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 southeast 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.

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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 (Th17) and type 3 innate lymphoid cell (ILC3) pathways that contribute to inflammatory cytokine production and

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Research in context

Evidence before this study

We searched PubMed for English language articles using the terms ''Crohn's disease", "biologic therapy", "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 in TNF antagonist-naive patients. Treatment with a second TNF 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 or the 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 superior to 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. Our trial 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 for the treatment of this serious chronic disease.

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 p19 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 (p 7).

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.

See Online for appendix

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 electrochemiluminescence 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

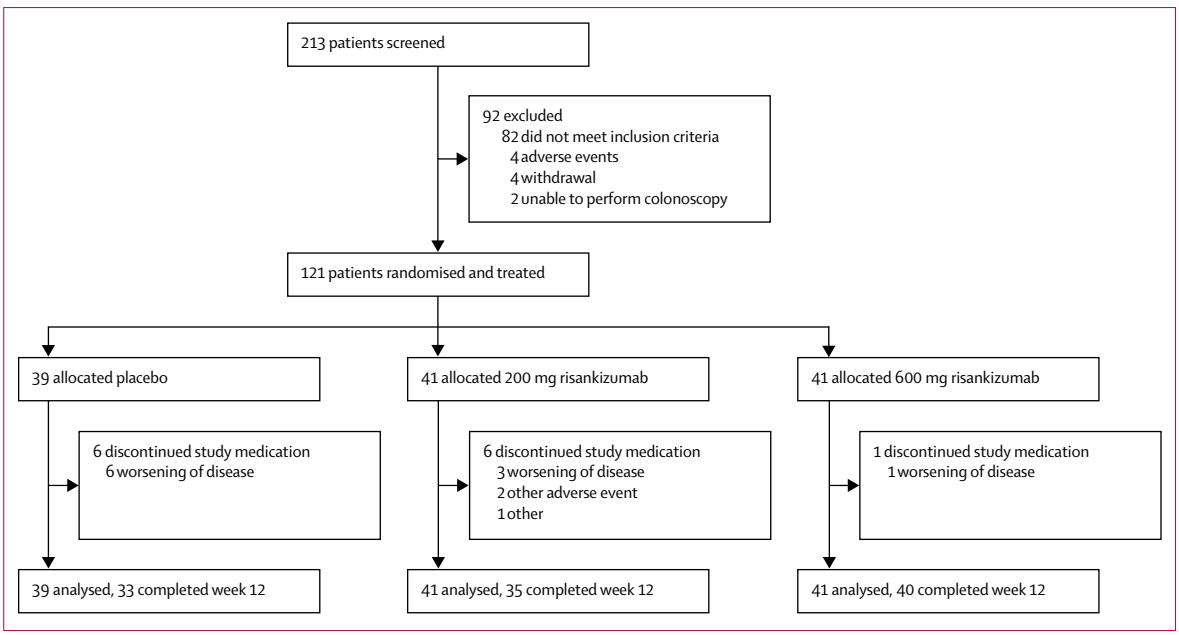


Figure 1: **Trial profile**

version 2.0), serious adverse events, tolerability, changes in vital signs and physical examination, discontinuation of therapy because of adverse events, and laboratory assessments.

Statistical analysis

We analysed the primary and secondary endpoints on an intention-to-treat basis. Pharmacokinetic data, immunogenicity, 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; p=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; p<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

	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.

***Table 1*: Baseline characteristics**

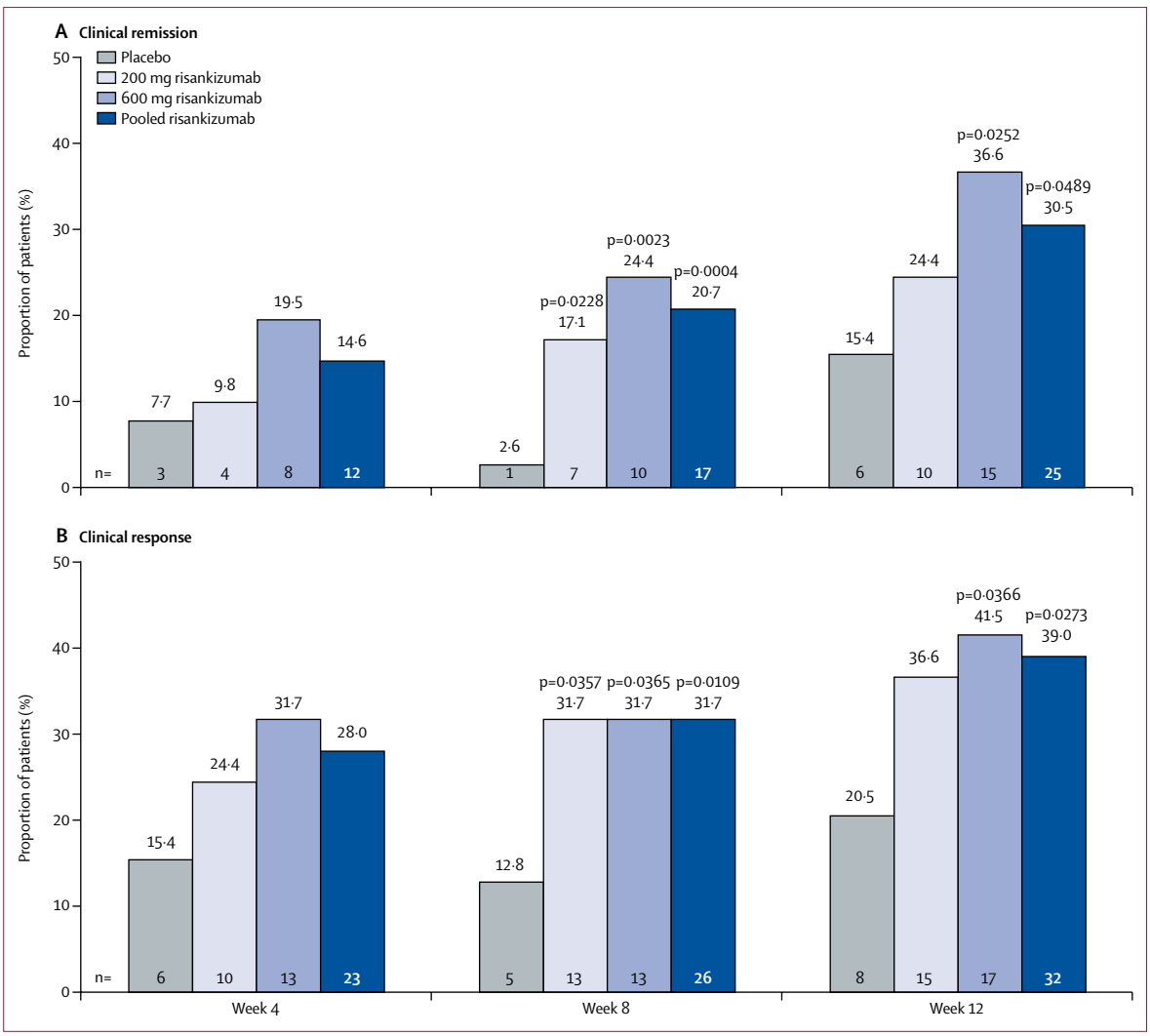


***Figure 2*: Clinical response and remission over 12 weeks**

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.

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,

	Placebo (n=39)	Risankizumab		
		200 mg (n=41)	600 mg (n=41)	Pooled (n=82)
Clinical remission (primary endpoint)				
n (%)	6 (15%)	10 (24%)	15 (37%)	25 (31%)
Difference *vs* placebo (95% CI, p value)	..	9·0% (–8·3 to 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)				
n (%)	8 (21%)	15 (37%)	17 (42%)	32 (39%)
Difference *vs* placebo (95% CI, p value)	..	16·0% (–3·2 to 35·2, p=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)				
n (%)	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)				
n (%)	5 (13%)	11 (27%)	15 (37%)	26 (32%)
Difference *vs* placebo (95% CI, p value)	..	14·1% (–2·8 to 30·9, p=0·10)	23·5% (5·5 to 41·5, p=0·0106)	18·7% (4·4 to 33·0, p=0·0104)
Mucosal healing (secondary endpoint)				
n (%)	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% (–4·6 to 14·3, p=0·31)	2·4% (–4·5 to 9·2, p=0·50)
Deep remission (secondary endpoint)				
n (%)	0	1 (2%)	5 (12%)	6 (7%)
Difference *vs* placebo (95% CI, p value)	..	2·4% (–2·3 to 7·1, p=0·31)	12·4% (2·3 to 22·5, p=0·0164)	7·4% (1·7 to 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.

***Table 2*: Efficacy endpoints at week 12**

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.

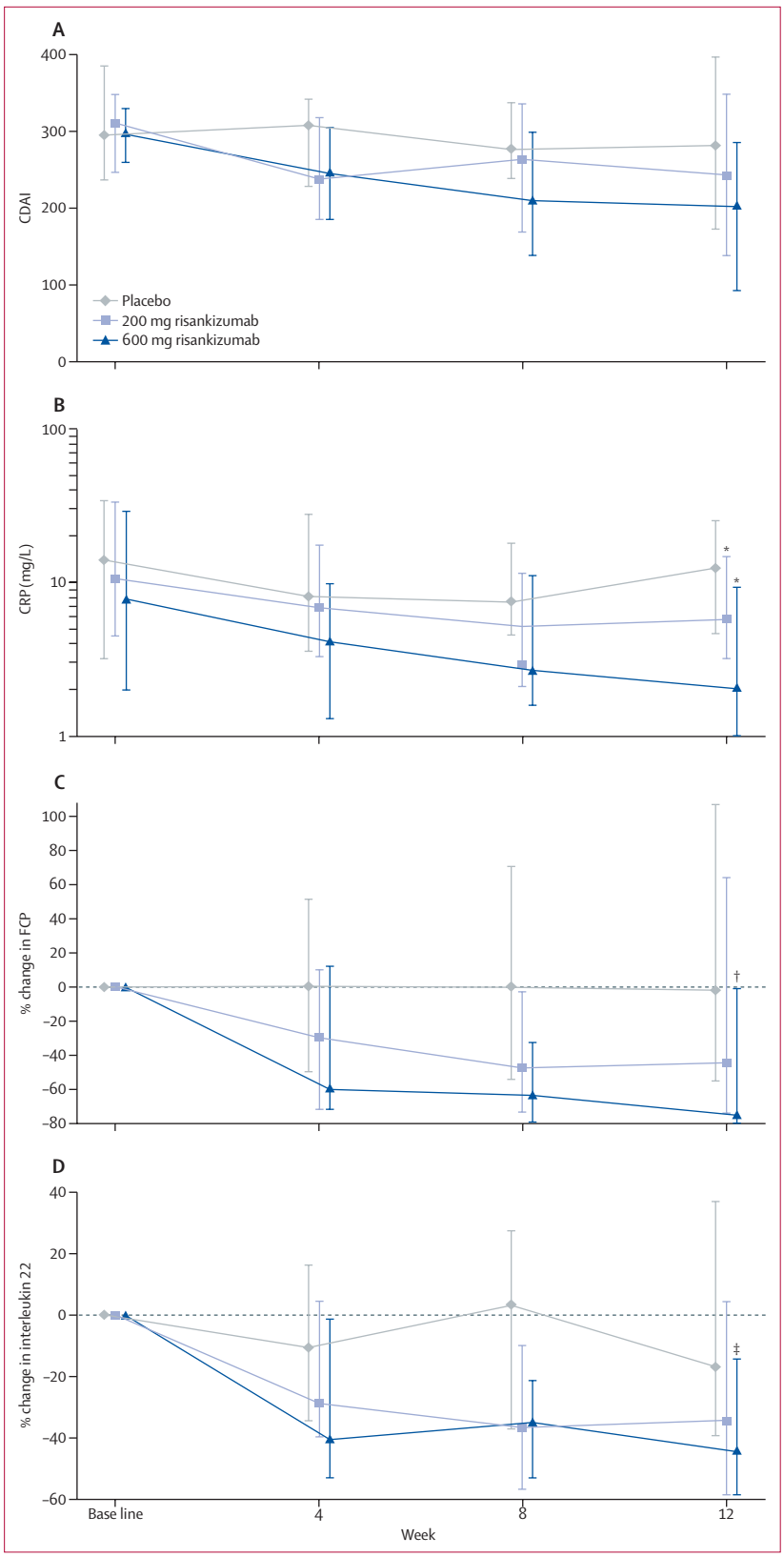
Treatment-emergent anti-drug antibodies were detected in 4% of patients receiving risankizumab (three of 76 patients). Anti-drug antibody titre values were low (≤8) and no neutralising antibodies were detected. Pre-existing anti-drug antibodies were observed in five patients in the risankizumab dose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

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 were downregulated by 12 weeks 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

***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=0·0180 for median percentage change from baseline in serum interleukin 22 versus placebo.

interleukin-23 axis. Collectively, these data suggest that selective inhibition of interleukin-23 through targeting of the interleukin-23 p19 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 p19 might be a viable therapeutic approach in Crohn's disease and warrants further investigation in larger studies with longer duration.

	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.

Table 3: **Adverse events (on treatment at week 12)**

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

BGF reports personal fees from Receptos, during the conduct of the study; grants from Sanofi; grants and personal fees from AbbVie, Amgen, AstraZeneca, Bristol-Myers Squibb, Janssen Biotech/Centocor, Johnson & Johnson/Janssen, Pfizer, Receptos, and Takeda; personal fees from Actogenix, Akros, Albireo Pharma, Allergan, Avaxia Biologics Inc, Avir Pharma, Axcan, Baxter Healthcare Corporation, Biogen Idec, Boehringer Ingelheim, Calypso Biotech, Celgene, Elan/Biogen, enGene, Ferring, Genentech/Roche, GiCare Pharma, Gilead, Given Imaging, GlaxoSmithKline, Ironwood, Kyowa Hakko Kirin Co, Ltd, Lilly, Lycera Biotech, Merck, Mesoblast Pharma, Millennium, Nestlé, Novo Nordisk, Novartis, Prometheus Therapeutics and Diagnostics, Protagonist, Salix, Shire, Sigmoid Pharma, Synergy Pharma, Teva Pharma, TiGenix, Tillotts, UCB, Vertex, VHsquared, Wyeth, Zealand, and Zyngenia, outside the submitted work. BGF is CEO and Senior Scientific Director of Robarts Clinical Trials (Western University, London, ON, Canada). WJS reports grants, personal fees, and non-financial support from Boehringer Ingelheim during the conduct of the study; grants from Exact Sciences, the American College of Gastroenterology, and the Broad Foundation; grants and personal fees from Prometheus Laboratories, AbbVie, Amgen, Boehringer Ingelheim, Takeda, Atlantic Pharmaceuticals, Janssen, Bristol-Myers Squibb, Gilead Sciences, GlaxoSmithKline, Genentech, Pfizer, Nutrition Science Partners, and Receptos; personal fees from Kyowa Hakko Kirin, Millennium Pharmaceuticals, Celgene Cellular Therapeutics, Santarus, Salix Pharmaceuticals, Catabasis Pharmaceuticals, Vertex Pharmaceuticals, Warner Chilcott, Cosmo Pharmaceuticals, Ferring Pharmaceuticals, Sigmoid Biotechnologies, Tillotts Pharma, Am Pharma BV, Dr August Wolff GmbH & Co KG, Avaxia Biologics, Zyngenia, Ironwood Pharmaceuticals, Index Pharmaceuticals, Nestle, Lexicon Pharmaceuticals, UCB Pharma, Orexigen, Luitpold Pharmaceuticals, Baxter Healthcare, Ferring Research Institute, Novo Nordisk, Mesoblast, Shire, Ardelyx, Actavis, Seattle Genetics, MedImmune (AstraZeneca), ActoGeniX NV, Lipid Therapeutics Gmbh, Eisai, Qu Biologics, Toray

Industries, Teva Pharmaceuticals, Eli Lilly, Chiasma, TiGenix, Adheron Therapeutics, Immune Pharmaceuticals, Celgene, Arena Pharmaceuticals, Ambrx, Akros Pharma, Vascular Biogenics, Theradiag, Forward Pharma, Regeneron, Galapagos, Seres Health, Ritter Pharmaceuticals, Theravance Biopharma, Palatin, Biogen, and the University of Western Ontario (owner of Robarts Clinical Trials), outside the submitted work. WJS reports patents related to the use of topical azathioprine to treat inflammatory bowel disorders (US 5 691 343), topical formulations of azathioprine to treat inflammatory bowel disorders (US 5,905,081), colonic delivery of nicotine to treat inflammatory bowel disease (South African patent 97/1020; US 5,846,983, 5,889,028, and 6,166,044; Mexico patent 209636; Europe patents 0954337 and 893998; Hong Kong patent HK1019043; China patent ZL97192177; Czech patent 293616; Canada patent 2,246,235), the use of azathioprine to treat CD (US 5,733,915), azathioprine compositions for colonic administration (New Zealand patent 306062; Singapore patent 45647; Australia patent 707168; Czech patent 290428), intestinal absorption of nicotine to treat nicotine responsive conditions (Australia patent 718052; US 6,238,689), the use of topical azathioprine and thioguanine to treat colorectal adenomas (US 6,166,024), enema and enteric-coated oral dosage forms of azathioprine (US 6,432,967), a pharmaceutical composition for the treatment of inflammatory bowel disease (US 7341741), intestinal absorption of nicotine to treat nicotine responsive conditions (Canada patent 2,260,909), and obesity treatment and device (US 7,803,195 B2). GD'H reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from AbbVie, Ablynx, Amakem, AM Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Celgene, Celltrion, Cosmo, Covidien, Engene, Ferring, Galapagos, GlaxoSmithKline, Hospira, Johnson and Johnson, Medimetrics, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Novo Nordisk, Pfizer, Prometheus Laboratories/Nestlé, Receptos, Robarts Clinical Trials, Salix, Sandoz, Setpoint, Shire, Teva, Tillotts, TopiVert, Versant, and Vifor, outside the submitted work. JP reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from AbbVie, Galapagos, Genentech Roche, Pfizer, Takeda, TiGenix, and TopiVert, outside the submitted work. AK reports grants, and non-financial support from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, Ferring, Genentech, GlaxoSmithKline, Hospira, Janssen, Kymab, Second Genome, and VHsquared, outside the submitted work. MF reports personal fees and non-financial support from Boehringer Ingelheim, during the conduct of the study; grants, personal fees, and non-financial support from Takeda, personal fees and non-financial support from AbbVie, Falk, Ferring, Janssen, MSD, and Tillotts; personal fees from Chiesi, Mitsubishi Tanabe, and Zeria Pharmaceutical Co., outside the submitted work. EL reports grants, personal fees, and non-financial support from AbbVie and MSD; personal fees from Ferring, Takeda, Celltrion, Mundipharma, Hospira, and Janssen, outside the submitted work. DF reports educational grants, personal fees and non-financial support from AbbVie and MSD; personal fees from Amgen, Ferring, Takeda, Mundipharma, Hospira, and Pfizer, outside the submitted work. US reports grants from Boehringer Ingelheim, during the conduct of the study; grants from Pfizer, Janssen, Roche, Gilead, Salix, and Mitsubishi; personal fees from MSD; non-financial support from Takeda, outside the submitted work. MFN reports personal fees from MSD Sharp & Dohme GmbH, PPM Services SA, Index Pharmaceuticals AB, Shire GmbH, Boehringer Ingelheim GmbH & Co. KG, Janssen-Cilag GmbH, Pentax Europe GmbH, Tillotts Pharma AG, e.Bavarian Health GmbH, and Takeda Pharma GmbH & Co. KG; grants from German Research Council and German Cancer Aid, outside the submitted work. In addition, MFN has a patent anti-interleukin-12 therapy in Crohn's disease issued. SS reports personal fees from Boehringer Ingelheim, during the conduct of the study; personal fees from Boehringer Ingelheim, MedImmune, and Janssen, outside the submitted work. OD and K-JK report no competing interests. PS, CP, BL, SV, SJP, IH, AS, DBH, and WOB are employed by Boehringer Ingelheim. PS, SV, SJP, and WOB report a patent BI case 09–0645-US-4 pending.

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References

1 Baumgart DC, Sandborn WJ. Crohn's disease. *Lancet* 2012; **380:** 1590–605.

2 Sandborn WJ, Feagan BG, Stoinov S, et al. Certolizumab pegol for the treatment of Crohn's disease. *N Engl J Med* 2007; **357:** 228–38.

3 Targan SR, Feagan BG, Fedorak RN, et al. Natalizumab for the treatment of active Crohn's disease: results of the ENCORE Trial. *Gastroenterology* 2007; **132:** 1672–83.

4 Peyrin-Biroulet L, Deltenre P, de Suray N, Branche J, Sandborn WJ, Colombel JF. Efficacy and safety of tumor necrosis factor antagonists in Crohn's disease: meta-analysis of placebo-controlled trials. *Clin Gastro Hepatol* 2008; **6:** 644–53.

5 Gordon JP, McEwan PC, Maguire A, Sugrue DM, Puelles J. Characterizing unmet medical need and the potential role of new biologic treatment options in patients with ulcerative colitis and Crohn's disease: a systematic review and clinician surveys. *Eur J Gastroenterol Hepatol* 2015; **27:** 804–12.

6 Lichtenstein GR, Sbreu MT, Cohen R, Tremaine W. American Gastroenterological Association Institute technical review on corticosteroids, immunomodulators, and infliximab in inflammatory bowel disease. *Rev Gastroenterol Mex* 2006; **71:** 351–401.

7 Neurath MF. IL-23: a master regulator in Crohn disease. *Nat Med* 2007; **13**: 26–8.

8 Duerr RH, Taylor KD, Brant SR, et al. A genome-wide association study identifies IL23R as an inflammatory bowel disease gene. *Science* 2006; **314:** 1461–63.

9 Geremia A, Arancibia-Carcamo CV, Fleming MP, et al. IL-23-responsive innate lymphoid cells are increased in inflammatory bowel disease. *J Exp Med* 2011; **208:** 1127–33.

10 Campa M, Mansouri B, Warren R, Menter A. A review of biologic therapies targeting IL-23 and IL-17 for use in moderate-to-severe plaque psoriasis. *Dermatol Ther* 2016; **6:** 1–12.

11 Sandborn WJ, Gasink C, Gao LL, et al. Ustekinumab induction and maintenance therapy in refractory Crohn's disease. *N Engl J Med* 2012; **367:** 1519–28.

12 Feagan BG, Sandborn WJ, Gasink C, et al. Ustekinumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2016; 375: 1946–60.

13 Hueber W, Sands BE, Lewitzky S, et al. Secikunmab, a human anti-IL-17a monoclonal antibody, for moderate to severe Crohn's disease: unpected results of a randomised, double-blind placebo-controlled trial. *Gut* 2012; **61:** 1693–700.

14 Targan SR, Feagan B, Vermeire S, et al. A randomised, double-blind, placebo-controlled phase 2 study of brodalumab in patients with moderate-to-severe Crohn's disease. *Am J Gastroenterol* 2016; **111:** 1599–607

15 Singh S, Kroe-Barrett RR, Canada KA, et al. Selective targeting of the IL23 pathway: generation and characterization of a novel high-affinity humanized anti-IL23A antibody. *mAbs* 2015; **7:** 778–91.

16 Brunda MJ, Luistro L, Warrier RR, et al. Antitumor and antimetastatic activity of interleukin 12 against murine tumors. *J Exp Med* 1993; **178:** 1223–30.

17 Stobie L, Gurunathan S, Prussin C, et al. The role of antigen and IL-12 in sustaining Th1 memory cells in vivo: IL-12 is required to maintain memory/effector Th1 cells sufficient to mediate protection to an infectious parasite challenge. *Proc Natl Acad Sci USA* 2000; **97:** 8427–32.

18 Krueger JG, Ferris LK, Menter A, et al. Anti-IL-23A mAb BI 655066 for treatment of moderate-to-severe psoriasis: safety, efficacy, pharmacokinetics, and biomarker results of a single-rising-dose, randomized, double-blind, placebo-controlled trial. *J Allergy Clin Immunol* 2015; **136:** 116–24.

19 Levesque BG, Sandborn WJ, Ruel J, et al. Converging goals of treatment of inflammatory bowel disease from clinical trials and practice. *Gastroenterology* 2015; **148:** 37–51.

20 Irvine EJ, Feagan B, Rochon J, et al. Quality of life: a valid and reliable measure of therapeutic efficacy in the treatment of inflammatory bowel disease. Canadian Crohn's Relapse Prevention Trial Study Group. *Gastroenterology* 1994; **106:** 287–96.

21 Matsuoka K, Kanai T. Mechanism and therapeutic strategy of secondary failure to anti-tumor necrosis factor-alpha monoclonal antibody treatment for Crohn's disease. *Digestion* 2013; **88:** 17–19.

22 Terdiman JP, Gruss CB, Heidelbaugh JJ, et al. American Gastroenterological Association Institute guideline on the use of thiopurines, methotrexate, and anti-TNF-alpha biologic drugs for the induction and maintenance of remission in inflammatory Crohn's disease. *Gastroenterology* 2013; **145:** 1459–63.

23 Gisbert JP, Marin AC, McNicholl AG, Chaparro M. Systematic review with meta-analysis: the efficacy of a second anti-TNF in patients with inflammatory bowel disease whose previous anti-TNF treatment has failed. *Aliment Pharmacol Ther* 2015; **41:** 613–23.

24 Sandborn WJ, Feagan BG, Rutgeerts P, et al. Vedolizumab as induction and maintenance therapy for Crohn's disease. *N Engl J Med* 2013; **369:** 711–21.

25 Targan SR, Hanauer SB, van Deventer SJ, et al. A short-term study of chimeric monoclonal antibody cA2 to tumor necrosis factor alpha for Crohn's disease. Crohn's Disease cA2 Study Group. *N Engl J Med* 1997; **337:** 1029–35.

26 Hanauer SB, Sandborn WJ, Rutgeerts P, et al. Human anti-tumor necrosis factor monoclonal antibody (adalimumab) in Crohn's disease: the CLASSIC-I trial. *Gastroenterology* 2006; **130**: 323–33.

27 Peyrin-Biroulet L, Reinisch W, Colombel JF, et al. Clinical disease activity, C-reactive protein normalisation and mucosal healing in Crohn's disease in the SONIC trial. *Gut* 2014; **63:** 88–95.

28 Rutgeerts P, Van Assche G, Sandborn WJ, et al. Adalimumab induces and maintains mucosal healing in patients with Crohn's disease: data from the EXTEND trial. *Gastroenterology* 2012; **142:** 1102–11.

29 Papp K, Blauvelt A, Bukhalo M, et al. Selective blockade of IL-23p19 with BI 655066 is associated with clinical responses superior to ustekinumab in patients with moderate-to-severe plaque psoriasis: Results from a 48-week Phase II study. *J Am Acad Dermatol* 2016; **74** (suppl 1)**:** AB274.

30 Ordas I, Feagan BG, Sandborn WJ. Therapeutic drug monitoring of tumor necrosis factor antagonists in inflammatory bowel disease. *Clin GastroHepatol* 2012; **10:** 1079–87.

31 Brandse JF, van den Brink GR, Wildenberg ME, et al. Loss of infliximab into feces is associated with lack of response to therapy in patients with severe ulcerative colitis. *Gastroenterology* 2015; **149:** 350–55.

32 Kleinschek MA, Boniface K, Sadekova S, et al. Circulating and gut-resident human Th17 cells express CD161 and promote intestinal inflammation. *J Exp Med* 2009; **206:** 525–34.

33 van Schie KA, Wolbink GJ, Rispens T. Cross-reactive and pre-existing antibodies to therapeutic antibodies—effects on treatment and immunogenicity. *mAbs* 2015; **7:** 662–71.

34 Khanna R, Bouguen G, Feagan BG, et al. A systematic review of measurement of endoscopic disease activity and mucosal healing in Crohn's disease: recommendations for clinical trial design. *Inflamm Bowel Dis* 2014; **20:** 1850–61.

35 Vuitton L, Marteau P, Sandborn WJ, et al. IOIBD technical review on endoscopic indices for Crohn's disease clinical trials. *Gut* 2016; **20:** 1447–55.