Efficacy and safety of intravenous induction and subcutaneous maintenance therapy with guselkumab for patients with Crohn's disease (GALAXI-2 and GALAXI-3): 48-week results from two phase 3, randomised, placebo and active comparator-controlled, double-blind, triple-dummy trials

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Summary

Background Despite the availability of biological therapies, suboptimal disease control remains a problem for patients with Crohn's disease. We report the results of the GALAXI-2 and GALAXI-3 studies, which aimed to assess the efficacy and safety of intravenous induction followed by subcutaneous maintenance therapy with guselkumab over 48 weeks in adults with moderately to severely active Crohn's disease.

Methods GALAXI-2 and GALAXI-3 were identically designed, phase 3, randomised, double-blind, triple-dummy, treat-through trials with active and placebo comparators. Adult patients with moderately to severely active Crohn's disease (≥3 months duration) were enrolled at 257 sites across 40 countries. Eligible participants were randomly assigned (2:2:2:1) by use of a centralised computer-generated schedule to one of four treatment groups: (1) 200 mg intravenous guselkumab at weeks 0, 4, and 8, then 200 mg subcutaneous guselkumab every 4 weeks from week 12 to week 44 (guselkumab 200 mg group); (2) 200 mg intravenous guselkumab at weeks 0, 4, and 8, then 100 mg subcutaneous guselkumab every 8 weeks from week 16 to week 40 (guselkumab 100 mg group); (3) approximately 6 mg/kg intravenous ustekinumab at week 0, then 90 mg subcutaneous ustekinumab every 8 weeks from week 8 to week 40 (ustekinumab group); or (4) intravenous placebo every 4 weeks at weeks 0, 4, and 8 (placebo group). At week 12, participants without a clinical response to placebo received masked rescue therapy with ustekinumab; all other participants remained on their randomised regimen irrespective of response status at week 12. Participants, investigators, site personnel, and the funder were masked to study treatment until all participants had either completed the follow-up visit at week 48 or terminated study participation before week 48. Coprimary composite endpoints (comparing each guselkumab regimen with placebo) were (1) clinical response at week 12 and clinical remission at week 48 and (2) clinical response at week 12 and endoscopic response at week 48, measured in the primary analysis population of all randomly assigned participants who received at least one dose of the study agent and satisfied the Simple Endoscopic Score for Crohn's Disease (SES-CD) eligibility criteria introduced with the third protocol amendment as per health authority request. Safety was assessed in participants who received at least one dose of study treatment (all-treated analysis population). These trials are registered with ClinicalTrials.gov (NCT03466411).

Findings From Jan 8, 2020, to Oct 20, 2023, 1048 participants were randomly assigned, treated, and followed up until week 48, of whom 1021 participants were included in the primary analysis population: 508 (49·8%) in GALAXI-2 and 513 (50·2%) in GALAXI-3. Both guselkumab regimens were superior to placebo for the endpoint of clinical response at week 12 and clinical remission at week 48 in GALAXI-2, which was observed in 80 (55%) of 146 participants in the guselkumab 200 mg group, 70 (49%) of 143 in the guselkumab 100 mg group, and nine (12%) of 76 in the placebo group (adjusted treatment difference 43% [95% CI 32–54] in the guselkumab 200 mg group and 38% [27–49] in the guselkumab 100 mg group; p<0·0001), and in GALAXI-3, observed in 72 (48%) of 150 participants in the guselkumab 200 mg group, 67 (47%) of 143 in the guselkumab 100 mg group, and nine (13%) of 72 in the placebo group (35% [24–46] and 34% [23–45]; p<0·0001). Similarly, both guselkumab regimens were superior to placebo for the endpoint of clinical response at week 12 and endoscopic response at week 48 in GALAXI-2, observed in 56 (38%) participants in the guselkumab 200 mg group, 56 (39%) in the guselkumab 100 mg group, and four (5%) in the placebo group (33% [24–42] in the guselkumab 200 mg group and 34% [24–43] in the guselkumab 100 mg group; p<0·0001), and in GALAXI-3, observed in 54 (36%) participants in the guselkumab 200 mg group, 48 (34%) in the guselkumab 100 mg group, and four (6%) in the placebo group (31% [21–40] and 28% [19–37]; p<0·0001). Serious adverse events occurred in 21 (7%) participants in the guselkumab 200 mg group (incidence rate 9·7 events per 100 participant-years),

32 (11%) in the guselkumab 100 mg group (14·9 events per 100 participant-years), 35 (12%) in the ustekinumab group (18·4 events per 100 participant-years), and 23 (15%) in the placebo group (23·8 events per 100 participant-years). No deaths were reported.

Interpretation Intravenous induction followed by subcutaneous maintenance therapy with guselkumab was efficacious in participants with moderately to severely active Crohn's disease, showing superiority to placebo and ustekinumab at week 48 across multiple endpoints. Safety outcomes were favourable and consistent with the known profile of guselkumab in approved indications.

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Research in context

Evidence before this study

We surveyed the evidence base for biological therapies in Crohn's disease, searching PubMed for articles published in English between database inception and Nov 15, 2024, using the following search terms: "Crohn's disease", "biologic therapy", "biological therapy", "anti-integrin", and "selective Janus kinase inhibitor". To date, most trials assessing the efficacy of maintenance therapy with biological agents in patients with Crohn's disease did not include statistically robust, head-to-head comparisons with established therapies. Additionally, most trials used designs (eg, randomised withdrawal) that selected only participants with a response to induction therapy for the evaluation of maintenance therapy, making it difficult to apply their results to clinical practice. Inadequate response, loss of response over time, and discontinuation due to side-effects are common with available therapies for Crohn's disease. Guselkumab, an inhibitor of the p-19 subunit of IL-23, was approved in 2024 for the treatment of ulcerative colitis. In a phase 2 study enrolling participants with moderately to severely active Crohn's disease, induction with intravenous guselkumab followed by maintenance therapy with subcutaneous guselkumab for 48 weeks was associated with high rates of clinical and endoscopic efficacy and had an acceptable safety profile.

Added value of this study

GALAXI-2 and GALAXI-3 were two identically designed, phase 3, randomised, double-blind, triple-dummy, registrational trials with head-to-head comparisons with an active comparator (ustekinumab) and a placebo in the treat-through design. These studies provide consistent evidence of the long-term efficacy and safety of guselkumab in adults with moderately to severely active Crohn's disease. Endpoints were assessed at the participant level, adding to the robustness of the results. Both guselkumab dose regimens (intravenous induction with 200 mg every 4 weeks followed by subcutaneous maintenance with either 100 mg every 8 weeks or 200 mg every 4 weeks) showed efficacy at week 48 and provided greater improvements than did ustekinumab for endpoints including an objective endoscopic evaluation. The benefits of guselkumab were also evident among participants who were naive to biological therapy, and among those with a history of intolerance or inadequate response to biological therapy, a difficult-to-treat subpopulation. The use of a treat-through study design, in which clinical outcomes at a specific timepoint were not a prerequisite for maintenance therapy, more closely mimicked clinical practice than previous studies. Importantly, this study design also showed that a substantial proportion of participants without a clinical response after induction improved with subcutaneous guselkumab treatment. Guselkumab was well tolerated in participants with Crohn's disease, showing a safety profile consistent with its approved uses in patients with ulcerative colitis, plaque psoriasis, and psoriatic arthritis.

Implications of all the available evidence

GALAXI-2 and GALAXI-3 are the first registrational studies of an inhibitor of the p-19 subunit of IL-23 with a double-blind, triple-dummy design to show head-to-head superiority to ustekinumab in participants with moderately to severely active Crohn's disease, regardless of their previous history with biological therapy. In the prespecified pooled analyses, guselkumab was superior to ustekinumab for endpoints incorporating an objective endoscopic outcome, in which endoscopic response is integral to long-term disease control and aligned with treatment targets of the consensus of Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II). Superiority was also shown for composite endpoints that included both symptom and endoscopic measures in the same participant, such as deep remission. Other head-to-head trials in patients with Crohn's disease comparing inhibitors of the p-19 subunit of IL-23 with ustekinumab either did not show superiority to ustekinumab (ie, mirikizumab in the VIVID-1 study) or used an open-label design and were conducted in participants with previous inadequate response or intolerance to TNF antagonists only (ie, rizankizumab in the SEQUENCE study). Overall, based on the observed benefit and favourable safety profile of guselkumab, the results of GALAXI-2 and GALAXI-3—in particular, the head-to-head comparison with ustekinumab, a standard of care in patients with moderate to severe Crohn's disease—could position guselkumab as a first-line or second-line option in this patient group.

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See **Online** for appendix

Introduction

Crohn's disease, a chronic and progressive inflammatory condition characterised by patchy, transmural lesions that can occur anywhere in the gastrointestinal tract from the mouth to the anus, is associated with decreased quality of life and increased use of health-care resources.[1] Complications and comorbidities, including extra-intestinal manifestations, are common,[1] and the estimated 10-year risk of surgery exceeds 25%.[2]

Many patients with moderately to severely active Crohn's disease are suboptimally treated with currently available therapies and continue to have signs and symptoms of disease. Although biological agents such as infliximab have been a mainstay of Crohn's disease management for decades, traditionally classified conventional therapies, such as corticosteroids, azathioprine, mercaptopurine, and methotrexate, continue to be widely used.[3] Patients often have an inadequate response to existing treatments, discontinue treatment due to side-effects, or lose response to treatment over time.[1] New treatment options that confer increased efficacy with an acceptable safety profile are needed. To evaluate the efficacy of these new treatments, researchers and regulators are placing increasing emphasis on endpoints that signify control of inflammatory disease activity, such as endoscopic outcomes.[4] The Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE-II) consensus highlights endoscopic healing as an important treatment goal in patients with Crohn's disease.[5]

IL-23 plays an essential role in the pathogenesis of Crohn's disease and other immune-mediated inflammatory diseases, in part by regulating the balance of pathogenic and regulatory T-cell subsets.[6,7] Guselkumab is a dual-acting inhibitor of the p-19 subunit of IL-23 that potently neutralises IL-23 and binds to CD64,[8] a receptor on cells that produce IL-23. As such, guselkumab is structurally and functionally different from other inhibitors of the p-19 subunit of IL-23. Guselkumab was first approved in the USA for the treatment of patients with ulcerative colitis in 2024 and is now approved for this indication in other regions worldwide.[9]

The phase 2/3 GALAXI programme consists of three efficacy and safety studies of intravenous induction and subcutaneous maintenance therapy with guselkumab in participants with moderately to severely active Crohn's disease. Each study uses a treat-through design, placebo control, and active comparator (ustekinumab). The phase 2 dose-finding study (GALAXI-1) evaluated three intravenous induction doses of guselkumab (200 mg, 600 mg, and 1200 mg) and showed similar efficacy across all doses compared with placebo.[10] An induction dose of 200 mg intravenous guselkumab was selected for use in the phase 3 studies. This dose followed by maintenance therapy with subcutaneous guselkumab (200 mg every 4 weeks or 100 mg every 8 weeks) showed high rates of clinical and endoscopic efficacy.[11] Herein, we report the results of the phase 3 GALAXI-2 and GALAXI-3 studies, which aimed to assess the efficacy and safety of induction with intravenous guselkumab followed by maintenance therapy with subcutaneous guselkumab over 48 weeks in adults with moderately to severely active Crohn's disease.

Methods

Study design

GALAXI-2 and GALAXI-3 were two identically designed, phase 3, randomised, double-blind, triple-dummy, registrational trials with head-to-head comparisons with an active comparator (ustekinumab) and a placebo in the treat-through design. Participants were enrolled at 257 hospitals, academic medical centres, clinical research units, and private practices across 40 countries (appendix pp 3–8). The study protocol was approved by an institutional review board or ethics committee at each study site and both studies were conducted in compliance with the Declaration of Helsinki, Good Clinical Practice guidelines, and applicable local regulations. Safety data were periodically reviewed by an independent data monitoring committee. The GALAXI-2 and GALAXI-3 trials are registered with ClinicalTrials.gov (NCT03466411).

Participants

Eligible participants were adults (aged ≥18 years) with moderately to severely active Crohn's disease of at least 3 months duration, defined as a Crohn's Disease Activity Index (CDAI) score of 220–450 (inclusive) with either a mean daily stool frequency count greater than 3 or a mean daily abdominal pain score greater than 1, and endoscopic evidence of Crohn's disease at the screening endoscopy with a Simple Endoscopic Score for Crohn's Disease (SES-CD) ≥6 (or ≥4 for participants with isolated ileal disease) and presence of ulceration in any one of the five ileocolonic segments (minimum scores of 1 for size of ulcer and ulcerated surface), as per central reader.

Participants were required to meet at least one of the following criteria regarding concomitant or previous medication for Crohn's disease: current treatment with oral corticosteroids, azathioprine, mercaptopurine, or methotrexate (alone or in combination); history of inadequate response or intolerance to previous therapy with oral corticosteroids, azathioprine, mercaptopurine, or methotrexate; history of corticosteroid dependence (ie, an inability to successfully taper corticosteroids without a return of the symptoms of Crohn's disease); or previous inadequate response or intolerance to a biological therapy for Crohn's disease (ie, tumour necrosis factor [TNF] antagonists [infliximab, adalimumab, certolizumab pegol], vedolizumab, or approved biosimilars; appendix pp 9–14). Participants with corticosteroid dependence or with inadequate response or intolerance to oral corticosteroids, azathioprine, mercaptopurine, or methotrexate could be naive to biological therapy or previously exposed to biological therapy without inadequate response or intolerance.

Key exclusion criteria were a current or suspected abscess, draining ostomy or stoma, complications of Crohn's disease (eg, symptomatic strictures or stenoses) that might require surgery or preclude the use of the CDAI to assess response to therapy, and the use of some medications or therapies within designated washout periods before baseline. Because ustekinumab was an active comparator in GALAXI-2 and GALAXI-3, participants who had previously received a biological therapy targeting IL-12 or IL-23 were ineligible, with the exception of participants with minimal previous ustekinumab exposure at approved dosages and intervals and no evidence of inadequate response or intolerance during previous treatment with ustekinumab. The full list of exclusion criteria and medication washout details are provided in the appendix (pp 15–22).

At baseline, participants were permitted oral corticosteroid therapy at a dose equivalent to prednisone at or below 40 mg/day (or budesonide 9 mg/day or beclomethasone 5 mg/day), with doses remaining stable during the induction period (weeks 0–12). Mandatory corticosteroid tapering began at week 12 according to a schedule recommended by the protocol. Other permitted concomitant therapies for Crohn's disease at baseline, such as oral aminosalicylates, azathioprine, mercaptopurine, and methotrexate, were to remain at stable doses until week 48 and new concomitant therapies should not have been initiated. Oral corticosteroid tapering schedules and prohibited changes in concomitant medications for Crohn's disease are described in the appendix (pp 23–24). Participant sex was self-reported. Before any study procedure, participants provided written informed consent.

Randomisation and masking

Following a screening period, eligible participants were randomly assigned (2:2:2:1) to one of four treatment groups that included both intravenous induction and subcutaneous maintenance administrations of guselkumab, ustekinumab, or placebo, for a total of 48 weeks of double-blinded study treatment. Eligible participants were first randomly assigned to GALAXI-2 or GALAXI-3 by use of permuted block randomisation with baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), documented history of inadequate response or intolerance to biological therapy (yes or no), and baseline corticosteroid use (yes or no) as stratification variables. Within each study, a minimum of 25% and a maximum of 50% of the total enrolled population were participants without a history of inadequate response or intolerance to biological therapy. A centralised computer-generated schedule prepared before the start of the study under the supervision of the sponsor was used to randomly assign participants to study treatment.

Participants, investigators, site personnel, and the sponsor were masked to study treatment until all participants had either completed the follow-up visit at week 48 or terminated study participation before week 48. Endoscopy central readers were masked to study treatment and visit.

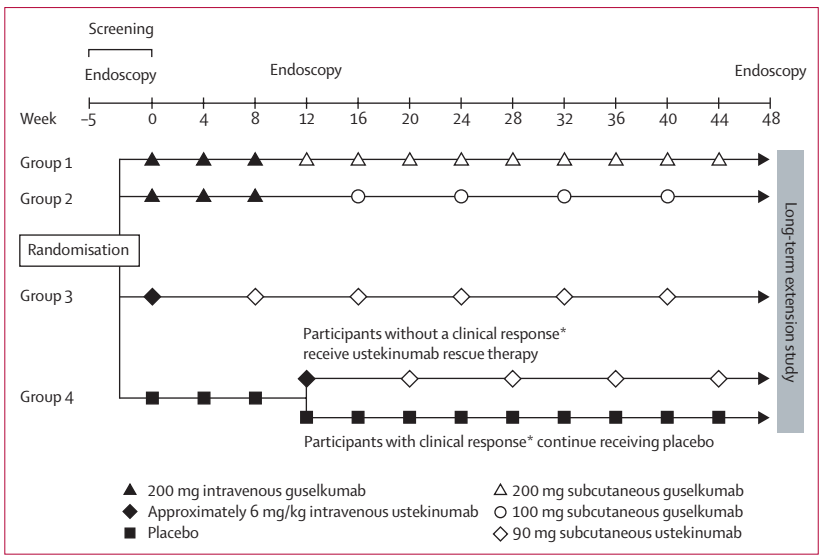

Figure 1: **Study treatment groups and timeline**
CDAI=Crohn's Disease Activity Index. *Clinical response: ≥100-point decrease in CDAI score from baseline or CDAI score of <150.

Procedures

Enrolled participants were randomly assigned to one of the following four treatment groups (figure 1): (1) 200 mg intravenous guselkumab at weeks 0, 4, and 8, then 200 mg subcutaneous guselkumab every 4 weeks from week 12 to week 44 (guselkumab 200 mg group); (2) 200 mg intravenous guselkumab at weeks 0, 4, and 8, then 100 mg subcutaneous guselkumab every 8 weeks from week 16 to week 40 (guselkumab 100 mg group); (3) approximately 6 mg/kg intravenous ustekinumab at week 0, then 90 mg subcutaneous ustekinumab every 8 weeks from week 8 to week 40 (ustekinumab group); or (4) intravenous placebo every 4 weeks at weeks 0, 4, and 8 (placebo group). Subsequent treatment for participants randomly assigned to placebo was established by clinical response status at week 12 (≥100-point decrease in CDAI score from baseline or a CDAI score <150). Participants in the placebo group without a clinical response at week 12 received masked rescue therapy with approximately 6 mg/kg intravenous ustekinumab at week 12, then 90 mg subcutaneous ustekinumab every 8 weeks from week 20 to week 44. Participants in the placebo group with a clinical response to placebo at week 12 received subcutaneous placebo every 4 weeks from week 12 to week 44. To maintain treatment blinding, all participants were evaluated for clinical response at week 12 and received an intravenous infusion of either placebo or ustekinumab. Consistent with the treat-through study design, participants in both guselkumab

	Definition
Clinical (symptom-based) outcomes	
Clinical response	≥100-point decrease in CDAI score from baseline or CDAI score <150
Clinical remission	CDAI score <150
90-day corticosteroid-free clinical remission	CDAI score <150 at designated timepoint and no receipt of corticosteroids for 90 days before timepoint
Fatigue response	Improvement from baseline of ≥7 points in PROMIS–Fatigue Short Form 7a score[12]
Outcomes with an endoscopic component	
Endoscopic response	≥50% improvement from baseline in SES-CD score or SES-CD score ≤2
Endoscopic remission	SES-CD score ≤4, ≥2-point reduction from baseline, and no SES-CD sub-score >1 in any individual component
Deep remission	Clinical remission and endoscopic remission

CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease.

Table 1: **Outcome definitions**

groups and the ustekinumab group remained in the treatment group they were initially allocated to, regardless of clinical response status at week 12. Selection of the two guselkumab maintenance dosing regimens is described in the appendix (pp 57–58).

Each active study intervention and its matching placebo were identical in appearance, and all participants received the same number and types of study drug administration at every visit. To maintain treatment blinding, all participants received intravenous infusions (active or placebo) at weeks 0, 4, 8, and 12. All participants received one subcutaneous injection (active or placebo) at week 8 (to conceal treatment in the ustekinumab group), two subcutaneous injections (active or placebo) at week 12, and three subcutaneous injections (active or placebo) at each visit from week 16 to week 44 (to conceal allocation to active treatment at every 4-week or 8-week interval).

The following CDAI components were recorded by the participant on a daily diary card: the total number of liquid or very soft stools; abdominal pain or cramping; use of antidiarrhoeal drugs, opiates, or both; and general wellbeing. The CDAI was evaluated at each study visit and a CDAI score was calculated if at least four of the eight components (ie, liquid or soft stool frequency, abdominal pain, general wellbeing, presence of complications, presence of an abdominal mass, use of antidiarrhoeal drugs, haematocrit, and bodyweight) were available at that visit. When at least four components were available, any missing components were imputed by carrying forward the last available component. If fewer than four components were available, the CDAI score was considered missing for that visit.

All participants underwent video-recorded ileocolonoscopies at screening and at weeks 12 and 48. All videos were scored by a masked central reader, assessed for the presence or absence of mucosal ulcerations, and scored with the SES-CD. Fatigue was assessed as a patient-reported outcome on the PROMIS–Fatigue Short Form 7a,[12] with a recall period of the previous 7 days at baseline and at weeks 8, 12, 24, and 48. Participants were evaluated for adverse events, serious adverse events, and hospitalisations and surgeries related to Crohn's disease at each study visit. Clinical laboratory assessments (including C-reactive protein [CRP]) were performed every 4 weeks until week 24, then every 8 weeks until week 48. Stool samples for faecal calprotectin assessment were obtained at baseline and at weeks 4, 8, 12, 24, and 48. Serum antibodies to guselkumab or ustekinumab were measured every 4 weeks until week 12, then every 8 weeks from week 24 by use of a validated, drug-tolerant assay. Additional assessments (eg, health-related quality of life and pharmacogenomic and pharmacokinetic evaluations) were performed as per the study schedule of activities; results associated with these assessments and other exploratory endpoints are not reported in this Article.

Adverse events were coded with MedDRA (version 26.0).[13] Occurrences of major adverse cardiovascular events were identified by clinical review. Terms for venous thromboembolism were based on customised MedDRA query. Hepatic disorder adverse events are defined as the narrow terms in the Standardised MedDRA Query of "Drug Related Hepatic Disorders—Comprehensive Search".[14]

Outcomes

Efficacy was assessed by various endpoints, which comprised specific outcomes evaluated at designated timepoints (table 1), including composite endpoints that evaluated more than one outcome. All composite endpoints were evaluated at the individual participant level: each participant must have reached both outcomes included in the composite, at the designated timepoints, to fulfil the criteria for meeting the overall composite endpoint.

The coprimary endpoints assessing the long-term efficacy of guselkumab compared with placebo were (1) clinical response at week 12 and clinical remission at week 48 and (2) clinical response at week 12 and endoscopic response at week 48. The two coprimary endpoints were also composite endpoints (each endpoint had two components), which were assessed at the individual participant level in each study.

Major secondary endpoints evaluating the short-term efficacy of guselkumab compared with placebo in each study were clinical remission at week 12, endoscopic response at week 12, the composite of clinical remission at week 12 and endoscopic response at week 12, and fatigue response at week 12. Major secondary endpoints evaluating the long-term efficacy of guselkumab compared with placebo (all composite endpoints with

assessments at week 12 and week 48) in each study were clinical response at week 12 and 90-day corticosteroid-free clinical remission at week 48, as well as clinical response at week 12 and endoscopic remission at week 48.

The head-to-head comparisons of guselkumab with ustekinumab at week 48 were first assessed in the pooled GALAXI-2 and GALAXI-3 dataset and then in each study individually. These long-term major secondary endpoints were endoscopic response at week 48, endoscopic remission at week 48, the composite of clinical remission at week 48 and endoscopic response at week 48, deep remission at week 48 (the composite of clinical remission at week 48 and endoscopic remission at week 48), and clinical remission at week 48.

All short-term (week 12) major secondary endpoints compared 200 mg intravenous guselkumab with placebo; data from participants in the two guselkumab treatment groups were combined for these short-term analyses given that participants in both groups received the same induction regimen of 200 mg intravenous guselkumab every 4 weeks before week 12. All endpoints with a week-48 assessment, including composite endpoints with an assessment at week 48 (eg, coprimary endpoints), separately compared each guselkumab induction and maintenance dose regimen with either placebo or ustekinumab, as specified. Efficacy analyses based on Crohn's disease medication history (subpopulations with inadequate response or intolerance to biological therapy and those naive to biological therapy) were prespecified for the individual studies and the pooled GALAXI-2 and GALAXI-3 dataset and were not controlled for multiplicity. Analyses of guselkumab efficacy at week 48 in participants with or without a clinical response at week 12 in the pooled GALAXI-2 and GALAXI-3 dataset were conducted post-hoc; similar analyses of the individual trials were prespecified.

Statistical analysis

A total sample size of approximately 980 participants (around 490 participants per study, consisting of 140 participants in each guselkumab treatment group, 70 participants in the placebo group, and 140 participants in the ustekinumab group) was calculated to provide at least 90% power for the coprimary endpoints in each study based on a Chi squared test at the two-sided 0·05 significance level. For this calculation, the assumption for the coprimary endpoints was that 8–10% of participants in the placebo group would have a clinical response at week 12 and clinical remission at week 48, and the difference between guselkumab and placebo would be 40–45%. For clinical response at week 12 and endoscopic response at week 12, the assumption was that 2–5% of participants in the placebo group would meet the endpoint, and the difference between guselkumab and placebo would be 30–35%.

GALAXI-2 and GALAXI-3 had separate, prespecified testing procedures, each with type I error control at the two-sided 0·05 significance level over the coprimary and major secondary endpoints (appendix p 25). The major secondary endpoints were separated into five ranked tiers and tested with the Hochberg procedure within each tier. The coprimary endpoints and major secondary endpoints in tiers 1, 4, and 5 were analysed for each study separately. Major secondary endpoints in tiers 2 and 3 were analysed with pooled data from both studies; data pooling was prespecified. Briefly, evaluation of each study began with sequential tests of superiority of each guselkumab dose regimen compared with placebo relative to the composite coprimary endpoints by use of a fixed-sequence testing procedure. In each study, if all p values were <0·05 for the coprimary endpoints, formal testing continued for the major secondary endpoints in tiers 1–5. If all comparisons within a tier were statistically significant (p<0·05), formal testing proceeded to the next tier. If a comparison was not statistically significant within a tier, other tests within the same tier could be declared significant if they reached the Hochberg thresholds, but formal testing did not proceed to the next tier. To address regional differences in regulatory requirements, a regional testing plan was also implemented (appendix p 26).

Counts and percentages were used to summarise categorical variables; 95% CIs for the proportion of participants meeting the endpoint in each treatment group were based on the normal approximation confidence limits. In cases of rare events, the exact confidence limits were provided. Adjusted treatment differences and associated 95% CIs and p values were based on the common risk difference by use of Mantel–Haenszel stratum weights and the Sato variance estimator with adjustment for stratification factors: baseline CDAI score (≤300 or >300), baseline SES-CD score (≤12 or >12), inadequate response or intolerance to biological therapy (yes or no; this factor was not used in analyses of subpopulations with inadequate response or intolerance to biological therapy and those naive to biological therapy), and baseline corticosteroid use (yes or no). Participants with a prohibited change in concomitant medications for Crohn's disease, discontinuation of study agent due to lack of efficacy, or an adverse event of worsening Crohn's disease were considered to not have reached dichotomous endpoints. Additionally, participants with missing data were considered to not have reached dichotomous endpoints (appendix pp 27–28).

Demographic baseline characteristics and efficacy analyses were based on the primary analysis population, which included all randomly assigned participants who received at least one dose of the study agent and satisfied the SES-CD eligibility criteria introduced with the third protocol amendment as per health authority request (ie, screening SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease]). Safety results are reported in the all-treated analysis population, which included all

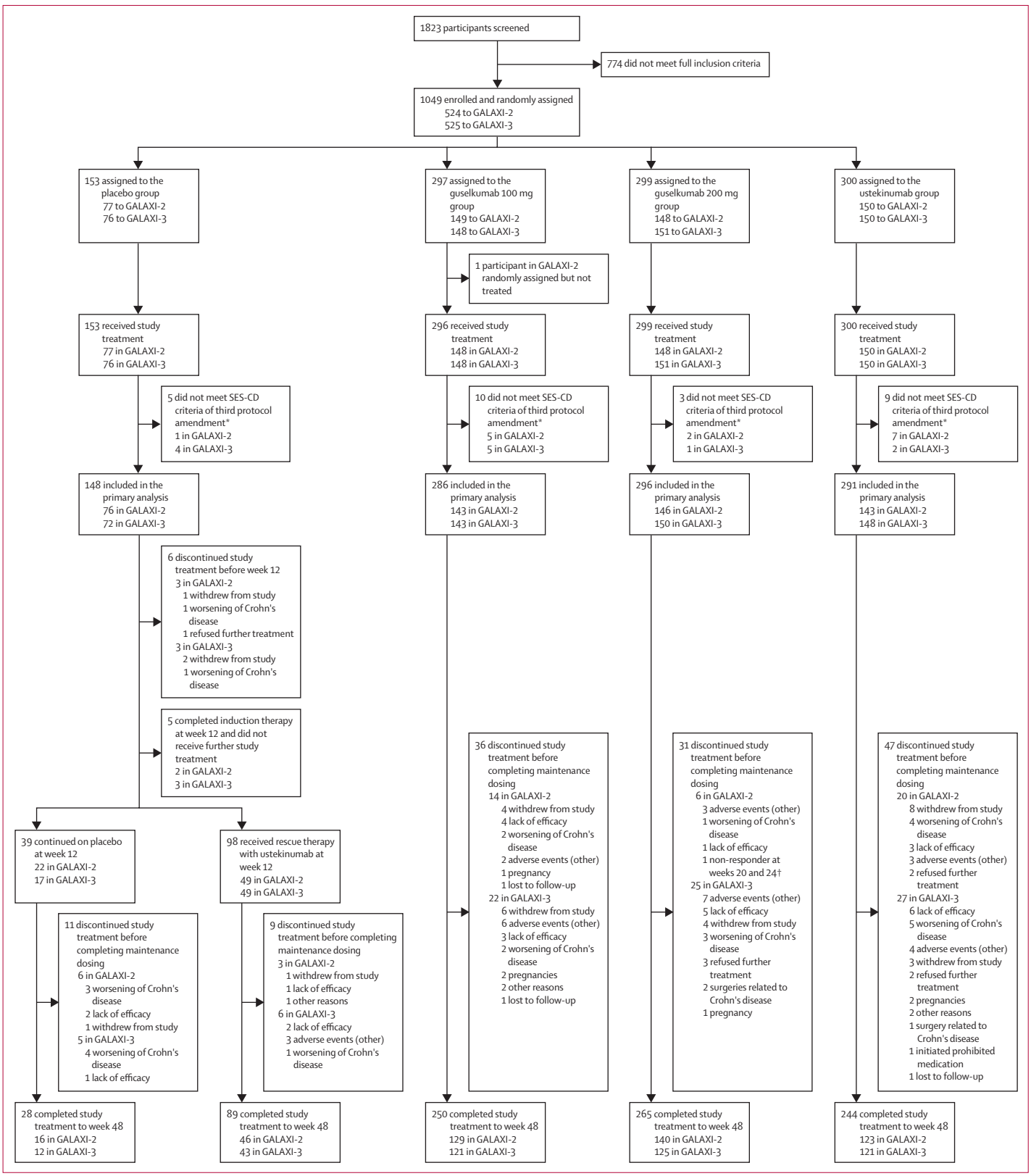

Figure 2: **Trial profile**

SES-CD=Simple Endoscopic Score for Crohn's Disease. CDAI=Crohn's Disease Actvity Index. *Screening SES-CD score of ≥6 (or ≥4 for participants with isolated ileal disease). †Change from baseline in CDAI score of <70 points and a CDAI score of >220 at weeks 20 and 24.

	GALAXI-2				GALAXI-3			
	Placebo group* (n=76)	Guselkumab 200 mg group (n=146)	Guselkumab 100 mg group (n=143)	Ustekinumab group† (n=143)	Placebo group* (n=72)	Guselkumab 200 mg group (n=150)	Guselkumab 100 mg group (n=143)	Ustekinumab group† (n=148)
Demographics								
Sex								
Male	41 (54%)	87 (60%)	69 (48%)	84 (59%)	47 (65%)	91 (61%)	85 (59%)	84 (57%)
Female	35 (46%)	59 (40%)	74 (52%)	59 (41%)	25 (35%)	59 (39%)	58 (41%)	64 (43%)
Age, years	32·0 (25·0–39·5)	33·5 (26·0–44·0)	34·0 (28·0–46·0)	36·0 (26·0–45·0)	33·0 (24·5–43·0)	35·0 (27·0–47·0)	33·0 (26·0–43·0)	35·0 (27·0–46·0)
Race								
Asian	17 (22%)	28 (19%)	34 (24%)	32 (22%)	18 (25%)	28 (19%)	38 (27%)	22 (15%)
Black or African American	0	1 (1%)	3 (2%)	3 (2%)	3 (4%)	1 (1%)	0	4 (3%)
Native Hawaiian or Other Pacific Islander	2 (3%)	0	0	0	2 (3%)	0	1 (1%)	1 (1%)
White	55 (72%)	115 (79%)	103 (72%)	104 (73%)	47 (65%)	117 (78%)	103 (72%)	115 (78%)
Not reported	2 (3%)	2 (1%)	3 (2%)	4 (3%)	2 (3%)	4 (3%)	1 (1%)	6 (4%)
Ethnicity								
Hispanic or Latinx	2 (3%)	8 (5%)	4 (3%)	5 (3%)	4 (6%)	5 (3%)	7 (5%)	11 (7%)
Not Hispanic or Latinx	70 (92%)	134 (92%)	135 (94%)	132 (92%)	67 (93%)	141 (94%)	132 (92%)	129 (87%)
Not reported	4 (5%)	4 (3%)	4 (3%)	6 (4%)	1 (1%)	4 (3%)	4 (3%)	8 (5%)
Region								
Asia	17 (22%)	28 (19%)	33 (23%)	31 (22%)	18 (25%)	28 (19%)	36 (25%)	22 (15%)
Eastern Europe	37 (49%)	72 (49%)	68 (48%)	69 (48%)	34 (47%)	66 (44%)	63 (44%)	63 (43%)
North America	3 (4%)	8 (5%)	11 (8%)	12 (8%)	7 (10%)	12 (8%)	12 (8%)	20 (14%)
Other	19 (25%)	38 (26%)	31 (22%)	31 (22%)	13 (18%)	44 (29%)	32 (22%)	43 (29%)
Disease characteristics								
Duration of Crohn's disease, years	4·1 (1·6–7·7)	4·7 (2·5–10·8)	6·0 (1·8–11·3)	4·6 (1·6–8·3)	5·7 (3·0–11·3)	3·6 (1·6–8·6)	4·5 (1·6–9·8)	5·6 (2·0–10·7)
CDAI								
Score	292·0 (51·7)	294·2 (51·7)	297·3 (52·6)	295·3 (52·4)	294·9 (54·1)	297·6 (53·9)	295·3 (56·1)	291·0 (51·7)
Stool frequency count >3	56 (74%)	100 (68%)	108 (76%)	108 (76%)	55 (76%)	120 (80%)	105 (73%)	115 (78%)
Abdominal pain score >1	71 (93%)	140 (96%)	136 (95%)	133 (93%)	67 (93%)	145 (97%)	136 (95%)	141 (95%)
SES-CD score	13·9 (7·8)	12·4 (7·1)	13·0 (7·0)	13·3 (7·5)	12·7 (7·3)	12·6 (7·4)	13·4 (7·8)	12·4 (6·6)
Endoscopic disease severity per SES-CD score								
<7	14 (18%)	29 (20%)	21 (15%)	26 (18%)	14 (19%)	41 (27%)	20 (14%)	31 (21%)
7–16	38 (50%)	79 (54%)	83 (58%)	75 (52%)	39 (54%)	68 (45%)	81 (57%)	84 (57%)
>16	24 (32%)	38 (26%)	39 (27%)	42 (29%)	19 (26%)	41 (27%)	42 (29%)	33 (22%)
Involved gastrointestinal areas (assessed by central reader)								
Ileum only	17 (22%)	39 (27%)	29 (20%)	25 (17%)	14 (19%)	41 (27%)	30 (21%)	30 (20%)
Colon only	29 (38%)	56 (38%)	62 (43%)	58 (41%)	33 (46%)	56 (37%)	51 (36%)	58 (39%)
Ileum and colon	30 (39%)	51 (35%)	52 (36%)	60 (42%)	25 (35%)	53 (35%)	62 (43%)	60 (41%)
Number of participants with ≥1 open or draining fistula	7 (9%)	7 (5%)	21 (15%)	9 (6%)	12 (17%)	17 (11%)	23 (16%)	16 (11%)
Number of participants with extra-intestinal manifestations	24 (32%)	25 (17%)	29 (20%)	29 (20%)	18 (25%)	37 (25%)	38 (27%)	36 (24%)
CRP concentration, mg/L	4·6 (1·7–15·8)	5·9 (2·1–17·1)	7·1 (1·9–17·1)	7·5 (2·8–17·8)	5·5 (1·4–16·1)	6·4 (3·0–22·6)	7·8 (3·0–27·6)	6·6 (2·0–21·5)
Faecal calprotectin								
Number of participants with baseline values	76 (100%)	145 (99%)	142 (99%)	138 (97%)	71 (99%)	149 (99%)	141 (99%)	146 (99%)
Concentration, µg/g	961·0 (257·5–2763·5)	962·0 (272·0–1790·0)	856·0 (388·0–1751·0)	1003·0 (351·0–1852·0)	962·0 (255·0–2481·0)	1242·0 (361·0–2167·0)	994·0 (499·0–2394·0)	773·0 (323·0–1855·0)

(Table 2 continues on next page)

	GALAXI-2				GALAXI-3			
	Placebo group* (n=76)	Guselkumab 200 mg group (n=146)	Guselkumab 100 mg group (n=143)	Ustekinumab group† (n=143)	Placebo group* (n=72)	Guselkumab 200 mg group (n=150)	Guselkumab 100 mg group (n=143)	Ustekinumab group† (n=148)
(Continued from previous page)								
Crohn's disease medication history								
No history of intolerance or inadequate response to biological therapy‡	37 (49%)	73 (50%)	66 (46%)	64 (45%)	33 (46%)	76 (51%)	67 (47%)	71 (48%)
Naive to biological therapy	34 (45%)	63 (43%)	58 (41%)	58 (41%)	27 (38%)	65 (43%)	58 (41%)	63 (43%)
Exposure to biological therapy‡ but no documented intolerance or inadequate response	3 (4%)	10 (7%)	8 (6%)	6 (4%)	6 (8%)	11 (7%)	9 (6%)	8 (5%)
Exposure to ustekinumab but no documented intolerance or inadequate response	1 (1%)	2 (1%)	0	1 (1%)	1 (1%)	3 (2%)	1 (1%)	4 (3%)
History of intolerance or inadequate response to previous biological therapy‡	39 (51%)	73 (50%)	77 (54%)	79 (55%)	39 (54%)	74 (49%)	76 (53%)	77 (52%)
≥1 TNF antagonist	39/39 (100%)	71/73 (97%)	74/77 (96%)	73/79 (92%)	37/39 (95%)	72/74 (97%)	75/76 (99%)	74/77 (96%)
≥2 TNF antagonists	10/39 (26%)	15/73 (21%)	16/77 (21%)	25/79 (32%)	13/39 (33%)	16/74 (22%)	15/76 (20%)	21/77 (27%)
Vedolizumab	4/39 (10%)	8/73 (11%)	13/77 (17%)	13/79 (16%)	9/39 (23%)	10/74 (14%)	12/76 (16%)	18/77 (23%)
Crohn's disease medications taken at baseline								
≥1 medication	47 (62%)	108 (74%)	106 (74%)	109 (76%)	49 (68%)	109 (73%)	101 (71%)	101 (68%)
Azathioprine, mercaptopurine, or methotrexate	21 (28%)	46 (32%)	43 (30%)	42 (29%)	19 (26%)	50 (33%)	44 (31%)	41 (28%)
Oral aminosalicylates	23 (30%)	61 (42%)	62 (43%)	64 (45%)	21 (29%)	55 (37%)	59 (41%)	55 (37%)
Antibiotics	4 (5%)	12 (8%)	6 (4%)	6 (4%)	3 (4%)	6 (4%)	6 (4%)	8 (5%)
Oral corticosteroids (including budesonide and beclomethasone)	25 (33%)	55 (38%)	54 (38%)	56 (39%)	26 (36%)	51 (34%)	55 (38%)	53 (36%)
Budesonide	8 (11%)	22 (15%)	17 (12%)	18 (13%)	10 (14%)	16 (11%)	19 (13%)	18 (12%)
Beclomethasone	0	0	0	0	0	0	0	0
Daily corticosteroid dose§ (excluding budesonide and beclomethasone), mg	15·0 (10·0–20·0)	20·0 (12·5–20·0)	20·0 (10·0–20·0)	20·0 (10·0–20·0)	20·0 (17·5–27·5)	20·0 (15·0–20·0)	20·0 (10·0–20·0)	20·0 (10·0–20·0)

Data are n (%), n/N (%), median (IQR), or mean (SD). CDAI=Crohn's Disease Activity Index. CRP=C-reactive protein. SES-CD=Simple Endoscopic Score for Crohn's Disease. TNF=tumour necrosis factor. *Including all participants randomly assigned to placebo. At week 12, participants with a clinical response continued placebo treatment and those without a clinical response received ustekinumab rescue therapy. †Including only participants randomly assigned to approximately 6 mg/kg intravenous ustekinumab at week 0 then 90 mg subcutaneous ustekinumab every 8 weeks from week 8 to week 40. ‡Biological therapies include infliximab, adalimumab, certolizumab pegol, or vedolizumab (and approved biosimilars). Participants who had previously received a biological therapy targeting IL-12 or IL-23 were ineligible, except for those with minimal exposure to ustekinumab and no history of intolerance or inadequate response. §Prednisone-equivalent dose.

Table 2: **Demographics, baseline disease characteristics, and Crohn's disease medication history in the primary analysis populations of GALAXI-2 and GALAXI-3**

randomly assigned and treated participants. All statistical analyses were performed with SAS Studio (version 3.8 on SAS 9.4 M6).

Role of the funding source

Employees of the study funder were involved in design of the study, data collection, data analysis, data interpretation, and writing of this report.

Results

From Jan 8, 2020, to Oct 20, 2023, 1048 participants were enrolled, randomly assigned, treated, and followed up until week 48 (figure 2). A total of 1021 participants fulfilled the SES-CD screening criteria of the third protocol amendment (SES-CD score ≥6 [or ≥4 for participants with isolated ileal disease] and presence of ulceration in any one of the five ileocolonic segments) and were included in the primary analysis population: 508 (49·8%) in GALAXI-2 and 513 (50·2%) in GALAXI-3 (figure 2). In GALAXI-2, 146 (29%) participants were included in the guselkumab 200 mg group, 143 (28%) in the guselkumab 100 mg group, 143 (28%) in the ustekinumab group, and 76 (15%) in the placebo group; in GALAXI-3, 150 (29%) participants were included in the guselkumab 200 mg group, 143 (28%) in the guselkumab 100 mg group, 148 (29%) in the ustekinumab group, and 72 (14%) in the placebo group.

53 (10%) of 508 participants in GALAXI-2 and 88 (17%) of 513 participants in GALAXI-3 discontinued treatment before completing maintenance dosing. In both trials combined, 31 (10%) of 296 participants in the guselkumab 200 mg groups, 36 (13%) of 286 participants in the guselkumab 100 mg groups, and 47 (16%) of 291 participants in the ustekinumab groups discontinued treatment before week 48. Compared with the guselkumab groups and the ustekinumab groups,

discontinuation rates were higher among participants in the placebo groups who had not received ustekinumab rescue therapy from week 12 (18 [36%] of 50 participants). When all 98 participants who had received ustekinumab rescue therapy in both trials were included, the discontinuation rate in the placebo group decreased (27 [18%] of 148 participants). Overall, the most common reasons for treatment discontinuation were withdrawal by participant, inadequate efficacy (lack of efficacy, non-responder at weeks 20 and 24, or an adverse event of worsening Crohn's disease), or an adverse event unrelated to efficacy. One participant discontinued treatment due to disruptions associated with the regional crisis in Ukraine and Russia; no participants discontinued treatment owing to logistical disruptions associated with the COVID-19 pandemic or an adverse event related to COVID-19.

Baseline demographics, disease characteristics, and Crohn's disease medication details were generally similar between treatment groups and across the two studies, except that the proportion of participants in the guselkumab 200 mg group with ileal disease only was somewhat greater than that of the other treatment groups (table 2). Across all treatment groups at baseline, mean CDAI scores were 295·0 (SD 52·0) in GALAXI-2 and 294·7 (53·8) in GALAXI-3 and mean SES-CD scores were 13·1 (7·3) in GALAXI-2 and 12·8 (7·3) in GALAXI-3. Endoscopic disease severity was moderate (SES-CD score 7–16) in 275 (54%) of 508 participants in GALAXI-2 and in 272 (53%) of 513 participants in GALAXI-3; it was severe (SES-CD score >16) in 143 (28%) participants in GALAXI-2 and in 135 (26%) participants in GALAXI-3.

Across all treatment groups, 268 (53%) participants in GALAXI-2 and 266 (52%) participants in GALAXI-3 had a history of intolerance or inadequate response to biological therapy. Of these participants, 257 (96%) in GALAXI-2 and 258 (97%) in GALAXI-3 had previous intolerance or inadequate response to at least one TNF antagonist, and 66 (25%) in GALAXI-2 and 65 (24%) in GALAXI-3 had previous intolerance or inadequate response to two or more TNF antagonists. Overall, 213 (42%) participants in both studies were naive to biological therapy; 27 (5%) participants in GALAXI-2 and 34 (7%) in GALAXI-3 were exposed to a previous biological therapy without documented intolerance or inadequate response, including four (1%) in GALAXI-2 and nine (2%) in GALAXI-3 with previous exposure to ustekinumab. Oral corticosteroids (prednisone or budesonide) were taken at baseline by 190 (37%) participants in GALAXI-2 and by 185 (36%) in GALAXI-3, with a median prednisone-equivalent daily dose of 20·0 mg (IQR 10·0–20·0) in both studies. Azathioprine, mercaptopurine, or methotrexate were taken at baseline by 30% of the study population in each trial: 152 participants in GALAXI-2 and 154 in GALAXI-3.

In both studies, the coprimary endpoints—composite endpoints with short-term (week 12) and long-term (week 48) components—were met for both guselkumab dose regimens. Both guselkumab regimens were superior to placebo for clinical response at week 12 and clinical remission at week 48 in GALAXI-2 (adjusted treatment difference 43% [95% CI 32–54] in the guselkumab 200 mg group and 38% [27–49] in the guselkumab 100 mg group; p<0·0001) and in GALAXI-3 (35% [24–46] and 34% [23–45]; p<0·0001). Similarly, both guselkumab regimens were superior to placebo for clinical response at week 12 and endoscopic response at week 48 in GALAXI-2 (33% [24–42] in the guselkumab 200 mg group and 34% [24–43] in the guselkumab 100 mg group; p<0·0001) and in GALAXI-3 (31% [21–40] and 28% [19–37]; p<0·0001; table 3). Rate differences by key baseline characteristics

	GALAXI-2			GALAXI-3		
	Placebo group (n=76)	Guselkumab 200 mg group (n=146)	Guselkumab 100 mg group (n=143)	Placebo group (n=72)	Guselkumab 200 mg group (n=150)	Guselkumab 100 mg group (n=143)
Clinical response* at week 12 and clinical remission† at week 48						
Number of participants (%)	9 (12%)	80 (55%)	70 (49%)	9 (13%)	72 (48%)	67 (47%)
95% CI	5–19	47–63	41–57	5–20	40–56	39–55
Adjusted treatment difference compared with placebo (95% CI)	..	43 (32–54)	38 (27–49)	..	35 (24–46)	34 (23–45)
p value	..	<0·0001	<0·0001	..	<0·0001	<0·0001
Clinical response* at week 12 and endoscopic response‡ at week 48						
Number of participants (%)	4 (5%)	56 (38%)	56 (39%)	4 (6%)	54 (36%)	48 (34%)
95% CI	0–10	31–46	31–47	0–11	28–44	26–41
Adjusted treatment difference compared with placebo (95% CI)	..	33 (24–42)	34 (24–43)	..	31 (21–40)	28 (19–37)
p value	..	<0·0001	<0·0001	..	<0·0001	<0·0001

CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Clinical response: ≥100-point decrease in CDAI score from baseline or CDAI score <150. †Clinical remission: CDAI score <150. ‡Endoscopic response: ≥50% improvement from baseline in SES-CD score or SES-CD score ≤2.

Table 3: **Long-term efficacy of guselkumab versus placebo measured by composite coprimary endpoints in GALAXI-2 and GALAXI-3**

for the coprimary endpoints in the pooled GALAXI-2 and GALAXI-3 dataset are provided in the appendix (pp 29–32).

In both GALAXI-2 and GALAXI-3, significantly higher rates of the major secondary endpoints of clinical remission at week 12, fatigue response at week 12, endoscopic response at week 12, and the composite of clinical remission at week 12 and endoscopic response at week 12 were observed among participants receiving 200 mg intravenous guselkumab at weeks 0, 4, and 8 than among those receiving placebo (table 4). Results of prespecified subpopulation analyses in the pooled GALAXI-2 and GALAXI-3 dataset highlight the consistent efficacy of guselkumab at week 12 compared with placebo in participants with a history of inadequate response or intolerance to biological therapies, and in participants naive to biological therapy. Rates of clinical remission at week 12 and endoscopic response at week 12 with intravenous guselkumab induction by subpopulation are shown in the appendix (pp 38–39).

Plots of clinical response until week 12 and clinical remission until week 48 (components of the composite coprimary endpoints) in the pooled GALAXI-2 and GALAXI-3 dataset showed that the response to guselkumab was evident at the first assessment timepoint (week 4) after the first intravenous dose (appendix p 40). Compared with placebo, the clinical benefit of induction with 200 mg intravenous guselkumab in improving symptoms, as measured by clinical response and clinical remission over time, was observed as early as week 4 and increased over time until week 12. Analyses of guselkumab and ustekinumab compared with placebo at week 12 in the pooled GALAXI-2 and GALAXI-3 dataset are provided in the appendix (p 41).

For major secondary endpoints evaluating the long-term efficacy of guselkumab compared with placebo, each guselkumab regimen was statistically superior in both studies (figure 3). In GALAXI-2, 74 (93%) of 80 participants in the 200 mg guselkumab group and 67 (96%) of 70 participants in the guselkumab 100 mg group with a clinical response at week 12 and clinical remission at week 48 were corticosteroid free for at least 90 days before week 48. In GALAXI-3, this outcome was observed in 67 (93%) of 72 participants in the 200 mg guselkumab group and in 65 (97%) of 67 participants in the guselkumab 100 mg group with a clinical response at week 12 and clinical remission at week 48. Among participants in GALAXI-2 receiving corticosteroids at baseline, corticosteroid elimination at week 48 was reported in 46 (84%) of 55 participants in the 200 mg guselkumab group, 39 (72%) of 54 participants in

	GALAXI-2		GALAXI-3	
	Placebo group (n=76)	Guselkumab groups combined* (n=289)	Placebo group (n=72)	Guselkumab groups combined* (n=293)
Clinical remission† at week 12				
Number of participants (%)	17 (22%)	136 (47%)	11 (15%)	138 (47%)
95% CI	13–32	41–53	7–24	41–53
Adjusted treatment difference compared with placebo (95% CI)	..	25% (14–36)	..	31% (21–41)
p value	..	<0·0001	..	<0·0001
Fatigue response‡ at week 12				
Number of participants (%)	22 (29%)	131 (45%)	13 (18%)	127 (43%)
95% CI	19–39	40–51	9–27	38–49
Adjusted treatment difference compared with placebo (95% CI)	..	16% (5–28)	..	26% (15–36)
p value	..	0·0064	..	<0·0001
Endoscopic response§ at week 12				
Number of participants (%)	8 (11%)	109 (38%)	10 (14%)	106 (36%)
95% CI	4–17	32–43	6–22	31–42
Adjusted treatment difference compared with placebo (95% CI)	..	28% (19–36)	..	22% (12–32)
p value	..	<0·0001	..	<0·0001
Clinical remission† and endoscopic response§ at week 12				
Number of participants (%)	3 (4%)	62 (21%)	2 (3%)	64 (22%)
95% CI	0–8	17–26	0–7	17–27
Adjusted treatment difference compared with placebo (95% CI)	..	18% (11–24)	..	19% (12–25)
p value	..	<0·0001	..	<0·0001

CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Participants randomly assigned to either guselkumab group. Until the assessment at week 12, participants in these groups had received 200 mg intravenous guselkumab only. †Clinical remission: CDAI score <150. ‡Fatigue response: improvement from baseline of ≥7 points in PROMIS–Fatigue Short Form 7a score.[12] §Endoscopic response: ≥50% improvement from baseline in SES-CD score or SES-CD score ≤2.

Table 4: **Short-term efficacy of guselkumab versus placebo measured by major secondary endpoints in GALAXI-2 and GALAXI-3**

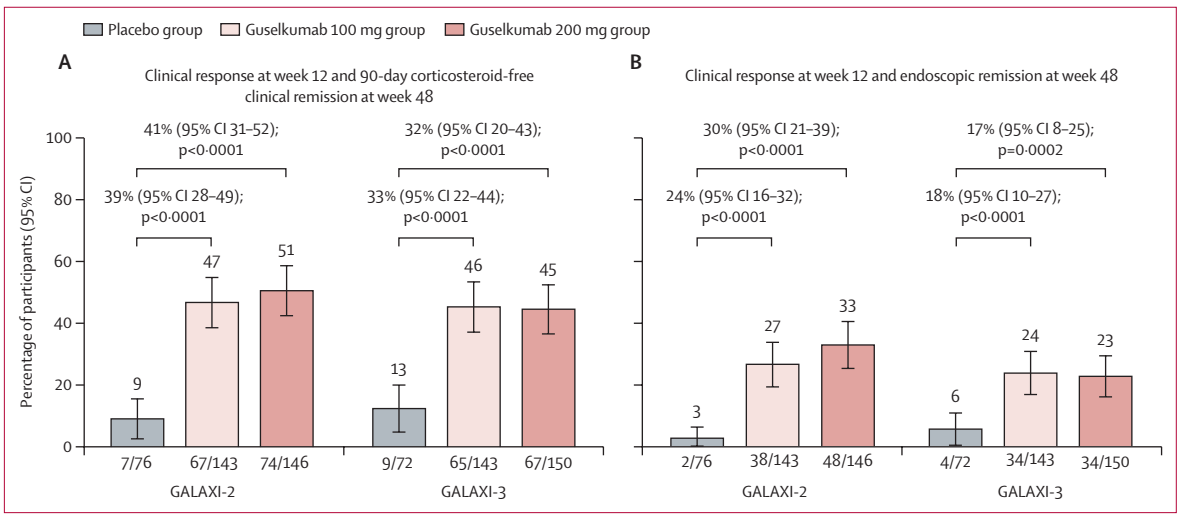

Figure 3: **Long-term efficacy of guselkumab versus placebo measured by major secondary endpoints in GALAXI-2 and GALAXI-3**
Long-term efficacy was assessed with two composite secondary endpoints: clinical response at week 12 and 90-day corticosteroid-free clinical remission at week 48 (A) and clinical response at week 12 and endoscopic remission at week 48 (B). Clinical response was defined as a ≥100-point decrease in CDAI score from baseline or a CDAI score <150. Corticosteroid-free clinical remission was defined as a CDAI score <150 at a designated timepoint and no receipt of corticosteroids for 90 days before that timepoint. Endoscopic remission was defined as a SES-CD score ≤4, a ≥2-point reduction from baseline, and no SES-CD sub-score >1 in any individual component. Efficacy of guselkumab is compared with that of placebo; adjusted treatment differences with 95% CI are presented. Values immediately above the 95% CI bars indicate the percentage of participants attaining the endpoint. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease.

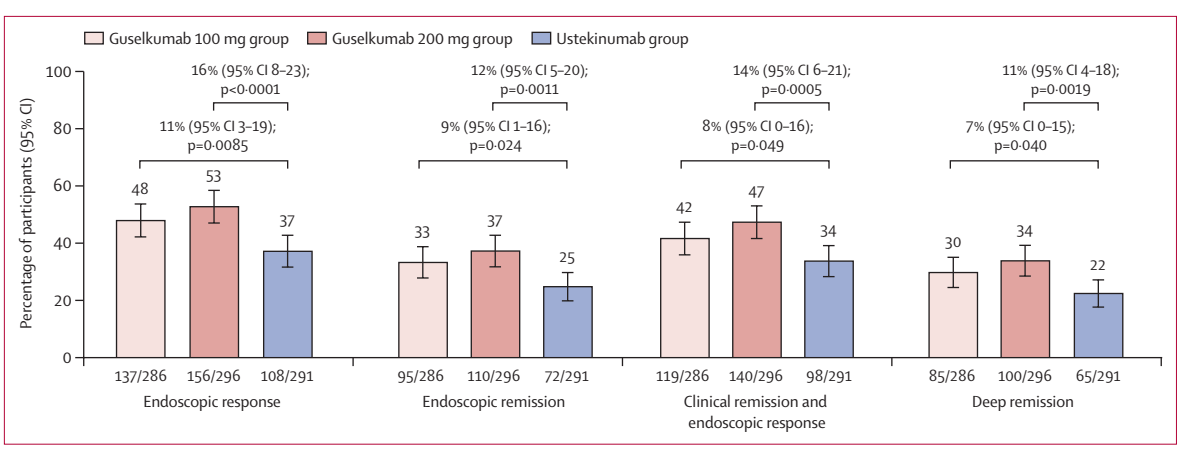

Figure 4: **Long-term efficacy of guselkumab versus ustekinumab measured by major secondary endpoints in the pooled GALAXI-2 and GALAXI-3 dataset**
Four secondary endpoints are presented: endoscopic response (≥50% improvement from baseline in SES-CD score or SES-CD score ≤2), endoscopic remission (SES-CD score ≤4, ≥2-point reduction from baseline, and no SES-CD sub-score >1 in any individual component), clinical remission (CDAI score <150) and endoscopic response, and deep remission (clinical remission and endoscopic remission). Values immediately above the 95% CI bars indicate the percentage of participants attaining the endpoint. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease.

the guselkumab 100 mg group, and 35 (63%) of 56 participants in the ustekinumab group. In GALAXI-3, this outcome was reported in 34 (67%) of 51 in the 200 mg guselkumab group, 39 (71%) of 55 participants in the guselkumab 100 mg group, and 38 (72%) of 53 in the ustekinumab group.

Prespecified, multiplicity-controlled analyses of the pooled GALAXI-2 and GALAXI-3 dataset showed that both guselkumab regimens were statistically superior (p<0·05) to ustekinumab at week 48 for endoscopic response; endoscopic remission; the composite of clinical remission and endoscopic response; and deep remission, which is the composite of clinical remission and endoscopic remission (figure 4; appendix pp 42–46). For attainment of clinical remission at week 48 in the pooled GALAXI-2 and GALAXI-3 dataset, guselkumab did not significantly differ from ustekinumab (63% [95% CI 57 to 68]) in the 200 mg guselkumab group (70% [65 to 75]; adjusted treatment difference 7% [0 to 15]) or the guselkumab 100 mg group (65% [60 to 71]; adjusted treatment difference 3% [–5 to 10]). Subsequent endpoints in the multiplicity-controlled testing procedure were not formally tested. Rate differences in the pooled GALAXI-2 and GALAXI-3 dataset by key baseline characteristics for

endoscopic response at week 48 and clinical remission at week 48 (guselkumab *vs* ustekinumab), as well as rates of durable clinical remission and remission based on the two patient-reported outcome components of the CDAI (total number of liquid or very soft stools and abdominal pain or cramping [PRO-2 remission]) at week 48, are reported in the appendix (pp 33–37, 47).

Results from the prespecified subpopulation analyses of the pooled GALAXI-2 and GALAXI-3 dataset show the consistent efficacy of guselkumab at week 48 in participants with a history of inadequate response or intolerance to biological therapies, as well as in participants naive to biological therapy (appendix pp 42–46). In the subpopulation of participants with inadequate response or intolerance to biological therapy in the guselkumab 200 mg group, the adjusted treatment differences compared with ustekinumab for the attainment of pooled secondary endpoints at week 48 were 15% (95% CI 5 to 26) for endoscopic response, 8% (–1 to 18) for endoscopic remission, 15% (5 to 26) for clinical remission and endoscopic response, 7% (–2 to 16) for deep remission, and 12% (0 to 23) for clinical remission. For those with inadequate response or intolerance to biological therapy in the guselkumab 100 mg group, these treatment differences were 11% (95% CI 1 to 22) for endoscopic response, 8% (–2 to 17) for endoscopic remission, 11% (1 to 22) for clinical remission and endoscopic response, 8% (–1 to 18) for deep remission, and 8% (–3 to 19) for clinical remission.

Supplemental analyses of the long-term efficacy of guselkumab showed that clinical remission, endoscopic response, or both, at week 48 were observed in most participants with a response to 12 weeks of guselkumab induction therapy (appendix p 48). Guselkumab efficacy at week 48 was also observed with both maintenance doses in participants without a response to induction therapy at week 12.

The effects of the study interventions on faecal calprotectin and CRP are outlined in the appendix (pp 49–50). Among participants with elevated baseline concentrations of CRP (>3 mg/L) or faecal calprotectin (>250 µg/g), guselkumab therapy was associated with clinically meaningful reductions in both of these markers of disease activity until week 48.

In the pooled GALAXI-2 and GALAXI-3 dataset, hospitalisations, surgeries, or both related to Crohn's disease until week 48 were reported in 27 (9%) of 291 participants in the ustekinumab group, compared with 15 (5%) of 296 participants in the 200 mg guselkumab group (nominal p=0·047) and 17 (6%) of 286 participants in the guselkumab 100 mg group (nominal p=0·139). Safety outcomes were similar across both studies. Key safety findings from the induction period (until week 12) are reported in the appendix for each trial separately and for the pooled dataset (pp 51–52). In the all-treated analysis population, the proportions of participants reporting one or more adverse events during the induction period were similar between the combined guselkumab groups (280 [47%]) and the placebo group (74 [48%]; appendix p 51). The proportions of participants with serious adverse events, adverse events leading to discontinuation of study agent, and serious infections during induction were low (≤3%) in the combined guselkumab groups and similar to the placebo group in the pooled GALAXI-2 and GALAXI-3 dataset (appendix p 51).

The proportions of participants who reported one or more adverse events until week 48 were generally similar across all active treatment groups in the pooled GALAXI-2 and GALAXI-3 dataset, ranging from 225 (76%) in the guselkumab 100 mg group to 236 (79%) in the ustekinumab group; with corresponding incidence rates of 327·3–353·5 adverse events per 100 participant-years across all active treatment groups (table 5). In the placebo group, 82 (54%) participants reported one or more adverse events while receiving placebo (those occurring after crossover to ustekinumab rescue therapy were not counted), with an incidence rate of 499·7 adverse events per 100 participant-years. The follow-up time for participants who received placebo only accounted for less than half of the overall follow-up time by participant years (table 5). The number of serious adverse events or adverse events leading to discontinuation of study treatment was broadly similar across the treatment groups; however, the incidence rates for serious adverse events were lower in both guselkumab groups than in the ustekinumab group and the placebo group (table 5). For adverse events leading to treatment discontinuation, incidence rates were similar across the active treatment groups and lower than in the placebo group. Key safety findings are reported separately for each trial in the appendix (p 53).

The most common adverse events until week 48 (reported in >10% of participants in any treatment group) were worsening of Crohn's disease and COVID-19. No deaths were reported. Compared with participants in the guselkumab 200 mg group (three [1%]; 1·1 events per 100 participant-years) or the guselkumab 100 mg group (one [<1%]; 0·4 events per 100 participant-years), the incidence of serious infections was higher among participants who received placebo (six [4%]; 6·1 events per 100 participant-years) or ustekinumab (12 [4%]; 5·7 events per 100 participant-years). Serious infections in the guselkumab groups were anal abscess (one case in the guselkumab 100 mg group) and intestinal abscess, intestinal fistula infection, and acute sinusitis (one case each in the guselkumab 200 mg group). Hepatic disorder was reported in less than 5% of participants across treatment groups (table 5). Most hepatic events were non-serious, transient, and did not result in discontinuation of the study agent. One participant receiving 200 mg intravenous induction therapy with guselkumab (guselkumab 100 mg group, GALAXI-2) met the biochemical criteria for Hy's law

	Placebo only* (n=153)	Placebo group† (n=153)	Guselkumab 200 mg group (n=299)	Guselkumab 100 mg group (n=296)	Ustekinumab group‡ (n=300)
Mean duration of follow-up, weeks	21·8	44·4	46·7	46·2	45·5
Total follow-up, participant-years	64·0	130·2	267·3	261·8	261·4
Participants with ≥1 adverse event	82 (54%)	113 (74%)	233 (78%)	225 (76%)	236 (79%)
Incidence rate, events per 100 participant-years	499·7	362·4	353·5	327·3	340·5
Participants with ≥1 serious adverse event	16 (10%)	23 (15%)	21 (7%)	32 (11%)	35 (12%)
Incidence rate, events per 100 participant-years	32·8	23·8	9·7	14·9	18·4
Deaths	0	0	0	0	0
Participants with adverse events leading to discontinuation of study agent	13 (8%)	17 (11%)	19 (6%)	21 (7%)	22 (7%)
Incidence rate, events per 100 participant-years	20·3	13·1	7·5	8·4	8·8
Participants with ≥1 serious infection	2 (1%)	6 (4%)	3 (1%)	1 (<1%)	12 (4%)
Incidence rate, events per 100 participant-years	6·3	6·1	1·1	0·4	5·7
Participants with ≥1 adverse event related to hepatic disorder§	3 (2%)	6 (4%)	14 (5%)	12 (4%)	7 (2%)
Incidence rate, events per 100 participant-years	4·7	5·4	8·2	6·9	3·8
Common adverse events¶					
Worsening of Crohn's disease	20 (13%)	28 (18%)	26 (9%)	26 (9%)	25 (8%)
COVID-19	10 (7%)	22 (14%)	53 (18%)	45 (15%)	40 (13%)
Upper respiratory tract infection	6 (4%)	12 (8%)	25 (8%)	29 (10%)	23 (8%)
Abdominal pain	9 (6%)	10 (7%)	14 (5%)	20 (7%)	27 (9%)
Pyrexia	8 (5%)	12 (8%)	16 (5%)	19 (6%)	26 (9%)
Arthralgia	5 (3%)	10 (7%)	25 (8%)	23 (8%)	20 (7%)
Headache	7 (5%)	8 (5%)	24 (8%)	15 (5%)	19 (6%)
Nasopharyngitis	5 (3%)	8 (5%)	21 (7%)	12 (4%)	19 (6%)
Anaemia	8 (5%)	10 (7%)	15 (5%)	15 (5%)	17 (6%)
Adverse events of interest					
Active tuberculosis	0	0	0	1 (<1%)	0
Malignancies	0	0	1 (<1%)	0	0
Anaphylactic or serum sickness reactions	0	0	0	0	2 (1%)
Opportunistic infections	1 (1%)	1 (1%)	2 (1%)	1 (<1%)	0
Major adverse cardiovascular event‖	0	0	0	1 (<1%)	0
Venous thromboembolism**	0	0	0	0	1 (<1%)

Data are n (%), unless otherwise indicated. The all-treated analysis population included all randomly assigned and treated participants. Adverse events were coded with MedDRA (version 26.0), unless otherwise noted. *Events attributed to participants randomly allocated to placebo only; events occurring after receiving ustekinumab rescue therapy are not counted. †All events in the placebo group, including those in participants who received ustekinumab rescue therapy. ‡Includes participants randomly allocated to approximately 6 mg/kg intravenous ustekinumab then 90 mg subcutaneous ustekinumab every 8 weeks; excludes participants allocated to placebo who received rescue therapy with ustekinumab. §Defined as the narrow terms in the Standardised MedDRA Query of "Drug Related Hepatic Disorders—Comprehensive Search".[14] ¶Participants with events (by preferred term) with a frequency of ≥5% in any group. Participants are counted only once for any given event, regardless of the number of times they experienced the event. ‖Occurrences of major adverse cardiovascular events were identified by clinical review. **Terms for venous thromboembolism were based on customised MedDRA query.

Table 5: **Adverse events reported in the all-treated analysis population until week 48 in the pooled GALAXI-2 and GALAXI-3 dataset**

(alanine transaminase [ALT] or aspartate aminotransferase [AST] concentrations ≥3 times the upper limit of normal and total bilirubin ≥2 times the upper limit of normal within 5 days) at the week 12 visit, before receiving subcutaneous guselkumab. Study intervention was interrupted, AST values returned to the normal range, and the participant resumed guselkumab treatment. Further evaluation presented a diagnosis of Gilbert's disease. During the induction phase, only two participants in the guselkumab groups had an ALT value at least three times the upper limit of normal, similar to what was observed in the placebo group. Until week 48, the incidence rates of elevated ALT values were also low and similar across treatment groups (appendix pp 54–55). In most cases, the increase in transaminases was transient and did not lead to discontinuation of study treatment. Across both studies, few participants had an adverse event of interest—eg, tuberculosis, malignancy, anaphylactic or serum sickness reaction, opportunistic infection, major adverse cardiovascular event, or venous thromboembolism (table 5). Brief case narratives are provided in the appendix (p 56).

In total, 39 (0·8%) of 4957 subcutaneous injections of active study treatment in the guselkumab 200 mg group,

three (0·3%) of 1072 in the guselkumab 100 mg group, and one (0·1%) of 1719 in the ustekinumab group were associated with injection-site reactions (most commonly injection-site erythema). No reported reactions were serious or severe; one case of injection-site hypersensitivity in the guselkumab 200 mg group led to discontinuation of study treatment. Across all treatment groups in GALAXI-2 and GALAXI-3, a total of 17 616 subcutaneous injections of placebo were administered. Injection-site reactions occurred with 35 (0·2%) of these placebo injections (most commonly injection-site erythema); no serious events were reported.

Among participants with appropriate samples for detection of antibodies to guselkumab or ustekinumab, 15 (5%) of 297 participants in the guselkumab 200 mg group, 15 (5%) of 295 in the guselkumab 100 mg group, and 12 (4%) of 298 in the ustekinumab group had antibodies to active treatment until week 48. Among participants with antibodies to active treatment, neutralising antibodies were present in no participants in the guselkumab 200 mg group, two (13%) participants in the guselkumab 100 mg group, and seven (58%) participants in the ustekinumab group. Efficacy outcomes were observed in a similar proportion of participants between those who tested positive and those who tested negative for antibodies to guselkumab. Due to the small number of participants testing positive for antibodies to guselkumab, the relationship between these antibodies and efficacy or safety could not be assessed.

Discussion

In GALAXI-2 and GALAXI-3, both guselkumab dose regimens (each including intravenous induction and subcutaneous maintenance) were superior to placebo for short-term (week 12) and long-term (week 48) endpoints, including the stringent, long-term, coprimary composite endpoints. Both guselkumab dose regimens were also superior to ustekinumab at week 48 in prespecified, multiplicity-controlled, treat-through analyses of the pooled GALAXI-2 and GALAXI-3 dataset for all endoscopic endpoints, including endoscopic response, endoscopic remission, and the more stringent composite endpoints containing both clinical and endoscopic components—namely, clinical remission and endoscopic response, as well as deep remission (ie, clinical remission and endoscopic remission).

The featured role of endoscopic outcomes in these studies highlights the importance of these objective endpoints as treatment targets that drive clinical decision making.[3–5,15] Furthermore, composite endpoints including symptom and objective improvement for a single participant are more clinically meaningful than separate symptom or endoscopic endpoints.

The results in the subpopulations of participants with an inadequate response or intolerance to biological therapy or who were naive to biological therapy were consistent with those in the overall population, in which both guselkumab dosing regimens showed efficacy at week 48 and provided greater improvements than did ustekinumab. The observed favourable outcomes with guselkumab in the refractory subpopulation of participants with inadequate response or intolerance to biological therapy have particular clinical importance: previous exposure to biological therapies is associated with reduced efficacy rates in randomised clinical trials.[16]

Both guselkumab regimens had the same induction dose of 200 mg intravenous guselkumab every 4 weeks. This dose was selected based on data from the phase 2b induction dose-ranging study, GALAXI-1,[10] in which clinical and endoscopic results at week 12 were similar across intravenous doses of 200, 600, or 1200 mg every 4 weeks. The maintenance doses of 100 mg subcutaneous guselkumab every 8 weeks and 200 mg subcutaneous guselkumab every 4 weeks were also administered in GALAXI-1;[11] however, GALAXI-1 was not designed or powered to evaluate the efficacy and safety of these maintenance doses. Pharmacokinetic data from GALAXI-1 showed that the maintenance dose of 200 mg subcutaneous guselkumab every 4 weeks resulted in approximately seven-fold greater median steady-state serum trough concentrations of guselkumab than did 100 mg subcutaneous guselkumab every 8 weeks (appendix pp 57–58). In the GALAXI-2 and GALAXI-3 trials, which were powered to evaluate the efficacy of induction and maintenance therapy with guselkumab, we found both dose regimens to be efficacious and no clinically meaningful differences between the maintenance doses of 100 mg every 8 weeks or 200 mg every 4 weeks, despite the substantial difference in steady-state serum trough concentrations of guselkumab.

GALAXI is the first registrational clinical development programme with a double-blind design in which a treatment for Crohn's disease showed head-to-head superiority to ustekinumab, a standard-of-care therapy, for endoscopic outcomes in a study population that included participants with inadequate response or intolerance to biological therapy and those naive to biological therapy. Two other head-to-head trials comparing inhibitors of the p-19 subunit of IL-23 with ustekinumab have been conducted in participants with Crohn's disease: the VIVID-1[17] and SEQUENCE trials.[18] The VIVID-1 study design was similar to that of the GALAXI studies in that it was a randomised, double-blind, triple-dummy, treat-through study that enrolled a mixed population of participants with inadequate response or intolerance to biological therapy and those naive to biological therapy. However, mirikizumab was not superior to ustekinumab for clinical nor endoscopic outcomes. Results of the open-label SEQUENCE trial found that risankizumab was non-inferior to ustekinumab for clinical remission at week 24 and superior for endoscopic remission at week 48 in participants with an inadequate response or intolerance

to anti-TNF agents. However, participants and investigators were aware of treatment assignments, while the assessors of endoscopic outcomes were masked.

Disease pathogenesis in Crohn's disease is primarily driven by IL-23.[19] Therefore, inhibition of IL-23 alone with a p-19 subunit inhibitor might be more effective at modulating inflammation than inhibition of both IL-12 and IL-23 with the p-40 subunit inhibitor, ustekinumab. Additionally, in-vitro studies have shown that both guselkumab and risankizumab have higher binding affinity for IL-23 than does ustekinumab.[20] Guselkumab differs from risankizumab and mirikizumab in that it binds to CD64 receptors on the myeloid cells in the gastrointestinal tract that produce IL-23. In-vitro studies showed that guselkumab binding to CD64 might result in greater functional potency at neutralising IL-23 than risankizumab[8] and mirikizumab.[21] The clinical relevance of these findings is being investigated; however, currently there are no head-to-head trials comparing the efficacy of inhibitors of the p-19 subunit of IL-23.

Guselkumab treatment in participants with moderately to severely active Crohn's disease was also evaluated in the GRAVITI study,[22] which had a fully subcutaneous induction and maintenance treatment regimen. Clinical and endoscopic outcomes reported with subcutaneous guselkumab induction in the GRAVITI study were similar to those in the phase 3 GALAXI studies following intravenous guselkumab induction. Although cross-trial comparisons must be made with caution, GALAXI and GRAVITI had similar study designs (eg, double-blind and treat-through), entry criteria, and study populations. Additionally, enrolled participants were from some of the same study sites during an overlapping time period. The data from these studies complement each other and show that both intravenous and subcutaneous induction with guselkumab are efficacious therapeutic options in patients with Crohn's disease. Intravenous and subcutaneous guselkumab induction were also similarly efficacious in participants with ulcerative colitis (the QUASAR[23] and ASTRO[24] studies).

Overall, guselkumab was well tolerated in participants with Crohn's disease, showing a safety profile consistent with the approved uses of guselkumab in ulcerative colitis, plaque psoriasis, and psoriatic arthritis.[9] The incidence of adverse events with guselkumab during induction was low and similar to placebo; guselkumab also had a similar safety profile to placebo and ustekinumab over approximately 1 year. Adverse events were not more frequent or severe in participants receiving the higher dose (200 mg) of guselkumab maintenance therapy.

The strengths of the GALAXI programme include the use of a treat-through design, in which randomisation occurred once. This design enabled the rigorous double-blinded evaluation of guselkumab efficacy in induction and maintenance regimens and head-to-head comparisons with ustekinumab in a manner that more closely reflects clinical practice. By contrast, trials with randomised withdrawal designs only randomly assign participants with a full induction response to maintenance therapy, which precludes evaluation in participants without a timely or complete induction response. The ability to assess outcomes in participants who might have a delayed response to induction therapy is clinically relevant. In both GALAXI-2 and GALAXI-3, more than half of the participants who had not shown response to guselkumab at week 12 reached clinical remission by week 48, with approximately 42% of this patient group showing endoscopic response. An additional strength of the GALAXI programme was the use of identical designs for GALAXI-2 and GALAXI-3, independent phase 3 trials that yielded strikingly consistent findings. Furthermore, composite endpoints were evaluated at the participant level, further increasing the robustness of these results.

As with all studies, the GALAXI studies had limitations. Adults with moderately to severely active Crohn's disease were eligible, so the results might not be generalisable to children, adolescents, or patients with mild forms of the disease. Because of the active comparison with ustekinumab, the study did not enrol participants with previous inadequate response or intolerance to ustekinumab. Therefore, the efficacy of guselkumab in this subpopulation could not be evaluated.

In conclusion, induction with intravenous guselkumab followed by maintenance with subcutaneous guselkumab was efficacious in participants with moderately to severely active Crohn's disease compared with placebo. Additionally, guselkumab showed superiority to ustekinumab at week 48 for endoscopic outcomes, which are associated with improved disease control in the long term. The safety profile of guselkumab was favourable and consistent with the well established profile of its approved indications.

Contributors

RP, BGF, AA, DTR, WR, JP, SD, TH, NAT, AS, MLV, JY, CH, MEF, KYYW, ZY, JJ, JMA, GRD'H, and BES contributed to the study design. MLV, CH, JY, NAT, LS, RVR, MEF, KYYW, ZY, and JJ assessed and verified the data. MEF, KYYW, ZY, and JJ conducted the statistical analysis. All authors participated in data acquisition and had full access to the study data. All authors were involved in interpretation of the data and preparation and critical review of the manuscript and approved the final version of the manuscript before submission. All authors had final responsibility for the decision to submit for publication.

Declaration of interests

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For **Johnson & Johnson Innovative Medicine** see https://innovativemedicine.jnj.com/our-innovation/clinical-trials/transparency

For **The Yale Open Data Access Project** see https://yoda.yale.edu

Data sharing

The data sharing policy of Johnson & Johnson is available at Johnson & Johnson Innovative Medicine. As noted on this site, requests for access to the study data can be submitted through The Yale Open Data Access Project.

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