Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials

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Summary

Background Risankizumab, an interleukin (IL)-23 p19 inhibitor, was evaluated for safety and efficacy as induction therapy in patients with moderately to severely active Crohn's disease.

Methods ADVANCE and MOTIVATE were randomised, double-masked, placebo-controlled, phase 3 induction studies. Eligible patients aged 16–80 years with moderately to severely active Crohn's disease, previously showing intolerance or inadequate response to one or more approved biologics or conventional therapy (ADVANCE) or to biologics (MOTIVATE), were randomly assigned to receive a single dose of intravenous risankizumab (600 mg or 1200 mg) or placebo (2:2:1 in ADVANCE, 1:1:1 in MOTIVATE) at weeks 0, 4, and 8. We used interactive response technology for random assignment, with stratification by number of previous failed biologics, corticosteroid use at baseline, and Simple Endoscopic Score for Crohn's disease (SES-CD). All patients and study personnel (excluding pharmacists who prepared intravenous solutions) were masked to treatment allocation throughout the study. Coprimary endpoints were clinical remission (defined by Crohn's disease activity index [CDAI] or patient-reported outcome criteria [average daily stool frequency and abdominal pain score]) and endoscopic response at week 12. The intention-to-treat population (all eligible patients who received at least one dose of study drug in the 12-week induction period) was analysed for efficacy outcomes. Safety was assessed in all patients who received at least one dose of study drug. Both trials were registered on ClinicalTrials.gov, NCT03105128 (ADVANCE) and NCT03104413 (MOTIVATE), and are now complete.

Findings Participants were enrolled between May 10, 2017, and Aug 24, 2020 (ADVANCE trial), and Dec 18, 2017 and Sept 9, 2020 (MOTIVATE trial). In ADVANCE, 931 patients were assigned to either risankizumab 600 mg (n=373), risankizumab 1200 mg (n=372), or placebo (n=186). In MOTIVATE, 618 patients were assigned to risankizumab 600 mg (n=206), risankizumab 1200 mg (n=205), or placebo (n=207). The primary analysis population comprised 850 participants in ADVANCE and 569 participants in MOTIVATE. All coprimary endpoints at week 12 were met in both trials with both doses of risankizumab (p values ≤0·0001). In ADVANCE, CDAI clinical remission rate was 45% (adjusted difference 21%, 95% CI 12–29; 152/336) with risankizumab 600 mg and 42% (17%, 8–25; 141/339) with risankizumab 1200 mg versus 25% (43/175) with placebo; stool frequency and abdominal pain score clinical remission rate was 43% (22%, 14–30; 146/336) with risankizumab 600 mg and 41% (19%, 11–27; 139/339) with risankizumab 1200 mg versus 22% (38/175) with placebo; and endoscopic response rate was 40% (28%, 21–35; 135/336) with risankizumab 600 mg and 32% (20%, 14–27; 109/339) with risankizumab 1200 mg versus 12% (21/175) with placebo. In MOTIVATE, CDAI clinical remission rate was 42% (22%, 13–31; 80/191) with risankizumab 600 mg and 40% (21%, 12–29; 77/191) with risankizumab 1200 mg versus 20% (37/187) with placebo; stool frequency and abdominal pain score clinical remission rate was 35% (15%, 6–24; 66/191) with risankizumab 600 mg and 40% (20%, 12–29; 76/191) with risankizumab 1200 mg versus 19% (36/187) with placebo; and endoscopic response rate was 29% (18%, 10–25; 55/191) with risankizumab 600 mg and 34% (23%, 15–31; 65/191) with risankizumab 1200 mg versus 11% (21/187) with placebo. The overall incidence of treatment-emergent adverse events was similar among the treatment groups in both trials. Three deaths occurred during induction (two in the placebo group [ADVANCE] and one in the risankizumab 1200 mg group [MOTIVATE]). The death in the risankizumab-treated patient was deemed unrelated to the study drug.

Interpretation Risankizumab was effective and well tolerated as induction therapy in patients with moderately to severely active Crohn's disease.

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Research in context

Evidence before this study

We searched PubMed for English language articles using the terms "Crohn's disease" and "interleukin-23" with clinical trial as the article type to identify controlled clinical trials of interleukin (IL)-23 inhibitors in patients with Crohn's disease published from database inception up to Sept 8, 2021. Of the 15 results, five described results from randomised controlled trials of an antibody targeting the p40 subunit of IL-12 or IL-23, and four reported results from randomised controlled trials of antibodies targeting the p19 subunit of IL-23. Although biologics are a major advance in the treatment of inflammatory bowel disease, many patients with moderately to severely active Crohn's disease do not respond, lose response over time, or have side-effects leading to discontinuation. Additional therapies with novel mechanisms of action are therefore needed. Risankizumab is a selective monoclonal antibody targeting the unique p19 subunit of the heterodimeric cytokine interleukin (IL)-23. Selective inhibition of IL-23 is highly effective and superior to anti-p40 drugs for the treatment of other immune-mediated inflammatory diseases, such as psoriasis. In treatment-experienced patients with moderately to severely active Crohn's disease, a phase 2 study has supported the efficacy of risankizumab in inducing and maintaining clinical remission.

Added value of this study

We present the results of two phase 3 induction studies of intravenous risankizumab (600 mg and 1200 mg) in patients with moderately to severely active Crohn's disease, who had previously shown intolerance or inadequate response to biologic therapy (ie, with previous bio-failure) or conventional therapy (ie, without previous bio-failure). These trials are the first completed phase 3 registrational studies in Crohn's disease that included centrally read endoscopic scores both as a selection criterion and coprimary outcome measure for all patients. In addition, novel endpoints of response and clinical remission as defined by the patient-reported outcomes of stool frequency and abdominal pain were assessed. In both trials, both doses of risankizumab achieved early symptom control by week 4, and endoscopic evidence of improvement of the mucosa at week 12. Furthermore, risankizumab as induction therapy was generally well tolerated and effective in patients with previous bio-failure and those without previous bio-failure.

Implications of all the available evidence

Selective blockade of IL-23 with risankizumab is a new mechanism of action being investigated for the treatment of moderately to severely active Crohn's disease. The ADVANCE and MOTIVATE induction studies indicated efficacy of risankizumab in patients with Crohn's disease with refractory disease to one or more lines of biologic therapies including anti-tumour necrosis factor drugs, anti-integrin drugs, and ustekinumab (an anti-p40 [anti-IL-12/23]) drug. The safety observed in ADVANCE and MOTIVATE is consistent with the known safety profile of risankizumab, further supporting its risk–benefit profile.

Introduction

Interleukin (IL)-23 inhibition is a promising therapeutic approach to treat Crohn's disease. IL-23 is an inflammatory cytokine comprising a distinct p19 subunit and a p40 subunit shared with IL-12.[1] IL-23 modulates intestinal inflammation through effector cytokines that include IL-22.[2] Elevated concentrations of IL-23 are present in the mucosa of patients with Crohn's disease, and genome-wide association studies have shown a strong correlation between polymorphisms of the IL-23 or IL-23 receptor (*IL-23R*) gene and inflammatory bowel diseases.[3–6] *IL-23R* gene variants have been shown to modulate IL-22 serum concentrations, which, in turn, have been shown to correlate with disease activity.[7–9] A phase 2a study examining anti-IL-23 therapy in patients with Crohn's disease identified a decrease in serum IL-22 concentrations after treatment, with greater clinical remission and response rates in patients with higher baseline serum IL-22.[10] Therefore, IL-22 might be clinically useful both as a downstream biomarker of Crohn's disease activity and as a pharmacodynamic biomarker of IL-23 activity.

Risankizumab is a monoclonal antibody that selectively binds to the IL-23 p19 subunit, inhibiting its interaction with the IL-23R complex, and is currently approved for the treatment of plaque psoriasis and psoriatic arthritis. In a randomised, double-masked, phase 2 study in patients with moderately to severely active Crohn's disease, intravenous induction therapy with risankizumab was well tolerated and efficacious at doses of 200 mg and 600 mg in patients who were naive to, or previously treated with, tumour necrosis factor (TNF) antagonist therapy or vedolizumab.[11] Higher efficacy was observed with the 600 mg dose; however, because a plateau of response was not reached, it was unknown if a dose higher than 600 mg would provide greater efficacy. Here, we report the primary results from the first 12 weeks of two phase 3 studies, ADVANCE and MOTIVATE. These trials evaluated the efficacy and safety of 600 mg and 1200 mg intravenous risankizumab as induction therapy in patients with moderately to severely active Crohn's disease who had previously shown intolerance or inadequate response to conventional or biologic therapies.

Methods

Study design and participants

ADVANCE and MOTIVATE were phase 3, multicentre, double-masked, randomised, placebo-controlled induction trials performed globally at 297 sites in 39 countries (ADVANCE) and 214 sites in 40 countries (MOTIVATE; appendix p 34). Sites included hospitals, academic medical centres, clinical research units, and private practices. Each study included a screening period

of up to 35 days, a 12-week induction period (induction period 1), an additional exploratory 12-week prolonged induction period (induction period 2) for patients not achieving clinical response (defined as ≥30% decrease from baseline in average daily stool frequency or ≥30% decrease from baseline in average daily abdominal pain score, or both, and neither worse than baseline; derived from the patient's electronic diary at week 12), and a 140-day follow-up period from the last dose of study drug. Patients achieving clinical response to risankizumab in ADVANCE or MOTIVATE were eligible for enrolment in FORTIFY, the proceeding 52-week maintenance withdrawal phase 3 study.[12] Only the results from the first 12-week induction period of ADVANCE and MOTIVATE are reported here.

The ADVANCE trial enrolled patients with demonstrated intolerance or inadequate response to conventional therapies (ie, without previous bio-failure) or biologic therapies (ie, with previous bio-failure), or to both conventional and biologic therapies; whereas, enrolment into the MOTIVATE trial was restricted to only patients with previous bio-failure. Conventional and biologic therapies are listed in the appendix (pp 14–15). Patients who received biologic therapy but discontinued due to reasons other than inadequate response or intolerance (eg, change in reimbursement coverage, well controlled disease) were considered biologic-exposed, but without previous bio-failure. In both studies, enrolment of patients with previous ustekinumab exposure was capped at 20%. Patients were enrolled (eg screened and consented) at routine check-ups.

In both trials, eligible patients were aged 16 to 80 years with a confirmed diagnosis of Crohn's disease for at least 3 months before baseline, and moderately to severely active disease defined by Crohn's disease activity index (CDAI) score of 220–450 at baseline, average daily stool frequency (≥4) or average daily abdominal pain score (≥2; or both stool frequency ≥4 and abdominal pain score ≥2), and endoscopic evidence of mucosal inflammation documented by the Simple Endoscopic Score for Crohn's disease (SES-CD ≥6, or ≥4 for isolated ileal disease; termed the original SES-CD, referring to the original SES-CD eligibility score before the protocol was amended to include patients with low SES-CD, described later). SES-CD values were calculated at screening. The eligibility score excluded the presence of the narrowing component. All patients needed to meet the eligibility SES-CD criteria to be enrolled and all SES-CD values were confirmed centrally. Predefined rules for imputation of missing SES-CD variables were used at baseline and follow-up (ie, missing variables were imputed as 0 unless more than eight individual variables were missing, in which case the entire SES-CD was considered missing). A subset of patients with an SES-CD of 3–5 for colonic or ileocolonic disease, or of 3 for isolated ileal disease (termed low SES-CD) were also randomly assigned and included in the study for exploratory analyses; these patients were included in safety analyses but not in the primary population for efficacy analyses. Full eligibility criteria are provided in the appendix (pp 14–22).

The studies were approved by independent ethics committees or institutional review boards at each study site. Studies were conducted and reported in accordance with the protocol, and in accordance with the International Conference on Harmonization Good Clinical Practice Guideline, applicable regulations, and the Declaration of Helsinki. Adult patients and parents or legal guardians of adolescent patients provided written informed consent before screening.

Randomisation and masking

Enrolled patients were randomly assigned with interactive response technology (2:2:1 in ADVANCE, 1:1:1 in MOTIVATE) to receive intravenous risankizumab 600 mg, intravenous risankizumab 1200 mg, or placebo over a 12-week period (induction period 1). Randomisation was stratified by the number of previous biologics that had failed to provide adequate response (0, 1, >1 in ADVANCE; 1, >1 in MOTIVATE), corticosteroid use at baseline (yes, no), and SES-CD (original, low). Patients without clinical response to risankizumab at week 12 entered induction period 2 and were randomly assigned (1:1:1) to receive intravenous risankizumab 1200 mg, subcutaneous risankizumab 360 mg, or subcutaneous risankizumab 180 mg with continued masking throughout induction period 2. Patients without clinical response to placebo at week 12 received intravenous risankizumab 1200 mg with continued masking of drug treatment. Because induction period 2 was exploratory in nature and the pivotal portion of the study assessed coprimary endpoints for the first 12 week period, the results for induction period 2 will be reported in a future publication. An unmasked pharmacist (or qualified designee) prepared the intravenous solutions. Saline of equal volume to study drug was administered as the placebo. Placebo and study drug were administered via covered syringes. In both trials, study investigators enrolled participants and randomisation was performed by Endpoint Clinical (San Francisco, California, USA). Study investigators, study site personnel, and patients were masked to treatment allocation throughout the study.

See Online for appendix

Procedures

Patients received a single dose of risankizumab or placebo intravenously at weeks 0, 4, and 8. A plus or minus 7 days window was permitted around all scheduled doses and study visits. The final study visit was scheduled for week 12 (or the date of premature discontinuation). Patients recorded symptoms related to Crohn's disease daily (including stool frequency, abdominal pain score, and general well being) in an electronic diary. An ileocolonoscopy was performed during screening and at week 12 (or at of premature discontinuation). Patients

who entered induction period 2 had an additional ileocolonoscopy at week 24 (12 weeks after induction period 1). Blood samples were collected throughout the study for laboratory testing, including assays to measure C-reactive protein (high-sensitivity [hs]-CRP, measured at baseline and weeks 4, 8, and 12) and IL-22 (measured at baseline and week 12). Stool samples for faecal calprotectin analysis were collected at baseline, and weeks 4 and 12. Risankizumab serum concentrations, antidrug antibody, and neutralising antibody were measured at weeks 4, 8, and 12 (without antibody isotyping; appendix p 31). Safety assessments, including adverse events, physical examination, vital signs, and clinical laboratory parameters, were done at weeks 4, 8, and 12 (or at premature discontinuation). Patients were expected to notify the principal investigator if any safety event occurred at any time.

Outcomes

The coprimary endpoints were clinical remission and endoscopic response at week 12. Due to regional differences in regulatory requirements (preference for CDAI-based endpoints in the USA and for endpoints based on patient-reported outcomes in Europe), clinical remission was defined as CDAI less than 150 (ie, CDAI clinical remission)[13] in the US analysis plan. In the non-US analysis plan, clinical remission was defined as average daily liquid or very soft stool frequency of 2·8 or less, plus average daily abdominal pain score of 1 or less, and both not worse than baseline (termed stool frequency and abdominal pain score clinical remission). Average daily stool frequency and abdominal pain score were calculated using the 7 most useable days of patient-report outcomes (ie, excluding days with missing entries or associated with endoscopy procedures) out of the 14 days before the visit. All patients were analysed for both clinical remission definitions. In both the US and non-US analysis plans, endoscopic response was defined as a greater than 50% decrease in SES-CD from baseline (or for isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), per central read. The cut-off criteria for stool frequency, abdominal pain score, and SES-CD were defined on the basis of a literature review and data analyses of adalimumab and risankizumab phase 2 studies, with alignment from regulatory agencies.[14–16]

Key secondary endpoints were CDAI clinical response at week 4 and week 12 (reduction in CDAI of ≥100 points from baseline), CDAI clinical remission at week 4 (CDAI <150), enhanced stool frequency and abdominal pain score clinical response at week 4 and week 12 (≥60% decrease from baseline in average daily stool frequency or ≥35% decrease from baseline in average daily abdominal pain score, or both, and neither worse than baseline, or stool frequency and abdominal pain score clinical remission), stool frequency remission at week 12 (average daily stool frequency ≤2·8 and not worse than baseline), abdominal pain score remission at week 12 (average daily abdominal pain score ≤1 and not worse than baseline), stool frequency and abdominal pain score clinical remission at week 4, endoscopic remission at week 12 (SES-CD ≤4 and at least a 2-point reduction *vs* baseline and no subscore >1 in any individual variable, as scored by a central reviewer), ulcer-free endoscopy at week 12 (ie, absence of ulceration; SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥1 at baseline, per central read), and a composite endpoint of clinical response and endoscopic response at week 12 (CDAI clinical response and endoscopic response, or enhanced stool frequency and abdominal pain score clinical response and endoscopic response, in the same patient). Several endpoints at additional timepoints (eg, week 8) are also reported (appendix p 11). Other planned secondary endpoints are not reported and will be reported in a future paper.

Safety was assessed according to the incidence of adverse events, abnormal findings at physical examination, changes in vital signs, and clinical laboratory parameters. Treatment-emergent adverse events were defined as events with onset after the first dose of study drug and within 140 days after the last dose of study drug administered in the 12-week induction period, or before the first dose of study drug in induction period 2 or the FORTIFY maintenance study (if applicable), whichever occurred first.[12] All adverse events were coded with the Medical Dictionary for Regulatory Activities (version 23.1) and graded with the National Cancer Institute Common Terminology Criteria for Adverse Events (version 4.03). Cardiovascular events and anaphylactic events were identified on the basis of a predefined search of adverse event terms and were adjudicated by independent external committees. Major adverse cardiovascular events (MACEs) were defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; extended MACEs were defined as MACEs along with hospitalisation for unstable angina and coronary revascularisation procedures.

Statistical analysis

Data from the ADVANCE and MOTIVATE trials were analysed independently. The sample size for each study was calculated to provide greater than 87% power to detect anticipated treatment differences in each coprimary endpoint between risankizumab and placebo with a Fisher's exact test at a two-sided significance level of 0·025. Statistical assumptions for power calculations are provided in the appendix (p 23).

Efficacy was analysed in the intention-to-treat (ITT) population, which included randomly assigned patients who received at least one dose of study drug in the first 12-week induction period and had a baseline eligible SES-CD (≥6, or ≥4 for isolated ileal disease). The coprimary endpoints (clinical remission and endoscopic response) and secondary endpoints (CDAI clinical response, enhanced stool frequency and abdominal pain

score clinical response, endoscopic remission, and ulcer-free endoscopy) were analysed between the subgroups with and without previous bio-failure in the ADVANCE trial. To ensure the consistency of drug efficacy across demographic and other baseline characteristics, subgroup analysis was performed for the coprimary endpoints for specified subgroups in the ITT population (appendix p 24; results not shown in this paper). Safety was analysed in all randomly assigned patients who received at least one dose of study drug in the first 12-week period, including patients with low SES-CD (3–5 for colonic or ileocolonic disease, or 3 for isolated ileal disease). Patients from one non-compliant site (without investigator oversight) were excluded from efficacy analyses but included in the safety analyses (five patients in ADVANCE [one in the placebo group, two in the risankizumab 600 mg group, and two in the risankizumab 1200 mg group] and 13 patients in MOTIVATE [five in the placebo group, four in the risankizumab 600 mg group, and four in the risankizumab 1200 mg group]).

The coprimary endpoints were analysed separately; each coprimary endpoint for the individual protocols had to meet the predefined success criteria (achievment of statistical significance for at least one risankizumab dose) to claim study success for each protocol. Secondary endpoints were ranked according to clinical significance and relevance. The difference between treatment groups for the coprimary efficacy endpoints and ranked secondary efficacy endpoints was tested with graphical multiplicity adjustment to ensure a strong control of family-wise type I error rate at a significance level of $\alpha=0\cdot05$ (two-sided; appendix pp 29–30).[17] Briefly, the testing used a sequence of hypothesis testing for the coprimary endpoints followed by the ranked secondary endpoints in the specified order. Testing began with each of the coprimary endpoints using $\alpha=0\cdot025$ (two-sided) for each dose compared with placebo. If both coprimary endpoints achieved statistical significance within a dose level, testing continued following a pre-specified weight of α allocation between the single hypothesis within the family, and between the families of hypotheses across the doses (appendix pp 28–30).

All categorical endpoints were analysed with the Cochran–Mantel–Haenszel test adjusted by stratification factors. Non-responder imputation incorporating multiple imputation for missing data due to COVID-19 infection or COVID-19 logistical restrictions was used for categorical endpoints; patients with missing data for all other reasons were counted as non-responders. Adjusted percentage difference with 95% CIs and p values was calculated based on Cochran–Mantel–Haenszel test adjusted for strata (number of previous biologics failed) and baseline steroid use for the comparison of two treatment groups.

Continuous endpoints were analysed by a mixed-effect model for repeated measures for endpoints with post-baseline measurements from multiple timepoints, and by ANCOVA for endpoints without repeated post-baseline measurement. In a post-hoc analysis, achievement of the composite endpoint of clinical remission (per CDAI or stool frequency and abdominal pain score) and endoscopic response at week 12 was assessed, as was the proportion of patients with baseline elevated concentrations of high-sensitivity C-reactive protein (hs-CRP; >5 mg/L) or faecal calprotectin (>250 mg/kg) who achieved normalisation in each parameter (hs-CRP, ≤5 mg/L; faecal calprotectin, ≤100 mg/kg [normal range], ≤250 mg/kg [below active disease range]) at week 12. Analyses were performed as described for other endpoints in the ITT population.

Safety, pharmacokinetic, and immunogenicity data were summarised descriptively. Statistical analysis for IL-22 is described in the appendix (pp 31–32). A two-sample t-test of baseline serum IL-22 concentrations was performed in pooled patient samples from both induction studies assessing patients who did not meet the endpoint versus those who did (geometric means were compared), in all patients who consented to sampling for exploratory analysis, received risankizumab, and had matched baseline and week 12 samples.

All statistical analyses were conducted with SAS (version 9.4). An external data monitoring committee oversaw the studies. Both trials were registered on ClinicalTrials.gov, NCT03105128 (ADVANCE) and NCT03104413 (MOTIVATE).

Role of the funding source

The study funder was involved in study design, data collection, data analysis, data interpretation, and writing of the report.

Results

In the ADVANCE trial, 931 patients were randomly assigned to receive intravenous risankizumab 600 mg (n=373), intravenous risankizumab 1200 mg (n=372), or intravenous placebo (n=186) between May 10, 2017, and Aug 24, 2020. 850 participants were included in the primary efficacy analysis (figure 1). In MOTIVATE, 618 patients were randomly assigned to receive intravenous risankizumab 600 mg (n=206), intravenous risankizumab 1200 mg (n=205), or placebo (n=207) between Dec 18, 2017, and Sept 9, 2020. 569 participants were included in the primary efficacy analysis (figure 1). In both studies, a greater proportion of patients discontinued study drug in the placebo groups (25 [14%] patients in ADVANCE; 26 [14%] patients in MOTIVATE) than in the risankizumab groups (16 [5%] patients receiving 600 mg and 12 [3%] patients receiving 1200 mg in ADVANCE; six [3%] patients receiving 600 mg and seven [4%] patients receiving 1200 mg in MOTIVATE). Primary reasons for drug discontinuation in both studies were adverse events (mainly worsening of Crohn's disease events), poor or no efficacy, and withdrawal by the patient, generally reported more often in the placebo groups (figure 1).

Patient demographics and baseline characteristics were similar between the risankizumab and placebo groups in both trials (table 1). The mean duration of Crohn's disease at study entry was 8·8 years (SD 8·3) in ADVANCE and 11·7 years (8·9) in MOTIVATE. Disease variables at baseline were similar across groups for both trials and reflective of moderately to severely active Crohn's disease (table 1). In ADVANCE, 491 (58%) of 850 patients were categorised as having previous bio-failure (239 [28%] with inadequate response or intolerance to one biologic and 252 [30%] with inadequate response or intolerance to more than one biologic) and 359 (42%) of 850 patients were without previous bio-failure. 45 (13%) of 359 patients without previous bio-failure were exposed to biologic therapy. Patients with previous bio-failure had longer disease duration (mean 10·2 years [SD 7·8]) than those without previous bio-failure (mean 7·0 years [8·7]; appendix p 4). In MOTIVATE, 268 (47%) of 569 patients had inadequate response or intolerance to one biologic and 301 (53%) had inadequate response or intolerance to more than one biologic. In the ITT populations, 110 (22%) of 491 patients in ADVANCE and 109 (19%) of 569 patients in MOTIVATE had inadequate response or intolerance to ustekinumab.

Both studies met the coprimary endpoints of clinical remission and endoscopic response at week 12 with both doses of risankizumab. In ADVANCE, significantly higher rates of CDAI clinical remission at week 12 were achieved with risankizumab 600 mg (45% [152/336]; adjusted difference 21% [95% CI 12–29]; p<0·0001) and risankizumab 1200 mg (42% [141/339]; 17% [8–25]; p<0·0001) versus placebo (25% [43/175]; figure 2, appendix p 3). Similarly, stool frequency and abdominal pain score clinical remission at week 12 was achieved in a significantly greater proportion of patients treated with risankizumab 600 mg (43% [146/336]; 22% [14–30]; p<0·0001) or risankizumab 1200 mg (41% [139/339]; 19% [11–27]; p<0·0001) versus placebo (22% [38/175]; figure 2). Endoscopic response at week 12 was also achieved by a significantly greater proportion of patients treated with

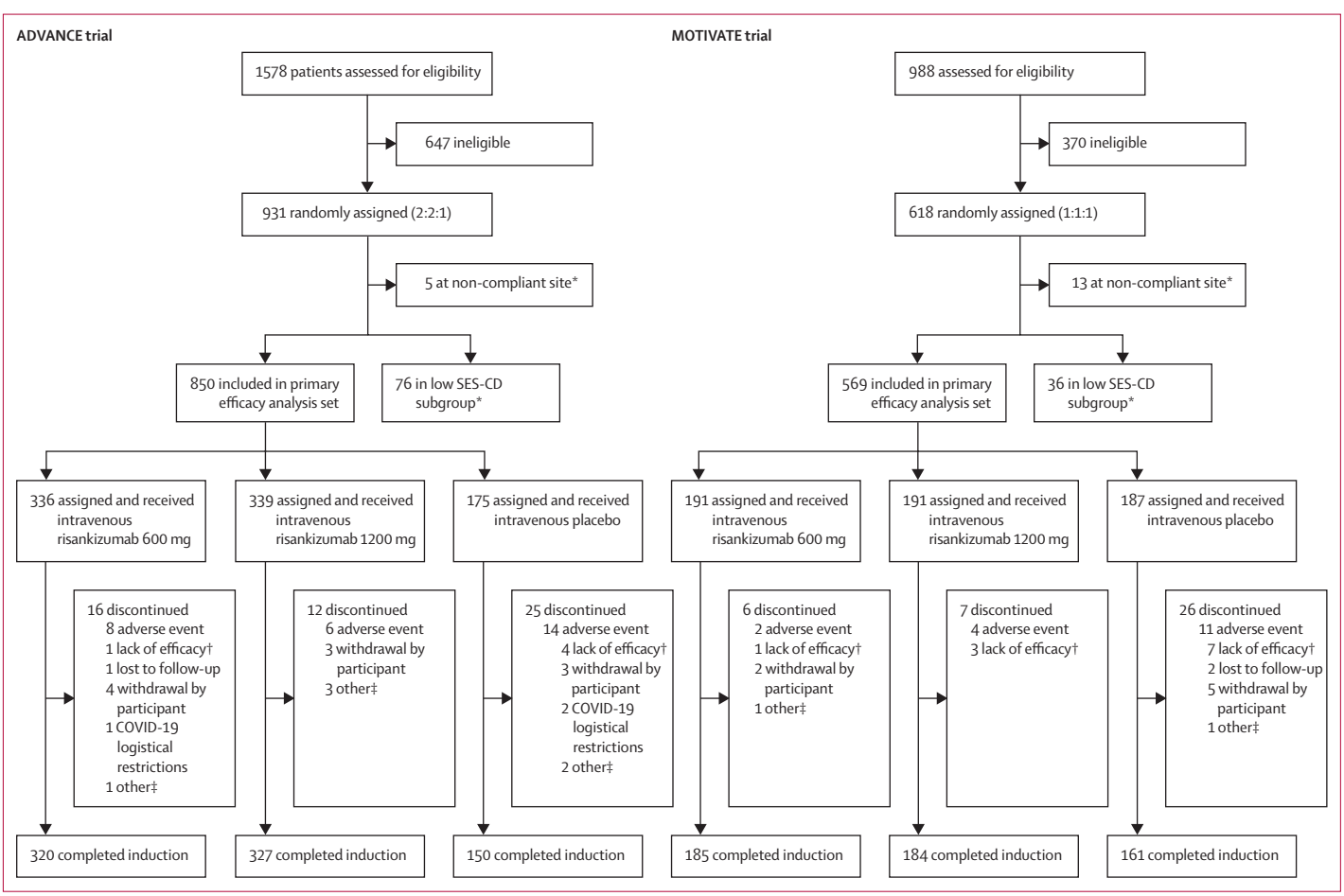

Figure 1: **Trial profiles**
IV=intravenous. SES-CD=Simple Endoscopic Score for Crohn's disease. *Received at least one dose of study drug and included in safety analyses. †Both participant and investigator decision due to poor or absent efficacy. ‡Other reasons for discontinuation in ADVANCE included non-compliance and worsening of Crohn's disease (risankizumab 600 mg), refused endoscopy, imprisonment, and inability to complete study visits due to COVID-19 restrictions (risankizumab 1200 mg), and non-compliance and inability to participate in study due to change in work situation (placebo); in MOTIVATE, discontinuation was due to the time commitment needed to complete study visits (risankizumab 600 mg) and pregnancy (placebo).

risankizumab 600 mg (40% [135/336]; 28% [21–35]; p<0·0001) or risankizumab 1200 mg (32% [109/339]; 20% [14–27]; p<0·0001) versus placebo (12% [21/175]; figure 2). In ADVANCE, numerically higher efficacy and effect size were observed in the subpopulation without previous bio-failure versus the subpopulation with previous bio-failure

	ADVANCE				MOTIVATE			
	Risankizumab 600 mg intravenous (n=336)	Risankizumab 1200 mg intravenous (n=339)	Placebo (n=175)	Total (n=850)	Risankizumab 600 mg intravenous (n=191)	Risankizumab 1200 mg intravenous (n=191)	Placebo (n=187)	Total (n=569)
Sex								
Female	147 (44%)	156 (46%)	87 (50%)	390 (46%)	99 (52%)	89 (47%)	88 (47%)	276 (49%)
Male	189 (56%)	183 (54%)	88 (50%)	460 (54%)	92 (48%)	102 (53%)	99 (53%)	293 (51%)
Age, years	38·3 (13·3)	37·0 (13·2)	37·1 (13·4)	37·5 (13·3)	40·2 (13·6)	39·3 (12·9)	39·3 (13·5)	39·6 (13·3)
Weight, kg	69·9 (17·7)	69·8 (19·5)	70·4 (18·2)	70·0 (18·5)	72·7 (20·2)	73·5 (17·6)	72·8 (19·1)	73·0 (19·0)
Race								
White	258 (77%)	247 (73%)	134 (77%)	639 (75%)	176 (92%)	168 (88%)	162 (87%)	506 (89%)
Black or African American	9 (3%)	13 (4%)	9 (5%)	31 (4%)	7 (4%)	8 (4%)	7 (4%)	22 (4%)
Asian	65 (19%)	74 (22%)	31 (18%)	170 (20%)	8 (4%)	14 (7%)	15 (8%)	37 (7%)
American Indian or Alaska Native	0	0	0	0	0	0	0	0
Native Hawaiian or Other Pacific Islander	0	1 (<1%)	1 (1%)	2 (<1%)	0	0	2 (1%)	2 (<1%)
Multiple	4 (1%)	4 (1%)	0	8 (1%)	0	1 (1%)	1 (1%)	2 (<1%)
Ethnicity								
Hispanic/Latino	11 (3%)	14 (4%)	10 (6%)	35 (4%)	16 (8%)	15 (8%)	19 (10%)	50 (9%)
Non-Hispanic/Latino	325 (97%)	325 (96%)	165 (94%)	815 (96%)	175 (92%)	176 (92%)	168 (90%)	519 (91%)
Disease duration, years	9·0 (8·8)	8·9 (8·4)	8·2 (7·1)	8·8 (8·3)	10·9 (7·7)	11·8 (9·1)	12·5 (9·7)	11·7 (8·9)
Disease location								
Ileal only*	52 (15%)	54 (16%)	19 (11%)	125 (15%)	33 (17%)	21 (11%)	26 (14%)	80 (14%)
Colonic only	115 (34%)	118 (35%)	70 (40%)	303 (36%)	75 (39%)	74 (39%)	73 (39%)	222 (39%)
Ileal-colonic	169 (50%)	167 (49%)	86 (49%)	422 (50%)	83 (43%)	96 (50%)	88 (47%)	267 (47%)
Corticosteroid use†	102 (30%)	101 (30%)	50 (29%)	253 (30%)	65 (34%)	62 (32%)	68 (36%)	195 (34%)
Immunomodulator use	88 (26%)	73 (22%)	42 (24%)	203 (24%)	36 (19%)	53 (28%)	40 (21%)	129 (23%)
Biologics failure history								
0‡	141 (42%)	140 (41%)	78 (45%)	359 (42%)	0	0	0	0
1	100 (30%)	98 (29%)	41 (23%)	239 (28%)	92 (48%)	88 (46%)	88 (47%)	268 (47%)
>1	95 (28%)	101 (30%)	56 (32%)	252 (30%)	99 (52%)	103 (54%)	99 (53%)	301 (53%)
Anti-tumour necrosis factor failure history								
0§	12/195 (6%)	12/199 (6%)	0/97	24/491 (5%)	14/191 (7%)	10/191 (5%)	6/187 (3%)	30/569 (5%)
1	110/195 (56%)	111/199 (56%)	57/97 (59%)	278/491 (57%)	101/191 (53%)	101/191 (53%)	103/187 (55%)	305/569 (54%)
>1	73/195 (37%)	76/199 (38%)	40/97 (41%)	189/491 (39%)	76/191 (40%)	80/191 (42%)	78/187 (42%)	234/569 (41%)
Ustekinumab failure history	43/195 (22%)	48/199 (24%)	19/97 (20%)	110/491 (22%)	36/191 (19%)	33/191 (17%)	40/187 (21%)	109/569 (19%)
Faecal calprotectin, mg/kg	960·0 (359·0–2140·0)	1045·0 (314·0–2411·0)	1200·0 (443·0–2601·0)	1045·0 (348·0–2360·0)	1367·0 (481·0–2797·0)	1220·0 (326·0–2816·0)	987·5 (322·0–2730·0)	1225·0 (355·0–2744·0)
High-sensitivity C-reactive protein, mg/L	7·3 (2·8–21·8)	7·6 (2·9–20·7)	8·4 (2·8–21·9)	7·7 (2·9–20·7)	9·3 (3·5–23·0)	11·7 (4·4–28·2)	9·4 (3·6–28·2)	9·6 (3·8–26·8)
Crohn's disease activity index	311·2 (62·4)	311·5 (68·4)	319·2 (59·4)	313·0 (64·3)	310·7 (63·6)	312·5 (61·2)	319·6 (69·8)	314·2 (64·9)
SES-CD	14·7 (7·7)	13·4 (6·5)	13·8 (6·8)	14·0 (7·1)	14·4 (7·6)	15·1 (7·6)	15·0 (8·1)	14·8 (7·8)
Average daily stool frequency	5·8 (2·7)	5·6 (2·8)	6·1 (2·8)	5·8 (2·8)	6·2 (3·1)	5·9 (2·8)	6·4 (2·9)	6·2 (2·9)
Average daily abdominal pain score	1·9 (0·6)	1·9 (0·5)	1·9 (0·6)	1·9 (0·5)	1·9 (0·5)	1·9 (0·6)	1·9 (0·5)	1·9 (0·5)

Data are n (%), n/N (%) among patients with available data, mean (SD), or median (IQR). The ITT population included randomly assigned participants who received at least one dose of study drug during the first 12-week induction period and had baseline eligible SES-CD (≥6; or ≥4 for isolated ileal disease). Baseline characteristics of the safety population are provided in the appendix (pp 1–2). ITT=intention to treat. SES-CD=Simple Endoscopic Score for Crohn's disease. *21 patients in ADVANCE and 20 in MOTIVATE who had isolated ileal disease at baseline had an SES-CD of 0 at week 12 (all of whom had their ileum intubated in determining SES-CD). †The maximum dose of steroids allowed at baseline was 20 mg/day of prednisone (or equivalent), 9 mg/day of budesonide, or 5 mg of beclomethasone; the patient had to be on the current course of steroids for at least 14 days before baseline and on a stable dose for at least 7 days before baseline. ‡In ADVANCE, 45 (13%) of 359 patients without previous bio-failure were exposed to biologic therapy. §Patients without a history of anti-TNF and patients exposed to anti-TNF therapy without treatment failure.

Table 1: **Baseline demographic and disease characteristics of the ITT population**

for both doses of risankizumab (figure 2). CDAI clinical remission rates in the risankizumab 600 mg and 1200 mg groups were 49% (69/141; adjusted difference *vs* placebo, 26% [13–38]) and 47% (66/140; 24% [12–37]) in patients without previous bio-failure versus 43% (83/195; 17% [6–28]) and 38% (75/199; 12% [1–23]) in patients with previous bio-failure. Stool frequency and abdominal pain score clinical remission rates in the risankizumab 600 mg and 1200 mg groups were 48% (67/141; 27% [15–39]) and 44% (62/140; 24% [12–36]) in patients without previous bio-failure versus 41% (79/195; 18% [7–29] and 39% (77/199; 16% [5–27]) in patients with previous bio-failure. Endoscopic response rates in the risankizumab 600 mg and 1200 mg groups were 50% (71/141; 38% [27–49]) and 44% (61/140; 31% [20–42]) in patients without previous bio-failure versus 33% (64/195; 21% [12–31]) and 24% (47/199; 12% [4–21]) in patients with previous bio-failure.

Similar results were observed in the MOTIVATE trial (all patients with previous bio-failure; figure 3, appendix p 3). Significantly higher CDAI clinical remission rates at week 12 were achieved with risankizumab 600 mg (42% [80/191]; adjusted difference 22% [95% CI 13–31]; p<0·0001) and risankizumab 1200 mg (40% [77/191]; 21% [12–29]; p<0·0001) versus placebo (20% [37/187]). Stool frequency and abdominal pain score clinical remission was also achieved in a significantly greater proportion of patients treated with risankizumab 600 mg (35% [66/191]; 15% [6–24]; p=0·0007) or risankizumab 1200 mg (40% [76/191]; 20% [12–29]; p<0·0001) versus placebo (19% [36/187]). Additionally, significantly greater rates of endoscopic response at week 12 were achieved with risankizumab 600 mg (29% [55/191]; 18% [10–25]; p<0·0001) and risankizumab 1200 mg (34% [65/191]; 23% [15–31]; p<0·0001) versus placebo (11% [21/187]). In general, similar results were observed between MOTIVATE and the population with previous bio-failure in ADVANCE. No significant increase in efficacy was observed with risankizumab 1200 mg versus risankizumab 600 mg for any of the coprimary endpoints in ADVANCE or MOTIVATE (figures 2 and 3).

In ADVANCE and MOTIVATE, significantly greater proportions of patients treated with risankizumab achieved the post-hoc composite endpoint of clinical remission (per CDAI or stool frequency and abdominal pain score criteria) and endoscopic response at week 12 than patients who received placebo (appendix p 5).

Most secondary endpoints measuring resolution of clinical symptoms and reductions in endoscopic inflammation were achieved by significantly greater proportions of patients in the risankizumab groups versus the placebo group in both the ADVANCE and MOTIVATE trials (table 2). Rates of stool frequency remission and abdominal pain score remission at week 12 were significantly higher with risankizumab

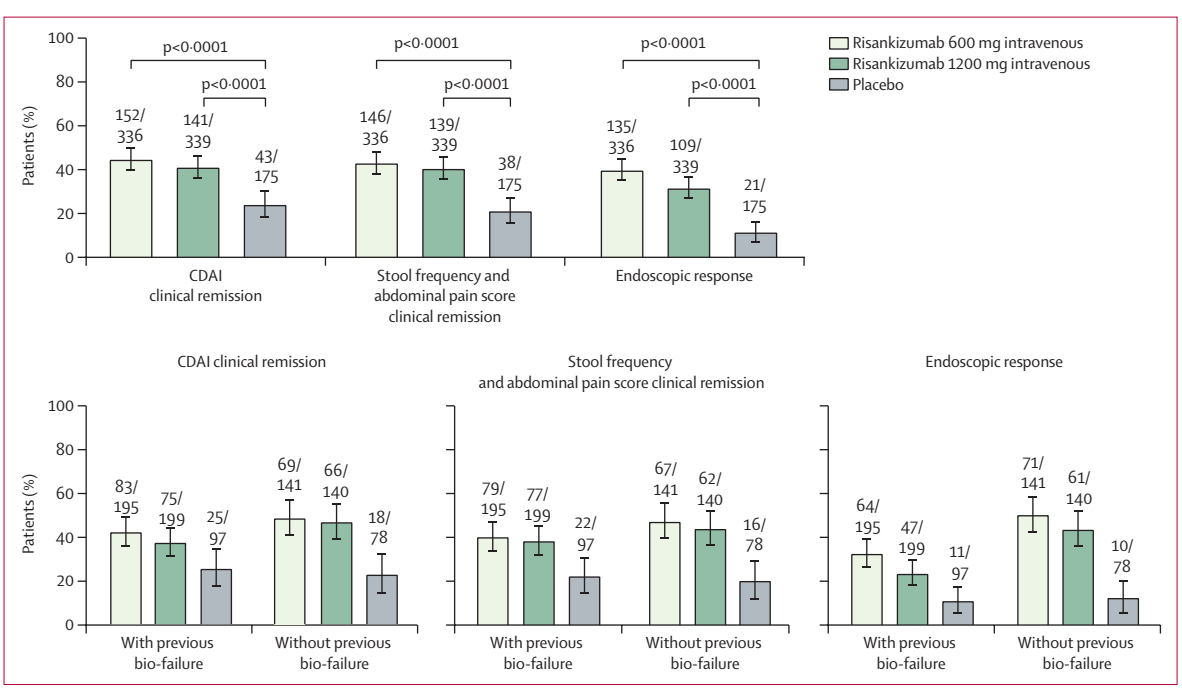

Figure 2: **Coprimary endpoints at week 12 of ADVANCE**

Error bars show 95% CIs. Numbers of patients are shown as n/N inside the bars. Endpoints were defined as follows: CDAI clinical remission (CDAI <150); stool frequency and abdominal pain score clinical remission (average daily stool frequency ≤2·8 and not worse than baseline and average daily abdominal pain score ≤1 and not worse than baseline); and endoscopic response (decrease in SES-CD of >50% from baseline; or for patients with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer. Patients with previous bio-failure are those with documented intolerance or inadequate response to one or more of the approved biologics for Crohn's disease; patients without previous bio-failure are those who had an inadequate response or intolerance to conventional therapy. Statistical analyses were not performed for subgroups. CDAI=Crohn's disease activity index. SES-CD=Simple Endoscopic Score for Crohn's disease.

than placebo (both outcomes, both doses of risankizumab, and in both studies, all p≤0·0003 compared with placebo; table 2). At the week 4 timepoint, following a single risankizumab dose (600 mg or 1200 mg), rates of CDAI clinical remission were significantly higher with risankizumab treatment versus placebo (ADVANCE: 600 mg, 18% [62/336], p=0·015, and 1200 mg 19% [64/339], p=0·0072, *vs* placebo, 10% [18/175]; MOTIVATE: 600 mg, 21% [40/191], p=0·010, and 1200 mg, 19% [37/191], p=0·023, *vs* placebo, 11% [21/187]; table 2, appendix p 9). Similarly, rates of stool frequency and abdominal pain score clinical remission at week 4 were significantly higher with risankizumab treatment (600 mg or 1200 mg) versus placebo (ADVANCE: 600 mg, 21% [71/336], and 1200 mg, 21% [72/339], *vs* 9% [16/175] for placebo; p≤0·0002 both comparisons; MOTIVATE: 600 mg, 17% [33/191], p=0·0059, and 1200 mg, 18% [35/191], p=0·0022, *vs* placebo, 8% [15/187]). Additional symptomatic endpoints, including CDAI clinical response and enhanced stool frequency and abdominal pain score clinical response, were also achieved at significantly higher rates at week 4 with risankizumab treatment (600 or 1200 mg) versus placebo, with increasing rates of efficacy observed over time for risankizumab up to week 12 (appendix p 11). At week 12, the endpoints of endoscopic remission and ulcer-free endoscopy (absence of ulceration), as well as composite clinical and endoscopic endpoints (CDAI clinical response and endoscopic response, and enhanced stool frequency and abdominal pain score clinical response and endoscopic response) were also achieved by a significantly greater proportion of patients treated with risankizumab (600 mg or 1200 mg) versus placebo (table 2).

Subgroup analysis of the symptomatic endpoints of CDAI clinical response and enhanced stool frequency and abdominal pain score clinical response in patients with and without previous bio-failure (ADVANCE) showed a treatment effect with risankizumab (600 mg or 1200 mg) versus placebo, with similar response rates in both subpopulations (appendix p 12). Slightly higher response rates were observed in the population without previous bio-failure (appendix p 12). For the endpoints of endoscopic remission and ulcer-free endoscopy (absence of ulceration), numerically higher rates were observed in the risankizumab (600 mg or 1200 mg) groups versus placebo; however, response rates were around twice as high in patients without previous bio-failure compared with patients with previous bio-failure (appendix p 12).

In ADVANCE, significant reductions in hs-CRP and faecal calprotectin were observed at week 4 and maintained up to week 12 with risankizumab treatment (600 mg or 1200 mg) versus placebo (figure 4). In MOTIVATE, hs-CRP was significantly reduced in the risankizumab groups between weeks 4 and 12. Faecal calprotectin concentrations were reduced in both risankizumab groups at week 4, although did not differ significantly

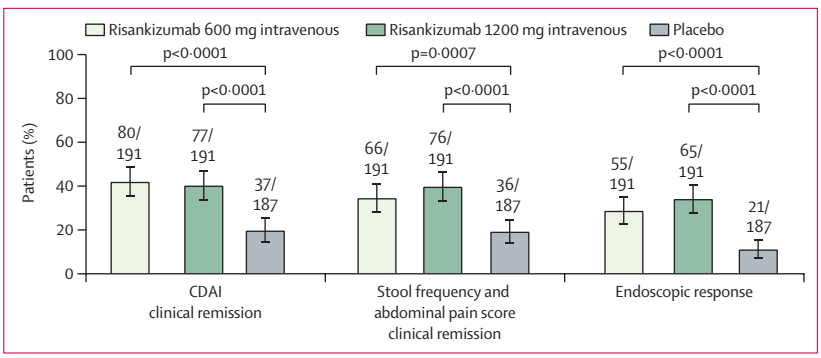

Figure 3: **Coprimary endpoints at week 12 of MOTIVATE**
Error bars show 95% CIs. Numbers of patients are shown as n/N inside the bars. Endpoints were defined as follows: CDAI clinical remission (CDAI <150); stool frequency and abdominal pain score clinical remission (average daily stool frequency ≤2·8 and not worse than baseline and average daily abdominal pain score ≤1 and not worse than baseline); and endoscopic response (decrease in SES-CD of >50% from baseline; or for patients with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central review. CDAI=Crohn's disease activity index. SES-CD=Simple Endoscopic Score for Crohn's disease.

compared with the placebo group. A significant reduction was observed at week 12 versus placebo in the risankizumab 600 mg group (figure 4). Although elevated hs-CRP or faecal calprotectin concentrations were not required for entry into ADVANCE or MOTIVATE, a post-hoc analysis was performed to examine the proportion of patients with baseline elevated concentrations of hs-CRP (>5 mg/L) or faecal calprotectin (>250 mg/kg) who achieved normalisation in each parameter (hs-CRP, ≤5 mg/L; faecal calprotectin, ≤100 mg/kg [normal range], ≤250 mg/kg [below active disease range]) at week 12 in each treatment group. Most of these comparisons showed a significantly greater proportion of patients treated with risankizumab (600 mg or 1200 mg) to have achieved normalisation of hs-CRP and faecal calprotectin versus patients who received placebo (appendix p 6).

In ADVANCE and MOTIVATE, serum concentrations of IL-22 were significantly decreased at week 12 in both risankizumab groups compared with the placebo group, in which IL-22 concentrations did not change (figure 4). A pooled analysis of 203 patients with Crohn's disease who received risankizumab in ADVANCE or MOTIVATE indicated that baseline serum IL-22 concentration was not predictive of week 12 stool frequency and abdominal pain score clinical remission, stool frequency and abdominal pain score clinical response, endoscopic response, or endoscopic remission (appendix p 7).

Risankizumab serum concentrations were generally dose-proportional across the time course for the 600 mg and 1200 mg intravenous dose regimens of risankizumab, reaching trough concentrations of 39·4 µg/mL (600 mg regimen) and 73·1 µg/mL (1200 mg regimen) at week 12 in ADVANCE, and 34·8 µg/mL (600 mg regimen) and 65·1 µg/mL (1200 mg regimen) at week 12 in MOTIVATE (appendix p 8). Based on population pharmacokinetic analyses, we observed no significant effect of previous use of biologics or concomitant immunomodulators on risankizumab exposure (data will be summarised in

a future publication). Treatment-emergent antidrug antibodies to risankizumab occurred in ten (1%) of 736 patients in the ADVANCE trial (seven patients who received risankizumab 600 mg and three who received risankizumab 1200 mg), and six (2%) of 397 patients in the MOTIVATE trial (five patients who received risankizumab 600 mg and one who received risankizumab 1200 mg). One patient in each study (risankizumab 600 mg group) was positive for neutralising antibodies (appendix p 9). The time to the first appearance of treatment-emergent antidrug antibodies ranged from 3·6 to 4·3 weeks after the first risankizumab treatment in ADVANCE, and 4·1 to 7·6 weeks in MOTIVATE. No apparent effect of antidrug antibodies on risankizumab exposure was observed (data not shown).

In both ADVANCE and MOTIVATE, the overall incidence of treatment-emergent adverse events during and after the 12-week induction period (up to 140 days after the last dose of study drug or up to the first dose of study drug in the FORTIFY maintenance study or induction period 2) was similar among all treatment groups (table 3). Rates of serious adverse events, severe

	ADVANCE			MOTIVATE		
	Risankizumab 600 mg intravenous (n=336)	Risankizumab 1200 mg intravenous (n=339)	Placebo (n=175)	Risankizumab 600 mg intravenous (n=191)	Risankizumab 1200 mg intravenous (n=191)	Placebo (n=187)
Stool frequency remission* at week 12†						
n (%; 95% CI)	182 (54%; 49 to 60)	183 (54%; 49 to 59)	52 (30%; 23 to 37)	88 (46%; 39 to 53)	93 (49%; 42 to 56)	53 (28%; 22 to 35)
Adjusted percentage difference compared with placebo (95% CI); p value	24% (16 to 33); p<0·0001	24% (15 to 32); p<0·0001	..	17% (8 to 27); p=0·0003	20% (11 to 30); p<0·0001	..
Abdominal pain score remission‡ at week 12†						
n (%; 95% CI)	200 (60%; 54 to 65)	197 (58%; 53 to 63)	67 (38%; 31 to 46)	111 (58%; 51 to 65)	113 (59%; 52 to 66)	68 (36%; 30 to 43)
Adjusted percentage difference compared with placebo (95% CI); p value	21% (12 to 30); p<0·0001	19% (10 to 28); p<0·0001	..	22% (12 to 32); p<0·0001	23% (13 to 32); p<0·0001	..
CDAI clinical remission§ at week 4†						
n (%; 95% CI)	62 (18%;14 to 23)	64 (19%;15 to 23)	18 (10%; 6 to 15)	40 (21%; 15 to 27)	37 (19%; 14 to 25)	21 (11%; 7 to 16)
Adjusted percentage difference compared with placebo (95% CI); p value	8% (2 to 14); p=0·015	8% (2 to 15); p=0·0072	..	10% (2 to 17); p=0·010	8% (1 to 15); p=0·023	..
CDAI clinical response¶ at week 4						
n (%; 95% CI)	137 (41%; 35 to 46)	126 (37%; 32 to 42)	44 (25%; 19 to 32)	70 (37%; 30 to 43)	62 (32%; 26 to 39)	39 (21%; 15 to 27)
Adjusted percentage difference compared with placebo (95% CI); p value	15% (7 to 24); p=0·0002	11% (3 to 19); p=0·0068	..	16% (7 to 25); p=0·0006	12% (3 to 21); p=0·0084	..
CDAI clinical response¶ at week 12						
n (%; 95% CI)	201 (60%; 55 to 65)	220 (65%; 60 to 70)	64 (37%; 30 to 44)	114 (60%; 53 to 66)	116 (61%; 54 to 68)	56 (30%; 23 to 37)
Adjusted percentage difference compared with placebo (95% CI); p value	23% (14 to 32); p<0·0001	28% (19 to 36); p<0·0001	..	29% (20 to 39); p<0·0001	31% (21 to 40); p<0·0001	..
Stool frequency and abdominal pain score clinical remission|| at week 4**						
n (%; 95% CI)	71 (21%; 17 to 25)	72 (21%; 17 to 26)	16 (9%; 5 to 13)	33 (17%; 12 to 23)	35 (18%; 13 to 24)	15 (8%; 4 to 12)
Adjusted percentage difference compared with placebo (95% CI); p value	11% (5 to 18); p=0·0002	12% (6 to 18); p=0·0001	..	9% (3 to 16); p=0·0059	10% [4 to 17]; p=0·0022	..
Enhanced stool frequency and abdominal pain score clinical response†† at week 4						
n (%; 95% CI)	155 (46%; 41 to 51)	147 (43%; 38 to 49)	54 (31%; 24 to 38)	86 (45%; 38 to 52)	74 (39%; 32 to 46)	59 (32%; 25 to 38)
Adjusted percentage difference compared with placebo (95% CI); p value	15% (6 to 23); p=0·0007	12% (3 to 20); p=0·0069	..	14% (4 to 23); p=0·0056	7% (–2 to 17); p=0·14	..
Enhanced stool frequency and abdominal pain score clinical response†† at week 12						
n (%; 95% CI)	211 (63%; 58 to 68)	218 (64%; 59 to 69)	73 (42%; 35 to 49)	118 (62%; 55 to 69)	113 (59%; 52 to 66)	73 (39%; 32 to 46)
Adjusted percentage difference compared with placebo (95% CI); p value	21% (12 to 30); p<0·0001	22% (13 to 30); p<0·0001	..	23% (13 to 33); p<0·0001	20·0% (10 to 30); p<0·0001	..
Endoscopic remission‡‡ at week 12						
n (%; 95% CI)	81 (24%; 20 to 29)	81 (24%; 19 to 28)	16 (9%; 5 to 13)	37 (19%; 14 to 25)	39 (20%; 15 to 26)	8 (4%; 1 to 7)
Adjusted percentage difference compared with placebo (95% CI); p value	15% (9 to 21); p<0·0001	15% (9 to 21); p<0·0001	..	15% (9 to 21); p<0·0001	16% (10 to 22); p<0·0001	..
Ulcer-free endoscopy§§ at week 12						
n (%; 95% CI)	71 (21%; 17 to 25)	55 (16%; 12 to 20)	13 (8%; 4 to 12)	26 (14%; 9 to 19)	29 (15%; 10 to 21)	8 (4%; 1 to 7)
Adjusted percentage difference compared with placebo (95% CI); p value	14% (8 to 19); p<0·0001	9% (4 to 15); p=0·0010	..	9% (4 to 15); p=0·0011	11% (5 to 17); p=0·0002	..

(Table 2 continues on next page)

	ADVANCE			MOTIVATE		
	Risankizumab 600 mg intravenous (n=336)	Risankizumab 1200 mg intravenous (n=339)	Placebo (n=175)	Risankizumab 600 mg intravenous (n=191)	Risankizumab 1200 mg intravenous (n=191)	Placebo (n=187)
(Continued from previous page)						
CDAI clinical response¶ and endoscopic response¶¶ at week 12*						
n (%; 95% CI)	101 (30%; 25 to 35)	78 (23%; 18 to 27)	10 (6%; 2 to 9)	39 (20%; 15 to 26)	44 (23%; 17 to 29)	10 (5%; 2 to 9)
Adjusted percentage difference compared with placebo (95% CI); p value	25% (19 to 30); p<0·0001	17% (12 to 23); p<0·0001	..	15% (9 to 21); p<0·0001	18% (11 to 24); p<0·0001	..
Enhanced stool frequency and abdominal pain score clinical response†† and endoscopic response¶¶ at week 12†						
n (%; 95% CI)	104 (31%; 26 to 36)	79 (23%; 19 to 28)	14 (8%; 4 to 12)	40 (21%; 15 to 27)	46 (24%; 18 to 30)	13 (7%; 3 to 11)
Adjusted percentage difference compared with placebo (95% CI); p value	23% (17 to 30); p<0·0001	15% (9 to 21); p<0·0001	..	14% (7 to 21); p<0·0001	17% (10 to 24); p<0·0001	..

Efficacy analyses include randomly assigned participants who received at least one dose of study drug during the first 12-week induction period and had baseline eligible SES-CD (≥6; or ≥4 for isolated ileal disease). All patients were analysed for endpoints defined in the US and non-US analysis plans. CDAI=Crohn's disease activity index. SES-CD=Simple Endoscopic Score for Crohn's disease. *Stool frequency remission was defined as average daily stool frequency ≤2·8 and not worse than baseline. †US analysis plan. ‡Abdominal pain score remission was defined as average daily AP score ≤1 and not worse than baseline. §CDAI clinical remission was defined as CDAI <150. ¶CDAI clinical response was defined as a reduction in CDAI of ≥100 points from baseline. ||Stool frequency and abdominal pain score clinical remission was defined as average daily stool frequency ≤2·8 and not worse than baseline and average daily AP score ≤1 and not worse than baseline. **Analysis plan for outside the USA. ††Enhanced stool frequency and abdominal pain score clinical response was defined as ≥60% decrease in average daily stool frequency and/or ≥35% decrease in average daily AP score, neither worse than baseline, or stool frequency and abdominal pain score clinical remission. ‡‡Endoscopic remission was defined as SES-CD ≤4 and at least a 2-point reduction versus baseline and no subscore greater than 1 in any individual variable, as scored by a central reviewer. §§Ulcer-free endoscopy was defined as a SES-CD ulcerated surface subscore of 0 in patients with SES-CD ulcerated surface subscore ≥1 at baseline, as scored by a central reviewer. ¶¶Endoscopic response was defined as a decrease in SES-CD >50% from baseline (or for patients with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by central reviewer.

Table 2: **Key clinical and endoscopic secondary endpoints**

adverse events, and adverse events leading to discontinuation of study drug were numerically higher in the placebo group, with most events related to underlying Crohn's disease. Across both studies, the most frequently reported adverse events (≥5% patients in any group) in the risankizumab groups were headache and nasopharyngitis, whereas the most common adverse events in the placebo groups were Crohn's disease (worsening of Crohn's disease), abdominal pain, nausea, and headache.

Three deaths were reported across both studies (one patient in the risankizumab 1200 mg group in MOTIVATE and two patients in the placebo group in ADVANCE). The death in the risankizumab-treated patient, who had a 40-year history of smoking (among other risk factors) and received one dose of risankizumab, was caused by acute respiratory failure due to invasive squamous cell carcinoma of the left lung (events beginning on day 8 after baseline risankizumab dose). This event was considered by the investigator to be unrelated to the study drug.

The incidence of adverse events of safety interest was similar across treatment groups in both ADVANCE and MOTIVATE, except for serious infections, which were slightly higher with placebo. In ADVANCE, five serious infections (appendicitis, leptospirosis [patient with possible environmental exposure to rodents], lower respiratory tract infection, pneumonia, and urinary tract infection) were reported in risankizumab-treated patients, each event in a single patient. All of these serious infection events were considered by the investigator to have no reasonable possibility of being related to study drug, and none resulted in study drug discontinuation. In MOTIVATE, three serious infection events were reported in risankizumab-treated patients (gastroenteritis [*Escherichia coli*], viral pharyngitis, and sepsis), and all were considered by the investigator to have no reasonable possibility of being related to study drug, and none led to study drug discontinuation. Three events of herpes zoster were reported in risankizumab-treated patients in ADVANCE who were on concomitant corticosteroid or azathioprine; all events were non-serious and mild in severity, and none led to study drug discontinuation. In ADVANCE, two events of active tuberculosis were reported, one of which occurred in the placebo group. The other event of active tuberculosis was in the risankizumab 600 mg group in a patient with a history of active tuberculosis. At screening, this patient had a positive tuberculosis test but normal chest x-ray and active tuberculosis was ruled out; no tuberculosis prophylaxis was initiated. This patient had numerous episodes of pyrexia starting a month before initiation of study drug, which were believed to be secondary to Crohn's disease. However, the patient was discontinued at week 8 after three doses of study drug due to a non-serious adverse event of persistent pyrexia. Final confirmation of active tuberculosis by chest x-ray occurred during the 140-day follow-up period. The investigator reported both events (pyrexia and tuberculosis) to have no reasonable possibility of being related to study drug. No adjudicated MACE, adjudicated extended MACE, or adjudicated anaphylactic reactions were reported in any treatment groups in either study. One event of serious hypersensitivity reaction (rash), accompanied by increased liver enzymes (alanine transaminase, aspartate transaminase, and total

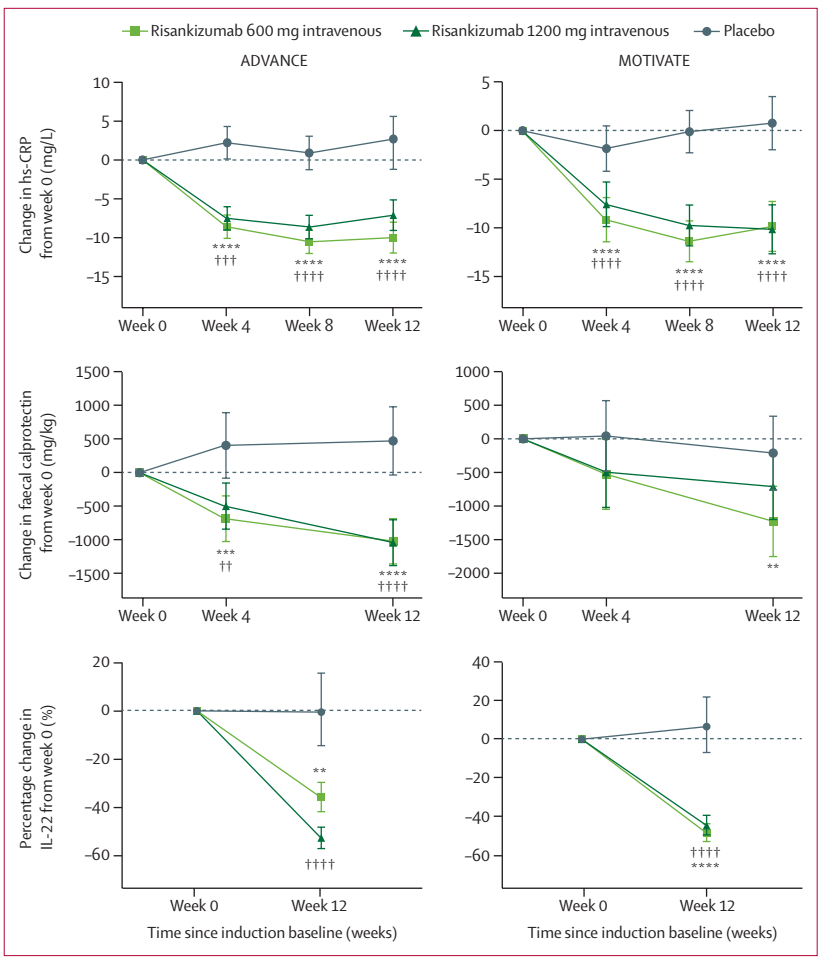

Figure 4: **Inflammatory and pharmacodynamic biomarkers**
Changes (based on least-square means) in hs-CRP, faecal calprotectin, and IL-22 from week 0. Error bars show 95% CIs. hs-CRP=high-sensitivity C-reactive protein. IL-22=interleukin 22. **p<0·01, ***p<0·001, and ****p<0·0001 for risankizumab 600 mg versus placebo. ††p<0·01, †††p<0·001, and ††††p<0·0001 for risankizumab 1200 mg versus placebo.

bilirubin) above clinical test thresholds, was reported in the risankizumab 600 mg group in ADVANCE 80 days after the first dose of study drug; the rash and increase in liver enzymes resolved after hospitalisation and steroid administration. This patient previously had a non-serious rash on day 55 which led to study drug discontinuation, with the final dose of study drug administered on day 29. The timing of the increase and resolution of liver enzymes was suggestive of an acute insult and not consistent with drug-induced liver injury. The rates of infusion-related reactions were similar across treatment groups in MOTIVATE and slightly numerically higher in the risankizumab groups versus placebo in ADVANCE; all events were either mild or moderate in severity and none occurred in patients with treatment-emergent antidrug antibodies. The rates of hepatic events were similar across all treatment groups (≤2%), with most events being non-serious and related to transient increases in liver enzymes. The proportion of patients meeting criteria for liver test elevations in alanine aminotransferase, aspartate aminotransferase, and total bilirubin in the risankizumab groups were low (<3%; appendix p 10).

Discussion

In patients with moderately to severely active Crohn's disease, a significantly greater proportion achieved the coprimary endpoints of clinical remission and endoscopic response with risankizumab treatment than with placebo treatment at week 12. Symptomatic improvement was evident at week 4, and endoscopic improvement was observed at week 12. Treatment effects of risankizumab were observed in patients with and without previous biofailure. Considering these strong results, risankizumab could be beneficial as a first-line therapy in newly diagnosed patients with moderate to severe Crohn's disease, or in patients who have shown inadequate response or intolerance to one or more biologics.

The ADVANCE and MOTIVATE studies are the first phase 3 induction trials completed in Crohn's disease to include the coprimary endpoints of clinical remission, using both the traditional CDAI outcome and patient-reported outcomes of stool frequency and abdominal pain score, and endoscopic response. These endpoints reflect a paradigm shift in Crohn's disease treatment whereby endoscopic healing, a target associated with improved long-term outcomes (eg, reduced risk of relapse, decreased hospitalisation rates, steroid-free remission, and fewer bowel resections), is now a primary treatment objective. In addition, updates to the Selecting Therapeutic Targets in IBD (STRIDE) clinical practice recommendations now include both short-term and intermediate-term goals of treating to target clinical and patient-reported remission (STRIDE-II).[18] The results from ADVANCE and MOTIVATE align with these emerging treatment goals.

ADVANCE and MOTIVATE included a higher risankizumab induction dose (1200 mg) than previously evaluated.[11] CDAI clinical remission rates across the phase 3 studies showed significantly greater efficacy versus placebo with 600 mg risankizumab, but no additional efficacy was conferred by the higher 1200 mg dose. Indeed, for most clinical, endoscopic, and composite endpoints examined across the studies, both in the overall population and in subgroup analyses, 1200 mg risankizumab yielded no better efficacy than 600 mg, despite higher serum concentrations with the higher dose. These data suggest that the exposures at both the 600 mg and 1200 mg doses might have reached the plateau of the exposure-response curve near the maximum for efficacy by fully saturating the target at the site of action. Importantly, no dose-dependent safety findings were observed.

Key strengths of the ADVANCE and MOTIVATE studies include comprehensive assessment of disease activity with use of CDAI, stool frequency and abdominal pain score, and centrally read endoscopy in all patients,

and use of the SES-CD to define endoscopic improvement.[19] One limitation was the requirement that corticosteroid doses be kept stable during the induction period, precluding evaluation of early steroid tapering with risankizumab induction therapy. Additionally, few adolescents aged 16–17 years participated in ADVANCE and MOTIVATE (n=14), limiting direct evidence obtained for risankizumab in this patient population. Further analyses of predictors of response to risankizumab are also warranted. These studies also lacked an active-comparator group, and further studies are necessary to compare the efficacy and safety of risankizumab to other advanced therapies with different mechanisms of action, such as ustekinumab, a dual IL-12 and IL-23 inhibitor targeting the p40 subunit of both proteins. In the treatment of psoriasis, risankizumab has shown superior efficacy to ustekinumab, indicating potential benefits of selective IL-23 p19 inhibition.[20,21] A study investigating

	ADVANCE			MOTIVATE		
	Risankizumab 600 mg IV (n=373)	Risankizumab 1200 mg IV (n=372)	Placebo (n=186)	Risankizumab 600 mg IV (n=206)	Risankizumab 1200 mg IV (n=205)	Placebo (n=207)
Adverse events	210 (56%)	191 (51%)	105 (56%)	98 (48%)	121 (59%)	137 (66%)
Severe adverse events	22 (6%)	18 (5%)	18 (10%)	7 (3%)	12 (6%)	25 (12%)
Serious adverse events	27 (7%)	14 (4%)	28 (15%)	10 (5%)	9 (4%)	26 (13%)
Adverse events leading to discontinuation of study drug	9 (2%)	7 (2%)	14 (8%)	2 (1%)	5 (2%)	17 (8%)
Adverse events related to COVID-19	1 (<1%)	0	2 (1%)	0	0	1 (<1%)
Most frequent adverse events*						
Crohn's disease (worsening)	10 (3%)	6 (2%)	25 (13%)	8 (4%)	4 (2%)	33 (16%)
Nasopharyngitis	22 (6%)	22 (6%)	5 (3%)	8 (4%)	8 (4%)	11 (5%)
Arthralgia	15 (4%)	11 (3%)	7 (4%)	8 (4%)	9 (4%)	9 (4%)
Headache	24 (6%)	20 (5%)	8 (4%)	11 (5%)	10 (5%)	11 (5%)
Nausea	17 (5%)	13 (3%)	10 (5%)	5 (2%)	3 (1%)	11 (5%)
Abdominal pain	8 (2%)	10 (3%)	10 (5%)	5 (2%)	3 (1%)	11 (5%)
Diarrhoea	2 (1%)	5 (1%)	4 (2%)	3 (1%)	2 (1%)	2 (1%)
Anaemia	11 (3%)	10 (3%)	6 (3%)	5 (2%)	6 (3%)	11 (5%)
Adverse events of safety interest						
Infections						
Serious infections	3 (1%)	2 (1%)	7 (4%)	1 (<1%)	2 (1%)	5 (2%)
Opportunistic infection, excluding tuberculosis and herpes zoster	0	1 (<1%)	0	0	0	3 (1%)
Herpes zoster	2 (1%)	1 (<1%)	0	0	0	1 (<1%)
Active tuberculosis	1 (<1%)	0	1 (1%)	0	0	0
Asymptomatic COVID-19	0	0	1 (1%)	0	0	0
COVID-19	1 (<1%)	0	1 (1%)	0	0	1 (<1%)
Adjudicated MACE	0	0	0	0	0	0
Adjudicated extended MACE	0	0	0	0	0	0
Non-melanoma skin cancer	0	0	0	0	0	0
Malignancies excluding non-melanoma skin cancer	0	0	0	0	1 (<1%)	0
Infusion-related reactions	4 (1%)	9 (2%)	1 (1%)	1 (<1%)	3 (1%)	3 (1%)
Serious hypersensitivity reactions	1 (<1%)	0	0	0	0	0
Adjudicated anaphylactic reaction	0	0	0	0	0	0
Hepatic events†	9 (2%)	6 (2%)	4 (2%)	1 (<1%)	2 (1%)	2 (1%)
Death	0	0	2 (1%)	0	1 (<1%)‡	0

Data are number of participants (%). MACE=major adverse cardiovascular event. MedDRA=Medical Dictionary for Regulatory Activities. *Occurring in ≥5% of patients in any group. †All hepatic events were identified with search criteria covering the standardised MedDRA queries of "hepatic failure, fibrosis and cirrhosis and other liver damage-related conditions", "hepatitis, non-infectious", "cholestasis and jaundice of hepatic origin", "liver related investigations, signs and symptoms", and "liver-related coagulation and bleeding disturbances".‡ After receiving one dose of study drug, patient with risk factors was hospitalised on day 8 after the baseline dose for shortness of breath and chest tightness. A nodule in the left upper lobe of lung was discovered, biopsied, and confirmed to be squamous cell lung cancer. Study drug was discontinued. The patient had Leriche syndrome leading to above knee amputation. The patient then developed acute respiratory failure and gram-negative bacteraemia. Hypoxia worsened, supportive care was withdrawn, and the patient died the same day; death was determined by the investigator to have no reasonable possibility of being related to study drug.

Table 3: **Overview of treatment-emergent adverse events (safety analysis set)**

the efficacy of risankizumab versus ustekinumab in patients with moderately to severely active Crohn's disease is in its recruitment phase (SEQUENCE, NCT04524611).

To conclude, in patients with moderately to severely active Crohn's disease, induction treatment with intravenous risankizumab was well tolerated and resulted in early, statistically significant, and clinically meaningful improvements versus placebo treatment across coprimary and key secondary endpoints in populations with and without previous bio-failure. IL-22, a pharmacodynamic biomarker of IL-23 activity, was reduced at week 12 with risankizumab treatment (600 mg and 1200 mg) while unchanged with placebo, and baseline serum IL-22 concentrations were not found be predictive of clinical or endoscopic improvement at week 12 of induction treatment with risankizumab. Early symptom control was accompanied by reductions in hs-CRP and faecal calprotectin. The safety profile of risankizumab in Crohn's disease was consistent with previous risankizumab studies in other indications,[21,22] with no new safety risks identified.

Contributors

GD'H was coordinating investigator for ADVANCE and RP was coordinating investigator for MOTIVATE; both contributed equally to the conduct of the studies. All authors participated in data acquisition. JS, BGF, EN, AS, YP, BH, JK, XL, AR, and KW participated in study design. All authors had full access to all the data in the study. BH and XL assessed and verified the data. BH and XL participated in statistical analysis. All authors were involved in the interpretation of the data and preparation and critical review of the manuscript, and approved the final version of the manuscript.

Declaration of interests

GD'H reports being a consultant or speaker for AbbVie, ActoGeniX, AIM, Allergan, Amgen, Arena, Boehringer Ingelheim, Celgene (formerly Receptos), Celltrion, Cosmo Technologies, Elan, Eli Lilly, enGene, Dr Falk Pharma, Ferring, Galapagos, Genentech, Gilead Sciences, Giuliani, Given Imaging, GlaxoSmithKline (GSK), Gossamer Bio, Janssen Biologics, Merck, Sharp & Dohme (MSD), Neovacs, Norgine, Novo Nordisk, Otsuka, PDL BioPharma, Prometheus Laboratories, Progenity, Pfizer, Alimentiv (formerly Robarts Clinical Trials), Salix, Seres and Nestle, Schering-Plough, SetPoint, Shire, Takeda, Tillotts, Tramedico, UCB, Versant, and Vifor; and reports research grants from AbbVie, Dr Falk Pharma, Given Imaging, Janssen, MSD, and PhotoPill. 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Data sharing

AbbVie is committed to responsible data sharing regarding the clinical trials it sponsors. This includes access to anonymised, individual, and trial-level data (analysis datasets), and other information (eg, protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. More information on the process and the portal to submit requests are available online.

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