INDUCTION THERAPY WITH THE SELECTIVE INTERLEUKIN-23 INHIBITOR RISANKIZUMAB IN PATIENTS WITH MODERATE-TO-SEVERE CROHN'S DISEASE: A RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED PHASE 2 STUDY

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SUMMARY

Background The interleukin-23 pathway is implicated genetically and biologically in the pathogenesis of Crohn's disease. We aimed to assess the efficacy and safety of risankizumab (BI 655066, Boehringer Ingelheim, Ingelheim, Germany), a humanised monoclonal antibody targeting the p19 subunit of interleukin-23, in patients with moderately-to-severely active Crohn's disease.

Methods In this randomised, double-blind, placebo-controlled phase 2 study, we enrolled patients at 36 referral sites in North America, Europe, and south-east Asia. Eligible patients were aged 18-75 years, with a diagnosis of Crohn's disease for at least 3 months, assessed as moderate-to-severe Crohn's disease at screening, defined as a Crohn's Disease Activity Index (CDAI) of 220-450, with mucosal ulcers in the ileum or colon, or both, and a Crohn's Disease Endoscopic Index of Severity (CDEIS) of at least 7 (≥4 for patients with isolated ileitis) on ileocolonoscopy scored by a masked central reader. Patients were randomised 1:1:1 using an interactive response system to a double-blind investigational product, and stratified by previous exposure to TNF antagonists (yes vs no). Patients received intravenous 200 mg risankizumab, 600 mg risankizumab, or placebo, at weeks 0, 4, and 8. The primary outcome was clinical remission (CDAI <150) at week 12 (intention-to-treat population). Safety was assessed in patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT02031276.

Findings Between March, 2014, and September, 2015, 213 patients were screened, and 121 patients randomised. At baseline, 113 patients (93%) had been previously treated with at least one tumour necrosis factor (TNF) antagonist (which had failed in 96 [79%]). At week 12, 25 (31%) of 82 risankizumab patients (pooled 41 patients in 200 mg and 41 patients in 600 mg arms) had clinical

remission versus six (15%) of 39 placebo patients (difference vs placebo 15 · 0%, 95% CI 0•1 to 30-1; p=0·0489). Ten (24%) of 41 patients who received 200 mg risankizumab had clinical remission (9-0%, -8-3 to 26-2; p=0·31) and 15 (37%) of 41 who received the 600 mg dose (20·9%, 2·6 to 39·2; p=0·0252). 95 (79%) patients had adverse events (32 in the placebo group, 32 randomised to 200 mg risankizumab, 31 randomised to 600 mg risankizumab); 18 had severe adverse events (nine, six, three); 12 discontinued (six, five, one); 24 had serious adverse events (12, nine, three). The most common adverse event was nausea and most common serious adverse event was worsening of underlying Crohn's disease. No deaths occurred.

Interpretation In this short-term study, risankizumab was more effective than placebo for inducing clinical remission in patients with active Crohn's disease. Therefore, selective blockade of interleukin-23 via inhibition of p19 might be a viable therapeutic approach in Crohn's disease.

Research in context

EVIDENCE BEFORE THIS STUDY

We searched PubMed for English language articles using the terms "Crohn's disease", "biologictherapy", "adalimumab", "infliximab", "certolizumab pegol", "vedolizumab", "ustekinumab", and "IL-23" to identify controlled clinical trials published up to June 17,2016, with no start date restrictions. Biological therapies approved for Crohn's disease include the tumour necrosis factor (TNF) antagonists adalimumab, infliximab, and certolizumab pegol. Treatment with these drugs has resulted in some induction of clinical remission inTNF antagonist-naive patients. Treatment with a secondTNF antagonist is effective in patients who have lost response or were intolerant to their previous TNF antagonist, but a response to a second TNF antagonist after primary TNF antagonist failure is not well studied and is generally very low. The integrin inhibitor vedolizumab has been approved for Crohn's disease.

The interleukin-23 pathway is implicated in the pathogenesis of psoriasis and Crohn's disease. Biological agents that abrogate this axis, through targeted inhibition of interleukin 17 orthe interleukin 17 receptor, interleukin 23, or interleukin 12 and interleukin 23, have shown efficacy in clinical trials for the treatment of psoriasis.

ADDED VALUE OF THIS STUDY

In this proof-of-concept phase 2 clinical trial for risankizumab, a monoclonal antibody that targets the interleukin-23 p19 subunit, in treatment-experienced patients with moderate-to-severe Crohn's disease, risankizumab was superiorto placebo in achieving clinical response or remission at week 12 in patients with moderate-to-severe Crohn's disease.

IMPLICATIONS OF ALL THE AVAILABLE EVIDENCE

Biological agents that abrogate the interleukin-23 pathway axis have shown efficacy in clinical trials for the treatment of psoriasis, but agents that specifically target interleukin 17 or the interleukin 17 receptor exacerbate Crohn's disease, indicating a dichotomy between the activity of interleukin 12/ interleukin 23 and interleukin 17 in psoriasis versus Crohn's disease. Ourtrial of risankizumab in treatment-experienced patients with moderate-to-severe Crohn's disease suggests that specific blockade of interleukin 23 with risankizumab might be a promising new therapeutic approach with a unique mode of action forthe treatment of this serious chronic disease.

Introduction

Crohn's disease is a chronic inflammatory bowel disease characterised by ulceration and transmural inflammation.[1] Management consists of controlling inflammation through administration of broadly acting immunosuppressive drugs such as corticosteroids, thiopurines, or methotrexate, or selective targeting of cytokines or integrins with biological agents.[2-4] These therapies are not consistently effective and can cause adverse events including infection.[4-6] About a third of patients treated with a TNF antagonist show a primary non-response, with another third developing secondary failure or intolerance to treatment. Patients with primary non-response or secondary failure to a TNF antagonist have a lower chance of responding to subsequent treatment with different TNF antagonists or the integrin antagonist vedolizumab.

Interleukin-23 receptor gene polymorphisms are associated with susceptibility to Crohn's disease, and interleukin-23 is a key regulator of the T-helper-17 cell (Thl7) and type 3 innate lymphoid cell (ILC3) pathways that contribute to inflammatory cytokine production and tissue inflammation.[7-9] The interleukin-23 pathway is implicated in the pathogenesis of several immune-mediated chronic inflammatory diseases including psoriasis and Crohn's disease. Biological agents that abrogate this axis, either through targeted inhibition of the interleukin-17/interleukin-17 receptor (brodalumab, ixekizumab, secukinumab), interleukin-23 (guselkumab, risankizumab, tildrakizumab), or interleukin-12 and interleukin-23 (ustekinumab), have shown efficacy in clinical trials for the treatment of psoriasis.[10] In Crohn's disease, interleukin 12 and interleukin-23 p40 subunit inhibition by ustekinumab appears beneficial with effect sizes for induction of clinical remission of 9-18% in patients with previous tumour necrosis factor (TNF) antagonist failure and 23-27% in TNF-antagonist-experienced patients.[11,12] However, whether its efficacy is driven by the inhibition of interleukin-12, interleukin-23, or both cytokines, is unclear. In the absence of direct comparator trials, these effect sizes must be interpreted with caution while considering the differences in study population and design that affect such cross-trial comparison. By contrast, agents that specifically target interleukin-17 or interleukin-17 receptor exacerbate Crohn's disease, indicating a dichotomy between the activity of interleukin-12/interleukin-23 and interleukin-17 in psoriasis versus Crohn's disease.[13,14] To our knowledge, no treatments that specifically target interleukin-23 in Crohn's disease are approved and only limited clinical trial data for such agents exist.

Risankizumab (BI 655066, Boehringer Ingelheim, Ingelheim, Germany) is a humanised monoclonal antibody that targets the pl9 subunit, which is specific to interleukin-23.[15] Thus, treatment with risankizumab might downregulate interleukin-23-mediated inflammation without affecting interleukin-12-dependent T-cell pathways which, in animal models, are important for infection and cancer immunity.[16,17] This selective approach might have advantages over agents that target both cytokines.

Preliminary data indicate that risankizumab is an effective treatment for psoriasis, a chronic inflammatory skin disease in which the interleukin-23 pathway is implicated.[18] On the basis of these observations, we aimed to assess the safety and efficacy of risankizumab in patients with active Crohn's disease.

Methods

STUDY DESIGN

In this multicentre, randomised, placebo-controlled, phase 2 study, we enrolled patients at 36 referral sites in North America, Europe, and southeast Asia (appendix). The study had three treatment periods: a 12-week double-blinded intravenous therapy period (period 1); a 12-week open-label intravenous therapy or wash-out period (period 2); and a 26-week subcutaneous therapy period (period 3). We report the primary, secondary, and additional endpoints—including biomarker, pharmacokinetic, and anti-drug antibody assessments—for period 1; endpoints for periods 2 and 3 will be reported after completion of the study. The complete study design is shown in the appendix (p7).

The study protocol was approved by the institutional review board or ethics committee at each participating centre. Safety data were periodically evaluated by an independent data monitoring committee.

PATIENTS

Eligible patients were aged 18-75 years, with a diagnosis of Crohn's disease for at least 3 months that was assessed as moderate-to-severe Crohn's disease at screening, defined as a Crohn's Disease Activity Index (CDAI)[19] of 220-450, with mucosal ulcers in the ileum or colon, or both, and a Crohn's Disease Endoscopic Index of Severity (CDEIS)[19] of at least 7 (≥4 for patients with isolated ileitis) on ileocolonoscopy scored by a masked central reader (descriptions of CDAI and CDEIS are in the appendix, p 5). Patients could have had previous treatment with one or more tumour necrosis factor (TNF) antagonists or vedolizumab. Patients previously treated with ustekinumab were excluded, as were patients who had received any other biological agent (including agents targeting integrins) within 8 weeks or five half-lives before randomisation. Patients continued stable doses of oral corticosteroids, oral 5-aminosalicylates, azathioprine, 6-mercaptopurine, methotrexate, and antibiotics throughout the trial if they were on these at the start. A full description of the inclusion and exclusion criteria is in the appendix (pp 3-4). All patients provided written informed consent.

RANDOMISATION AND MASKING

Before the first 12-week period, we randomly assigned patients (1:1:1) to receive 200 mg risankizumab, 600 mg risankizumab, or placebo. We used an interactive response system to assign a double-blind investigational product to every patient. Randomisation was stratified by previous exposure to TNF antagonists (yes vs no). A randomisation list was generated using a validated system, which involved a pseudorandom number generator to guarantee the reproducibility of the assignments. This randomisation list was checked by an independent statistician and used to assign randomisation numbers to eligible patients. Access to the randomisation code was controlled and documented. All people directly involved in the conduct and analysis of the trial (including patients, investigators, and study personnel) were fully masked to the treatment allocation before the week 12 database lock. To maintain masking, study drug packaging was identical irrespective of treatment and was only distinguishable by medication number, which was managed by the central randomisation centre. Both risankizumab and placebo appeared as clear solutions.

PROCEDURES

Patients received either 200 mg risankizumab, 600 mg risankizumab, or placebo by intravenous infusion at weeks 0, 4, and 8 (appendix, p 7). Patients were followed through week 12, every 4 weeks, and were then eligible to enter subsequent phases of the trial.

OUTCOMES

The primary outcome was clinical remission in the pooled risankizumab dose groups, defined by a CDAI <150 at week 12. Secondary outcomes (all evaluated at week 12) including clinical response (defined by either CDAI <150 or a CDAI reduction from baseline of ≥100), endoscopic remission (CDEIS score of ≤4; ≤2 for patients with isolated ileitis), endoscopic response (>50% CDEIS reduction from baseline), mucosal healing (absence of mucosal ulceration), and deep remission (clinical remission and endoscopic remission) are reported here. All further endpoints relating to period 1 are listed in the appendix (p 4) and will be reported after completion of the study. Of these, we report CDAI throughout period 1, change from baseline to week 12 in Inflammatory Bowel Disease Questionnaire (IBDQ), C-reactive protein (CRP) throughout period 1, and percentage change from baseline in faecal calprotectin (FCP). Additionally, percentage change from baseline in serum interleukin 22 was reported because activated T helper 17 and ILC3 cells from patients with inflammatory bowel disease characteristically produce interleukin 22, as well as biomarker gene changes to week 12,

pharmacokinetic data (where data permitted), and anti-drug antibody assessments. Additional post-hoc analyses were the proportion of patients achieving normalisation of CRP and FCP.

Health-related quality of life (HRQoL) was assessed at baseline and at week 12 by asking patients to complete the 32 questions of the IBDQ, which has been established as a valid, reliable, and responsive tool to scale the impact of bowel-related symptoms, systemic complaints, social functions, and emotional status of patients with ulcerative colitis, with higher scores indicating better HRQoL.20

At each study visit, data were obtained for CDAI, adverse events, concomitant medications, FCP, and serum CRP concentration. Biomarkers relevant to the interleukin 23 pathway were evaluated in tissue biopsies obtained at baseline and at week 12, and in whole blood samples (appendix p 5). CDEIS scores and presence or absence of mucosal ulcers were determined by masked central readers at baseline and week 12. Plasma samples for pharmacokinetic analysis and immunogenicity assessments were collected at each visit. The schedule for collection and assay methodology is described in the appendix (pp 4—5). The anti-drug antibody electro-chemiluminescence assay was sensitive and drug tolerant.

Safety endpoints were adverse events (coded using version 18.1 of the Medical Dictionary for Drug Regulatory Activities [MedDRA], severity grading based on the Rheumatology Common Toxicity Criteria version 2.0), serious adverse events, tolerability changes in vital signs and physical examination, discontinuation of therapy because of adverse events, and laboratory assessments.

Figure 1: Trial profile
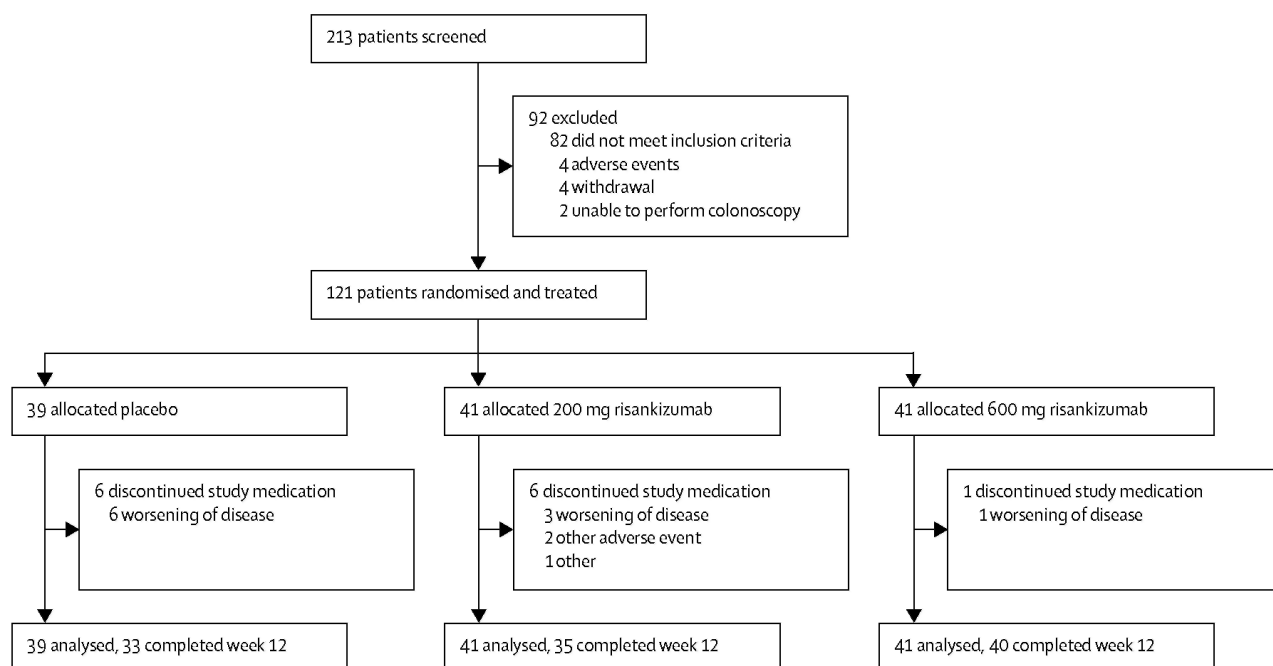
STATISTICAL ANALYSIS

We analysed the primary and secondary endpoints on an intention-to-treat basis. Pharmacokinetic data, immuno-genicity and biomarker endpoints were analysed on all evaluable patients who received at least one dose of study drug. Differences in pairwise comparisons for the primary and secondary endpoints were analysed using a stratified Cochran-Mantel-Haenszel test, with previous exposure to TNF antagonists as the stratification variable; confidence intervals were calculated by normal approximation of the variance of Mantel-Haenszel stratified risk difference. Continuous outcomes including change or percentage change from baseline in CDAI, CRP, FCP, and plasma interleukin-22 concentrations were summarised descriptively and baseline values were assigned from time of

treatment initiation; a Wilcoxon two-sample test was used post hoc to compare the median differences from baseline between treatments.

We predicted that both the 200 mg risankizumab and 600 mg risankizumab dose groups would be effective; thus, the primary analysis was based on a comparison of week 12 remission rates in the pooled risankizumab dose groups with placebo. We estimated that randomisation of 120 patients in a 2:1 ratio between risankizumab (200 mg and 600 mg, pooled) and placebo would provide 82% power using a two-sided test with a type 1 error of 0·10, which we used to increase the sensitivity of identifying a treatment effect for the primary endpoint. A 30% clinical remission rate for the combined risankizumab dose groups and a 9% rate for placebo was the basis for the calculation. For secondary endpoints, statistical significance was based on two-sided p values less than 0·05. Non-response imputation was used for missing values and analysis. Patients missing their week 12 CDEIS assessment were counted as endoscopic failures; patients in whom prohibited concomitant medication to treat Crohn's disease was used before week 12 and those with missing CDAI items were considered to be treatment failures. We did not adjust for multiplicity for clinical and endoscopic endpoints; for RNA biomarker analyses, we applied the Bonferroni's correction for multiple comparisons.

Safety analyses included patients who underwent randomisation and received at least one dose of study drug. We report frequencies of adverse events descriptively. This trial is registered with ClinicalTrials. gov, number NCT02031276.

ROLE OF THE FUNDING SOURCE

The funder of the study was involved in the study design and the data collection and analysis. All authors had full access to all data in the study, made the decision to submit these data for publication, were involved in writing the manuscript, and agreed upon the final content of the paper. The study funder provided funding for editorial assistance in manuscript preparation. The corresponding author had final responsibility for the decision to submit for publication.

Results

Between March, 2014, and September, 2015, 213 patients were screened and 121 were randomised (figure 1). The main reason for screening failures was insufficient clinical or endoscopic activity. Less frequent reasons included the presence of Crohn's complications, concomitant diseases, or insufficient wash-out time of prohibited medications. 13 patients discontinued study participation before week 12 (figure 1). Baseline demographics and disease characteristics of patients were similar in treatment groups (table 1). Mean duration of Crohn's disease was 13 years (SD 9) at study entry.

Clinical remission at week 12 was achieved by ten (24%) of 41 patients in the 200 mg risankizumab group and 15 (37%) of 41 patients in the 600 mg risankizumab group, compared with six patients (15%) in the placebo group (figure 2, table 2). At week 12, the observed difference between the pooled risankizumab dose groups and placebo was 15·0% (95% CI 0·1 to 30·1; p=0·0489). The observed difference between the 200 mg risankizumab arm and placebo was 9·0% (95% CI -8·3 to 26·2, p=0·31; table 2) and between the 600 mg risankizumab arm and placebo was 20·9% (2·6 to 39·2, p=0·0252; table 2). The difference in clinical remission between risankizumab and placebo at week 8 was 14·5% (2·0 to 27·0; ρ=0·0228) in the 200 mg risankizumab arm and 21·7% (7·7 to 35·7; p=0·0023) in the 600 mg risankizumab arm (figure 2, table 2).

The proportion of patients with clinical response, endoscopic response, or deep remission at week 12 did not differ between the 200 mg risankizumab group and placebo but an increased proportion of patients in the 600 mg risankizumab group had these outcomes (figure 2, table 2). An increased proportion of patients had clinical response at week 8 with both risankizumab doses. More patients had endoscopic remission at week 12 in the 200 mg and 600 mg risankizumab dose groups compared

with placebo (table 2). The proportion of patients with mucosal healing did not differ between risankizumab treatment and placebo (table 2).

The IBDQ assessment indicated a reduced HRQoL of the randomised study population at baseline. Treatment with risankizumab resulted in a dose-dependent increase from baseline to week 12 by 7·3 points for placebo, 21·7 points for 200 mg risankizumab, and 34·7 points for 600 mg risankizumab (difference for 600 mg risankizumab vs placebo 27·3, 95% CI 11·7 to 43·0, p=0·0009; appendix, p 8).

Median CRP concentrations were reduced in both risankizumab arms compared with placebo at week 12 (-6·2 mg/L [IQR -17·0 to 0·2] for 200 mg risankizumab, -2·8 mg/L [-22·2 to -0·1] for 600 mg risankizumab, vs 2·7 mg/L [-1·2 to 10·1] or placebo; ρ<0·0001 for each arm vs placebo; figure 3). In the post-hoc analysis, normalisation of CRP to less than the upper limit of normal (2·87 mg/L) at week 12 in patients with elevated CRP at baseline was observed in eight (24%) of 33 patients who received 200 mg risankizumab, eight (29%) of 28 patients in the 600 mg risankizumab arm, and two (7%) of 28 patients in the placebo arm. Treatment with 600 mg risankizumab decreased median FCP levels compared with placebo (median % change from baseline to week 12 -74·4% [IQR -91·7 to -1·0] vs -2·5% [-55·5 to 107·1], p=0·0003; figure 3). In the post-hoc analysis, normalisation of FCP to less than the upper limit of normal (50 µg/g) at week 12 in patients with elevated FCP at baseline was observed in one (3%) of 29 patients in the 200 mg risankizumab arm, five (16%) of 31 patients in the 600 mg risankizumab arm, and two (7%) of 30 patients in the placebo arm. Additionally, plasma interleukin-22 concentration was lower with 600 mg risankizumab treatment than with placebo (median % change from baseline to week 12 -44·2 [IQR-58·8 to-14·3] vs-16·7 [IQR-39·0 to 36·8]; p=0·0180; figure 3).

Colon or ileum tissue was collected at baseline and at week 12 from a subset of patients (26 [63%] for colon and 30 [73%] for ileum in the 200 mg risankizumab group; 27 [66%] for colon and 26 [63%] for ileum in the 600 mg risankizumab group; and 26 [67%] for colon and 22 [56%] for ileum in the placebo group). Significant reductions in the expression of selected genes associated with interleukin-23 immune-related pathways were observed in the colon biopsies of this subset of risankizumab-treated patients compared with placebo (appendix, p 9).

Interleukin-22 gene expression was significantly reduced from baseline to week 12 in the ileum biopsies from the subset of pooled risankizumab-treated patients (log2 fold change -1·94; p=0·003; appendix p 9).

No dose-related increases for any adverse events were associated with risankizumab treatment (table 3). The most frequent adverse events were associated with the gastrointestinal tract. The most common serious adverse event was worsening of underlying Crohn's disease (appendix p 15). No deaths occurred, although serious infections were reported in three patients (abdominal, anal, and rectal abscesses, and pneumonia) in the placebo arm, one patient (pneumonia) in the 200 mg risankizumab group, and two patients (osteomyelitis and anal abscess) in the 600 mg risankizumab group (appendix p 15). Infusion-related reactions were mild or moderate and were reported in two (5%) patients in the placebo group and one (2%) patient in each of the 200 mg and 600 mg risankizumab groups. No differences between treatment groups were observed in physical examination, vital signs, electrocardiograph monitoring, and safety laboratory analyses.

Treatment-emergent anti-drug antibodies were detected in 4% of patients receiving risankizumab (three of 76 patients). Anti-drug antibody titre values were low (≤8) and no neutralising antibodies were detected. Preexisting anti-drug antibodies were observed in five patients in the risankizumab dose groups and three patients in the placebo group.

Table 1: **Baseline characteristics**

	Placebo (n=39)	Risankizumab		
		200 mg (n=41)	600 mg (n=41)	Pooled (n=82)
Age (years)	36 (14)	39 (13)	40 (13)	39 (13)
Sex				
Male	16 (41%)	15 (37%)	16 (39%)	31 (38%)
Female	23 (59%)	26 (63%)	25 (61%)	51 (62%)
White	32 (82%)	36 (88%)	34 (83%)	70 (85%)
Bodyweight (kg)	68 (22)	66 (15)	67(13)	67 (14)
Current smoker	7(18%)	12 (29%)	13 (32%)	25 (30%)
Duration of disease, years	12 (9)	14(9)	14 (10)	14(9)
Disease site				
Ileum only	5 (13%)	6(15%)	10 (24%)	16 (20%)
Ileum and colon	16 (41%)	25 (61%)	16 (39%)	41 (50%)
Colon only	18 (46%)	10 (24%)	14 (34%)	24 (29%)
History of fistulising disease	9 (23%)	7 (17%)	5 (12%)	12 (15%)
Draining fistulae at baseline	0	2 (5%)	2(5%)	4(5%)
Previous intestinal resection for Crohn's disease	1(3%)	0	1(2%)	1 (1%)
CDAI	295 (237-386)	311 (247-375)	298 (259-330)	300 (247-349)
CDEIS	11 (8-18)	12 (9-17)	12 (8-16)	12 (9-17)
CRP (mg/L)	14 (3-34)	11 (5-34)	8 (2-29)	10 (4-33)
FCP(µg/g)	1747 (672-2792)	1364 (527-2319)	1101 (434-3539)	1243 (509-2487)
Haemoglobin (g/L)	125 (17)	126 (15)	127 (15)	126 (14)
Corticosteroids or IM, or both				
Corticosteroids only	6(15%)	7 (17%)	9 (22%)	16 (20%)
Corticosteroids and IM	5 (13%)	3 (7%)	3 (7%)	6 (7%)
IM only	8 (21%)	7 (17%)	5 (12%)	12 (15%)
Previous TNF antagonist use				
1	12 (31%)	9 (22%)	9 (22%)	18 (22%)
2	20 (51%)	23 (56%)	24 (59%)	47 (57%)
≥3	5 (13%)	7(17%)	4 (10%)	11 (13%)
Missing	2 (5%)	2 (5%)	4 (10%)	6 (7%)
Worst outcome of ≥1 previous TNF antagonists				
Inadequate response	10 (26%)	16 (39%)	11 (27%)	27(33%)
Loss of response	21 (54%)	13 (32%)	17 (41%)	30 (37%)
Unacceptable adverse events	1(3%)	2 (5%)	5 (12%)	7(9%)
Other	2 (5%)	3 (7%)	1(2%)	4(5%)
Unknown	1(3%)	3 (7%)	2 (5%)	5 (6%)

Data are mean (SD), n (%), or median (IQR). CDAI=Crohn's Disease Activity Index. CDEIS=Crohn's Disease Endoscopic Index of Severity. CRP=C-reactive protein. FCP=faecal calprotectin. IM=immunomodulators. TNF=tumour necrosis factor.

***Table2:* Efficacy endpoints at week 12**

	Placebo (n=39)	Risankizumab		
		200 mg (n=41)	600 mg (n=41)	Pooled (n=82)
Clinical remission (primary endpoint)				
η(%)	6 (15%)	10 (24%)	15 (37%)	25 (31%)
Difference vs placebo (95% CI, p value)		9·0% (-8·3to 26·2, p=0·31)	20·9% (2·6 to 39·2, p=0·0252)	15·1% (0·1 to 30·1, p=0·0489)
Clinical response (secondary endpoint)				
η(%)	8 (21%)	15 (37%)	17(42%)	32 (39%)
Difference vs placebo (95% CI, p value)		16·0% (-3·2 to 35·2, ρ=0·10)	20·3% (1·3 to 39·4, p=0·0366)	18·4% (2·1 to 34·8, p=0·0273)
Endoscopic remission (secondary endpoint)				
η(%)	1(3%)	6 (15%)	8 (20%)	14 (17%)
Difference vs placebo (95% CI, p value)		12·1% (0·8 to 23·4, p=0·0357)	16·8% (3·9 to 29·7, p=0·0107)	14·5%(5·5 to 23·5,p=0·0015)
Endoscopic response (secondary endpoint)				
η(%)	5 (13%)	11 (27%)	15 (37%)	26 (32%)
Difference vs placebo (95% CI, p value)		141% (-2·8 to 30·9, ρ=0·10)	23-5% (5·5 to 41·5, ρ=0·0106)	18·7% (4·4 to 33·0, p=0·0104)
Mucosal healing (secondary endpoint)				
η(%)	1(3%)	1(2%)	3 (7%)	4(5%)
Difference vs placebo (95% CI, p value)		-0·1%(-7·0 to 6·7,p=0·97)	4·9% (-4·6to 14·3, p=0·31)	24%(-45to9·2,p=0·50)
Deep remission (secondary endpoint)				
η(%)	0	1(2%)	5 (12%)	6 (7%)
Difference vs placebo (95% CI, p value)		2·4%(-2·3 to 7·1,p=0·31)	124% (2·3 to 22·5, p=0·164)	7·4% (1·7to 13·0, p=0·0107)

Clinical remission is defined as a CDAI score <150. Clinical response is either a CDAI score <150 or a CDAI reduction of ≥100 from baseline. Endoscopic remission is a CDEIS score of ≤4 at week 12 (≤2 for patients with initial isolated ileitis). Endoscopic response is a >50% reduction in CDEIS score from baseline to week 12. Mucosal healing is defined as the absence of mucosal ulceration. Deep remission is clinical remission and endoscopic remission. Full analysis set was used for this analysis, using non-response imputation for missing values and stratified Cochran-Mantel-Haenszel tests. CDAI=Crohn's Disease Activity Index. CDEIS=Crohn's Disease Endoscopic Index of Severity.

Figure 2: Clinical response and remission over 12 weeks

Proportion of patients with clinical remission (A) or clinical response (B). Clinical remission is defined as a CDAI score <150. Clinical response is either a CDAI score <150 or a CDAI reduction of ≥100 from baseline. Patients in whom prohibited concomitant medication to treat Crohn's disease was used before week 12 were considered as treatment failures. Intention-to-treat group was used for this analysis, using non-response imputation for missing values. CDAI=Crohn's Disease Activity Index.
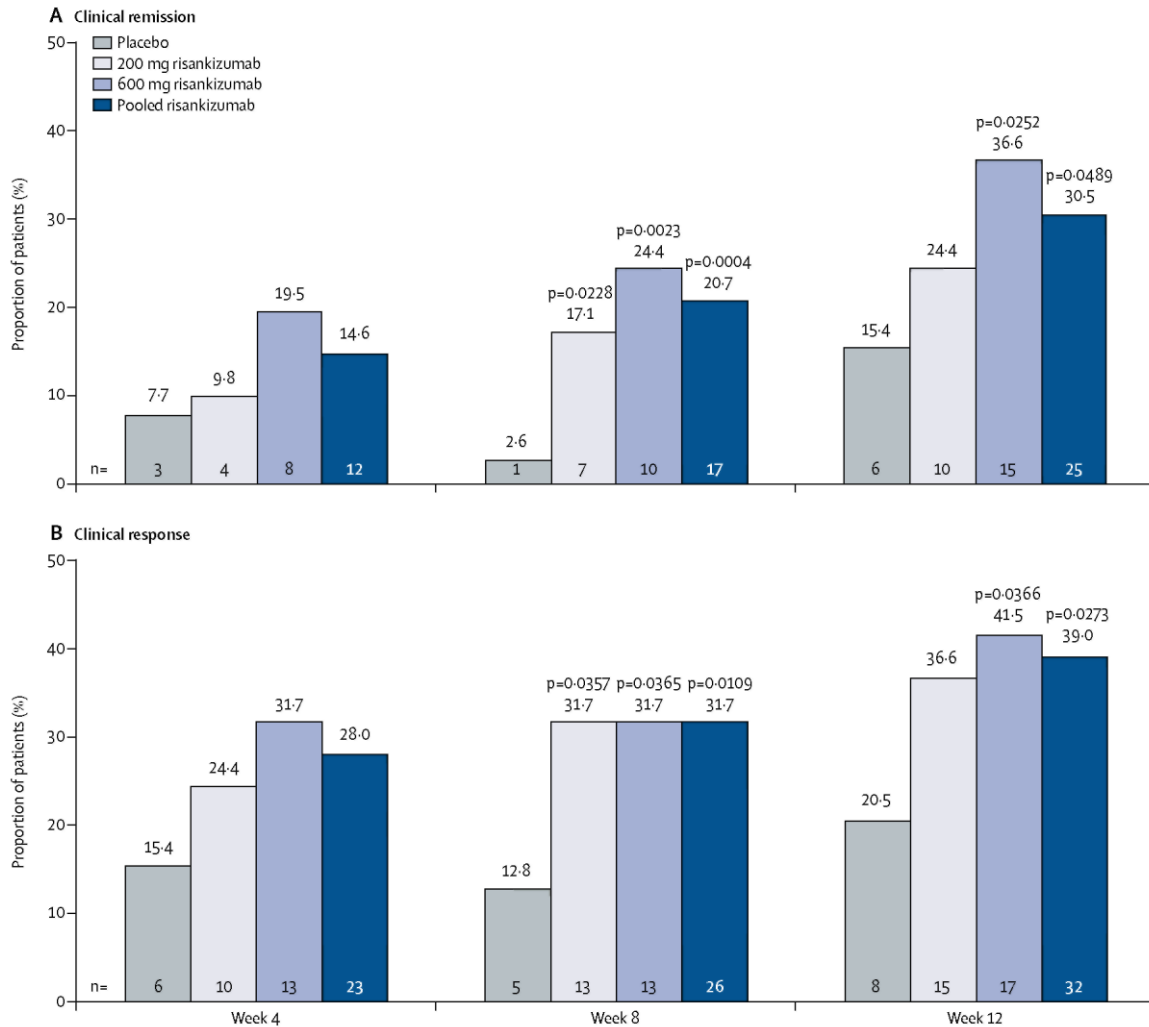
Table 3: Adverse events (on treatment at week 12)

	Placebo (n=39)	Risankizumab	
		200 mg (n=41)	600 mg (n=41)
Any adverse event	32 (82%)	32 (78%)	31 (76%)
Severe	9 (23%)	6(15%)	3 (7%)
Drug related	8 (21%)	10 (24%)	5 (12%)
Leading to discontinuation	6(15%)	5 (12%)	1(2%)
Serious adverse events*	12 (31%)	9 (22%)	3 (7%)
Persistent or significant disability or incapacity	0	1(2%)	0
Requiring or prolonging hospitalisation	10 (26%)	8 (20%)	2 (5%)
Other medically important serious event	4 (10%)	1(2%)	1(2%)
Common adverse events†			
Nausea	4 (10%)	8 (20%)	3 (7%)
Worsening of Crohn's disease	6(15%)	2(5%)	0
Abdominal pain	4 (10%)	6(15%)	3 (7%)
Arthralgia	3 (8%)	6(15%)	6 (15%)
Anaemia	4 (10%)	0	2 (5%)
Headache	4 (10%)	6(15%)	4 (10%)
Vomiting	4 (10%)	3 (7%)	2 (5%)

Data are n (%). *A serious adverse event was defined as any that results in death, is immediately life-threatening, results in persistent or significant disability or incapacity, requires or prolongs patient hospital stay, is a congenital anomaly or birth defect, or is an important medical event, based upon appropriate medical judgment that might jeopardise the patient and might require medical or surgical intervention. †Common adverse events were those reported in at least 10% of patients in any study arm.

***Figure 3*: Change from baseline in CDAI and selected biomarkers** Median CDAI (A), median CRP (B), median percentage change from baseline in FCP (C), and median percentage change from baseline in serum interleukin 22 (D). Bars are IQR. BL=baseline. CDAI=Crohn's Disease Activity Index. CRP=C-reactive protein. FCP=faecal calprotectin.*p<0·0001 for change from baseline in CRP for versus placebo. †p=0·0003 for median percentage change from baseline in FCP versus placebo. ‡p=0·0160 for median percentage change from baseline in serum interleukin 22 versus placebo
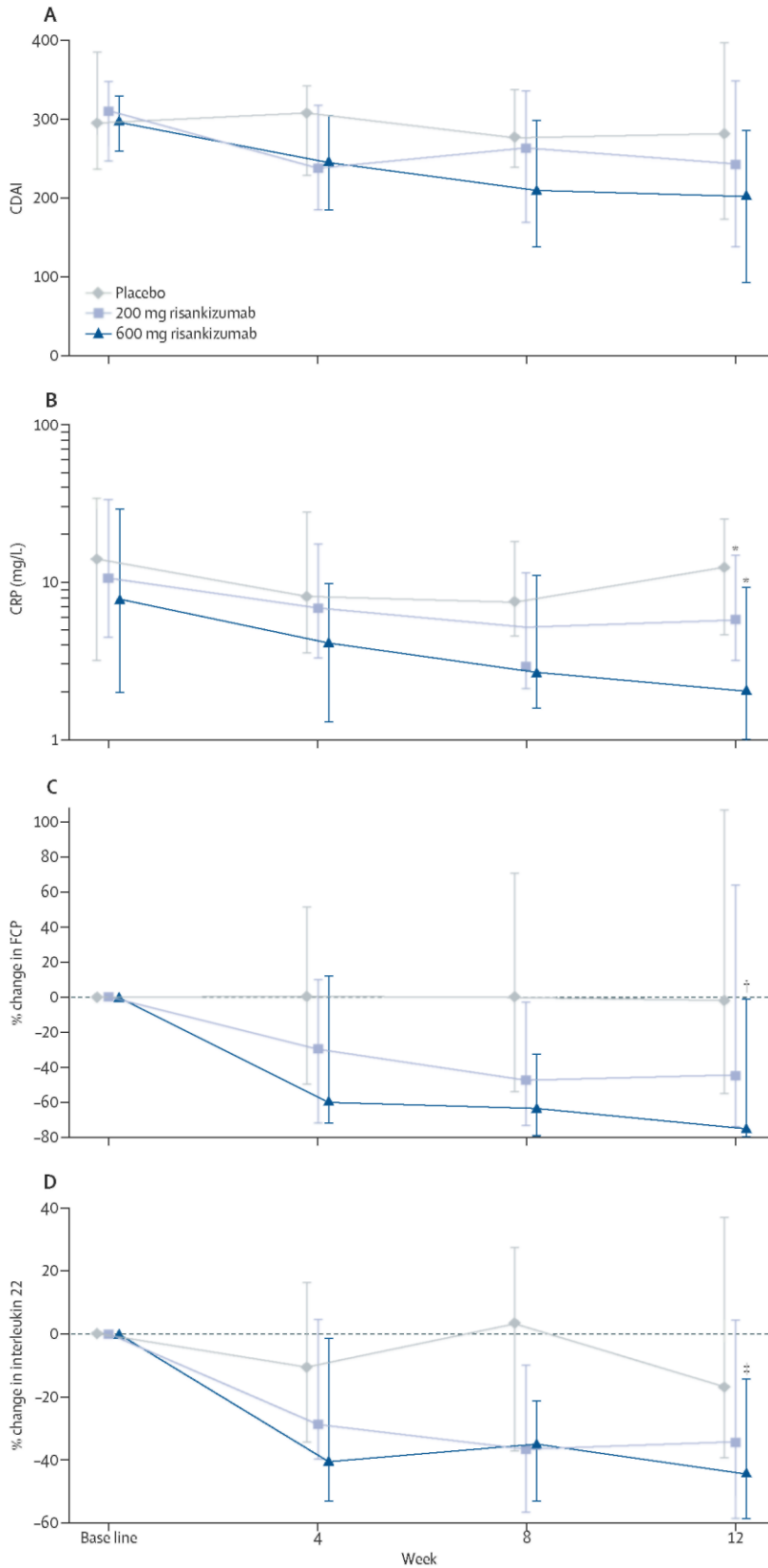
Discussion

Despite the introduction of biological therapies, an unmet need exists for patients with moderate-to-severe Crohn's disease because of high rates of treatment failure with conventional and biological therapies.[21,22] About a third of patients treated with a TNF antagonist have a primary non-response, and another third develop secondary failure or intolerance to treatment.[4] Patients who have had a primary non-response or secondary failure to a TNF antagonist have a lower chance of responding to subsequent treatment with different TNF antagonists[23] or the integrin antagonist vedolizumab.[24] Those patients who do not respond to the second-line biological therapy are at higher risk for poor outcomes. In this phase 2 trial, selective inhibition of interleukin-23 with risankizumab was superior to placebo in achieving clinical remission and response at week 12 in patients with moderate-to-severe treatment-refractory Crohn's disease.

The differences observed for clinical response and remission between the pooled risankizumab groups and placebo were statistically significant but were also clinically meaningful in this treatment-refractory population, in which 83 (69%) of 121 patients had previously been exposed to at least two TNF antagonists and 96 (79%) of 121 patients had failed at least one such treatment (because of inadequate response, loss of response, or intolerance). The difference for the 600 mg dose achieving clinical remission compared with placebo was 20.9% (p=0.025), which represents a benefit similar to those reported for induction with infliximab or adalimumab in TNF antagonist-naive patients.[25,26]

Although the near resolution of symptoms associated with Crohn's disease assessed as clinical remission represents one important treatment target, clinical activity in Crohn's disease correlates poorly with objective signs of gut inflammation.[27] Because chronic inflammation can lead to long-term complications such as strictures, fistulae, and dysplasia, we included endoscopic assessments in this trial to assess objectively the effects of treatment on the inflammatory process. In accordance with the observed clinical endpoints, the observed rates of endoscopic remission and deep remission, which are challenging endpoints to meet in a short-term induction study,[28] also indicate the superiority of the high-dose regimen versus the lower-dose regimen and placebo.

We also found clinically meaningful increases in IBDQ for risankizumab compared with placebo. A mean change of 16 points is considered clinically meaningful for the IBDQ score[20] and both the 200 mg and 600 mg risankizumab groups exceeded this threshold, with 600 mg risankizumab statistically significant versus placebo.

Both dose levels that we tested for induction in Crohn's disease were several times higher than those tested in plaque psoriasis, for which risankizumab regimens of 90 mg and 180 mg given subcutaneously at weeks 0, 4, and 12 showed superior efficacy versus ustekinumab at 12 weeks in a phase 2 study.[29] Our dose selection was based on observations with TNF antagonists that indicated the need for higher induction doses in Crohn's disease compared with other indications, which might result from lower drug exposure because of intestinal protein loss or a larger burden of target molecules in the inflamed gut in inflammatory bowel diseases, or both.[30,31] In keeping with this hypothesis, all efficacy outcomes favoured the 600 mg dose. The observed associations between risankizumab exposure and CDAI response and remission as well as endoscopic activity (CDEIS response) should be evaluated in future studies.

Reductions in expression of biomarkers in blood and tissue were consistent with blockade of interleukin-23-mediated gut inflammation.[7] Larger decreases in serum CRP and FCP concentrations were observed at 12 weeks in the risankizumab groups in comparison with the placebo group. Changes in gene expression observed in colon tissue indicated that multiple pathways associated with the interleukin-23 axis weredownregulatedby12weeks in patients treated with risankizumab. Activated Th17 and ILC3 cells from patients with inflammatory bowel disease characteristically produce interleukin-22,[9,32] and treatment with risankizumab decreased interleukin-22 expression in ileum biopsies and in circulation, consistent with the expected effects of blockade of the interleukin-23 axis. Collectively, these data suggest that selective inhibition of interleukin-23 through targeting of the

interleukin-23 pl9 subunit might be an effective induction therapy for moderate-to-severe Crohn's disease.

In this short-term trial, risankizumab showed a favourable safety profile. We observed no association between drug dose and the incidence of adverse events, and we detected no dose-dependent safety signal. The most common serious adverse event was worsening of underlying Crohn's disease. However, the limited duration of the trial and the small number of patients evaluated did not allow an exhaustive assessment of the safety and tolerability of the drug. Treatment-emergent anti-drug antibodies were detected in 4% of patients but were of low titres and were not neutralising. The observation of low titre pre-existing anti-drug antibodies in eight patients is not unusual using highly sensitive assays and such antibodies are not usually clinically relevant.[33]

A key strength of this study was its design. To be enrolled, patients needed to have baseline clinical and endoscopic activity, which was scored using central reading by a masked reviewer. Endoscopic outcome was also assessed in all patients as a secondary endpoint.

The major limitations of our study were the low number of patients evaluated, resulting in relatively imprecise estimates of treatment effects, and the short study duration. Although the small number of TNF antagonist-naive patients randomised in this trial precludes the extrapolation of the observed effects beyond the study population, past trials[12,23] in TNF antagonist-experienced patients with different biological treatments have generally shown a lower treatment effect in TNF antagonist-naive patients. Another methodological limitation inherent to all clinical trials in patients with Crohn's disease is the lack of clinical validation of endoscopic endpoints. However, the operating properties of the CDEIS used in this study are well characterised and have been successfully used in previous clinical trials.[34] Furthermore the definition of endoscopic remission is consistent with expert panel recommendations.[35]

In this short-term proof-of-concept trial in patients with moderate-to-severe Crohn's disease, in most of whom treatment with a TNF antagonist had previously failed, treatment with risankizumab achieved higher clinical and endoscopic remission rates than placebo at week 12. These results suggest that specific blockade of interleukin-23 via inhibition of pl9 might be a viable therapeutic approach in Crohn's disease and warrants further investigation in larger studies with longer duration.

Contributors

BGF wrote the initial draft. All authors approved the manuscript for submission and vouch for the veracity and completeness of the data and the fidelity of the study to the protocol. The study site and investigator details are in the appendix (p 2). BGF, WJS, GD'H, JP, AK, SS, PS, SV, SJP, DBH, and WOB contributed to study design. BGF, WJS, GD'H, JP, AK, MF, EL, DF, OD, US, K-JK, MFN, and SS contributed to data collection. All listed authors contributed to data analysis, data interpretation, and writing and review of the manuscript.

Declaration of interests

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