Canada's Drug Agency
L'Agence des médicaments du Canada

Reimbursement Recommendation

Reimbursement Recommendation

(Confidential Draft)

Guselkumab (Tremfya)

Indication: For the treatment of adult patients with moderately to severely active Crohn's disease.

Sponsor: Janssen Inc.

Recommendation: Reimburse with Conditions

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Recommendation

The CDA-AMC Canadian Drug Expert Committee (CDEC) recommends that guselkumab be reimbursed for the treatment of adult patients with moderately to severely active Crohn disease (CD), only if the conditions listed in **Error! Reference source not found.** are met.

Rationale for the Recommendation

Two phase III, double-blind, placebo and active-controlled (versus ustekinumab) trials (GALAXI 2, N = 523; and GALAXI 3, N = 525), along with 1 phase III, placebo-controlled trial (GRAVITI, N = 347) demonstrated that treatment with guselkumab — administered as either a 200 mg intravenous or 400 mg subcutaneous induction, followed by 100 mg subcutaneous (SC) maintenance (regimen 1) or 200 mg subcutaneous maintenance (regimen 2)—results in added clinical benefits in adults with moderately to severely active CD who had an inadequate response to, or were unable to tolerate, previous conventional or advanced therapy. Comparative evidence versus placebo from the GALAXI 2 and GALAXI 3 trials demonstrated that guselkumab results in a clinically important improvement in clinical response at Week 12 and clinical remission at Week 48 (adjusted between-group difference = 40.4%; 95% CI, 31.0 to 49.7, and 34.4%; 95% CI, 24.7 to 44.1, respectively), clinical response at Week 12 and endoscopic response at Week 48 (33.4%; 95% CI, 25.9 to 41.0, and 29.1%; 95% CI, 21.5 to 36.7, respectively). Evidence from the GRAVITI trial demonstrated that, compared to placebo, guselkumab results in a clinically important improvement in clinical remission at Weeks 12 (adjusted between-group difference = 34.9%; 95% CI, 25.1 to 44.6) and 48 (45.9%; 95% CI, 36.6 to 55.1), endoscopic response at Week 48 (40.9%; 95% CI, 32.9 to 48.9). Additionally, these trials showed evidence of high certainty that, compared to placebo, guselkumab treatment results in a clinically important improvement in clinical and endoscopic outcomes, clinical response and 90–day corticosteroid-free clinical remission, at Weeks 12 and 48; and evidence of moderate-to-high certainty that guselkumab treatment improves HRQoL (as assessed by Inflammatory Bowel Disease Questionnaire [IBDQ] remission and patient-reported outcome 2 [PRO-2] remission) at Weeks 12 and 48. Comparative evidence versus ustekinumab from the pooled analysis of the GALAXI 2 and GALAXI 3 trials showed added benefits with guselkumab treatment with respect to endoscopic response, endoscopic remission, and combined clinical remission and endoscopic response at Week 48; however, based on the analyses of individual trials, clinically important benefits with guselkumab treatment was not consistently observed for some outcomes, which reduces certainty of the evidence. Further, evidence from the GALAXI trials suggested that there is little to no clinically important difference between guselkumab and ustekinumab in clinical remission at Week 48 (moderate certainty) and IBDQ remission at Week 48 (low and moderate certainty for regimen 1 and 2, respectively).

The sponsor-submitted indirect treatment comparison (ITC) demonstrated that guselkumab frequently showed potential superiority over vedolizumab in achieving clinical remission and response; however, comparisons with other agents— such as adalimumab, infliximab, ustekinumab, risankizumab, and upadacitinib —yielded more inconsistent results. Due to limitations of the ITC and imprecision in the treatment effect estimates, no definitive conclusions can be drawn regarding the relative efficacy of guselkumab compared with other relevant comparators.

Patients identified a need for accessible and effective treatment options that provide a convenient route of administration, reduce symptoms and achieve clinical remission, including corticosteroid-free remission, improve HRQoL, and minimize side effects. CDEC concluded that guselkumab met some important needs identified by patients, such as achieving clinical response and remission, endoscopic response and remission, improved HRQoL, offering an additional advanced therapy option. CDEC noted that no new safety signals were identified and that the safety profile of guselkumab was consistent with that of the drug class.

At the sponsor submitted price for guselkumab and publicly listed price for comparators, guselkumab was more costly than most other reimbursed advanced therapies for adult patients with moderately to severely active CD who have an inadequate response to or failure to tolerate conventional or advanced therapy. As no definitive conclusions can be drawn regarding the relative efficacy of guselkumab compared to other advanced therapies, the total drug cost of guselkumab should not exceed the total drug cost of the least costly relevant advanced therapy reimbursed in this patient population.

Table 1: Reimbursement Conditions and Reasons

Reimbursement condition	Reason	Implementation guidance
Initiation, renewal, discontinuation, and prescribing		
1. Eligibility for reimbursement of guselkumab should be based on the criteria used by each of the public drug plans for initiation, renewal, discontinuation, and prescribing of other advanced therapies for the treatment of adults with moderately to severely active CD.	CDEC considered it appropriate to align the reimbursement conditions for guselkumab with the reimbursement criteria used by public drug plans for the treatment of adults with moderately to severely active CD.	—
Pricing		
2. Guselkumab should be negotiated so that it does not exceed the drug program cost of treatment with the least costly available relevant advanced therapy reimbursed for the treatment of adult patients with moderately to severely active CD.	The comparative efficacy and safety of guselkumab relative to other relevant advanced therapies available for moderately to severely active CD is uncertain due to limitations with the sponsor's NMA which precluded the CDA-AMC clinical review from drawing conclusions regarding the relative efficacy and safety of guselkumab. As such, there is insufficient evidence to justify a cost premium for guselkumab over the least costly relevant advanced therapy reimbursed for adult patients with moderately to severely active CD.	—

CD = Crohn disease; CDEC = Canadian Drug Expert Committee; NMA = network meta-analysis.

Discussion Points

- **Unmet need:** Patients and clinicians identified a need for additional effective advanced therapy options for CD. The clinical experts consulted by CDA-AMC indicated that in clinical practice, some patients have inadequate response or loss of response to currently available advanced therapies, and require alternative treatments. CDEC noted that currently, there are several approved advanced therapies available for CD. Based on the submitted evidence, CDEC concluded that guselkumab does not meet the unmet needs identified by patients when compared to other advanced therapies; however, the evidence is supportive of guselkumab as an additional effective treatment option for patients with moderately to severely active CD, specifically in those who have disease that failed conventional or advanced therapy as per the GALAXI 2, GALAXI 3, and GRAVITI trial populations. CDEC also acknowledged that the availability of SC formulation for induction therapy may be an advantage as it may be more convenient to administer than the IV formulation.
- **Direct comparative efficacy versus placebo**: CDEC highlighted that the evidence from GALAXI 2 and GALAXI 3 trials (IV induction followed by SC maintenance) was of high certainty, per the Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) assessment that guselkumab, compared with placebo, results in a clinically important improvement in the following outcomes: clinical response at Week 12 and clinical remission at Week 48, clinical response at Week 12 and endoscopic response at Week 48, as well as 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. Compared with placebo, evidence from the GRAVITI trial (SC induction followed by SC maintenance) demonstrated with high certainty that guselkumab results in a clinically important increase in achieving clinical remission at Weeks 12 and 48, endoscopic response at Weeks 12 and 48, endoscopic remission at Week 48, and clinical remission and endoscopic response at Week 48. In the GALAXI and GRAVITI trials, IBDQ remission was evaluated as an exploratory outcome. In the GALAXI trials, there is high-certainty evidence that guselkumab regimen 1 (100 mg maintenance) results in a clinically meaningful improvement in IBDQ remission at Week 12 compared with placebo. For guselkumab regimen 2 (200 mg maintenance), there is moderate-certainty evidence suggesting it

likely results in a clinically important increase in the proportion of patients achieving IBDQ remission at Week 12 compared with placebo. In the GRAVITI trial, there is moderate-certainty evidence that guselkumab likely results in a clinically meaningful improvement in IBDQ remission at Week 48 and high certainty evidence that guselkumab results in a clinically meaningful improvement in PRO-2 remission at Week 48, compared to placebo.

- **Direct comparative efficacy versus ustekinumab**: The results of the pre-specified, multiplicity-controlled pooled analysis of GALAXI 2 and GALAXI 3 demonstrated that both dosing regimens of guselkumab were favored over ustekinumab across secondary end points, including endoscopic response, endoscopic remission, combined clinical remission and endoscopic response at Week 48. However, results from the analyses of individual trials did not consistently suggest clinically important benefits with guselkumab treatment for some outcomes, which reduces certainty of the evidence. Per the GRADE assessment, evidence showed clinically important improvements in endoscopic response, and combined clinical remission and endoscopic response at Week 48 (low certainty for 100 mg maintenance; high certainty for 200 mg maintenance), and endoscopic remission at Week 48 (moderate certainty) with guselkumab treatment, compared to ustekinumab. Additionally, the evidence suggests that, compared with ustekinumab, guselkumab has little to no difference in clinical remission at Week 48 (moderate certainty), and IBDQ remission at Week 48 (low certainty for 100 mg maintenance; moderate certainty for 200 mg maintenance).
- **Long-term evidence:** The long-term safety and efficacy of guselkumab were evaluated in the long-term extension (LTE) phase of the GALAXI trials, with comparative assessments relative to ustekinumab. However, these findings were considered exploratory and only supportive of the primary trial results, as outcomes assessed in the LTE phase were not subject to formal hypothesis testing and no adjustments were made for multiplicity in the statistical analyses. Similar limitations were identified with the LTE of the GALAXI 1 trial with up to 152 weeks of data submitted by the sponsor.
- **Indirect evidence:** The results of the sponsor-submitted NMA demonstrated that, compared with active treatments, guselkumab often showed potential superiority over vedolizumab in achieving clinical remission and response; however, its comparative efficacy against other agents—such as ustekinumab, risankizumab, and upadacitinib—was more variable, with results differing across specific analyses and outcome measures. Due to limitations of the ITC, primarily related to the heterogeneity across studies, unverifiable assumptions made in the analysis, and imprecision in the treatment effect estimates, no definitive conclusions can be drawn regarding the relative efficacy of guselkumab compared with other relevant comparators. No comparative evidence was presented for subcutaneous guselkumab induction.
- **Safety:** In all 3 RCTs, serious treatment-emergent adverse events (TEAEs), TEAEs leading to discontinuation of treatment, notable harms (i.e., infections), and deaths were infrequent and similar across the treatment groups. CDEC agreed with the clinical experts that there was no new safety signals identified and that the safety of guselkumab was consistent with the known safety profile of the drug class. No safety outcomes were included in the NMA; therefore, CDEC could not draw any conclusions about the safety of guselkumab compared to relevant comparators based on this analysis.
- **Induction and maintenance regimens:** CDEC discussed that 2 maintenance dosing regimens (100 mg and 200 mg) of guselkumab were evaluated. CDEC considered input from the clinical experts that, in clinical practice, clinicians would typically initiate treatment with the 100 mg maintenance dose, reserving the 200 mg dose for patients with more severe disease characteristics, such as higher endoscopic activity, perianal disease, or a history of prior intestinal surgery. CDEC acknowledged that the availability of 2 maintenance dosing options may offer flexibility to tailor treatment based on individual patient needs and response to therapy.
- **Implementing the price condition:** Guselkumab has different dosing regimens to achieve dose optimization. CDEC discussed that there is no clinical evidence of a dose-response between the maintenance dosing regimens (i.e., 100 mg every 8 weeks and 200 mg every 4 weeks) nor evidence comparing the different routes of administration of guselkumab (i.e., IV and SC). CDEC noted that the clinical experts consulted on the review expected 60% of patients would receive low dose guselkumab maintenance therapy while the remainder would be on high dose guselkumab maintenance therapy. This information should be considered when negotiating the price of guselkumab to ensure that the total cost of treatment is no more costly than the least costly relevant comparator (i.e., advanced therapy) reimbursed for adults with moderately to severely active CD.

Background

Crohn disease (CD) is a chronic form of inflammatory bowel disease (IBD) that can affect any part of the gastrointestinal tract, but most commonly affects the ileum (i.e., small intestine), colon (i.e., beginning of the large intestine), and rectum. CD is typically diagnosed in adolescents and young adults, most commonly between the ages of 20 and 30 years. In 2023, the incidence of IBD in Canada was estimated at 30 per 100,000 individuals, with CD accounting for 12.2 per 100,000. CD can manifest in 3 phenotypical forms: inflammatory, stricturing, and penetrating (fistulas and abscesses). Common symptoms of CD include abdominal pain, rectal bleeding, fatigue, vomiting, diarrhea, perianal disease, weight loss, and bloating. Potential complications of include malnutrition, anemia, bowel obstructions, fistulas, anal fissures, and intra-abdominal or other abscesses and ulcers. Risk factors for CD include cigarette smoking, a family history of IBD, prior infectious gastroenteritis, and frequent use of non-steroidal anti-inflammatory drugs.

The diagnosis of CD is established through a comprehensive assessment that integrates clinical evaluation with endoscopic, histological, radiological, and/or biochemical investigations. Therapeutic goals include inducing and maintaining clinical and endoscopic remission. Pharmaceutical treatments for CD include immunosuppressants, corticosteroids, tumour necrosis factor alpha (TNF alpha) antagonists, interleukin (IL) inhibitors, Janus Kinase inhibitors (JAK) inhibitors, and integrin inhibitors. Medical management of CD generally follows a stepwise approach, in which therapies are initiated sequentially and escalated to more advanced agents or higher doses in cases of inadequate response. Not all patients respond to available treatments and their disease may become refractory to the current treatment regimens.

The indication under review for guselkumab is for the treatment of adult patients with moderately to severely active CD, and the sponsor's submitted reimbursement criteria align with this indication. The recommended induction dosage of guselkumab is either 200 mg administered by intravenous infusion, or 400 mg of guselkumab administered by subcutaneous injection at Weeks 0, 4, and 8. For maintenance therapy, the recommended dosage of guselkumab is 100 mg administered by SC injection at Week 16 and every 8 weeks thereafter, or 200 mg administered by SC injection at Week 12 and every 4 weeks thereafter.

Sources of Information Used by the Committee

To make its recommendation, the committee considered the following information:

- a review of 3 phase III, double blind, randomized controlled trials in adults with moderately to severely active CD.
- 1 long-term extension study
- 1 indirect treatment comparison
- 2 additional studies addressing gaps in evidence
- patients' perspectives gathered by 2 patient groups, Crohn's and Colitis Canada and the Gastrointestinal Society
- input from public drug plans that participate in the reimbursement review process
- 2 clinical specialists with expertise in diagnosing and treating patients with CD
- a review of the pharmacoeconomic model and report submitted by the sponsor

Perspectives of Patients, Clinicians, and Drug Programs

Patient Input

Two patient inputs were summarized for this review. The GI Society is a national charity with programs and services that supports research, advocates for appropriate patient access to health care, and promotes gastrointestinal and liver health. Crohn and Colitis Canada is a national, volunteer-based health charity focused on finding the cures for CD and ulcerative colitis. Information from both inputs were gathered from varied sources which included published perspectives, online surveys, interviews with patients and questionnaires.

The patient groups noted that CD often has a profound effect on patients' quality of life affecting both physical, emotional, and social factors of patients at home, school, or workplace. Disease severity may fluctuate, thus, requiring routine testing, reassessments, and medication changes. The Gastrointestinal (GI) Society noted that patients with CD preferred sustained remission and treatment response over relieving any 1 symptom. In the survey conducted by Crohn's and Colitis Canada, most respondents with moderate IBD (53%) and severe IBD (60%) believed that access to different treatment options could make them feel better. Both groups noted that treating CD requires a multifaceted strategy that allows for the management of symptom and disease consequences with therapies that target and reduce the underlying inflammation. Respondents in both patient group inputs highlighted they had experience with the following treatment options: systemic steroids, biologics and biosimilars, immunomodulators and antibiotics, sulfasalazine, 5-aminosalicylates, and non-systemic steroids. The majority of patients with moderate to severe CD who participated in the surveys expressed they continued to experience symptoms with current treatment options. Both patient groups expressed that patients need effective treatment options that mitigate symptoms and improve quality of life, are convenient, and can be accessed in timely manner. Patients expressed that they desired fewer medications, treatments that are safe, those that can minimize the use of steroids, and can be administered at home and taken as pills.

Major concerns regarding the existing treatments identified by the GI Society included limited access to adequate treatment supplies and continuity of care given that some patients respond differently to various medications, and in some cases may stop responding to medications after using them for some time. Both groups noted that patients have varied preferences for medication administration, influenced by a range of factors. One group noted the importance of varied treatment options that can cater to individual needs, without a requirement to trial conventional therapies before accessing targeted treatments. Therefore, there is a need for new, effective treatments for patients that could improve quality of life and eliminate symptoms, pain, frustration, and hardship.

Clinician Input

Input From Clinical Experts Consulted for This Review

According to the clinical experts consulted by CDA-AMC, although a variety of treatment options are available for CD, not all patients respond adequately to existing therapies. The clinical experts consulted emphasized the importance of introducing highly effective treatments early in the disease treatment to optimize patient outcomes. Furthermore, the clinical experts identified a significant barrier to accessing biologics: the requirement for patients to fail conventional therapies (i.e., immunomodulators) before initiating biologic treatment. Additionally, the clinical experts noted that the absence of clear guidance on the optimal sequencing of biologic therapies contributes to clinical uncertainty, often leading to treatment decisions being made without the support of robust comparative evidence.

The clinical expert indicated that guselkumab is unlikely to dramatically shift the current treatment paradigm for CD and is expected to be used similarly to other biologic therapies. Nonetheless, the clinical experts agreed that guselkumab should be accessible as a treatment option for patients with moderately to severely active CD and that it should not be reserved only for those who are intolerant to or have contraindications for other biologic agents. The clinical experts also highlighted a favorable safety profile makes it a viable alternative for patients who have experienced adverse effects with other therapies, such as anti-TNF agents. According to the clinical experts consulted, guselkumab is considered appropriate for a broad population, including both biologic-naïve and biologic-experienced patients, particularly those who have failed or are intolerant to conventional therapies or other biologics. Patients best suited should have an established diagnosis of CD based on ileocolonoscopy with active disease.

The clinical expert noted the following outcomes are used to determine patient response to treatment: clinical response or remission, endoscopic response or remission, and improved health-related quality of life (HRQoL). According to the clinical experts consulted, clinicians monitor response using a combination of symptom burden, endoscopic assessment, and biomarkers such as fecal calprotectin and C-reactive protein (CRP). The clinical experts indicated that discontinuation of guselkumab may be considered in cases of primary nonresponse, worsening patient-reported outcomes, rising biomarkers, or adverse events that cannot be adequately managed. The clinical expert emphasized that patients receiving guselkumab should be diagnosed, treated, and monitored by a specialist, such as a gastroenterologist or an internal medicine physician.

Clinician Group Input

No clinical group input was submitted for this review.

Drug Program Input

Input was obtained from the drug programs that participate in the CDA-AMC reimbursement review process.

Table 2: Responses to Questions from the Drug Programs

Implementation issues	Response
Relevant comparators	
The proposed place in therapy for guselkumab is within the moderately or severely active CD treatment landscape for patients who have disease that failed conventional therapy and patients who have disease that failed previous biologic treatments. Gulselkumab is a second in class IL-23 inhibitor (risankizumab being the first). Ustekinumab was the active comparator in the GALAXI trials and is a IL12/23 inhibitor. The proposed place in therapy is in line with the trials and ustekinumab is a reasonable comparator in the drug plans' opinion.	*This is a comment from the drug plans to inform CDEC deliberations.*
Considerations for initiation of therapy	
GALAXI trials included adults (18 years and older) with moderately or severely active CD of at least 3 months duration and the following disease criteria at baseline: • Clinically active CD: Baseline Crohn's disease activity index (CDAI) score ≥ 220 but ≤ 450 and either a mean daily stool frequency (SF) count >3 or mean daily abdominal pain (AP) score > 1. • Endoscopic evidence of ileocolonic CD: Screening simple endoscopic score for Crohn's disease (SES-CD) score ≥ 6 (or ≥ 4 for patients with isolated ileal disease) GRAVITI trials included adults (18 years and older) with a CD diagnosis of at least 3 months' duration with colitis, ileitis, or ileocolitis, confirmed at any time in the past by radiography, histology, and/or endoscopy and with the following criteria at baseline: • Clinically active CD: Baseline Crohn's disease activity index (CDAI) score ≥ 220 but ≤ 450 and either a mean daily stool frequency (SF) count ≥ 4 or mean daily abdominal pain (AP) score ≥ 2. • Endoscopic evidence of active ileocolonic CD: Screening simple endoscopic score for CD (SES-CD) score ≥ 6 (or ≥ 4 for patients with isolated ileal disease) and the presence of ulceration in at least one of the five ileocolonic segments. Are the scores used in the clinical trials reflective of what is used in clinical practice or is the Harvey Bradshaw Index score a more commonly used score? Which scoring tool should be used?	The clinical experts noted that that Harvey Bradshaw Index score is typically used to assess treatment eligibility in clinical practice. Although not universally used, some clinicians also apply the SES-CD for endoscopic assessment. The clinical experts noted that the CDAI is primarily used in clinical trials and not practical for day-to-day care due to its complexity. Despite the disconnect between trial and clinical tools, the clinical experts noted that the use of CDAI in trials is not a barrier to interpreting or applying trial results in practice, as clinicians are familiar with its components. CDEC agreed with the clinical experts and noted that scoring tools, such as CDAI, SES-CD, and Harvey Bradshaw Index, may be used to assess treatment eligibility.

Implementation issues	Response
Trials excluded patients under the age of 18 years, patients with complications of CD (e.g., symptomatic strictures or stenoses, short gut syndrome), current or suspected abscess, had a draining stoma or ostomy, prior exposure to IL12/23 or IL23 drugs (exception for those with limited exposure and no failure/intolerance to ustekinumab). • Could this be considered in patients under 18 years of age? • Are there specific complications of CD that would preclude use of guselkumab? • Should patients who had previous exposure to an IL/23 (risankizumab) or IL12/23 be eligible for treatment with guselkumab?	• CDEC agreed with the clinical experts that they were unable to comment on the use of guselkumab in patients under 18 years old since such patients were not included in the pivotal trials. The clinical experts noted that the lack of timely regulatory approvals in the pediatric population is a significant challenge that delays access to effective treatments for children. • CDEC agreed with the clinical experts that allergies to any component of the medications or preservatives would preclude the use of guselkumab. The clinical experts noted that patients with stricturing or penetrating disease are usually excluded from clinical trials due to limited expected efficacy, as these cases often require surgical intervention rather than reflecting safety concerns. CDEC acknowledged the responses from the clinical experts and noted that it may be reasonable to leave the treatment eligibility decision to the treating physician's judgement. • CDEC noted that no evidence for guselkumab treatment in patients who had prior exposure to IL-12/23 or IL-23 agents was reviewed. CDEC considered clinical expert input that in clinical practice, patients may respond to different formulations of advanced therapies in the same drug class. CDEC agreed with the clinical experts that patients who had previous exposure to an IL/23 or IL12/23 should be eligible for treatment with guselkumab.
Per the manufacturers submitted info, the proposed place in therapy for guselkumab is within the treatment options for moderately to severely active CD in patients for whom conventional therapy has failed, or who have not responded to previous biologic treatments Should patients whose disease has failed a biologic be eligible for treatment with gulselkumab?	CDEC agreed with the clinical experts that guselkumab should be available for patients who are biologic therapy-naïve and -experienced, including those whose disease failed biologic therapy.
Consider alignment with reimbursement criteria used by each of the drugs plans for other biologics for the treatment of CD.	*This is a comment from the drug plans to inform CDEC deliberations.*
Considerations for continuation or renewal of therapy	
Consider alignment with renewal criteria used by each of the drug plans for other biologics for the treatment of CD.	*This is a comment from the drug plans to inform CDEC deliberations.*
Considerations for discontinuation of therapy	
Question for the expert: How would loss of response be defined? Would loss of response, absence of clinical benefit, or disease progression be determined by the scores related to clinical response (i.e., changes in CDAI scores) and endoscopic response (i.e., changes in SES-CD scores) used in the trials?	The clinical experts noted that it would be reasonable to use Harvey Bradshaw Index score to determine response to therapy. They noted that SES-CD score may also be used but could potentially be limited by how quickly a repeat colonoscopy can be completed in clinical practice. The clinical experts emphasized the importance of objective measures beyond clinical symptoms, including biomarkers (CRP, fecal calprotectin) and imaging modalities, such as intestinal ultrasound, CTE, or MRE. The clinical experts noted that treatment response should be assessed 12 weeks after treatment initiation. The clinical experts also noted that increasing corticosteroid use without objective evidence of disease activity is not appropriate and may indicate

Implementation issues	Response
	lack of treatment response. The clinical experts noted that dose escalation may be considered for patients who do not respond to guselkumab at a dose of 100 mg. Treatment with guselkumab should not be discontinued solely based on limited improvement at Week 12, recommending reassessment and consideration of dose escalation, or the addition of immunomodulators or corticosteroids. CDEC acknowledged input from the clinical experts and ultimately considered it appropriate to align the discontinuation criteria for guselkumab with the criteria of other advanced therapies used by the public drug plans for the treatment of adults with moderately to severely active CD.
Considerations for prescribing of therapy	
The recommended induction dosage is 200 mg of guselkumab administered by intravenous (IV) infusion or 400 mg of guselkumab administered by subcutaneous (SC) injection at Week 0, Week 4, and Week 8. For the SC formulation, each 400 mg dose is given as two injections of 200 mg. The recommended maintenance dosage is 100 mg of guselkumab administered by SC injection at Week 16 and every 8 weeks thereafter. A dose of 200 mg administered by SC injection at Week 12 and every 4 weeks thereafter may be considered for patients who do not show adequate therapeutic benefit to guselkumab, or according to clinical judgement.	*This is a comment from the drug plans to inform CDEC deliberations.*
Consider alignment with prescribing criteria used by each of the drug plans for other biologics for the treatment of CD.	*This is a comment from the drug plans to inform CDEC deliberations.*
System and economic issues	
The submitted unit price of guselkumab is $3,059.7400 for the 100 mg/1.0 mL solution for subcutaneous injection, $3,059.7400 for the 200 mg/2.0 mL solution for subcutaneous injection, and $3,059.7400 for the 200 mg/20.0 mL vial for intravenous infusion. Based on the sponsor's submitted BIA, from the perspective of the Canadian public payer drug plans (excluding Quebec), the increase in net expenditure attributable to guselkumab was estimated to be $3,387,771, $3,965,366, and $7,911,414 in Year 1 (2026), Year 2 (2027), and Year 3 (2028), respectively, resulting in a 3-year total budget impact of $15,264,551.	*This is a comment from the drug plans to inform CDEC deliberations.*
Some comparators have successfully gone through price negotiations for the same indication	*This is a comment from the drug plans to inform CDEC deliberations.*

CD = Crohn disease; AZA = azathioprine; CDAI = Crohn Disease Activity Index; CDEC = Canadian Drug Expert Committee; IL = interleukin; IV = intravenous; SES-CD = Simple Endoscopic Score for Crohn Disease; SC = subcutaneous.

Clinical Evidence

Systematic Review

Description of Studies

Three multicenter, double-blind, randomized controlled trials (RCTs)—GALAXI 2 (N = 508), GALAXI 3 (N= 513), and GRAVITI (N = 347)—were included in the sponsor-submitted systematic literature review.

The GALAXI 2 and GALAXI 3 trials are identically designed, Phase 3, randomized, double-blind, placebo- and active-controlled (versus ustekinumab) parallel-group, multicenter trials. The primary objectives of both trials were to evaluate the clinical and endoscopic efficacy, and safety of guselkumab in patients with moderately to severely active CD who have demonstrated an inadequate response or failure to tolerate previous conventional therapy (oral corticosteroids and/or immunomodulators), or biologic therapy. Each trial included a 48–week main treatment phase, consisting of a 12–week induction period followed by a 36–week maintenance. In both trials, patients in the guselkumab group received an induction dose of 200 mg intravenously (IV) every 4 weeks, followed by maintenance treatment with either 100 mg subcutaneously (SC) every 8 weeks (guselkumab regimen 1 [low dose]) or 200 mg SC every 4 weeks (guselkumab regimen 2 [high dose]). In the active control group, patients received a single weight-based IV dose of ustekinumab at Week 0 (approximately 6 mg/kg), followed by SC maintenance dosing of 90 mg every 8 weeks. Patients were enrolled at 186 centers from 36 countries or territories (including 31 sites in Canada) in the GALAXI 2 trial, and 198 centers across 39 countries or territories (including 31 sites in Canada) in the GALAXI 3 trial.

The GRAVITI trial is a Phase 3, randomized, double-blind, placebo-controlled parallel-group, multicentre study. The primary objectives of the GRAVITI trials were to evaluate the efficacy and safety of guselkumab in patients with moderately to severely active CD who had demonstrated an inadequate response or intolerance to prior conventional therapy, or biologic treatments. The 24–week main treatment phase included a 12–week induction period followed by a 12–week maintenance period and was followed by the extension treatment phase that included 72–week maintenance period. During the GRAVITI trial, patients received guselkumab at a dose of 400 mg SC at Weeks 0, 4, and 8 for induction, followed by either 100 mg SC every 8 weeks (guselkumab regimen 1 [low dose]) or 200 mg SC every 4 weeks (guselkumab regimen 2 [high dose]) for maintenance. Patients were enrolled at 143 centers from 23 countries or territories, including 5 sites in Canada.

Efficacy Results

Clinical Response at Week 12 and Clinical Remission at Week 48

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance)

In GALAXI 2, the adjusted between-group difference compared to placebo was 38.1% (95% confidence interval [CI], 27.3 to 48.9; P value < 0.001) for guselkumab regimen 1 (low dose) and 42.8% (95% CI, 31.6 to 53.9; P value < 0.001) for guselkumab regimen 2 (high dose). In GALAXI 3, the adjusted between-group difference compared to placebo was 34.2% (95% CI, 23.2 to 45.3; P value < 0.001) for guselkumab regimen 1 and 35.0% (95% CI, 23.5 to 46.5; P value < 0.001) for guselkumab regimen 2. Sensitivity, supportive, and subgroup analysis — including those conducted in patients with a history of biologic therapy failure or intolerance (BIO-Failure group) and those with a history of conventional therapy failure or intolerance (CON-Failure group)—were consistent with the primary analyses in both trials.

Clinical Response at Week 12 and Endoscopic Response Week 48

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance)

In GALAXI 2, the adjusted between-group difference compared to placebo was 33.7% (95% CI, 24.1 to 43.2; P value < 0.001) for guselkumab regimen 1 and 32.9% (95% CI, 23.5 to 42.4; P value < 0.001) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to placebo was 27.9% (95% CI, 18.7 to 37.1; P value < 0.001) for guselkumab regimen 1 and 30.8% (95%CI, 21.3 to 40.3; P value < 0.001) for guselkumab regimen 2. Sensitivity, supportive, and subgroup analysis —including those conducted in the BIO-Failure and CON-Failure subpopulations—were consistent with the primary analyses in both trials.

Clinical Response at Week 12 and 90–day Corticosteroid-free Clinical Remission at Week 48

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance)

In GALAXI 2, the adjusted between-group difference compared to placebo was 38.7% (95% CI, 28.4 to 48.9; P value < 0.001) for guselkumab regimen 1 and 41.3% (95% CI, 30.6 to 52.0; P value < 0.001) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to placebo was 32.6% (95% CI, 21.7 to 43.6; P value < 0.001) for guselkumab regimen 1 and 31.5% (95% CI, 20.1 to 42.8; P value < 0.001) for guselkumab regimen 2.

Clinical Response at Week 12 and Endoscopic Remission at Week 48

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance)

In GALAXI 2, the adjusted between-group difference compared to placebo was 24.0% (95% CI, 15.8 to 32.2; P value < 0.001) for guselkumab regimen 1 and 30.0% (95% CI, 21.4 to 38.5; P value < 0.001) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to placebo was 18.2% (95% CI, 9.5 to 26.9; P value < 0.001) for guselkumab regimen 1 and 16.7% (95% CI, 8.0 to 25.4; P value < 0.001) for guselkumab regimen 2.

Clinical Remission at Week 12

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance), GRAVITI (SC induction and SC maintenance)

In GALAXI 2, the combined guselkumab induction dose group demonstrated an adjusted between-group difference of 25.1% (95% CI, 14.1 to 36.2; P value < 0.001) compared to placebo. In GALAXI 3, the combined guselkumab induction dose group demonstrated an adjusted between-group difference of 31.2% (95% CI, 21.1 to 41.3; P value < 0.001) compared to placebo.

In GRAVITI, the combined guselkumab induction dose group demonstrated an adjusted between-group difference of 34.9% (95% CI, 25.1 to 44.6; P value < 0.001) compared to placebo. Sensitivity and subgroup analysis —including those in the BIO-Failure and CON-Failure subpopulations—were consistent with the primary analyses.

Clinical Remission at Week 48

GRAVITI (SC induction and SC maintenance)

In GRAVITI, the adjusted between-group difference compared to placebo was 42.8% (95% CI, 31.6 to 54.0; P value < 0.001) for guselkumab regimen 1 and 48.9% (95% CI, 37.9 to 59.9; P value < 0.001) for guselkumab regimen 2.

Endoscopic Response at Week 12

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance), GRAVITI (SC induction and SC maintenance)

In GALAXI 2, the combined guselkumab induction dose group showed an adjusted between-group difference of 27.7% (95% CI, 19.3 to 36.1; P value < 0.001) compared to placebo. In GALAXI 3, the combined guselkumab induction dose group demonstrated an adjusted between-group difference of 22.1% (95% CI, 12.2 to 31.9; P value < 0.001) compared to placebo.

In GRAVITI, the combined guselkumab induction dose group demonstrated an adjusted between-group difference of 19.9% compared to placebo (95% CI, 10.2 to 29.6; P value < 0.001). Sensitivity and subgroup analysis — including those conducted in the BIO-Failure and CON-Failure subpopulations — were consistent with the primary analyses.

Endoscopic Response at Week 48

GRAVITI (SC induction and SC maintenance)

The adjusted between-group difference compared to placebo was 37.5% (95% CI, 27.3 to 47.7; P value < 0.001) for guselkumab regimen 1 and 44.6% (95% CI, 34.1 to 55.0; P value < 0.001) for guselkumab regimen 2.

Endoscopic remission at Week 48

GRAVITI (SC induction and SC maintenance)

The adjusted between-group difference compared to placebo was 24.5% (95% CI, 15.2 to 33.9; P value < 0.001) for guselkumab regimen 1 and 32.4% (95% CI, 22.6 to 42.3; P value < 0.001) for guselkumab regimen 2.

Clinical Response at Week 12

GRAVITI (SC induction and SC maintenance)

The combined guselkumab induction dose group demonstrated an adjusted between-group difference of 40.3% compared to placebo (95% CI, 29.9 to 50.7; P value < 0.001).

Deep Remission at Week 48

GRAVITI (SC induction and SC maintenance)

The adjusted between-group difference compared to placebo was 21.8% (95% CI, 13.1 to 30.6; P value < 0.001) for guselkumab regimen 1 and 29.8% (95% CI, 20.5 to 39.2; P value < 0.001) for guselkumab regimen 2.

Patient-Reported Outcomes

IBDQ Remission Week 12

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance), GRAVITI (SC induction and SC maintenance)

In GALAXI 2, the adjusted between-group difference compared to placebo was 19.1% (95% CI, 6.7 to 31.5; P value = 0.003) for guselkumab regimen 1 and 10.5% (95% CI, –2.3 to 23.2; P value = 0.108) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to placebo was 23.7% (95% CI, 11.1 to 36.4; P value < 0.001) for guselkumab regimen 1 and 16.5% (95% CI, 3.0 to 30.1; P value = 0.017) for guselkumab regimen 2. In GRAVITI, the adjusted between-group difference compared to placebo was 29.2% (95% CI, 17.4 to 41.0; P value < 0.001) for guselkumab regimen 1 and 20.8% (95% CI, 9.2 to 32.4; P value < 0.001) in guselkumab regimen 2.

IBDQ remission at Week 48

GRAVITI (SC induction and SC maintenance)

The adjusted between-group difference compared to placebo was 36.6% (95% CI, 25.4 to 47.8; P value < 0.001) for guselkumab regimen 1 and 30.7% (95% CI, 19.2 to 42.1; P value < 0.001) for guselkumab regimen 2.

PRO–2 Remission at Week 48

GRAVITI (SC induction and SC maintenance)

At Week 48, the adjusted between-group difference compared to placebo was 41.1 (95% CI, 30.1 to 52.1; P value < 0.001) for guselkumab regimen 1 and 53.2 (95% CI, 42.6 to 63.7; P value < 0.001) for guselkumab regimen 2.

Summary of Efficacy Outcomes (Guselkumab versus Ustekinumab)

GALAXI 2 and GALAXI 3 (IV induction and SC maintenance)

Clinical Remission at Week 48 and Endoscopic Response at Week 48

Following the pooling of data from the GALAXI 2 and GALAXI 3 trials, the adjusted between-group differences compared to ustekinumab were 7.8% (95% CI, 0.1 to 15.6; P value = 0.049) for guselkumab regimen 1 and 13.6% (95% CI, 5.9 to 21.3; P value <

0.001) for regimen 2. Comparisons from the individual GALAXI 2 and GALAXI 3 trials were not formally tested due to the failure of the statistical testing hierarchy. In GALAXI 2, the adjusted between-group difference compared to ustekinumab was 2.8% (95% CI, –0.6 to 21.0) for guselkumab regimen 1 and 10.2% (95% CI, –0.6 to 21.0) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to ustekinumab was 12.7% (95% CI, 1.7 to 23.7) for guselkumab regimen 1 and 16.9 % (95% CI, 5.8 to 27.9) for guselkumab regimen 2.

Clinical Remission at Week 48

Following the pooling of data from the GALAXI 2 and GALAXI 3 trials, the adjusted between-group differences compared to ustekinumab were 2.6% (95% CI, –5.1 to 10.2; P value = 0.512) for guselkumab regimen 1 and 7.3% (95% CI, –0.2 to 14.8; P value = 0.058) for regimen 2. Comparisons from the individual GALAXI 2 and GALAXI 3 trials were not formally tested due to the failure of the statistical testing hierarchy. In GALAXI 2, the adjusted between-group difference compared to ustekinumab was –0.6% (95% CI, –11.6 to 10.5) for guselkumab regimen 1 and 9.5% (95% CI, –0.7 to 19.8) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to ustekinumab was 5.6% (95% CI, –5.2 to 16.5) for guselkumab regimen 1 and 5.0% (95% CI, –6.1 to 16.1) for guselkumab regimen 2.

Endoscopic Response at Week 48

Following the pooling of data from the GALAXI 2 and GALAXI 3 trials, the adjusted between-group differences compared to ustekinumab were 10.6% (95% CI, 2.7 to 18.5; P = 0.009) for guselkumab regimen 1 and 15.6% (95% CI, 7.9 to 23.4; P < 0.001) for regimen 2. Comparisons from the individual GALAXI 2 and GALAXI 3 trials were not formally tested due to the failure of the statistical testing hierarchy. In GALAXI 2, the adjusted between-group compared to ustekinumab was 7.0% (95% CI, –4.4 to 18.3;) for guselkumab regimen 1 and 14.5% (95% CI, 3.6 to 25.4) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group compared to ustekinumab was 14.1% (95% CI, 2.9 to 25.2) for guselkumab regimen 1 and 16.8% (95% CI, 5.7 to 28.0) for guselkumab regimen 2.

Endoscopic Remission at Week 48

Following the pooling of data from the GALAXI 2 and GALAXI 3 trials, the adjusted between-group differences compared to ustekinumab were 8.5% (95% CI, 1.1 to 15.9; P = 0.024) for guselkumab regimen 1 and 12.3% (95% CI, 4.9 to 19.7; P = 0.001) for regimen 2. Comparisons from the individual GALAXI 2 and GALAXI 3 trials were not formally tested due to the failure of the statistical testing hierarchy. In GALAXI 2, the adjusted between-group treatment difference compared to ustekinumab was 6.4% (95% CI, –4.3 to 17.1) for guselkumab regimen 1 and 17.9% (95% CI, 7.3 to 28.4) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to ustekinumab was 10.5% (95% CI, 0.1 to 20.9) for guselkumab regimen 1 and 6.9% (95% CI, –3.3 to 17.0) for guselkumab regimen 2.

Deep Remission at Week 48

Following the pooling of data from the GALAXI 2 and GALAXI 3 trials, the adjusted between-group differences compared to ustekinumab were 7.4% (95% CI, 0.3 to 14.6; P = 0.040) for guselkumab regimen 1 and 11.3% (95% CI, 4.2 to 18.5; P = 0.002) for regimen 2. Comparisons from the individual GALAXI 2 and GALAXI 3 trials were not formally tested due to the failure of the statistical testing hierarchy. In GALAXI 2, the adjusted between-group difference compared to ustekinumab was 4.2% (95% CI, –6.2 to 14.7) for guselkumab regimen 1 and 13.0% (95% CI, 2.7 to 23.4) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to ustekinumab was 10.4% (95% CI, 0.4 to 20.4) for guselkumab regimen 1 and 9.6% (95% CI, –0.1 to 19.4) for guselkumab regimen 2.

IBDQ Remission at Week 48

In GALAXI 2, the adjusted between-group difference compared to ustekinumab was 1.6% (95% CI, –9.9 to 13.2; P value = 0.783) for guselkumab regimen 1 and 5.6% (95% CI, –5.5 to 16.7; P value = 0.322) for guselkumab regimen 2. In GALAXI 3, the adjusted between-group difference compared to ustekinumab was 10.1% (95% CI, –1.2 to 21.5; P value = 0.080) for guselkumab regimen 1 and 2.1% (95% CI, –9.4 to 13.6; P value = 0.725) for guselkumab regimen 2.

Harms Results

GALAXI 2 and GALAXI 3: IV induction and SC maintenance

Induction Period

In GALAXI 2, the proportion of patients experiencing at least 1 adverse event (AE) was 38.5% in the guselkumab regimen 1 group, 47.3% in the guselkumab regimen 2 group, 48.3% in the ustekinumab group, and 40.8% in the placebo group. In GALAXI 3, the proportion of patients experiencing at least 1 AE was 51.7% in the guselkumab regimen 1 group, 50.7% in the guselkumab regimen 2 group, 44.6% in the ustekinumab group, and 55.6% in the placebo group. In GALAXI 2, the proportion of patients experiencing at least 1 serious adverse event (SAE) was 3.5% in the guselkumab regimen 1 group, 1.4% in the guselkumab regimen 2 group, 2.4% in the ustekinumab group, and 2.6% in the placebo group. In GALAXI 3, the proportion of patients experiencing at least 1 SAE was 3.5% in the guselkumab regimen 1 group, 2.7% in the guselkumab regimen 2 group, 5.4% in the ustekinumab group, and 9.7% in the placebo group. In GALAXI 2, the proportion of patients who discontinued study treatment due to AE was 2.6% in the placebo group, 0% in the guselkumab regimen 1 group, 1.4% in the guselkumab regimen 2 group, and 2.1% in the ustekinumab group. In GALAXI 3, the corresponding discontinuation rates due to AE were 6.9%, 2.8%, 3.3%, and 3.4%, respectively. No deaths occurred during the induction period in either trial.

Maintenance Period

In GALAXI 2, the proportion of patients experiencing at least 1 AE was higher in the guselkumab regimen 1 (74.1%), guselkumab regimen 2 (78.8%), and ustekinumab (78.3%) groups, compared with the placebo group (50.0%). In GALAXI 3, the proportion of patients experiencing at least 1 AE was higher in the guselkumab regimen 1 (79.0%), guselkumab regimen 2 (76.7%), and ustekinumab (79.1%) groups, compared with the placebo group (56.9%). In GALAXI 2, the proportion of patients experiencing at least 1 SAE was higher in the guselkumab regimen 1 and ustekinumab groups (12.6% each), compared to the guselkumab regimen 2 (4.1%) and placebo (7.9%) groups. In GALAXI 3, the proportion of patients experiencing at least 1 SAE was 8.4% in the guselkumab regimen 1 group, 10.0% in the guselkumab regimen 2 group, and 10.8% in the ustekinumab group, and 13.9% in the placebo group. In GALAXI 2, the proportion of patients who discontinued study treatment due to AE during the maintenance period was 6.6% in the placebo group, 5.6% in the guselkumab regimen 1 group, 4.1% in the guselkumab regimen 2 group, and 6.3% in the ustekinumab group. In GALAXI 3, the corresponding discontinuation rates due to AE were 11.1%, 8.4%, 8.7%, and 8.8%, respectively. No deaths occurred during the maintenance period in either trial.

Notable Harms

In GALAXI 2, 1 patient (0.7%) in the guselkumab regimen 1 group experienced major adverse cardiovascular events and 1 patient (0.7%) in the ustekinumab group experienced venous thromboembolism. In GALAXI 3, 1 patient (0.7%) in the guselkumab regimen 1 group experienced active tuberculosis, and 1 patient (0.7%) experienced a malignancy in the guselkumab regimen 2 group. Additionally, 4 patients experienced opportunistic infections, including 1 (1.4%) in the placebo group, 1 (0.7%) in the guselkumab regimen 1 group, and 2 (1.3%) in the guselkumab regimen 2 group.

GRAVITI - SC Induction and SC Maintenance

Induction period

The proportions of patients who experienced at least 1 AE were 49.6% in the placebo group, 51.3% in the guselkumab regimen 1 group and 41.7% in the guselkumab regimen 2 group. The proportion of patients experiencing at least 1 SAE was 2.6% in the guselkumab regimen 1 group, 1.7% in the guselkumab regimen 2 group, and 7.7% in the placebo group. The proportion of patients who discontinued study treatment during the induction period was 2.6% in the placebo group, 0% in the guselkumab regimen 1 group, and 0.9% in the guselkumab regimen 2 group. No deaths occurred during the induction period in the GRAVITI trial.

Maintenance period

The proportions of patients who experienced at least 1 AE were 65.8% in the placebo group, 82.6% in the guselkumab regimen 1 group and 80.0% in the guselkumab regimen 2 group. The proportion of patients experiencing at least 1 SAE during the

maintenance period 13.0% in the regimen 1 guselkumab group, 7.8% in the guselkumab regimen 2 group, and 13.7% in the placebo group. The proportion of patients who discontinued study treatment was 8.5% in the placebo group, 3.5% in the guselkumab regimen 1 group, 2.6% in the guselkumab regimen 2 group. During the maintenance period, 1 patient (0.9%) died in the guselkumab regimen 1 group.

Notable Harms

In GRAVITI, 1 patient (0.7%) in the regimen 1 guselkumab group experienced a malignancy, while in the placebo group, 1 patient (0.9%) experienced an opportunistic infection and 1 patient (0.9%) venous thromboembolism.

Critical Appraisal

Randomization and allocation concealment for all 3 studies were conducted using appropriate methodology. A stratified, computerized randomization scheme was employed, and allocation concealment was ensured using interactive web response technology. Although there was some imbalance in baseline characteristics across the treatment groups in GALAXI and GRAVITI trials (e.g., race, sex, several disease characteristics), these did not systematically favour any treatment group, and clinical experts did not believe these would impact the results of the pivotal trials. Additionally, they noted that the stratification factors used across all 3 trials (e.g., baseline CDAI and SES-CD scores, prior biologic exposure) were deemed appropriate for minimizing confounding and ensuring balanced treatment groups. Major protocol deviations occurred in 17.5% of patients in the GALAXI 2 trial and 23.3% in the GALAXI 3 trial. These deviations were balanced across treatment groups and did not appear to be related to the trial context. In the GRAVITI trial, major protocol deviations were reported in 36.8% of patients in the placebo group, 26.1% in the guselkumab regimen 1 group, and 24.3% in the guselkumab regimen 2 group through Week 48. The uneven distribution of protocol deviations across treatment groups may potentially result in imbalanced comparisons of efficacy and safety of guselkumab relative to placebo. However, patients who received prohibited concomitant medications were addressed using a composite strategy, under which they were classified as nonresponders; this approach was considered reasonable by the review team. Both the GALAXI and GRAVITI trials utilized a treat-through design, whereby participants remained on their assigned treatment regimen beyond the initial induction phase without re-randomization. Additionally, all 3 trials were conducted using a double-blind design, where patients, investigators, and outcome assessors were masked to treatment allocation from the time of randomization until unblinding as specified in the study protocols. In all 3 trials, the rate of treatment discontinuation prior to Week 48 was higher in the placebo group compared to the active treatment groups. In both GALAXI trials, 49 patients crossed over to ustekinumab at Week 12 due to clinical nonresponse but were still analyzed as part of the as-randomized placebo group at Week 48, despite having received ustekinumab treatment from Week 12 onward. In the GRAVITI trial, 44 patients in the placebo group meeting predefined criteria rescued with guselkumab treatment at Weeks 12 or 16. As a result, in all 3 trials, patients in the guselkumab groups who completed the study were exposed to treatment for a longer duration, potentially providing more opportunity to demonstrate efficacy or experience safety events. Dropouts for various reasons were reflected as intercurrent events (ICEs) within the trial estimands and typically considered as non-response, which was considered appropriate in most cases. Some drop-outs were not clearly related to lack of efficacy and the non-response imputation (NRI) could have introduced bias, though rates of such ICEs were relatively limited in the GALAXI trials. At longer time points in GRAVITI, dropouts due to reasons potentially unrelated to lack of response were increased in the placebo group compared to the guselkumab groups, which could inflate the treatment effect estimates. After consideration of the ICEs, there were few missing data. In general, the end points reported in all 3 trials were validated for use in patients with moderately to severely active CD. The statistical methods used to analyze the primary and secondary outcomes across all 3 trials were deemed appropriate. Multiplicity adjustments were adequately implemented for primary and secondary outcomes across all 3 trials. However, in the GALAXI trials, formal statistical testing of the long-term secondary endpoints comparing guselkumab with ustekinumab within the individual trials was precluded due to failure of the hierarchical testing strategy. Subgroup analyses, including those conducted in the BIO-Failure and CON-Failure subpopulations, of the co-primary endpoints, were conducted in all 3 trials as part of this review. However, the subgroup analyses were not adjusted for multiplicity and were likely underpowered to detect differences between subgroups; therefore, the findings should be considered supportive only. In all 3 trials, the use of concomitant therapies was generally balanced across treatment groups and, according to clinical experts, was unlikely to have confounded the study results. Overall, the proportion of patients who experienced serious adverse events was low across all 3 trials, with similar rates observed among all treatment groups.

In terms of external validity, the inclusion and exclusion criteria across all 3 trials were generally appropriate and reflective of patients eligible for guselkumab treatment in clinical practice. The clinical experts consulted noted that while certain exclusion criteria, such as strictures or previous colectomy, are considered typical for clinical trials, they do not always reflect real-world practice, where treatment decisions are often based on individual clinical judgment and may include patients typically excluded from trials. The Health Canada indication for guselkumab is for the treatment of adult patients with moderately to severely active CD. However, both the GALAXI and GRAVITI trials included patients with moderately to severely active CD who have demonstrated an inadequate response or failure to tolerate previous conventional therapy or biologic therapy. The clinical experts noted that the trial design reflects real-world clinical practice; however, they emphasized that the distribution of biologic-naïve versus biologic-experienced patients may differ between community and tertiary care settings. In the GALAXI 2 and GALAXI 3 trials, guselkumab was evaluated against both an active comparator (ustekinumab) and placebo. The active comparator used in these trials was appropriate as ustekinumab is currently used in clinical practice. These end points included in the trials were considered appropriate by the clinical expert, although they noted that the Harvey-Bradshaw Index is more commonly used in Canadian clinical practice than the Crohn's Disease Activity Index (CDAI) score. Although there is a disconnect between tools used in trials and in clinical practice, clinical experts emphasized that the use of CDAI in trials does not pose a barrier to applying the results, since clinicians are well familiar with its components. The clinical experts considered the 48–week maintenance period following the 12–week induction period to be appropriate and sufficient for evaluating the long-term efficacy and safety of guselkumab in patients with CD.

GRADE Summary of Findings and Certainty of the Evidence

For pivotal studies and RCTs identified in the sponsor's systematic review, GRADE was used to assess the certainty of the evidence for outcomes considered most relevant to inform expert committee deliberations, and a final certainty rating was determined as outlined by the GRADE Working Group.[10,11]

The selection of outcomes for GRADE assessment was based on the sponsor's Summary of Clinical Evidence, consultation with clinical experts, and input received from patient and clinician groups and public drug plans. The following list of outcomes was finalized in consultation with expert committee members:

- Guselkumab compared with placebo: clinical response at Week 12 and clinical remission at Week 48, clinical response at Week 12 and endoscopic response at Week 48, clinical response at Week 12 and 90–day corticosteroid-free clinical remission at Week 48, clinical response at Week 12 and endoscopic remission at Week 48, IBDQ remission at Week 12, Clinical remission at Weeks 12 and 48, Endoscopic response at Weeks 12 and 48, Endoscopic remission at Week 48, IBDQ remission at Week 48, and PRO–2 remission at Week 48.
- Guselkumab compared with ustekinumab: clinical remission at Week 48, endoscopic response at Week 48, endoscopic remission at Wee 48, clinical remission and endoscopic repose at Week 48, and IBDQ remission at Week 48.
- Harms: serious adverse events

Results of GRADE Assessments

Table 3 and Table 4 present the GRADE summary of findings for guselkumab versus placebo (IV induction and SC maintenance, high and low dose) in the GALAXI and GRAVITI trials (SC induction and SC maintenance, high and low dose), respectively. Table 5 presents the GRADE summary of findings for guselkumab versus ustekinumab in the GALAXI 2 and GALAXI 3 trials (IV induction and SC maintenance, high and low dose).

Table 3: Summary of Findings for Guselkumab Versus Placebo for Patients with Crohn Disease: GALAXI Trials – IV Induction and SC Maintenance (regimen 1 and regimen 2)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Clinical response and clinical remission				

Proportion of patients with clinical response[a] at Week 12 and clinical remission[b] at Week 48	365 (GALAXI 2)
	
	365 (GALAXI 3)
		GALAXI 2
		• Guselkumab (combined[g]): 519 patients per 1,000
		• Placebo[h]: 118 patients per 1,000
		• Difference (combined[g]): 404 more patients per 1,000 (95% CI, 310 to 497 more patients per 1,000)
		  ○ Difference (regimen 1[g]): 381 more patients per 1,000 (95% CI, 273 to 489 more patients per 1,000)
		  ○ Difference (regimen 2[g]): 428 more patients per 1,000 (95% CI, 316 to 539 more patients per 1,000)
		
		GALAXI 3
		• Guselkumab (combined[g]): 474 patients per 1,000
		• Placebo[h]: 125 patients per 1,000
		• Difference (combined[g]): 344 more patients per 1,000 (95% CI, 247 to 441 more patients per 1,000)
		  ○ Difference (regimen 1[g]): 342 more patients per 1,000 (95% CI, 232 to 453 more patients per 1,000)
		  ○ Difference (regimen 2[g]): 350 more patients per 1,000 (95% CI, 235 to 465 more patients per 1,000)
			High[i]	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with clinical response at Week 12 and clinical remission at Week 48 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Clinical response and endoscopic response				

Proportion of patients with clinical response[a] at Week 12 and endoscopic response[c] at Week 48	365 (GALAXI 2)
	
	365 (GALAXI 3)
		GALAXI 2
		• Guselkumab (combined[g]): 388 patients per 1,000
		• Placebo[h]: 53 patients per 1,000
		• Difference (combined[g]): 334 more patients per 1,000 (95% CI, 259 to 410 more patients per 1,000)
		  ○ Difference (regimen 1[g]): 337 more patients per 1,000 (95% CI, 241 to 432 more patients per 1,000)
		  ○ Difference (regimen 2[g]): 329 more patients per 1,000 (95% CI, 235 to 424 more patients per 1,000)
		
		GALAXI 3
		• Guselkumab (combined[g]): 348 patients per 1,000
		• Placebo[h]: 56 patients per 1,000
		• Difference (combined[g]): 291 more patients per 1,000 (95% CI, 215 to 367 more patients per 1,000)
		  ○ Difference (regimen 1[g]): 279 more patients per 1,000 (95% CI, 187 to 371 more patients per 1,000)
		  ○ Difference (regimen 2[g]): 308 more patients per 1,000 (95% CI, 213 to 403 more patients per 1,000)
			High[i]	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with clinical response at Week 12 and endoscopic response at Week 48 when compared with placebo.

Clinical response and 90–day corticosteroid-free clinical remission				
Proportion of patients with clinical response[a] at Week 12 and 90–	365 (GALAXI 2)	GALAXI 2 • Guselkumab (combined[g]): 488 patients per 1,000 • Placebo[h]: 92 patients per 1,000	High[i]	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with clinical response at Week 12 and 90–day

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
day corticosteroid-free clinical remission[d] at Week 48	365 (GALAXI 3)	• Difference (combined[g]): 399 more patients per 1,000 (95% CI, 312 to 486 more patients per 1,000) ○ Difference (regimen 1[g]): 387 more patients per 1,000 (95% CI, 284 to 489 more patients per 1,000) ○ Difference (regimen 2[g]): 413 more patients per 1,000 (95% CI, 306 to 520 more patients per 1,000) GALAXI 3 • Guselkumab (combined[g]): 451 patients per 1,000 • Placebo[i]: 125 patients per 1,000 • Difference (combined[g]): 318 more patients per 1,000 (95% CI, 223 to 414 more patients per 1,000) ○ Difference (regimen 1[g]): 326 more patients per 1,000 (95% CI, 217 to 436 more patients per 1,000) ○ Difference (regimen 2[g]): 315 more patients per 1,000 (95% CI, 201 to 428 more patients per 1,000)		corticosteroid-free clinical remission at Week 48 when compared with placebo.
Clinical response and endoscopic remission				
Proportion of patients with clinical response[a] at Week 12 and endoscopic remission[e] at Week 48	365 (GALAXI 2) 365 (GALAXI 3)	GALAXI 2 • Guselkumab (combined[g]): 298 patients per 1,000 • Placebo[h]: 26 patients per 1,000 • Difference (combined[g]): 271 more patients per 1,000 (95% CI, 206 to 336 more patients per 1,000) ○ Difference (regimen 1[g]): 240 more patients per 1,000	High[i]	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with clinical response at Week 12 and endoscopic remission at Week 48 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		(95% CI, 158 to 322 more patients per 1,000) ○ Difference (regimen 2[g]): 300 more patients per 1,000 (95% CI, 214 to 385 more patients per 1,000) GALAXI 3 • Guselkumab (combined[g]): 232 patients per 1,000 • Placebo[h]: 56 patients per 1,000 • Difference (combined[g]): 173 more patients per 1,000 (95% CI, 100 to 245 more patients per 1,000) ○ Difference (regimen 1[g]): 182 more patients per 1,000 (95% CI, 95 to 269 more patients per 1,000) ○ Difference (regimen 2[g]): 167 more patients per 1,000 (95% CI, 80 to 254 more patients per 1,000)		
HRQoL: IBDQ remission				
Proportion of patients with IBDQ remission[f] Follow up: 12 weeks	365 (GALAXI 2) 365 (GALAXI 3)	GALAXI 2 • Guselkumab (combined[g]): 446 patients per 1,000 • Placebo: 303 patients per 1,000 • Difference (combined[g]): 145 more patients per 1,000 (95% CI, 31 to 258 more patients per 1,000) ○ Difference (regimen 1[g]): 191 more patients per 1,000 (95% CI, 67 to 315 more patients per 1,000) ○ Difference (regimen 2[g]): 105 more patients per 1,000 (95% CI, 23 less to 232 more patients per 1,000)	Guselkumab regimen 1[g]: High[i] Guselkumab regimen 2[g]: Moderate[j]	Guselkumab regimen 1 results in a clinically important increase in the proportion of patients with IBDQ remission at Week 12 when compared with placebo. Guselkumab regimen 2 likely results in a clinically important increase in the proportion of patients with IBDQ remission at Week 12 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens

		GALAXI 3
		• Guselkumab (combined[g]): 478 patients per 1,000
		• Placebo[h]: 278 patients per 1,000
		• Difference (combined[g]): 197 more patients per 1,000 (95% CI, 79 to 315 more patients per 1,000)
		  ○ Difference (regimen 1[g]): 237 more patients per 1,000 (95% CI, 111 to 364 more patients per 1,000)
		  ○ Difference (regimen 2[g]): 165 more patients per 1,000 (95% CI, 30 to 301 more patients per 1,000)		

Harms				

Proportion of patients with serious adverse events
 	
Follow up: 12 weeks
	365 (GALAXI 2)
	
	365 (GALAXI 3)
		GALAXI 2
		• Guselkumab (combined[g]): 24 patients per 1,000
		• Placebo: 26 patients per 1,000
		• Difference (combined[g]): [redacted]
		  ○ Difference (regimen 1[g]): [redacted]
		Difference (regimen 2[g]): [redacted]
		GALAXI 3
		• Guselkumab (combined[g]): 31 patients per 1,000
		• Placebo: 97 patients per 1,000
		• Difference (combined[g]): [redacted]
		  ○ Difference (regimen 1[g]): [redacted]
		Difference (regimen 2[g]): [redacted]
			Low[k]	Guselkumab regimens 1 and 2 may result in little to no difference in serious adverse events at Week 12 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens

Proportion of patients with serious adverse events
 	
Follow up: 48 weeks
	365 (GALAXI 2)
	
	365 (GALAXI 3)
		GALAXI 2
		• Guselkumab (combined[g]): 83 patients per 1,000
		• Placebo[i]: 79 patients per 1,000
		• Difference (combined[g]): [redacted]
		  ○ Difference (regimen 1[g]): [redacted]
		  ○ Difference (regimen 2[g]): [redacted]
		
		GALAXI 3
		• Guselkumab (combined[g]): 92 patients per 1,000
		• Placebo[h]: 139 patients per 1,000
		• Difference (combined[g]): [redacted]
		  ○ Difference (regimen 1[g]): [redacted]
		  ○ Difference (regimen 2[g]): [redacted]
			Low[k,l]	Guselkumab regimen 1 may result in little to no difference in serious adverse events at Week 48 when compared with placebo.
				
				Guselkumab regimen 2 may result in a clinically important decrease in serious adverse events at Week 12 when compared with placebo.

AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; MID = minimal importance difference; NR = not reported; PRO = patient-reported outcome; RCT = randomized controlled trial; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Note: The statistical testing for IBDQ remission and PRO-2 remission was not adjusted for multiplicity in both GALAXI trials and should be considered as supportive evidence.

[a] The clinical response is defined as either a reduction of 100 or more points from the baseline in the CDAI score or achieving a CDAI score of less than 150.

[b] Clinical remission is defined as CDAI score less than150.

[c] Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD Score of 2 or higher.

[d] Endoscopic remission is defined as SES-CD Score 4 or less and at least a 2–point reduction from baseline and no subscore greater than 1 in any individual component.

[e] 90–day corticosteroid-free clinical remission was defined as not receiving corticosteroids for 90 days.

[f] IBDQ remission is defined as IBDQ total score at least 170. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[g] Combined guselkumab induction dose group: 200 mg every 4 weeks, administered via intravenous injection. Guselkumab regimen 1 (low dose) = 200 mg IV every 4 weeks, followed by 100 mg SC every 8 weeks: guselkumab regimen 2 (high dose) = 200 mg IV every 4 weeks followed by 200 mg SC every 4 weeks.

[h] Included patients in the placebo group who crossed over to ustekinumab after Week 12.

[i] An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[j] The level of evidence was rated down 1 level for imprecision. Based on the MID identified by clinical experts (a difference of 5% between the groups), the 95% CI for the between-group difference crossed the MID threshold (i.e., includes the possibility of little-to-no difference) for guselkumab regimen 2 in both GALAXI trials. Additionally, notable between-group imbalances in missing data were observed after applying the intercurrent event handling strategies.

[k] An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 3-5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome. The level of evidence was rated down 2 levels for imprecision and indirectness, the estimate is informed by a very low number of events and may be unstable. Additionally, there was indirectness related to the inclusion of worsening CD and other CD-related events as a serious adverse event (SAE). This complicates interpretation.

[l] An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 3-5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome. The level of evidence was rated down 2 levels for imprecision and indirectness, the estimate is informed by a very low number of events and may be unstable. There was some inconsistency in result for regimen 1. Additionally, there was indirectness related to the inclusion of worsening CD and other CD-related events as a serious adverse event (SAE). This complicates interpretation, as it is difficult to explain findings such as lower SAE rates with guselkumab compared with placebo at Week 48 in GALAXI 3. A greater number of patients in the placebo group discontinued treatment, while discontinuation rates were lower in the guselkumab groups; therefore, differences in treatment discontinuation and exposure between the study groups may influence the interpretation of harm outcomes.

Source: Clinical Study Reports for GALAXI 2, and GALAXI 3. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 4: Summary of Findings for Guselkumab Versus Placebo for Patients with Crohn Disease: GRAVITI trial – SC Induction and SC Maintenance (regimen 1 and regimen 2)

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Clinical remission at Week 12				
Proportion of patients with clinical remission[a] Follow up: 12 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 561 patients per 1,000 • Placebo: 124 patients per 1,000 • Difference (combined[f]): 349 more patients per 1,000 (95% CI, 251 to 446 more patients per 1,000)	High	Guselkumab induction results in a clinically important increase in the proportion of patients with clinical remission at Week 12 when compared with placebo.
Clinical remission at Week 48				

Proportion of patients with clinical remission[a]
 	
Follow up: 48 weeks
	347 (GRAVITI)	• Guselkumab (combined[f]): 630 patients per 1,000
		• Placebo[g]: 171 patients per 1,000
		• Difference (combined[f]): 459 more patients per 1,000 (95% CI, 366 to 551 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 428 more patients per 1,000 (95% CI, 316 to 540 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 489 more patients per 1,000 (95% CI, 379 to 599 more patients per 1,000)
			High	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with clinical remission at Week 48 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Endoscopic response at Week 12				
Proportion of patients with endoscopic response[b] Follow up: 12 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 413 patients per 1,000 • Placebo: 214 patients per 1,000 • Difference (combined[f]): 199 more patients per 1,000 (95% CI, 102 to 296 more patients per 1,000)	High	Guselkumab induction results in a clinically important increase in the proportion of patients with endoscopic response at Week 12 when compared with placebo.
Endoscopic response at Week 48				

Proportion of patients with endoscopic response[b]
 	
Follow up: 48 weeks
	347 (GRAVITI)	• Guselkumab (combined[f]): 478 patients per 1,000
		• Placebo[g]: 68 patients per 1,000
		• Difference (combined[f]): 409 more patients per 1,000 (95% CI, 329 to 489 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 375 more patients per 1,000 (95% CI, 273 to 477 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 446 more patients per 1,000 (95% CI, 341 to 550 more patients per 1,000)
			High	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with endoscopic response at Week 48 when compared with placebo.

Endoscopic remission				

Proportion of patients with endoscopic remission[c]
 	
Follow up: 48 weeks
	347 (GRAVITI)	• Guselkumab (combined[f]): 343 patients per 1,000
		• Placebo[g]: 60 patients per 1,000
		• Difference (combined[f]): 284 more patients per 1,000 (95% CI, 210 to 358 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 245 more patients per 1,000 (95% CI, 152 to 339 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 324 more patients per 1,000 (95% CI, 226 to 423 more patients per 1,000)
			High	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with endoscopic remission at Week 48 when compared with placebo.

Clinical remission and endoscopic response				
Clinical remission and endoscopic response Follow up: 48 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 413 patients per 1,000 • Placebo[g]: 51 patients per 1,000 • Difference (combined[f]): 362 more patients per 1,000 (95% CI, 286 to 437 more patients per 1,000)	High	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with clinical remission and endoscopic response at Week 48 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		○ Difference (regimen 1[f]): 331 more patients per 1,000 (95% CI, 233 to 428 more patients per 1,000) ○ Difference (regimen 2[f]): 394 more patients per 1,000 (95% CI, 294 to 494 more patients per 1,000)		
HRQoL: IBDQ remission				
Proportion of patients with IBDQ remission[d] Follow up: 48 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 517 patients per 1,000 • Placebo[g]: 179 patients per 1,000 • Difference (combined[f]): 337 more patients per 1,000 (95% CI, 243 to 430 more patients per 1,000) ○ Difference (regimen 1[f]): 366 more patients per 1,000 (95% CI, 254 to 478 more patients per 1,000) ○ Difference (regimen 2[f]): 307 more patients per 1,000 (95% CI, 192 to 421 more patients per 1,000)	Moderate[h]	Guselkumab regimens 1 and 2 likely results in a clinically important increase in the proportion of patients with IBDQ remission at Week 48 when compared with placebo.
HRQoL: PRO–2 remission				
Proportion of patients with PRO-2 remission[e] Follow up: 48 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 591 patients per 1,000 • Placebo[g]: 120 patients per 1,000 • Difference (combined[f]): 472 more patients per 1,000 (95% CI, 385 to 560 more patients per 1,000) ○ Difference (regimen 1[f]): 411 more patients per 1,000 (95% CI, 301 to 521 more patients per 1,000) ○ Difference (regimen 2[f]): 532 more patients per 1,000 (95% CI, 426 to 637 more patients per 1,000)	High	Guselkumab regimens 1 and 2 result in a clinically important increase in the proportion of patients with PRO–2 remission at Week 48 when compared with placebo.
Harms				
Proportion of patients with serious adverse events Follow up: 12 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 22 patients per 1,000 • Placebo: 77 patients per 1,000 • Difference (combined[f]): [redacted] ○ Difference (regimen 1[f]): [redacted] [redacted]Difference (regimen 2[f]): [redacted]	Low[i]	Guselkumab regimens 1 and 2 may result in a clinically important decrease in the serious adverse events at Week 12 when compared with placebo.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Proportion of patients with serious adverse events Follow up: 48 weeks	347 (GRAVITI)	• Guselkumab (combined[f]): 104 patients per 1,000 • Placebo[g]: 137 patients per 1,000 ○ Difference (combined[f]): [redacted] Difference (regimen 1[f]): [redacted] Difference (regimen 2[f]): [redacted]	Low[j]	Guselkumab regimen 1 may result in little-to-no clinically important difference in the serious adverse events at Week 48 compared to placebo. Guselkumab regimen 2 may result in a clinically important decrease in the serious adverse events at Week 48 when compared with placebo.

AP = abdominal pain; CDAI = Crohn's Disease Activity Index; CI = confidence interval; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; MID = minimal importance difference; NR = not reported; PRO = patient-reported outcome; RCT = randomized controlled trial; SES-CD = Simple Endoscopic Score for Crohn's Disease; SF = stool frequency.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Note: The statistical testing for IBDQ remission was not adjusted for multiplicity in the GRAVITI trial and should be considered as supportive evidence.

Note: The statistical testing for endoscopic remission was not adjusted for multiplicity in the GRAVITI trial and should be considered as supportive evidence.

Note: In the GRAVITI trial, the Week 12 end points were based on comparisons between the combined guselkumab induction dose group and the placebo group. The end points assessed after Week 12 were based on comparisons between each individual guselkumab group and the placebo group.

Note: ICE 5 methodology was used to handle treatment discontinuations, which is an approach accepted by regulatory authorities. However, as the exact reasons for discontinuations were not always clearly reported (e.g., whether they were linked to lack of efficacy), there remains some uncertainty regarding potential bias. No downgrading for risk of bias was applied for the end points at Week 48, although some risk may exist. Additional context is provided in the Executive Summary.

[a] Clinical remission is defined as CDAI score less than150. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 12% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[b] Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[c] Endoscopic remission is defined as SES-CD Score 4 or less and at least a 2–point reduction from baseline and no subscore greater than 1 in any individual component. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[d] IBDQ remission is defined as IBDQ total score at least 170. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[e] PRO–2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[f] Combined guselkumab induction dose group: 400 mg SC at Weeks 0, 4, and 8, administered via subcutaneous injection. Guselkumab SC regimen 1 (low dose) = guselkumab 400 SC every 4 weeks, followed by 100 mg SC every 8 weeks, guselkumab SC regimen 2 (high dose) = guselkumab 400 SC every 4 weeks, followed by 200 mg SC every 4 weeks.

[g] Includes placebo patients who were rescued with guselkumab after Week 12.

[h] The level of evidence was rated down 1 level for serious study limitations. Notable between-group imbalances in missing data were observed after applying the intercurrent event handling strategies.

[i] An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 3-5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome. The level of evidence was rated down 2 levels for imprecision and indirectness, the estimate is informed by a very low number of events and may be unstable. Additionally, there

was indirectness related to the inclusion of worsening CD and other CD-related events as a serious adverse event (SAE). This complicates interpretation, as it is difficult to explain findings such as lower SAE rates with guselkumab compared with placebo

[j] An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 3-5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome. The level of evidence was rated down levels for imprecision and indirectness, the estimate is informed by a very low number of events and may be unstable. Additionally, there was indirectness related to the inclusion of worsening CD and other CD-related events as a serious adverse event (SAE). This complicates interpretation, as it is difficult to explain findings such as lower SAE rates with guselkumab compared with placebo. A greater number of patients in the placebo group discontinued treatment, while discontinuation rates were lower in the guselkumab groups; therefore, differences in treatment discontinuation and exposure between the study groups may influence the interpretation of harm outcomes.

Source: Clinical Study Report for GRAVITI. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Table 5: Summary of Findings for Guselkumab (regimen 1 and regimen 2) Versus Ustekinumab with Crohn Disease: GALAXI Trials – IV Induction and SC Maintanance

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Clinical remission				

Proportion of patients with clinical remission[a]
 	
Follow up: 48 weeks
	432 (GALAXI 2)
	
	441 (GALAXI 3)
		Pooled GALAXI 2 and GALAXI 3[f]:
		• Guselkumab (pooled regimen 1[f]): 654 patients per 1,000
		• Guselkumab (pooled regimen 2[f]): 703 patients per 1,000
		• Ustekinumab[g]: 629 patients per 1,000
		  ○ Difference (regimen 1[f]): 26 more patients per 1,000 (95% CI, 51 less to 102 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 73 more patients per 1,000 (95% CI, 2 less to 148 more patients per 1,000)
		
		GALAXI 2
		• Guselkumab (combined[h]): 696 patients per 1,000
		• Ustekinumab[g]: 650 patients per 1,000
		• Difference (combined[h]): 44 more patients per 1,000 (95% CI, 49 less to 137 more patients per 1,000)
		  ○ Difference (regimen 1[h]): 6 less patients per 1,000 (95% CI, 116 less to 105 more patients per 1,000)
		  ○ Difference (regimen 2[h]): 95 more patients per 1,000 (95% CI, 7 less to 198 more patients per 1,000)
		
		GALAXI 3
		• Guselkumab (combined[h]): 662 patients per 1,000
		• Ustekinumab[g]: 608 patients per 1,000
			Moderate[i]	Guselkumab regimens 1 and 2 likely result in little to no clinically important difference in the proportion of patients with clinical remission at Week 48 when compared with ustekinumab.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens

		• Difference (combined[h]): 53 more patients per 1,000 (95% CI, 42 less to 148 more patients per 1,000)
		  ○ Difference (regimen 1[h]): 56 more patients per 1,000 (95% CI, 52 less to 165 more patients per 1,000)
		  ○ Difference (regimen 2[h]): 50 more patients per 1,000 (95% CI, 61 less to 161 more patients per 1,000)		

Endoscopic response				

Proportion of patients with endoscopic response[b]
 	
Follow up: 48 weeks
	432 (GALAXI 2)
	
	441 (GALAXI 3)
		Pooled GALAXI 2 and GALAXI 3[f]:
		• Guselkumab (pooled regimen 1[f]): 479 patients per 1,000
		• Guselkumab (pooled regimen 2[f]): 527 patients per 1,000
		• Ustekinumab[g]: 371 patients per 1,000
		  ○ Difference (regimen 1[f]): 106 more patients per 1,000 (95% CI, 27 to 185 more patients per 1,000)
		  ○ Difference (regimen 2[f]):156 more patients per 1,000 (95% CI, 79 to 234 more patients per 1,000)
		
		GALAXI 2
		• Guselkumab (combined[f]): 526 patients per 1,000
		• Ustekinumab[g]: 420 patients per 1,000
		• Difference (combined[f]): 107 more patients per 1,000 (95% CI, 11 more to 137 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 7 more patients per 1,000 (95% CI, 44 less to 183 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 145 more patients per 1,000 (95% CI, 36 to 254 more patients per 1,000)
		
		GALAXI 3
		• Guselkumab (combined[f]): 481 patients per 1,000
		• Ustekinumab[g]: 324 patients per 1,000
		• Difference (combined[f]): 154 more patients per 1,000 (95% CI, 58 to 137 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 141 more patients per 1,000 (95% CI, 29 to 252 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 168 more patients per 1,000 (95% CI, 57 to 280 more patients per 1,000)
			Guselkumab regimen 1: Low[j]
			
			Guselkumab regimen 2: High
				Guselkumab regimen 1 may result in a clinically important increase in the proportion of patients with endoscopic response at Week 48 when compared with ustekinumab.
				
				Guselkumab regimen 2 results in a clinically important increase in the proportion of patients with endoscopic response at Week 48 when compared with ustekinumab.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Endoscopic remission				

Proportion of patients with endoscopic remission[c]
 	
Follow up: 48 weeks
	432 (GALAXI 2)
	
	441 (GALAXI 3)
		Pooled GALAXI 2 and GALAXI 3[f]:
		• Guselkumab (pooled regimen 1[f]): 332 patients per 1,000
		• Guselkumab (pooled regimen 2[f]): 372 patients per 1,000
		• Ustekinumab[g]: 247 patients per 1,000
		  ○ Difference (regimen 1[f]): 85 more patients per 1,000 (95% CI, 11 to 156 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 123 more patients per 1,000 (95% CI, 49 to 197 more patients per 1,000)
		
		GALAXI 2
		• Guselkumab (combined[f]): 388 patients per 1,000
		• Ustekinumab[g]: 266 patients per 1,000
		• Difference (combined[f]): 122 more patients per 1,000 (95% CI, 31 more to 213 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 64 more patients per 1,000 (95% CI, 43 less to 171 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 179 more patients per 1,000 (95% CI, 73 to 284 more patients per 1,000)
		
		GALAXI 3
		• Guselkumab (combined[f]): 317 patients per 1,000
		• Ustekinumab[g]: 230 patients per 1,000
		• Difference (combined[f]): 87 more patients per 1,000 (95% CI, 1 less to 174 more patients per 1,000)
		  ○ Difference (regimen 1[f]): 105 more patients per 1,000 (95% CI, 1 to 209 more patients per 1,000)
		  ○ Difference (regimen 2[f]): 69 more patients per 1,000 (95% CI, 33 less to 170 more patients per 1,000)
			Moderate[k]	Guselkumab regimens 1 and 2 likely result in a clinically important increase in the proportion of patients with endoscopic remission at Week 48 when compared with ustekinumab.

Clinical remission and endoscopic response				
Proportion of patients with clinical remission and endoscopic response	432 (GALAXI 2) 441 (GALAXI 3)	Pooled GALAXI 2 and GALAXI 3[f]: • Guselkumab (pooled regimen 1[f]): 416 patients per 1,000 • Guselkumab (pooled regimen 2[f]): 473 patients per 1,000 • Ustekinumab[g]: 337 patients per 1,000	Guselkumab regimen 1: Low[l] Guselkumab regimen 2: High	Guselkumab regimen 1 may result in a clinically important increase in the proportion of patients with clinical remission and endoscopic response

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
Follow up: 48 weeks		○ Difference (regimen 1[f]): 78 more patients per 1,000 (95% CI, 10 to 156 more patients per 1,000) ○ Difference (regimen 2[f]): 136 more patients per 1,000 (95% CI, 59 to 213 more patients per 1,000) GALAXI 2 • Guselkumab (combined[f]): 457 patients per 1,000 • Ustekinumab[g]: 392 patients per 1,000 • Difference (combined[f]): 65 more patients per 1,000 (95% CI, 3 less to 174 more patients per 1,000) ○ Difference (regimen 1[f]): 28 more patients per 1,000 (95% CI, 84 less to 141 more patients per 1,000) ○ Difference (regimen 2[f]): 102 more patients per 1,000 (95% CI, 6 less to 210 more patients per 1,000) GALAXI 3 • Guselkumab (combined[f]): 433 patients per 1,000 • Ustekinumab[g]: 284 patients per 1,000 • Difference (combined[f]): 147 more patients per 1,000 (95% CI, 53 to 174 more patients per 1,000) ○ Difference (regimen 1[f]): 127 more patients per 1,000 (95% CI, 17 to 237 more patients per 1,000) ○ Difference (regimen 2[f]): 169 more patients per 1,000 (95% CI, 58 to 497 more patients per 1,000)		at Week 48 when compared with ustekinumab. Guselkumab regimen 2 results in a clinically important increase in the proportion of patients with clinical remission and endoscopic response at Week 48 when compared with ustekinumab.
HRQoL: IBDQ remission				
Proportion of patients with IBDQ remission[d] Follow up: 48 weeks	432 (GALAXI 2) 441 (GALAXI 3)	GALAXI 2 • Guselkumab (combined[f]): 557 patients per 1,000 • Ustekinumab[g]: 524 patients per 1,000 • Difference: 33 more patients per 1,000 (95% CI, 65 less to 131 more patients per 1,000) ○ Difference (regimen 1[f]): 16 more patients per 1,000 (95% CI, 99 less to 132 more patients per 1,000)	Guselkumab regimen 1: Low[l] Guselkumab regimen 2: Moderate[m]	Guselkumab regimen 1 may result in little to no clinically important difference in the proportion of patients with IBDQ remission at Week 48 when compared with ustekinumab. Guselkumab likely results in little to no clinically important difference in

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		○ Difference (regimen 2[f]): 56 more patients per 1,000 (95% CI, 55 less to 167 more patients per 1,000) GALAXI 3 • Guselkumab (combined[f]): 553 patients per 1,000 • Ustekinumab[g]: 493 patients per 1,000 • Difference (combined[f]): 59 more patients per 1,000 (95% CI, 40 less to 158 more patients per 1,000) ○ Difference (regimen 1[f]): 101 more patients per 1,000 (95% CI, 12 less to 215 more patients per 1,000) ○ Difference (regimen 2[f]): 21 more patients per 1,000 (95% CI, 94 less to 136 more patients per 1,000)		the proportion of patients with IBDQ remission at Week 48 when compared with ustekinumab.
Harms				
Proportion of patients with serious adverse events Follow up: 12 weeks	432 (GALAXI 2) 441 (GALAXI 3)	GALAXI 2 • Guselkumab (combined[f]): 24 patients per 1,000 • Ustekinumab[g]: 56 patients per 1,000 Difference (combined[f]): [redacted]Difference (regimen 1[f]): [redacted] Difference (regimen 2[f]): [redacted] GALAXI 3 • Guselkumab (combined[f]): 31 patients per 1,000 • Ustekinumab[g]: 54 patients per 1,000 ○ Difference (combined[f]): [redacted] Difference (regimen 1[f]): [redacted] Difference (regimen 2[f]): [redacted]	Low[n]	Guselkumab regimens 1 and 2 may result in little to no clinically important difference in the serious adverse events at Week 12 when compared with ustekinumab.
Proportion of patients with serious adverse events Follow up: 48 weeks	432 (GALAXI 2) 441 (GALAXI 3)	GALAXI 2 • Guselkumab (combined[f]): 83 patients per 1,000 • Ustekinumab[g]: 126 patients per 1,000 Difference (combined[f]): [redacted] Difference (regimen 1[f]): [redacted] Difference (regimen 2[f]): [redacted] GALAXI 3	Low[n]	Guselkumab regimens 1 and 2 may result in little to no clinically important difference in the serious adverse events at Week 48 when compared with ustekinumab.

Outcome and follow-up	Patients (studies), N	Effect	Certainty	What happens
		• Guselkumab (combined[f]): 92 patients per 1,000 • Ustekinumab[g]: 108 patients per 1,000 ○ Difference (combined[f]): [redacted] Difference (regimen 1[f]): [redacted] Difference (regimen 2[f]): [redacted]		

AP = abdominal pain; CI = confidence interval; HRQoL = health-related quality of life; IBDQ = Inflammatory Bowel Disease Questionnaire; MID = minimal importance difference; NR = not reported; PRO = patient-reported outcome; RCT = randomized controlled trial; SF = stool frequency.

Note: Study limitations (which refers to internal validity or risk of bias), inconsistency across studies, indirectness, imprecision of effects, and publication bias were considered when assessing the certainty of the evidence. All serious concerns in these domains that led to the rating down of the level of certainty are documented in the table footnotes.

Note: In the GALAXI trials, the hierarchical testing strategy precluded formal statistical testing of the long-term secondary end points comparing guselkumab with ustekinumab, as the adjusted treatment difference for clinical remission at Week 48 did not reach statistical significance.

Note: In both GALAXI trials, all long-term end points comparing guselkumab relative to ustekinumab were analyzed separately, comparing each individual guselkumab regimen against ustekinumab.

[a] Clinical remission is defined as CDAI score less than150. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 12% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[s] Endoscopic response is defined as at least 50% improvement from baseline in SES-CD score or SES-CD Score of 2 or higher. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[c] Endoscopic remission is defined as SES-CD Score 4 or less and at least a 2–point reduction from baseline and no subscore greater than 1 in any individual component. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome.

[d] IBDQ remission is defined as IBDQ total score at least 170.

[e] PRO–2 remission is defined as AP mean daily score at or below 1 and SF mean daily score at or below 3, and no worsening of AP or SF from baseline. An empirically derived MID was not identified for the between-group difference for this outcome.

[f] Data were pooled for each guselkumab treatment group from GALAXI 2 and GALAXi 3 and compared with the ustekinumab treatment.

[g] Ustekinumab: ~6 mg/kg IV, followed by 90 mg SC every 8 weeks.

[h] Guselkumab regimen 1 (low dose) = 200 mg IV every 4 weeks, followed by 100 mg SC every 8 weeks: guselkumab regimen 2 (high dose) = 200 mg IV every 4 weeks followed by 200 mg SC every 4 weeks.

[i] The level of evidence was rated down 1 level for serious imprecision. An empirically derived MID was not identified for the between-group difference for this outcome. Based on the MID identified by clinical experts (a difference of 12% between the groups), the point estimate suggested little to no difference, and the 95% CI for the between-group difference crossed the MID threshold.

[j] The level of evidence was rated down 2 levels for serious imprecision and inconsistency. An empirically derived MID was not identified for the between-group difference for this outcome. Based on the MID identified by clinical experts (a difference of 5% between the groups), the point estimate suggested a benefit, and the 95% CI for the between-group difference crossed the MID threshold to include little-to-no difference. Additionally, inconsistency was observed between studies: while 1 study demonstrated a benefit based on the point estimate, the other study showed little to no difference. This inconsistency reduces the overall certainty of the evidence

[k] The level of evidence was rated down 1 level for serious imprecision. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome, the point estimate suggests a benefit and the 95% CI for the between-group difference crossed the MID threshold to include little-to-no difference.

[l] The level of evidence was rated down 2 levels for serious imprecision and inconsistency. An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome, and the 95% CI for the between-group difference crossed the MID threshold. Additionally, inconsistency was observed between studies: while 1 study demonstrated a benefit based on the point estimate, the other study showed little to no difference. This inconsistency reduces the overall certainty of the evidence.

[m] The level of evidence was rated down 1 level for study limitations. An empirically derived MID was not identified for the between-group difference for this outcome. Based on the MID identified by clinical experts (a difference of 5% between the groups), the 95% CI for the between-group difference crossed the MID threshold. Notable between-group imbalances in missing data were observed after applying the intercurrent event handling strategies.

[n] An empirically derived MID was not identified for the between-group difference for this outcome. A difference of 3-5% between the groups was identified by the clinical expert consulted by CDA-AMC as a threshold of clinical importance for this outcome. The level of evidence was rated down 2 levels for imprecision and indirectness, the estimate is informed by a very low number of events and may be unstable. Additionally, there was indirectness related to the inclusion of worsening CD and other CD-related events as a serious adverse event (SAE). This complicates interpretation.

Source: Clinical Study Reports for GALAXI 2, and GALAXI 3. Details included in the table are from the sponsor's Summary of Clinical Evidence.

Long-Term Extension Studies

Description of Studies

The parent pivotal studies, GALAXI 2 and GALAXI 3, were randomized, double-blind, placebo- and active controlled, parallel-group, multicenter studies to evaluate the efficacy and safety of guselkumab in patients with moderately to severely active CD. The LTEs were designed to evaluate the long-term efficacy of clinical and endoscopic outcomes, safety, to evaluate the benefit of treatment adjustment for patients with inadequate response between Week 52 through Week 80, and impact of guselkumab on health-related quality of life (HRQOL). Patients continued with their assigned treatments throughout the LTE phase. Patients on guselkumab or ustekinumab maintained their dosages, while those on placebo were discontinued after unblinding at Week 48. The study is ongoing and Week 96 results are presented.

Efficacy Results

In the primary efficacy analysis set (All randomized patients with screening SES-CD score of at least 6 [or at least 4 for participants with isolated ileal disease] who received ≥1 (partial or complete) dose of study drug), rates of clinical remission were 59.4% in pooled regimen 1 (guselkumab 200 mg IV every 4 weeks to 100 mg SC every 8 weeks), 63.2% in pooled regimen 2 (guselkumab 200 mg IV every 4 weeks to 200 mg SC every 4 weeks), versus [redacted] in the ustekinumab group at Week 96. The rates of patients achieving corticosteroid-free clinical remission were 57% in the pooled regimen 1 group, 60.8% in the pooled regimen 2 group, and [redacted] in the pooled ustekinumab group at Week 96. The rate of patients who achieved endoscopic response were 44.1%, 44.6%, vs [redacted] in the pooled regimen 1, regimen 2, and ustekinumab groups respectively at Week 96. The rates of patients achieving clinical remission and endoscopic response were 40.6%, 41.6% in the pooled regimen 1 and regimen 2 groups compared to [redacted] in the pooled ustekinumab at Week 96. In the primary efficacy analysis set, the rate of patients who achieved deep remission (clinical remission and endoscopic response) were 26.2%, 29.4%, and [redacted] in the pooled regimen 1, regimen 2, and ustekinumab group at Week 96. Data on HRQoL was not presented.

In the LTE efficacy analysis set (consisting of all patients who had entered the LTE and had received ≥1 [partial or complete] dose of study drug during the LTE), the rates of patients who achieved clinical remission were 75.1%, 78.1%, and [redacted] in the pooled regimen 1, regimen 2, and ustekinumab groups, respectively at week 96. The rates of patients who achieved endoscopic response was 53.6%, 55.4%, and [redacted] in the pooled regimen 1, regimen 2, and ustekinumab group at week 96. The rate of patients who achieved endoscopic remission was 34.6%, 39.3%, vs [redacted] in the pooled regimen 1, regimen 2, and ustekinumab groups at week 96.

Harms Results

In the LTE Safety Analysis set (consisting of randomized patients who entered the LTE and received ≥1 dose of study intervention [including a partial dose] during the LTE phase), 61.4%, 58.8%, and [redacted] of patients in the regimen 1, regimen 2, and ustekinumab group, respectively reported at least 1 AE. In total, 5.2%, 5.8%, and [redacted] of patients reported at least 1 serious AE in the regimen 1, regimen 2, and ustekinumab groups, respectively. Adverse events leading to discontinuation were generally similar across treatment groups in the LTE. In total, 2%, 1.6%, [redacted] in regimen 1, regimen 2, and ustekinumab groups respectively discontinued treatments in the LTE. There were no deaths reported in the guselkumab treatment groups. In total, [redacted] patient died in the ustekinumab group. Notable harms were not reported in the guselkumab treatment groups in the LTE phase. [redacted] patients in the ustekinumab reported 1 or more malignancies, and [redacted] patient reported a major adverse cardiovascular event.

Critical Appraisal

Both pivotal studies of the LTEs (GALAXI 2 and 3), were randomized, double-blind, placebo-controlled, parallel-group trials. There is a risk for selection bias for the main estimand (LTE patients), as only patients with continued treatment benefit (approximately 80% of randomized patients) in the opinion of the investigator were included.

The LTE phase was unblinded at week 48, which may introduce bias in patient management, the reporting of AEs, and the assessment of subjective clinical outcomes. Concomitant treatments were provided or adjusted at the discretion of the investigator; the impact on estimates of efficacy cannot be quantified.

Overall, the statistical methods in the LTEs were appropriate. The strategy used to handle ICEs for the main estimands (LTE patients) was relevant and aligned with the guidance of regulatory bodies. However, it is not clear how many patients discontinued for reasons other than lack of efficacy or AE (ICE3) or who chose not to enter the LTE (ICE7). Since these ICE are not clearly related to lack of efficacy, imbalances in these occurrences could introduce bias in the randomized comparisons. However, no information was reported to adequately access the proportion of patients with these ICEs. There was no defined hierarchal testing procedure for the LTE phases in both LTEs and statistical analyses were not controlled for multiplicity. Thus, the results were considered exploratory. Rates of study discontinuation were generally low in both LTE studies and similar between groups, mostly attributed to withdrawal by patients, AEs and lack of efficacy. Non-responder imputation was performed for missing data in the primary LTE analysis. The extent of missing data was not clear, therefore any potential for risk of bias arising from the imputation methods used cannot be ascertained.

In general, the population requested for reimbursement aligns with the Health Canada indication. The dosing and administration of guselkumab in the LTEs were consistent with the product monograph. According to the clinical experts, the patient eligibility criteria and baseline characteristics of the parent studies were generalizable to adults with moderately to severely active CD in the Canadian clinical setting. However, HRQoL was not reported in the LTE. Therefore, the impact of guselkumab on HRQoL in long-term is uncertain.

Indirect Comparisons

Description of Studies

A sponsor-submitted indirect treatment comparison (ITC) evaluated guselkumab versus relevant comparators (including adalimumab, infliximab, vedolizumab, ustekinumab, risankizumab, and upadacitinib) for moderately to severely active CD. A systematic literature review (SLR) (July 2023) identified 58 unique randomized controlled trials (RCTs); of these, 37 double-blind RCTs informed the network meta-analysis (NMA). Analyses considered adults with conventional-therapy failure (CON-Failure) and biologic-therapy failure (BIO-Failure), assessed induction (approximately 12 weeks) and maintenance (approximately 1 year), and examined clinical remission, clinical response, endoscopic response, and a joint outcome of remission plus endoscopic response. The ITC used Bayesian random effects NMAs, often adjusted for differences in baseline placebo response during induction. No safety data were included in these indirect comparisons.

Efficacy Results

During induction, results showed that in both the CON-Failure and BIO-Failure populations, no active comparator significantly outperformed guselkumab. There were instances in which guselkumab appeared numerically more effective than vedolizumab or ustekinumab, albeit with wide credible intervals that highlight uncertainty in these estimates.

In the maintenance phase (with or without delayed responders), numerical trends suggested that guselkumab may potentially exceed the efficacy of some comparators (for example, vedolizumab or certain doses of upadacitinib), no significant advantage for any other active treatment over guselkumab was observed. Overall, there is not clear evidence showing any comparator to be more efficacious; however, wide credible intervals in several comparisons suggest that caution is needed when interpreting the relative treatment effects.

Harms Results

No safety or harms outcomes were included in the sponsor's submitted ITC.

Critical Appraisal

The SLR's search was last conducted in July 2023 and the NMA restricted evidence to double-blind RCTs, which may have excluded relevant open-label trials and more recent evidence. The GRAVITI trial was not included in the NMA, precluding conclusions about SC induction. Maintenance analyses incorporated complex normalization of different trial designs, including re-randomization, but relied on untested assumptions that may affect interpretability. Baseline-risk adjustment was only applied during induction, despite potentially greater heterogeneity in the maintenance phase. Variations across trials—encompassing population differences, definitions of response, and outcome timepoints ranging from 4 to 64 weeks—further introduce potential bias due to violation of the

underlying transitivity assumption and imprecision. Safety endpoints were not evaluated, limiting any comparative benefit–risk assessment. Additionally, data extraction and risk-of-bias assessment were conducted by a single reviewer with only secondary validation, which may introduce human-error bias. Several included trials had risk of bias concerns.

Studies Addressing Gaps in the Evidence From the Systematic Review

GALAXI 1 Long-term Extension

Description of Studies

The GALAXI 1 study is a phase 2, randomized, double-blind, placebo- and active-controlled, multicenter trial with a long-term extension (LTE) component, designed to evaluate the efficacy and safety of guselkumab in adults with moderately to severely active Crohn's disease (CD). The LTE phase extended treatment to approximately 152 weeks and included patients who continued to derive benefit according to the investigator at the end of the 48-week maintenance period. The study was unblinded at 48 weeks. The study enrolled 220 patients in the guselkumab group and 71 in the ustekinumab group, with 151 and 48 patients, respectively, entering the LTE. Participants continued on their assigned subcutaneous treatment regimens throughout the extension period. The primary endpoint was clinical remission, defined by a CDAI score of less than 150 at Week 144, with additional assessments of patient-reported outcomes and endoscopic endpoints. The study was not powered to detect differences between guselkumab and ustekinumab, and all outcomes beyond Week 12 were considered exploratory. Three cohorts were defined: the all-randomized non-responder imputation (NRI) set included every patient dosed from Week 0, imputing discontinuations, non-entry, and intercurrent events as non-responders; the LTE NRI set comprised those dosed during LTE with the same ICE rules plus CD-related surgery and AE-related discontinuation, assessed through Week 144 using NRI; and lastly, the LTE observed set, which included only patients on treatment without dose changes, reporting observed rates without imputations.

Efficacy Results

By Week 144, clinical remission — as measured by the CDAI — remained stable in patients treated with guselkumab. In the LTE NRI cohort, 68.2% (103/151) of guselkumab-treated patients achieved CDAI remission, while 54.1% (100/185) achieved remission in the all-randomized NRI cohort and 95.4% (103/108) in the LTE observed cohort. Ustekinumab yielded similar results: 64.6% (31/48) of patients in the LTE NRI cohort and 83.8% (31/37) in the LTE observed cohort were in CDAI remission, and 46.0% (29/63) in the all-randomized NRI analysis. Patient-reported outcomes (PRO-2 remission) followed the same pattern—64.2% and 51.4% of guselkumab-treated patients reached PRO-2 remission in the LTE NRI and all-randomized NRI cohorts, respectively, while 58.3% of ustekinumab patients did so in the LTE NRI cohort.

Endoscopic assessments likewise demonstrated maintained benefit through Week 144. In the guselkumab group, endoscopic response rates were 43.0% (LTE NRI) and 34.7% (all-randomized NRI), and endoscopic remission rates were 28.9% and 23.3%, respectively. Ustekinumab patients achieved a 25.5% endoscopic response and 17.0% endoscopic remission in the LTE NRI cohort.

Harms Results

Guselkumab was well tolerated through 152 weeks, with overall AE rates comparable to ustekinumab. In the guselkumab group, there were 279.8 events per 100 patient-years and 87.3% of patients experienced ≥1 AE; serious AEs occurred at 10.6 per 100 patient-years in 11.4% of patients, and 13.2% discontinued due to AEs. Infections affected 51.8% of guselkumab-treated patients (65.8 events/100 patient-years [PY]), with serious infections in 5.5% (3.3/100 PY), versus 46.5% (44.7/100 PY) and 7.0% (5.0/100 PY) in the ustekinumab group.

The most frequent individual AEs for guselkumab were COVID-19 (15.0%; 8.5 events/100 PY), headache (13.6%; 10.1/100 PY), nasopharyngitis (12.7%; 12.9/100 PY), Crohn's-disease events (10.9%; 7.5/100 PY) and pyrexia (9.5%; 8.0/100 PY). By comparison, ustekinumab-treated patients reported lower rates of COVID-19 (7.0%; 3.6/100 PY) but similar frequencies of headache (11.3%; 5.7/100 PY) and nasopharyngitis (11.3%; 7.1/100 PY)

Critical Appraisal

The GALAXI 1 LTE employed a robust "treat-through" design (i.e., participants remained on their originally randomized therapy through Week 152). The prespecified analysis sets (all-randomized NRI, LTE NRI, LTE observed) ensured methodological

transparency. However, because only 80% of randomized patients entered the extension (investigator-judged to be benefiting), the LTE cohort lost its randomized basis and is susceptible to selection bias. Unblinding at Week 48 may have influenced patient management, adverse event reporting, and subjective efficacy assessments, while investigator-driven adjustments to concomitant medications further clouds causal inference. Although intercurrent events were handled per regulatory guidance, the absence of a complete ICE inventory and unclear extent of missing data mean that imputation methods — and thus overall efficacy estimates — cannot be fully appraised.

Participants included biologic-naïve and biologic-experienced patients with moderate-to-severe Crohn's disease, reflecting a real-world treatment landscape and supporting broad applicability of safety and efficacy findings. The exclusion of individuals with certain comorbidities or complex complications limits the relevance of the results to the sickest or those with more severe or multifactorial disease presentations.

Neff-Baro et al. (2024)

Additional evidence by Neff-Baro et al, (2024) was reviewed to assess the predictive impact of endoscopic response after maintenance treatment (approximately 48 weeks) and long-term outcomes (approximately 96 weeks) in patients with moderately to severely active CD. A pooled post-hoc analysis was conducted with data from treatment arms (placebo excluded) of 2 RCTs (IM-UNITI [phase III maintenance trial of ustekinumab] and GALAXI 1 [phase II treat-through trial of guselkumab, total n = 461]) which enrolled adult patients diagnosed with moderately to severely active CD of at least 3 months' duration (confirmed through CDAI).

Efficacy Results

Efficacy results at end of maintenance (EOM): Overall, 75.3% of patients with endoscopic response at end of maintenance (EOM) were in long-term clinical remission (i.e., Week 92 for IM-UNITI and W96 for GALAXI 1) compared to 48.5% without endoscopic response. The odds ratio for endoscopic response at EOM was 1.91 (95% CI 1.11 to 3.28). In total 78.5% of patients with endoscopic response at EOM were in long-term clinical response compared to 56.9% patients without endoscopic response (OR= 1.65 [95% CI, 0.97-2.83]). A total of 75.0% versus 54.4%, respectively of patients with endoscopic response at EOM were in long-term IBDQ remission compared to patients without endoscopic response (OR = 1.99 [95% CI, 1.16 to 3.41]).

Harms Results

There were no harms results presented.

Critical Appraisal

The pooled post hoc analysis is limited by lack of pre-specification and an increased risk of type I error due to multiple group testing, thus the evidence is exploratory. The model aimed to provide an indication of the ability of endoscopic response at week 48 to predict later outcomes among individual patients. It is not clear how variables were selected for inclusion within the regression models. It is possible that important predictors (confounders) were missed which might alter the observed associations had they been included. In general, the associations were estimated with imprecision which indicates uncertainty in the estimated magnitude of association between endoscopic response at week 48 and later outcomes. There is a risk of bias in the estimated associations due to substantial missing data (approximately 15 to 35%) across the available outcomes, which does not appear to have been imputed. Finally, the study provides some information to suggest an association between endoscopic response at 48 weeks and later outcomes. However, the ideal evidence to validate a surrogate end point comes from RCTs that demonstrate the ability of the treatment effect (i.e., guselkumab vs. placebo or other comparator) at 48 weeks to predict a clinically relevant treatment effect on patient-important outcomes at later time points.

Economic Evidence

Cost and Cost-Effectiveness

- Guselkumab is available as a solution for injection (100 mg/ mL or 200 mg/ 2mL). At the submitted price of $3,059.74 per vial, the annual cost of guselkumab is expected to range from $23,016 to $49,092 per patient in the first year of treatment and $19,957 to $39,913 per patient in subsequent years (depending on dose), based on the Health Canada recommended dosage.
- Clinical efficacy in the economic analysis was derived from a sponsor-submitted network meta-analysis (NMA), with the efficacy of guselkumab informed by the GALAXI trials. Indirect evidence submitted by the sponsor suggests that guselkumab showed potential superiority over vedolizumab in achieving clinical remission and response; although its comparative efficacy against other agents—such as ustekinumab, risankizumab, and upadacitinib—was more variable, with results differing across specific analyses (e.g., by treatment phase [i.e., induction or maintenance], by patient populations [i.e., CT failure or biologic failure]) and outcome measures. However, owing to the limitations of the NMA relating to the heterogeneity across studies and imprecision in the treatment effect estimates, no definitive conclusions can be drawn regarding the relative efficacy of guselkumab compared with other biologics.
- Whether guselkumab will be associated with higher or lower drug costs to the health care system versus other biologics will depend on the proportion of patients on high versus low doses of guselkumab. Owing to the individualized approach to dosing in clinical practice, the relative total treatment costs of guselkumab compared to other biologics is uncertain.
- The sponsor estimated that the budget impact of reimbursing guselkumab for the treatment of adult patients with moderately to severely active CD will be $15,264,551 over the first 3 years of reimbursement compared to the amount currently spent on comparators, with an estimated expenditure of $80,378,863 on guselkumab over this period. CDA-AMC was unable to provide a more robust estimate. The actual budget impact of reimbursing guselkumab will depend on the proportion of patients on high compared to low dose guselkumab.

CDEC Information

Members of the Committee:

Dr. Peter Jamieson (Chair), Dr. Kerry Mansell (Vice Chair), Dr. Sally Bean, Daryl Bell, Dan Dunsky, Dr. Ran Goldman, Dr. Trudy Huyghebaert, Morris Joseph, Dr. Dennis Ko, Dr. Christine Leong, Dr. Alicia McCallum, Dr. Srinivas Murthy, Dr. Nicholas Myers, Dr. Krishnan Ramanathan, Dr. Marco Solmi, Dr. Edward Xie, and Dr. Peter Zed.

Meeting date: June 25, 2025

Regrets:

Four expert committee members did not attend.

Conflicts of interest:

None