Medicinrådet

Bilag til direkte indplacering af guselkumab i Medicinrådets evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til Crohns sygdom

Vers. 1.0

Bilagsoversigt

1. Forhandlingsnotat fra Amgros vedr. guselkumab
2. Ansøgers endelige ansøgning vedr. guselkumab

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12.08.2025

DBS/LSC

Forhandlingsnotat

Dato for behandling i Medicinrådet	03.09.2025
Leverandør	Johnsson and Johnson
Lægemiddel	Tremfya (guselkumab)
Ansøgt indikation	Tremfya er indiceret til behandling af voksne patienter med moderat til svært aktiv Crohns sygdom, som ikke har responderet tilstrækkeligt på, ikke længere responderer på eller er intolerante over for enten konventionel behandling eller en biologisk behandling
Nyt lægemiddel / indikationsudvidelse	Indikationsudvidelse – direkte indplacering i behandlingsvejledning

Prisinformation

Amgros har forhandlet pris på de nye styrker af Tremya (guselkumab).

[redacted]

Tabel 1: Forhandlingsresultat

Lægemiddel	Styrke (paknings-tørrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Rabat ift. AIP
Tremfya	200 mg, 1 stk. hætteglas	14.188,17	[redacted]	[redacted]
Tremfya	200 mg, 1 stk. pen	14.188,17	[redacted]	[redacted]

Prisen er betinget af Medicinrådets anbefaling. Det betyder, at hvis Medicinrådet ikke anbefaler Tremfya, indkøbes lægemidlet til AIP.

Amgros har følgende aftalepriser på Tremfya 100 mg pen og sprøjte:

Tabel 1: Aftalepriser

Lægemiddel	Styrke (Paknings-størrelse)	AIP (DKK)	Nuværende SAIP, (DKK)	Rabat ift. AIP
Tremfya	100 mg, 1 stk. pen/sprøjte	14.188,17	[redacted]	[redacted]

Aftaleforhold

[redacted]

Konkurrencesituationen

Denne direkte indplacering drejer sig om indplacering af Tremfya i de kliniske spørgsmål vedr. patienter:

- til behandling af voksne BMSL-naive patienter med moderat til svær aktiv Crohns sygdom
- til behandling af voksne BMSL-erfarne patienter med moderat til svær aktiv Crohns sygdom

[redacted]

Tabel 2 viser lægemiddeludgifter på udvalgte sammenlignelige lægemidler. Lægemiddeludgiften pr. patient er beregnet på 78 uger (18 måneders behandling) jf. det kliniske sammenligningsgrundlag i Medicinrådets

opsummering af evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til Crohns sygdom.

Tabel 2: Sammenligning af lægemiddeludgifter pr. patient

Lægemiddel	Styrke (pakningsstørrelse)	Dosering	Pris pr. pakning (SAIP, DKK)	Lægemiddeludgift pr. behandling på 78 uger (SAIP, DKK)*
Amgevita (biosimilær, adalimumab)	40 mg, 2 stk. sprøjte	**Induktion (s.c):** 160 mg uge 0, 80 mg uge 2. **Vedligeholdelse (s.c.):** 40 mg hver 2. uge.	[redacted]	[redacted]
Steqeyma (biosimilær, ustekinumab)	130 mg, 1 stk. hætteglas 90 mg, 1 stk. sprøjte	**Induktion (i.v.):** 390 mg (55-85 kg) uge 0. **Vedligeholdelse (s.c.):** 90 mg uge 8 og herefter hver 12. uge.	[redacted]	[redacted]
Tremfya (guselkumab)	200 mg, 1 stk. hætteglas **NY** 100 mg, 1 stk. pen/sprøjte	**Induktion (i.v.):** 200 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 100 mg hver 8. uge	[redacted]	[redacted]
Tremfya (guselkumab)	200 mg, 1 stk. hætteglas **NY** 200 mg, 1 stk. pen/sprøjte **NY**	**Induktion (i.v.):** 200 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 200 mg hver 4. uge	[redacted]	[redacted]
Tremfya (guselkumab)	200 mg, 1 stk. pen/sprøjte **NY** 100 mg, 1 stk. pen/sprøjte	**Induktion (i.v.):** 400 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 100 mg hver 8. uge	[redacted]	[redacted]
Tremfya (guselkumab)	200 mg, 1 stk. pen/sprøjte **NY**	**Induktion (i.v.):** 400 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 200 mg hver 4. uge	[redacted]	[redacted]

Zessly (infliximab)	100 mg, 3 stk. hætteglas	**Induktion (i.v.):** 5 mg/kg uge 0, 2 og 6. **Vedligehold (i.v.):** 5 mg/kg hver 8. uge.	[redacted]	[redacted]
Skyrizi (risankizumab)	600 mg, 1 stk. hætteglas 360 mg, 1 stk. pen	**Induktion (i.v.):** 600 mg uge 0, 4 og 8. **Vedligeholdelse (s.c.):** 360 mg hver 8. uge fra uge 12.	[redacted]	[redacted]
Entyvio (vedolizumab) *i.v. + s.c.*	300 mg, 1 stk. hætteglas 108 mg, 1 stk. pen/sprøjte	**Induktion (i.v.):** 300 mg uge 0 og 2. **Vedligeholdelse (s.c.):** 108 mg uge 6 og herefter 108 mg hver 2. uge.	[redacted]	[redacted]
Entyvio (vedolizumab) *i.v.*	300 mg, 1 stk. hætteglas	**Induktion (i.v.):** 300 mg uge 0, 2 og 6. **Vedligeholdelse (i.v.):** 300 mg hver 8. uge.	[redacted]	[redacted]

*jf. det kliniske sammenligningsgrundlag i Medicinrådets opsummering af evidensgennemgang vedrørende biologiske og målrettede syntetiske lægemidler til Crohns sygdom.
Note: Gennemsnitsvægt for en patient er estimeret til 75 kg.
[redacted]

Status fra andre lande

Tabel 1: Status fra andre lande

Land	Status	Link
Norge	Under vurdering	Link til status
England	Under vurdering	Link til status

Opsummering

[redacted]

Application for the assessment of guselkumab (Tremfya®) by updating the Danish Medicines Council's guideline regarding biological and targeted synthetic drugs for the treatment of Crohn's disease

Contact information

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Abbreviations

Abbreviations	Definition
AE	Adverse event
BMSL	Biological and targeted synthetic medicine
CD	Crohn's disease
CDAI	Crohn's Disease Activity Index
CD64	Fc-gamma receptor 1
CI	Confidence interval
COVID-19	Coronavirus disease-19
DMC	Danish Medicines Council
EIM	Extra-intestinal manifestations
EMA	European Medicines Agency
IBD	Inflammatory Bowel Disease
IBDQ	Inflammatory Bowel Disease Questionnaire
ICE	Intercurrent event
IL	Interleukin
IV	Intravenous
N/A	Not applicable
PBO	Placebo
Q4W	Every 4 weeks
Q8W	Every 8 weeks
SC	Subcutaneous
SD	Standard deviation

1. Regulatory information on the pharmaceutical

Table 1 Overview of guselkumab

Overview of the pharmaceutical	
Proprietary name	Tremfya®
Generic name	Guselkumab
Therapeutic indication as defined by EMA	Guselkumab for the treatment of adult patients with moderately to severely active Crohn's disease (CD) who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment (1).
Marketing authorization holder in Denmark	Johnson & Johnson
ATC code	L04AC16
Combination therapy and/or co-medication	No
(Expected) Date of EC approval	May 07th 2025
Has the pharmaceutical received a conditional marketing authorization?	No
Accelerated assessment in the European Medicines Agency (EMA)	No
Orphan drug designation (include date)	No
Other therapeutic indications approved by EMA	Guselkumab is indicated for the treatment of moderate to severe plaque psoriasis in adults who are candidates for systemic therapy (2). Guselkumab, alone or in combination with methotrexate, is indicated for the treatment of active psoriatic arthritis in adult patients who have had an inadequate response or who have been

Overview of the pharmaceutical	
	intolerant to a prior disease-modifying antirheumatic drug therapy (2). Guselkumab is indicated for the treatment of adult patients with moderately to severely active ulcerative colitis who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biologic treatment (1).
Other indications that have been evaluated by the Danish Medicines Council (DMC) (yes/no)	Yes. Guselkumab is indicated for psoriatic arthritis (3) and for plaque psoriasis (4, 5) and have previously been evaluated by the DMC.
Dispensing group	NBS
Packaging – types, sizes/number of units and concentrations	Guselkumab (Tremfya®) 100 mg solution for injection in pre-filled pen Guselkumab (Tremfya®) 100 mg solution for injection in pre-filled syringe Guselkumab (Tremfya®) 200 mg solution for injection in pre-filled pen* Guselkumab (Tremfya®) 200 mg solution for intravenous (IV) administration*

Abbreviations: CD = Crohn's disease; DMC = Danish Medicines Council; EMA = European Medicines Agency; IV = intravenous.
Note: * Not available from Medicinpriser.dk until June 2025.
Source: European Medicines Agency, 2024 (2); Danish Medicines Agency, 2024 (6); Johnson & Johnson [Data on file] (1).

2. Summary table

Table 2 Summary table

Summary	
Therapeutic indication relevant for the assessment	Guselkumab for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment (1).
Dosage regiment and administration	The recommended induction dose is 200 mg guselkumab IV infusion at Week 0, Week 4, and Week 8 or 400 mg subcutaneous (SC) at Week 0, Week 4, and Week 8 (1). The recommended and standard maintenance dose is 100 mg guselkumab SC injection starting at Week 16 and every 8 weeks (Q8W). Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg SC injection starting at Week 12 and every 4 weeks (Q4W) thereafter, may be

Summary	
	considered (1). As evident from section 5.2 and 6.2, the two maintenance regimens show comparable efficacy.
Choice of comparator [if any]	Ustekinumab is a relevant comparator as ustekinumab is included in the existing treatment guideline for CD. Placebo is also included as a comparator.
Most important efficacy endpoints (Difference/gain compared to comparator)	GALAXI 2 BMSL-naïve Clinical remission (Week 12), adjusted treatment difference: guselkumab 100mg vs PBO = 30.9%, guselkumab 200mg vs PBO = 33.4%. Corticosteroid-free clinical remission (Week 48), adjusted treatment difference: guselkumab 100mg vs uste = -3.7%, guselkumab 200mg vs uste = 10.1% GALAXI 3 BMSL-naïve Clinical remission (Week 12), adjusted treatment difference: guselkumab 100mg vs PBO = 33.7%, guselkumab 200mg vs PBO = 31.2%. Corticosteroid-free clinical remission (Week 48), adjusted treatment difference: guselkumab 100mg vs uste = -10.3%, guselkumab 200mg vs uste = 11.2% GRAVITI BMSL-naïve Clinical remission (Week 12), adjusted treatment difference: guselkumab 100mg vs PBO = 29.8%; guselkumab 200mg vs PBO = 20.7%. GALAXI 2 BMSL-experienced Clinical remission (Week 12), adjusted treatment difference: guselkumab 100mg vs PBO = 17.7%, guselkumab 200mg vs PBO = 26.2%. Corticosteroid-free clinical remission (Week 48), adjusted treatment difference: guselkumab 100mg vs uste = 2.3%, guselkumab 200mg vs uste = 10.9% GALAXI 3 BMSL-experienced Clinical remission (Week 12), adjusted treatment difference: guselkumab 100mg vs PBO = 36.0%, guselkumab 200mg vs PBO = 28.4%. Corticosteroid-free clinical remission (Week 48), adjusted treatment difference: guselkumab 100mg vs uste = 19.9%, guselkumab 200mg vs uste = 17.9% GRAVITI BMSL-experienced Clinical remission (Week 12), adjusted treatment difference: guselkumab 100mg vs PBO = 50.5%; guselkumab 200mg vs PBO = 35.7%
Most important serious adverse events for the intervention and comparator	In GALAXI 2, 2 (3.4%) patients experienced worsening of CD in the guselkumab 100 mg SC group, 0 in the guselkumab 200 mg SC group, and 0 in the ustekinumab group among BMSL-naïve patients by Week 48 (7).

Summary	
	In GALAXI 2, 3 (3.9%) patients experienced worsening of CD in the guselkumab 100 mg SC group, 0 in the guselkumab 200 mg SC group, and 3 (3.8%) in the ustekinumab group among BMSL-experienced patients by Week 48 (7). In GALAXI 3, 0 patients experienced worsening of CD in the guselkumab 100 mg SC group and 0 in the guselkumab 200 mg SC group among BMSL-naïve patients by Week 48 (8). In GALAXI 3, 1 (1.3%) patient experienced worsening of CD by Week 48 in the guselkumab 100 mg SC group, 2 (2.7) in the guselkumab 200 mg SC group, and 1 (1.3%) in the ustekinumab group among BMSL-experienced patients. 0 patients experienced anal fistula by Week 48 in the guselkumab 100 mg SC group, 0 in the guselkumab 200 mg SC group, and 0 in the ustekinumab group among BMSL-experienced patients (8). In GRAVITI, 4 (7.1%) in the guselkumab 100 mg SC group among BMSL-naïve patients experienced worsening of CD by Week 48. In comparison, 1 (3.7%) experienced worsening of CD in the placebo group, 1 (1.5%) in the guselkumab 200 mg SC group. No serious AEs were experienced by ≥5% in any treatment arm among the BMSL-experienced patients (9).

Abbreviations: AE = adverse event; CD = Crohn's disease; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: European Medicines Agency, 2024 (2); Johnson & Johnson [Data on file] (1, 7-9)

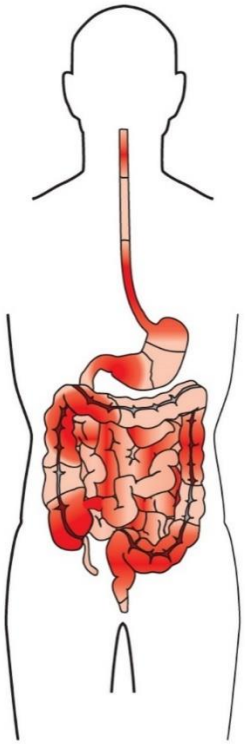
3. The patient population, intervention and relevant outcomes

3.1 The medical condition, patient population, current treatment options and choice of comparator(s)

3.1.1 Introduction to Crohn's disease

Inflammatory bowel disease (IBD) is characterized by chronic immune-mediated inflammation of the gastrointestinal (GI) tract (10-14). Crohn's disease and ulcerative colitis (UC) are the most common forms of IBD, with each presenting with distinct clinical features (10, 11, 13, 14). Whereas UC mainly affects the colon and the rectum, CD is characterised by transmural inflammation that can occur throughout the entirety of the GI tract, from the mouth to the anus (14-16). In particular, the ileum of the small intestine and the colon are the most frequently affected regions in patients with CD (14, 17). The inflammation of CD can be described as "patchy," with areas of inflammation distributed between normal areas along the GI tract (Figure 1) (18).

Figure 1 Inflammation sites of the GI tract in CD



Abbreviations: CD = Crohn's disease; GI = gastrointestinal.
Source: Adapted from Baumgart and Sandborn (19).

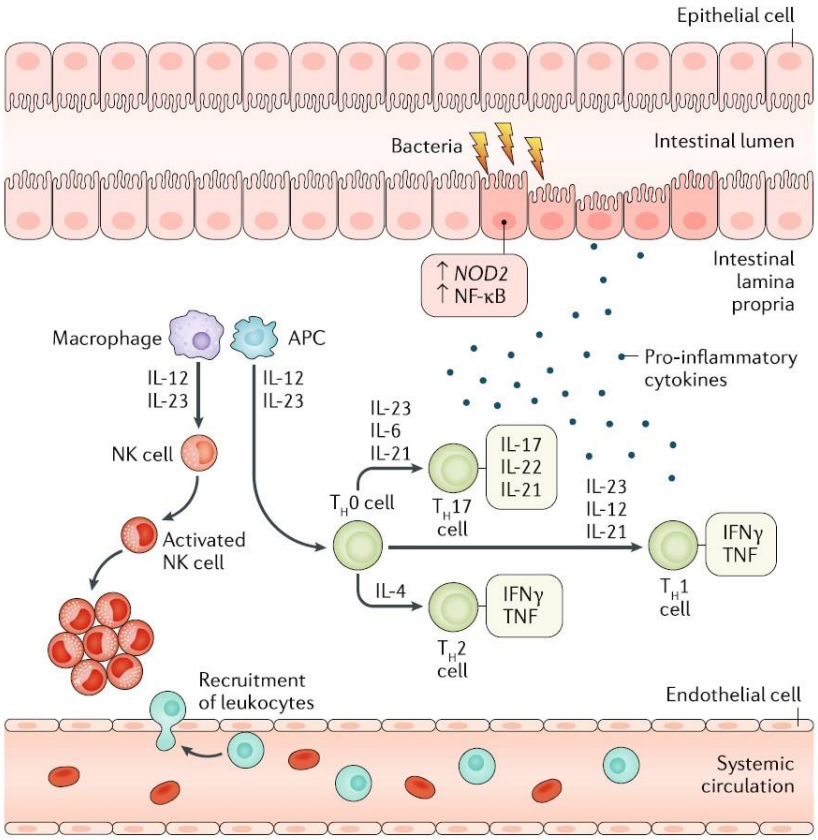
Disease onset typically occurs during early adulthood (14, 16), with the highest incidence rates among those 20 to 29 years of age (20). The condition typically presents in phases (13, 16), with alternating periods of clinical relapse and remission (14). Relapse occurs sporadically and is mostly unpredictable, with stable and prolonged symptom-free periods occurring in only 10% of patients (21). During active disease, patients with CD may experience symptoms such as diarrhoea, abdominal pain, rectal bleeding, and fatigue (16). As classifications of CD severity predominantly rely on symptomology (22), symptom burden increases as severity increases from mild to moderately or severely active (23).

It is important to note that CD has a progressive and destructive course (24-28). Over time, chronic inflammation drives disease progression and can lead to more serious complications that impair intestinal function, such as fibrosis, strictures, fistulas, fissures, and abscesses (24-28). Fibrosis (an excessive accumulation of scar tissue on the intestinal wall) is one of the most common and serious complications of CD, and can lead to narrowing of intestinal segments, impairing their function (29, 30). Fistulas (an abnormal connection between two epithelialized surfaces) are another common manifestation of CD, with approximately up to 40% of patients developing at least one fistula during their lifetime (30, 31). The treatment of patients with these complications is complex and often requires costly surgical intervention (30). Further, compromised GI function can result in impaired digestion and malabsorption, leading to other serious complications, such as malnutrition and extra-intestinal manifestations (EIMs), including anaemia, gall stones, and osteoporosis (16, 21, 32).

3.1.2 Pathobiology

Although the pathogenesis of CD is complex and remains elusive, it is believed to involve dysbiosis, epithelial barrier disruption, and dysregulated innate and adaptive immune system responses (12, 17, 33, 34). Genetic/immune drivers, environmental triggers, as well as lifestyle/diet can all contribute to a pre-disease state where IBD happens at a sub-clinical level (35). Microbes that are otherwise not harmful in patients without IBD transform to pathogenic microbes (pathobionts), resulting in immune activation, mucus depletion, and a compromised barrier. As the disease progresses, increased pathobionts and a decrease in beneficial microbes lead to active inflammation and mucosal damage (initial disease stage). Persistent inflammation and long-term dysbiosis then lead to immune imbalance and the inability for mucosal healing which maintains the inflammatory and dysbiotic state. This ultimately results in chronic inflammation of the intestinal mucosa and tissue, caused by abnormal and uncontrollable innate and adaptive immune responses to pathogens or environmental triggers (12-14, 36). The causes and inflammatory response of CD are shown in Figure 2**.**

Figure 2 Hypothetical model of CD pathogenesis



Abbreviations: APC = antigen-presenting cell; IFN = interferon; IL = interleukin; NF-κB = nuclear factor-κB; NK = natural killer; NOD2 = nucleotide binding oligomerization domain containing 2; TH0 = T helper; TH1 = T helper 1; TH2 = T helper 2; TH17 = T helper 17.
Source: Roda, Chien Ng (21).

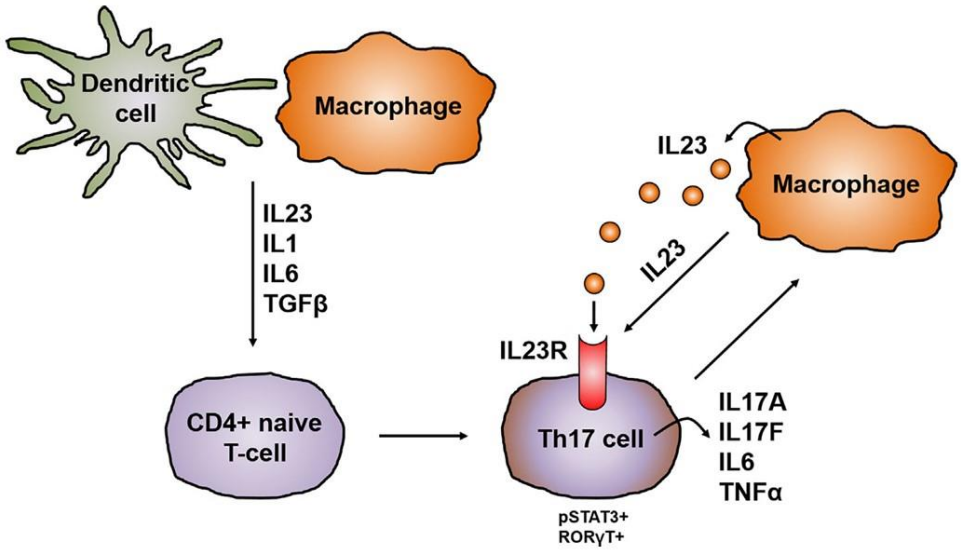
Interleukin (IL)-23 plays a key role in the pathophysiology of CD, as it mediates both innate and adaptive immunity, as well as in mucosal barrier function (12). Polymorphisms in the

gene encoding IL-23 receptor (IL23R) have been linked to the pathogenesis of IBD, indicating the important role of IL23 signalling in mucosal inflammation (12, 37). The importance of IL-23 in intestinal inflammation is further supported by findings that samples of inflamed mucosa from patients with CD have been shown to have elevated levels of IL-23, and IL-23 expression was positively correlated with the severity of lesions identified in endoscopy (12, 38-40).

As a crucial inflammatory mediator, IL-23 activates and promotes effector functions of T helper type 17 (Th17) cells and other IL-17 producing cells (12). Th17 cells mainly produce IL-17 and a range of other pro-inflammatory cytokines, including IL-6, IL-21, IL-22, interferon (IFN)-γ, and tumour necrosis factor (TNF; formerly known as TNF alpha) (12, 13). In addition to activating Th-17 cells, IL-23 can also stimulate innate immune cells such as natural killer (NK) cells and innate lymphoid cells (ILCs) (12). In particular, IL-23 can induce IFN-γ production by NK cells, and ILC3 cells respond to IL-23 by secreting pro-inflammatory cytokines such as IL-17, TNF, and IL-22 (12). IL-23 signalling has also been shown to suppress Treg differentiation (12, 13).

In chronic inflammation, antigen-presenting cells (APCs) such as dendritic cells and macrophages are the main producers of IL-23, along with IL-1, IL-6, and TGFβ, thereby promoting the development of IL-17–producing pathogenic Th17 cells from CD4+ helper T cells (see Figure 3) (12). Of interest, myeloid cells that express Fcγ receptor I (CD64) were found to be the primary cellular source of IL-23 in inflamed gut tissue of patients with IBD (41-43). In patients with CD, APCs produce an increased amount of IL-23 in the ileal and colonic wall of the intestine (11-13). The subsequent development of Th17 cells then leads to the upregulation of IL23R on Th17 cells and the release of several cytokines, including TNF-α, IFN-γ, IL-6, IL-17A, IL-17F, and IL-22, causing a macrophage-mediated production of more IL-23, which drives continued inflammation via downstream proinflammatory responses (12). Over time, these uncontrolled responses can result in chronic intestinal inflammation (13).

Figure 3 Role of the IL-23 pathway in CD



Abbreviations: CD = Crohn's disease; IL = interleukin; IL23R = IL-23 receptor; pSTAT3 = phosphorylated signal transducer and activator of transcription 3; RORγT = retinoid acid related-orphan nuclear receptor gamma; Th17 = T helper type 17; TGFβ = transforming growth factor-β; TNF-α = tumor necrosis factor-alpha.
Source: Schmitt, Neurath (12).

The resulting intestinal inflammation can lead to serious intestinal complications like fibrosis, strictures, and fistulas, which can impair GI function, as well as to EIMs like anaemia, gall stones, osteoporosis, inflammatory arthropathies, psoriasis and psoriatic arthritis.

In support for the key role of IL-23 in the pathogenesis of IBD, the inhibition of IL-23 with guselkumab was shown to restore intestinal immune homeostasis and promote epithelial repair in tissue samples from patients with UC (44). More specifically, treatment with guselkumab resulted in significant reduction in serum levels and colon tissue levels of the downstream effector cytokines IL-17A, IL-22, and IFNγ. Of interest, a recent *in vitro* study found that the ability of guselkumab to also bind to CD64 on IL-23—producing cells through guselkumab's native Fc region may contribute to its enhanced functional potency with respect to the inhibition of IL-23 signalling compared with risankizumab, which has a mutated Fc region (45). This suggests that guselkumab may be more effective at neutralising IL-23 by targeting IL-23 at its source of production.

3.2 The intervention

Table 3 Overview of guselkumab

Overview of guselkumab	
Therapeutic indication relevant for the assessment	Guselkumab for the treatment of adult patients with moderately to severely active CD who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic treatment (1).
Method of administration	Induction: IV infusion or SC injection Maintenance: SC injection
Dosing	The recommended induction dose is 200 mg guselkumab IV infusion at Week 0, Week 4 and Week 8 or 400 mg SC at Week 0, Week 4 and Week 8.The recommended maintenance dose is 100 mg guselkumab SC injection starting at Week 16 and Q8W. Alternatively, for patients who do not show adequate therapeutic benefit to induction treatment according to clinical judgement, a maintenance dose of 200 mg SC injection starting at Week 12 and Q4W thereafter, may be considered (1). As evident from section 5.2 and 6.2, the two maintenance regimens show comparable efficacy.
Should the pharmaceutical be administered with other medicines?	No

Overview of guselkumab	
Treatment duration / criteria for end of treatment	If a patient develops a clinically important or serious infection or is not responding to standard therapy, the patient should be monitored closely and treatment should be discontinued until the infection resolves. If a serious hypersensitivity reaction occurs, administration of guselkumab should be discontinued immediately (1).
Necessary monitoring, both during administration and during the treatment period	After proper training in SC injection technique, patients may inject guselkumab if a physician determines that this is appropriate. However, the physician should ensure appropriate medical follow up of patients (1). Patients receiving guselkumab should be monitored for signs and symptoms of active tuberculosis during and after treatment (1).
Need for diagnostics or other tests (e.g. companion diagnostics). How are these included in the model?	No diagnostic tests are required for patients (1). No model has been developed for this this application.
Package size(s)	Guselkumab (Tremfya®) 100 mg solution for injection in prefilled pen Guselkumab (Tremfya®) 100 mg solution for injection in prefilled syringe Guselkumab (Tremfya®) 200 mg solution for injection in prefilled pen* Guselkumab (Tremfya®) 200 mg solution for IV*

Abbreviations: CD = Crohn's disease; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; UC = ulcerative colitis.
Note: * Not available from Medicinpriser.dk until June 2025.
Source: European Medicines Agency, 2024 (2); Danish Medicines Agency, 2024 (6); Johnson & Johnson [Data on file] (1).

3.2.1 Mechanism of action

Guselkumab is a human IgG1λ monoclonal antibody that binds selectively to the interleukin (IL)-23 protein with high specificity and affinity through the antigen binding site. IL-23 is a cytokine that is involved in inflammatory and immune responses. By blocking IL-23 from binding to its receptor, guselkumab inhibits IL-23- dependent cell signalling and release of proinflammatory cytokines (2).

In patients with CD or UC, levels of IL-23 are elevated in the colon tissue. In *in vitro* models, guselkumab was shown to inhibit the bioactivity of IL-23 by blocking its interaction with cell surface IL-23 receptor, disrupting IL-23-mediated signalling, activation, and cytokine cascades. Guselkumab exerts clinical effects in plaque psoriasis, psoriatic arthritis, UC, and CD through blockade of the IL-23 cytokine pathway (2).

Notably, guselkumab is the only selective IL-23 inhibitor that is dual-binding (12, 41-43, 45). Myeloid cells expressing Fc-gamma receptor 1 (CD64) have been shown to be a predominant source of IL-23 in inflamed tissue in psoriasis, UC, and CD. 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 inflammation (2).

3.2.2 The intervention in relation to Danish clinical practice

In line with previously assessed IL-23s, the intervention is expected to be placed in the "use" category for biological and targeted synthetic medicine (BMSL)-naïve patients and BMSL-experienced patients in v2.3 of the DMC Crohn's disease treatment guideline (46).

Ustekinumab is considered a relevant comparator to determine clinical equivalency as it is included in the existing treatment guideline for CD. In additions, placebo is also included as a comparator.

4. Overview of literature

Table 4 presents the relevant literature included in this application (GALAXI studies and GRAVITI).

In agreement with the DMC and as the treatment guideline includes a network meta-analysis, a systematic literature search has not been conducted for this application. However, Johnson & Johnson have conducted and published a network meta-analysis of guselkumab vs available advanced therapies for moderately to severely active Crohn's disease (47).

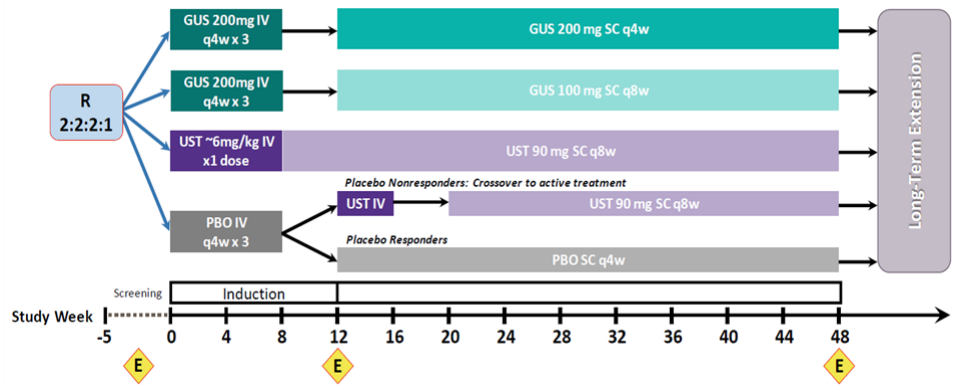
The GALAXI studies include GALAXI 1, 2, and 3 and are all registered under the same NCT number. As GALAXI 1 is a phase 2 dose-finding study, the study is not described further in this application.

GALAXI 2 and GALAXI 3 studies are randomized, double-blind, placebo-controlled, active-controlled (ustekinumab), parallel-group, multicenter studies. Both studies are conducted using a treat-through study design. Patients were randomised into either guselkumab 200 mg IV q4w, ustekinumab ~6mg/kg IV or placebo IV q4w during the induction phase (week 0 - week 8). During the maintenance phase (week 12 – week 48), guselkumab patients switch to either 200 mg SC q4w or 100 mg SC q8w, placebo patients who responded, where allowed to continue placebo treatment, whereas placebo patients who did not respond, were allowed to switch to ustekinumab. At week 8, ustekinumab patients switched to 90 mg SC q8w to through to week 48 (Figure 4).

As a result, in GALAXI 2 & 3, the comparison of efficacy between guselkumab vs placebo is only relevant during the induction phase, since during the maintenance phase, the placebo group will consist of patients who crossover to ustekinumab and will not be an appropriate comparator.

Conversely, the comparison of efficacy between guselkumab vs ustekinumab is only relevant during the maintenance phase.

Figure 4 GALAXI 2 & 3 trial design



GRAVITI is a phase 3, randomized, double-blind, placebo-controlled, parallel-group, multicenter study. GRAVITI will provide the main efficacy results for guselkumab vs placebo for this submission.

Table 4 Relevant literature included in the assessment of efficacy and safety [sample text in table for full paper and conference abstract]

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
GALAXI (consisting of GALAXI 1[Ω], GALAXI 2, and GALAXI 3), NCT03466411 Only the following publications, which describe GALAXI 1, are available: Danese et al. 2024 (48) and Sandborn et al. 2022 (49). GALAXI 2 and 3 publications are expected in mid-2025.	Double-blinded randomised placebo- and active-controlled phase 2/3 study†.	Induction phase through week 12 (I-12) and maintenance phase through week 48 (M-48).	Start: 13/04/18 Primary completion: 20/10/23 Estimated completion: 30/06/30 Data cut-off GALAXI 2: 20/10/23 Data cut-off GALAXI 3: 16/10/23 Future data cut-offs: No future data cut-offs for the randomised phase. Future data cut-offs are expected for the long-term extension study (NCT03466411) based on GALAXI 1, 2, and 3.	Participants with moderately to severely active CD who have demonstrated an inadequate response to or failure to tolerate previous conventional or biologic therapy. Both the BMSL-naïve and BMSL-experienced subpopulations are relevant.	Induction: 200 mg IV guselkumab Q4W (Weeks 0 through 8) Standard maintenance dose: 100 mg SC guselkumab Q8W (Weeks 16 through 40) Alternative maintenance dose: 200 mg SC guselkumab Q4W (Weeks 12 through 44)	Ustekinumab: Induction: 6 mg/kg IV at Week 0; Maintenance 90 mg SC Q8W (Week 8 through 40). Placebo: Induction: IV Q4W (Weeks 0 through 8). At week 12 responders continue treatment IV QW4 (Week 12 through Week 44) and nonresponders receive a single ustekinumab IV induction dose at Week 12 (6mg/kg) and ustekinumab 90 mg SC maintenance Q8W (Week 20 through 44).	1 and 2	Aligning with the DMC's template, primary and secondary outcomes in the study that are included in the treatment guideline are listed here. Secondary endpoints evaluating guselkumab vs. placebo were clinical remission and Inflammatory Bowel Disease Questionnaire (IBDQ) remission at Week 12 well as AEs. Secondary endpoints evaluating guselkumab vs. ustekinumab were corticosteroid-free clinical remission, endoscopic remission and IBDQ remission at Week 48. Clinical as well AEs.

Trial name, NCT identifier and reference (Full citation incl. reference number)*	Study design	Study duration	Dates of study (Start and expected completion date, data cut-off and expected data cut-offs)	Patient population (specify if a subpopulation in the relevant study)	Intervention	Comparator	Relevant for PICO nr. in treatment guideline	Outcomes and follow-up period
GRAVITI, NCT05197049. Hart et al. 2025 (50).	Double-blinded randomised placebo-controlled phase 3 study.	24 weeks main treatment phase (12-week induction period followed by 12-week maintenance period) followed by a 224-week extension.	Start: 19/01/22 Primary completion: 04/07/23 Estimated completion: 31/03/25 Data cut-off: 01/03/24 Future data cut-offs: No future data cut-offs for the main treatment phase. Future data cut-offs including data from Week 72 are expected for the long-term extension phase.	Participants with moderately to severely active CD with an inadequate response to or intolerance of prior conventional or biologic therapy. Both the BMSL-naïve and BMSL-experienced subpopulations are relevant.	Induction: 400 mg SC guselkumab at Weeks 0, 4, and 8 Standard maintenance dose: 100 mg SC guselkumab Q8W starting at Week 16 Alternative maintenance dose: 200 mg SC guselkumab Q4W starting at Week 12	Placebo SC Q4W from Week 0.	1 and 2	Aligning with the DMC's template, primary and secondary outcomes in the study that are also included in the treatment guideline are listed here. One of the co-primary endpoints were clinical remission at Week 12. Other endpoints included were corticosteroid-free clinical remission at Week 48, endoscopic remission at Week 48, IBDQ data at Week 12 and Week 48, as well as AEs.

Abbreviations: AE = adverse event; CD = Crohn's disease; DMC = Danish Medicines Council; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; N/A = not applicable; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Notes: * If there are several publications connected to a trial, include all publications used. Ω As GALAXI 1 is a phase 2 dose-finding study, the study is not described further in this application. † Only GALAXI 1 is as phase 2 study.

Source: ClinicalTrials.gov, 2018 (51); Janssen Research & Development, 2023 (52); Janssen Research & Development, 2024 (53); Janssen Research & Development, 2024 (54); ClinicalTrials.gov, 2022 (55); Janssen Research & Development, 2024 (56).

5. Clinical question(s) 1

5.1 Efficacy of guselkumab compared ustekinumab and placebo for BMSL-naïve patients with moderate to severe Crohn's disease

5.1.1 Relevant studies

The relevant studies are listed in Table 4. The application includes the pre-defined sub-population: biologically naïve patients defined as participants without prior exposure to biologic therapy (53, 54, 56) and will henceforth be referred to as BMSL-naïve patients.

5.1.2 Comparability of studies

The Danish treatment guideline for moderate to severe CD in BMSL-naïve patients are informed by 14 unique studies. The studies include randomised controlled, double-blinded and single-blinded studies, which are primarily phase 2 and 3 studies (57). The GALAXI and GRAVITI studies are randomised controlled, double-blinded, phase 2/3 trials, making them comparable to the studies informing the guideline. Both the GALAXI and GRAVITI studies are ongoing (the latest data cut-offs for GALAXI 2 & 3 were in 2023, and the latest data cut-off for GRAVITI was in 2024).

In GALAXI 2 & 3 and in GRAVITI, clinical remission was measured at Week 12 (53, 54, 56) in alignment with the treatment guideline including data from Week 4-12 (57). The DMC defines clinical remission as achieving a CDAI score of ≤150 (57, 58), similar to the definition applied in the studies included in this application (see section 5.2.1.1). In GALAXI 2 & 3 and in GRAVITI, corticosteroid-free clinical remission was measured at Week 48 (53, 54, 56) in alignment with the treatment guideline including data from Week 44-60 (57). The DMC defines systemic steroid-free remission as not receiving systemic corticosteroid treatment after 52 weeks and having a total CDAI score of ≤150 (57, 58), similar to the definition applied in this application (see section 5.2.1.1). In GALAXI 2 & 3 and in GRAVITI, endoscopic remission was measured at Week 48 (53, 54, 56).

The DMC does not specify the definition of endoscopic remission but suggests that Crohn's disease Endoscopic Index of Severity can be utilised. The definition of endoscopic remission applied in these studies is presented in section 0. Additionally, endoscopic remission is not included in the treatment guideline, as the data basis was insufficient (57). According to the DMC, AEs should be assessed quantitatively by number and percentage experiencing at least one serious AE and qualitatively (57, 58). Both a quantitative and qualitative description of AEs is reported in this application for GALAXI 2 & 3 and GRAVITI at Week 12 and 48. According to the DMC, quality of life should be measured as proportion of patients achieving a score ≥ 170 on the IBDQ and as change from baseline in IBDQ. This should be assessed at the longest follow-up (57, 58). In the treatment guideline, it is also stated that IBDQ is relevant to assess after induction treatment, i.e., at Week 6-8. However, the expert

committee found the available data to be too difficult to compare, and therefore IBDQ has not been assessed in the treatment guideline (57). In this application, both the proportion of patients achieving a score ≥ 170 on the IBDQ at Week 12 and Week 48 are included as well as change from baseline in in IBDQ.

5.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Table 5 presents the baseline characteristics of BMSL-naïve patients in GALAXI 2 and 3 as well as in GRAVITI. Overall, demographic and baseline characteristics as well as disease characteristics for the BMSL-naïve patients included in GALAXI 2 and 3 and GRAVITI were comparable across all treatment arms. For instance, patients were similar in terms of age (median age: 33.6-39.3) and race, with most patients being white (≥75%). In terms of disease characteristics, patients were similar across treatments arms. Although, CD duration was a bit longer in the placebo group in GALAXI 3 compared to all other treatment arms.

According to the DMC, the patient populations in the 14 studies informing the Danish treatment guideline for moderate to severe CD in BMSL-naïve patients are comparable and align with the Danish patient population (57). Compared with the baseline characteristics of the 14 studies informing the treatment guideline, the patients in GALAXI 2 and 3 and GRAVITI are similar in terms of age, sex, and disease characteristics such as CDAI and IBDQ score. For instance, the mean CDAI and IBDQ scores observed in GALAXI 2 and 3 and GRAVITI fall within the ranges observed in the DMC studies (mean CDAI of 288.7-301.2 across GRAVITI and GALAXI studies compared with 88-329.2 across the DMC studies, and mean IBDQ mean of 115.5-133.3 across GRAVITI and GALAXI studies compared with 116-200 across the DMC studies).

Furthermore, BMSL-naïve patients in the GALAXI and GRAVITI studies had a mean weight at baseline of 64.65-75.04 kg. This is in line with the Expert Committee's estimate that Danish BMSL-naïve patients with moderate to severe CD have an average weight of approximately 75 kg (57). Since the baseline characteristics of the BMSL-naïve patient populations in GALAXI 2 and 3 as well as in GRAVITI closely match those of these 14 studies informing the treatment guideline, it is expected that the BMSL-naïve patients in GALAXI 2 and 3 and GRAVITI are also comparable to the Danish patient population.

Table 5 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	GALAXI 2				GALAXI 3				GRAVITI		
	PBO[a] N=34	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=63	UST ~6 mg/kg IV → 90 mg SC Q8W N=58	PBO [a] N=27	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=65	UST ~6 mg/kg IV → 90 mg SC Q8W N=63	PBO N=56	GUS 400 mg SC Q4W → 100 mg SC Q8W N=53	GUS 400 mg SC Q4W → 200 mg SC Q4W N=52
Age in years, mean (standard deviation [SD])	33.6 (12.41)	39.3 (15.18)	38.1 (14.26)	34.8 (11.92)	35.8 (14.01)	33.7 (9.44)	36.4 (13.18)	37.1 (13.83)	36.04 (12.28)	38.21 (13.80)	38.98 (13.00)
Sex, n (%)											
Females	17 (50.0)	34 (58.6)	30 (47.6)	26 (44.8)	12 (44.4)	23 (39.7)	20 (30.8)	28 (44.4)	27 (48.2)	24 (45.3)	15 (28.8)
Males	17 (50.0)	24 (41.4)	33 (52.4)	32 (55.2)	15 (55.6)	35 (60.3)	45 (69.2)	35 (55.6)	29 (51.8)	29 (54.7)	37 (71.2)
Race, n (%)											
Asian	2 (5.9)	8 (13.8)	5 (7.9)	5 (8.6)	1 (3.7)	7 (12.1)	8 (12.3)	3 (4.8)	5 (8.9)	7 (13.2)	10 (19.2)
Black or African American	0	0	1 (1.6)	0	0	0	0	0	1 (1.8)	0	0
Native Hawaiian or Other	2 (5.9)	0	0	0	2 (7.4)	0	0	0	0	0	0

	GALAXI 2				GALAXI 3				GRAVITI		
	PBO[a] N=34	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=63	UST ~6 mg/kg IV → 90 mg SC Q8W N=58	PBO [a] N=27	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=65	UST ~6 mg/kg IV → 90 mg SC Q8W N=63	PBO N=56	GUS 400 mg SC Q4W → 100 mg SC Q8W N=53	GUS 400 mg SC Q4W → 200 mg SC Q4W N=52
Pacific Islander											
White	30 (88.2)	50 (86.2)	57 (90.5)	53 (91.4)	23 (85.2)	51 (87.9)	57 (87.7)	59 (93.7)	46 (82.1)	44 (83)	39 (75)
Not reported	0	0	0	0	1 (3.7)	0	0	1 (1.6)	4 (7.1)	2 (3.8)	3 (5.8)
Weight in kg, mean (SD)	65.57 (12.92)	66.20 (14.93)	68.60 (15.83)	66.44 (16.18)	70.46 (19.28)	69.14 (17.28)	70.77 (15.82)	75.04 (19.48)	67.91 (12.86)	74.06 (19.31)	74.9 (18.87)
Height in cm, mean (SD)	170.80 (10.86)	169.18 (10.50)	170.98 (9.45)	170.55 (10.04)	171.98 (9.61)	172.43 (9.53)	174.09 (10.56)	172.00 (10.39)	168.08 (9.64)	172.73 (9.20)	173.15 (9.40)
CD duration (years), mean (SD)	3.70 (4.45)	5.00 (6.18)	5.95 (7.06)	4.24 (4.52)	7.03 (6.98)	4.68 (4.57)	4.79 (6.78)	5.34 (6.76)	5.79 (7.55)	5.76 (6.13)	5.41 (5.44)
CDAI score, mean (SD)	290.5 (48.07)	300.0 (55.28)	296.0 (56.22)	293.4 (49.39)	288.8 (45.68)	290.6 (53.52)	292.4 (49.15)	288.7 (52.99)	291.3 (49.88)	301.2 (58.07)	298.2 (55.79)
Simple Endoscopic Score for CD	12.4 (6.36)	12.8 (7.36)	12.2 (6.89)	12.2 (6.72)	9.2 (4.59)	11.5 (6.69)	11.9 (7.25)	12.0 (6.33)	10.5 (5.23)	10.6 (5.20)	10.4 (5.69)

	GALAXI 2				GALAXI 3				GRAVITI		
	PBO[a] N=34	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=63	UST ~6 mg/kg IV → 90 mg SC Q8W N=58	PBO [a] N=27	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=65	UST ~6 mg/kg IV → 90 mg SC Q8W N=63	PBO N=56	GUS 400 mg SC Q4W → 100 mg SC Q8W N=53	GUS 400 mg SC Q4W → 200 mg SC Q4W N=52
(SES-CD), mean (SD)											
IBDQ, mean (SD)	127.0 (35.72), n=33	128.5 (31.62)	125.5 (28.14)	124.6 (28.67)	123.2 (31.75)	127.6 (35.33), n=55	127.1 (28.39)	133.3 (30.42), n=61	123.7 (32.21), n=52	126.5 (34.21), n=51	115.5 (31.51), n=51

Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; N/A = not applicable; Q4W =every 4 weeks; Q8W =every 8 weeks; SC = subcutaneous; SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Notes: [a] Placebo column includes all subjects randomised to placebo. At Week 12, subjects who were clinical responders continued placebo treatment and those who were nonresponders crossed over to ustekinumab.

Source: Johnson & Johnson; [Data on file] (7-9)

5.2 Comparative analyses of efficacy and safety

5.2.1 Efficacy and safety – results per study

The efficacy data presented in this dossier is based on the BMSL-naïve subgroup analyses of the ITT populations for the GALAXI and GRAVITI studies in order to comply with the Danish treatment guideline patient population scope.

Study discontinuations and the respective reasons for discontinuations for GALAXI and GRAVITI for both the induction phase (I-12) and maintenance phase (M-48) are described below.

Table 6 Discontinuation in GALAXI 2 prior to Week I-12 (BMSL-naïve subgroup)

	PBO N=34	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=63
Subjects who discontinued, n (%)	0 (0.0)	0 (0.0)	0 (0.0)
Reason for discontinuation, n (%)			
Adverse event	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: I = induction; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7)

Table 7 Discontinuation in GALAXI 2 prior to Week M-48 (BMSL-naïve subgroup)

	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=63	UST ~6 mg/kg IV → 90 mg SC Q8W N=58
Subjects who discontinued, n (%)	2 (3.4)	0 (0.0)	8 (13.8)
Reason for discontinuation, n (%)			
Worsening of CD	0 (0.0)	0 (0.0)	2 (3.4)
Other adverse event	0 (0.0)	0 (0.0)	1 (1.7)
Lack of efficacy	1 (1.7)	0 (0.0)	1 (1.7)

Withdrawal by subject	1 (1.7)	0 (0.0)	4 (6.9)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CD = Crohn's disease; IV = intravenous; M = maintenance; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7)

Table 8 Discontinuation in GALAXI 3 prior to Week I-12 (BMSL-naïve subgroup)

	PBO N=27	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=65
Subjects who discontinued, n (%)	0 (0.0)	1 (1.7)	1 (1.5)
Reason for discontinuation, n (%)			
Worsening of CD	0 (0.0)	0 (0.0)	1 (1.5)
Withdrawal by subject	0 (0.0)	1 (1.7)	0 (0.0)
CD-related surgery	0 (0.0)	0 (0.0)	0 (0.0)
Other	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: CD = Crohn's disease; I = induction; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (8)

Table 9 Discontinuation in GALAXI 3 prior to Week M-48 (BMSL-naïve subgroup)

	GUS 200 mg IV Q4W → 100 mg SC Q8W N=58	GUS 200 mg IV Q4W → 200 mg SC Q4W N=65	UST ~6 mg/kg IV → 90 mg SC Q8W N=63
Subjects who discontinued, n (%)	7 (12.1)	10 (15.4)	6 (9.5)
Reason for discontinuation, n (%)			
Worsening of CD	1 (1.7)	1 (1.5)	0 (0.0)
Other adverse event	2 (3.4)	4 (6.2)	0 (0.0)
Lost to follow-up	1 (1.7)	0 (0.0)	1 (1.6)

Pregnancy	0 (0.0)	0 (0.0)	2 (3.2)
Subject refused further study treatment	0 (0.0)	2 (3.1)	0 (0.0)
Withdrawal by subject	2 (3.4)	2 (3.1)	1 (1.6)
CD-related surgery	0 (0.0)	1 (1.5)	1 (1.6)
Other	2 (3.4)	0 (0.0)	1 (1.6)

Abbreviations: CD = Crohn's disease; IV = intravenous; M = maintenance; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (8)

Table 10 Discontinuation in GRAVITI prior to Week I-12 (BMSL-naïve subgroup)

	PBO N=56	GUS 400 mg SC Q4W → 100 mg SC Q8W N=53	GUS 400 mg SC Q4W → 200 mg SC Q4W N=52
Subjects who discontinued, n (%)	4 (7.1)	0 (0.0)	0 (0.0)
Reason for discontinuation, n (%)			
Withdrawal by subject	3 (5.4)	0 (0.0)	0 (0.0)
Protocol deviation	1 (1.8)	0 (0.0)	0 (0.0)

Abbreviations: CD = Crohn's disease; I-# = XX; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (9)

Table 11 Discontinuation in GRAVITI prior to Week M-48 (BMSL-naïve subgroup)

	PBO N=56	GUS 400 mg SC Q4W → 100 mg SC Q8W N=53	GUS 400 mg SC Q4W → 200 mg SC Q4W N=52
Subjects who discontinued, n (%)	12 (21.4)	2 (3.8)	1 (1.9)
Reason for discontinuation, n (%)			
Withdrawal by subject	3 (5.4)	0 (0.0)	0 (0.0)

Lack of efficacy	1 (1.8)	1 (1.9)	0 (0.0)
Worsening of CD	2 (3.6)	0 (0.0)	1 (1.9)
Other adverse event	0 (0.0)	1 (1.9)	0 (0.0)
Pregnancy	1 (1.8)	0 (0.0)	0 (0.0)
Week 20/24 non-responder	1 (1.8)	0 (0.0)	0 (0.0)
Lost to follow-up	1 (1.8)	0 (0.0)	0 (0.0)
Initiated prohibited medication	1 (1.8)	0 (0.0)	0 (0.0)
Protocol deviation	1 (1.8)	0 (0.0)	0 (0.0)
Other	1 (1.8)	0 (0.0)	0 (0.0)

Abbreviations: CD = Crohn's disease; IV = intravenous; M = maintenance; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (9)

5.2.1.1 Clinical remission at Week 12

Table 12 presents clinical remission at Week 12 defined as CDAI score <150. As shown in the table below, guselkumab 100mg and 200mg SC demonstrated similar results vs placebo, therefore no differences in efficacy between the 2 doses were observed.

Table 12 Clinical remission at Week 12 (BMSL-naïve subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	28 (48.3)	Vs. PBO: 30.9%	11.9%, 49.9%	0.0014
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	32 (50.8)	Vs. PBO: 33.4%	14.8%, 52.0%	0.0004
	PBO	34	6 (17.6)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	29 (50.0)	Vs. PBO: 33.7%	13.5%, 53.9%	0.0011
	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	32 (49.2)	Vs. PBO: 31.2%	12.3%, 50.1%	0.0012

	PBO	27	4 (14.8)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	29 (54.7)	29.8%	11.8%, 47.8%	0.0012
	GUS 400 mg SC Q4W → 200 mg SC Q4W	52	23 (44.2)	20.7%	3.5%, 38.0%	0.0185
	PBO	56	14 (25.0)	Reference		

Abbreviations: AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; COVID-19 = coronavirus disease-19; ICE = intercurrent event; IV = intravenous; PBO = placebo; Q4W = every 4 weeks; Q8W = ever 8 weeks; SC = subcutaneous.
Notes: [a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy or an AE of worsening CD [ICE3] or discontinued study agent for any other reason other than coronavirus disease-19 (COVID-19) related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12. [b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI at Week 12 were considered not having achieved the endpoint at Week 12. [c] Composite strategy: subjects who met ICE categories 1, 2, 3, 5 (here defined as discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4), or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: subjects who met ICE4 had their observed data used, if available.
Source: Johnson & Johnson; [Data on file] (7-9)

5.2.1.2 Corticosteroid-free clinical remission at Week 48

Table 13 presents corticosteroid-free clinical remission at Week 48, which is defined as CDAI score <150 at Week 48 and not receiving corticosteroids at Week 48. As with clinical remission results, guselkumab 100mg and 200mg SC demonstrated similar results vs ustekinumab in corticosteroid-free clinical remission, therefore no differences in efficacy between the 2 doses were observed.

Table 13 Corticosteroid-free clinical remission at Week 48* (BMSL-naïve subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	44 (75.9)	Vs. UST: 3.7%	-12.8%, 20.2%	0.6618
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	52 (82.5)	Vs. UST: 10.1%	-4.5%, 24.7%	0.1770
	UST ~6 mg/kg IV → 90 mg SC Q8W	58	42 (72.4)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	38 (65.5)	Vs. UST: -10.3%	-26.3%, 5.7%	0.2076

	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	42 (64.6)	Vs. UST: -11.2%	-27.6%, 5.1%	0.1782
	UST ~6 mg/kg IV → 90 mg SC Q8W	63	47 (74.6)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	33 (62.3)	40.8%	23.9%, 57.8%	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	52	35 (67.3)	46.5%	29.9%, 63.0%	<0.0001
	PBO	56	12 (21.4)	Reference		

Abbreviations: AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; COVID-19 = coronavirus disease-19; ICE = intercurrent event; IV = intravenous; Q4W = every 4 weeks; Q8W = ever 8 weeks; SC = subcutaneous.
Notes: * Region-specific endpoint.
[a] ICE strategies: Subjects who had a ICE1, a ICE2, or ICE3 or ICE5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not having achieved the endpoint at Week 48.
[c] Composite strategy: subjects who met ICE categories 1, 2, 3, 5 (here defined as discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4), or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: subjects who met ICE4 had their observed data used, if available.
Source: Johnson & Johnson; [Data on file] (7-9)

5.2.1.3 Endoscopic remission at Week 48

Table 14 presents endoscopic remission at Week 48, which is defined as SES-CD ≤4 with at least a 2-point reduction from baseline and no subscore greater than 1 in any individual subcomponent. This definition has also been applied in the application for direct placement of risankizumab into the CD treatment guideline (59). Guselkumab 100mg and 200mg SC demonstrated similar results vs ustekinumab in endoscopic remission, therefore no differences in efficacy between the 2 doses were observed.

Table 14 Endoscopic remission at Week 48* (BMSL-naïve subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	25 (43.1)	Vs. UST: 9.4%	-9.2%, 28.8%	0.3228
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	35 (55.6)	Vs. UST: 22.7%	5.5%, 39.8%	0.0096
	UST ~6 mg/kg IV → 90 mg SC Q8W	58	19 (32.8)	Reference		

GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	26 (44.8)	Vs. UST: 16.4%	-0.8%, 33.6%	0.0617
	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	24 (36.9)	Vs. UST: 8.6%	-8.3%, 25.5%	0.3199
	UST ~6 mg/kg IV → 90 mg SC Q8W	63	17 (27.0)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	22 (41.5)	30.8%	15.3%, 46.3%	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	52	22 (42.3)	32.0%	16.1%, 47.8%	<0.0001
	PBO	56	6 (10.7)	Reference		

Abbreviations: AE = adverse event; CD = Crohn's disease; CI = confidence interval; COVID-19 = coronavirus disease-19; ICE = intercurrent event; IV = intravenous; Q4W = every 4 weeks; Q8W = ever 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.
Notes: * Global endpoint.
[a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 nonresponder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 48.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing SES-CD at Week 48 were considered not having achieved the endpoint at Week 48.
[c] Composite strategy: subjects who met ICE categories 1, 2, 3, 5 (here defined as discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4), or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: subjects who met ICE4 had their observed data used, if available.
Source: Johnson & Johnson; [Data on file] (7-9)

5.2.1.4 IBDQ remission at Week 12

Table 15 presents IBDQ remission at Week 12, which is defined as IBDQ total score ≥ 170.

Table 15 IBDQ remission at Week 12 (BMSL-naïve subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	30 (51.7)	Vs. PBO: 18.9%	-0.5%, 38.3%	0.0568
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	26 (41.3)	Vs. PBO: 9.5%	-9.8%, 28.8%	0.3333
	PBO	34	11 (32.4)	Reference		

GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	30 (51.7)	Vs. PBO: 30.0%	10.9%, 49.1%	0.0021
	GUS 200 mg IV Q4W → 200 mg SC Q4W	58	30 (51.7)	Vs. PBO: 19.6%	-1.3%, 40.4%	0.0664
	PBO	27	6 (22.2)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	28 (52.8)	28.8%	11.6%, 46.0%	0.001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	52	15 (28.8)	5.8%	-10.4%, 22.0%	0.4837
	PBO	56	13 (23.2)	Reference		

Abbreviations: CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes:
[a] ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 12.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 12 were considered not having achieved the endpoint at Week 12.
[c] Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available.
Source: Johnson & Johnson; [Data on file] (7-9)

5.2.1.5 IBDQ remission at Week 48

Table 16 presents IBDQ remission at Week 48. Consistent results were observed for guselkumab 100 mg and 200 mg across studies, with statistically significant results demonstrated in the GRAVITI study vs placebo.

Table 16 IBDQ remission at Week 48 (BMSL-naïve subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	38 (65.5)	Vs. UST: 8.4%	-9.8%, 26.5%	0.3659
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	42 (66.7%)	Vs. UST: 11.2%	-5.3%, 27.7%	0.1848
	UST ~6 mg/kg IV → 90 mg SC Q8W	58	33 (56.9)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	35 (60.3)	Vs. UST: 1.4%	-16.3%, 19.1%	0.8759

	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	31 (47.7)	Vs. UST: -10.2%	-27.8%, 7.5%	0.2581
	UST ~6 mg/kg IV → 90 mg SC Q8W	63	37 (58.7)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	30 (56.6)	36.3%	19.1%, 53.4%	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	52	23 (44.2)	24.4%	7.0%, 41.8%	0.0059
	PBO	56	11 (19.6)	Reference		

Abbreviations: CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes:
[a] ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 48 were considered not having achieved the endpoint at Week 48.
Source: Source: Johnson & Johnson; [Data on file] (7-9)

5.2.1.6 CFB in IBDQ total score at Week 48

Table 17 and Table 18 present mean CFB in IBDQ total score at Week 48. Consistent results were observed for guselkumab 100 mg and 200 mg across studies, with statistically significant results demonstrated in the GRAVITI study vs placebo.

Table 17 CFB in mean IBDQ total score at Week 48, GUS vs. PBO (BMSL-naïve subgroup)

Study	Treatment arm	N [a]	LS Mean CFB (SE) [b]	Difference in LS mean CFB	95% CI	p-value
GRAVITI	GUS 400 mg SC Q4W → 100 mg SC Q8W	49	42.015 (4.34)	24.358	12.44, 36.27	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	48	44.339 (4.231)	25.811	14.10, 37.53	<0.0001
	PBO	45	Vs. GUS 100: 17.657 (4.49)	Reference		
			Vs. GUS 200: 18.188 (4.38)	Reference		

Abbreviations: CFB = change from baseline; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes: [a] N is number of subjects with IBDQ measurements at baseline and at Week 48. [b] Least squares means are derived based on a pairwise comparison Mixed-effects Model for Repeated Measures (MMRM) with N number

of subjects with IBDQ measurements at baseline and at Week 48. Analyses were performed without stratification to avoid numerical issues.
Source: Source: Johnson & Johnson; [Data on file] (7-9)

Table 18 CFB in mean IBDQ total score at Week 48, GUS vs. UST (BMSL-naïve subgroup)

Study	Treatment arm	N [a]	LS Mean CFB (SE) [b]	Difference in LS mean CFB	95% CI	p-value
GALAXI 2	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	50.017 (3.72)	3.303	-7.00, 13.61	0.5282
	GUS 200 mg IV Q4W → 200 mg SC Q4W	60	58.225 (3.66)	11.535	1.380, 21.61	0.0262
	UST ~6 mg/kg IV → 90 mg SC Q8W	58	Vs. GUS 100: 46.722 (3.75)	Reference		
			Vs. GUS 200: 46.690 (3.75)	Reference		
GALAXI 3	GUS 200 mg IV Q4W → 100 mg SC Q8W	54	43.949 (3.91)	2.893	-7.56, 13.35	0.5860
	GUS 200 mg IV Q4W → 200 mg SC Q4W	62	37.403 (3.63)	-5.171	-15.3, 4.914	0.3136
	UST ~6 mg/kg IV → 90 mg SC Q8W	59	Vs. GUS 100: 41.055 (3.69)	Reference		
			Vs. GUS 200: 42.574 (3.69)	Reference		

Abbreviations: CFB = change from baseline; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes: [a] N is number of subjects with IBDQ measurements at baseline and at Week 48. [b] Least squares means are derived based on a pairwise comparison Mixed-effects Model for Repeated Measures (MMRM) with N number of subjects with IBDQ measurements at baseline and at Week 48. Analyses were performed without stratification to avoid numerical issues.
Source: Johnson & Johnson; [Data on file] (7-9)

5.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

The safety data presented in this dossier is based on the BMSL-naïve subgroup analyses of the ITT populations for the GALAXI and GRAVITI studies in order to comply with the Danish treatment guideline patient population scope.

Guselkumab 100 mg and 200 mg were generally well tolerated across both the GALAXI and GRAVITI studies, with only a few additional AE's occurred from Week 12 to Week 48. No differences in AE's were observed between the 100 mg and 200mg guselkumab dose. Compared to placebo, similar frequencies of AE's were observed, particularly in Week48.

Guselkumab compared to ustekinumab in the GALAXI studies demonstrated no additional safety signals and were generally consistent with each other.

Table 19 Serious adverse events by System organ class (GALAXI 2 – BMSL-naïve – Week 12)

	Placebo N = 34	Guselkumab 100 mg N = 58	Guselkumab 200 mg N = 63
Subjects with one or more SAEs, n (%)	0 (0.0)	3 (5.2)	1 (1.6)
Gastrointestinal disorders	0 (0.0)	1 (1.7)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	0 (0.0)	1 (1.6)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.7)	0 (0.0)
Investigations	0 (0.0)	1 (1.7)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	1 (1.6)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 20 Serious adverse events by System organ class (GALAXI 2 – BMSL-naïve – Week 48)

	Guselkumab 100 mg N = 58	Guselkumab 200 mg N = 63	Ustekinumab N = 58
Subjects with one or more SAEs, n (%)	6 (10.3)	2 (3.2)	5 (8.6)
Gastrointestinal disorders	3 (5.2)	0 (0.0)	0 (0.0)

Cardiac disorders	1 (1.7)	1 (1.6)	0 (0,0)
General disorders and administration site conditions	0 (0.0)	1 (1.6)	0 (0.0)
Hepatobiliary disorders	1 (1.7)	0 (0.0)	1 (1.7)
Infections and infestations	1 (1.7)	0 (0.0)	2 (3.4)
Injury, poisoning and procedural complications	1 (1.7)	0 (0.0)	0 (0.0)
Investigations	1 (1.7)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	1 (1.6)	0 (0.0)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	1 (1.7)
Reproductive system and breast disorders	0 (0.0)	0 (0.0)	1 (1.7)
Social circumstances	0 (0.0)	0 (0.0)	1 (1.7)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 21 Serious adverse events (GALAXI 3 – BMSL-naïve – Week 12)

	Placebo N = 27	Guselkumab 100 mg N = 58	Guselkumab 200 mg N = 65
Subjects with one or more SAEs, n (%)	1 (3.7)	4 (6.9)	2 (3.1)
Gastrointestinal disorders	1 (3.7)	4 (6.9)	2 (3.1)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 22 Serious adverse events (GALAXI 3 – BMSL-naïve – Week 48)

	Guselkumab 100 mg N = 58	Guselkumab 200 mg N = 65	Ustekinumab N = 63
Subjects with one or more SAEs, n (%)	7 (12.1)	7 (10.8)	5 (7.9)
Gastrointestinal disorders	5 (8.6)	7 (10.8)	2 (3.2)
Musculoskeletal and connective tissue disorders	1 (1.7)	0 (0.0)	0 (0.0)
Pregnancy, puerperium and perinatal conditions	1 (1.7)	0 (0.0)	1 (1.6)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	1 (1.6)
Infections and infestations	0 (0.0)	0 (0.0)	1 (1.6)
Renal and urinary disorders	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 23 Serious adverse events (GRAVITI – BMSL-naïve – Week 12)

	Placebo N = 56	Guselkumab 100 mg N = 53	Guselkumab 200 mg N = 52
Subjects with one or more SAEs, n (%)	3 (5.4)	2 (3.8)	1 (1.9)
Gastrointestinal disorders	2 (3.6)	0 (0.0)	1 (1.9)
Cardiac disorders	0 (0.0)	1 (1.9)	0 (0.0)
General disorders and administration site conditions	0 (0.0)	1 (1.9)	0 (0.0)
Hepatobiliary disorders	1 (1.8)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 24 Serious adverse events (GRAVITI – BMSL-naïve – Week 48)

	Placebo N = 56	Guselkumab 100 mg N = 53	Guselkumab 200 mg N = 52
Subjects with one or more SAEs, n (%)	7 (12.5)	10 (18.9)	5 (9.6)
Gastrointestinal disorders	4 (7.1)	4 (7.5)	1 (1.9)
Infections and infestations	0 (0.0)	2 (3.8)	1 (1.9)
Reproductive system and breast disorders	0 (0.0)	2 (3.8)	0 (0.0)
Cardiac disorders	0 (0.0)	0 (0.0)	1 (1.9)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (1.9)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	1 (1.9)
Metabolism and nutrition disorders	0 (0.0)	1 (1.9)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (1.9)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (1.9)	0 (0.0)
Blood and lymphatic systems disorders	1 (1.8)	0 (0.0)	0 (0.0)
General disorders and administration site conditions	1 (1.8)	0 (0.0)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.8)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

5.2.3 Method of synthesis

N/A

5.2.4 Results from the comparative analysis

N/A

Table 25 Results from the comparative analysis of [intervention] vs. [comparator] for [patient population]

Outcome measure	[Intervention] (N=x)	[Comparator] (N=x)	Result
N/A	N/A	N/A	N/A

6. Clinical question(s) 2

6.1 Efficacy of guselkumab compared ustekinumab and placebo for BMSL-experienced patients with moderate to severe Crohns disease

6.1.1 Relevant studies

The relevant studies are listed in Table 26. The application includes the pre-defined subpopulation 'biologic failure' meaning that participants must have had 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 and will henceforth be referred to as BMSL-experienced patients. Inadequate response was defined as primary nonresponse (i.e., no initial response) or secondary nonresponse (i.e., response initially but subsequently lost response) (53, 54, 56). In GALAXI 2 & 3, participants who had demonstrated an inadequate response to or had failed to tolerate ustekinumab were not eligible for study entry (53, 54).

6.1.2 Comparability of studies

The Danish treatment guideline for moderate to severe CD in BMSL-experienced patients are informed by 12 unique studies. The studies include randomised controlled, double-blinded and single-blinded studies, which are primarily phase 2 and 3 studies (57). The GALAXI and GRAVITI studies are randomised controlled, double-blinded, phase 2/3 trials, making them comparable to the studies informing the guideline. Both the GALAXI and

GRAVITI studies are ongoing (the latest data cut-offs for GALAXI 2 & 3 were in 2023, and the latest data cut-off for GRAVITI was in 2024).

In the DMC's treatment guideline, clinical question 2 concerns BMSL-experienced patients, i.e., it is not specified whether the patients should have failed a biologic treatment. In this application, BMSL-experienced subgroups from GALAXI studies and GRAVITI are included.

In GALAXI 2 & 3 and in GRAVITI, clinical remission was measured at Week 12 (53, 54, 56), similar to the treatment guideline including data from Week 4-8 (57). The DMC defines clinical remission as achieving a CDAI score of ≤150 (57, 58), similar to the definition applied in the studies included in this application (see section 5.2.1.1). In GALAXI 2 & 3 and in GRAVITI, corticosteroid-free clinical remission was measured at Week 48 (53, 54, 56), similar to the treatment guideline including data from Week 52 (57). The DMC defines systemic steroid-free remission as not receiving systemic corticosteroid treatment after 52 weeks and having a total CDAI score of ≤150 (57, 58), similar to the definition applied in this application (see section 5.2.1.1). In GALAXI 2 & 3 and in GRAVITI, endoscopic remission was measured at Week 48 (53, 54, 56). The DMC does not specify the definition of endoscopic remission but suggests that Crohn's disease Endoscopic Index of Severity can be utilised. The definition of endoscopic remission applied in these studies is presented in section 0. Additionally, endoscopic remission is not included in the treatment guideline, as the data basis was insufficient (57). According to the DMC, AEs should be assessed quantitatively by number and percentage experiencing at least one serious AE and qualitatively (57, 58). Both a quantitative and qualitative description of AEs is reported in this application for GALAXI 2 & 3 and GRAVITI at Week 12 and 48.

According to the DMC, quality of life should be measured as proportion of patients achieving a score ≥ 170 on the IBDQ and as change from baseline in IBDQ. This should be assessed at the longest follow-up (57, 58). In the treatment guideline, it is also stated that IBDQ is relevant to assess after induction treatment, i.e., at Week 6-8. However, the expert committee found the available data to be too difficult to compare, and therefore IBDQ has not been assessed in the treatment guideline (57). In this application, both the proportion of patients achieving a score ≥ 170 on the IBDQ at Week 12 and Week 48 are included as well as change from baseline in in IBDQ.

6.1.3 Comparability of patients across studies and with Danish patients eligible for treatment

Table 26 presents the baseline characteristics of BMSL-experienced patients in GALAXI 2 and 3 as well as GRAVITI. Overall, demographic and baseline characteristics as well as disease characteristics for the BMSL-experienced patients included in GALAXI 2 and 3 and GRAVITI were comparable across all treatment arms. For instance, patients were similar in terms of age (median age: 34.9-39.2 years), sex, and race. Most patients were white (59.0-69.9%), with a slight overweight of males relative to females in all treatment arms. In terms of disease characteristics, patients were similar across treatments arms. However, CD duration was a bit longer in the 'guselkumab 400 mg SC Q4W → 100 mg SC Q8W' in GRAVITI compared to all other treatment arms.

According to the DMC, the patient populations in the 12 studies informing the Danish treatment guideline for moderate to severe CD in BMSL-experienced patients are comparable and align with the Danish patient population (57). Compared with the baseline characteristics of the 12 studies informing the treatment guideline, the patients in GALAXI 2 and 3 and GRAVITI are similar in terms of age, sex, and disease characteristics such as CDAI and IBDQ. For instance, the mean CDAI and IBDQ scores observed in GALAXI 2 and 3 and GRAVITI fall within the ranges observed in the DMC studies (mean CDAI of 289.1-300.4 across the GRAVITI and GALAXI studies compared with 288-338.0 across the DMC studies, and mean IBDQ of 119.8-132.5 across the GRAVITI and GALAXI studies compared with 118.2-151.6 across the DMC studies). Furthermore, BMSL-experienced patients in the GRAVITI and GALAXI studies had a mean weight at baseline of 63.59-71.53 kg (Table 26). This range for the mean baseline weight is similar to, although slightly lower than, the Expert Committee's estimate that Danish BMSL-experienced patients with moderate to severe CD have an average weight of approximately 75 kg (57). Since the baseline characteristics of the BMSL-experienced populations in GALAXI 2 and 3 as well as in GRAVITI closely match those of these 12 studies informing the treatment guideline, it is expected that the BMSL-experienced patients in GALAXI 2 and 3 and GRAVITI are also comparable to the Danish patient population.

Table 26 Baseline characteristics of patients in studies included for the comparative analysis of efficacy and safety

	GALAXI 2				GALAXI 3				GRAVITI		
	PBO[a] N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=77	GUS 200 mg IV Q4W → 200 mg SC Q4W N=73	UST ~6 mg/kg IV → 90 mg SC Q8W N=79	PBO[a] N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=76	GUS 200 mg IV Q4W → 200 mg SC Q4W N=74	UST ~6 mg/kg IV → 90 mg SC Q8W N=77	PBO N=53	GUS 400 mg SC Q4W → 100 mg SC Q8W N=55	GUS 400 mg SC Q4W → 200 mg SC Q4W N=53
Age in years, mean (SD)	34.9 (11.89)	35.6 (10.91)	34.7 (11.97)	38.8 (13.34)	37.1 (11.34)	35.3 (12.85)	38.7 (14.44)	39.2 (13.72)	35.64 (13.75)	37.65 (13.24)	39.19 (11.67)
Sex, n (%)											
Females	16 (41.0)	36 (46.8)	28 (38.4)	32 (40.5)	12 (30.8)	32 (42.1)	34 (45.9)	33 (42.9)	19 (35.8)	24 (43.6)	25 (47.2)
Males	23 (59.0)	41 (53.2)	45 (61.6)	47 (59.5)	27 (69.2)	44 (57.9)	40 (54.1)	44 (57.1)	34 (64.2)	31 (56.4)	28 (52.8)
Race, n (%)											
Asian	14 (35.9)	25 (32.5)	20 (27.4)	24 (30.4)	14 (35.9)	28 (36.8)	19 (25.7)	18 (23.4)	23 (43.4)	17 (30.9)	11 (20.8)
Black or African American	0	3 (3.9)	0	3 (3.8)	3 (7.7)	0	1 (1.4)	4 (5.2)	4 (7.5)	0	3 (5.7)
Native Hawaiian or Other Pacific Islander	0	0	0	0	0	1 (1.3)	0	1 (1.3)	0	0	0

	GALAXI 2				GALAXI 3				GRAVITI		
	PBO[a] N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=77	GUS 200 mg IV Q4W → 200 mg SC Q4W N=73	UST ~6 mg/kg IV → 90 mg SC Q8W N=79	PBO[a] N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=76	GUS 200 mg IV Q4W → 200 mg SC Q4W N=74	UST ~6 mg/kg IV → 90 mg SC Q8W N=77	PBO N=53	GUS 400 mg SC Q4W → 100 mg SC Q8W N=55	GUS 400 mg SC Q4W → 200 mg SC Q4W N=53
White	23 (59.0)	46 (59.7)	51 (69.9)	48 (60.8)	21 (53.8)	46 (60.5)	50 (67.6)	49 (63.6)	18 (34)	30 (54.5)	32 (60.4)
Not re-ported	2 (5.1)	3 (3.9)	2 (2.7)	4 (5.1)	1 (2.6)	1 (1.3)	4 (5.4)	5 (6.5)	8 (15.1)	8 (14.5)	7 (13.2)
Weight in kg, mean (SD)	63.59 (17.59)	66.85 (16.67)	66.02 (15.48)	68.92 (17.01)	70.61 (22.51)	67.40 (18.30)	68.02 (18.87)	68.30 (17.86)	67.78 (19.30)	68.25 (19.02)	71.53 (20.47)
Height in cm, mean (SD)	169.88 (8.49)	169.26 (9.62)	169.88 (9.89)	170.72 (10.48)	172.37 (10.36)	170.09 (9.20)	168.74 (9.42)	170.14 (9.70)	168.83 (9.20)	167.41 (9.58)	169.25 (9.46)
CD duration (years), mean (SD)	8.59 (8.96)	9.78 (6.80)	8.31 (6.48)	8.08 (7.26)	8.75 (8.40)	7.30 (6.74)	7.87 (8.09)	9.71 (8.67)	7.65 (7.66)	12.44 (10.42)	10.00 (8.04)
CDAI score, mean (SD)	297.6 (54.57)	292.4 (48.45)	289.1 (46.47)	298.7 (55.68)	295.9 (57.18)	295.4 (57.96)	300.4 (58.47)	291.0 (47.60)	294.5 (50.69)	294.6 (50.56)	297.9 (56.87)
SES-CD, mean (SD)	15.4 (8.94)	13.4 (6.85)	12.8 (7.64)	13.9 (7.42)	14.2 (7.57)	14.7 (8.55)	13.5 (7.70)	12.5 (6.09)	13.6 (8.16)	13.7 (8.01)	13.3 (8.17)

			GALAXI 2			GALAXI 3			GRAVITI		
	PBO[a] N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=77	GUS 200 mg IV Q4W → 200 mg SC Q4W N=73	UST ~6 mg/kg IV → 90 mg SC Q8W N=79	PBO[a] N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=76	GUS 200 mg IV Q4W → 200 mg SC Q4W N=74	UST ~6 mg/kg IV → 90 mg SC Q8W N=77	PBO N=53	GUS 400 mg SC Q4W → 100 mg SC Q8W N=55	GUS 400 mg SC Q4W → 200 mg SC Q4W N=53
IBDQ, mean (SD)	125.8 (26.06)	121.3 (32.41), n=76	128.7 (31.65), n=70	129.1 (32.57), n=76	132.5 (39.23)	125.2 (28.53)	126.2 (29.09), n=71	125.4 (31.91), n=74	127.6 (37.67), n=52	123.2 (30.61), n=50	119.8 (29.26), n=50

Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; N/A = not applicable; Q4W =every 4 weeks; Q8W =every 8 weeks; SC = subcutaneous; SD = standard deviation; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Notes: [a] Placebo column includes all subjects randomised to placebo. At Week 12, subjects who were clinical responders continued placebo treatment and those who were nonresponders crossed over to ustekinumab.

Source: Johnson & Johnson; [Data on file] (7-9)

6.2 Comparative analyses of efficacy and safety

6.2.1 Efficacy and safety – results per study

As with the BMSL-naïve subgroup for clinical question 1, the efficacy data presented in this dossier is based on the BMSL-experienced subgroup analyses of the ITT populations for the GALAXI and GRAVITI studies in order to comply with the Danish treatment guideline patient population scope.

Study discontinuations and the respective reasons for discontinuations for GALAXI and GRAVITI for both the induction phase (I-12) and maintenance phase (M-48) are described below.

Table 27 Discontinuation in GALAXI 2 prior to Week I-12 (BMSL-experienced subgroup)

	PBO N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=77	GUS 200 mg IV Q4W → 200 mg SC Q4W N=73
Subjects who discontinued, n (%)	3 (7.7)	0 (0.0)	2 (2.7)
Reason for discontinuation, n (%)			
Worsening of CD	1 (2.6)	0 (0.0)	0 (0.0)
Other adverse event		0 (0.0)	2 (2.7)
Subject refused further study treatment	1 (2.6)	0 (0.0)	0 (0.0)
Withdrawal by subject	1 (2.6)	0 (0.0)	0 (0.0)

Abbreviations: CD = Crohn's disease; I = induction; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: Johnson & Johnson; [Data on file] (7-9)

Table 28 Discontinuation in GALAXI 2 prior to Week M-48 (BMSL-experienced subgroup)

	GUS 200 mg IV Q4W → 100 mg SC Q8W N=77	GUS 200 mg IV Q4W → 200 mg SC Q4W N=73	UST ~6 mg/kg IV → 90 mg SC Q8W N=79
Subjects who discontinued, n (%)	11 (14.3)	6 (8.2)	12 (15.2)

Reason for discontinuation, n (%)			
Worsening of CD	2 (2.6)	1 (1.4)	2 (2.5)
Other adverse event	2 (2.6)	3 (4.1)	2 (2.5)
Lack of efficacy	3 (3.9)	1 (1.4)	2 (2.5)
Pregnancy	1 (1.3)	0 (0.0)	0 (0.0)
Landmark visit non-responder	0 (0.0)	1 (1.4)	0 (0.0)
Subject refused further study treatment	0 (0.0)	0 (0.0)	2 (2.5)
Withdrawal by subject	3 (3.9)	0 (0.0)	4 (5.1)

Abbreviations: CD = Crohn's disease; IV = intravenous; M = maintenance; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: Johnson & Johnson; [Data on file] (7-9)

Table 29 Discontinuation in GALAXI 3 prior to Week I-12 (BMSL-experienced subgroup)

	PBO N=39	GUS 200 mg IV Q4W → 100 mg SC Q8W N=76	GUS 200 mg IV Q4W → 200 mg SC Q4W N=74
Subjects who discontinued, n (%)	3 (7.7)	2 (2.6)	1 (1.4)
Reason for discontinuation, n (%)			
Worsening of CD	1 (2.6)	0 (0.0)	0 (0.0)
Other adverse event	0 (0.0)	0 (0.0)	0 (0.0)
Initiated prohibited medication	0 (0.0)	0 (0.0)	0 (0.0)
Pregnancy	0 (0.0)	1 (1.3)	0 (0.0)
Subject refused further study treatment	0 (0.0)	0 (0.0)	1 (1.4)

Withdrawal by subject	2 (5.1)	1 (1.3)	0 (0.0)

Abbreviations: CD = Crohn's disease; I = induction; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: Johnson & Johnson; [Data on file] (7-9)

Table 30 Discontinuation in GALAXI 3 prior to Week M-48 (BMSL-experienced subgroup)

	GUS 200 mg IV Q4W → 100 mg SC Q8W N=76	GUS 200 mg IV Q4W → 200 mg SC Q4W N=74	UST ~6 mg/kg IV → 90 mg SC Q8W N=77
Subjects who discontinued, n (%)	12 (15.8)	14 (18.9)	20 (26)
Reason for discontinuation, n (%)			
Worsening of CD	1 (1.3)	2 (2.7)	5 (6.5)
Other adverse event	2 (2.6)	3 (4.1)	3 (3.9)
Initiated prohibited medication	0 (0.0)	0 (0.0)	1 (1.3)
Lack of efficacy	3 (3.9)	4 (5.4)	6 (7.8)
Pregnancy	2 (2.6)	1 (1.4)	0 (0.0)
Subject refused further study treatment	0 (0.0)	1 (1.4)	2 (2.6)
Withdrawal by subject	3 (3.9)	2 (2.7)	2 (2.6)
CD-related surgery	0 (0.0)	1 (1.4)	0 (0.0)
Other	1 (1.3)	0 (0.0)	1 (1.3)

Abbreviations: CD = Crohn's disease; IV = intravenous; M = maintenance; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: Johnson & Johnson; [Data on file] (7-9)

Table 31 Discontinuation in GRAVITI prior to Week I-12 (BMSL-experienced subgroup)

	PBO N=53	GUS 400 mg SC Q4W → 100 mg SC Q8W N=55	GUS 400 mg SC Q4W → 200 mg SC Q4W N=53
Subjects who discontinued, n (%)	6 (11.3)	2 (3.6)	1 (1.9)

Reason for discontinuation, n (%)			
Withdrawal by subject	3 (5.7)	0 (0.0)	0 (0.0)
Lack of efficacy	2 (3.8)	0 (0.0)	0 (0.0)
Other adverse event	1 (1.9)	0 (0.0)	1 (1.9)
Death	0 (0.0)	1 (1.8)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (1.8)	0 (0.0)

Abbreviations: I = induction; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: Johnson & Johnson; [Data on file] (7-9)

Table 32 Discontinuation in GRAVITI prior to Week M-48 (BMSL-experienced subgroup)

	PBO N=53	GUS 400 mg SC Q4W → 100 mg SC Q8W N=55	GUS 400 mg SC Q4W → 200 mg SC Q4W N=53
Subjects who discontinued, n (%)	14 (26.4)	9 (16.4)	3 (5.7)
Reason for discontinuation, n (%)			
Withdrawal by subject	5 (9.4)	1 (1.8)	1 (1.9)
Lack of efficacy	2 (3.8)	2 (3.6)	1 (1.9)
Worsening of CD	3 (5.7)	2 (3.6)	
Other adverse event	2 (3.8)	1 (1.8)	1 (1.9)
Pregnancy	0 (0.0)	0 (0.0)	0 (0.0)
Week 20/24 non-responder	0 (0.0)	1 (1.8)	0 (0.0)
Death	0 (0.0)	1 (1.8)	0 (0.0)
Lost to follow-up	0 (0.0)	1 (1.8)	0 (0.0)
Other	2 (3.8)	0 (0.0)	0 (0.0)

Abbreviations: CD = Crohn's disease; IV = intravenous; M = maintenance; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Source: Johnson & Johnson; [Data on file] (7-9)

6.2.1.1 Clinical remission at Week 12

Table 33 presents clinical remission at Week 12. As shown in the table below, guselkumab 100mg and 200mg SC demonstrated similar results vs placebo, therefore no differences in efficacy between the 2 doses were observed.

Table 33 Clinical remission at Week 12 (BMSL-experienced subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	31 (40.3)	Vs. PBO: 17.7%	1.6%, 33.8%	0.0314
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	36 (49.3)	Vs. PBO: 26.2%	8.5%, 44.0%	0.0037
	PBO	39	9 (23.1)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	39 (51.3)	Vs. PBO: 36.0%	20.2%, 51.7%	<0.0001
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	32 (43.2)	Vs. PBO: 28.4%	13.0%, 43.8%	0.0003
	PBO	39	6 (15.4)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	37 (67.3)	50.5%	35.2%, 65.8%	<0.001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	53	28 (52.8)	35.7%	19.1%, 52.2%	<0.001
	PBO	53	9 (17.0)	Reference		

Abbreviations: AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; COVID-19 = coronavirus disease-19; ICE = intercurrent event; IV = intravenous; Q4W = every 4 weeks; Q8W = ever 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Notes: [a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy or an AE of worsening CD [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 12. [b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI at Week 12 were considered not having achieved the endpoint at Week 12. [c] Composite strategy: subjects who met ICE categories 1, 2, 3, 5 (here defined as discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4), or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: subjects who met ICE4 had their observed data used, if available. [d] The CIs for the proportion of subjects meeting the endpoint were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided. [e] The adjusted treatment difference(s), CI(s), and p-value(s) were based on the common risk difference by

use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300) and baseline SES-CD score (≤12 or >12).
Source: Johnson & Johnson; [Data on file] (7-9)

6.2.1.2 Corticosteroid-free clinical remission at Week 48

Table 34 presents corticosteroid-free clinical remission at Week 48. As with clinical remission results, guselkumab 100mg and 200mg SC demonstrated similar results vs ustekinumab in corticosteroid-free clinical remission, therefore no differences in efficacy between the 2 doses were observed.

Table 34 Corticosteroid-free clinical remission at Week 48* (BMSL-experienced subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	41 (53.2)	Vs. UST: 2.3%	-13.0%, 17.6%	0.7682
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	45 (61.6)	Vs. UST: 10.9%	-5.1%, 27.0%	0.1816
	UST ~6 mg/kg IV → 90 mg SC Q8W	79	40 (50.6)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	50 (65.8)	Vs. UST: 19.9%	5.0%, 34.8%	0.0089
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	47 (63.5)	Vs. UST: 17.9%	2.1%, 33.6%	0.0260
	UST ~6 mg/kg IV → 90 mg SC Q8W	77	35 (45.5)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	31 (56.4)	47.0%	31.7%, 62.4%	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	53	33 (62.3)	52.9%	37.6%, 68.1%	<0.0001
	PBO	53	5 (9.4)	Reference		

Abbreviations: AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; COVID-19 = coronavirus disease-19; ICE = intercurrent event; IV = intravenous; Q4W = every 4 weeks; Q8W = ever 8 weeks; SC = subcutaneous.
Notes: * Region-specific endpoint. [a] ICE strategies: Subjects who had a ICE1, a ICE2, or ICE3 or ICE5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48. [b] Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not having achieved the endpoint at Week 48.
Source: Johnson & Johnson; [Data on file] (7-9)

6.2.1.3 Endoscopic remission at Week 48

Table 35 presents endoscopic remission at Week 48. Guselkumab 100mg and 200mg SC demonstrated similar results vs ustekinumab in endoscopic remission, therefore no differences in efficacy between the 2 doses were observed.

Table 35 Endoscopic remission at Week 48* (BMSL-experienced subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	22 (28.6)	Vs. UST: 5.8%	-7.7%, 19.4%	0.3996
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	23 (31.5)	Vs. UST: 9.0%	-4.9%, 22.9%	0.2045
	UST ~6 mg/kg IV → 90 mg SC Q8W	79	18 (22.8)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	21 (27.6)	Vs. UST: 9.3%	-4.5%, 23.1%	0.1871
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	19 (25.7)	Vs. UST: 7.8%	-5.5%, 21.2%	0.2504
	UST ~6 mg/kg IV → 90 mg SC Q8W	77	14 (18.2)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	11 (20.0)	20.4%	9.8%, 31.0%	0.0002
	GUS 400 mg SC Q4W → 200 mg SC Q4W	53	20 (37.7)	37.4%	24.3%, 50.5%	<0.0001
	PBO	53	0 (0.0)	Reference		

Abbreviations: AE = adverse event; CD = Crohn's disease; CI = confidence interval; COVID-19 = coronavirus disease-19; ICE = intercurrent event; IV = intravenous; Q4W = every 4 weeks; Q8W = ever 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.

Notes: * Global endpoint. [a] ICE strategies: Subjects who had a CD-related surgery [ICE1], a prohibited change in concomitant CD medication [ICE2], or discontinued study agent due to lack of efficacy, an AE of worsening CD or Week 20/24 nonresponder [ICE3] or discontinued study agent for any other reason other than COVID-19 related reasons or regional crisis [ICE5] prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had discontinued study agent due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis [ICE4] had their observed data used, if available, to determine responder and nonresponder status at Week 48. [b] Missing data imputation: After accounting for ICE strategies, subjects who were missing SES-CD at Week 48 were considered not having achieved the endpoint at Week 48.

Source: Johnson & Johnson; [Data on file] (7-9)

6.2.1.4 IBDQ remission at Week 12

Table 36 presents IBDQ remission at Week 12. Similar results were observed for guselkumab 100 mg and 200 mg doses across both studies, with statistically significant results demonstrated in GRAVITI vs placebo.

Table 36 IBDQ remission at Week 12 (BMSL-experienced subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	34 (44.2)	Vs. PBO: 21.5%	5.0%, 38.1%	0.0108
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	27 (37)	Vs. PBO: 13.8%	-3.3%, 30.8%	0.1128
	PBO	39	9 (23.1)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	40 (52.6)	Vs. PBO: 22.1%	4.3%, 40.0%	0.0150
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	35 (47.3)	Vs. PBO: 16.9%	-1.8%, 35.5%	0.0760
	PBO	39	12 (30.8)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	29 (52.7)	32.9%	16.2%, 49.5%	0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	53	26 (49.1)	29.5%	13.0%, 45.9%	0.0004
	PBO	53	11 (20.8)	Reference		

Abbreviations: CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes:
[a] ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 12.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 12 were considered not having achieved the endpoint at Week 12.
[c] Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available.
Source: Johnson & Johnson; [Data on file] (7-9)

6.2.1.5 IBDQ remission at Week 48

Table 37 presents IBDQ remission at Week 48. Similar results were observed for guselkumab 100 mg and 200 mg doses across both studies, with statistically significant results demonstrated in GRAVITI vs placebo.

Table 37 IBDQ remission at Week 48 (BMSL-experienced subgroup)

Study	Treatment arm	N	n (%)	Adjusted treatment difference	95% CI	p-value
GALAXI 2 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	34 (44.2)	Vs. UST: -2.9%	-18.7%, 12.9%	0.7187
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	35 (47.9)	Vs. UST: 2.1%	-14.0%, 18.1%	0.8011
	UST ~6 mg/kg IV → 90 mg SC Q8W	79	37 (46.8)	Reference		
GALAXI 3 [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	44 (57.9)	Vs. UST: 17.5%	2.0%, 33.1%	0.0272
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	40 (54.1)	Vs. UST: 14.2%	-1.5%, 29.9%	0.0754
	UST ~6 mg/kg IV → 90 mg SC Q8W	77	31 (40.3)	Reference		
GRAVITI [b, c]	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	30 (54.5)	39.2%	23.7%, 54.7%	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	53	25 (47.2)	32.1%	15.7%, 48.5%	<0.0001
	PBO	53	8 (15.1)	Reference		

Abbreviations: CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes:
[a] ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48.
[b] Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 48 were considered not having achieved the endpoint at Week 48.
Source: Johnson & Johnson; [Data on file] (7-9)

6.2.1.6 CFB in IBDQ total score at Week 48

Table 38 and Table 39 present mean CFB in IBDQ total score at Week 48 for guselkumab vs. placebo and ustekinumab, respectively. Consistent results were observed for

guselkumab 100 mg and 200 mg across both studies, with statistically significant results demonstrated in the GRAVITI study vs placebo.

Table 38 CFB in mean IBDQ total score at Week 48, GUS vs. PBO (BMSL-experienced subgroup)

Study	Treatment arm	N [a]	LS Mean CFB (SE) [b]	Difference in LS mean CFB	95% CI	p-value
GRAVITI	GUS 400 mg SC Q4W → 100 mg SC Q8W	45	45.37 (3.94)	35.710	24.99, 46.43	<0.0001
	GUS 400 mg SC Q4W → 200 mg SC Q4W	46	45.977 (4.34)	36.221	24.42, 48.02	<0.0001
	PBO	49	Vs. GUS 100: 9.620 (3.80)	Reference		
			Vs. GUS 200: 9.756 (4.2)	Reference		

Abbreviations: CFB = change from baseline; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes: [a] N is number of subjects with IBDQ measurements at baseline and at Week 48. [b] Least squares means are derived based on a pairwise comparison Mixed-effects Model for Repeated Measures (MMRM) with N number of subjects with IBDQ measurements at baseline and at Week 48. Analyses were performed without stratification to avoid numerical issues.
Source: Johnson & Johnson; [Data on file] (7-9)

Table 39 CFB in mean IBDQ total score at Week 48, GUS vs. UST (BMSL-experienced subgroup)

Study	Treatment arm	N [a]	LS Mean CFB (SE) [b]	Difference in LS mean CFB	95% CI	p-value
GALAXI 2	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	36.970 (3.69)	-2.081	-12.0, 7.823	0.6795
	GUS 200 mg IV Q4W → 200 mg SC Q4W	68	41.246 (3.83)	3.506	-6.40, 13.41	0.4863

	UST ~6 mg/kg IV → 90 mg SC Q8W	76	Vs. GUS 100: 39.051 (3.64)	Reference		
			Vs. GUS 200: 37.739 (3.59)	Reference		
GALAXI 3	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	40.456 (3.69)	7.730	-2.32, 17.78	0.1313
	GUS 200 mg IV Q4W → 200 mg SC Q4W	71	39.234 (3.96)	7.061	-3.51, 17.64	0.1898
	UST ~6 mg/kg IV → 90 mg SC Q8W	71	Vs. GUS 100: 32.727 (3.753)	Reference		
			Vs. GUS 200: 32.172 (3.88)	Reference		

Abbreviations: CFB = change from baseline; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous.
Notes: [a] N is number of subjects with IBDQ measurements at baseline and at Week 48. [b] Least squares means are derived based on a pairwise comparison Mixed-effects Model for Repeated Measures (MMRM) with N number of subjects with IBDQ measurements at baseline and at Week 48. Analyses were performed without stratification to avoid numerical issues.
Source: Johnson & Johnson; [Data on file] (7-9)

6.2.2 Please provide a qualitative description of safety data. Differences in definitions of outcomes between studies

The safety data presented in this dossier is based on the BMSL-experienced subgroup analyses of the ITT populations for the GALAXI and GRAVITI studies in order to comply with the Danish treatment guideline patient population scope.

As was also demonstrated in the BMSL-naïve subgroup, Guselkumab 100 mg and 200 mg were generally well tolerated across both the GALAXI and GRAVITI studies, with only a few additional AE's occurred from Week 12 to Week 48. No differences in AE's were observed between the 100 mg and 200mg guselkumab dose.

Table 40 Serious adverse events by System organ class (GALAXI 2 – BMSL-experienced – Week 12)

	Placebo	Guselkumab 100 mg	Guselkumab 200 mg
	N = 39	N = 77	N = 73

Subjects with one or more SAEs, n (%)	2 (5.1)	2 (2.6)	1 (1.4)
Gastrointestinal disorders	2 (5.1)	2 (2.6)	1 (1.4)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	0 (0.0)
Psychiatric disorders	0 (0.0)	0 (0.0)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 41 Serious adverse events by System organ class (GALAXI 2 – BMSL-experienced – Week 48)

	Guselkumab 100 mg N = 77	Guselkumab 200 mg N = 73	Ustekinumab N = 79
Subjects with one or more SAEs, n (%)	12 (15.6)	3 (4.1)	11 (13.9)
Gastrointestinal disorders	9 (11.7)	1 (1.4)	5 (6.3)
Infections and infestations	0 (0.0)	1 (1.4)	4 (5.1)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.4)	0 (0.0)
Musculoskeletal and connective tissue disorders	1 (1.3)	0 (0.0)	0 (0.0)
Nervous system disorders	1 (1.3)	0 (0.0)	0 (0.0)

Pregnancy, puerperium and perinatal conditions	1 (1.3)	0 (0.0)	0 (0.0)
Blood and lymphatic system disorders	0 (0.0)	0 (0.0)	2 (2.5)
Investigations	0 (0.0)	0 (0.0)	0 (0.0)
Metabolism and nutrition disorders	0 (0.0)	0 (0.0)	1 (1.3)
Psychiatric disorders	0 (0.0)	0 (0.0)	1 (1.3)
Respiratory, thoracic and mediastinal disorders	0 (0.0)	0 (0.0)	0 (0.0%)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 42 Serious adverse events by System organ class (GALAXI 3 – BMSL-experienced – Week 12)

	Placebo N = 39	Guselkumab 100 mg N = 76	Guselkumab 200 mg N = 74
Subjects with one or more SAEs, n (%)	6 (15.4)	1 (1.3)	2 (2.7)
Gastrointestinal disorders	6 (15.4)	1 (1.3)	2 (2.7)
Infections and infestations	0 (0.0)	0 (0.0)	1 (1.4)
Injury, poisoning and procedural complications	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 43 Serious adverse events by System organ class (GALAXI 3 – BMSL-experienced – Week 48)

	Guselkumab 100 mg N = 76	Guselkumab 200 mg N = 74	Ustekinumab N = 77
Subjects with one or more SAEs, n (%)	5 (6.6)	7 (9.5)	10 (13.0)
Gastrointestinal disorders	4 (5.3)	5 (6.8)	8 (10.4)

Blood and lymphatic system disorders	0 (0.0)	1 (1.4)	0 (0.0)
Injury, poisoning and procedural complications	0 (0.0)	1 (1.4)	1 (1.3)
Metabolism and nutrition disorders	0 (0.0)	1 (1.4)	0 (0.0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0 (0.0)	1 (1.4)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (1.4)	0 (0.0)
Skin and subcutaneous tissue disorders	1 (1.3)	0 (0.0)	0 (0.0)
Infections and infestations	0 (0.0)	0 (0.0)	3 (3.9)
Musculoskeletal and connective tissue disorders	0 (0.0)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 44 Serious adverse events by System organ class (GRAVITI – BMSL-experienced – Week 12)

	Placebo N = 43	Guselkumab 100 mg N = 55	Guselkumab 200 mg N = 53
Subjects with one or more SAEs, n (%)	5 (11.6)	1 (1.8)	1 (1.9)
Gastrointestinal disorders	5 (9.4)	0 (0.0)	1 (1.9)
Infections and infestations	1 (1.9)	1 (1.8)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

Table 45 Serious adverse events by System organ class (GRAVITI – BMSL-experienced – Week 48)

	Placebo N = 53	Guselkumab 100 mg N = 55	Guselkumab 200 mg N = 53
Subjects with one or more SAEs, n (%)	7 (9.4)	4 (7.3)	3 (5.7)
Gastrointestinal disorders	5 (9.4)	2 (3.6)	2 (3.8)
Eye disorders	0 (0.0)	0 (0.0)	1 (1.9)
Hepatobiliary disorders	0 (0.0)	0 (0.0)	1 (1.9)
Injury, poisoning and procedural complications	1 (1.9)	1 (1.8)	0 (0.0)
Respiratory, thoracic and mediastinal disorders	1 (1.9)	1 (1.8)	0 (0.0)
Cardiac disorders	1 (1.9)	0 (0.0)	0 (0.0)
Endocrine disorders	1 (1.9)	0 (0.0)	0 (0.0)
Infections and infestations	1 (1.9)	0 (0.0)	0 (0.0)
Vascular disorders	1 (1.9)	0 (0.0)	0 (0.0)

Abbreviations: BMSL = biological and targeted synthetic medicine; MS = maintenance study; q4w = every 4 weeks; q8w = every 8 weeks; SAE = serious adverse event; SC = subcutaneous.

Source: Johnson & Johnson; [Data on file] (7-9)

6.2.3 Method of synthesis

N/A

6.2.4 Results from the comparative analysis

N/A

Table 46 Results from the comparative analysis of [intervention] vs. [comparator] for [patient population]

Outcome measure	[Intervention] (N=x)	[Comparator] (N=x)	Result
N/A	N/A	N/A	N/A

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Appendix A. Main characteristics of studies included

The GALAXI study includes GALAXI 1, 2, and 3, all registered under the same NCT number. However, as GALAXI 1 is not relevant to this submission, only information relating to GALAXI 2 and 3 is presented in Table 47.

Table 47 Main characteristics of GALAXI 2 and 3

Trial name: GALAXI (GALAXI 2 and 3)	NCT number: NCT03466411
Objective	The purpose of this study is to evaluate the clinical efficacy (GALAXI 1), clinical and endoscopic efficacy (GALAXI 2 and GALAXI 3), and safety of guselkumab in participants with CD.
Publications – title, author, journal, year	Only the following publications, which describe GALAXI 1, are available: Efficacy and safety of 48 weeks of guselkumab for patients with CD: maintenance results from the phase 2, randomised, double-blind GALAXI-1 trial. Danese S, Panaccione R, Feagan BG, Afzali A, Rubin DT, Sands BE, Reinisch W, Panés J, Sahoo A, Terry NA, Chan D, Han C, Frustaci ME, Yang Z, Sandborn WJ, Hisamatsu T, Andrews JM, D'Haens GR; GALAXI-1 Study Group. Lancet Gastroenterol Hepatol. 2024 (48) Guselkumab for the Treatment of CD: Induction Results From the Phase 2 GALAXI-1 Study. Sandborn WJ, D'Haens GR, Reinisch W, Panés J, Chan D, Gonzalez S, Weisel K, Germinaro M, Frustaci ME, Yang Z, Adedokun OJ, Han C, Panaccione R, Hisamatsu T, Danese S, Rubin DT, Sands BE, Afzali A, Andrews JM, Feagan BG; GALAXI-1 Investigators. Gastroenterology. 2022 (49)
Study type and design	Treat-through, double-blinded randomised placebo- and active-controlled phase 2/3† study. GALAXI 2 and 3 were both 48-week phase 3 confirmatory studies, following the 48-week, phase 2, dose-ranging GALAXI 1 study. Participants were randomly assigned to GALAXI 2 or GALAXI 3, using a permuted block randomisation with the stratification variables as described below. Within each stratum, participants in each study were randomly assigned in a 2:2:2:1 ratio to receive one of two dose regimens of guselkumab, ustekinumab, or placebo, respectively, based on a computer-generated randomisation schedule prepared before the study by or under the supervision of the Sponsor. The randomisation was balanced by using randomly permuted blocks and was stratified by baseline CDAI score (≤300 or >300), baseline Simple SES-CD score (≤12 or >12), prior biologic failure status (Yes/No), and baseline corticosteroid use (Yes/No) as the stratification variables. At Week 12, participants continued treatment based on their clinical response status (placebo responders continued placebo treatment, while non-responders received ustekinumab).

Trial name: GALAXI (GALAXI 2 and 3)	NCT number: NCT03466411
	GALAXI long term extension study is ongoing.
Sample size (n)	524 randomised in GALAXI 2 and 525 randomised in GALAXI 3
Main inclusion criteria	• Have CD or fistulising CD 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 moderate to severe CD as assessed by CDAI, stool frequency, and abdominal pain 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 CD
Main exclusion criteria	• Current diagnosis of ulcerative colitis or indeterminate colitis • Has complications of CD, such as symptomatic strictures or stenoses, short gut syndrome, or any other manifestation • Unstable doses of concomitant CD therapy • Receipt of CD approved biologic agents, investigational agents, or procedures outside of permitted timeframe as specified in the protocol • Any medical contraindications preventing study participation
Intervention	**Guselkumab 200 mg IV Q4W (Weeks 0 through 8) → 100 mg SC Q8W (Weeks 16 through 40)**: 149 patients were randomised to this regimen in GALAXI 2 (including 58 BMSL-naïve and 77 BMSL-experienced patients). 148 patients were randomised to this regimen in GALAXI 3 (including 58 BMSL-naïve and 76 BMSL-experienced patients). **Guselkumab 200 mg IV Q4W (Weeks 0 through 8) → 200 mg SC Q4W (Weeks 12 through 44)**: 148 patients were randomised to this regimen in GALAXI 2 (including 63 BMSL-naïve and 73 BMSL-experienced patients). 151 patients were randomised to this regimen in GALAXI 3 (including 65 BMSL-naïve and 74 BMSL-experienced patients).
Comparator(s)	**Ustekinumab ~6 mg/kg IV at Week 0 → 90 mg SC Q8W (Week 8 through 40):** 150 patients were randomised to this regimen in GALAXI 2 (including 58 BMSL-naïve and 79 BMSL-experienced patients). 150 patients were randomised to this regimen in GALAXI 3 (including 63 BMSL-naïve and 77 BMSL-experienced patients). **Placebo** Induction: IV Q4W (Weeks 0 through 8). At week 12 responders continue treatment SC QW4 (Week 12 through Week 44) and non-responders receive a single ustekinumab IV induction dose at Week 12 (6mg/kg) and ustekinumab 90 mg SC maintenance Q8W (Week 20 through 44). 70 patients were randomised to this regimen. 77 patients were randomised to this regimen in GALAXI 2 (including 34 BMSL-naïve and 39

Trial name: GALAXI (GALAXI 2 and 3)	NCT number: NCT03466411
	BMSL-experienced patients). 76 patients were randomised to this regimen in GALAXI 3 (including 27 BMSL-naïve and 39 BMSL-experienced patients).
Follow-up time	**GALAXI 2** The average duration of follow-up through Week 48 in the safety analysis set was 45.0 weeks in the combined placebo (as randomised) group[a], 47.1 weeks in the guselkumab 200 mg IV Q4W → 100 mg SC Q8W, 47.8 weeks in the guselkumab 200 mg IV Q4W → 200 mg SC Q4W, and 45.8 weeks in the Ustekinumab ~6 mg/kg IV → 90 mg SC Q8W. **GALAXI 3** The average duration of follow-up through Week 48 in the safety analysis set was 43.5 weeks in the combined placebo (as randomised) group[a], 45.3 weeks in the guselkumab 200 mg IV Q4W → 100 mg SC Q8W, 45.5 weeks in the guselkumab 200 mg IV Q4W → 200 mg SC Q4W, and 44.9 weeks in the Ustekinumab ~6 mg/kg IV → 90 mg SC Q8W.
Primary, secondary and exploratory endpoints	**Endpoints included in this application from GALAXI 2 and 3*** Secondary endpoints evaluating guselkumab vs. placebo and included in this application were: clinical remission and IBDQ remission at Week 12 as well as AEs. at Week 48, as well as AEs were also analysed. Secondary endpoints evaluating guselkumab vs. ustekinumab and included in this application were: corticosteroid-free clinical remission, endoscopic remission and IBDQ remission at Week 48, as well AEs were also analysed. **Other endpoints from GALAXI 2 and 3*** The co-primary endpoints evaluating guselkumab vs. placebo were "clinical response at Week 12 and clinical remission at Week 48" and "clinical response at Week 12 and endoscopic response at Week 48". Secondary endpoints evaluating guselkumab vs. placebo were clinical response at Week 4; endoscopic response at Week 12; fatigue response at Week 12; clinical remission at Week 12 and endoscopic response at Week 12; endoscopic remission at Week 12; clinical response at Week 12 and 90-day corticosteroid-free clinical remission at Week 48; and clinical response at Week 12 and endoscopic remission at Week 48. Secondary endpoints evaluating guselkumab vs. ustekinumab were clinical remission at Week 48, endoscopic response at Week 48, clinical remission at Week 48 and endoscopic response at Week 48, and deep remission at Week 48.
Method of analysis	All efficacy analyses were intention-to-treat analyses presented for the BMSL-naïve and BMSL-experienced subgroup. All efficacy analyses include the presentation of numbers, percentages, and CIs as well as adjusted treatment difference. The adjusted treatment difference and corresponding CIs were based on the Wald statistic

Trial name: GALAXI (GALAXI 2 and 3)	NCT number: NCT03466411
	with Cochran-Mantel-Haenszel weight. Similarly, the p-values were based on Cochran-Mantel-Haenszel tests with stratification.
Subgroup analyses	**GALAXI 2** Pre-specified subgroup analyses were conducted for the global co-primary endpoints and global major secondary endpoints for the BMSL-experienced , conventional therapy failure, and BMSL-naïve subgroups. Furthermore, efficacy results for the global co-primary endpoints were also assessed by region, country, and site subgroups. Subgroup analyses of demographics, baseline disease characteristics, concomitant CD medication use at baseline, and CD-related medication history were conducted for global co-primary and selected major secondary endpoints. **GALAXI 3** Pre-specified subgroup analyses were conducted for the global co-primary endpoints and global major secondary endpoints for the BMSL-experienced, conventional therapy failure, and BMSL-naïve subgroups. Furthermore, efficacy results for the global co-primary endpoints were also assessed by region, country, and site subgroups. Subgroup analyses of demographics, baseline disease characteristics, concomitant CD medication use at baseline, and CD-related medication history were conducted for global co-primary and selected major secondary endpoints.
Other relevant information	N/A

Abbreviations: AE = adverse event; CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; CI = confidence interval; IBDQ = Inflammatory Bowel Disease Questionnaire; IV = intravenous; N/A = not applicable; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.
Notes: † Only GALAXI 1 is as phase 2 study. [a] This includes all events in the randomised placebo group regardless of crossover to ustekinumab at or after week 12. * The primary and secondary endpoints are the same in GALAXI 2 and GALAXI 3.
Sources: ClinicalTrials.gov, 2018 (51); Janssen Research & Development, 2023 (52); Janssen Research & Development, 2024 (53); Janssen Research & Development, 2024 (54).

Table 48 Main characteristics of GRAVITI

Trial name: GRAVITI	NCT number: NCT05197049
Objective	The purpose of this study is to evaluate the efficacy and safety of guselkumab in participants with CD.
Publications – title, author, journal, year	Efficacy and Safety of Guselkumab Subcutaneous Induction and Maintenance in Participants With Moderately to Severely Active Crohn's Disease: Results From the Phase 3 GRAVITI Study. Hart A, Panaccione R, Steinwurz F, Danese S, Hisamatsu T, Cao Q, Ritter T, Seidler U, Olurinde M, Vetter ML, Yee J, Yang Z, Wang Y, Johanns J, Han C, Sahoo A, Terry NA, Sands BE, D'Haens G. Gastroenterology. 2025 (50)

Trial name: GRAVITI	NCT number: NCT05197049
Study type and design	Double-blinded randomised placebo-controlled phase 3 study. Eligible participants were randomly assigned in a 1:1:1 ratio to either one of two guselkumab treatment regimens or placebo. The randomisation was stratified by baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and biologic failure status (Yes or No) at baseline (Week 0). No crossover was allowed. The participants and investigator were masked. The study is ongoing, although the recruitment is complete.
Sample size (n)	350 participants were randomised and 347 were included in the full analysis set and in the safety analysis set.
Main inclusion criteria	• Diagnosis of CD of at least 3 months in duration. • Have moderate to severe CD as assessed by CDAI, stool frequency, and abdominal pain score, and SES-CD. • Demonstrated intolerance or inadequate response to conventional or to biologic therapy for CD.
Main exclusion criteria	• Current diagnosis of ulcerative colitis or indeterminate colitis. • Complications of CD that require surgical intervention or confound efficacy assessments. • Unstable doses of concomitant CD therapy
Intervention	Guselkumab 400 mg SC at Weeks 0, 4, and 8 followed by guselkumab 100 mg SC Q8W starting at Week 16 (n=115, among these 53 are in the BMSL-naïve group and 55 are in the BMSL-experienced group). Guselkumab 400 mg SC at Weeks 0, 4, and 8 followed by guselkumab 200 mg SC Q4W starting at Week 12 (n=115, among these 52 are in the BMSL-naïve group and 53 are in the BMSL-experienced group).
Comparator(s)	Placebo SC Q4W from Week 0 (n=117, among these 56 are in the BMSL-naïve group and 53 are in the BMSL-experienced group).
Follow-up time	The average duration of follow-up through week 48 in the safety analyses set was 30.0 weeks in the placebo group (all placebo subjects excluding data after a subject is rescued with guselkumab [the average duration of follow-up was 30.6 weeks in placebo subjects who were rescued with guselkumab]). In the guselkumab 400 mg SC Q4W followed by 100 mg Q8W group, the average duration of follow-up was 47.0 weeks. In the guselkumab 400 mg SC Q4W followed by 200 mg Q4W group, the average duration of follow-up was 48.0 weeks.
Primary, secondary and exploratory endpoints	**Endpoints included in this application:** One of the co-primary endpoints, clinical remission at Week 12, were included in this application. Other endpoints included corticosteroid-

Trial name: GRAVITI	NCT number: NCT05197049
	free clinical remission at Week 48, endoscopic remission at Week 48, IBDQ data at Week 12 and Week 48, as well as AEs. **Other endpoints:** The other co-primary endpoint, endoscopic response at Week 12, was not included in this application. Secondary endpoints were clinical remission at Week 24, patient-reported outcome-2 remission at Week 12, and clinical response at Week 12. Multiplicity-controlled Week 48 endpoints were clinical remission at Week 48 and endoscopic response at Week 48.
Method of analysis	All efficacy analyses were intention-to-treat analyses presented for the BMSL-naïve and BMSL-experienced subgroup. All efficacy analyses include the presentation of numbers, percentages, and CIs as well as adjusted treatment difference. The adjusted treatment difference and corresponding CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.
Subgroup analyses	Pre-specified subgroup analyses were performed to evaluate consistency of treatment effect over baseline demographics, baseline disease characteristics, and prior and baseline CD-related medication use. Subgroups were also analysed by serum guselkumab concentration (based on quartiles).
Other relevant information	N/A

Abbreviations: CD = Crohn's disease; CDAI = Crohn's Disease Activity Index; IBDQ = Inflammatory Bowel Disease Questionnaire; N/A = not applicable; Q4W = every 4 weeks; Q8W = every 8 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease.
Sources: ClinicalTrials.gov, 2022 (55); Janssen Research & Development, 2024 (56).

Appendix B. Efficacy results per study

Results per study (GALAXI 2)

Table 49 Results per study (GALAXI 2)

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
Clinical remission, BMSL-naïve subgroup (12 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 28 (48.3%)	N/A	N/A	N/A	Vs. PBO: 30.9%	11.9%, 49.9%	0.0014	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 12. Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI at Week 12 were considered not having achieved the endpoint at Week 12. The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	n = 32 (50.8%)	N/A	N/A	N/A	Vs. PBO: 33.4%	14.8%, 52.0%	0.0004		
	PBO	34	n = 6 (17.6%)	N/A	N/A	N/A	Reference	Reference	Reference		

Results of GALAXI 2 (NCT03466411)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
Clinical remission, BMSL-experienced subgroup (12 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	n = 31 (40.3%)	N/A	N/A	N/A	Vs. PBO: 17.7%	1.6%, 33.8%	0.0314	The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	n = 36 (49.3%)	N/A	N/A	N/A	Vs. PBO: 26.2%	8.5%, 44.0%	0.0037		
	PBO	39	n = 9 (23.1%)	N/A	N/A	N/A	Reference	Reference	Reference		
Corticosteroid-free clinical remission, BMSL-naïve subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 44 (75.9%)	N/A	N/A	N/A	Vs. UST: 3.7%	-12.8%, 20.2%	0.6618	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48.	Johnson & Johnson (7)

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	n = 52 (82.5%)	N/A	N/A	N/A	Vs. UST: 10.1%	-4.5%, 24.7%	0.1770	Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not having achieved the endpoint at Week 48. The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	
	UST	58	n = 42 (72.4%)	N/A	N/A	N/A	Reference	Reference	Reference		
Corticosteroid-free clinical remission, BMSL-experienced subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	n = 41 (53.2%)	N/A	N/A	N/A	Vs. UST: 2.3%	-13.0%, 17.6%	0.7682		Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	n = 45 (61.6%)	N/A	N/A	N/A	Vs. UST: 10.9%	-5.1%, 27.0%	0.1816		

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
	UST	79	n = 40 (50.6%)	N/A	N/A	N/A	Reference	Reference	Reference		
Endoscopic remission, BMSL-naïve subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 25 (43.1%)	N/A	N/A	N/A	Vs. UST: 9.4%	-9.2%, 28.8%	0.3228	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48. Missing data imputation: After accounting for ICE strategies, subjects who were missing SES-CD at Week 48 were considered not having achieved the endpoint at Week 48. The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	n = 35 (55.6%)	N/A	N/A	N/A	Vs. UST: 22.7%	5.5%, 39.8%	0.0096		
	UST	58	n = 19 (32.8%)	N/A	N/A	N/A	Reference	Reference	Reference		
Endoscopic remission BMSL-	GUS 200 mg IV Q4W →	77	n = 22 (28.6%)	N/A	N/A	N/A	Vs. UST: 5.8%	-7.7%, 19.4%	0.3996		

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
experienced subgroup (48 weeks)	100 mg SC Q8W									>300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	n = 23 (31.5%)	N/A	N/A	N/A	Vs. UST: 9.0%	-4.9%, 22.9%	0.2045		
	UST	79	n = 18 (22.8%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-naïve subgroup (12 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 30 (51.7%)	N/A	N/A	N/A	Vs. PBO: 18.9%	-0.5%, 38.3%	0.0568	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 12.	Johnson & Johnson (7)
	GUS 200 mg IV Q4W →	63	n = 26 (41.3%)	N/A	N/A	N/A	Vs. PBO: 9.5%	-9.8%, 28.8%	0.3333		

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
	200 mg SC Q4W									Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ score at Week 12 were considered not having achieved the endpoint at Week 12. The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	
	PBO	34	n = 11 (32.4%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-experienced subgroup (12 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	n = 34 (44.2%)	N/A	N/A	N/A	Vs. PBO: 21.5%	5.0%, 38.1%	0.0108		Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	n = 27 (37.0%)	N/A	N/A	N/A	Vs. PBO: 13.8%	-3.3%, 30.8%	0.1128		
	PBO	39	n = 9 (23.1%)	N/A	N/A	N/A	Reference	Reference	Reference		

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
IBDQ remission, BMSL-naïve subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 38 (65.5%)	N/A	N/A	N/A	Vs. UST: 8.4%	-9.8%, 26.5%	0.3659	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48. Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 48 were considered not having achieved the endpoint at Week 48. The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	63	n = 42 (66.7%)	N/A	N/A	N/A	Vs. UST: 11.2%	-5.3%, 27.7%	0.1848		
	UST	58	n = 33 (56.9%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-experienced subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	77	n = 34 (44.2%)	N/A	N/A	N/A	Vs. UST: -2.9%	-18.7%, 12.9%	0.7187		Johnson & Johnson (7)

Results of GALAXI 2 (NCT03466411)										
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
	GUS 200 mg IV Q4W → 200 mg SC Q4W	73	n = 35 (47.9%)	N/A	N/A	N/A	Vs. UST: 2.1%	-14.0%, 18.1%	0.8011		
	UST	79	n = 37 (46.8%)	N/A	N/A	N/A	Reference	Reference	Reference		
CFB in IBDQ total score, BMSL-naïve subgroup, GUS vs. UST (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	LS mean: 50.017 (3.72)	N/A	N/A	N/A	3.303	-7.00, 13.61	0.5282	The LS Mean and SE for each treatment group, LS Mean difference between the treatment groups and p-values for the comparisons of each guselkumab treatment group with the ustekinumab group were based on MMRM analysis including change from baseline in IBDQ score as the response; treatment group, visit, baseline IBDQ score, BIO-Failure status (Yes, No), baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), baseline corticosteroid use (Yes or No), an interaction term of visit with treatment group and an interaction term of visit with baseline IBDQ score as explanatory variables.	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	60	LS mean: 58.225 (3.66)	N/A	N/A	N/A	11.535	1.380, 21.61	0.0262		

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
	UST	58	Vs. GUS 100: 46.722 (3.76) Vs. GUS 200: 46.690 (3.75)	N/A	N/A	N/A	Reference				
CFB in IBDQ total score, BMSL-experienced subgroup, GUS vs. UST (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	LS mean: 36.970 (3.69)	N/A	N/A	N/A	-2.081	-12.0, 7.823	0.6795	The LS Mean and SE for each treatment group, LS Mean difference between the treatment groups and p-values for the comparisons of each guselkumab treatment group with the ustekinumab group were based on MMRM analysis including change from baseline in IBDQ score as the response; treatment group, visit, baseline IBDQ score, BIO-Failure status (Yes, No), baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), baseline corticosteroid use (Yes or No), an interaction term of visit with treatment group and an interaction term of visit with baseline IBDQ score as explanatory variables.	Johnson & Johnson (7)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	68	LS mean: 41.246 (3.83)	N/A	N/A	N/A	3.506	-6.40, 13.41	0.4863		

Results of GALAXI 2 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	P value	Difference	95% CI	P value		
	UST	76	Vs. GUS 100: 39.051 (3.64) Vs. GUS 200: 37.739 (3.59)	N/A	N/A	N/A	Reference				

ICE categories: ICE 1 = A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.); ICE 2 = A prohibited change in CD medication; ICE 3 = Discontinuation of study intervention due to lack of efficacy or an AE of worsening of CD; ICE 4 = Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis; ICE 5 = Discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4; ICE 6 = Meet rescue criteria (only applicable after Week 16).

Results per study (GALAXI 3)

Table 50 Results per study (GALAXI 3)

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Clinical remission, BMSL-naïve subgroup (12 weeks) [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 29 (50.0%)	N/A	N/A	N/A	Vs. PBO: 33.7%	13.5%, 53.9%	0.0011	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 12. Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI at Week 12 were considered not having achieved the endpoint at Week 12. The adjusted treatment difference and the CIs were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.	Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	n = 32 (49.2%)	N/A	N/A	N/A	Vs. PBO: 31.2%	12.3%, 50.1%	0.0012		
	PBO	27	n = 4 (14.8%)	N/A	N/A	N/A	Reference	Reference	Reference		
Clinical remission, BMSL-experienced subgroup (12 weeks) [a, b]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	n = 39 (51.3%)	N/A	N/A	N/A	Vs. PBO: 36.0%	20.2%, 51.7%	<0.0001		Johnson & Johnson (8)
	GUS 200 mg IV Q4W →	74	n = 32 (43.2%)	N/A	N/A	N/A	Vs. PBO: 28.4%	13.0%, 43.8%	0.0003		

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
	200 mg SC Q4W									The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	
	PBO	39	n = 6 (15.4%)	N/A	N/A	N/A	Reference	Reference	Reference		
Corticosteroid-free clinical remission, BMSL-naïve subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 38 (65.5)	N/A	N/A	N/A	Vs. UST: -10.3%	-26.3%, 5.7%	0.2076	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48. Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI score at Week 48 were considered not	Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	n = 42 (64.6)	N/A	N/A	N/A	Vs. UST: -11.2%	-27.6%, 5.1%	0.1782		
	UST [c, d]	63	n = 47 (74.6%)	N/A	N/A	N/A	Reference	Reference	Reference		

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Corticosteroid-free clinical remission , BMSL-experienced subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	n = 50 (65.8%)	N/A	N/A	N/A	Vs. UST: 19.9%	5.0%, 34.8%	0.0089	having achieved the endpoint at Week 48. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	n = 47 (63.5%)	N/A	N/A	N/A	Vs. UST: 17.9%	2.1%, 33.6%	0.0260		
	UST [c, d]	77	n = 35 (45.5%)	N/A	N/A	N/A	Reference	Reference	Reference		
Endoscopic remission, BMSL-naïve subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 26 (44.8%)	N/A	N/A	N/A	Vs. UST: 16.4%	-0.8%, 33.6%	0.0617	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who had ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48.	Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	n = 24 (36.9%)	N/A	N/A	N/A	Vs. UST: 8.6%	-8.3%, 25.5%	0.3199		

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	UST	63	n = 17 (27.0%)	N/A	N/A	N/A	Reference	Reference	Reference	Missing data imputation: After accounting for ICE strategies, subjects who were missing SES-CD at Week 48 were considered not having achieved the endpoint at Week 48. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	
Endoscopic remission BMSL-experienced subgroup (48 weeks) [f, g]	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	n = 21 (27.6%)	N/A	N/A	N/A	Vs. UST: 9.3%	-4.5%, 23.1%	0.1871		Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	n = 19 (25.7%)	N/A	N/A	N/A	Vs. UST: 7.8%	-5.5%, 21.2%	0.2504		
	UST	77	n = 14 (18.2%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-naïve subgroup (12 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	58	n = 30 (51.7%)	N/A	N/A	N/A	Vs. PBO: 30.0%	10.9%, 49.1%	0.0021	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available, to determine respond-	Johnson & Johnson (8)
	GUS 200 mg IV Q4W →	65	n = 29 (44.6%)	N/A	N/A	N/A	Vs. PBO: 19.6%	-1.3%, 40.4%	0.0664		

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	200 mg SC Q4W									er and nonresponder status at Week 12.	
	PBO	27	n = 6 (22.2%)	N/A	N/A	N/A	Reference	Reference	Reference	Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 12 were considered not having achieved the endpoint at Week 12.	
IBDQ remission, BMSL-experienced subgroup (12 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	n = 40 (52.6%)	N/A	N/A	N/A	Vs. PBO: 22.1%	4.3%, 40.0%	0.0150		Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	n = 35 (47.3%)	N/A	N/A	N/A	Vs. PBO: 16.9%	-1.8%, 35.5%	0.0760	The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.	
	UST	39	n = 12 (30.8%)	N/A	N/A	N/A	Reference	Reference	Reference	The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No), and baseline corticosteroid use (Yes or No).	
	GUS 200 mg IV Q4W →	58	n = 35 (60.3%)	N/A	N/A	N/A	Vs. Ust: 1.4%	-16.3%, 19.1%	0.8759	ICE strategies: Subjects who met ICE categories 1, 2, 3 or 5 prior to	Johnson & Johnson (8)

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
IBDQ remission, BMSL-naïve subgroup (48 weeks)	100 mg SC Q8W									the analysis timepoint were considered not to have met the endpoint criteria. Subjects who met ICE4 had their observed data used, if available, to determine responder and nonresponder status at Week 48. Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ total score at Week 48 were considered not having achieved the endpoint at Week 48. The p-values were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification variables used are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), biologic failure status (Yes or No),	
	GUS 200 mg IV Q4W → 200 mg SC Q4W	65	n = 31 (47.7%)	N/A	N/A	N/A	Vs. Ust: 10.2%	-27.8%, 7.5%	0.2581		
	UST	63	n = 37 (58.7%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-experienced subgroup (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	n = 44 (57.9%)	N/A	N/A	N/A	Vs. UST: 17.5%	2.0%, 33.1%	0.0272		Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	74	n = 40 (54.1%)	N/A	N/A	N/A	Vs. UST: 14.2%	-1.5%, 29.9%	0.0754		
	UST	77	n = 31 (40.3%)	N/A	N/A	N/A	Reference	Reference	Reference		

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
CFB in IBDQ total score, BMSL-naïve subgroup, GUS vs. UST (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	54	LS mean: 43.949 (3.91)	N/A	N/A	N/A	2.893	-7.56, 13.35	0.5860	and baseline corticosteroid use (Yes or No).	Johnson & Johnson (8)
	GUS 200 mg IV Q4W → 200 mg SC Q4W	62	LS mean: 37.403 (3.63)	N/A	N/A	N/A	-5.171	-15.3, 4.914	0.3136		
	UST	59	Vs. GUS 100: 41.055 (3.69)	N/A	N/A	N/A	Reference				
			Vs. GUS 200: 42.574 (3.69)								
CFB in IBDQ total score, BMSL-experienced subgroup, GUS vs. UST (48 weeks)	GUS 200 mg IV Q4W → 100 mg SC Q8W	76	LS mean: 40.456 (3.69)	N/A	N/A	N/A	7.730	-2.32, 17.78	0.1313		Johnson & Johnson (8)
	GUS 200 mg IV Q4W →	71	LS mean: 39.234 (3.96)	N/A	N/A	N/A	7.061	-3.51, 17.64	0.1898		

Results of GALAXI 3 (NCT03466411)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	200 mg SC Q4W										
	UST	71	Vs. GUS 100: 32.727 (3.75)	N/A	N/A	N/A	Reference				
			Vs. GUS 200: 32.172 (3.88)								

ICE categories: ICE 1 = A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.); ICE 2 = A prohibited change in CD medication; ICE 3 = Discontinuation of study intervention due to lack of efficacy or an AE of worsening of CD; ICE 4 = Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis; ICE 5 = Discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4; ICE 6 = Meet rescue criteria (only applicable after Week 16).

Results per study (GRAVITI)

Table 51 Results per study (GRAVITI)

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	Study arm	N	Result (CI)	Difference	95% CI	*P* value	Difference	95% CI	*P* value		
Clinical remission, BMSL-naïve subgroup (12 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	n = 29 (54.7%)	N/A	N/A	N/A	29.8%	11.8%, 47.8%	0.0012	Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: Subjects who met ICE4 had their observed data used, if available. Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI at Week 12 were considered not having achieved the endpoint at Week 12. The CIs for the proportion of subjects meeting the endpoint were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided. The adjusted treatment difference(s), CI(s), and p-value(s) were based	Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	52	n = 23 (44.2%)	N/A	N/A	N/A	20.7%	3.5%, 38.0%	0.0185		
	PBO	56	n = 14 (25.9%)	N/A	N/A	N/A	Reference				
Clinical remission, BMSL-experienced	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	n = 37 (67.3%)	N/A	N/A	N/A	50.5	35.2, 65.8	<0.001		Johnson & Johnson (9)

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
subgroup (12 weeks)	GUS 400 mg SC Q4W → 200 mg SC Q8W	53	n = 28 (52.8%)	N/A	N/A	N/A	35.7	19.1, 52.2	<0.001	on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator.	
	PBO	53	n = 9 (17.0%)	N/A	N/A	N/A	Reference	Reference	Reference		
Corticosteroid-free clinical remission, BMSL-naïve subgroup (48 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	n = 33 (62.3%)	N/A	N/A	N/A	40.8%	23.9%, 57.8%	<0.0001	Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: Subjects who met ICE4 had their observed data used, if available. Missing data imputation: After accounting for ICE strategies, subjects who were missing CDAI at Week 48 were considered not having achieved the endpoint at Week 48. The CIs for the proportion of subjects meeting the endpoint were based on the normal approximation confidence limits. In cases of rare events, the exact	Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	52	n = 35 (67.3%)	N/A	N/A	N/A	46.5%	29.9%, 63.0%	<0.0001		
	PBO	56	n = 12 (21.4%)	N/A	N/A	N/A	Reference				
Corticosteroid-free clinical	GUS 400 mg SC Q4W →	55	n = 31 (56.4%)	N/A	N/A	N/A	47.0%	31.7%, 62.4%	<0.0001		Johnson & Johnson (9)

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
remission, BMSL-experienced subgroup (48 weeks)	100 mg SC Q8W									confidence limits were provided. The adjusted treatment difference(s), CI(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).	
	GUS 400 mg SC Q4W → 200 mg SC Q8W	53	n = 33 (62.3%)	N/A	N/A	N/A	52.9%	37.6%, 68.1%	<0.0001		
	PBO	53	n = 5 (9.4%)	N/A	N/A	N/A	Reference	Reference	Reference		
Endoscopic remission, BMSL-naïve subgroup (48 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	n = 22 (41.5%)	N/A	N/A	N/A	30.8%	15.3%, 46.3%	<0.0001	Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: Subjects who met ICE4 had their observed data used, if available. Missing data imputation: After accounting for ICE strategies, subjects who were missing SES-CD at	Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	52	n = 22 (42.3%)	N/A	N/A	N/A	32.0%	16.1%, 47.8%	<0.0001		
	PBO	56	n = 6 (10.7%)	N/A	N/A	N/A	Reference				

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
Endoscopic remission, BMSL-experienced subgroup (48 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	n = 11 (20.0%)	N/A	N/A	N/A	20.4%	9.8%, 31.0%	0.0002	Week 48 were considered not having achieved the endpoint at Week 48. The CIs for the proportion of subjects meeting the endpoint were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided. The adjusted treatment difference(s), CI(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).	Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	53	n = 20 (37.7%)	N/A	N/A	N/A	37.4%	24.3%, 50.5%	<0.0001		
	PBO	53	n = 0 (0.0%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-naïve subgroup (12 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	n = 28 (52.8%)	N/A	N/A	N/A	28.8%	11.6%, 46.0%	0.0010	Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria. Treatment policy strategy: Subjects who met ICE4 had their observed data used, if available.	Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	52	n = 23 (44.2%)	N/A	N/A	N/A	20.7%	3.5%, 38.0%	0.0185		

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	PBO	56	n = 14 (25.0%)	N/A	N/A	N/A	Reference	Reference	Reference	Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ score at Week 12 were considered not having achieved the endpoint at Week 12. The CIs for the proportion of subjects meeting the endpoint were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided. The adjusted treatment difference(s), CI(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).	
IBDQ remission, BMSL-experienced subgroup (12 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	n = 29 (52.7%)	N/A	N/A	N/A	32.9%	16.2%, 49.5%	0.0001		Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	53	n = 26 (49.1%)	N/A	N/A	N/A	29.5%	13.0%, 45.9%	0.0004		
	PBO	53	n = 11 (20.8%)	N/A	N/A	N/A	Reference	Reference	Reference		
IBDQ remission, BMSL-naïve subgroup (48 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	53	n = 30 (56.6%)	N/A	N/A	N/A	30.8%	15.3%, 46.3%	<0.0001	Composite strategy: Subjects who met ICE categories 1, 2, 3, 5, or 6 (meet rescue criteria [only applicable after Week 16]) prior to the analysis timepoint were considered not to have met the endpoint criteria.	Johnson & Johnson (9)
	GUS 400 mg SC Q4W →	52	n = 23 (44.2%)	N/A	N/A	N/A	32.0%	16.1%, 47.8%	<0.0001		

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	200 mg SC Q8W									Treatment policy strategy: Subjects who met ICE4 had their observed data used, if available. Missing data imputation: After accounting for ICE strategies, subjects who were missing IBDQ score at Week 48 were considered not having achieved the endpoint at Week 48. The CIs for the proportion of subjects meeting the endpoint were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided. The adjusted treatment difference(s), CI(s), and p-value(s) were based on the common risk difference by use of Mantel-Haenszel stratum weights and the Sato variance estimator. The stratification factors are baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), and BIO-failure status at baseline (yes or no).	
	PBO	56	n = 11 (19.6%)	N/A	N/A	N/A	Reference				
IBDQ remission, BMSL-experienced subgroup (48 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	55	n = 30 (54.5%)	N/A	N/A	N/A	39.2%	23.7%, 54.7%	<0.0001		Johnson & Johnson (9)
	GUS 400 mg SC Q4W → 200 mg SC Q8W	53	n = 25 (47.2%)	N/A	N/A	N/A	32.1%	15.7%, 48.5%	<0.0001		
	PBO	53	n = 8 (15.1%)	N/A	N/A	N/A	Reference	Reference	Reference		
CFB in IBDQ total score, BMSL-naïve	GUS 400 mg SC Q4W → 100 mg SC Q8W	49	LS mean: 42.015 (4.34)	N/A	N/A	N/A	24.358	12.44, 36.27	<0.0001	Composite strategy: subjects who met ICE categories 1, 2, 3, 5, or 6 prior to the analysis timepoint have zero CFB at the analysis timepoint.	Johnson & Johnson (9)

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
subgroup (48 weeks)	GUS 400 mg SC Q4W → 200 mg SC Q8W	48	LS mean: 44.339 (4.23)	N/A	N/A	N/A	25.811	14.10, 37.53	<0.0001	Treatment policy strategy: subjects who met ICE 4 had their observed data used, if available. The LS mean, LS mean difference, confidence interval, and p-value were based on the MMRM (Mixed Model Repeated Measures) model with treatment group, visit, applicable baseline score, biologic failure status at baseline (yes or no), baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), visit by treatment group interaction, and visit by applicable baseline score interaction.	
	PBO	45	Vs. GUS 100: 17.66 (4.49) Vs. GUS 200: 18.19 (4.38)	N/A	N/A	N/A	Reference				
CFB in IBDQ total score, BMSL-experienced subgroup (48 weeks)	GUS 400 mg SC Q4W → 100 mg SC Q8W	45	LS mean: 45.37 (3.94)	N/A	N/A	N/A	35.710	24.99, 46.43	<0.0001	Composite strategy: subjects who met ICE categories 1, 2, 3, 5, or 6 prior to the analysis timepoint have zero CFB at the analysis timepoint. Treatment policy strategy: subjects who met ICE 4 had their observed data used, if available. The LS mean, LS mean difference, confidence interval, and p-value were based on the MMRM (Mixed	Johnson & Johnson (9)
	GUS 400 mg SC Q4W →	46	LS mean: 45.977 (4.34)	N/A	N/A	N/A	36.221	24.42, 48.02	<0.0001		

Results of GRAVITI (NCT05197049)											
				Estimated absolute difference in effect			Estimated relative difference in effect			Description of methods used for estimation	References
Outcome	**Study arm**	**N**	**Result (CI)**	**Difference**	**95% CI**	***P* value**	**Difference**	**95% CI**	***P* value**		
	200 mg SC Q8W									Model Repeated Measures) model with treatment group, visit, applicable baseline score, biologic failure status at baseline (yes or no), baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), visit by treatment group interaction, and visit by applicable baseline score interaction.	
	PBO	49	Vs. GUS 100: 9.62 (3.80)	N/A	N/A	N/A	Reference				
			Vs. GUS 200: 9.76 (4.20)								

ICE categories: ICE 1 = A CD-related surgery (with the exception of minor procedures such as drainage of a superficial abscess or seton placement, etc.); ICE 2 = A prohibited change in CD medication; ICE 3 = Discontinuation of study intervention due to lack of efficacy or an AE of worsening of CD; ICE 4 = Discontinuation of study intervention due to COVID-19 related reasons (excluding COVID-19 infection) or regional crisis; ICE 5 = Discontinuation of study intervention due to COVID-19 infection or for reasons other than those specified in ICE categories 3 and 4; ICE 6 = Meet rescue criteria (only applicable after Week 16).

Appendix C. Comparative analysis of efficacy

N/A

Appendix D. Literature searches for the clinical assessment

N/A

Appendix E. Clinical basis for comparison

In Table 52, we present our suggestion for the placement of guselkumab in the DMC's clinical sequence of medications for adult patients with CD who are BMSL-naïve (corresponding to Table 1-1 in Medicinrådet, 2024 (60)).

Table 52 Suggestion for the DMC's clinical sequence of medications for adult patients with CD who are BMSL-naïve

BMSL-naïve patients	Drug	Administration and dose
Use among at least 70% of the population*	Adalimumab (SC)	Induction dose: 160 mg at Week 0, 80 mg at Week 2. Maintenance dose: 40 mg every 2 weeks.
	Guselkumab (IV + SC)	Induction dose (IV): 200 mg at Week 0, Week 4, and Week 8. Maintenance dose (SC): 100 mg starting at Week 16 and Q8W.
	Guselkumab (SC + SC)	Induction dose (SC): 400 mg at Week 0, Week 4, and Week 8. Maintenance dose (SC): 100 mg starting at Week 16 and Q8W.
	Infliximab (IV)	Induction dose: 5 mg/kg at Week 0, 2, and 6. Maintenance dose: 5 mg/kg Q8W.
	Risankizumab (IV + SC)	Induction dose (IV): 600 mg at Week 0, 4, and 8. Maintenance dose (SC): 360 mg Q8W from Week 12.
	Ustekinumab (IV + SC)	Induction dose (IV): 260 mg (≤55 kg); 390 mg (>55 kg - ≤85 kg); 520 mg (>85 kg) at Week 0. Maintenance dose (SC): 90 mg at Week 8, hereafter every 12 weeks.
	Vedolizumab (IV)	Induction dose: 300 mg at Week 0, 2, and 6. Maintenance dose: 300 mg Q8W.

	Vedolizumab (IV + SC)	Induction dose (IV): 300 mg at Week 0 and 2. Maintenance dose (SC): 108 mg at Week 6, hereafter 108 every 2 weeks.
Consider	-	-
Do not use routinely	Upadacitinib (per os)	Induction dose: 45 mg daily for 12 weeks. Maintenance dose: 15 or 30 mg daily.

Abbreviations: BMSL = biological and targeted synthetic medicine; CD = Crohn's disease; DMC = Danish Medicines Council; IV = intravenous; Q8W = every 8 weeks; SC = subcutaneous.
Notes: * The percentage describes the proportion of the patient population that should, at a minimum, begin treatment with the medication recommended as the first choice in the treatment recommendation.
Source: Based on Table 1-1 in Medicinrådet, 2024 (60).

In Table 53, we present our suggestion for the placement of guselkumab in the DMC's clinical sequence of medications for adult patients with CD who are BMSL-experienced (corresponding to Table 1-3 in Medicinrådet, 2024 (60)).

Table 53 Suggestion for the DMC's clinical sequence of medications for adult patients with CD who are BMSL-experienced

BMSL-naïve patients	Drug	Administration and dose
Use among at least 70% of the population*	Adalimumab (SC)	Induction dose: 160 mg at Week 0, 80 mg at Week 2. Maintenance dose: 40 mg every 2 weeks.
	Guselkumab (IV + SC)	Induction dose (IV): 200 mg at Week 0, Week 4, and Week 8. Maintenance dose (SC): 100 mg starting at Week 16 and Q8W.
	Guselkumab (SC + SC)	Induction dose (SC): 400 mg at Week 0, Week 4, and Week 8. Maintenance dose (SC): 100 mg starting at Week 16 and Q8W.
	Infliximab (IV)	Induction dose: 5 mg/kg at Week 0, 2, and 6. Maintenance dose: 5 mg/kg Q8W.
	Risankizumab (IV + SC)	Induction dose (IV): 600 mg at Week 0, 4, and 8. Maintenance dose (SC): 360 mg Q8W from Week 12.

	Ustekinumab (IV + SC)	Induction dose (IV): 260 mg (≤55 kg); 390 mg (>55 kg - ≤85 kg); 520 mg (>85 kg) at Week 0. Maintenance dose (SC): 90 mg at Week 8, hereafter every 12 weeks.
	Vedolizumab (IV)	Induction dose: 300 mg at Week 0, 2, and 6. Maintenance dose: 300 mg Q8W.
	Vedolizumab (IV + SC)	Induction dose (IV): 300 mg at Week 0 and 2. Maintenance dose (SC): 108 mg at Week 6, hereafter 108 every 2 weeks.
Consider	Upadacitinib (per os)	Induction dose: 45 mg daily for 12 weeks. Maintenance dose: 15 or 30 mg daily.

Abbreviations: BMSL = biological and targeted synthetic medicine; CD = Crohn's disease; DMC = Danish Medicines Council; IV = intravenous; Q8W = every 8 weeks; SC = subcutaneous.
Notes: * The percentage describes the proportion of the patient population that should, at a minimum, begin treatment with the medication recommended as the first choice in the treatment recommendation.
Notes: Based on Table 1-3 in Medicinrådet, 2024 (60).

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