Guselkumab in patients with moderately to severely active ulcerative colitis (QUASAR): phase 3 double-blind, randomised, placebo-controlled induction and maintenance studies

David T Rubin, Jessica R Allegretti, Julián Panés, Nicole Shipitofsky, Shadi S Yarandi, Kuan-Hsiang Gary Huang, Matthew Germinaro, Rebbecca Wilson, Hongyan Zhang, Jewel Johanns, Brian G Feagan, Tadakazu Hisamatsu, Gary R Lichtenstein, Brian Bressler, Laurent Peyrin-Biroulet, Bruce E Sands, Axel Dignass, on behalf of the QUASAR Study Group

Summary

Background Interleukin-23 inhibition is effective in treating ulcerative colitis. Guselkumab is a dual-acting, human IgG1, interleukin-23p19 subunit inhibitor that potently neutralises interleukin-23 and can bind to CD64. We aimed to evaluate the efficacy and safety of guselkumab as induction and maintenance therapy in patients with ulcerative colitis.

Methods The primary populations of these two phase 3, randomised, double-blind, placebo-controlled studies (QUASAR phase 3 induction and maintenance) included randomised and treated adults with moderately to severely active ulcerative colitis (induction baseline modified Mayo score from 5 to 9) with inadequate response or intolerance to conventional or advanced ulcerative colitis therapy. Patients were randomly assigned (3:2) to receive guselkumab 200 mg given intravenously or placebo at weeks 0, 4, and 8 (phase 3 induction study). All patients were randomly assigned using web-based interactive response technology. Patients in clinical response 12 weeks after guselkumab induction given intravenously (from QUASAR phase 2b and phase 3 induction studies) were randomly assigned (1:1:1) at maintenance week 0 to guselkumab 200 mg given subcutaneously every 4 weeks or 100 mg every 8 weeks or placebo for 44 weeks (maintenance). Primary endpoints were clinical remission at induction week 12 and maintenance week 44. This study is registered with ClinicalTrials.gov, NCT04033445.

Findings The induction study primary population included 701 patients (guselkumab 200 mg given intravenously 60% [421 patients]; placebo 40% [280 patients]). The maintenance study primary population included 568 guselkumab induction responders randomly assigned to receive guselkumab 200 mg given subcutaneously every 4 weeks (190 [33%] patients) or 100 mg every 8 weeks (188 [33%] patients) or placebo (guselkumab withdrawal 190 [33%] patients). A significantly greater proportion of patients treated with guselkumab given intravenously had clinical remission at induction week 12 (23% [95 of 421 patients]) than did placebo-treated patients (8% [22 of 280 patients]; adjusted treatment difference 15%, 95% CI 10–20; p<0·0001). Clinical remission at maintenance week 44 was achieved by a significantly greater proportion of patients treated with guselkumab 200 mg given subcutaneously every 4 weeks (50% [95 of 190 patients]; adjusted treatment difference 30%, 95% CI 21–38; p<0·0001) and 100 mg every 8 weeks (45% [85 of 188 patients]; adjusted treatment difference 25%, 16–34; p<0·0001) than with placebo (19% [36 of 190 patients]). The overall safety profile was favourable and consistent with that of guselkumab in approved indications. In the induction study, adverse events were reported by 49% of patients in both groups (208 of 421 guselkumab-treated patients and 138 of 280 placebo-treated patients), serious adverse events were reported by 3% (12 of 421) of guselkumab-treated patients and 7% (20 of 280) of placebo-treated patients, and adverse events leading to treatment discontinuation were reported by 2% (seven of 421) of guselkumab-treated patients and 4% (11 of 280) of placebo-treated patients. In the maintenance study, adverse event rates were similar among groups, and the most frequently reported adverse events in all groups were ulcerative colitis, COVID-19, and arthralgia. No active tuberculosis, anaphylaxis, serum sickness, or clinically important hepatic disorders were reported in either study.

Interpretation Guselkumab was effective and safe as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis.

Funding Janssen Research and Development.

Lancet 2025; 405: 33–49

Published **Online** December 17, 2024 https://doi.org/10.1016/S0140-6736(24)01927-5

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University of Chicago Medicine Inflammatory Bowel Disease Centre, Chicago, IL, USA (D T Rubin MD); **Division of Gastroenterology, Hepatology and Endoscopy, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA** (J R Allegretti MD); **Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain** (J Panés MD); **Janssen Research and Development, Spring House, PA, USA** (N Shipitofsky PharmD, S S Yarandi MD, K-H G Huang MD, M Germinaro MD, R Wilson DrPH, H Zhang PhD, J Johanns PhD); **Western University, London, ON, Canada** (B G Feagan MD); **Kyorin University, Tokyo, Japan** (T Hisamatsu MD); **University of Pennsylvania, Philadelphia, PA, USA** (G R Lichtenstein MD); **University of British Columbia, Vancouver, BC, Canada** (B Bressler MD); **University of Lorraine, Inserm, NGERE, F-54000 Nancy, France and Groupe Hospitalier privé Ambroise Paré-Hartmann, Paris IBD Centre, Neuilly-sur-Seine, France** (L Peyrin-Biroulet MD); **Dr Henry D Janowitz Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY, USA** (Prof B E Sands MD); **Department of Medicine I, Agaplesion Markus Hospital, Goethe University, Frankfurt, Germany** (Prof A Dignass MD)

Correspondence to:
Dr David T Rubin, University of Chicago Medicine Inflammatory Bowel Disease Centre, Chicago, IL 60637, USA
drubin@medicine.bsd.uchicago.edu

Research in context

Evidence before this study

We searched PubMed on June 20, 2024, using the search terms "ulcerative colitis", "moderate to severe", and "treatment". We searched for articles published between Jan 1, 2019, and May 1, 2024, in English. Our search yielded 507 articles describing the efficacy and safety of agents used to treat patients with moderately to severely active ulcerative colitis. The goal for the management of ulcerative colitis is induction and long-term maintenance of clinical remission, endoscopic and histological improvement, restoration of quality of life, and absence of disability. Patients with ulcerative colitis often have an inadequate response or intolerance to one or more conventional ulcerative colitis therapies (ie, corticosteroids and immunosuppressants) or biologics, Janus kinase (JAK) inhibitors, or sphingosine 1-phosphate modulators. Additional options for effective treatment of ulcerative colitis are needed. Guselkumab is a dual-acting selective IL-23p19 subunit inhibitor that potently neutralises IL-23 and can bind to CD64, a receptor on myeloid cells that are one of the cell types that produce IL-23 as well as other cytokines. It is approved for the treatment of moderate-to-severe plaque psoriasis and active psoriatic arthritis, and has been shown to be effective in treating Crohn's disease. In the phase 2b, randomised, double-blind, placebo-controlled, dose-ranging induction study (QUASAR Ph2b Induction Study, NCT04033445), clinical response was significantly greater with guselkumab induction given intravenously compared with placebo in patients with moderately to severely active ulcerative colitis.

Added value of this study

The QUASAR phase 3 randomised, double-blind, placebo-controlled studies evaluated guselkumab as induction and maintenance therapy in patients with moderately to severely active ulcerative colitis. In these studies, compared with patients receiving placebo, significantly greater proportions of patients achieved clinical remission 12 weeks after receiving guselkumab induction therapy given intravenously and after 44 weeks of maintenance therapy with guselkumab 200 mg given subcutaneously every 4 weeks or 100 mg every 8 weeks. Seven of nine prespecified, multiplicity-controlled major secondary endpoints, including clinical, endoscopic, histological, symptomatic, and patient-reported outcome measures were met in the induction study and all nine were met in the maintenance study for both dose regimens. In addition, the guselkumab treatment effect was evident in biologic-naive and JAK inhibitor-naive patients and in patients with a history of inadequate response or intolerance to biologics or JAK inhibitors. No new safety concerns were observed.

Implications of all the available evidence

IL-23 plays a crucial role in ulcerative colitis pathogenesis, and IL-23 inhibition is effective in treating ulcerative colitis, including the promotion of epithelial repair. The results of the QUASAR phase 3 studies show that guselkumab is effective for induction and maintenance treatment in patients with moderately to severely active ulcerative colitis. In addition, the efficacy achieved in biologic and JAK inhibitor-naive patients and biologic or JAK inhibitor-refractory patients, in conjunction with the demonstrated safety profile, suggests that guselkumab is a compelling treatment option in both populations. We also propose that the substantive endoscopic and histological efficacy observed with guselkumab can be related to the dual-acting mechanism of guselkumab.

Introduction

Ulcerative colitis is a chronic, immune-mediated, inflammatory bowel disorder involving the surface mucosa, the crypt epithelium, and the submucosa of the colon.[1–3] Ulcerative colitis is associated with diarrhoea, rectal bleeding, abdominal pain, bowel urgency, fatigue, and impaired quality of life.[4–6] The primary goal for the management of ulcerative colitis is induction and long-term maintenance of clinical remission, while minimising the need for corticosteroids.[2,7] Endoscopic improvement, restoration of quality of life, and absence of disability are long-term goals, whereas histological remission is an emerging long-term therapeutic target.[7]

Ulcerative colitis therapies are frequently limited by non-response to primary therapy, efficacy therapeutic ceiling, loss of clinical benefit over time, and adverse reactions such as infections, malignancies, and cardiovascular events;[8–12] thus, additional treatment options are needed.

IL-23 inhibition is effective in treating ulcerative colitis, including the promotion of epithelial repair.[10,13–16] Guselkumab is a dual-acting, human IgG1, IL-23p19 subunit inhibitor that potently neutralises IL-23 and can bind to CD64, a receptor on myeloid cells, which are one of the cell types that produce IL-23 in addition to other cytokines.[17]

In the phase 2b/3 clinical development programme for guselkumab in ulcerative colitis (QUASAR programme, NCT04033445), the efficacy and safety of guselkumab were evaluated in patients with moderately to severely active ulcerative colitis.[18] In the QUASAR phase 2b, dose-ranging, induction study, both intravenous guselkumab induction doses (200 mg and 400 mg every 4 weeks) were safe and showed clinically meaningful efficacy compared with placebo at week 12, with no apparent incremental benefit with the guselkumab 400 mg dose across key efficacy measures and clinically relevant subgroups.[18] Thus, guselkumab given intravenously 200 mg was selected as the phase 3 induction dose.

Here, we aimed to report the efficacy and safety results of guselkumab from the pivotal QUASAR phase 3 induction and maintenance studies.

Methods

Study design and participants

The QUASAR multicentre, randomised, double-blind, placebo-controlled clinical programme consisted of a phase 2b induction study (results previously reported),[18] a phase 3 induction study, and a phase 3 maintenance study (figure 1). The programme was conducted at 254 hospital and community centres in 32 countries or territories. The eligibility criteria for the phase 3 induction study were the same as those for the previously published phase 2b induction study (appendix pp 15–20);[18] but briefly, patients were aged at least 18 years with a confirmed diagnosis of moderately to severely active ulcerative colitis for at least 3 months before screening and a history of an inadequate response or intolerance (or both) to corticosteroids, immunosuppressants, biologics, or Janus kinase (JAK) inhibitors. At induction baseline, patients had a modified Mayo (mMayo) score from 4 to 9, a Mayo rectal bleeding subscore of at least 1, and a Mayo endoscopic subscore of at least 2. Although the protocol allowed the enrolment of patients who had an mMayo score of 4 (limited to ≤5% of the total enrolled population), in response to health authority feedback, the primary analysis population included only patients with an mMayo score from 5 to 9. Patient eligibility for the maintenance study was dependent on induction study participation (figure 1).

Previous use of a biologic IL-12 or IL-23 inhibitor, including ustekinumab, was prohibited. Unless discontinuation or dose reduction was deemed necessary by the investigator for each study site, a stable dose of ulcerative colitis-specific concomitant medications permitted at induction baseline was maintained through maintenance week 44 except for oral corticosteroids (permitted at ≤20 mg per day prednisone or equivalent; appendix p 21).[18] Corticosteroid tapering was mandatory beginning at maintenance week 0 unless it was not medically feasible (appendix p 21).

See Online for appendix

The independent ethics committee or institutional review board at each study site approved the study materials before patient enrolment. The trials were conducted in accordance with the International Council for Harmonisation guidelines, applicable regulations, and the Declaration of Helsinki. All participants provided written informed consent. Data on sex were self-reported

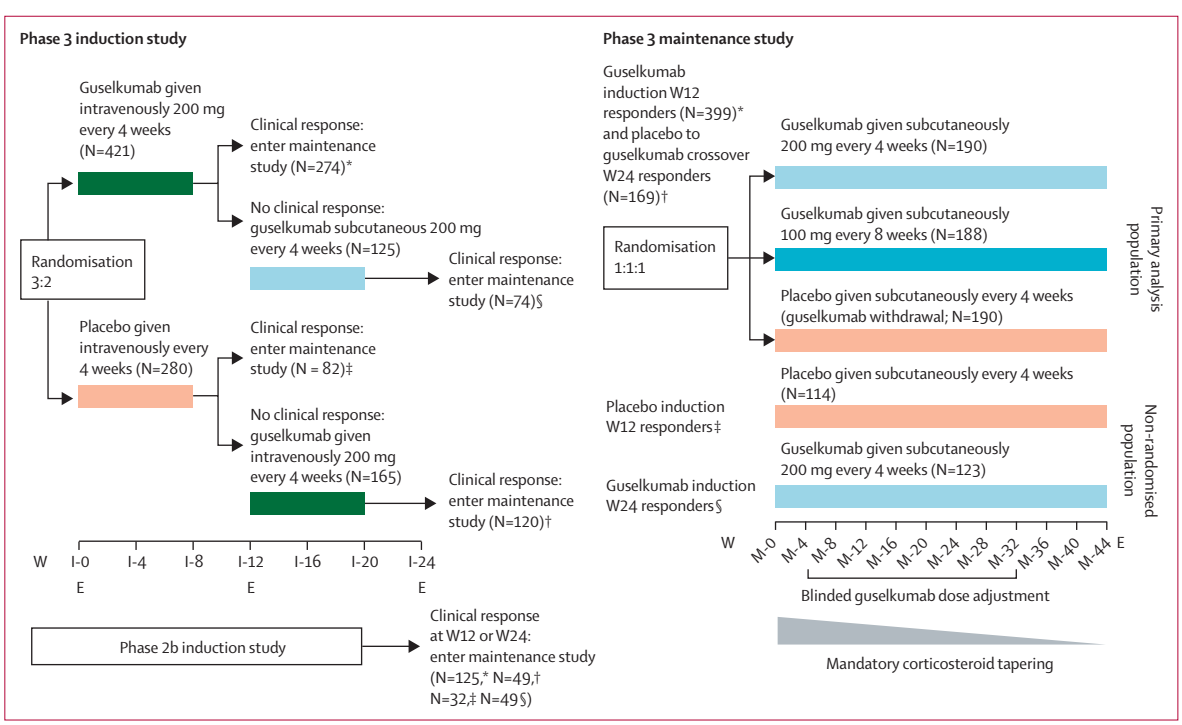

Figure 1: **The QUASAR programme**

Population numbers include patients with a baseline modified Mayo (mMayo) score from 5 to 9 only. Clinical response was based on the interactive web response system data using the Mayo endoscopic subscore assigned by the blinded local endoscopist. Four groups of patients from the induction studies entered the maintenance study: *guselkumab induction week 12 responders (randomised); †placebo to guselkumab crossover week 24 induction responders (randomised); ‡placebo week 12 induction responders (non-randomised); and §guselkumab week 24 induction responders (non-randomised). Randomised patients meeting loss of clinical response criteria between maintenance weeks 8 and 32 were eligible for a blinded dose adjustment as follows: placebo given subcutaneously to guselkumab 200 mg given subcutaneously every 4 weeks (rescue treatment), guselkumab 100 mg given subcutaneously every 8 weeks to guselkumab 200 mg given subcutaneously every 4 weeks, guselkumab 200 mg given subcutaneously every 4 weeks to guselkumab 200 mg given subcutaneously every 4 weeks (sham dose adjustment). Detailed study design figures for the QUASAR phase 3 induction study and maintenance study have been shown in the appendix (p 44), and detailed patient dispositions for the QUASAR phase 3 induction study primary analysis population and for the maintenance study primary analysis population and non-randomised population have been shown in the appendix (p 50). E=endoscopy. I=induction. M=maintenance. W=week.

by patients and collected on an electronic case report form with the options of male, female, unknown, or undifferentiated.

Randomisation and masking

In the phase 2b induction study, patients were randomised (1:1:1) to receive guselkumab (200 mg or 400 mg given intravenously) or placebo given intravenously at induction weeks 0, 4, and 8.[18] Based on the absence of dose response in the phase 2b induction study, the 200 mg dose was selected for the phase 3 induction study. In the phase 3 induction study, patients were randomly assigned (3:2) to receive guselkumab (200 mg given intravenously) or placebo at induction weeks 0, 4, and 8 in the phase 3 induction study (appendix p 44).

Guselkumab intravenous induction responders at induction week 12 from both induction studies were randomly assigned (1:1:1) at maintenance week 0 to receive guselkumab (200 mg every 4 weeks given subcutaneously), guselkumab (100 mg every 8 weeks given subcutaneously), or placebo (guselkumab withdrawal) maintenance therapy (appendix p 45). Guselkumab intravenous induction non-responders at induction week 12 received guselkumab (200 mg given subcutaneously at induction weeks 12, 16, and 20); those in clinical response at induction week 24 received guselkumab (200 mg every 4 weeks given subcutaneously) starting at week 0 in the maintenance study (non-randomised).

Patients who were randomly assigned to placebo induction who were in clinical response at induction week 12 received placebo in the maintenance study (non-randomised). Patients randomly assigned to placebo induction who were not in clinical response at induction week 12 received guselkumab (200 mg given intravenously) at induction weeks 12, 16, and 20; those in clinical response at induction week 24 were randomly assigned in the maintenance study at maintenance week 0 as described earlier.

In all studies, principal investigators enrolled patients at their respective investigative centres, and an interactive web response system was used to assign patients to treatment groups using permuted block randomisation by distinct stratification variables. For the induction study, stratification variables were previous inadequate response or intolerance to biologics or JAK inhibitors (yes or no), region (eastern Europe, Asia, or rest of the world), and concomitant use of corticosteroids at baseline (yes or no). In the maintenance study, stratification variables were clinical remission status at maintenance week 0 (yes or no based on the local Mayo endoscopic subscore), concomitant use of corticosteroids at maintenance baseline (yes or no), and induction treatment (guselkumab 400 mg given intravenously, guselkumab 200 mg given intravenously, or placebo crossover [guselkumab 200 mg given intravenously]).

The sponsor, study investigators, site personnel, central laboratory, central readers, and patients were masked to the treatment assignment throughout all studies. Matching intravenous or subcutaneous placebo was administered to all week 12 non-responders in the induction studies to maintain blinding. In the maintenance study, all patients received either guselkumab or matching placebo every 4 weeks to maintain blinding.

Patients randomly assigned into the maintenance study who met loss of clinical response criteria, which was based on the mMayo score and required an endoscopic assessment between maintenance weeks 8 and 32, could receive a blinded dose adjustment: placebo to guselkumab (200 mg given subcutaneously every 4 weeks; rescue treatment), guselkumab (100 mg given subcutaneously every 8 weeks) to guselkumab (200 mg given subcutaneously every 4 weeks), or guselkumab (200 mg given subcutaneously every 4 weeks) to guselkumab (200 mg given subcutaneously every 4 weeks; sham adjustment; appendix pp 21, 46–47). 12 weeks after loss of clinical response, patients in partial Mayo response continued the study.

Procedures

The Mayo stool frequency and rectal bleeding subscores were determined at induction weeks 0, 1, 2, and 4, and then every 4 weeks through maintenance week 44. The physician global assessment was assessed every 4 weeks from induction week 0 to maintenance week 44. Endoscopies and biopsies were performed at induction weeks 0, 12, 24, and maintenance week 44 (appendix p 21). The Inflammatory Bowel Disease Questionnaire and the Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a (PROMIS-Fatigue SF-7a) were assessed at induction weeks 0, 12, 24, maintenance week 28, and maintenance week 44. Blood samples for C-reactive protein were collected every 4 weeks from induction week 0 to induction week 24 and then every 8 weeks from maintenance week 4 to maintenance week 44, and stool samples for faecal calprotectin were collected at induction weeks 0, 4, 12, 24, maintenance week 28, and maintenance week 44. Adverse events were coded using the Medical Dictionary for Regulatory Activities (version 26.0).

Outcomes

The primary endpoints were clinical remission at induction week 12 in the phase 3 induction study and clinical remission at maintenance week 44 in the maintenance study (panel). Major secondary endpoints evaluated at week 12 (unless otherwise indicated) in the induction study were clinical response, endoscopic improvement, histo-endoscopic mucosal improvement, endoscopic remission (normalisation), Inflammatory Bowel Disease Questionnaire remission,[19] fatigue response, and symptomatic remission (induction

***Panel*: Score components and endpoint definitions**

Score components

- Mayo score (score range 0 [normal] to 12 [severely active disease]): RBS (0–3), SFS (0–3), PGA (0–3), and MES (0–3)
- mMayo score (score range 0–9): RBS (0–3), SFS (0–3), and MES (0–3)
- Partial Mayo score (score range 0–9): RBS (0–3), SFS (0–3), and PGA (0–3)
- Symptomatic Mayo score (score range 0–6): RBS (0–3) and SFS (0–3)

Endpoints

- Clinical remission: Mayo SFS of 0 or 1 and not increased from induction baseline, a Mayo RBS of 0, and an MES of 0 or 1 with no friability present on endoscopy
- Clinical response: decrease from induction baseline in the mMayo score by at least 30% and at least 2 points, with either a 1-point or more decrease from induction baseline in the Mayo RBS or a Mayo RBS of 0 or 1
- Corticosteroid-free clinical remission: clinical remission without any use of corticosteroids for at least 8 weeks before assessment
- Corticosteroid elimination: among patients who were receiving oral corticosteroids at maintenance baseline, no use of oral corticosteroids from the specified timepoint during maintenance week 44
- C-reactive protein normalisation: C-reactive protein concentration of 3 mg/L or less among patients with a C-reactive protein concentration of more than 3 mg/L at induction baseline
- Endoscopic improvement: MES of 0 or 1 with no friability present on endoscopy
- Endoscopic remission (normalisation): MES of 0
- Fatigue response: at least 7-point improvement from induction baseline in PROMIS-Fatigue SF-7a
- Faecal calprotectin normalisation: faecal calprotectin concentration 250 mg/kg or less among patients with a faecal calprotectin concentration of more than 250 mg/kg at induction baseline
- Histo-endoscopic mucosal improvement: combination of histological improvement and endoscopic improvement endpoints
- Histo-endoscopic mucosal remission: combination of histological remission and endoscopic remission endpoints
- Histological improvement: neutrophil infiltration in less than 5% of crypts, no crypt destruction, and no erosions, ulcerations, or granulation tissue according to the Geboes grading system (ie, Geboes score ≤3·1)
- Histological remission: 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); equivalent to RHI-based definition of histological remission in which RHI 3 or less with subscores of 0 for lamina propria neutrophils and neutrophils in the epithelium and without ulcers or erosion
- Histological remission (NHI based): NHI of 1 or less
- Inflammatory Bowel Disease Questionnaire remission: total Inflammatory Bowel Disease Questionnaire score of at least 170
- Maintenance of clinical remission: clinical remission at maintenance week 44 among patients in clinical remission at maintenance baseline (maintenance week 0)
- Maintenance of clinical response: clinical response at maintenance week 44 among patients in clinical response at maintenance baseline
- Partial Mayo response: a decrease from induction baseline of at least 2 in the partial Mayo score
- Symptomatic remission: Mayo SFS of 0 or 1 and not increased from induction baseline, and a Mayo RBS of 0 (deep symptomatic remission: Mayo SFS of 0 and a Mayo RBS of 0)
- Symptomatic response: decrease from induction baseline in the symptomatic Mayo score by at least 30% and at least 1 point, with either at least 1-point decrease from induction baseline in the Mayo RBS or a Mayo RBS of 0 or 1

CRP=C-reactive protein. IBDQ=Inflammatory Bowel Disease Questionnaire. mMayo=modified Mayo. MES=Mayo endoscopic subscore. NHI=Nancy Histological Index. PGA=Physician's Global Assessment. PROMIS-Fatigue SF-7a=Patient-Reported Outcome Measurement Information System Fatigue Short Form 7a. RBS=rectal bleeding subscore. RHI=Robarts Histopathology Index. SFS=stool frequency subscore.

weeks 2, 4, and 12). These outcomes were also evaluated at induction week 24 among week 12 induction non-responders. Major secondary endpoints evaluated at maintenance week 44 in the maintenance study were corticosteroid-free clinical remission, maintenance of clinical remission, maintenance of clinical response, endoscopic improvement, histo-endoscopic mucosal improvement, endoscopic remission, Inflammatory Bowel Disease Questionnaire remission, fatigue response, and symptomatic remission. Among patients who had a blinded dose adjustment during the maintenance study, symptomatic response and symptomatic remission were analysed 0, 4, 8, and 12 weeks after dose adjustment. All other efficacy endpoints reported for both studies are listed in the appendix (pp 24–28). All reported endpoints were prespecified unless otherwise noted. All prespecified endpoints in both studies and whether they were reported in this manuscript are listed in the appendix (pp 29–41).

Safety assessments included reporting of adverse events, physical examinations, and laboratory tests. Prespecified targeted adverse events (eg, opportunistic infections, serious infections, active tuberculosis, major adverse cardiovascular events, clinically important hepatic disorders, and malignancies) were analysed.

In all studies, the presence of anti-guselkumab antibodies in serum was determined using a validated, sensitive, drug-tolerant electrochemiluminescence method using the Meso Scale Discovery platform (Gaithersburg, MD, USA).[20] Positive samples were further characterised for anti-guselkumab neutralising antibodies (NAbs).

Statistical analysis

The primary efficacy and safety populations for both studies included all randomised patients with a baseline mMayo score from 5 to 9 who received at least one dose of study treatment, analysed according to their assigned treatment. In both studies, primary and major secondary endpoints were analysed by clinically relevant subpopulations and subgroups, including by biologic or JAK inhibitor history and induction baseline mMayo score (post hoc for the induction study; appendix pp 24–28).

A hierarchical testing procedure was used in both studies to control the overall type 1 error rate at the 0·05 significance level for the primary and major secondary endpoints. The primary endpoints were tested using a fixed-sequence testing procedure. A major secondary endpoint for a dose regimen was considered significant only if the previous endpoints in the hierarchy and the current endpoint tested positive at the two-sided 0·05 level of significance. If an endpoint was not significant, all subsequent tests were considered not significant (appendix pp 48–49).

Categorical endpoints in both studies were analysed using the Cochran–Mantel–Haenszel χ^2 test adjusted by stratification factors. Stratification factors were history of inadequate response or intolerance to biologics or JAK inhibitors (yes or no) and concomitant use of corticosteroids at baseline (yes or no) for the induction study, and clinical remission status at maintenance baseline (yes or no), and induction treatment (guselkumab [400 mg given intravenously], guselkumab [200 mg given intravenously], or placebo given intravenously crossover to guselkumab [200 mg given intravenously]) for the maintenance study. Adjusted treatment differences and confidence intervals were based on the Wald statistic with Cochran–Mantel–Haenszel weight. In both studies, for categorical endpoints, after accounting for intercurrent event strategies, patients who were missing a value at a timepoint were classified as non-responders (appendix p 42). For continuous endpoints measured at more than one post-baseline visit (after applying intercurrent event strategies), a mixed-effect model for repeated measures was used to account for missing data, under the missing-at-random assumption.

The phase 3 induction study sample size was calculated to provide 90% power at a significance level of 0·05 (two-sided) for the primary endpoint and more than 90% power for the major secondary endpoints except for histo-endoscopic mucosal improvement and endoscopic improvement at induction week 12 and symptomatic remission at induction week 2, and to provide enough participants in conjunction with the phase 2b induction study for the primary population of the maintenance study (appendix p 42). The maintenance study sample size was calculated to provide 90% power at a significance level of 0·05 (two-sided) for the primary endpoint and at least 90% power for the major secondary endpoints, except for maintenance of clinical remission and endoscopic remission at maintenance week 44. The actual number of patients in the primary analysis population of the maintenance study depended on the number of guselkumab clinical responders at induction week 12 and placebo to guselkumab clinical responders at induction week 24 from the induction studies.

Safety data were summarised descriptively. Selected safety summaries were also provided for all treated patients, regardless of baseline mMayo score, including randomised and non-randomised patients.

All statistical analyses were done with SAS (version 9.4). An external data monitoring committee was established and routinely reviewed unblinded safety data. Both studies were registered on ClinicalTrials.gov, NCT04033445, and EudraCT, 2018–004002–25.

Role of the funding source

The study protocols and analysis plans were written by the sponsor, Janssen Research and Development, in collaboration with the steering committee. The sponsor and investigators jointly conducted the studies and gathered data. Data were analysed by statisticians employed by the sponsor. All authors, including those employed by the funder, 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 funder, reviewed and provided feedback on all subsequent versions of the manuscript and made the decision to submit the manuscript for publication.

Results

Between May 18, 2021, and June 2, 2022, 736 patients were randomly assigned to treatment in the phase 3 induction study; the primary analysis population included 701 treated patients with an mMayo score from 5 to 9 (guselkumab given intravenously 200 mg, 60% [421 of 701 patients]; placebo 40% [280 patients]; appendix p 50). Overall, 6% (42 of 701) of patients discontinued study treatment before induction week 12 (4% [18 of 421] of patients treated with guselkumab and 9% [24 of 280] of patients treated with the placebo). The primary reasons for discontinuation were the adverse event of worsening ulcerative colitis (1% [nine of 701 patients]; <1% [one of 421] of patients treated with guselkumab and 3% [eight of 280] of patients treated with the placebo) and patient withdrawal (2% [17 of 701];

1% [six of 421] of patients treated with guselkumab and 4% [11 of 280] of patients treated with the placebo).

Induction baseline disease characteristics were representative of patients with moderately to severely active ulcerative colitis and were similar to those in the phase 2b induction study.[18] Overall, mean ulcerative colitis duration was 7·5 (SD 7·3) years, and 64% (452 of 701) of patients had an mMayo score of 7–9. Further, 68% (476 of 701 patients) had a Mayo endoscopic subscore of 3, 48% (335 patients) had extensive disease,

	Induction study*		Maintenance study†		
	Placebo given intravenously every 4 weeks (N=280)	Guselkumab 200 mg given intravenously every 4 weeks (N=421)	Placebo given subcutaneously (guselkumab withdrawal; N=190)	Guselkumab 100 mg given subcutaneously every 8 weeks (N=188)	Guselkumab 200 mg given subcutaneously every 4 weeks (N=190)
Age, years	39·8 (13·4)	41·0 (13·9)	41·2 (13·6)	40·3 (13·0)	40·6 (14·7)
Sex					
Male	161 (58%)	238 (57%)	109 (57%)	102 (54%)	100 (53%)
Female	119 (42%)	183 (43%)	81 (43%)	86 (46%)	90 (47%)
Race					
Asian	62 (22%)	88 (21%)	34 (18%)	38 (20%)	44 (23%)
Black or African American	3 (1%)	4 (1%)	2 (1%)	2 (1%)	2 (1%)
White	205 (73%)	303 (72%)	142 (75%)	139 (74%)	135 (71%)
Not reported, multiple, or other‡	10 (4%)	26 (6%)	12 (6%)	9 (5%)	9 (5%)
Weight, kg	71·8 (17·0)	72·9 (16·7)	73·6 (17·0)	70·7 (16·8)	70·9 (16·6)
Ulcerative colitis disease duration, years	7·1 (6·5)	7·8 (7·7)	7·3 (6·3)	7·8 (8·5)	8·4 (8·4)
Extensive ulcerative colitis	147 (52%)	188 (45%)	95 (50%)	79 (42%)	83 (44%)
Mayo score (0–12)	9·2 (1·3)	9·1 (1·4)	9·2 (1·4)	9·0 (1·4)	9·2 (1·4)
mMayo score (0–9)	6·9 (1·1)	6·9 (1·1)	7·0 (1·1)	6·8 (1·2)	6·9 (1·1)
mMayo score (7–9; severe)	178 (64%)	274 (65%)	125 (66%)	114 (61%)	124 (65%)
Mayo endoscopic subscore of 3 (severe)	180 (64%)	296 (70%)	129 (68%)	125 (66%)	123 (65%)
Partial Mayo score	6·5 (1·2)	6·4 (1·2)	6·5 (1·2)	6·3 (1·3)	6·5 (1·2)
Geboes total score§	278/280 (99%)	418/421 (99%)	187/190 (98%)	184/188 (98%)	188/190 (99%)
Mean (SD)	11·9 (4·3)	11·8 (4·4)	12·3 (4·2)	12·1 (4·6)	11·7 (4·8)
Extraintestinal manifestation present¶	30 (11%)	60 (14%)	23 (12%)	22 (12%)	23 (12%)
C-reactive protein§	278/280 (99%)	416/421 (99%)	190/190 (98%)	185/188 (98%)	187/190 (99%)
Median (IQR), mg/L	3·8 (1·6–9·1)	4·3 (1·5–11·2)	4·2 (1·6–8·4)	3·9 (1·4–10·4)	3·6 (1·4–9·1)
Abnormal (>3 mg/L)	160 (58%)	248 (60%)	117 (62%)	104 (56%)	104 (56%)
Faecal calprotectin§	253/280 (90%)	370/421 (88%)	175/190 (92%)	160/188 (85%)	171/190 (90%)
Median (IQR), mg/kg	1606·0 (654·0–3077·0)	1651·0 (647·0–3479·0)	1642·0 (663·0–3498·0)	1675·0 (806·0–3543·5)	1487·0 (603·0–3019·0)
Abnormal (>250 mg/kg)	225 (89%)	333 (90%)	154 (88%)	141 (88%)	150 (88%)
Albumin (g/L)	43·0 (41·0–46·0)	43·0 (41·0–46·0)	43·0 (27–55)	44·0 (16–54)	43·0 (31–52)
IBDQ total score (32–224)§	271/280 (97%)	407/421 (97%)	185/190 (97%)	179/188 (95%)	182/190 (96%)
Mean (SD)	126·3 (31·7)	125·8 (31·5)	128·3 (30·4)	127·0 (31·8)	127·2 (33·4)
PROMIS-Fatigue SF-7a§	271/280 (97%)	407/421 (97%)	185/190 (97%)	179/188 (95%)	182/190 (96%)
Mean (SD)	56·4 (8·9)	56·0 (8·8)	55·6 (8·1)	56·3 (9·2)	56·5 (9·2)
Receiving corticosteroids, immunosuppressants, or aminosalicylates for ulcerative colitis treatment at induction baseline	247 (88%)	365 (87%)	168 (88%)	164 (87%)	166 (87%)
Oral corticosteroids	120 (49%)	182 (50%)	77 (46%)	74 (45%)	76 (46%)
Immunosuppressants	54 (22%)	92 (25%)	43 (26%)	41 (25%)	42 (25%)
Oral aminosalicylates	204 (83%)	304 (83%)	145 (86%)	146 (89%)	147 (89%)
No history of inadequate response or intolerance to a biologic or JAK inhibitor‖	144 (51%)	213 (51%)	115 (61%)	111 (59%)	102 (54%)
Biologic or JAK inhibitor experienced‖	7 (5%)	11 (5%)	7 (6%)	6 (5%)	6 (6%)
Biologic and JAK inhibitor naive‖	137 (95%)	202 (95%)	108 (94%)	105 (95%)	96 (94%)

(Table 1 continues on next page)

	Induction study*		Maintenance study†		
	Placebo given intravenously every 4 weeks (N=280)	Guselkumab 200 mg given intravenously every 4 weeks (N=421)	Placebo given subcutaneously (guselkumab withdrawal; N=190)	Guselkumab 100 mg given subcutaneously every 8 weeks (N=188)	Guselkumab 200 mg given subcutaneously every 4 weeks (N=190)
(Continued from previous page)					
History of inadequate response or intolerance to a biologic or JAK inhibitor‖	136 (49%)	208 (49%)	75 (39%)	77 (41%)	88 (46%)
One biologic or JAK inhibitor‖	63 (46%)	95 (46%)	36 (48%)	36 (47%)	52 (59%)
At least two therapies (biologics or JAK inhibitors)‖	73 (54%)	113 (54%)	39 (52%)	41 (53%)	36 (41%)
Any TNFα antagonist	119 (88%)	182 (88%)	65 (87%)	70 (91%)	76 (86%)
One TNFα antagonist	90 (66%)	139 (67%)	46 (61%)	55 (71%)	61 (69%)
At least two TNFα antagonists	29 (21%)	43 (21%)	19 (25%)	15 (19%)	15 (17%)
TNFα antagonists only	55 (40%)	86 (41%)	36 (48%)	31 (40%)	44 (50%)
One TNFα antagonist only	46 (34%)	72 (35%)	28 (37%)	29 (38%)	40 (45%)
Vedolizumab	74 (54%)	112 (54%)	35 (47%)	44 (57%)	39 (44%)
Vedolizumab only	16 (12%)	18 (9%)	7 (9%)	6 (8%)	10 (11%)
Tofacitinib	22 (16%)	40 (19%)	18 (24%)	20 (26%)	10 (11%)
Tofacitinib only	1 (1%)	5 (2%)	1 (1%)	1 (1%)	2 (2%)

Data are n (%), median (IQR), mean (SD), or n/N (%), unless stated otherwise. IBDQ=Inflammatory Bowel Disease Questionnaire. JAK=Janus kinase. mMayo=modified Mayo. PROMIS-Fatigue SF-7a=Patient-Reported Outcomes Measurement Information System Fatigue Short Form 7a. TNFα=tumour necrosis factor α. *Values at induction baseline for the phase 3 induction study primary efficacy population. †Values at induction baseline (in either the phase 2b or phase 3 induction study) for the phase 3 maintenance study primary efficacy population. ‡Includes American Indian or Alaska Native, Native Hawaiian, or other Pacific Islander. §Data are n/N (%) patients who were evaluated for this outcome. ¶Extraintestinal manifestations assessed were arthritis or arthralgia, aphthous stomatitis, erythema nodosum, iritis or uveitis, primary sclerosing cholangitis, and pyoderma gangrenosum. ‖Biologics refers to TNFα antagonists and vedolizumab, and JAK inhibitors refers to tofacitinib.

Table 1: **Induction baseline demographics and disease characteristics among randomised and treated patients in the phase 3 induction study and the maintenance study (primary efficacy populations)**

43% (302 patients) were using oral corticosteroids and 21% (146 patients) were using immunosuppressants at baseline, 49% (344 patients) had a previous inadequate response or intolerance to biologics or JAK inhibitors, and 48% (339 patients) were biologic naive and JAK inhibitor naive (table 1).

Between July 31, 2020, and Nov 11, 2022, 846 patients (267 from the phase 2b induction study and 579 from the phase 3 induction study) were enrolled into the maintenance study (appendix p 51). The primary analysis population included 568 randomly assigned and treated patients with an induction baseline mMayo score from 5 to 9 (guselkumab 100 mg given subcutaneously every 8 weeks, 33% [188 of 568 patients]; guselkumab 200 mg given subcutaneously every 4 weeks, 33% [190 patients]; and placebo [guselkumab withdrawal] 33% [190 patients]). Of these, 11% (65 of 568 patients) had received guselkumab 400 mg given intravenously for induction treatment, and the remaining patients received guselkumab 200 mg given intravenously for induction treatment.[18] Overall, 12% (68 of 568) of patients discontinued study treatment before maintenance week 44: 11% (20 of 188 patients) who received guselkumab 100 mg given subcutaneously every 8 weeks, 12% (22 of 190 patients) who received guselkumab 200 mg given subcutaneously every 4 weeks, and 14% (26 of 190 patients) who received placebo. The primary reasons for discontinuation were the adverse event of worsening ulcerative colitis (3% [19 of 568 patients]; 2% [three of 188 patients], 4% [eight of 190 patients], and 4% [eight of 190 patients] in the guselkumab 100 mg given subcutaneously every 8 weeks group, guselkumab 200 mg given subcutaneously every 4 weeks group, and placebo group, respectively) and patient withdrawal (3% [19 of 568 patients]; 2% [four of 188 patients], 4% [seven of 190 patients], and 4% [eight of 190 patients] in the guselkumab 100 mg given subcutaneously every 8 weeks group, guselkumab 200 mg given subcutaneously every 4 weeks group, and the placebo group, respectively). A higher proportion of patients randomly assigned to the placebo group (36% [69 of 190 patients]) experienced loss of clinical response and received rescue treatment with guselkumab (10% [19 of 188 patients] and 16% [30 of 190 patients] in the guselkumab 100 mg given subcutaneously every 8 weeks group and guselkumab 200 mg given subcutaneously every 4 weeks group, respectively), which could have reduced the proportion of placebo-treated patients discontinuing study intervention.

Disease characteristics at induction baseline for the maintenance primary population were consistent with those of the overall induction study populations. Overall, mean ulcerative colitis duration was 7·8 (SD 7·8) years,

and 64% (363 of 568) of patients had a Mayo score of 7–9. Further, 66% (377 of 568 patients) had a Mayo endoscopic subscore of 3, and 40% (227 patients) were using oral corticosteroids and 22% (126 patients) were using immunosuppressants. 42% (240 of 568 patients) had a previous inadequate response or intolerance to biologics or JAK inhibitors, and 54% (309 patients) were biologic naive and JAK inhibitor naive (table 1). Supplementary demographics and disease characteristics at maintenance study baseline are reported in the appendix (p 53).

Treatment disposition of the 237 patients in the maintenance study non-randomised population is shown in the appendix (p 52). Disease characteristics at induction and maintenance baseline in the week 24 guselkumab induction responders (n=123) reflected a higher amount of disease activity and refractoriness than induction week 12 guselkumab induction responders (n=568; table 1; appendix pp 53–54).

In the phase 3 induction study, a significantly greater proportion of patients treated with guselkumab achieved clinical remission at week 12 (primary endpoint; 23% [95 of 421 patients]) than did placebo-treated patients (8% [22 of 280 patients]; adjusted treatment difference 15%, 95% CI 10–20; figure 2). Relative to placebo, achievement of the multiplicity-controlled major secondary endpoints was significantly greater with guselkumab except for symptomatic remission at induction week 2 (p=0·21) and endoscopic remission at induction week 12 (nominal p<0·0001, given testing hierarchy). Achievement of additional combined histological and endoscopic endpoints was also greater

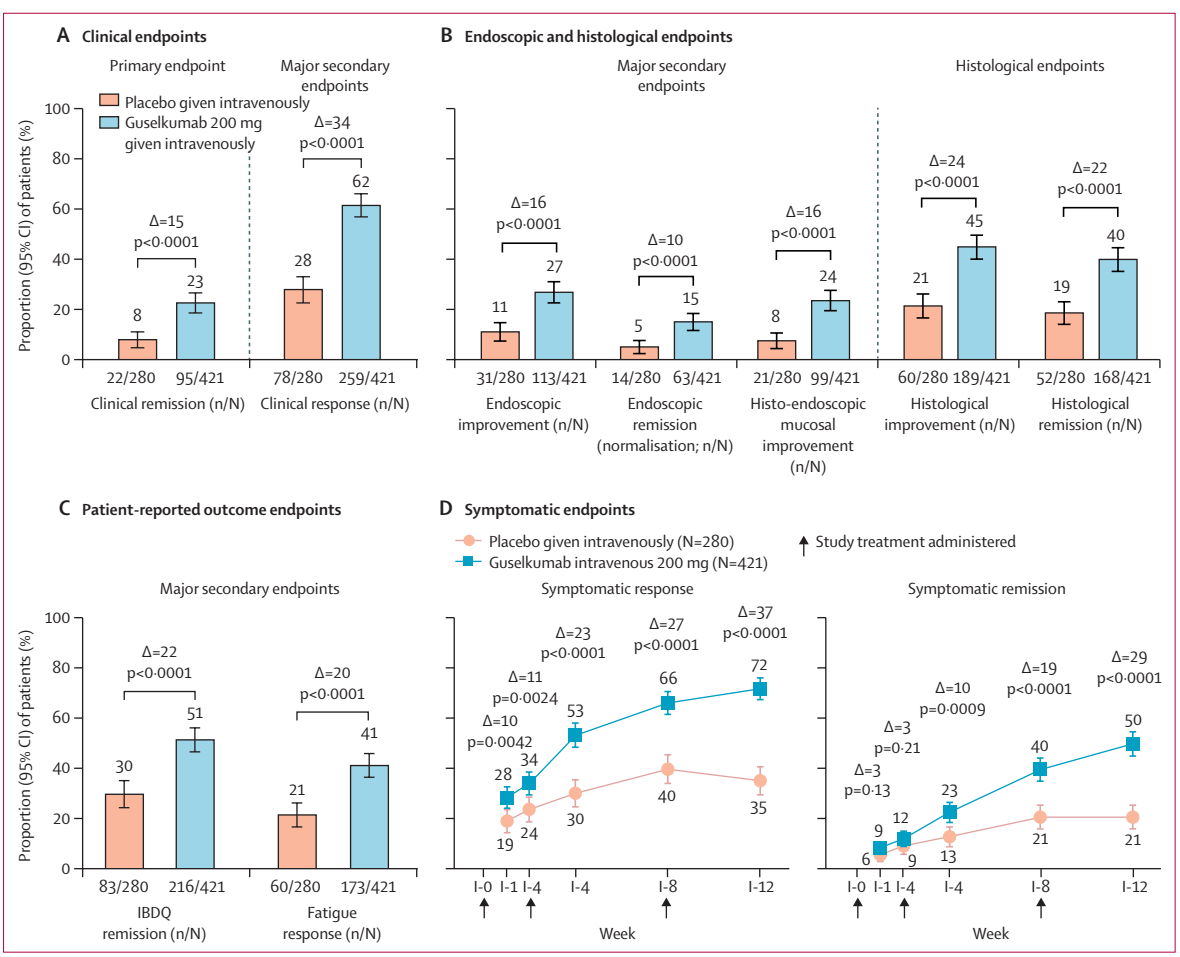

Figure 2: **Primary, major secondary, and histological endpoints at induction week 12 in the phase 3 induction study (primary analysis population)**
Comparisons between guselkumab and placebo for all endpoints were multiplicity controlled except endoscopic remission (nominal p<0·0001, given testing hierarchy), histological improvement, histological remission, and all symptomatic endpoints (except for symptomatic remission at induction weeks 2, 4, and 12, which were multiplicity-controlled major secondary endpoints). p values for endpoints that were not multiplicity controlled are nominal. Symptomatic response up to induction week 12 and symptomatic remission at induction week 1 were post hoc. Adjusted treatment differences (95% CIs) were as follows: clinical remission, 15% (95% CI 10 to 20); clinical response, 34% (27 to 41); endoscopic improvement, 16% (11 to 21); endoscopic remission, 10% (6 to 14); histo-endoscopic mucosal improvement, 16% (11 to 21); histological improvement, 24% (17 to 30); histological remission, 22% (15 to 28); IBDQ remission, 22% (15 to 29); fatigue response, 20% (13 to 26); symptomatic response at induction week 1, 10% (3 to 16), induction week 2, 11% (4 to 17), induction week 4, 23% (16 to 30), induction week 8, 27% (20 to 34), and induction week 12, 37% (30 to 44); and symptomatic remission at induction week 1, 3% (–1 to 7), induction week 2, 3% (–2 to 8), induction week 4, 10% (4 to 15), induction week 8, 19% (13 to 26), and induction week 12, 29% (23 to 36). I=induction. IBDQ=Inflammatory Bowel Disease Questionnaire.

at induction week 12 with guselkumab versus placebo (appendix p 55).

Symptomatic improvement was observed as early as induction week 1 (first assessed timepoint) with greater proportions of guselkumab-treated than placebo-treated patients achieving symptomatic response and a stool frequency subscore of 0 or 1 at induction week 1 and each subsequent timepoint to induction week 12 (figure 2; appendix p 56). Relative to placebo, significantly greater proportions of patients treated with guselkumab achieved symptomatic remission at induction weeks 4 and 12 (major secondary endpoints), and greater improvements in rectal bleeding were observed from induction week 1 to induction week 12. Achievement of the more stringent deep symptomatic remission endpoint was also greater in patients treated with guselkumab at induction weeks 8 and 12. Consistent with clinical endpoints, improvements in health-related quality of life endpoints at induction week 12 were greater in patients treated with guselkumab compared with placebo-treated patients (appendix p 58).

Guselkumab efficacy was shown in both biologic-naive and JAK inhibitor-naive patients, and in patients with a history of inadequate response or intolerance to biologics or JAK inhibitors (figure 3; appendix p 57). Clinical response at induction week 12 by different subsets of inadequate response or intolerance to biologics or JAK inhibitors has been shown in the appendix (p 59). Clinical remission at induction week 12 by induction baseline demographic, disease characteristic, and ulcerative colitis-related medication subgroups has been shown in the appendix (pp 60–61). Additionally, greater proportions of guselkumab-treated than placebo-treated patients achieved clinically meaningful improvement in abdominal pain and bowel urgency symptoms and social impact at induction week 12 (appendix pp 62–63).

Greater reductions in C-reactive protein and faecal calprotectin concentrations with guselkumab induction compared with placebo were observed as early as induction week 4 (first assessed timepoint) and maintained to induction week 12 (appendix p 64). Among patients with baseline elevated C-reactive protein (>3 mg/L) or faecal calprotectin (>250 mg/kg) concentrations, greater proportions of guselkumab-treated than placebo-treated patients achieved normalisation as early as induction week 4 (first assessed timepoint) that were maintained to induction week 12.

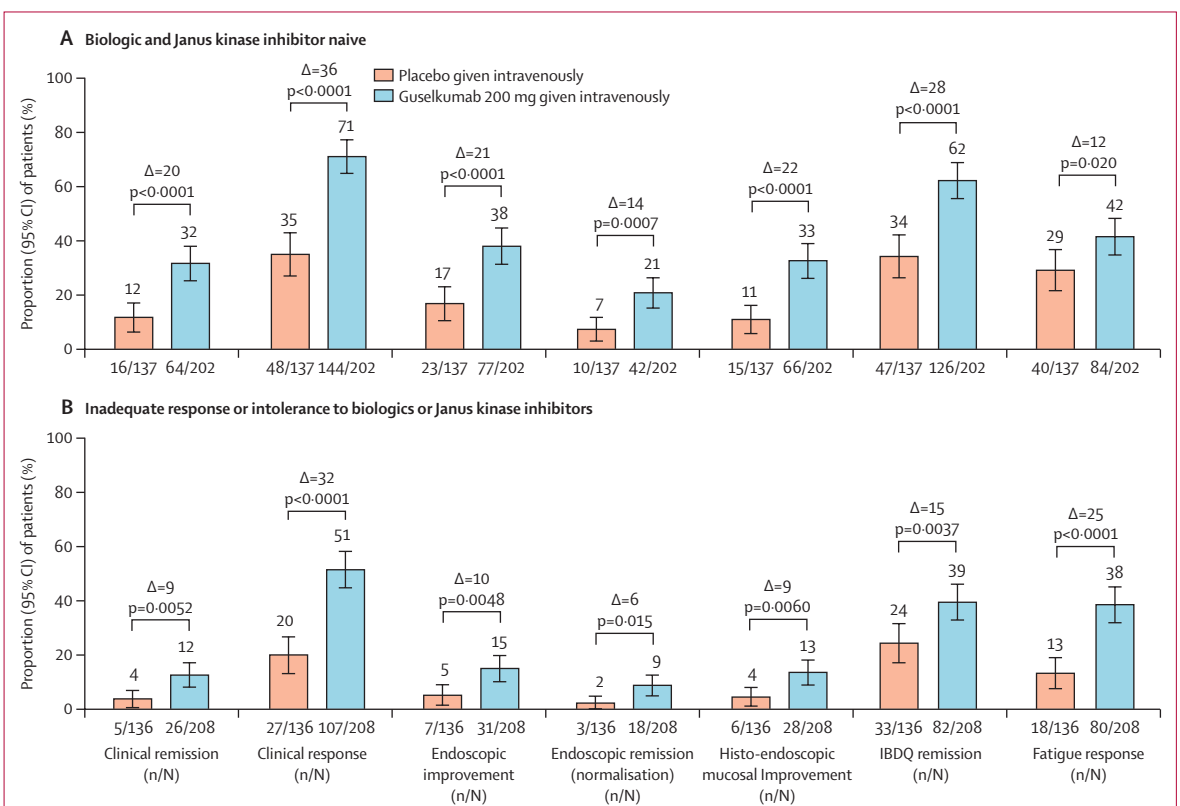

Figure 3: **Efficacy at induction week 12 among patients who were biologic naive and JAK inhibitor naive (A) and patients with a history of inadequate response or intolerance to biologics or JAK inhibitors (B)**

All p values are nominal. All patients had a modified Mayo score from 5 to 9 at induction baseline. 18 patients (seven patients in the placebo group and 11 patients in the guselkumab group) were biologic or JAK inhibitor experienced without a documented inadequate response or intolerance to biologics or JAK inhibitors. I=induction. IBDQ=Inflammatory Bowel Disease Questionnaire. JAK=Janus kinase.

Among the 120 patients who were week 12 guselkumab induction non-responders who received additional guselkumab treatment, including 74 patients with a previous inadequate response or intolerance to biologics or JAK inhibitors, 55% (66 of 120 patients) achieved clinical response at induction week 24 (appendix p 65). Among all patients initially randomly assigned to receive guselkumab induction, 77% (325 of 421 patients) achieved clinical response either at induction week 12 or 24.

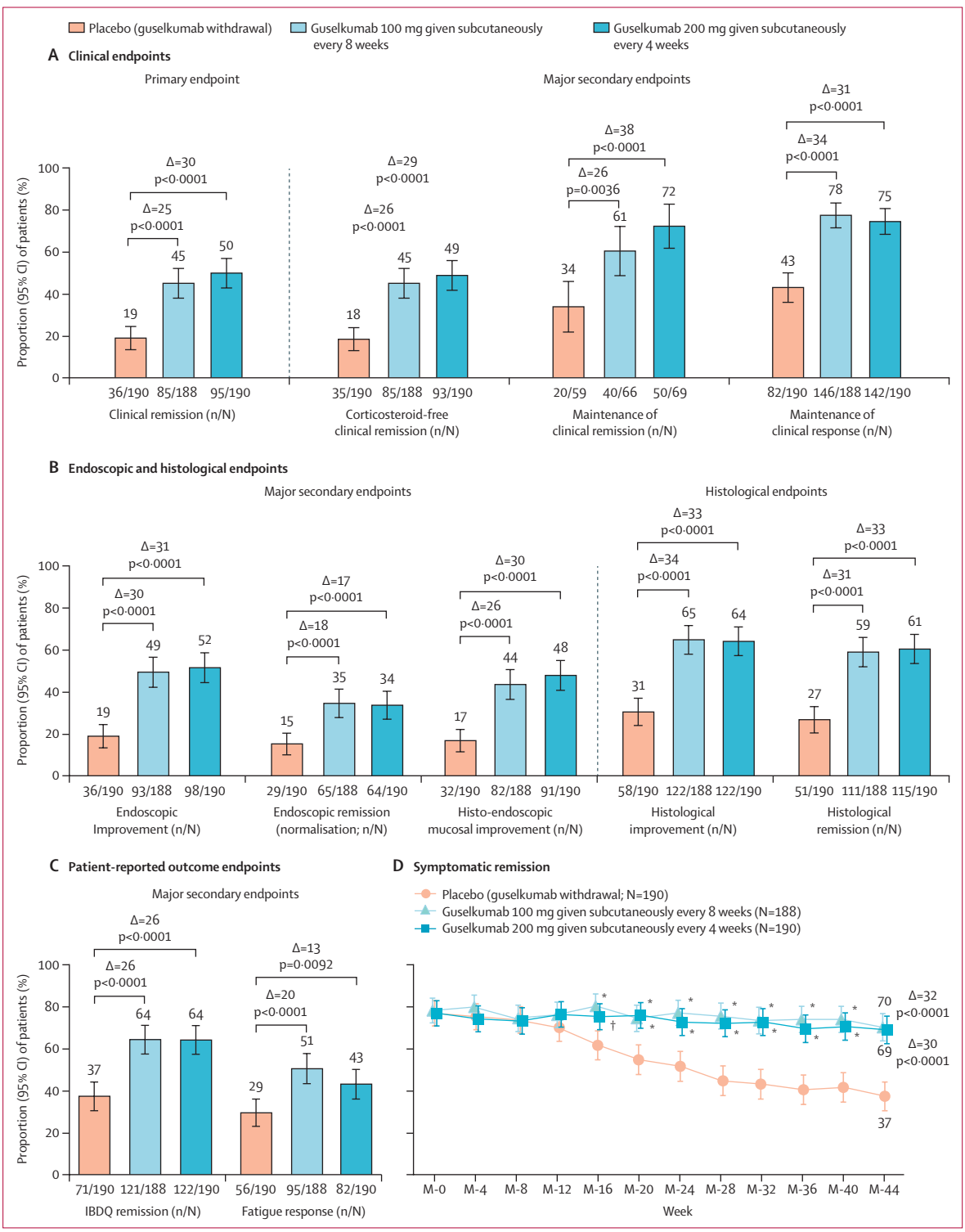

Figure 4: **Primary, major secondary, and histological endpoints at maintenance week 44 in the maintenance study (primary analysis population including randomised and treated patients only)**
All endpoints for guselkumab and placebo were multiplicity controlled except for histological improvement, histological remission, and symptomatic remission (except for maintenance week 44, which was a multiplicity-controlled major secondary endpoint). Adjusted treatment differences (95% CIs) for guselkumab 100 mg given subcutaneously every 8 weeks and guselkumab 200 mg given subcutaneously every 4 weeks, respectively, were 25% (95% CI 16–34) and 30% (21–38) for clinical remission, 26% (17–34) and 29% (21–38) for corticosteroid-free clinical remission, 26% (9–42) and 38% (23–54) for maintenance of clinical remission, 34% (24–43) and 31% (22–40) for maintenance of clinical response, 30% (21–38) and 31% (22–40) for endoscopic improvement, 18% (10–27) and 17% (9–25) for endoscopic remission, 26% (17–34) and 30% (21–38) for histo-endoscopic mucosal improvement, 34% (24–43) and 33% (23–42) for histological improvement, 31% (22–41) and 33% (24–42) for histological remission, 26% (17–36) and 26% (16–35) for IBDQ remission, 20% (11–30) and 13% (3–22) for fatigue response, and 32% (23–41) and 30% (21–40) for symptomatic remission at maintenance week 44. IBDQ=Inflammatory Bowel Disease Questionnaire. M=maintenance. *Nominal p<0·0001 versus placebo. †Nominal p=0·0066 versus placebo.

Among the 165 patients who were week 12 placebo induction non-responders who then received guselkumab induction intravenously, guselkumab efficacy at induction week 24 was consistent with that observed at induction week 12 among patients initially randomly assigned to receive guselkumab induction (appendix p 66).

When guselkumab induction efficacy was evaluated among 44 patients with a baseline mMayo score of 4, guselkumab induction efficacy relative to placebo was consistent with that observed among patients with a baseline mMayo score from 5 to 9 (appendix p 67).

In the maintenance study, both guselkumab dose regimens showed superior efficacy compared with placebo as measured by clinical remission at maintenance week 44 (primary endpoint) and all major secondary endpoints at maintenance week 44 (figure 4). Clinical remission at maintenance week 44 was achieved by a significantly greater proportion of patients treated with guselkumab 200 mg given subcutaneously every 4 weeks (50% [95 patients]; adjusted treatment difference 30%, 95% CI 21–38; p<0·0001) and 100 mg every 8 weeks (45% [85 of 188 patients]; 25%, 16–34; p<0·0001) compared with placebo (19% [36 of 190 patients]). Overall, 34% (129 of 378) of patients in the guselkumab groups achieved endoscopic remission at maintenance week 44. However, among the 180 patients in the guselkumab groups in clinical remission at maintenance week 44, 124 (69%) of 180 were in endoscopic remission (appendix p 68). Consistent with the primary and major secondary endpoint results, the proportions of patients who achieved histological improvement and histological remission (figure 4) and additional combined histological and endoscopic outcomes (appendix p 69) were greater at maintenance week 44 with guselkumab compared with placebo. With guselkumab maintenance treatment, some patients who were in clinical response but not clinical remission at maintenance week 0 subsequently achieved clinical remission at maintenance

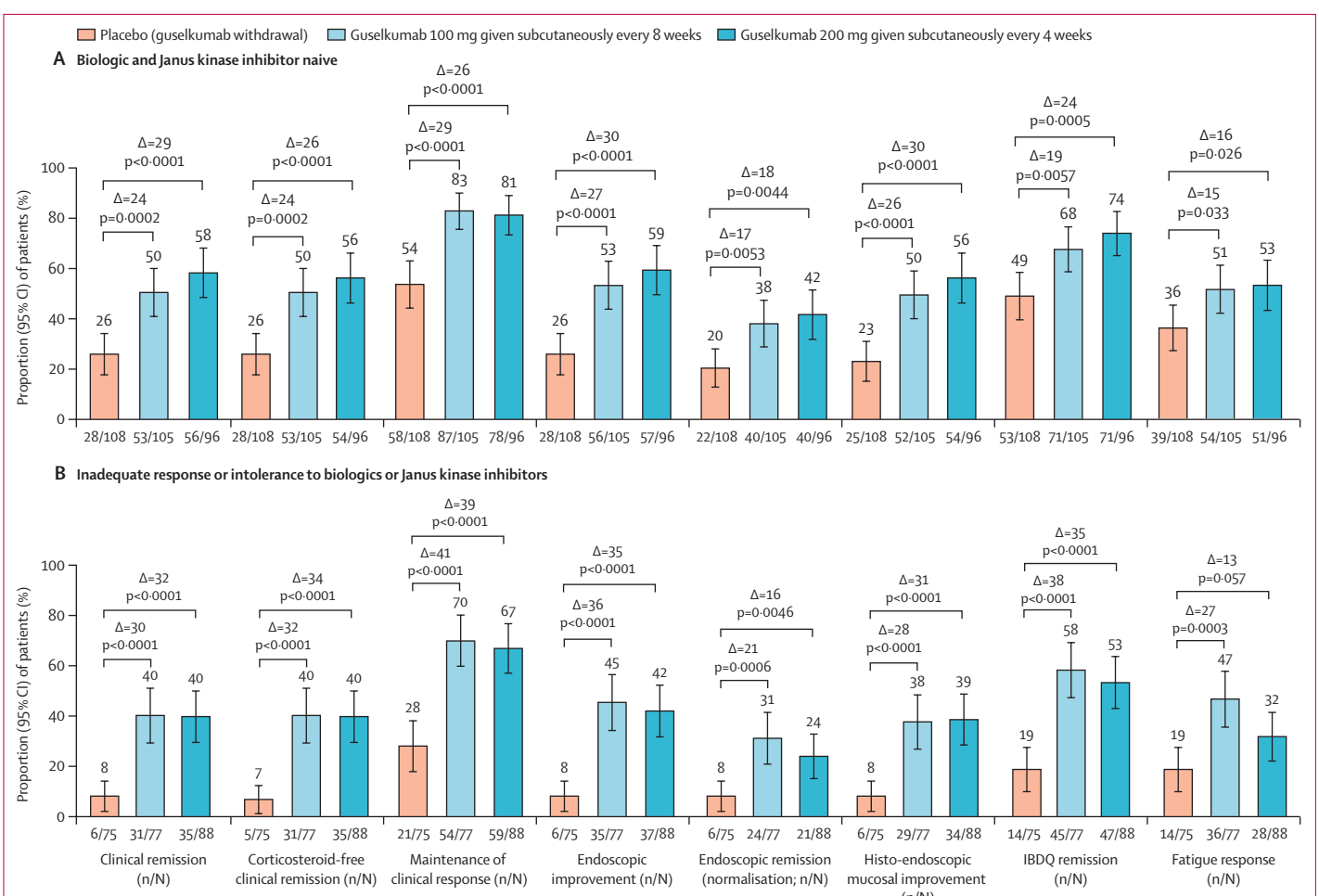

Figure 5: **Efficacy at maintenance week 44 among patients who were biologic naive and JAK inhibitor naive (A) and patients with a history of inadequate response or intolerance to biologics or JAK inhibitors (B) at induction baseline (randomised and treated patients only)**

All p values are nominal. All patients had a modified Mayo score from 5 to 9 at induction baseline. IBDQ=Inflammatory Bowel Disease Questionnaire. JAK=Janus kinase. M=maintenance.

week 44 (appendix pp 70–71), with similar relative increases also being observed for endoscopic and histological endpoints at maintenance week 44.

Among patients who received guselkumab and were in clinical remission at maintenance week 44, 99% (178 of 180 patients) were corticosteroid-free for at least 8 weeks before maintenance week 44. Among patients receiving oral corticosteroids at maintenance baseline, greater proportions of patients in both guselkumab groups eliminated oral corticosteroids as early as maintenance week 8 and continued to maintenance week 44 compared with placebo (appendix p 72).

Symptomatic remission and deep symptomatic remission achieved with guselkumab induction was generally maintained to maintenance week 44 with guselkumab relative to placebo (figure 4; appendix pp 73). Consistent with clinical endpoints, improvements in health-related quality of life endpoints at maintenance week 44 were better sustained in patients treated with guselkumab compared with placebo-treated patients (appendix p 75).

Guselkumab efficacy in the maintenance study was evident among both biologic-naive and JAK inhibitor-naive patients and in individuals with a history of inadequate response or intolerance to biologics or JAK inhibitors (figure 5; appendix p 74). Efficacy at maintenance week 44 by subsets of inadequate response or intolerance to biologics or JAK inhibitors have been shown in the appendix (pp 76–77). Clinical remission at maintenance week 44 by induction baseline demographic,

	Induction study		Maintenance study		
	Placebo given intravenously every 4 weeks (N=280)	Guselkumab 200 mg given intravenously every 4 weeks (N=421)	Placebo given subcutaneously (guselkumab withdrawal; N=192)	Guselkumab 100 mg given subcutaneously every 8 weeks (N=186)	Guselkumab 200 mg given subcutaneously every 4 weeks (N=190)
Mean duration of follow-up, weeks	11·9	12·2	34·0	40·5	39·2
Mean exposure (number of administrations)	2·9	2·9	8·2	9·9	9·6
Adverse events	138 (49%)	208 (49%)	131 (68%)	120 (65%)	133 (70%)
Serious adverse events	20 (7%)	12 (3%)	1 (1%)	5 (3%)	12 (6%)
Deaths	2 (1%)*	1 (0·2%)†	0	0	0
Adverse events leading to discontinuation of study agent	11 (4%)	7 (2%)	13 (7%)	7 (4%)	5 (3%)
Most frequent adverse events (≥5% of patients in any treatment group)					
Ulcerative colitis	23 (8%)	10 (2%)	57 (30%)	17 (9%)	25 (13%)
Anaemia	19 (7%)	21 (5%)	5 (3%)	4 (2%)	6 (3%)
COVID-19	12 (4%)	21 (5%)	27 (14%)	24 (13%)	18 (9%)
Headache	8 (3%)	13 (3%)	12 (6%)	7 (4%)	8 (4%)
Arthralgia	6 (2%)	6 (1%)	13 (7%)	8 (4%)	15 (8%)
Upper respiratory tract infection	1 (0·4%)	3 (1%)	8 (4%)	6 (3%)	13 (7%)
Targeted adverse events					
Serious infections‡	1 (0·4%)	3 (1%)	0	1 (1%)	2 (1%)
Opportunistic infections‡	1 (0·4%)§	0	0	0	0
Active tuberculosis	0	0	0	0	0
Major adverse cardiovascular event	2 (1%)¶	2 (0·5%)‖	0	0	1 (1%)**
Clinically important hepatic disorders††	0	0	0	0	0
Malignancies‡‡	0	0	2 (1%)§§	0	1 (1%)¶¶
Non-melanoma skin cancer	0	2 (0·5%)	2 (1%)	0	0
Anaphylactic reactions	0	0	0	0	0
Serum sickness reactions	0	0	0	0	0

Data are number of patients experiencing adverse event (%), unless stated otherwise. For both studies, the primary safety populations included randomised, treated patients with a modified Mayo score from 4 to 9 at induction baseline. For the maintenance study, two patients who were randomly assigned to the guselkumab 100 mg given subcutaneously every 8 weeks group only received placebo at maintenance week 0 and discontinued the study intervention before their first scheduled guselkumab dose at maintenance week 4; these patients were included in the placebo subcutaneous treatment group for safety analyses. For the maintenance study, data are from maintenance week 0 to maintenance week 44 or up to time of dose adjustment in patients who had a dose adjustment. *Natural causes and cardiac arrest. †Fatal acute myocardial infarction in a patient with pre-existing cardiac risk factors. ‡Infections were defined as any adverse event that was coded to the Medical Dictionary for Regulatory Activities system (version 26·0). §Cytomegalovirus colitis. ¶Natural causes and cardiac arrest. ||Non-fatal myocardial infarction and fatal acute myocardial infarction in patients with pre-existing cardiac risk factors. **Haemorrhagic stroke. ††Defined as hepatic adverse events reported as serious adverse events or adverse events leading to study drug discontinuation. ‡‡Excludes non-melanoma skin cancer. §§Breast cancer. ¶¶Rectal adenocarcinoma.

Table 2: **Overall summary of adverse events to induction week 12 in the QUASAR phase 3 induction study and from maintenance week 0 to maintenance week 44 in the QUASAR maintenance study (primary safety populations)**

disease characteristic, and ulcerative colitis-related medication subgroups has been shown in the appendix (pp 78–81).

Among patients with abnormal concentrations at induction baseline, reductions in markers of inflammation (C-reactive protein and faecal calprotectin) and normalisation of concentrations that were observed after induction were maintained in the maintenance study in the guselkumab groups, whereas the concentrations in the placebo group worsened (appendix p 82).

Consistent with the results of the clinical outcomes, clinically meaningful improvement in abdominal pain and symptoms of bowel urgency was sustained at maintenance week 44 in a greater proportion of patients treated with guselkumab than placebo-treated patients (appendix pp 83–84).

Among patients who lost clinical response and had a blinded guselkumab dose adjustment (placebo to guselkumab 200 mg given subcutaneously every 4 weeks, guselkumab 100 mg given subcutaneously every 8 weeks to 200 mg every 4 weeks, guselkumab 200 mg given subcutaneously every 4 weeks to 200 mg every 4 weeks [sham]), symptomatic response (78, 53, and 43 percentage-point improvement, respectively), and symptomatic remission (61, 26, and 23 percentage-point improvement, respectively) improved 12 weeks after dose adjustment (appendix pp 85–86).

Efficacy of guselkumab maintenance therapy at maintenance week 44 among randomised patients in the maintenance study with an induction baseline mMayo score of 4 (5% [31 of 599 patients]) was consistent with that of the primary analysis population (appendix p 87).

Efficacy results among week 24 guselkumab induction responders assigned to guselkumab maintenance treatment (non-randomised) show the benefit of guselkumab maintenance in this treatment-refractory patient population (appendix pp 88–89).

The incidences of anti-guselkumab antibodies and NAbs were low in both the induction and maintenance studies (appendix p 90). Among the patients who did develop anti-guselkumab antibodies, titres were low and did not affect serum concentration, efficacy, or safety.

Overall, in the phase 3 induction study, the proportions of patients with adverse events, serious adverse events, and adverse events leading to treatment discontinuation in induction week 12 were similar between groups (table 2). Adverse events were reported in 49% (208 of 421) of patients treated with guselkumab and 49% (138 of 280) of placebo-treated patients, with serious adverse events in 3% (12 of 421 patients) and 7% (20 of 280 patients), respectively, and adverse events leading to discontinuation in 2% (seven of 421 patients) and 4% (11 of 280 patients), respectively. The most frequently reported adverse events (≥5% in any group) in induction week 12 were ulcerative colitis, anaemia, and COVID-19. Two non-melanoma skin cancer events (both in the guselkumab group) and four major adverse cardiovascular events (two in the placebo group [both fatal] and two in the guselkumab group [one fatal]) were reported in induction week 12. No deaths were considered treatment related.

Overall, in the maintenance study, the proportion of patients with adverse events was similar across treatment groups (guselkumab 100 mg every 8 weeks, 65% [120 of 186 patients]; guselkumab 200 mg every 4 weeks, 70% [133 of 190 patients]; and placebo group, 68% [131 of 192 patients; table 2). The most frequently reported adverse events were ulcerative colitis, COVID-19, arthralgia, headache, and upper respiratory tract infection. The incidences of serious adverse events and adverse events leading to treatment discontinuation, respectively, were 3% (five of 186 patients) and 4% (seven of 186 patients) in the guselkumab 100 mg group, 6% (12 of 190 patients) and 3% (five of 190 patients) in the guselkumab 200 mg group, and 1% (one of 192 patients) and 7% (13 of 192 patients) in the placebo (guselkumab withdrawal) group. The serious adverse events reported in either study did not have a clear pattern with respect to event or class, and most were considered unrelated to guselkumab. No serious adverse event was reported in more than two patients treated with guselkumab in either study except for ulcerative colitis (n=8 total across studies).

From maintenance week 0 to maintenance week 44, non-melanoma skin cancer occurred in 0·4% (two of 568 patients; both in the placebo group), other malignancies occurred in 0·5% (three of 568 patients; two in the placebo group and one in the guselkumab 200 mg group) of patients, and a major adverse cardiovascular event occurred in 0·2% (one of 568 patients; in the guselkumab 200 mg group) of patients; no deaths were reported.

No cases of active tuberculosis, anaphylaxis, serum sickness, Hy's Law, or clinically important hepatic disorders were reported in patients receiving guselkumab in either study.

Overall, safety results in the all-treated populations in both studies were consistent with those in the primary analysis populations (appendix pp 91–92). Notably, the incidence of serious adverse events in the maintenance study was balanced across groups in this population (guselkumab 100 mg every 8 weeks, 3% [five of 197 patients]; guselkumab 200 mg every 4 weeks, 6% [24 of 422 patients]; and placebo group, 5% [15 of 314 patients]), which includes all randomised and non-randomised patients in the maintenance study regardless of baseline mMayo score.

Discussion

The QUASAR confirmatory phase 3 induction study has shown significant efficacy of guselkumab 200 mg given intravenously every 4 weeks induction in patients with moderately to severely active ulcerative colitis, as measured by the primary endpoint of clinical remission at induction week 12, and seven of nine major secondary endpoints. Importantly, symptomatic improvements

were observed as early as induction week 1 (first timepoint assessed). Efficacy and safety in the phase 3 induction study were similar to those observed in the phase 2b induction study.[18]

In the pivotal maintenance study, the clinical benefits observed in guselkumab intravenous induction responders from both induction studies were sustained or further improved to maintenance week 44 with guselkumab given subcutaneously and worsened in patients who received placebo (guselkumab withdrawal). The primary endpoint of clinical remission at maintenance week 44 and all nine major secondary endpoints were met with both guselkumab maintenance dose regimens. In addition, nearly all patients in clinical remission at maintenance week 44 were corticosteroid free, and more than half of patients receiving corticosteroids at the beginning of maintenance were able to eliminate them.

The robust treatment effect of guselkumab for induction and maintenance in patients with ulcerative colitis was shown by clinically meaningful differences compared with placebo across clinical, endoscopic, histological, symptomatic, and patient-reported outcome measures in both studies and among clinically relevant patient subgroups. The substantial improvement of fatigue with guselkumab is also notable given that fatigue is a prevalent, debilitating symptom in patients with ulcerative colitis.[7]

Although head-to-head comparison data with other IL-23 antagonists are currently not available, we observed substantive rates of objective measures of disease remission, including endoscopic and histological remission endpoints at maintenance week 44 in the QUASAR phase 3 maintenance study.[10,14,21,22] Importantly, complete mucosal healing is associated with improved long-term outcomes,[23,24] and favourable outcomes beyond 1 year are anticipated among patients who achieved these histological and endoscopic endpoints.[7]

The primary analysis populations were treatment refractory; approximately 50% of patients had a history of inadequate response or intolerance to one or more biologic or JAK inhibitor, and approximately half of these patients had an inadequate response or intolerance to two or more agents. Furthermore, induction baseline disease activity was high as evidenced by the proportions of patients with an mMayo score or a Mayo endoscopic subscore indicating severe disease or elevated inflammatory biomarkers. The efficacy of guselkumab was shown in both biologic and JAK inhibitor-naive patients and in patients with a history of inadequate response or intolerance to biologics or JAK inhibitors. In conjunction with the demonstrated safety profile, these data suggest that guselkumab is a compelling treatment option for both subpopulations. Additionally, guselkumab has a suitable profile for combination treatment strategies in inflammatory bowel disease with proof-of-concept shown in ulcerative colitis.[15]

Patients with an induction baseline mMayo score of 4, including a Mayo endoscopic subscore of at least 2 and a rectal bleeding subscore of at least 1, had a lower disease burden than the primary analysis population but still had clinically active ulcerative colitis with substantial symptoms. Guselkumab induction and maintenance efficacy was observed in this subpopulation, although the number of patients was relatively small.

Across the QUASAR programme, safety results were consistent with the known and favourable safety profile of guselkumab in its approved indications. Rates of adverse events, serious adverse events, and adverse events leading to treatment discontinuation generally did not occur more frequently in patients treated with guselkumab versus placebo-treated patients. In the maintenance study, apparent differences in the incidence of serious adverse events with guselkumab versus placebo could have been driven by a lower-than-expected serious adverse event incidence in the placebo group, which was not observed in the all-treated population. In addition, the placebo serious adverse event rates in other studies, including other IL-23 antagonists, are higher than the observed randomised maintenance placebo serious adverse event rate and comparable with the guselkumab serious adverse event rate in the QUASAR programme.[10,14,21,22] Furthermore, no incremental safety risks were observed between induction and maintenance, and there were no clinically meaningful differences in safety between the two maintenance dose regimens.

Limitations of the study should be considered when interpreting the results. The efficacy observed at maintenance week 44 should be interpreted within the context of the induction randomised-withdrawal study design. The primary analysis population for the maintenance study included only guselkumab induction responders following 12 weeks of intravenous treatment; therefore, efficacy results would be different if all patients entered the maintenance study regardless of their clinical response to induction therapy. Maintenance outcomes in week 24 guselkumab induction responders were evaluated without a placebo comparator, and these patients only received the higher subcutaneous dose regimen in the maintenance study. In addition, while the QUASAR programme was enrolling, additional ulcerative colitis therapies were approved, and patients with an inadequate response to these therapies, including ustekinumab, are not represented in the study population. Follow-up beyond 44 weeks of maintenance treatment is not available. A long-term extension of the study is ongoing.

Taken together, the results from the QUASAR programme show the efficacy and safety of guselkumab for induction with guselkumab 200 mg given intravenously every 4 weeks and maintenance therapy for 1 year with both guselkumab 200 mg given subcutaneously every 4 weeks and 100 mg given subcutaneously every 8 weeks maintenance dose regimens in patients with moderately to severely active ulcerative colitis.

Contributors

DTR, JRA, JP, K-HGH, MG, HZ, JJ, BGF, TH, GRL, BB, LP-B, BES, and AD contributed to the study design. RW, HZ, JJ, and BB assessed and verified the data. RW, HZ, 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.

Declaration of interests

DTR reports consulting, speaker fees, and advisory board participation for AbbVie, Altrubio, Apex, Avalo, Bristol Myers Squibb, Buhlmann Diagnostics, Celgene, Connect BioPharma, Iterative Health, Janssen (Johnson & Johnson), Lilly, Pfizer, Samsung Neurologica, and Takeda; Altrubio, Datos Health, and Iterative Health stock options; grants from Takeda; and is on the Board of Directors of Cornerstones Health and on the Crohn's & Colitis Foundation's Board of Trustees. JRA reports research support from Merck and Pfizer; consulting and speaker fees from AbbVie, Artugen Therapeutics, Bristol Myers Squibb, Ferring, Finch Therapeutics, Iterative Scopes, Janssen, Merck, Pfizer, and Seres Therapeutics; and is a steering committee member and investigator for Janssen. JP reports consulting fees from AbbVie, Alimentiv, Athos, Boehringer Ingelheim, Celsius, Ferring, Galapagos, Genentech (a subsidiary of Roche), GlaxoSmithKline, Janssen, Mirum, Nimbus, Pfizer, Progenity, Prometheus, Protagonis, Revolo, Sanofi, Sorriso, Surrozen, Takeda, and Wasserman; and fees for data safety monitoring board or advisory board participation from Alimentiv, Sanofi, Sorriso, and Surrozen. NS, SSY, K-HGH, MG, RW, HZ, and JJ are employees of Janssen Research & Development, which is a wholly owned subsidiary of Johnson & Johnson, and might own stock in Johnson & Johnson. BGF reports consulting and speaker fees from AbbVie, AbolerIS, AgomAB Therapeutics, Allianthera, Amgen, AnaptysBio, Applied Molecular Transport, Arena, Avoro Capital Advisors, Atomwise, BioJamp, Biora (Progenity), Boehringer-Ingelheim, Boxer, Business Intelligence Pharma, Celsius Therapeutics, Celgene (a subsidiary of Bristol-Myers Squibb), Connect BioPharma, Cytoki Pharma, Disc Medicine, Duality, EcoR1 Capital, Equillium, Ermium, First Wave, First Word Group, Galapagos, Galen Atlantica, Genentech (a subsidiary of Roche), Gilead, Gossamer Bio, GlaxoSmithKline, Hinge Bio, Hot Spot Therapeutics, Imhotex, Immunic Therapeutics, InDex Pharmaceuticals, JAKAcademy, Janssen, Japan Tobacco, Kaleido Biosciences, Landos Biopharma, Leadiant, L.E.K. Consulting, LifeSci Capital, Lilly, Lument AB, Millennium, MiroBio, Morphic Therapeutic, Mylan, OM Pharma, Origo BioPharma, Orphagen, Pandion Therapeutics, Pendopharm, Pfizer, PlayToKnow AG, Prometheus Therapeutics and Diagnostics, Protagonist, PTM Therapeutics, Q32 Bio, Rebiotix, REDX Pharma, Roche, Sandoz, Sanofi, Seres Therapeutics, Silverback Therapeutics, Surrozen, Takeda, Teva, Thelium, Tigenix, Tillotts, Ventyx Biosciences, VHsquared, Viatris, Ysios, Ysopia, and Zealand Pharma; payment for expert testimony from Morgan Lewis and Lenczner Slaght; support for meeting attendance and travel from AbbVie, Business Intelligence Pharma, Janssen, Pfizer, and Takeda; data safety monitoring board or advisory board participation for AbbVie, Amgen, AMT Pharma, AnaptysBio, Axio Research, Biora (Progenity), Boehringer-Ingelheim, Celgene, EcoR1 Capital, Genentech (a subsidiary of Roche), GlaxoSmithKline, InDex Pharmaceuticals, Janssen, Lilly, MiroBio, Morphic Therapeutic, Origo BioPharma, Pfizer, Prometheus Biosciences, REDX Pharma, Sanofi, Takeda, Teva, and Tillotts; and stock or stock option ownership in Gossamer Bio. TH reports research grants from AbbVie, Boston Scientific, Daiichi-Sankyo, EA Pharma Co, JIMRO Co, Mitsubishi Tanabe Pharma Corporation, Kissei Pharmaceutical, Kyorin Pharmaceutical Co, Mochida Pharmaceutical Co, Nippon Kayaku Co, Pfizer, Takeda Pharmaceutical Co, Zeria Pharmaceutical Co; and consulting fees and honoraria from AbbVie GK, Bristol Myers Squibb, EA Pharma Co, Gilead Sciences, Janssen Pharmaceutical, Kyorin Pharmaceutical Co, Lilly, Mitsubishi Tanabe Pharma Corp, Nichi-Iko Pharmaceutical Co, Pfizer, Takeda Pharmaceutical Co, and Zeria Pharmaceutical Co. GRL reports consulting fees, speaker fees, and meeting attendance or travel support from AbbVie, Allergan, American Gastroenterological Association, American Regent (Creative Educational Concepts), Amgen (continuing medical education sponsor), Boehringer Ingelheim (continuing medical education sponsor), Bristol Meyers Squibb, Celgene, Exact Sciences (continuing medical education sponsor), Ferring, Focus Medical Communications, Gilead, IBD Horizon, Ironwood, Janssen (continuing medical education sponsor), Janssen Biotech (continuing medical education sponsor), Janssen Orthobiotech, Janssen Scientific (continuing medical education sponsor), Lilly, MedEd Consultants, Pennsylvania Society of Gastroenterology, Pfizer, Pharmacosmos, Physician Education Resource, Prometheus Laboratories, Salix (continuing medical education sponsor), Sandoz, Sanofi (continuing medical education sponsor), Seres Pharmaceuticals (continuing medical education sponsor), Takeda, UCB, and Vindico; research support from Bristol Meyers Squibb, Celgene, Janssen Orthobiotech, Pfizer, Takeda, and UCB; data safety monitoring board participation with Lilly; honoraria from Gastroenterology and Hepatology (Gastro-Hep Communications; editor), Springer Science and Business Media (editor), and Up-To-Date-Walters Kluwer (author); royalties from SLACK (book royalty) and Professional Communications (textbook royalty); and Chair, Professional Education Committee and Member of the National Scientific Advisory Committee for Crohn's Colitis Foundation. BB reports consulting and speaker fees from AbbVie, Alimentiv, Amgen, Bausch Health, BioJamp Pharma, Bristol Myers Squibb, Celgene, Celltrion, Eupraxia, Ferring, Fresenius Kabi, Gilead, Iterative Health, Janssen, Lifelabs, Lilly, Merck, Mylan, Novartis, Organon, Pendopharm, Pfizer, Sandoz, Takeda, and Viatris; serves on a data safety monitoring board or advisory board for Eupraxia; and owns Qu Biologic stock. LP-B reports grants or contracts from Celltrion, Fresenius Kabi, Medac, Merck Sharp & Dohme, and Takeda; consulting and payment or honoraria and data safety monitoring board or advisory board participation for AbbVie, Abivax, Adacyte, Alfasigma, Alimentiv, Amgen, Applied Molecular Transport, Arena, Banook, Biogen, Bristol Myers Squibb, Celltrion, Connect Biopharm, Cytoki Pharma, Enthera, Ferring, Fresenius Kabi, Galapagos, Genentech, Gilead, Gossamer Bio, GlaxoSmithKline, IAC Image Analysis, Index Pharmaceuticals, Inotrem, Janssen, Kern Pharma, Lilly, Medac, Mopac, Morphic, Merck Sharp & Dohme, Nordic Pharma, Novartis, Oncodesign Precision Medicine, ONO Pharma, OSE Immunotherapeutics, Pandion Therapeutics, Par' Immune, Pfizer, Prometheus, Protagonist, Roche, Samsung, Sandoz, Sanofi, Satisfay, Takeda, Telavant, Theravance, Thermo Fischer, Tigenix, Tillots, Viatris, Vectivbio, Ventyx, and Ysopia; and meeting attendance and travel support from AbbVie, Alfasigma, Amgen, Celltrion, Connect Biopharm, Ferring, Galapagos, Genentech, Gilead, Gossamer Bio, Janssen, Lilly, Medac, Morphic, Merck Sharp & Dohme, Pfizer, Sandoz, Takeda, Thermo Fischer, and Tillots. BES reports medical writing support from AbbVie, Abivax, Bristol Myers Squibb, Celltrion, Janssen (a subsidiary of Johnson & Johnson), Lilly, Merck, Pfizer, and Takeda; institutional grants or contracts from Bristol Myers Squibb and Janssen (a subsidiary of Johnson & Johnson); consulting fees and payment or honoraria and data safety monitoring board or advisory board participation for AbbVie, Abivax, Adiso Therapeutics, Agomab, Alimentiv, Amgen, AnaptysBio, Arena Pharmaceuticals, Artugen Therapeutics, AstraZeneca, Biolojic Design, Biora Therapeutics, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Calibr, Celgene, Celltrion, ClostraBio, Equilium, Enthera, Enveda Biosciences, Evommune, Ferring, Fresenius Kabi, Galapagos, Genentech (Roche), Gilead Sciences, Glaxo SmithKline, Gossamer Bio, Imhotex, Immunyx Pharmaceuticals, Index Pharmaceuticals, Innovation Pharmaceuticals, Inotrem, Janssen, Johnson & Johnson, Kaleido, Kallyope, Lilly, Merck, Microbiotics, Mitsubishi Tanabe, Mobius Care, Morphic Therapeutics, MRM Health, Nexus Therapeutics, Nimbus Discovery, Odyssey Therapeutics, Palisade Bio, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Rasayana Therapeutics, Recludix Therapeutics, Reistone Biopharma, Sanofi, Sorriso Therapeutics, Spyre Therapeutics, Sun Pharma, Surrozen, Takeda, Target RWE, Teva, Theravance Biopharma, TLL Pharmaceutical, Tr1X, Union Therapeutics, and Ventyx Bioscience; meeting attendance and travel support from Janssen, Lilly, Mitsubishi Tanabe, and Pfizer; and stock in Ventyx Bioscience. AD reports consulting and speaker fees from AbbVie, Abivax, Amgen, Arena, Biogen, Bristol Myers Squibb, Celgene (a subsidiary of Bristol Myers Squibb), Celltrion, Falk Foundation, Ferring, Fresenius Kabi, Galapagos, Gilead, High5MD, Janssen, Lilly, Materia Prima, MedToday, Novartis, Pfizer, Pharmacosmos, Roche (a subsidiary of Genentech),

Sandoz, Sandoz (a subsidiary of Hexal), Streamed-Up, Takeda, Tillotts, and Vifor and payment for manuscript preparation from Biogen, Falk Foundation, Janssen, Takeda, and Thieme.

Data sharing

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this website, requests for access to the study data can be submitted through the Yale Open Data Access project site at http://yoda.yale.edu.

Acknowledgments

We thank the patients, investigators, study site personnel, and the QUASAR Clinical and Cross-Functional Trial Teams. The study was funded by Janssen Research and Development. Holly Capasso-Harris (Certara) provided writing assistance under the direction of the authors in accordance with Good Publication Practice guidelines. Writing assistance was funded by Janssen Global Services.

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