Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial

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Summary

Background There is a great unmet need for new therapeutics with novel mechanisms of action for patients with Crohn's disease. The ADVANCE and MOTIVATE studies showed that intravenous risankizumab, a selective p19 anti-interleukin (IL)-23 antibody, was efficacious and well tolerated as induction therapy. Here, we report the efficacy and safety of subcutaneous risankizumab as maintenance therapy.

Methods FORTIFY is a phase 3, multicentre, randomised, double-blind, placebo-controlled, maintenance withdrawal study across 273 clinical centres in 44 countries across North and South America, Europe, Oceania, Africa, and the Asia-Pacific region that enrolled participants with clinical response to risankizumab in the ADVANCE or MOTIVATE induction studies. Patients in ADVANCE or MOTIVATE were aged 16–80 years with moderately to severely active Crohn's disease. Patients in the FORTIFY substudy 1 were randomly assigned again (1:1:1) to receive either subcutaneous risankizumab 180 mg, subcutaneous risankizumab 360 mg, or withdrawal from risankizumab to receive subcutaneous placebo (herein referred to as withdrawal [subcutaneous placebo]). Treatment was given every 8 weeks. Patients were stratified by induction dose, post-induction endoscopic response, and clinical remission status. Patients, investigators, and study personnel were masked to treatment assignments. Week 52 co-primary endpoints were clinical remission (Crohn's disease activity index [CDAI] in the US protocol, or stool frequency and abdominal pain score in the non-US protocol) and endoscopic response in patients who received at least one dose of study drug during the 52-week maintenance period. Safety was assessed in patients receiving at least one dose of study medication. This study is registered with ClinicalTrials.gov, NCT03105102.

Findings 712 patients were initially assessed and, between April 9, 2018, and April 24, 2020, 542 patients were randomly assigned to either the risankizumab 180 mg group (n=179), the risankizumab 360 mg group (n=179), or the placebo group (n=184). Greater clinical remission and endoscopic response rates were reached with 360 mg risankizumab versus placebo (CDAI clinical remission was reached in 74 (52%) of 141 patients *vs* 67 (41%) of 164 patients, adjusted difference 15% [95% CI 5–24]; stool frequency and abdominal pain score clinical remission was reached in 73 (52%) of 141 *vs* 65 (40%) of 164, adjusted difference 15% [5–25]; endoscopic response 66 (47%) of 141 patients *vs* 36 (22%) of 164 patients, adjusted difference 28% [19–37]). Higher rates of CDAI clinical remission and endoscopic response (but not stool frequency and abdominal pain score clinical remission [p=0·124]) were also reached with risankizumab 180 mg versus withdrawal (subcutaneous placebo; CDAI clinical remission reached in 87 [55%] of 157 patients, adjusted difference 15% [95% CI 5–24]; endoscopic response 74 [47%] of 157, adjusted difference 26% [17–35]). Results for more stringent endoscopic and composite endpoints and inflammatory biomarkers were consistent with a dose–response relationship. Maintenance treatment was well tolerated. Adverse event rates were similar among groups, and the most frequently reported adverse events in all treatment groups were worsening Crohn's disease, arthralgia, and headache.

Interpretation Subcutaneous risankizumab is a safe and efficacious treatment for maintenance of remission in patients with moderately to severely active Crohn's disease and offers a new therapeutic option for a broad range of patients by meeting endpoints that might change the future course of 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 before 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. The ADVANCE and MOTIVATE phase 3 induction studies examined the safety and efficacy of risankizumab, a selective anti-IL-23 antibody, as induction therapy versus withdrawal to placebo. More patients who received intravenous risankizumab at 600 mg and 1200 mg doses met the week-12 co-primary endpoints of clinical remission and endoscopic response than did patients who received placebo. These improvements were accompanied by a reduction of inflammatory (ie, high-sensitivity CRP and faecal calprotectin) and pharmacodynamic (ie, IL-22) biomarkers. Treatment effects of risankizumab were evident in patients with and without previous bio-failure. These findings align with those from the risankizumab phase 2 study where clinical remission was reached following induction or reinduction with intravenous risankizumab (600 mg) in patients with moderately to severely active Crohn's disease, most of whom had disease that did not respond to previous therapy with one or more TNF antagonists. Risankizumab was also well tolerated and effective for maintaining clinical remission in patients who received open-label subcutaneous risankizumab (180 mg) for a period of 26 weeks up to, or exceeding, 3 years of dosing.

Added value of this study

The pivotal placebo-controlled, 52-week, maintenance withdrawal study of FORTIFY substudy 1 (SS1), described herein, evaluated efficacy and safety of subcutaneous risankizumab as maintenance therapy in patients with moderately to severely active Crohn's disease who responded to 12 weeks of intravenous risankizumab induction therapy. FORTIFY SS1 was also the first pivotal maintenance study in patients with Crohn's disease to use an endoscopic co-primary endpoint and to include novel endpoints of clinical remission and response, as defined by patient-reported outcomes of stool frequency and abdominal pain score. Maintenance therapy with risankizumab provided superior efficacy versus withdrawal (subcutaneous placebo) as evidenced by a significantly greater proportion of patients reaching the co-primary endpoints of clinical remission and endoscopic response and secondary endpoints, including the more stringent endoscopic endpoint of remission and composite endpoints (eg, deep remission). Efficacy was observed irrespective of intolerance or inadequate response to other advanced therapies. Even accounting for the prolonged effects of risankizumab in patients who were randomly assigned to the withdrawal (subcutaneous placebo) group, a greater proportion of patients reached the objective endoscopic and biomarker endpoints at week 52, underscoring the importance of continuing risankizumab as maintenance therapy. Risankizumab subcutaneous maintenance therapy was safe and well tolerated in patients with moderately to severely active Crohn's disease.

Implications of all the available evidence

The data reported here support the favourable benefit–risk profile of risankizumab for maintenance therapy of patients with moderately to severely active Crohn's disease that responded to risankizumab intravenous induction, regardless of previous intolerance or inadequate response to biological therapy. These results will allow for a broad range of use in clinical practice, ranging from first-line advanced therapy to treatment of patients with inadequate response or intolerance to multiple advanced therapies. Additionally, the robust endoscopic data could translate into changing the course of disease, which is important to all stakeholders.

Introduction

Current therapies to treat moderately to severely active Crohn's disease might not result in adequate disease control. Factors contributing to treatment discontinuation include pathophysiology, immunogenicity, enhanced drug clearance, and side-effects or complications. New treatment options with novel mechanisms of action that deliver robust and sustained improvements in disease outcomes and offer improved benefit–risk profiles are needed. Interleukin (IL)-23 is a key player in the development and pathogenesis of Crohn's disease.[1–9] Stimulation of activated T cells by IL-23 induces expression of proinflammatory cytokines, such as IL-22. Risankizumab is a humanised IgG1 monoclonal antibody that selectively binds to the p19 subunit of IL-23, distinguishing it from biological therapies that target the shared IL-12 and IL-23 p40 subunit (eg, ustekinumab).

The pivotal phase 3 induction studies ADVANCE and MOTIVATE were multicentre, randomised, double-blind, 12-week, placebo-controlled evaluations of 600 mg and 1200 mg intravenous risankizumab, dosed every 4 weeks, in patients with moderately to severely active Crohn's disease with and without previous inadequate response or intolerance to biologics (ie, bio-failure).[10] For both studies, across the co-primary and key secondary endpoints, risankizumab showed significant and clinically meaningful resolution of signs and symptoms of Crohn's disease as compared with withdrawal (herein referred to as withdrawal [subcutaneous placebo]). Reductions in symptoms and inflammatory biomarkers were observed as early as week 4, with further improvements observed at week 12. Significantly higher rates of endoscopic response and endoscopic remission were observed at week 12 with risankizumab than with

placebo, and efficacy of risankizumab over placebo was shown in patients with and without previous bio-failure.[10]

Phase 2 studies reported that maintenance treatment with 180 mg subcutaneous risankizumab was well tolerated for up to 184 weeks and effective in maintaining clinical remission for a period of up to 26 weeks.[11,12] Because a subcutaneous dose higher than 180 mg had not been studied in patients with Crohn's disease, it was unknown whether an efficacy plateau had been achieved; therefore, a higher subcutaneous dose of 360 mg was evaluated in FORTIFY to establish whether greater efficacy could be achieved than with 180 mg.

Here we report the results of FORTIFY substudy 1 (SS1), in which the efficacy of continuing subcutaneous risankizumab as maintenance therapy was evaluated. In FORTIFY SS1, patients with clinical response to 12-week induction therapy in the ADVANCE or MOTIVATE induction studies were randomly assigned to receive either 180 mg or 360 mg subcutaneous risankizumab or were withdrawn from risankizumab to receive subcutaneous placebo (ie, withdrawal). Dosing occurred every 8 weeks over a 52-week period. The pharmacokinetic properties, immunogenicity, and the pharmacodynamic effects of risankizumab were also evaluated.

Methods

Study design and participants

FORTIFY SS1 is a multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 study conducted at 273 clinical centres in 44 countries across North and South America, Europe, Oceania, Africa, and the Asia-Pacific region. Patients with clinical response (defined as ≥30% decrease in mean stool frequency of daily values reported for 7 days before the scheduled assessment visit or ≥30% decrease in mean daily abdominal pain score, both not worse than baseline of the induction study) to intravenous risankizumab induction therapy at week 12 or at week 24 of induction period 2 in ADVANCE (NCT03105128) or MOTIVATE (NCT03104413) were eligible to enter FORTIFY. Complete FORTIFY eligibility criteria are provided in the appendix (pp 9–10). Patients in ADVANCE or MOTIVATE were aged 16–80 years with moderately to severely active Crohn's disease, as determined by CDAI 220–450, mean daily stool frequency of at least 4 or mean abdominal pain score of at least 2, and Simple Endoscopic Score for Crohn's disease (SES-CD) at least 6 (or ≥4 for isolated ileal disease).[10] Patients with an SES-CD of 3–5 for colonic or ileocolonic disease, or 3 for isolated ileal disease, (termed low SES-CD) were also included for exploratory purposes. ADVANCE enrolled patients with demonstrated intolerance or disease with inadequate response to conventional (ie, without previous bio-failure) or biological (ie, with previous bio-failure) therapies, whereas MOTIVATE exclusively enrolled patients with previous bio-failure. Patients that entered, but were not randomly assigned to a treatment group, in FORTIFY included those who had a clinical response to subcutaneous risankizumab at week 24 of induction period 2 in ADVANCE or MOTIVATE or clinical response to placebo in ADVANCE or MOTIVATE; these patients were excluded from efficacy analyses but included in safety analyses. There were no high-sensitivity (hs)-CRP, faecal calprotectin, or endoscopy eligibility criteria for entry into this maintenance study. Participants with a clinical response in ADVANCE or MOTIVATE were invited to enrol in FORTIFY, which was approved by independent ethics committees or institutional review boards at each study site. The study was conducted and reported in accordance with the protocol and with the International Conference on Harmonization guidelines, 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

Patients in FORTIFY SS1 were randomly assigned again (in a 1:1:1 ratio) via interactive response technology to receive 180 mg of subcutaneous risankizumab (risankizumab 180 mg group), 360 mg subcutaneous risankizumab (risankizumab 360 mg group), or withdrawal from risankizumab to receive subcutaneous placebo (placebo group; appendix p 22) every 8 weeks. Re-randomisation was stratified by endoscopic response (ie, 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; yes, no], and stool frequency and abdominal pain score clinical remission status [mean daily stool frequency ≤2·8 and not worse than baseline and mean daily abdominal pain score ≤1 and not worse than baseline status; yes, no]) at the final visit of induction; and risankizumab induction final dose (1200 mg or 600 mg). All endoscopies were centrally read for the purposes of data analyses, but local reads for endoscopic response were used for the maintenance stratification variable. Patients with a low SES-CD at the induction study baseline, patients who received 24 weeks of induction dosing, and patients from a non-compliant site (ie, without investigator oversight) were also randomly assigned and were included in the safety population, but not in the efficacy population. Patients, investigators, and study personnel involved in the trial conduct or analyses were masked to treatment assignments until study completion. To maintain blinding, risankizumab and placebo kits were identical in appearance. Study investigators enrolled participants. Interactive response technology determined assignment of participants to a treatment group.

See Online for appendix

Procedures

Patients received subcutaneous injections of risankizumab or placebo (ie, four 90 mg injections in the risankizumab 360 mg group, two 90 mg risankizumab

injections and two placebo injections of equal volume in the risankizumab 180 mg group, and four placebo injections of equal volume to each 90 mg risankizumab injection in the placebo group) at weeks 0, 8, 16, 24, 32, 40, and 48. Each scheduled dose was administered within plus or minus 7 days. Patients with Crohn's disease that did not respond adequately could receive open-label risankizumab rescue therapy (ie, one single intravenous dose of 1200 mg followed by 360 mg (ie, four 90 mg injection subcutaneously every 8 weeks thereafter) starting at the week 16 visit on the basis of increased symptom activity and confirmation with objective markers of inflammation (appendix p 12). The final study visit was at week 52 (or the date of premature discontinuation of treatment). Patients recorded symptoms related to Crohn's disease in a daily diary. Blood samples were collected throughout the study for laboratory testing, including assays to measure concentrations of CRP (hs-CRP) at weeks 0, 24, and 52; IL-22 at weeks 0 and 52; and serum risankizumab, antidrug antibody, and neutralising antibody at weeks 0, 8, 16, 24, 32, 40, 48, and 52 (without antibody isotyping). Stool samples for faecal calprotectin analysis were collected before starting bowel preparations for endoscopy. Test methods are listed in the appendix (p 14). An ileo-colonoscopy was performed at the week 52 (or early termination) visit and was evaluated by use of SES-CD. Pharmacokinetic analysis is reported for all patients with available data, except for those receiving rescue treatment. Primary and secondary efficacy outcomes were assessed at week 52. Safety was monitored throughout the study and included adverse events, changes in vital signs, physical examination, product complaints ongoing during maintenance treatment (at weeks 0, 8, 16, 24, 32, 40, and 52, or at premature discontinuation); electrocardiogram assessments (at weeks 8 and 52, or premature discontinuation); and clinical laboratory parameters (at weeks 0, 24, and 52, or premature discontinuation). Study investigators monitored each patient for clinical and laboratory evidence of adverse events on a routine basis at each study site. Study investigators also assessed and recorded any adverse event in detail, including the date of onset, event diagnosis (if known) or sign or symptom, severity, time course (ie, end date, ongoing, and intermittent), relationship of the adverse event to the study drug, and any actions taken.

Outcomes

FORTIFY SS1 co-primary endpoints were clinical remission and endoscopic response at week 52 in the primary efficacy population. Due to regional differences in regulatory requirements (a preference for CDAI-based endpoints in the USA and patient-reported outcome-based endpoints in Europe), clinical remission was defined as CDAI less than 150 (hereafter referred to as CDAI clinical remission) in the US analysis plan. In the non-US plan, clinical remission was defined as mean daily liquid or very soft stool frequency of 2·8 or less and not worse than baseline, plus mean daily abdominal pain score of 1 or less and not worse than baseline of induction (hereafter referred to as stool frequency and abdominal pain score clinical remission). All patients were analysed for both clinical remission definitions. In both analysis plans, endoscopic response was defined as a decrease in SES-CD of more than 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). Secondary endpoints were multiplicity controlled. Among the key secondary endpoints examined were stool frequency remission, abdominal pain remission, CDAI clinical response, enhanced stool frequency and abdominal pain score clinical response, ulcer-free endoscopy (ie, absence of ulceration), endoscopic remission, composite endpoint of clinical remission and endoscopic response, CDAI deep remission (ie, composite of clinical remission and endoscopic remission), stool frequency and abdominal pain score clinical response at week 52. Definitions of these endpoints are provided in the appendix (p 16). Other planned secondary endpoints, including durability of clinical remission (ie, CDAI and stool frequency and abdominal pain score) at week 52, change from baseline in the Functional Assessment of Chronic Illness Therapy-Fatigue measure at week 52, steroid-free CDAI clinical remission at week 52, change from baseline in the Inflammatory Bowel Disease Questionnaire total score, and change from baseline in the 36-Item Short Form Survey at week 52, are not reported here and will be reported in a future publication.

Safety analyses included the incidence of adverse events, changes in vital signs, physical examination results, electrocardiogram, and clinical laboratory parameters in all patients who received at least one dose of the study drug. Treatment-emergent adverse events were collected from the time of study drug administration until 140 days from the final dose of study drug had elapsed. Serious adverse events and non-serious adverse events related to the protocol were collected from the time the participant signed the study-specific informed consent. Adverse events were coded with the Medical Dictionary for Regulatory Activities (version 23.1). 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 event was defined as cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke; extended major adverse cardiovascular event was defined as major adverse cardiovascular event with admission to hospital for unstable angina and coronary revascularisation procedures. An independent data monitoring committee assessed all potential safety signals and were not masked to treatment allocation. The committee reviewed the unmasked safety data on a cohort level, at a minimum of 6-month intervals throughout the course of the study.

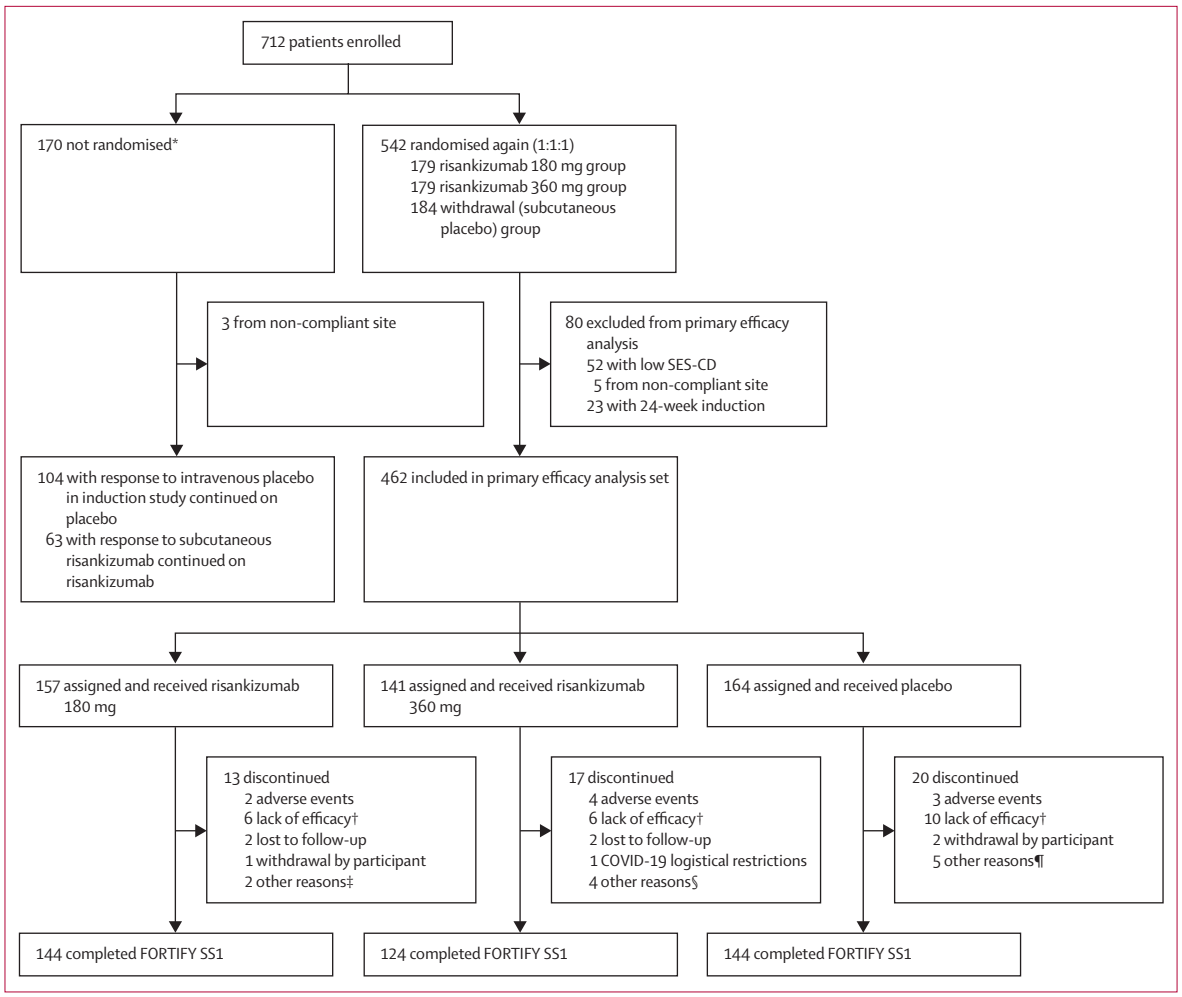

Figure 1: **Trial profile**

SES-CD=Simple Endoscopic Score for Crohn's Disease. SS1=substudy 1. *Patients with a clinical response after subcutaneous risankizumab at week 24 of the induction period 2 in ADVANCE or MOTIVATE were subsequently assigned to receive masked subcutaneous risankizumab 180 mg or 360 mg at the same dose that they received during induction period 2 of ADVANCE or MOTIVATE, and therefore were excluded from the primary efficacy analysis. Patients with clinical response to placebo in ADVANCE or MOTIVATE were subsequently assigned to continue to receive masked placebo, and therefore were excluded from the primary efficacy analysis. †Decided by participant or investigator. ‡One participant was removed at the principal investigator's discretion. One participant could no longer commit the time needed for the study due to geographical move, but has agreed to prematurely discontinue visit and 140-day follow-up. §One participant withdrew to commence a dermatology study, two participants withdrew due to pregnancy, and one participant became pregnant during the study, so was withdrawn per the protocol. ¶One participant did not comply with scheduled visits, two participants withdrew due to pregnancy, one participant was non-compliant with inclusion criteria 3 of the protocol and prematurely discontinued, and one participant was withdrawn by principal investigator decision after reviewing the patient.

Statistical analysis

The sample size was calculated to provide more than 87% power to detect anticipated treatment differences in each co-primary endpoint between risankizumab and placebo by use of a Fisher's exact test at a two-sided significance level of 0·05. The rate assumption and power calculation details are presented in the appendix (p 13). Briefly, the week 52 CDAI clinical remission rate was assumed to be 46% for one of the risankizumab groups, and 28% for the withdrawal (subcutaneous placebo) group; the week 52 stool frequency and abdominal pain score clinical remission rate was assumed to be 39% for one of the risankizumab groups, and 20% for the withdrawal (subcutaneous placebo) group; and the week 52 endoscopic response rate was assumed to be 33% for one of the risankizumab groups and 10% for the withdrawal (subcutaneous placebo) group.

The primary efficacy population included participants from the ADVANCE and MOTIVATE induction studies who had a baseline SES-CD of at least 6 (≥4 for isolated ileal disease), had a clinical response to 12 weeks of intravenous risankizumab at the end of induction, and received at least one dose of study drug during the 52-week FORTIFY maintenance study. The primary safety analysis population additionally included randomly assigned patients who received 24 weeks of risankizumab during the induction studies, patients from a non-compliant site

(ie, without investigator oversight), patients with low SES-CD at induction baseline, and patients who were not randomly assigned to study groups (ie, those with clinical response after masked subcutaneous risankizumab 180 mg or 360 mg at week 24 of induction period 2 in ADVANCE or MOTIVATE and those with clinical response to placebo at week 12 in ADVANCE or MOTIVATE).

The co-primary endpoints of clinical remission and endoscopic response were analysed separately for each protocol. The co-primary endpoints were tested at a two-sided significance level of 0·05 for the risankizumab 360 mg group versus withdrawal (subcutaneous placebo) group, followed sequentially by testing each of the co-primary endpoints at a two-sided significance level of 0·05 for the risankizumab 180 mg group versus placebo group. For the study to claim success, the co-primary endpoints had to meet the predefined criteria for that protocol (ie, both co-primary endpoinds should be $p<0·05$ for the risankizumab 360 mg group). If both co-primary endpoints reached significance for both risankizumab doses, continued testing of the secondary endpoints for 360 mg and 180 mg, ranked according to clinical relevance, would follow the multiplicity adjustment using the graphic α spending method (appendix pp 13–15). The overall type 1

	Risankizumab 180 mg group (n=157)	Risankizumab 360 mg group (n=141)	Withdrawal group (subcutaneous placebo; n=164)
Baseline of induction (in ADVANCE or MOTIVATE)			
Sex			
Female	89 (57%)	60 (43%)	75 (46%)
Male	68 (43%)	81 (57%)	89 (54%)
Age, years	39·1 (14·8)	37·0 (12·8)	38·0 (13·0)
Weight, kg	69·2 (16·2)	70·4 (17·5)	71·8 (19·2)
Race			
White	127 (81%)	111 (79%)	126 (77%)
Black or African American	4 (3%)	8 (6%)	10 (6%)
Asian	22 (14%)	20 (14%)	28 (17%)
American Indian or Alaska Native	0	0	0
Native Hawaiian or Other Pacific Islander	1 (1%)	0	0
Multiple	3 (2%)	2 (1%)	0
Ethnicity			
Hispanic or Latino	8 (5%)	7 (5%)	7 (4%)
Non-Hispanic or non-Latino	149 (95%)	134 (95%)	157 (96%)
Disease duration, years	10·8 (10·2)	9·3 (8·1)	9·6 (8·8)
Disease location			
Ileal only	15 (10%)	15 (11%)	23 (14%)
Colonic only	70 (45%)	59 (42%)	62 (38%)
Ileal-colonic	72 (46%)	67 (48%)	79 (48%)
Corticosteroid use	51 (32%)	42 (30%)	51 (31%)
Immunomodulator use	41 (26%)	40 (28%)	40 (24%)
Biologics failure history			
0	44 (28%)	39 (28%)	41 (25%)
1	42 (27%)	51 (36%)	60 (37%)
>1	71 (45%)	51 (36%)	63 (38%)
Anti-TNF failure history*			
0†	6/113 (5%)	11/102 (11%)	4/123 (3%)
1	52/113 (46%)	49/102 (48%)	71/123 (58%)
>1	55/113 (49%)	42/102 (41%)	48/123 (39%)
Ustekinumab failure history*	18/113 (16%)	17/102 (17%)	15/123 (12%)
Faecal calprotectin, mg/kg	1561·00 (452·00–2749·50)	1543·00 (573·00–2879·00)	794·50 (237·00–2245·00)
High-sensitivity CRP, mg/L	8·415 (3·955–22·500)	10·050 (3·960–33·050)	7·670 (2·750–21·500)
CDAI	323·2 (67·6)	308·9 (61·1)	307·4 (64·9)
SES-CD	14·7 (7·1)	14·3 (7·4)	14·0 (7·1)
Mean daily stool frequency	6·1 (3·2)	5·9 (2·6)	5·8 (2·7)
Mean daily abdominal pain score	2·0 (0·5)	1·8 (0·5)	1·9 (0·5)

(Table 1 continues on next page)

	Risankizumab 180 mg group (n=157)	Risankizumab 360 mg group (n=141)	Withdrawal group (subcutaneous placebo; n=164)
(Continued from previous page)			
FORTIFY, week 0‡			
Faecal calprotectin, mg/kg	412·50 (137·00–1084·00)	424·00 (143·50–1455·50)	307·00 (97·00–904·00)
High-sensitivity CRP, mg/L	3·7·30 (1·490–7·840)	3·900 (1·530–8·170)	4·070 (1·270–8·325)
CDAI	132·8 (75·8)	137·2 (67·7)	133·6 (80·6)
SES-CD	7·9 (6·4)	8·5 (7·3)	7·6 (6·6)
Mean daily stool frequency	2·2 (2·0)	2·1 (1·8)	1·8 (1·8)
Mean daily abdominal pain score	0·7 (0·6)	0·7 (0·6)	0·7 (0·6)
Patients in stool frequency or abdominal pain score clinical remission	92/157 (59%)	72/139 (52%)	91/163 (56%)
Patients in CDAI clinical remission	96/157 (61%)	81/138 (59%)	96/163 (59%)
Patients with endoscopic response	66/151 (44%)	55/136 (40%)	73/162 (45%)
Patients in endoscopic remission	44/151 (29%)	39/136 (29%)	46/162 (28%)

Data are mean (SD), n (%), or median (IQR). Intention-to-treat population includes participants who were randomly assigned and received at least one dose of study drug during the 52-week maintenance period, received only one 12-week period of risankizumab induction, and had baseline eligible SES-CD of ≥6 (≥4 for isolated ileal disease). All groups received intravenous risankizumab induction. CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Denominator based on the bio-failure population. †Participants who are naive to anti-TNF therapy or who discontinued anti-TNF therapy for reasons other than inadequate response or intolerance (eg, change of insurance), the percentage of response is only summarised for patients with available assessments. ‡Based on as observed data, and the statistics were calculated on non-missing values.

Table 1: **Demographic and disease characteristics of the intention-to-treat population**

error rate of efficacy evaluation based on the co-primary and ranked secondary endpoints for the two doses was strongly controlled at a 0·05 (two-sided) level. Co-primary and categorical secondary efficacy endpoints were analysed by use of the Cochran–Mantel–Haenszel test stratified by the randomisation stratification factors of week 0 clinical remission status, week 0 endoscopic response status, and risankizumab induction dose. A Cochran–Mantel–Haenszel-based two-sided 95% CI for the difference between treatment groups was constructed. Non-responder imputation incorporating multiple imputation for missing data due to COVID-19 infection or logistical restrictions was used for categorical endpoints; patients with missing data for all other reasons were counted as non-responders. Participants who received rescue therapy were considered as non-responders for categorical endpoints.

Continuous endpoints with repeated measures were analysed by a mixed-effect model for repeated measures, whereas those with only one post-baseline measure were analysed by an analysis of covariance model. The randomisation stratification factors and the measurements at induction baseline and at week 0 have been included as covariates in the model. Data after receiving rescue therapy were not used in the analysis of continuous endpoints.

Baseline demographics and characteristics, safety data, and pharmacokinetic data were summarised by descriptive statistics. Pharmacokinetic analyses were done by use of a non-linear mixed-effects population modelling approach based on a previously developed two-compartment population pharmacokinetic model with first order absorption and elimination that described risankizumab pharmacokinetics in patients with moderate to severe plaque psoriasis and Crohn's disease. Statistical analysis for IL-22 measurements is described in the appendix (pp 14–15). All statistical analyses were conducted with SAS version 9.4. This study is registered with ClinicalTrials.gov, NCT03105102.

Role of the funding source

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

Results

Between April 9, 2018, and April 24, 2020, 712 patients were initially assessed and 542 patients from ADVANCE and MOTIVATE were randomly assigned again in FORTIFY SS1 to either the risankizumab 180 mg group (n=157), the risankizumab 360 mg group (n=141), or the withdrawal (subcutaneous placebo) group (n=164). Most patients completed the maintenance period across the treatment groups (144 [92%] of 157 patients in the risankizumab 180 mg group; 124 [88%] of 141 patients in the risankizumab 360 mg group; and 144 [88%] of 164 patients in the placebo group). The most frequent primary reasons for study discontinuation were participant or investigator decision due to lack of efficacy (numerically highest in the withdrawal [subcutaneous placebo] group) and adverse events (similar across groups; figure 1).

Induction baseline patient demographics and disease characteristics were similar among the risankizumab and withdrawal (subcutaneous placebo) groups (table 1).

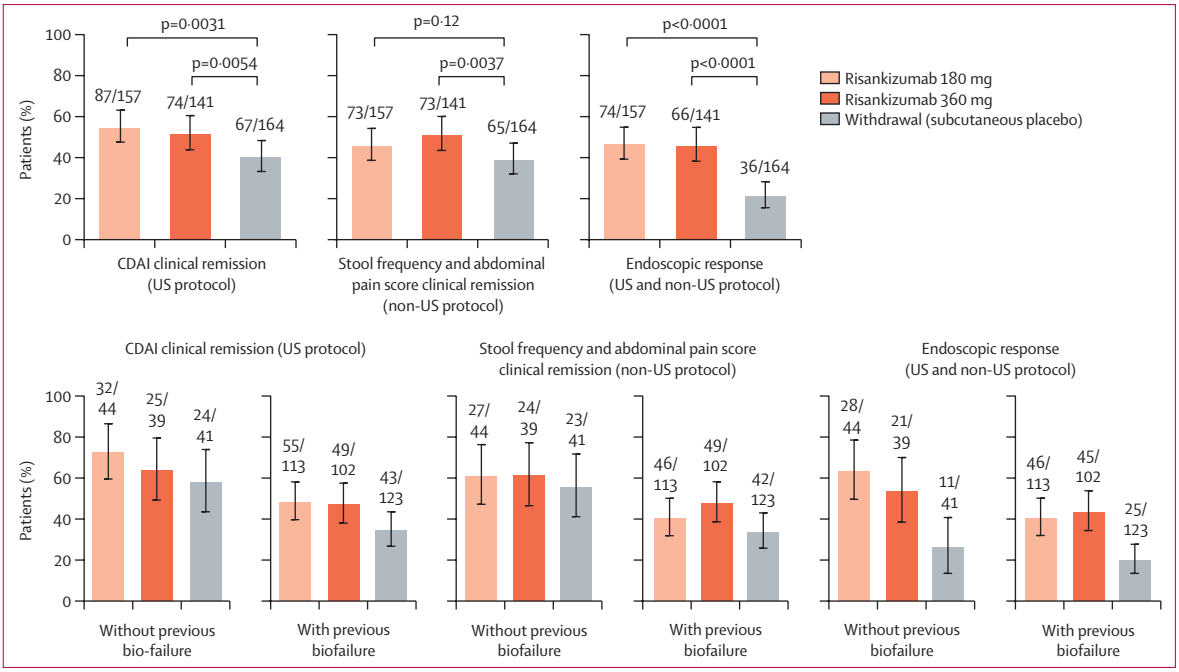

Figure 2: **Co-primary endpoints at week 52 of FORTIFY**

Error bars show 95% CIs. Numbers of patients are shown as n/N. With previous bio-failure indicates patients with documented intolerance or with disease with inadequate response to one or more of the approved biologics for Crohn's disease. Without previous bio-failure indicates patients with disease that had an inadequate response or who had intolerance to conventional therapy and patients who received biologic therapy in the past but stopped therapy on the basis of reasons other than an inadequate response or intolerance (eg, change in reimbursement coverage or well controlled disease). CDAI clinical remission was defined as CDAI less than 150. Stool frequency and abdominal pain score clinical remission was defined as mean daily stool frequency of 2·8 or less and not worse than baseline and mean daily abdominal pain score of 1 or less and not worse than baseline. Endoscopic response was defined as a decrease in SES-CD of more than 50% from baseline of the induction study (or for patients with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline of the induction study), as scored by central reviewer (Alimentiv). All patients in the withdrawal (subcutaneous placebo) group were exposed to risankizumab in the induction study and withdrawn from risankizumab to receive placebo in FORTIFY. CDAI=Crohn's Disease Activity Index.

Disease variables at FORTIFY week 0, such as CDAI, SES-CD, mean daily stool frequency and abdominal pain score, hs-CRP, and faecal calprotectin analysis were similar across groups, as were the proportions of patients with clinical remission (CDAI and stool frequency and abdominal pain score), endoscopic response, and endoscopic remission (table 1). Overall, 338 (73%) of 462 patients were categorised as with previous bio-failure (153 [33%] of 462 patients had disease that did not respond to one biologic and 185 [40%] of 462 patients had disease that did not respond to more than one biologic). Of patients with previous bio-failure, 50 [15%] of 338 patients showed intolerance or disease with inadequate response to ustekinumab.

At week 52, the adjusted treatment difference between risankizumab 360 mg and withdrawal (subcutaneous placebo) for CDAI clinical remission was 15% (95% CI 4–25; figure 2). The adjusted treatment difference between risankizumab 360 mg and withdrawal (subcutaneous placebo) for stool frequency and abdominal pain score clinical remission was 15% (95% CI 5–25). The adjusted treatment difference between risankizumab 360 mg and withdrawal (subcutaneous placebo) for endoscopic response was 28% (95% CI 19–37). In the risankizumab 180 mg group, the co-primary endpoints at week 52 were met for the US analysis plan; the adjusted treatment difference between risankizumab 180 mg and withdrawal (subcutaneous placebo) for CDAI clinical remission was 15% (95% CI 5–25), and the adjusted treatment difference for endoscopic response was 26% (17–35). For the non-US analysis, the adjusted treatment difference between risankizumab 180 mg and withdrawal (subcutaneous placebo) for stool frequency and abdominal pain score clinical remission was 8% (95% CI –2 to 18); however, the adjusted treatment difference was not significant. As a result, the hierarchical testing plan prevented testing of significance for all secondary endpoints in the hierarchy. Patients with and without previous bio-failure were analysed to establish the efficacy of risankizumab maintenance dosing in these subpopulations (figure 2). Results in both cohorts favoured risankizumab over placebo for primary endpoints. Numerically higher rates of efficacy were generally observed with risankizumab in the patients without previous bio-failure.

Week 52 results for key secondary endpoints are presented in table 2. Higher rates of efficacy were shown for the objective endpoints of endoscopic remission and ulcer-free endoscopy (ie, absence of ulceration), composite endpoints of clinical remission and endoscopic response, and deep remission in the risankizumab treatment

	Risankizumab 180 mg group (n=157)	Risankizumab 360 mg group (n=141)	Withdrawal group (subcutaneous placebo; n=164)
Stool frequency remission* at week 52			
n (%; 95% CI)	81 (52%; 44 to 59)	80 (57%; 49 to 65)	73 (45%; 37 to 52)
Adjusted percentage difference compared with placebo (95% CI)	8% (–1·9 to 18·0); p=0·11	15% (5 to 25); p=0·0041	..
Abdominal pain remission† at week 52			
n (%; 95% CI)	89 (57%; 49 to 64)	80 (57%; 48 to 65)	76 (46%; 39 to 54)
Adjusted percentage difference compared with placebo (95% CI)	11% (1 to 21); p=0·038	13% (3 to 24); p=0·014	..
CDAI clinical response‡ at week 52			
n (%; 95% CI)	105 (67%; 60 to 74)	87 (62%; 54 to 70)	79 (48%; 41 to 56)
Adjusted percentage difference compared with placebo (95% CI)	19% (9 to 29); p=0·0002	16 (6 to 27); p=0·0025	..
Enhanced clinical response§ at week 52†			
n (%; 95% CI)	97 (62%; 54 to 69)	84 (59%; 51 to 68)	81 (49%; 42 to 57)
Adjusted percentage difference compared with placebo (95% CI)	13% (3 to 23); p=0·013	13% (2 to 23); p=0·018	..
Maintenance of stool frequency or abdominal pain score clinical remission¶			
n/N (%; 95% CI)	59/92 (64%; 54 to 74)	50/72 (69%; 58 to 80)	46/91 (51%; 40 to 61)
Adjusted percentage difference compared with placebo (95% CI)	14% (1 to 28); p=0·042	21% (6 to 35); p=0·0046	..
Ulcer-free endoscopy‖ at week 52			
n/N (%; 95% CI)	38/157 (24%; 18 to 31)	43/141 (31%; 23 to 38)	17/162 (10%; 6 to 15)
Adjusted percentage difference compared with placebo (95% CI)	14% (7 to 21); p=0·0002	22% (14 to 30); p<0·0001	..
Endoscopic remission at week 52**			
n (%; 95% CI)	47 (30%; 23 to 37)	55 (39%; 31 to 47)	21 (13%; 8 to 18)
Adjusted percentage difference compared with placebo (95% CI)	17% (9 to 25); p<0·0001	28% (20 to 37); p<0·0001	..
CDAI clinical remission†† and endoscopic response‡‡ at week 52*			
n (%; 95% CI)	60 (38%; 31 to 46)	51 (36%; 28 to 44)	26 (16%; 10 to 21)
Adjusted percentage difference compared with placebo (95% CI)	23% (15 to 31); p<0·0001	23% (14 to 32); p<0·0001	..
Stool frequency or abdominal pain score clinical remission§§ and endoscopic response‡‡ at week 52			
n (%; 95% CI)	50 (32%; 25 to 39)	49 (35%; 27 to 43)	27 (16%; 11 to 22)
Adjusted percentage difference compared with placebo (95% CI)	16% (8 to 24); p<0·0001	22% (13 to 30); p<0·0001	..
CDAI deep remission¶¶ at week 52*			
n (%; 95% CI)	40 (25%; 19 to 32)	41 (29%; 22 to 37)	17 (10%; 6 to 15)
Adjusted percentage difference compared with placebo (95% CI)	15% (8 to 22); p=0·0001	21% (13 to 29); p<0·0001	..
Stool frequency or abdominal pain score deep remission‖‖‖ at week 52†			
n (%; 95% CI)	35 (22%; 16 to 29)	39 (28%; 20 to 35)	16 (10%; 5 to 14)
Adjusted percentage difference compared with placebo (95% CI)	13% (5 to 20); p=0·0006	20% (12 to 28); p<0·0001	..

All p values are nominal. Adjusted treatment difference, 95% CI, and p values for comparison of binary endpoints between risankizumab and withdrawal (subcutaneous placebo) were calculated using Cochran-Mantel-Haenszel test adjusted for randomisation stratification factors (ie, endoscopic response at week 0 [yes or no], clinical remission status at week 0 [yes or no], and last intravenous dose during risankizumab induction periods [1200 mg or 600 mg]). CDAI=Crohn's Disease Activity Index. SES-CD=Simple Endoscopic Score for Crohn's Disease. *Stool frequency remission, mean daily stool frequency ≤2·8 and not worse than baseline. †Abdominal pain remission, mean daily abdominal pain score ≤1 and not worse than baseline. ‡CDAI clinical response, reduction of CDAI ≥100 points from baseline. §Enhanced clinical response, ≥60% decrease in mean daily stool frequency or ≥35% decrease in mean daily abdominal pain score and both not worse than baseline, or clinical remission. ¶Maintenance of clinical remission, clinical remission at week 52 in patients with clinical remission at week 0. ‖Ulcer-free endoscopy, SES-CD ulcerated surface subscore of 0 in participants with SES-CD ulcerated surface subscore ≥1 at baseline, as scored by a central reviewer (response rate calculated using the Net Reclassification Index-C method with multiple imputation). **Endoscopic remission, 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. ††CDAI clinical remission, CDAI <150. ‡‡Endoscopic response, decrease in SES-CD >50% from baseline (or for subjects with isolated ileal disease and a baseline SES-CD of 4, at least a 2-point reduction from baseline), as scored by a central reviewer. §§Stool frequency or abdominal pain score clinical remission, mean daily stool frequency ≤2·8 and not worse than baseline of the induction study, and mean daily abdominal pain score ≤1 and not worse than baseline of the induction study. ¶¶CDAI clinical remission and endoscopic remission. ‖‖‖Stool frequency or abdominal pain score clinical remission and endoscopic remission.

Table 2: **Key clinical and endoscopic secondary endpoints in the intention-to-treat population**

groups versus the withdrawal (subcutaneous placebo) group, and a greater treatment effect was generally observed with the 360 mg versus 180 mg dose (appendix p 5). Additionally, a clear treatment effect was observed in patients with and without previous bio-failure, with a generally higher response rate observed for patients without previous bio-failure.

An assessment of the clinical secondary endpoints CDAI clinical response, stool frequency and abdominal pain score clinical response, enhanced stool frequency and abdominal pain score clinical response, stool frequency remission, and abdominal pain remission at week 52 showed similar effect sizes of approximately 10% in the risankizumab versus the withdrawal (subcutaneous

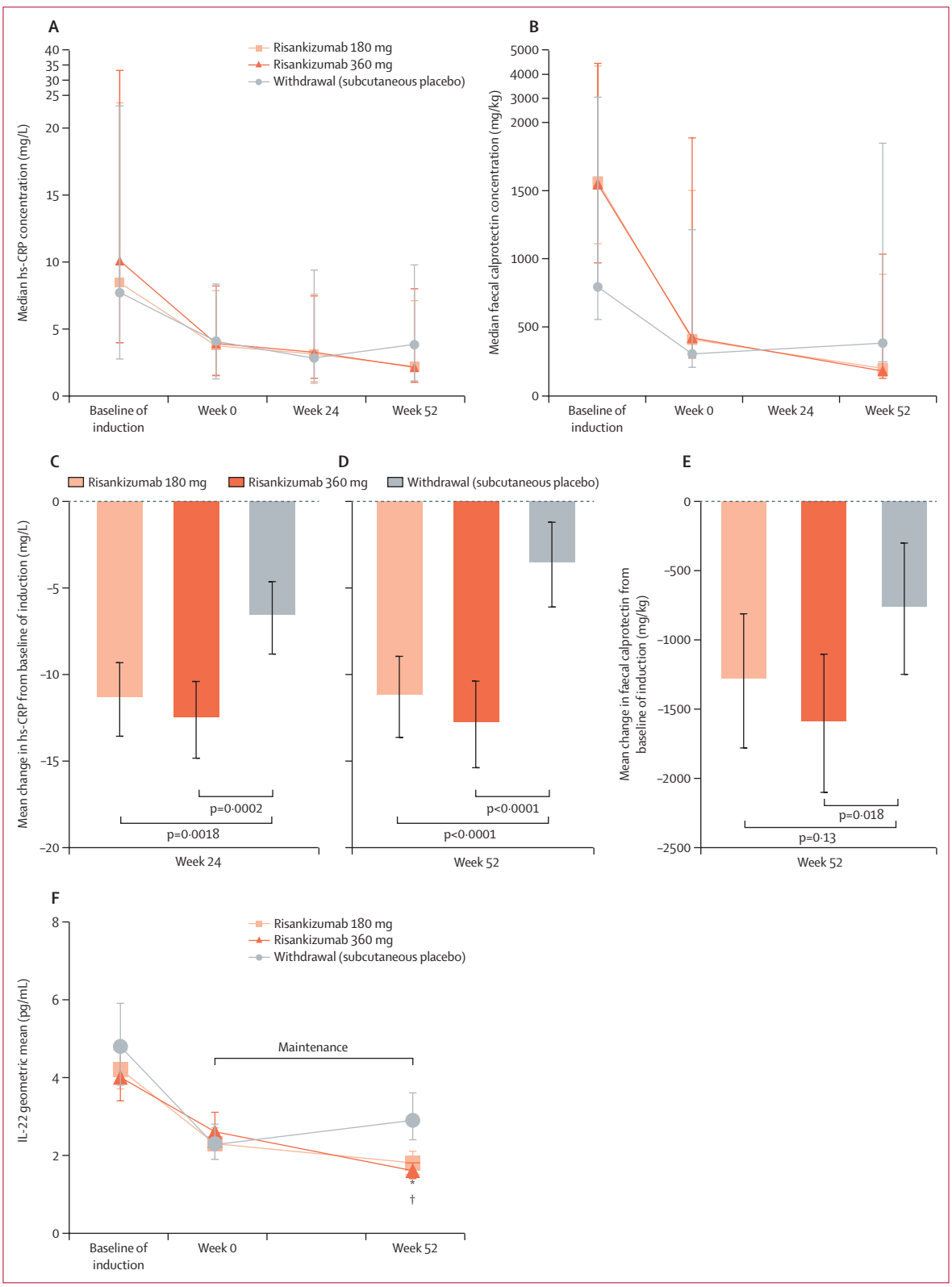

Figure 3: **Inflammatory and pharmacodynamic biomarkers**
Error bars show 95% CIs (C,D,E, and F) or IQR (A, B). All patients in the withdrawal (subcutaneous placebo) group were exposed to risankizumab in the induction study and withdrawn from risankizumab to receive placebo in FORTIFY. hs-CRP=high-sensitivity-CRP. IL-22=interleukin-22. *360 mg *vs* withdrawal (subcutaneous placebo), nominal p=0·036. †360 mg, week 52 *vs* week 0, p<0·001.

placebo) treatment groups. However, efficacy rates were similar across treatment groups until week 16, indicative of prolonged efficacy of induction in the withdrawal group (subcutaneous placebo; appendix p 6). Of patients who had stool frequency and abdominal pain score clinical remission at week 0, the proportion of patients maintaining clinical remission at week 52 was greater in the risankizumab treatment groups than in the withdrawal (subcutaneous placebo) group.

The therapeutic efficacy of risankizumab over the 52-week maintenance study was accompanied by a decrease in faecal calprotectin and hs-CRP relative to week 0 of FORTIFY, with week 52 concentrations of both significantly lower in the risankizumab treatment groups than in the withdrawal (subcutaneous placebo) treatment group (figure 3). Concentrations of faecal calprotectin and hs-CRP in the withdrawal (subcutaneous placebo) group increased at week 52 relative to week 0 of FORTIFY.

	Risankizumab 180 mg group (n=179; 169·3 person-years)		Risankizumab 360 mg group (n=179; 166·4 person-years)		Withdrawal group (subcutaneous placebo; n=184; 160·4 person-years)	
	n (%)	Events per 100 person-years	n (%)	Events per 100 person-years	n (%)	Events per 100 person-years
Overall adverse events						
Adverse events	128 (72%)	480 (283·5)	129 (72%)	448 (269·3)	135 (73%)	545 (339·7)
Severe adverse events	12 (7%)	15 (8·9)	21 (12%)	26 (15·6)	23 (13%)	33 (20·6)
Serious adverse events	22 (12%)	33 (19·5)	24 (13%)	35 (21·0)	23 (13%)	31 (19·3)
Adverse events leading to discontinuation of study drug	3 (2%)	4 (2·4)	6 (3%)	8 (4·8)	6 (3%)	6 (3·7)
Adverse events related to COVID-19	1 (1%)	1 (0·6)	4 (2%)	4 (2·4)	1 (1%)	1 (0·6)
Most frequent adverse events*						
Worsening Crohn's disease	19 (11%)	19 (11·2)	21 (12%)	23 (13·8)	32 (17%)	34 (21·2)
Nasopharyngitis	17 (9%)	21 (12·4)	17 (9%)	21 (12·6)	25 (14%)	30 (18·7)
Arthralgia	15 (8%)	16 (9·5)	17 (9%)	17 (10·2)	20 (11%)	20 (12·5)
Headache	9 (5%)	15 (8·9)	11 (6%)	11 (6·6)	11 (6%)	16 (10·0)
Nausea	9 (5%)	9 (5·3)	4 (2%)	4 (2·4)	13 (7%)	15 (9·3)
Abdominal pain	8 (4%)	9 (5·3)	9 (5%)	9 (5·4)	13 (7%)	15 (9·3)
Diarrhoea	6 (3%)	8 (4·7)	4 (2%)	5 (3·0)	10 (5%)	11 (6·9)
Anaemia	9 (5%)	9 (5·3)	8 (4%)	8 (4·8)	8 (4%)	9 (5·6)
Adverse events of safety interest						
Infections						
Serious infections	5 (3%)	5 (3·0)	8 (4%)	10 (6·0)	7 (4%)	8 (5·0)
Opportunistic infection, excluding tuberculosis and herpes zoster	1 (1%)	1 (0·6)	1 (1%)	1 (0·6)	0	0
Herpes zoster	2 (1%)	2 (1·2)	0	0	1 (1%)	1 (0·6)
Active tuberculosis	0	0	0	0	0	0
Asymptomatic COVID-19	0	0	0	0	1 (1%)	1 (0·6)
COVID-19	1 (1%)	1 (0·6)	4 (2%)	4 (2·4)	0	0
Adjudicated MACE events†	0	0	1 (1%)†	1 (0·6)†	1 (1%)	1 (0·6)
Adjudicated extended MACE events	0	0	1 (1%)	1 (0·6)	1 (1%)	1 (0·6)
Malignancies, excluding non-melanoma skin cancer	0	0	1 (1%)	1 (0·6)	0	0
Non-melanoma skin cancer	0	0	0	0	1 (1%)	1 (0·6)
Injection site reactions	9 (5%)	16 (9·5)	11 (6%)	23 (13·8)	9 (5%)	13 (8·1)
Serious hypersensitivity reactions	0	0	0	0	0	0
Adjudicated anaphylactic reaction	0	0	0	0	0	0
Hepatic events‡	5 (3%)	8 (4·7)	7 (4%)	9 (5·4)	4 (2%)	4 (2·5)
Death	0		0		0	

Safety analysis population included participants who were randomly assigned to a group who received at least one dose of study medication in 52-week maintenance period. MACE=major adverse cardiovascular event. *Occurring in ≥5% of patients in any dose group. †Previous history of dyslipidaemia and a smoker for 34 years, experienced a severe adverse event of acute myocardial infarction (adjudicated as non-fatal myocardial infarction) on day 411 (day 322 of substudy 1) after 6 doses of study drug. The event was considered by the investigator to have no reasonable possibility of being related to study drug. ‡Hepatic events were identified using the 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".

Table 3: **Overview of treatment-emergent adverse events in the safety analysis population**

IL-22, a downstream pharmacodynamic biomarker of IL-23 activity, was measured in a subset of patients (n=92) in FORTIFY SS1. Risankizumab maintenance dosing led to decreased IL-22 in the induction studies and a further decrease from week 0 to week 52 of FORTIFY SS1, with the 360 mg subcutaneous treatment group showing a decrease from 2·6 pg/mL to 1·6 pg/mL (nominal p=0·0060). In patients in the withdrawal (subcutaneous placebo) group, however, IL-22 concentrations increased from 2·3 pg/mL at FORTIFY week 0 to 2·9 pg/mL at week 52 but were well below induction baseline concentration (4·8 pg/mL; figure 3). Week 52 IL-22 concentrations in the risankizumab 360 mg group (1·6 pg/mL) were lower than those in the withdrawal (subcutaneous placebo) group (2·9 pg/mL; nominal p=0·0093). A pooled analysis of 52 patients with Crohn's disease who received risankizumab in ADVANCE or MOTIVATE and FORTIFY, however, showed that induction baseline serum IL-22 concentrations were not predictive of week 52 stool frequency and abdominal pain score clinical remission, stool frequency and abdominal pain score clinical response, endoscopic response, or endoscopic remission (appendix p 1).

Patients who were randomly assigned to the withdrawal (subcutaneous placebo) group in FORTIFY SS1 retained residual risankizumab exposures from induction treatment due to the long elimination half-life of risankizumab (approximately 21 days in patients with Crohn's disease, based on population pharmacokinetic analyses). Measurable risankizumab serum exposures were observed throughout the duration of FORTIFY SS1 in patients in the withdrawal (subcutaneous placebo) group, with geometric mean trough concentrations of 2·070 µg/mL at week 16, 0·198 µg/mL at week 32, 0·031 µg/mL at week 48, and 0·027 µg/mL at week 52 (appendix p 2). Maintenance risankizumab concentrations were depicted by the simulated pharmacokinetic profiles using population pharmacokinetic modelling (appendix p 8).

Serum risankizumab concentrations were generally dose proportional at the 180 mg and 360 mg subcutaneous doses (appendix p 2). Low incidence of treatment-emergent antidrug antibodies was observed across all groups, with four (2%) of 224 patients with antidrug antibodies for the risankizumab groups combined and four (4%) of 92 patients with antidrug antibodies for the withdrawal (subcutaneous placebo) group (appendix p 5). The time to the first appearance of treatment-emergent antidrug antibodies was 48·1 weeks (n=1) for the risankizumab 360 mg group and from 15·6 weeks to 48·3 weeks for the risankizumab 180 mg group. No apparent effect of antidrug antibodies on risankizumab exposure was observed. One patient in FORTIFY SS1 was positive for neutralising antibodies but still had clinical remission and endoscopic response at week 52.

Among participants who were randomly assigned to a group, the number of patients who reported at least one adverse event in the risankizumab groups was similar to the number in the withdrawal (subcutaneous placebo) group (table 3). The most common adverse events (ie, occurring in ≥5·0% of patients) across the treatment groups were worsening Crohn's disease, nasopharyngitis, arthralgia, headache, abdominal pain, and nausea. The most common adverse events also included anaemia for the risankizumab treatment groups and diarrhoea for the withdrawal (subcutaneous placebo) group. The proportion of patients with serious adverse events and adverse events leading to discontinuation was similar between patients treated in the risankizumab group and those in the withdrawal (subcutaneous placebo) group, without dose-dependency among the two risankizumab doses (table 3). There were no deaths in the 52-week withdrawal (subcutaneous placebo)-controlled maintenance period of FORTIFY SS1.

The incidence of infectious adverse events was lower in both risankizumab treatment groups (34% [51·4 events per 100 person-years] for the risankizumab 180 mg group; 34% [57·7 events per 100 person-years] for the risankizumab 360 mg group) than in the withdrawal subcutaneous placebo group (40% [76·0 events per 100 person-years]). Rates of serious infections were similar across the treatment groups (3·0 events per 100 person-years for the risankizumab 180 mg group, 6·0 events per 100 person-years for the risankizumab 360 mg group, and 5·0 events per 100 person-years for the withdrawal subcutaneous placebo group). The most frequently reported serious infections were viral infections (three participants in the risankizumab 360 mg group) and appendicitis (two participants in the risankizumab 180 mg group). The remainder of serious infections were reported in a single patient receiving risankizumab; none of the serious infections in risankizumab groups led to study drug discontinuation. Two events of herpes zoster were reported in the risankizumab 180 mg group, and two events of opportunistic infections, one oral fungal infection (oral candidiasis) in the risankizumab 180 mg group and one intestinal *Aeromonas* infection in the risankizumab 360 mg group, were reported; all events were mild to moderate in severity, all were resolved, and none led to discontinuation of study drug. One malignancy, HER2-positive breast cancer, was reported in one patient in the risankizumab 360 mg group and considered by the investigator to be unrelated to the study drug. Rates of hypersensitivity reactions were similar between the risankizumab 180 mg group (18 [10%] of 179 [12·4 events per 100 person-years]), risankizumab 360 mg group (12 [7%] of 179 [12·6 events per 100 person-years]), and the withdrawal (subcutaneous placebo) group (17 [9%] of 184 [11·8 events per 100 person-years]). Rates of injection site reactions were similar between the risankizumab 180 mg group and the withdrawal (subcutaneous placebo) group (9 [5%] of 179 [9·5 events per 100 person-years] *vs* 9 [5%] of 184 [8·1 events per 100 person-years]) and were numerically higher in the risankizumab 360 mg group (11 [6%] of 179 [13·8 events per 100 person-years]).

One adjudicated major adverse cardiovascular event was reported during the maintenance study in the risankizumab 360 mg group. This event was a non-fatal myocardial infarction in a 49-year-old white man with a previous history of dyslipidaemia and 34 years of smoking, which are known risk factors for major adverse cardiovascular events, and the event was considered by the investigator to be unrelated to the study drug and did not result in study drug discontinuation. Hepatic events were reported in less than 4% of participants across treatment groups (4·7 events per 100 person-years in the risankizumab 180 mg group, 5·4 events per 100 person-years in the risankizumab 360 mg group, and 2·5 events per 100 person-years in the withdrawal subcutaneous placebo group). Most hepatic events were liver enzyme increases and did not result in a change in study drug treatment, and none of the events were serious or severe in nature or led to a change in study drug treatment. The proportion of patients meeting criteria for liver test elevations in alanine aminotransferase, aspartate aminotransferase, and total bilirubin concentrations in the risankizumab groups was low (ie, <3%; appendix p 4). There were no events of active tuberculosis, serious hypersensitivity, or adjudicated anaphylactic reactions.

Discussion

Results from FORTIFY SS1 showed the value of continuing risankizumab maintenance treatment following successful intravenous induction, meeting the co-primary endpoints of CDAI clinical remission and endoscopic response at the 180 mg and 360 mg risankizumab subcutaneous doses at week 52 and stool frequency and abdominal pain score clinical remission at the 360 mg subcutaneous dose at week 52. A greater proportion of patients had clinical response (CDAI and stool frequency and abdominal pain score) and enhanced clinical response at week 52 with risankizumab than with withdrawal (subcutaneous placebo), and also had more stringent, objective endoscopic endpoints, for which a dose–response was observed.

180 mg and 360 mg subcutaneous risankizumab doses were generally well tolerated over the maintenance period. Safety analyses, including adverse events, adverse events of special interest, laboratory tests, and vital signs, did not show any dose-dependent patterns. No new safety risks were identified, and the overall safety profile was consistent with the known safety profile of risankizumab.

Demonstration of efficacy of Crohn's disease therapeutics now requires both symptomatic relief, as determined by patient-reported outcome measures, and (more objectively) improvement of mucosal disease as measured by ileocolonoscopy.[13] FORTIFY SS1 is the first completed pivotal phase 3 maintenance study to measure endoscopic disease activity in all enrolled patients with Crohn's disease, prospectively test novel clinical response and clinical remission endpoints with the patient-reported outcomes of stool frequency and abdominal pain score, and evaluate clinical remission and endoscopic response as co-primary endpoints.[10]

To date, all approved biologics have been studied in a population with disease that did not respond to conventional therapy or a population with disease that did not respond to single or multiple anti-TNF treatments, or both. The ADVANCE, MOTIVATE, and FORTIFY studies differentiated from these studies by including patients with disease that did not respond to ustekinumab or vedolizumab, or both, or solely conventional therapy (ie, corticosteroids and immunosuppressants). Efficacy with risankizumab was observed in patients with and without previous bio-failure in both induction studies and FORTIFY.

High responder rates in the withdrawal (subcutaneous placebo) group indicate prolonged durability of risankizumab induction therapy. This durability was evident for symptomatic endpoints and hs-CRP at week 24 (because all patients entering FORTIFY had received 12 weeks of induction risankizumab and were clinical responders), and IL-22 concentrations at week 52 stayed below those at induction baseline, indicating a residual pharmacodynamic effect. The high clinical response rate in the withdrawal (subcutaneous placebo) group is in contrast to endoscopic outcomes, further emphasising the importance of objective markers and underscoring the limitations of relying solely on symptomatic clinical endpoints.[14] By contrast, inflammatory biomarker concentrations in the withdrawal (subcutaneous placebo) group increased at week 52. Sustained or improved efficacy rates were also observed with risankizumab for more objective endoscopic endpoints and composite endpoints (ie, endoscopic and clinical endpoints together in the same patient), whereas efficacy rates decreased in the withdrawal (subcutaneous placebo) group at week 52. These results underscore the need for continued risankizumab maintenance treatment.

As with all studies, FORTIFY SS1 had limitations. Despite the SES-CD being a validated scoring system and the increasingly accepted definition of endoscopic response as SES-CD higher than 50%, its operating characteristics have not been fully explored, and the thresholds defining endoscopic remission and endoscopic response have not been validated.[15] Likewise, it is unclear whether the differences observed for stool frequency and abdominal pain score clinical remission and the subjective (ie, wellbeing) components of CDAI clinical remission reflect differences in sensitivity of the endpoints to detect symptom changes or suggest a need for validation of the patient-reported outcomes.[16] Although stool frequency and abdominal pain score and CDAI clinical remission are generally well correlated, any differences in clinical remission rates in FORTIFY, such as in the risankizumab 180 mg group, might be due to the differences in the components of the stool frequency and abdominal pain

score and CDAI definitions; stool frequency and abdominal pain score solely relies on subjective components, whereas CDAI incorporates both subjective and objective components (eg, haematocrit, bodyweight, abdominal mass, the use of medications, and extraintestinal manifestations).

In terms of limitations of the study design, biomarker sample collection occurred less frequently than symptomatic endpoints were evaluated, preventing comprehensive assessment of the relationship between symptom improvement and inflammation across all study visits and a precise establishment of when biomarkers began to differ between the withdrawal (subcutaneous placebo) and risankizumab groups. Occasional discrepancies observed between symptoms, biomarker changes, and endoscopic endpoints in the withdrawal (subcutaneous placebo) group align with previous reports documenting a general absence of convergence of these endpoints in patients with Crohn's disease. Lastly, although risankizumab maintenance therapy was more efficacious than placebo, there are inherent limitations of a withdrawal (placebo) study design of therapies with long half-lives, and prolonged pharmacodynamic effects might require increased study durations. Additionally, withdrawal study designs are limited in their ability to quantify the benefits of active therapy versus a true placebo and assess their effect on disease modification over the long term.

High rates of primary and secondary treatment failure, adverse events, and reduced effectiveness of biologics over time underscore the importance of continued development of new treatment methods for moderately to severely active Crohn's disease with and without previous treatment failure.[17–23] FORTIFY SS1, together with ADVANCE and MOTIVATE, are the first phase 3 studies to show the efficacy and safety of a new class of biologics that selectively target IL-23 via the p19 subunit.

Contributors

MF was the coordinating investigator for FORTIFY. MF and RP contributed equally to the conduct of the studies. MF, RP, FB, PB, J-FC, SD, MD, BGF, TH, AL, JOL, EVL, JP, LP-B, ZR, DTR, WJS, SS, EN, AS, KK, YP, VP, SB, WRD, BH, JK, XL, AR, KW, and GDH participated in data acquisition. WJS, BGF, EN, AS, YP, BH, JK, XL, AR, and KW participated in study design. BH and XL accessed and verified the data. BH and XL participated in statistical analysis. All authors were involved in the interpretation of the data, preparation, and critical review of the manuscript, and approved the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Declaration of interests

MF reports being a consultant or speaker for AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Dr Falk, Ferring, Janssen-Cilag, Lamepro, Eli Lilly, Medtronic, Merck Sharp & Dohme (MSD), Mylan, Pfizer, Regeneron, Samsung Bioepis, Sandoz, Takeda, Thermo Fisher Scientific, and Truvion Healthcare; and research grants from AbbVie, Amgen, Biogen, Janssen, Pfizer, and Takeda. RP reports being a consultant or speaker for AI4GI, AbbVie, Arena, Amgen, Atlantic Healthcare, BioBalance, Boehringer Ingelheim, Bristol-Myers Squibb (BMS), Celgene, Coronado Biosciences, Cosmo Technologies, Eagle, Eisai Medical Research, Elan, Eli Lilly, EnGene, Ferring, Genentech, Gilead, Given Imaging, GlaxoSmithKline (GSK), Janssen, Lycera, Meda, Merck & Co, Merck Research, MerckSerono, Novo Nordisk, PDL Biopharma, Pfizer, Prometheus, Protagonist, Celgene, Alimentiv, Salix, Soz, Sanofi Genzyme, Shire, Sigmoid, Sublimity, Takeda, and Theravance. FB reports being a consultant or speaker for AbbVie, Arena, Celltrion, Falk, Ferring, Janssen, Mundipharma, MSD, Pfizer, Sandoz, Takeda, Vifor; and received research grants from AbbVie, Amgen, Chiesi, Ipsen, Janssen, and MSD. PB has received financial support for research from AbbVie, Amgen, Janssen, Mundipharma, Mylan, and Pfizer; lecture fees from AbbVie, Celltrion, Janssen, Pfizer, and Takeda; and advisory board fees from AbbVie, Arena Pharmaceuticals, BMS, Hospira, Janssen, Lilly, Merck, Mundipharma, Pentax Medical, Pfizer, PSI CRO, Roche, Sandoz, and Takeda. J-FC reports research grants from AbbVie, Janssen Pharmaceuticals, and Takeda; received payment for lectures from AbbVie, Amgen, Allergan, Ferring Pharmaceuticals, Shire, and Takeda; received consulting fees from AbbVie, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, BMS, Celgene, Eli Lilly, Ferring Pharmaceuticals, Galmed Research, Genentech, GSK, Janssen Pharmaceuticals, Kaleido Biosciences, Imedex, Immunic, Iterative Scopes, Merck, Microba, Novartis, PBM Capital, Pfizer, Sanofi, Takeda, TiGenix, and Vifor; and holds stock options in Intestinal Biotech Development. SD reports research grants from AbbVie, Alimentiv, Amgen, Genentech, Gilead, Janssen, Pfizer, Celgene, Seres Therapeutics, Takeda, and UCB; and has been a consultant for AbbVie, Allergan, Amgen, BMS, Celgene, Celltrion, Janssen, Lilly, Pfizer, Takeda, and UCB. MD reports being a consultant for AbbVie, Arena, BMS, Boehringer Ingelheim, Celgene, Eli Lilly, Gilead, Janssen, Merck, Pfizer, Prometheus Labs, Takeda, and UCB; and received research grants from Janssen, AbbVie, and Prometheus Labs. 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TH reports speaker or consultant fees from Mitsubishi Tanabe Pharma Corporation, EA Pharma, AbbVie, JIMRO, Zeria Pharmaceutical, Kyorin Pharmaceutical, Takeda Pharmaceutical, Pfizer Japan, Mochida Pharmaceutical, Celgene, Janssen Pharmaceutical, and Nichi-Iko Pharmaceutical; and reports research grants from Alfresa Pharma, EA pharma, Mitsubishi Tanabe Pharma Corporation, AbbVie, JIMRO, Zeria Pharmaceutical, Daiichi-Sankyo, Kyorin Pharmaceutical, Nippon Kayaku, Takeda Pharmaceutical, Pfizer, and Mochida Pharmaceutical. AL reports being a consultant, speaker, or stockholder with AbbVie, Takeda, Janssen, and Ferring; and reports research grants from AbbVie, Takeda, Janssen, and Eli Lilly. JOL reports advisory board membership or speaker fees from AbbVie, Allergan, BMS, Celgene, Celtrion, Ferring, Gilead, GSK, Janssen, MSD, Napp, Pfizer, and Takeda; and research grants from AbbVie, Gilead, Takeda, and Pfizer. 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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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