Efficacy and safety of subcutaneous guselkumab induction therapy in participants with moderately to severely active ulcerative colitis (ASTRO): a double-blind, treat-through, randomised, placebo-controlled, phase 3 trial

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Summary

Background Approved IL-23p19 subunit inhibitors, including guselkumab, require intravenous induction dosing in patients with ulcerative colitis. We aimed to evaluate the efficacy and safety of subcutaneous guselkumab induction in adults with moderately to severely active ulcerative colitis.

Methods The ASTRO double-blind, treat-through, randomised, placebo-controlled, phase 3 trial enrolled adults (≥18 years) at 153 sites (community centres or hospitals) in 25 countries with moderately to severely active ulcerative colitis (modified Mayo score 5–9 with a Mayo endoscopic subscore [MES] ≥2 and a Mayo rectal bleeding subscore [RBS] ≥1) and current or history of inadequate response or intolerance to corticosteroids, azathioprine, 6-mercaptopurine, biologics, JAK inhibitors, or sphingosine 1-phosphate receptor (S1P) inhibitors or a history of corticosteroid dependence. By permuted blocks and stratified by inadequate response or intolerance to biologics, JAK inhibitors, or S1P inhibitors (yes/no) and baseline MES (2 or 3), eligible participants were randomly assigned (1:1:1) to receive either subcutaneous guselkumab 400 mg at weeks 0, 4, and 8 followed by 100 mg every 8 weeks (400/100 mg group), subcutaneous guselkumab 400 mg at weeks 0, 4, and 8 followed by 200 mg every 4 weeks (400/200 mg group), or matched subcutaneous placebo. Investigators, study-site personnel, and participants were masked to treatment assignment. Participants who met rescue criteria at week 16 received subcutaneous guselkumab 400 mg at weeks 16, 20, and 24 followed by 100 mg every 8 weeks (placebo group) or continued their assigned guselkumab treatment (sham rescue). The primary outcome of clinical remission at week 12 (defined as Mayo stool frequency subscore of 0 or 1 and not increased from baseline, Mayo RBS of 0, and MES of 0, or 1 with no friability) was assessed among all participants who were randomly assigned and received at least one dose of study drug according to the treatment group to which they were assigned. Safety was assessed until week 24 among all participants who were randomly assigned and received at least one dose of study drug according to the treatment they received. This trial is registered with ClinicalTrials.gov, NCT05528510, and is ongoing.

Findings Between Sept 13, 2022, and April 2, 2024, 651 participants were screened for eligibility and 418 participants were randomly assigned to the guselkumab 400/100 mg group (n=139), the guselkumab 400/200 mg group (n=140), and the placebo group (n=139). Mean age was 41·7 years (SD 14·2), 256 (61%) of 418 participants were male, and 162 (39%) were female. Mean ulcerative colitis duration was 7·6 years (SD 6·7) and mean modified Mayo score was 6·7 (1·2). A significantly greater proportion of participants receiving guselkumab 400 mg induction versus placebo had clinical remission at week 12 (77 [28%] of 279 *vs* nine [6%] of 139; adjusted treatment difference 21 percentage points, 95% CI 14–28; p<0·0001). At week 24, 49 (35%) participants in the guselkumab 400/100 mg group, 51 (36%) in the guselkumab 400/200 mg group, and 13 (9%) in the placebo group were in clinical remission (the difference between both guselkumab groups and placebo was statistically significant). The frequencies of adverse events in the guselkumab groups (74 [53%] of 139 for 400/100 mg and 85 [61%] of 140 for 400/200 mg) were similar to that in the placebo group (91 [65%] of 139). There were no treatment-related deaths, and no new safety concerns were identified. The most frequently reported adverse events were worsening of ulcerative colitis (14 [10%] in the 400/100 mg group, nine [6%] in the 400/200 mg group, and 29 [21%] in the placebo group), arthralgia (11 [8%], seven [5%], and three [2%]), and upper respiratory tract infection (ten [7%], five [4%], and nine [6%]). Serious adverse events occurred in five (4%) participants in the 400/100 mg group, six (4%) in the 400/200 mg group, and 17 (12%) in the placebo group.

Interpretation Subcutaneous guselkumab induction and maintenance was safe and efficacious for 24 weeks in participants with moderately to severely active ulcerative colitis, establishing a fully subcutaneous guselkumab regimen as a treatment option in this patient population.

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Introduction

A variety of biologics and small-molecule drugs are available for the treatment of moderately to severely active ulcerative colitis; however, there continues to be an unmet need for safe and effective therapies with convenient dosing options for both induction and maintenance.[1] Interleukin (IL)-23 inhibitors approved for ulcerative colitis treatment, including guselkumab, mirikizumab, and risankizumab, require induction treatment administered intravenously followed by maintenance treatment administered subcutaneously.[2–5]

Guselkumab is a selective, dual-acting IL-23p19 subunit inhibitor that potently blocks IL-23 and binds to CD64, a receptor on immune cells that produce IL-23.[6] In the QUASAR programme, participants with moderately to severely active ulcerative colitis who received intravenous guselkumab induction (three doses of 200 mg or 400 mg at induction weeks 0, 4, and 8) followed by subcutaneous guselkumab maintenance (100 mg every 8 weeks or 200 mg every 4 weeks) had significant improvements across symptomatic, endoscopic, and histological outcomes at induction week 12 and maintenance week 44 compared with those assigned to placebo.[7,8] Guselkumab was approved for intravenous induction and subcutaneous maintenance for ulcerative colitis by the US Food and Drug Administration in September, 2024, and by the European Medicines Agency in April, 2025.[2,3] Both intravenous and subcutaneous guselkumab induction were approved for Crohn's disease by the US Food and Drug Administration in March, 2025, and by the European Medicines Agency in May, 2025.[2,3,9–11]

See Online for appendix 1

Flexibility in the route of administration of induction therapy (intravenous or subcutaneous) is an important factor in treatment decisions by patients and health-care providers.[12–16] Intravenous infusions are more expensive and time-consuming than subcutaneous injections, because they are primarily administered in infusion centres.[13,17–20] Including travel and infusion time, infusions can take several hours and often require that patients take a day off from work and other activities, substantially adding to the burden of disease.[18] A fully subcutaneous treatment regimen for ulcerative colitis could optimise resources, lower disease burden, and provide greater flexibility and ease of administration in a patient's preferred setting.[21]

Therefore, we aimed to evaluate the efficacy and safety of guselkumab using fully subcutaneous induction and maintenance treatment regimens in participants with moderately to severely active ulcerative colitis.

Methods

Study design and participants

The ASTRO double-blind, treat-through, parallel-group, randomised, placebo-controlled, phase 3 trial was done at 153 sites (community or hospital) in 25 countries (appendix 1 pp 2–8). Eligible participants were aged 18 years or older with moderately to severely active ulcerative colitis for at least 12 weeks before screening, confirmed by histology and either radiology or endoscopy. Inclusion criteria included a modified Mayo (mMayo) score from 5 to 9, with a Mayo endoscopic subscore (MES) of at least 2 (based on endoscopy at screening) and a Mayo rectal bleeding subscore (RBS) of at least 1. Current or history of inadequate response or intolerance to corticosteroids, azathioprine, or 6-mercaptopurine or to biologics, JAK inhibitors, or sphingosine 1-phosphate receptor (S1P) inhibitors (ozanimod) or a history of corticosteroid dependence was also required. Exclusion criteria included previous exposure to an IL-12 or IL-23 inhibitor and use of anti-TNF therapy within 2 months of the first dose of study drug, vedolizumab within 3 months, JAK inhibitors within

Research in context

Evidence before this study

We searched PubMed using the search terms "ulcerative colitis" or "Crohn's disease" and "interleukin (IL)-23p19" for articles published between database inception and May 21, 2025. Our search yielded 118 articles describing the role of IL-23 pathway inhibition in the treatment of patients with inflammatory bowel disease. Randomised, controlled studies of IL-23 inhibitors used intravenous induction. No studies evaluated administration of an IL-23 inhibitor using subcutaneous induction in participants with ulcerative colitis.

Added value of this study

The ASTRO study was the first to evaluate fully subcutaneous induction and maintenance treatment regimens of an IL-23 inhibitor in participants with ulcerative colitis.

Implications of all the available evidence

IL-23 has a crucial role in ulcerative colitis pathogenesis, and IL-23 inhibition is effective in treating inflammatory bowel disease, including ulcerative colitis. The efficacy of guselkumab subcutaneous induction in participants with moderately to severely active ulcerative colitis suggests that guselkumab is the first treatment for ulcerative colitis that both blocks the IL-23p19 subunit and allows for the option of a fully subcutaneous regimen, providing greater convenience and flexibility for patients with ulcerative colitis. Subcutaneous induction with guselkumab was approved for ulcerative colitis by the US Food and Drug Administration in September, 2025, and by the European Medicines Agency in October, 2025.

2 weeks or five half-lives, whichever was longer, S1P inhibitors or investigational therapy within 4 weeks or five half-lives, whichever was longer, natalizumab within 1 year, and drugs that deplete B or T cells (eg, rituximab or alemtuzumab) within 24 weeks.

Doses of oral 5-aminosalicylic acid compounds, azathioprine, 6-mercaptopurine, or methotrexate at baseline had to be stable and maintained up to week 48. Doses of oral corticosteroids (≤20 mg per day prednisone or equivalent, ≤9 mg per day budesonide, and ≤5 mg per day beclomethasone) had to be stable and maintained until week 12, when mandatory tapering (appendix 1 p 14) was initiated unless not medically feasible. For the full list of inclusion and exclusion criteria see appendix 1 (pp 8–14).

The ASTRO protocol was approved by investigational review boards or ethics committees at each site, and is published as appendix 2. The central investigational review board was Advarra (approval number Pro00064182). All participants provided written informed consent. ASTRO was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice. This trial is registered with ClinicalTrials.gov, NCT05528510, and is ongoing.

Randomisation and masking

A computer-generated randomisation schedule was prepared using an interactive web response system. Investigators enrolled participants, and the interactive web response system was used to randomly assign participants (1:1:1) to receive either subcutaneous guselkumab 400 mg at weeks 0, 4, and 8 then 100 mg every 8 weeks (400/100 mg group), subcutaneous guselkumab 400 mg at weeks 0, 4, and 8 then 200 mg every 4 weeks (400/200 mg group), or matched subcutaneous placebo (placebo group). Randomisation was balanced by permuted blocks (block size 6) and stratified by inadequate response or intolerance to biologics, JAK inhibitors, or S1P inhibitors (inadequate response or intolerance to BIO/JAKi/S1Pi [BIO/JAKi/S1Pi-IR]; yes/no) and baseline MES (moderate [2] or severe [3]).

To maintain blinding, all treatment groups received two identical subcutaneous injections at weeks 0, 4, and 8 (two active or two matching placebo; appendix 1 p 14). All treatment groups received one subcutaneous injection (active or matching placebo) at week 12 and up to three identical injections (active and/or matching placebo) per visit from week 16 onwards, depending upon if rescue criteria were met (appendix 2 p 51). Investigators, study-site personnel, and participants were masked to study drug until week 48. Select sponsor personnel were unmasked for week-24 analyses.

Procedures

ASTRO consisted of a screening phase (up to 8 weeks), a 24-week main treatment phase, and an extension phase (appendix 1 p 18). Participants in the 400/100 mg group received subcutaneous guselkumab 400 mg at weeks 0, 4, and 8, then 100 mg every 8 weeks (weeks 16 and 24 in the main treatment phase). Participants in the 400/200 mg group received subcutaneous guselkumab 400 mg at weeks 0, 4, and 8, then 200 mg every 4 weeks (weeks 12, 16, 20, and 24 in the main treatment phase). Participants in the placebo group received subcutaneous placebo (see appendix 2 pp 51 for full dosing schedules). Study drug was administered by masked study-site personnel following preparation by unmasked study-site personnel not otherwise involved in the study. The guselkumab dose regimen selected for induction was based on data from the QUASAR phase 2b dose-ranging study,[7] in which there was no clear dose–response or exposure–response between intravenous guselkumab 200 mg and 400 mg induction at induction weeks 0, 4, and 8. The 200 mg intravenous induction dose regimen was selected for the guselkumab QUASAR phase 3 studies.[8] Pharmacokinetic analyses demonstrated a bioavailability of approximately 50% with subcutaneous administration,[22] which determined the subcutaneous induction dose of 400 mg for ASTRO.

See Online for appendix 2

At week 16, all participants were assessed for rescue criteria: no decrease from baseline in MES at week 12 (central review) and a less than 2-point decrease from baseline in partial Mayo score at both weeks 12 and 16. The interactive web response system was used to manage rescue treatment assignments. Participants assigned to placebo who met rescue criteria received subcutaneous guselkumab 400 mg at weeks 16, 20, and 24, then 100 mg every 8 weeks (rescue treatment). Participants assigned to guselkumab who met rescue criteria continued their assigned treatment regimen and received blinded sham rescue with matching subcutaneous placebo injections at weeks 16, 20, and 24. All participants who did not meet rescue criteria continued their assigned treatment.

All participants who reached the week-24 visit and were benefiting from study treatment in the opinion of the investigator were eligible for the study extension with treatment up to week 248. Extension participants continued the same treatment regimen they were receiving before week 24. Study drug discontinuations were required or had to be strongly considered for several conditions, including safety or tolerability reasons, initiation of prohibited therapy, or worsening of ulcerative colitis (appendix 1 p 15).

Study visits were scheduled every 4 weeks up to week 24. Endoscopic assessments were performed at screening and weeks 12 and 24. Biopsy samples for histological assessments were taken at screening and week 12. The symptom-based and Physician Global Assessment components of the Mayo score (ie, the partial Mayo score) were collected at at all study visits (and daily up to week 4 for stool frequency subscore [SFS] and RBS). C-reactive protein (CRP) was assessed at week 0 then every 4 weeks, and faecal calprotectin was assessed at weeks 0, 4, 12,

and 24. Health-related quality of life was evaluated using the Inflammatory Bowel Disease Questionnaire (IBDQ) at weeks 0, 12, and 24 and the Ulcerative Colitis Patient-Reported Outcomes Signs and Symptoms (UC-PRO/SS) instrument at week 0 then every 4 weeks. At every study visit, physical examinations, vital sign assessments, and laboratory tests (eg, haematology and liver and kidney chemistry evaluations) were performed, and concomitant medications, adverse events, signs and symptoms of tuberculosis and other infections, and ulcerative colitis-related procedures and surgeries were reviewed. Adverse events were reported as they occurred, at any time during the study. Relationship of adverse events to study treatment was assessed by the investigator. Adverse event severity was assessed by the investigator using criteria defined in appendix 2 (p 111). Serum samples collected at weeks 0, 4, 8, 12, 20, and 24 were evaluated for anti-guselkumab antibodies using a validated, drug-tolerant assay (not commercially available) with an acid dissociation step to improve detection of antibodies to guselkumab in the presence of excess guselkumab.

Additional assessments, such as the 29-item Patient-Reported Outcomes Measurement Information System (known as PROMIS-29) and pharmacokinetic evaluations, were performed as per the study schedule of activities (appendix 2 pp 15–25); results associated with these assessments and other exploratory endpoints are not reported in this Article.

Outcomes

The primary endpoint was clinical remission at week 12 (Mayo SFS of 0 or 1 and not increased from baseline, RBS of 0, and MES of 0, or 1 with no friability; centrally assessed). Multiplicity-controlled secondary endpoints were symptomatic remission (SFS of 0 or 1 and not increased from baseline and RBS of 0), endoscopic improvement (MES of 0, or 1 with no friability), clinical response (mMayo score decrease from baseline by ≥30% and ≥2 points with either a ≥1-point decrease from baseline in RBS or RBS of 0 or 1), and histo-endoscopic mucosal improvement (combination of histological improvement [neutrophil infiltration in <5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue per Geboes grading system (ie, Geboes score ≤3·1)] and endoscopic improvement), all at week 12, and clinical remission, symptomatic remission, endoscopic improvement, and clinical response, all at week 24.

Prespecified exploratory efficacy endpoints included corticosteroid-free clinical remission at week 24 (among all participants and among participants receiving corticosteroids at baseline); endoscopic remission (normalisation; MES of 0) at weeks 12 and 24; histological improvement at week 12; histological remission at week 12 (absence of neutrophils from the mucosa [both lamina propria and epithelium], no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system [ie, Geboes score ≤2B·0]); histological remission (alternative definition) at week 12 (Nancy Histological Index ≤1); and histo-endoscopic mucosal remission (combined histological remission [primary definition] and endoscopic remission) at week 12.

Additional exploratory efficacy endpoints were symptomatic remission at weeks 2 and 4 then every 4 weeks; SFS and RBS change from baseline at weeks 2 and 4 then every 4 weeks; RBS of 0 at weeks 2 and 4 then every 4 weeks; SFS of 0 or 1 at weeks 2 and 4 then every 4 weeks; and change from baseline in absolute stool number at weeks 2 and 4 then every 4 weeks. Week 2 timepoint analyses were post-hoc. Another post-hoc outcome was symptomatic response (decrease from baseline in the symptomatic Mayo score [sum of SFS and RBS] by ≥30% and ≥1 point, with either a ≥1-point decrease from baseline in the RBS or an RBS of 0 or 1) at weeks 2 and 4 then every 4 weeks.

Additional prespecified exploratory endpoints included a CRP concentration of 3 mg/L or less (normalisation) at week 4 then every 4 weeks among participants with a baseline CRP concentration of more than 3 mg/L; a faecal calprotectin concentration of 150 mg/kg or less at weeks 4, 12, and 24 among participants with a baseline concentration of more than 150 mg/kg; IBDQ remission (total IBDQ score ≥170) at weeks 12 and 24; no bowel urgency (rounded weekly mean score of 0 for UC-PRO/SS question 7) at week 0 then every 4 weeks; no abdominal pain (rounded weekly mean score of 0 for UC-PRO/SS question 8) at week 0 then every 4 weeks; resolution of bowel urgency and resolution of abdominal pain (rounded weekly mean scores of 0 for questions 7 and 8, respectively, among participants with a respective baseline rounded weekly mean score ≥1) at week 4 then every 4 weeks; and incidence of anti-guselkumab antibodies, including neutralising antibodies, up to week 24.

Frequency and type of adverse events, including serious adverse events, up to week 24 were secondary outcomes; targeted adverse events, serious infections, adverse events leading to treatment discontinuation, and injection-site reactions were also evaluated up to week 24.

Statistical analysis

Sample size was determined assuming an 8% clinical remission rate at week 12 in the placebo group and 22% in the combined guselkumab group.[7,23] 399 participants (133 per treatment group) would provide a statistical power of more than 95% for the primary endpoint of clinical remission at week 12 at a significance level of 0·05 (two-sided) and at least 85% power for all secondary endpoints, also at a significance level of 0·05 (two-sided). Any withdrawals were accounted for by the treatment failure and missing data handling rules.

Efficacy and safety analyses comprised all randomly assigned participants who received at least one dose of

study drug (the "full analysis set" and "safety analysis set", respectively). The efficacy population was analysed according to the treatment group to which they were assigned, regardless of the treatment they received. The safety population was analysed according to the treatment they received.

Because the guselkumab groups received identical subcutaneous induction regimens up to week 12, these groups were combined for all efficacy analyses up to week 12. The primary and all secondary efficacy endpoints were analysed using a multiplicity-controlled testing procedure to control the type I error rate at the 0·05 (two-sided) significance level following a fixed-sequence hierarchical approach (appendix 1 p 19). The primary endpoint was tested at the full significance level and secondary endpoints were tested in a confirmatory manner if this test was significant.

Participants who met treatment failure criteria (appendix 1 p 16; except for treatment discontinuation due to COVID-19-related reasons [excluding SARS-CoV-2 infection] or regional crisis in Russia and Ukraine, in which some study sites were located, were considered not to have reached binary endpoints from that timepoint onwards or had baseline values assigned from that timepoint onwards (continuous endpoints). Observed data were used, if available, for participants who discontinued study drugs due to COVID-19-related reasons (excluding SARS-CoV-2 infection) or regional crisis from that timepoint onwards. Participants in any treatment group who met rescue criteria were considered non-responders for endpoints after week 16, enabling comparisons between guselkumab and placebo groups after placebo-treated participants received rescue treatment. Participants with missing binary endpoint values at the designated analysis timepoint, including missing endoscopy data, after accounting for treatment failure and rescue criteria handling rules, were also considered not to have met binary endpoints at that timepoint.

The proportions of participants reaching each endpoint were summarised by treatment group. Adjusted treatment differences and 95% CIs between the combined or individual subcutaneous guselkumab induction groups and the placebo group were based on the common risk difference using Mantel–Haenszel stratum weights and the Sato variance estimator. p values were based on a two-sided Mantel–Haenszel test stratified by BIO/JAKi/S1Pi-IR status (yes/no) and baseline MES (moderate [2] or severe [3]). The primary endpoint was also analysed by prespecified subgroups according to baseline demographics, ulcerative colitis disease characteristics, and ulcerative colitis-related medication history and concomitant medications, and the primary endpoint and secondary endpoints were also evaluated in the prespecified BIO/JAKi/S1Pi-naive and BIO/JAKi/S1Pi-IR subpopulations.

For continuous endpoints, after accounting for treatment failure and rescue criteria handling rules, a mixed-effects model for repeated measures was used to account for missing data under the assumption of missing at random. Missing data were accounted for through correlation of repeated measures in the model. Treatment differences between guselkumab groups and placebo groups were estimated by the difference in least-squares means, and p values were based on the mixed-effects model for repeated measures.

Because placebo-treated participants who met the prespecified criteria could be rescued with guselkumab treatment at week 16, the average duration of follow-up was expected to be shorter in the placebo group versus the guselkumab treatment groups; therefore, prespecified, follow-up, time-adjusted analyses (ie, number of events per 100 person-years) were performed for adverse events, serious adverse events, adverse events leading to treatment discontinuation, infections, and serious infections.

To identify any potential differences in efficacy between subcutaneous and intravenous guselkumab induction treatment, we conducted a prespecified inverse probability weighting analysis[24] comparing ASTRO induction efficacy data with QUASAR phase 3 induction study efficacy data.[8] These analyses adjusted for differences in the two study populations using weights calculated from a propensity score model that included variables associated with imbalances across studies, clinical remission in the placebo group, and guselkumab treatment effects (using a 0·10 two-sided significance level threshold; appendix 1 pp 16–17).

All analyses were conducted using SAS version 9.4. An independent data monitoring committee was not used for the ASTRO study because the safety profile for guselkumab was well established, data monitoring committees were being used in larger ongoing studies in similar populations, the study had a short duration, and regular medical review throughout the study was planned.

Role of the funding source

The study protocol and analysis plan were written by the sponsor, Johnson & Johnson, in collaboration with the steering committee. The sponsor and investigators jointly conducted the study and gathered data. Data were analysed by statisticians employed by the sponsor. All authors, including those employed by the sponsor, contributed to data interpretation. The first draft of the manuscript was written under the direction of the authors by medical writers funded by the sponsor. All authors, including those employed by the sponsor, reviewed and provided feedback on all subsequent versions of the manuscript and made the decision to submit the manuscript for publication.

Results

Between Sept 13, 2022, and April 2, 2024, 651 patients were screened for eligibility and 418 participants were

randomly assigned, received at least one dose of study drug, and included in the efficacy and safety analysis population: 139 in the placebo group, 139 in the guselkumab 400/100 mg group, and 140 in the guselkumab 400/200 mg group (figure 1). Mean participant age was 41·7 years (SD 14·2), and 256 (61%) of 418 participants were men and 162 (39%) were women (table 1). Mean ulcerative colitis duration was 7·6 years (SD 6·7), mean mMayo score was 6·7 (1·2), 234 (56%) of 418 participants had an MES of 3, 238 (57%) of 414 participants had CRP concentrations of more than 3 mg/L, and 368 (96%) of 385 participants had faecal calprotectin concentrations of more than 150 mg/kg. At baseline, 323 (77%) of 418 participants were receiving oral aminosalicylates, 137 (33%) oral corticosteroids, and 84 (20%) immunosuppressants. 168 (40%) of 418 participants had a history of BIO/JAKi/S1Pi-IR, and 163 (97%) of these 168 participants had an inadequate response or intolerance to at least one biologic. 243 (58%) of 418 participants were naive to BIO/JAKi/S1Pi therapy and seven (2%) had been exposed to BIO/JAKi/S1Pi therapy but were not BIO/JAKi/S1Pi-IR.

Seven (2%) of 418 participants discontinued study drug before week 12 (one [1%] of 139 in the guselkumab 400/100 mg group, three [2%] of 140 in the guselkumab 400/200 mg group, and three [2%] of 139 in the placebo

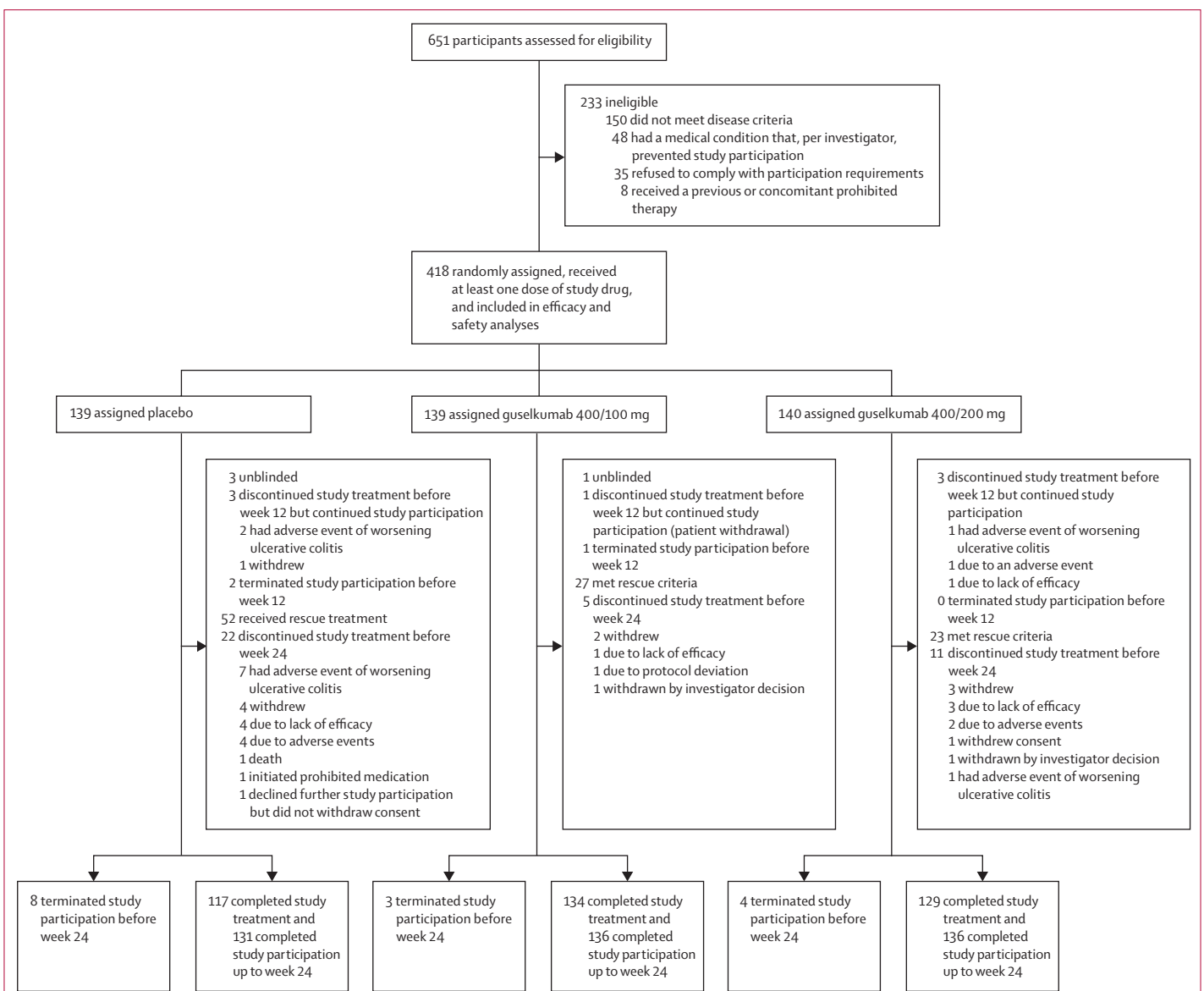

Figure 1: **Trial profile**
A potential participant could fail screening for more than one reason and could be counted more than once. All unblinding code breaks were initiated by the site investigator in the setting of worsening ulcerative colitis or to inform future treatment options. Week 24 numbers are inclusive of week 12 numbers.

group; figure 1). The primary reason across groups for treatment discontinuation before week 12 was an adverse event of worsening ulcerative colitis (three [1%]). Overall, by week 24, 38 (9%) of 418 participants had discontinued study drug (five [4%] of 139 in the 400/100 mg group, 11 [8%] of 140 in the 400/200 mg group, and 22 [16%] of 139 in the placebo group). The primary reasons across groups for treatment discontinuation up to week 24 were withdrawal by participant (nine [2%] of 418), an adverse event of worsening ulcerative colitis (eight [2%]), and lack of efficacy as determined by investigators (eight [2%]). The mean duration of follow-up was 24·0 weeks for the guselkumab 400/100 mg group, 24·2 weeks for the guselkumab 400/200 mg group, and 20·7 weeks for

	Subcutaneous placebo (n=139)	Subcutaneous guselkumab			Total (n=418)
		400/100 mg (n=139)	400/200 mg (n=140)	Combined (n=279)	
Mean age, years (SD)	39·5 (13·6)	42·1 (14·6)	43·6 (14·3)	42·9 (14·4)	41·7 (14·2)
Sex*					
Male	90 (65%)	79 (57%)	87 (62%)	166 (59%)	256 (61%)
Female	49 (35%)	60 (43%)	53 (38%)	113 (41%)	162 (39%)
Race					
White	94 (68%)	85 (61%)	91 (65%)	176 (63%)	270 (65%)
Asian	40 (29%)	41 (29%)	40 (29%)	81 (29%)	121 (29%)
Black or African American	1 (1%)	6 (4%)	6 (4%)	12 (4%)	13 (3%)
American Indian or Alaska Native	0	4 (3%)	0	4 (1%)	4 (1%)
Multiple (more than one race reported)	1 (1%)	1 (1%)	1 (1%)	2 (1%)	3 (1%)
Not reported	3 (2%)	2 (1%)	2 (1%)	4 (1%)	7 (2%)
Ethnicity					
Hispanic or Latino	23 (17%)	30 (22%)	26 (19%)	56 (20%)	79 (19%)
Not Hispanic or Latino	112 (81%)	102 (73%)	112 (80%)	214 (77%)	326 (78%)
Not reported	3 (2%)	5 (4%)	2 (1%)	7 (3%)	10 (2%)
Unknown	1 (1%)	2 (1%)	0	2 (1%)	3 (1%)
Weight, kg	71·5 (15·9)	71·0 (15·2)	71·7 (18·2)	71·4 (16·7)	71·4 (16·4)
Ulcerative colitis disease duration, years	6·6 (6·2)	8·4 (7·3)	7·7 (6·4)	8·0 (6·8)	7·6 (6·7)
Modified Mayo score (0–9)†	6·8 (1·1)	6·8 (1·2)	6·6 (1·2)	6·7 (1·2)	6·7 (1·2)
Modified Mayo score of 7–9 (severe)	87/138 (63%)	95/139 (68%)	77/140 (55%)	172/279 (62%)	259/417 (62%)
Mayo endoscopic subscore of 3 (severe)	78 (56%)	78 (56%)	78 (56%)	156 (56%)	234 (56%)
Extensive ulcerative colitis‡	73 (53%)	69 (50%)	82 (59%)	151 (54%)	224 (54%)
C-reactive protein, mg/L§	3·8 (1·2–10·9)	3·7 (1·3–7·2)	4·7 (1·7–9·1)	4·1 (1·5; 8·2)	4·1 (1·4–8·9)
C-reactive protein >3 mg/L	77/138 (56%)	75/136 (55%)	86/140 (61%)	161/276 (58%)	238/414 (57%)
Faecal calprotectin, mg/kg¶	1749·0 (617·0–3202·0)	1351·5 (609·0–2805·0)	1594·0 (838·0–3336·0)	1494·5 (678·0–2963·0)	1566·0 (641·0–2964·0)
Faecal calprotectin >150 mg/kg	124/131 (95%)	119/126 (94%)	125/128 (98%)	244/254 (96%)	368/385 (96%)
BIO/JAKi/S1Pi-naive	79 (57%)	81 (58%)	83 (59%)	164 (59%)	243 (58%)
BIO/JAKi/S1Pi-experienced without history of BIO/JAKi/S1Pi-IR	4 (3%)	1 (1%)	2 (1%)	3 (1%)	7 (2%)
BIO/JAKi/S1Pi-IR	56 (40%)	57 (41%)	55 (39%)	112 (40%)	168 (40%)
≥1 biologic	54/56 (96%)	56/57 (98%)	53/55 (96%)	109/112 (97%)	163/168 (97%)
≥1 JAKi/S1Pi	13/56 (23%)	9/57 (16%)	11/55 (20%)	20/112 (18%)	33/168 (20%)
≥1 biologic and ≥1 JAKi/S1Pi	11/56 (20%)	8/57 (14%)	9/55 (16%)	17/112 (15%)	28/168 (17%)
1 BIO/JAKi/S1Pi class	39/56 (70%)	40/57 (70%)	38/55 (69%)	78/112 (70%)	117/168 (70%)
2 BIO/JAKi/S1Pi classes	13/56 (23%)	10/57 (18%)	11/55 (20%)	21/112 (19%)	34/168 (20%)
3 BIO/JAKi/S1Pi classes	4/56 (7%)	7/57 (12%)	6/55 (11%)	13/112 (12%)	17/168 (10%)
≥2 BIO/JAKi/S1Pi classes	17/56 (30%)	17/57 (30%)	17/55 (31%)	34/112 (30%)	51/168 (30%)
≥1 anti-TNF (regardless of other BIO/JAKi/S1Pi)	39/56 (70%)	42/57 (74%)	46/55 (84%)	88/112 (79%)	127/168 (76%)
Vedolizumab (regardless of other BIO/JAKi/S1Pi)	25/56 (45%)	30/57 (53%)	19/55 (35%)	49/112 (44%)	74/168 (44%)
Ozanimod (regardless of other BIO/JAKi/S1Pi)	2/56 (4%)	0/57	3/55 (5%)	3/112 (3%)	5/168 (3%)
JAKi (regardless of other BIO/JAKi/S1Pi)	11/56 (20%)	9/57 (16%)	10/55 (18%)	19/112 (17%)	30/168 (18%)

(Table 1 continues on next page)

	Subcutaneous placebo (n=139)	Subcutaneous guselkumab			Total (n=418)
		400/100 mg (n=139)	400/200 mg (n=140)	Combined (n=279)	
(Continued from previous page)					
Participants receiving any of the following medications at baseline for ulcerative colitis	120 (86%)	122 (88%)	117 (84%)	239 (86%)	359 (86%)
Oral aminosalicylates	107 (77%)	110 (79%)	106 (76%)	216 (77%)	323 (77%)
Immunosuppressants	28 (20%)	26 (19%)	30 (21%)	56 (20%)	84 (20%)
6-mercaptopurine or azathioprine	26 (19%)	26 (19%)	30 (21%)	56 (20%)	82 (20%)
Methotrexate	2 (1%)	0	0	0	2 (<1%)
Oral corticosteroids	46 (33%)	50 (36%)	41 (29%)	91 (33%)	137 (33%)
Prednisone-equivalent dose, mg/day‖	20 (15–20)	20 (10–20)	15 (10–20)	20 (10–20)	20 (10–20)

Data are n (%), n/N (%), median (IQR), or mean (SD). "Unknown" is reported by the patient; "not reported" is not reported by the patient. BIO/JAKi/S1Pi=biologic, JAK inhibitor, or sphingosine 1-phosphate inhibitor. BIO/JAKi/S1Pi-IR=inadequate response or intolerance to BIO/JAKi/S1Pi. *Data on sex were self-reported by participants and collected on an electronic case report form with the options of male, female, unknown, or undifferentiated. †Placebo data for n=138; total n=417. ‡Defined as any ulcerative colitis not limited to the left side of the colon. §Placebo data for n=138; guselkumab 400/100 mg data for n=136; combined n=276; total N=414. ¶Placebo data for n=131; guselkumab 400/100 mg data for n=126; guselkumab 400/200 mg data for n=128; combined n=254; total n=385. ‖Among participants receiving corticosteroids other than budesonide and beclomethasone dipropionate at baseline.

Table 1: **Baseline demographics and disease characteristics (full analysis set)**

the placebo group. The shorter follow-up duration for the placebo group was due to the number of participants who met rescue criteria and crossed over to guselkumab.

At week 16, 52 (37%) of 139 participants in the placebo group met the rescue criteria and switched to guselkumab. 27 (19%) of 139 participants in the guselkumab 400/100 mg group and 23 (16%) of 140 in the guselkumab 400/200 mg group met rescue criteria and continued to receive their originally assigned guselkumab dose regimen (sham rescue). At week 24, median guselkumab concentrations were 8·7 µg/mL (IQR 5·1–12·0) in the 400/200 mg group and 1·5 µg/mL (0·8–2·7) in the 400/100 mg group.

A significantly greater proportion of participants in the combined guselkumab group versus the placebo group had clinical remission at week 12 (77 [28%] of 279 *vs* nine [6%] of 139; adjusted treatment difference 21 percentage points, 95% CI 14–28; p<0·0001; figure 2A). Additionally, significantly greater proportions of guselkumab-treated versus placebo-treated participants reached the week-12 secondary endpoints of symptomatic remission, endoscopic improvement, clinical response, and histo-endoscopic mucosal improvement (figure 2B–E). Similarly, significantly greater proportions of participants in each of the guselkumab groups versus the placebo group reached the week-24 secondary endpoints of clinical remission, symptomatic remission, endoscopic improvement, and clinical response (figure 3).

Consistent with the overall population, in BIO/JAKi/S1Pi-naive and BIO/JAKi/S1Pi-IR subpopulations, clinically meaningful differences were observed between guselkumab-treated and placebo-treated participants for the primary endpoint and all secondary endpoints (figures 2, 3). The proportion of participants who achieved clinical remission at week 12 (primary endpoint) was also greater among guselkumab-treated versus placebo-treated participants in most evaluated subgroups, including participants with a baseline MES of 3, and efficacy was generally consistent across bodyweight quartiles (appendix 1 p 20).

At week 24, 48 (35%) of 139 participants in the guselkumab 400/100 mg group (adjusted treatment difference *vs* placebo 25 percentage points, 95% CI 16–34; nominal p<0·0001) and 49 (35%) of 140 participants in the 400/200 mg group (26 percentage points, 16–35; nominal p<0·0001) had corticosteroid-free clinical remission compared with 13 (9%) of 139 participants in the placebo group. Results were consistent among participants receiving corticosteroids at baseline (400/100 mg group 16 [32%] of 50, adjusted treatment difference 24 percentage points [95% CI 9–39]; nominal p=0·0022; 400/200 mg group nine [22%] of 41, 16 percentage points [2–31]; nominal p=0·030; placebo group four [9%] of 46).

Greater proportions of guselkumab-treated versus placebo-treated participants had endoscopic remission at weeks 12 and 24 (figure 4A, B). Greater proportions of guselkumab-treated versus placebo-treated participants reached histological endpoints at week 12: histological improvement, Geboes-based histological remission, histo-endoscopic mucosal remission, and Nancy Histological Index-based histological remission (124 [44%] of 279 *vs* 28 [20%] of 139, adjusted treatment difference 24 percentage points [95% CI 16–33]; nominal p<0·0001; figure 4C; appendix 1 p 23).

Early, sustained achievement of symptomatic endpoints was observed with guselkumab treatment. As early as week 2 for symptomatic response and week 4 for symptomatic remission, clinically meaningful differences were observed in the proportions of participants

reaching these endpoints in the guselkumab group compared with the placebo group (appendix 1 pp 24–25). Early clinically meaningful differences in SFS of 0 or 1 (as early as week 2) and RBS of 0 (as early as week 4) were also observed for guselkumab versus placebo (appendix 1 p 26). Additionally, clinically meaningful differences in mean changes from baseline in SFS, RBS, and absolute stool number with guselkumab versus placebo were observed as early as week 2 and maintained until week 24 (appendix 1 pp 26–27).

Greater improvement in concentrations of inflammatory biomarkers was observed with guselkumab compared with placebo. Among participants with baseline CRP concentrations of more than 3 mg/L, greater proportions of guselkumab-treated versus placebo-treated participants reached normalisation (≤3 mg/L) as early as week 4 (the earliest assessment) and up until week 24 (appendix 1 p 28). Among participants with baseline faecal calprotectin concentrations of more than 150 mg/kg, clinically meaningful differences were observed in the proportions of guselkumab-treated versus placebo-treated participants reaching normalisation (≤150 mg/kg) as early as week 4 and until week 24 (appendix 1 p 28).

At both weeks 12 and 24, the proportions of participants who had IBDQ remission were greater with guselkumab versus placebo (appendix 1 p 29). Overall, clinically meaningful differences were observed in the proportions of guselkumab-treated versus placebo-treated participants with no bowel urgency and no abdominal pain as early as week 4 (the earliest assessment) and until week 24 (appendix 1 pp 30–31). Similarly, among participants who had baseline bowel urgency or abdominal pain (rounded weekly mean score ≥1), clinically meaningful differences were observed in the proportions of guselkumab-treated versus placebo-treated participants reaching resolution as early as week 8 for bowel urgency and week 4 for abdominal pain until week 24 (appendix 1 pp 30–31).

We compared subcutaneous guselkumab 400 mg induction efficacy data from the current ASTRO study with that of intravenous guselkumab 200 mg induction from the previously reported QUASAR study[8] using inverse probability weighting to adjust for study population differences. No substantial differences in efficacy between intravenous and subcutaneous guselkumab induction were observed, as measured by symptomatic, endoscopic, and histological outcomes (appendix 1 p 32). In the unweighted analyses of clinical remission at week 12 of guselkumab induction, there was no significant difference in guselkumab treatment effect in ASTRO compared with QUASAR (risk difference *vs* placebo 21 percentage points [95% CI 14 to 28] *vs* 15 percentage points [10 to 20]; difference in risk differences 6 percentage points [95% CI –2 to 15]; nominal p=0·13; appendix 1 p 32). In the adjusted analysis of clinical remission at week 12 of guselkumab induction, there was even less of a difference in treatment effects (risk difference vs placebo 18 percentage points [95% CI 10 to 25] *vs* 16 percentage points [10 to 21]; difference in risk differences 2 percentage points [95% CI –7 to 11]; nominal p=0·70). Similar results were observed for other endpoints evaluated (appendix 1 p 32).

Overall, by week 24, the proportions of participants reporting adverse events, serious adverse events, adverse events leading to treatment discontinuation, and infections were numerically lower in the guselkumab versus placebo groups (table 2). Across treatment groups, adverse events were reported in 74 (53%) of 139 participants in the guselkumab 400/100 mg group (342·3 events per 100 person-years), 85 (61%) of 140 participants in the guselkumab 400/200 mg group (333·2 events per 100 person-years), and 91 (65%) of 139 participants in the placebo group (372·3 events per 100 person-years). The most frequently reported adverse events across groups were worsening of ulcerative colitis (52 [12%] of 418), arthralgia (21 [5%]), and upper respiratory tract infection (24 [6%]).

By week 24, five (4%) of 139 participants in the guselkumab 400/100 mg group, six (4%) of 140 participants in the guselkumab 400/200 mg group, and 17 (12%) of 139 participants in the placebo group had a serious adverse event. Three (2%) participants in the guselkumab 400/100 mg group, four (3%) in the guselkumab 400/200 mg group, and 12 (9%) in the placebo group had an adverse event leading to treatment discontinuation. All adverse events reported by week 24 and risk differences between placebo and the combined guselkumab group for serious adverse events and targeted adverse events at week 12 are shown in the appendix 1 (pp 33–40).

Four (1%) guselkumab-treated participants had events categorised as serious infections, all of which did not interrupt study drug and resolved. In the 400/200 mg group, one participant developed pilonidal disease described as an abscess in a previously reported pilonidal cyst and two were diagnosed with appendicitis, and one participant in the 400/100 mg group developed gastroenteritis (table 2). All serious infections in the guselkumab groups were of moderate severity except for one case of appendicitis that was considered severe. One participant in the placebo group had a serious infection (pneumonia) of moderate severity; study drug was not interrupted and the infection resolved. In terms of targeted adverse events, in the guselkumab groups, one participant had an opportunistic infection (cytomegalovirus colitis), one had two malignancies (breast cancer and lymphoma), and one had a major adverse cardiovascular event (cerebral infarction). In the placebo group, there was one case of adenocarcinoma of the colon. No cases of active tuberculosis, venous thromboembolism, anaphylaxis, serum sickness, or clinically important hepatic disorders were reported in any group. One death (due to a road traffic accident) occurred in the

placebo group. Injection-site reactions were infrequently reported in all groups (table 2). The proportions of injections with injection-site reactions were also low in all groups (five [0·4%] of 1171 in the placebo group, 11 [0·8%] of 1420 in the guselkumab 400/100 mg group, and 22 [1·6%] of 1408 in the guselkumab 400/200 mg group).

Of the 279 participants who received guselkumab, by week 24, 24 (9%) were positive for anti-guselkumab antibodies. Of these 24 participants, three (13%) were

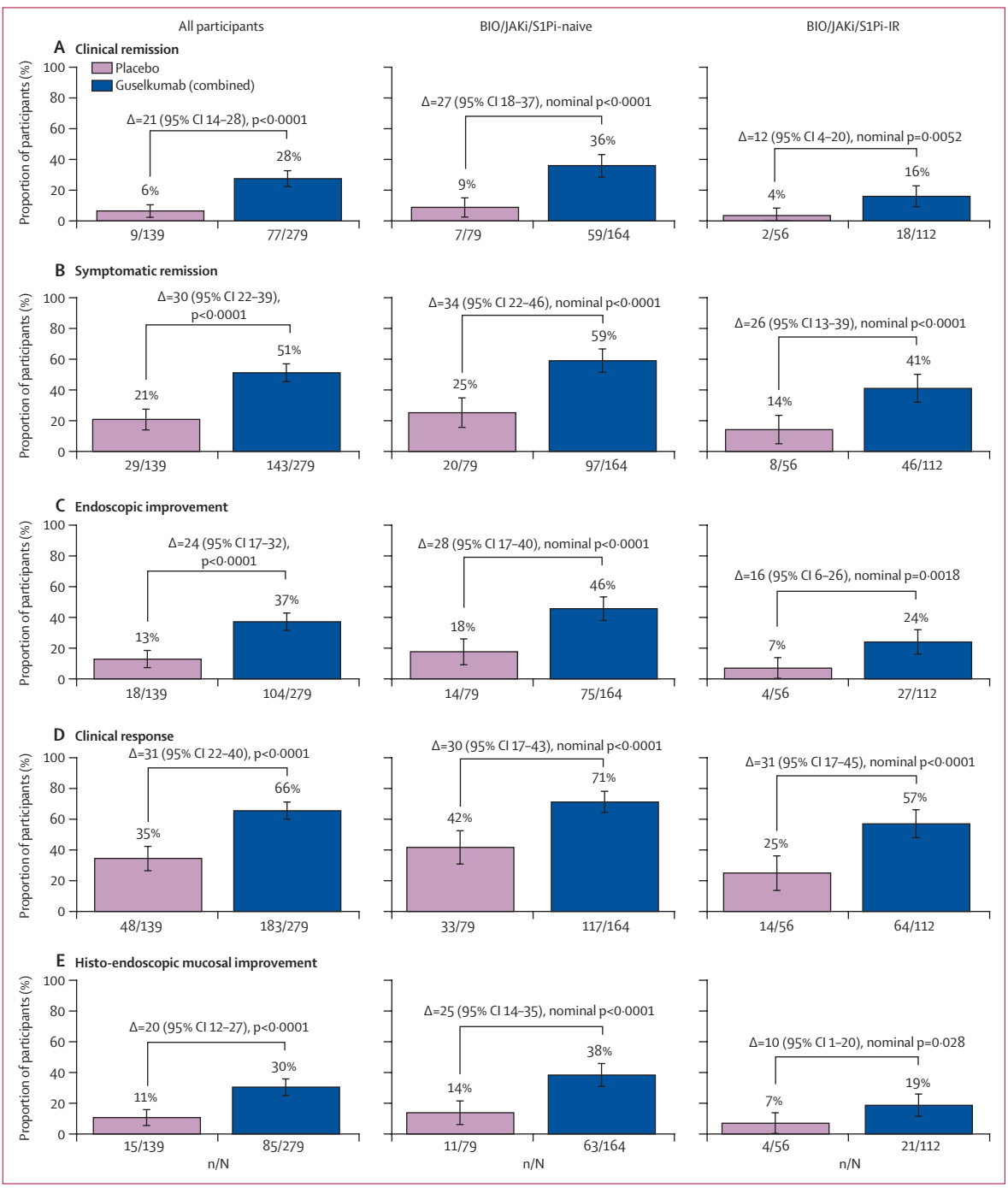

Figure 2: **Primary endpoint and 12-week secondary endpoints for the full analysis set and subgroups**
(A) Clinical remission. (B) Symptomatic remission. (C) Endoscopic improvement. (D) Clinical response. (E) Histo-endoscopic mucosal improvement. Δ=adjusted treatment difference. BIO/JAKi/S1Pi=biologic, JAK inhibitor, or sphingosine 1-phosphate receptor inhibitor. BIO/JAKi/S1Pi-IR=inadequate response or intolerance to BIO/JAKi/S1Pi.

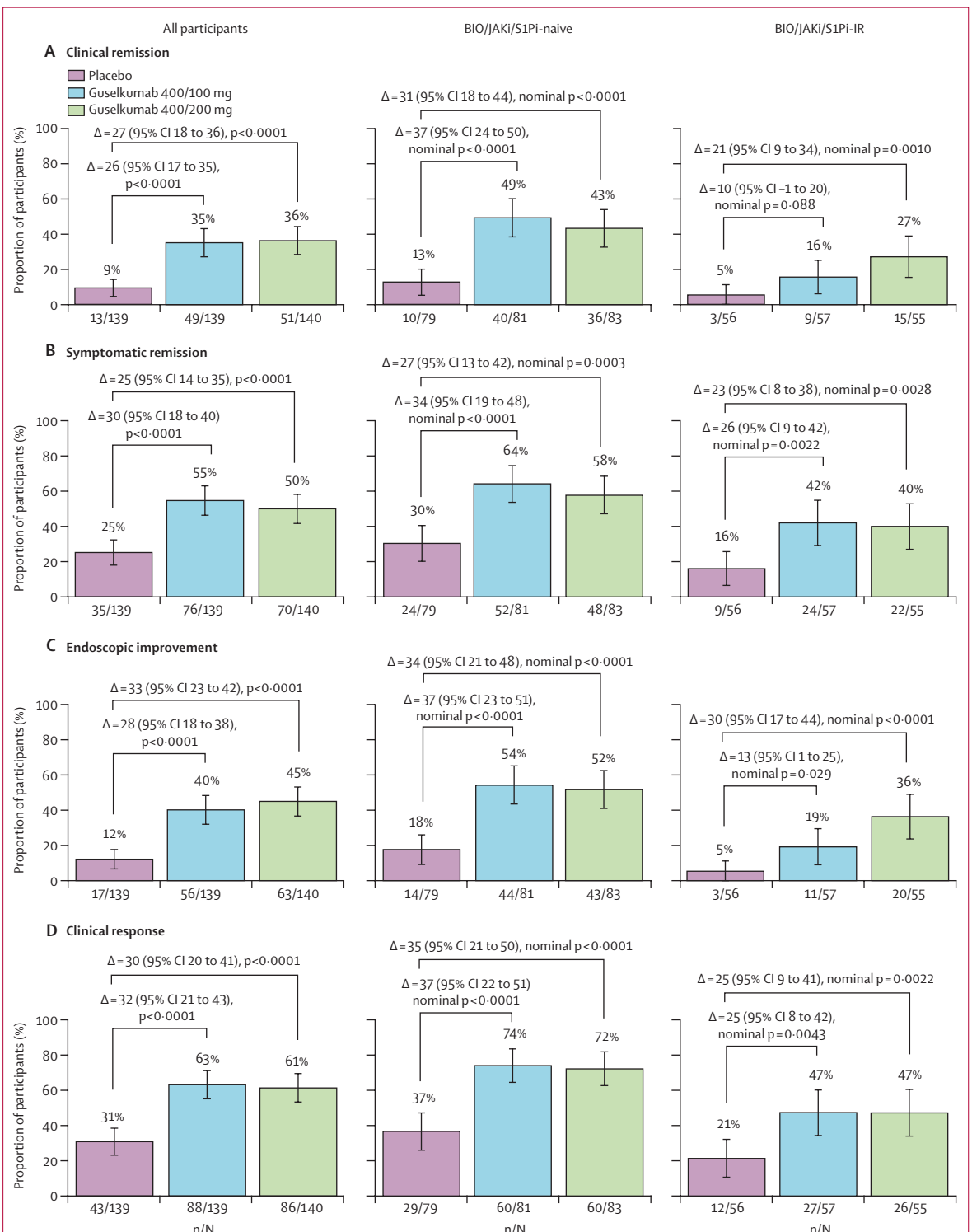

***Figure 3*: 24-week secondary endpoints for the full analysis set and subgroups**
(A) Clinical remission. (B) Symptomatic remission. (C) Endoscopic improvement. (D) Clinical response. Δ=adjusted treatment difference. BIO/JAKi/S1Pi=biologic, JAK inhibitor, or sphingosine 1-phosphate receptor inhibitor. BIO/JAKi/S1Pi-IR=inadequate response or intolerance to BIO/JAKi/S1Pi.

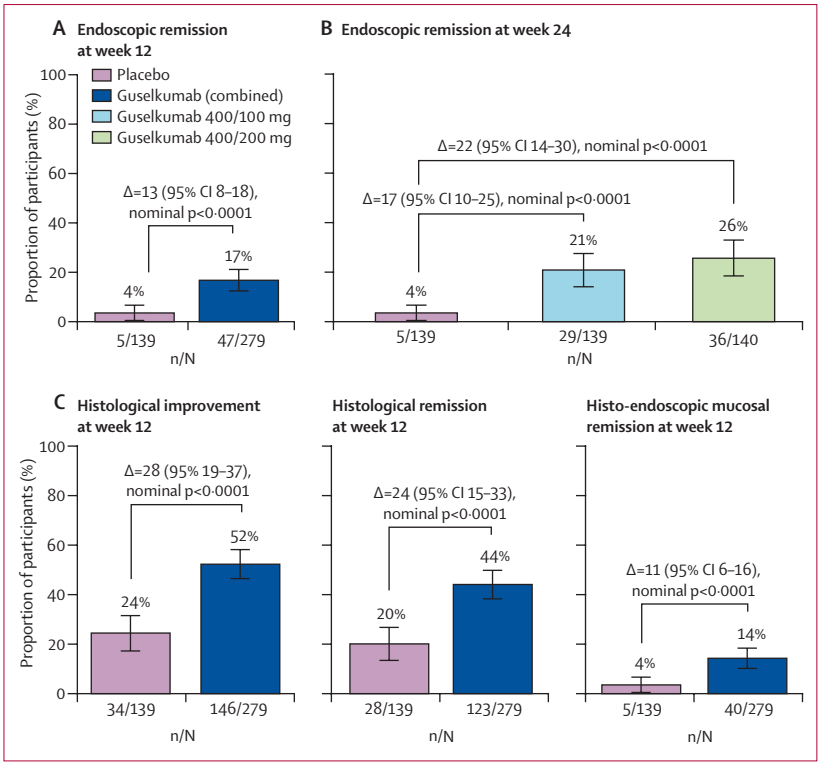

Figure 4: **Additional exploratory endoscopic and histological endpoints in the full analysis set**
(A) Endoscopic remission (normalisation) at week 12. (B) Endoscopic remission (normalisation) at week 24. (C) Histological endpoints. Histological remission was according to the Geboes grading system. Δ=adjusted treatment difference.

positive for neutralising antibodies (ie, 1% of guselkumab-treated participants). Most participants with anti-guselkumab antibodies had low peak titres (data not shown).

Discussion

ASTRO demonstrated the efficacy of subcutaneous guselkumab induction in participants with moderately to severely active ulcerative colitis. The primary endpoint of 12-week clinical remission and all multiplicity-controlled secondary endpoints, including symptomatic, endoscopic, and histological outcomes, were met. Among most clinically relevant subgroups evaluated, there was a consistent clinically meaningful treatment effect of guselkumab on 12-week clinical remission, including among participants with a history of BIO/JAKi/S1Pi-IR and those with severe endoscopic disease (baseline MES of 3).

Subcutaneous guselkumab induction resulted in rapid symptom improvement, with separation from placebo observed as early as week 2 for symptomatic response and week 4 for symptomatic remission. Early reductions in SFS and RBS were also observed in guselkumab-treated participants. Additionally, greater proportions of guselkumab-treated versus placebo-treated participants had no abdominal pain and no bowel urgency as early as week 4. Greater proportions of participants also had normalised inflammatory biomarkers with guselkumab subcutaneous induction relative to placebo at the earliest assessment (week 4).

To understand the relative efficacy of subcutaneous versus intravenous guselkumab induction, an inverse probability weighting analysis was performed. This analysis accounted for potential baseline differences between the ASTRO (subcutaneous induction) and QUASAR (intravenous induction)[8] study populations and showed no evidence of substantial differences in efficacy between subcutaneous and intravenous induction, as measured by symptomatic, endoscopic, and histological outcomes.

In ASTRO, subcutaneous induction with guselkumab was followed by subcutaneous maintenance with guselkumab 100 mg every 8 weeks or 200 mg every 4 weeks. These are the same maintenance regimens evaluated following guselkumab intravenous induction in participants with ulcerative colitis in the QUASAR maintenance study[8] and following intravenous or subcutaneous guselkumab induction in participants with Crohn's disease in the GALAXI[10,11] and GRAVITI[9] studies, respectively. In each of these previous studies, both guselkumab maintenance dose regimens were efficacious for around 1 year of follow-up. In ASTRO, these maintenance dose regimens were evaluated until week 24, and both were efficacious compared with placebo in the overall population. In the subgroup of participants with previous BIO/JAKi/S1Pi-IR, those who received subcutaneous guselkumab 200 mg every 4 weeks for maintenance appeared to have numerically greater rates of clinical remission and endoscopic improvement at week 24 than those who received 100 mg every 8 weeks. However, the number of participants in this subgroup was relatively small, and this finding was not observed in the corresponding subgroup in the larger QUASAR maintenance study.[8] The maintenance phase of ASTRO is ongoing and longer-term efficacy and safety data from the study will be reported in the future, which might further elucidate the clinical relevance of these findings. In a separate publication, we will report detailed ASTRO pharmacokinetic data. We will also compare subcutaneous induction pharmacokinetic data from ASTRO with intravenous induction pharmacokinetic data from QUASAR.

By week 24, the proportions of participants reporting at least one adverse event, serious adverse event, adverse event leading to treatment discontinuation, and infection were numerically lower in the guselkumab treatment groups compared with placebo. No new safety concerns were identified. Safety data were consistent with the well characterised safety profile of guselkumab in other approved indications,[2,3,25–27] and the most commonly reported adverse events in ASTRO are consistent with other IL-23 antagonists, including mirikizumab and risankizumab.[4,5]

	Subcutaneous placebo (n=139)*	Subcutaneous guselkumab		
		400/100 mg (n=139)	400/200 mg (n=140)	Combined (n=279)
Mean (SD) duration of follow-up, weeks	20·7 (4·4)	24·0 (1·8)	24·2 (1·8)	24·1 (1·8)
Deaths	1 (1%)†	0	0	0
Adverse events	91 (65%)	74 (53%)	85 (61%)	159 (57%)
Events per 100 person-years (95% CI)	372·3 (323·1–426·9)	342·3 (298·5–390·8)	333·2 (290·3–380·8)	337·7 (306·7–371·0)
Mild‡	49 (35%)	42 (30%)	48 (34%)	90 (32%)
Moderate‡	30 (22%)	27 (19%)	30 (21%)	57 (20%)
Severe‡	12 (9%)	5 (4%)	7 (5%)	12 (4%)
Treatment-related adverse events	17 (12%)	28 (20%)	18 (13%)	46 (16%)
Serious adverse events	17 (12%)	5 (4%)	6 (4%)	11 (4%)
Events per 100 person-years (95% CI)	38·1 (23·6–58·3)	7·8 (2·5–18·2)	10·8 (4·3–22·3)	9·3 (4·8–16·3)
Adverse events leading to treatment discontinuation	12 (9%)§	3 (2%)¶	4 (3%)	7 (3%)
Events per 100 person-years (95% CI)	21·8 (11·3–38·1)	4·7 (1·0–13·7)	6·2 (1·7–15·8)	5·4 (2·2–11·2)
Infections‖	36 (26%)	33 (24%)	32 (23%)	65 (23%)
Events per 100 person-years (95% CI)	85·4 (62·7–113·5)	75·0 (55·3–99·5)	74·1 (54·6–98·2)	74·5 (60·4–91·0)
Serious infections**	1 (1%)	1 (1%)	3 (2%)	4 (1%)
Events per 100 person-years (95% CI)	1·8 (0·1–10·1)	1·6 (0·0–8·7)	4·6 (1·0–13·5)	3·1 (0·9–8·0)
Most common adverse events with guselkumab (≥5%)				
Worsening of ulcerative colitis	29 (21%)	14 (10%)	9 (6%)	23 (8%)
Arthralgia	3 (2%)	11 (8%)	7 (5%)	18 (6%)
Upper respiratory tract infection	9 (6%)	10 (7%)	5 (4%)	15 (5%)
Targeted adverse events				
Active tuberculosis††	0	0	0	0
Malignancy††	1 (1%)‡‡	0	1 (1%)§§	1 (<1%)
Anaphylactic or serum-sickness reactions	0	0	0	0
Opportunistic infections	0	0	1 (1%)¶¶	1 (<1%)
Major adverse cardiovascular events	0	1 (1%)‖‖	0	1 (<1%)
Venous thromboembolism	0	0	0	0
Clinically important hepatic disorders	0	0	0	0
Injection-site reactions	4 (3%)	7 (5%)	9 (6%)	16 (6%)

Data are n (%), unless otherwise specified. All participants who had a targeted adverse event had risk factors for the event. Clinically important hepatic disorders were defined as hepatic disorder adverse events (standardised MedDRA query [SMQ] Drug-related Hepatic Disorders–Comprehensive Search narrow scope search) reported as serious adverse events or adverse events leading to discontinuation of study drug. Adverse events leading to treatment discontinuation, including adverse events that occurred until week 24, are reported; however, in five cases (one in the placebo group, three in the guselkumab 400/100 mg group, and one in the guselkumab 400/200 mg group) discontinuation occurred after week 24 and, therefore, these cases are not captured in figure 1. Participants are counted only once for any given event, regardless of the number of times they actually experienced the event. Adverse events are coded using MedDRA Version 26.1. MedDRA=Medical Dictionary for Regulatory Activities. *Includes all participants assigned placebo, excluding data after a participant was rescued with guselkumab. †Due to a road traffic accident. ‡The worst severity event experienced by the participant is used. §One case of high-grade dysplasia of the colon was deemed related to treatment. ¶One case of worsening of ulcerative colitis was deemed related to treatment. ‖Infections were defined as any adverse event that was coded to the MedDRA system organ class "Infections and infestations". **Serious infections were one case each of pilonidal disease (400/200 mg group) and gastroenteritis (400/100 mg group), both moderate severity, did not interrupt study drug, and resolved, and two cases of appendicitis (one moderate, one severe; both 400/200 mg group), neither of which interrupted study drug and both events resolved. The serious infection in the placebo group was pneumonia of moderate severity, did not interrupt study drug, and resolved. ††Adverse events of special interest. ‡‡Adenocarcinoma of the colon. §§Breast cancer and lymphoma. ¶¶Cytomegalovirus colitis. ‖‖Cerebral infarction.

Table 2: **Safety summary by week 24 (safety population)**

A patient's individual preference with respect to the route of drug administration is an important factor in treatment selection. Subcutaneous drug delivery might be preferred by some patients and health-care providers because it lowers disease burden by offering greater flexibility, requiring less time to administer, and minimising discomfort associated with intravenous infusion.[18,20] Subcutaneous administration can also reduce drug delivery-related health-care costs and resource use.[17] In the USA, a fully subcutaneous induction and maintenance regimen requires only one health insurance authorisation compared with the two for intravenous and subcutaneous strategies, which are more cumbersome on the health-care team to obtain and have been shown to result in delayed transitions to maintenance.[28] The availability of both subcutaneous and intravenous guselkumab induction for the treatment of ulcerative colitis will enable patients and health-care professionals to choose their preferred route for induction treatment.

A strength of ASTRO is the treat-through study design, which mimics real-world treatment and follows the full randomised population on active treatment. A limitation is that participants with an inadequate response to therapies targeting IL-12 or IL-23 (eg, ustekinumab, mirikizumab, and risankizumab) are not represented in the study population. This is because one of ASTRO's aims was to replicate the QUASAR population as much as possible and the QUASAR programme was initiated before certain ulcerative colitis therapies were approved. The lack of histological assessments at week 24 is also a study limitation.

Rescue treatment was provided to participants assigned to placebo in an attempt to mitigate the inherent risk of worsening ulcerative colitis when using a placebo control in studies in which participants have moderately to severely active disease. Participants in all treatment groups who met rescue criteria were considered not to have reached endpoints after week 16. Thus, the week-24 endpoints might not fully capture the efficacy of delayed responders to guselkumab. Results at week 48 in the rescue population will be reported in a future publication.

In conclusion, the results presented here show that subcutaneous guselkumab induction was highly efficacious compared with placebo, with no evidence of a substantial difference in efficacy compared with intravenous guselkumab induction, establishing a fully subcutaneous guselkumab induction and maintenance regimen as safe and efficacious in participants with moderately to severely active ulcerative colitis. Thus, guselkumab is the first treatment for ulcerative colitis that both potently blocks IL-23 and allows for the option of a simple, fully subcutaneous regimen, combining efficacy and safety with greater convenience and flexibility for patients with ulcerative colitis. Subcutaneous induction with guselkumab has now been approved for ulcerative colitis by the US Food and Drug Administration (September, 2025) and by the European Medicines Agency (October, 2025).

For the **Johnson & Johnson clinical trial data transparency webpage** see https://innovativemedicine.jnj.com/our-innovation/clinical-trials/transparency

For the **Yale Open Data Access Project site** see http://yoda.yale.edu

Contributors

ML, JRA, SD, MG, TB, MK, CH, SJ, HZ, TH, DTR, and LP-B contributed to study design. All authors participated in data acquisition. ML, SJ, LJ, and HZ assessed and verified the data. SJ, LJ, and HZ conducted the statistical analysis. All authors had full access to all the data in the study, were involved in interpretation of the data and preparation and critical review of the manuscript, and had final responsibility for the decision to submit for publication.

Declaration of interests

ML reports research support from Celltrion, Lilly, Pfizer, and Takeda, and consulting for AbbVie, Bristol Myers Squibb, Celltrion, Intercept, Johnson & Johnson, Lilly, Pfizer, Prometheus, Roivant, Sanofi, Spyre, Takeda, and Target RWE. JRA reports consulting fees from Celltrion, Ferring, Genentech, GlaxoSmithKline, Merck, Pfizer, Roivant, Seres Therapeutics, Shattuck Labs, TRXBio, Vedanta, and Xencor; consulting and speaker fees from AbbVie, Bristol Myers Squibb, and Johnson & Johnson; and is a steering committee member and investigator for Johnson & Johnson. SD reports consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Enthera, Ferring, Gilead, Hospira, Inotrem, Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity, Takeda, TiGenix, UCB, and Vifor; and lecture fees from AbbVie, Amgen, Ferring, Gilead, Johnson & Johnson, Mylan, Pfizer, and Takeda. MG, TB, YA, MK, CH, SJ, LJ, and HZ are employees of Johnson & Johnson. TZ reports research grants from AbbVie, Boston Scientific, Daiichi-Sankyo, EA Pharma, JIMRO, Mitsubishi Tanabe Pharma Corporation, Kissei Pharmaceutical, Kyorin Pharmaceutical, Mochida Pharmaceutical, Nippon Kayaku, Pfizer, Takeda Pharmaceutical, and Zeria Pharmaceutical, and consulting fees and/or honoraria from AbbVie, Bristol Myers Squibb, EA Pharma, Gilead Sciences, Johnson & Johnson Pharmaceutical, Kyorin Pharmaceutical, Lilly, Mitsubishi Tanabe Pharma, Nichi-Iko Pharmaceutical, Pfizer, Takeda Pharmaceutical, and Zeria Pharmaceutical. DTR reports consulting and/or speaker fees and/or advisory board participation for AbbVie, Abivax, Altrubio, Avalo Therapeutics, Bausch Health, Bristol-Myers Squibb, Buhlmann Diagnostics Corp, Celltrion, ClostraBio, Connect BioPharma, Douglas Pharmaceuticals, Foresee, Genentech (Roche), Image Analysis Group, InDex Pharmaceuticals, Iterative Health, Johnson & Johnson, Lilly, Odyssey Therapeutics, Pfizer, Sanofi, Takeda Pharmaceuticals, Throne, and Vedanta. LP-B reports grants or contracts from Celltrion, Fresenius Kabi, Medac, MSD, and Takeda; consulting for AbbVie, Abivax, Adacyte, Alfasigma, Alimentiv, Amgen, Applied Molecular Transport, Arena, Banook, Bristol Myers Squibb, Celltrion, Cytoki Pharma, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, GlaxoSmithKline, IAG Image Analysis, Index Pharmaceuticals, Inotrem, Iterative Health, Johnson & Johnson, LifeMine, Lilly, Medac, Mopac, Morphic, MSD, Nordic Pharma, Novartis, Oncodesign, Precision Medicine, ONO Pharma, OSE Immunotherapeutics, Par' Immune, Pfizer, Prometheus, Roche, Roivant, Samsung, Sandoz, Sanofi, Sorriso, Spyre, Takeda, Teva, ThirtyfiveBio, Tillots, Vectivbio, Vedanta, and Ventyx; lecture fees from AbbVie, Alfasigma, Amgen, Arena, Biogen, Celltrion, Ferring, Galapagos, Genentech, Gilead, Iterative Health, Johnson & Johnson, Lilly, Medac, MSD, Nordic Pharma, Pfizer, Sandoz, Takeda, and Tillots; and travel support from AbbVie, Alfasigma, Amgen, Arena, Celltrion, Ferring, Galapagos, Genentech, Gilead, Johnson & Johnson, Lilly, Medac, Morphic, MSD, Pfizer, Sandoz, and Takeda.

Data sharing

The data sharing policy of Johnson & Johnson is available on the Johnson & Johnson clinical trial data transparency webpage. As noted on this site, requests for access to the trial data can be submitted through the Yale Open Data Access Project site.

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