

Title: Open-label extension of a phase 2 trial of risankizumab in patients with moderate-to-severe Crohn's disease

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Background: Risankizumab, an anti-interleukin-23 antibody, was superior to placebo in achieving clinical and endoscopic remission at week 12 in a randomised, phase 2 induction study in patients with moderately to severely active Crohn's disease. The efficacy and safety of extended intravenous induction and/or subcutaneous maintenance therapy with risankizumab was assessed.

Methods: Following 12-week, double-blind, randomised, induction treatment comparing 200 mg or 600 mg intravenous risankizumab to placebo every 4 weeks, patients without deep remission, defined as clinical (Crohn's Disease Activity Index <150) and endoscopic remission (Crohn's Disease Endoscopic Index of Severity [CDEIS] ≤ 4 [≤ 2 for patients with isolated ileitis]), received open-label 600 mg intravenous risankizumab (every 4 weeks) and patients in deep remission underwent washout until week 26 (Period 2). At week 26, patients in clinical remission received maintenance treatment (Period 3) with 180 mg subcutaneous risankizumab (every 8 weeks). Efficacy endpoints included clinical and endoscopic response and remission at weeks 26 (Period 2) and 52 (Period 3) respectively; safety was assessed through both periods. Study registration: ClinicalTrials.gov, NCT02031276.

Findings: In Period 2, 101 patients were treated with 600 mg risankizumab resulting in an increase in clinical remission rates at week 26 versus week 12 for all original designated treatment groups: 55% versus 18%, 59% versus 21%, and 47% versus 26% for placebo, 200, and 600 mg risankizumab, respectively. Of the 62 patients receiving maintenance treatment, 54 completed treatment. At week 52, clinical remission was maintained by 71% of patients; endoscopic remission and response (>50% CDEIS reduction from baseline) was achieved by 35% and 55% of patients, respectively, and 29% of patients achieved deep remission. Risankizumab was well tolerated with no new safety signals.

Interpretation: Extended induction treatment with open-label intravenous risankizumab was effective in increasing clinical response and remission rates at week 26. Open-label subcutaneous risankizumab maintained remission till week 52 in most patients who were in clinical remission at week 26. Selective blockade of interleukin-23 warrants further evaluation as treatment for Crohn's disease.

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Research in context

Evidence before this study

We searched PubMed for English language articles using the terms “Crohn’s disease”, “biologic therapy”, “adalimumab”, “infliximab”, “certolizumab pegol”, “vedolizumab”, “ustekinumab”, and “IL-23” to identify controlled clinical trials published up to 28 March 2018, with no start date restrictions. In the US and Europe, current biologic therapies approved for the treatment of moderate-to-severe Crohn’s disease include tumour necrosis factor (TNF) antagonists adalimumab, infliximab, and certolizumab pegol, the integrin antagonists, vedolizumab and natalizumab (US only), and the interleukin-12 and interleukin-23 inhibitor, ustekinumab. Treatment regimens are aimed at inducing remission followed by maintenance therapy. Despite more therapeutic options, there are a number of patients in who these therapies have limited efficacy (primary nonresponse) or who lose response over time (secondary nonresponse) or evoke adverse effects; thus, new therapies targeting different inflammatory pathways are needed.

Previously, we reported phase 2 clinical trial results of induction treatment with two intravenous (IV) dose levels (200 mg and 600 mg every 4 weeks) of risankizumab, a monoclonal antibody targeting 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, demonstrating proof-of-concept.

Added value of this study

This study reports the findings for two further treatment periods from the previously reported phase 2 clinical trial (Period 1): a second open-label IV induction treatment with 600 mg risankizumab every 4 weeks (Period 2) for those patients not in deep remission after the first 12 weeks induction treatment; and an open-label maintenance treatment period with subcutaneous (SC) 180 mg risankizumab every 8 weeks (Period 3) for patients in clinical remission at the end of Period 2. For patients not in deep remission at week 12, the results at week 26 demonstrate that further open-label induction treatment with IV 600 mg risankizumab every 4 weeks was effective in achieving greater clinical remission rates than those observed at week 12. Period 3 results suggest that open-label SC 180 mg risankizumab

every 8 weeks was an effective therapy to maintain clinical remission up to week 52 in patients who were in clinical remission at week 26.

Implications of all the available evidence

Evidence from studies with other biological agents suggests that some patients, particularly those previously exposed to TNF antagonists, may take longer to achieve remission than TNF antagonist-naïve patients. Ninety-three percent of patients enrolled in this study had been previously treated with at least one TNF antagonist and 79% had failed at least one such treatment due to inadequate response, loss of response, or intolerance. Extended open-label induction treatment with IV 600 mg risankizumab in patients who were not in deep remission at week 12 was effective in increasing clinical response and remission rates at week 26. The results also suggest that open-label SC 180 mg risankizumab was effective for maintenance of clinical remission at week 52, although a maintenance placebo arm was not included in this phase II study. Based upon these results, specific blockade of interleukin-23 with risankizumab appears to be a promising new approach for the induction of response and maintenance treatment of Crohn's disease, and is currently undergoing phase III evaluation.

Introduction

Crohn's disease is a life-long, relapsing, remitting inflammatory disease of the gastrointestinal tract with symptoms of abdominal pain, weight loss, and chronic diarrhoea.^{1,2} The medical management of Crohn's disease is based upon the use of corticosteroids, and immunosuppressive agents such as thiopurines or methotrexate, with the aim of controlling mucosal inflammation and inducing clinical remission.^{1,3} Whilst corticosteroids are successful for induction of remission, they are ineffective as maintenance therapy and are associated with an increased risk of adverse events such as serious infection.¹ The advent of biological agents that selectively target cytokines or integrins provides an alternative treatment option for patients with moderate-or-severe Crohn's disease; however, these therapies are not universally effective, lose effectiveness over time, and may also predispose patients to infections.^{1,4-6}

Interleukin-23 plays a key role in the induction and function of T helper 17-type cells, innate lymphoid cells, $\gamma\delta$ T cells, and natural killer cells responsible for tissue inflammation, destruction, and aberrant tissue repair involved in the pathology of several immune-related disorders, including Crohn's disease.⁷⁻¹² Furthermore, polymorphisms in the interleukin-23 receptor gene are associated with susceptibility to both Crohn's disease and ulcerative colitis.⁷ Blockade of the interleukin-23 pathway by biologics that target interleukin-17 or its receptor (brodalumab, ixekizumab, secukinumab), interleukin-23 (guselkumab, risankizumab, tildrakizumab), or interleukin-12 and interleukin-23 (ustekinumab) have shown efficacy for the treatment of psoriasis, and both risankizumab and ustekinumab have also shown efficacy in Crohn's disease.¹³⁻¹⁶ Conversely, biological agents that specifically target interleukin-17 or the interleukin-17 receptor exacerbate Crohn's disease, indicating differences between the role of interleukin-12/interleukin-23 and interleukin-17 in psoriasis compared with Crohn's disease.¹⁷⁻¹⁹

Risankizumab (BI 655066/ABBV-066) is a humanised monoclonal IgG1 antibody targeting the interleukin-23 p19 subunit,²⁰ currently under evaluation in Crohn's disease, psoriasis, psoriatic arthritis, and asthma. In a randomised, double-blind, phase 2 study in patients with moderately to severely active Crohn's disease, most of whom had previously received at least two TNF α antagonists, intravenous induction therapy with risankizumab (200 mg or 600 mg at weeks 0, 4, and 8) was superior to placebo in achieving clinical remission and endoscopic remission at week 12.²¹ The greatest treatment response was achieved with 600 mg

risankizumab, which resulted in clinical remission for 37% of patients compared with 15% of patients receiving placebo (difference 20.9%; $p=0.025$). Since evidence from studies with other biological agents suggests that some patients, particularly those with extensive previous treatment with TNF antagonists, may take longer to achieve remission,^{1,22} this study included a 12-week second phase (Period 2) of open-label induction treatment with intravenous 600 mg risankizumab every 4 weeks for patients who did not achieve deep remission, defined as both clinical remission (Crohn's Disease Activity Index [CDAI] of <150) and endoscopic remission (Crohn's Disease Endoscopic Index of Severity [CDEIS] ≤ 4 [≤ 2 for patients with isolated ileitis]) at week 12; followed by 26 weeks of open-label maintenance therapy (Period 3) with subcutaneous 180 mg risankizumab every 8 weeks for patients in clinical remission. Herein, we report the safety and additional efficacy endpoints from these open-label treatment periods.

Methods

Study design

This randomised, double-blind, placebo-controlled phase 2 study enrolled patients with moderate-to-severe active Crohn's disease at multiple sites in North America, Europe, and Southeast Asia.²¹ There were three treatment periods: Period 1 (weeks 0–12), double-blind intravenous therapy; Period 2 (weeks 14–26), open-label intravenous therapy (or washout for patients in deep remission at week 12); and Period 3 (weeks 26–52), subcutaneous therapy (see appendix, p 3). The primary efficacy endpoint (i.e. the proportion of patients in clinical remission, defined by a CDAI of <150 at the end of Period 1 (week 12), has been previously reported;²¹ here, we report additional and exploratory endpoints for Periods 2 and 3.

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. Written, informed consent was provided by all patients.

Patients

A complete description of the inclusion and exclusion criteria has been reported previously.²¹ In brief, eligible patients were adults (aged 18–75 years) who had been diagnosed with Crohn's disease for at least 3 months and who had moderate-to-severe symptoms at screening, defined by a CDAI²³ of 220–450, with mucosal ulcers in the ileum or colon (or

both), and a CDEIS²³ of at least 7 (or ≥ 4 for patients with isolated ileitis) on ileocolonoscopy scored by a blinded central reader.

Randomisation and masking

During the previously reported Period 1 of the study, patients were randomised (1:1:1, with stratification by previous exposure to TNF antagonists) to receive 200 mg risankizumab, 600 mg risankizumab, or placebo.²¹ Periods 2 and 3 were open label and were not randomised.

Procedures

In Period 1, patients received either risankizumab 200 mg, risankizumab 600 mg, or placebo by intravenous infusion at weeks 0, 4, and 8. In Period 2, patients who were not in deep remission (defined as clinical and endoscopic remission) at the end of Period 1 (week 12) received open-label risankizumab 600 mg intravenous infusion at weeks 14, 18, and 22. Patients who were in deep remission at week 12 entered a washout phase until week 26. If these patients experienced a disease flare during this period (including the week 26 visit), defined as an increase in CDAI of ≥ 70 points compared to week 12, and a CDAI of ≥ 220 , patients underwent an ileocolonoscopy. If the CDEIS was ≤ 4 (or ≤ 2 for patients with initial isolated ileitis), patients were to continue washout until week 26; otherwise they were to restart Period 2 and receive open-label risankizumab 600 mg intravenous infusions every 4 weeks for 12 weeks. At the end of Period 2 (week 26), patients who were not in clinical remission stopped the study. Patients who were in clinical remission at week 26 could enter Period 3, and receive maintenance therapy with subcutaneous risankizumab 180 mg at weeks 26, 34, 42, and 50. The maintenance dosing regime was selected based on the pharmacokinetics and available formulation of risankizumab, and the clinical results observed in patients with plaque psoriasis that suggested an extended clinical effect and the expectation of higher clearance in patients with CD.²⁴

Outcomes

Efficacy outcomes during Period 2 included the proportions of patients in clinical remission (CDAI of < 150) or clinical response (CDAI of < 150 or a reduction from baseline of at least 100 points). Period 3 outcomes included clinical remission or response, endoscopic remission (CDEIS ≤ 4 or ≤ 2 for patients with baseline-isolated ileitis), endoscopic response ($> 50\%$ CDEIS reduction from baseline), mucosal healing (absence of mucosal ulceration), and deep remission (clinical remission plus endoscopic remission). In addition, serum C-reactive

protein (CRP), faecal calprotectin (FCP), and faecal lactoferrin (LF) concentrations were measured.

During Periods 2 and 3, the CDAI was assessed at every treatment visit as well as at the end of each period (weeks 26 and 52). CDEIS was assessed by a blinded and independent central reader at the end of Period 3 (week 52). CRP, FCP, and LF were assessed at weeks 18, 26, 34, 50, and 52. Plasma samples were collected at every study visit and were used to determine risankizumab concentrations and to assess the immunogenicity of risankizumab. Assay methodologies have been previously described.²¹

Safety endpoints consisted of adverse events, serious adverse events, tolerability, changes in vital signs and physical examination, discontinuation of therapy because of adverse events, laboratory assessments at all study visits, and 12-lead electrocardiogram at weeks 26 and 52.

Statistical methods

Endpoints for Periods 2 and 3 were summarised descriptively, unless specified. The efficacy analysis population for Period 2 included patients who received at least one dose of 600 mg intravenous risankizumab during Period 2 (P2-treated) and did not include patients who were in washout. For Period 3, the efficacy analysis population included all patients who received at least one dose of study drug during the open-label subcutaneous period (full analysis set; FAS-P3). Post-hoc, stepwise selection logistic regression analyses were used to explore the predictive potential of baseline factors (CDAI, duration of disease, abdominal pain, stool frequency, corticosteroids use, TNF antagonist use, and the presence of draining fistulas) for week 52 clinical or endoscopic remission or response. These post-hoc regression analyses were conducted using the FAS-P3 Period 1 treatment group assignment as one factor.

The full safety population included all randomised patients who received at least one dose of the study drug, and was further divided by study period. The incidence of treatment-emergent adverse events per 100 patient-years was estimated for exposure to 200 mg or 600 mg intravenous risankizumab during Period 1, 600 mg intravenous risankizumab during Period 2, 180 mg subcutaneous risankizumab during Period 3, and for all patients exposed to risankizumab (all-exposure safety population; Periods 1–3).

This trial is registered with ClinicalTrials.gov, number NCT02031276.

Role of the funding source

The study funder was involved in the study design, data collection, and data analysis. All authors had full access to all data in the study, agreed 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 baseline demographics and disease characteristics of patients, which have been reported previously,²¹ were similar across treatment groups; key parameters are reported in table 1. The mean (standard deviation) duration of Crohn's disease at study entry was 13 (9) years. Of the 121 patients randomised for Period 1, 115 received at least one dose of risankizumab (all-exposure safety population). A total of 107 patients continued to Period 2: 13 discontinued during Period 1²¹ and one patient declined to continue participation.

Among the 107 patients from the three original randomised groups entering Period 2, 101 (those not in deep remission) received treatment with 600 mg intravenous risankizumab (P2-treated): 33 from the Period 1 placebo group and 34 from each of the Period 1 risankizumab groups (figure 1). Six patients who were in deep remission at week 12 (five from the 600 mg risankizumab group and one from the 200 mg risankizumab group) entered the washout phase, did not meet flare criteria during Period 2, and did not receive treatment with risankizumab during Period 2.

The proportion of P2-treated patients with clinical response or remission increased steadily from week 12 to week 26 (figure 2A). In all three original randomisation groups, the proportion of patients with clinical remission at week 26 was greater than that observed at week 12, respectively (table 2): 18/33 (55%) versus 6/33 (18%) for the placebo group, 20/34 (59%) versus 7/34 (21%) for the 200 mg risankizumab group, and 16/34 (47%) versus 9/34 (26%) for the 600 mg risankizumab group (see appendix, p 4). Seven patients discontinued intravenous 600 mg risankizumab during Period 2 due to patient withdrawal (n=3),

worsening disease (n=1), and other reasons (lack of efficacy; n=3). Mean CDAI decreased from week 12 to week 26 (figure 2B)

Period 3 (FAS-P3) included 55 P2-treated patients who were in clinical remission at week 26, six patients who had been in deep remission at week 12 (all of whom were in clinical remission at week 26), plus one more patient included in a deviation from protocol despite not achieving clinical remission at the end of Period 2 (figure 1). Eight patients discontinued subcutaneous risankizumab during Period 3 due to: protocol violation (n=2, including the aforementioned patient), patient withdrawal (n=3), adverse events (n=2), and other (n=1). The remaining 54 patients completed 52 weeks of treatment.

During Period 3, the proportion of patients in clinical remission declined slightly by week 34, but was then stable to the end of the study (figure 2A). At week 52, the proportion of patients in clinical remission was 71% and the proportion with clinical response was 81% (table 2). Clinical remission and response rates were similar across the three original Period 1 randomization groups; however, rates of endoscopic remission/response and mucosal healing were highest in patients who had been treated with the 600 mg dose of risankizumab in Period 1 (table 2). Mean CDAI was stable through Period 3 (figure 2B)

At week 52, 18 patients in total were in deep remission. Five of the six patients who had been in deep remission at week 12 were also in deep remission at week 52. During Periods 2 and 3, four patients maintained clinical remission at all visits, another patient maintained remission despite a brief increase in CDAI to 154.5 during Period 2, while the other patient showed fluctuating CDAI and lost remission at the last visit (see appendix, p 5). All patients who were in deep remission at week 12 were characterised by a steep decrease in CDAI during Period 1 (see appendix, p 5).

C-reactive protein, FCP, and LF concentrations were all reduced in patients receiving risankizumab. Reductions from baseline were similar between Periods 1 and 2 and maintained throughout Period 2; during Period 3, which only included patients in clinical remission, concentrations of C-reactive protein, FCP, and LF were further reduced and maintained to week 52 (figure 3).

Logistic regression analysis of the FAS-P3 population with Period 1 treatment group assignment as one factor did not identify any baseline factors (CDAI, duration of disease, disease location [ileal/colonic], abdominal pain, stool frequency, corticosteroids use, TNF antagonist use, or the presence of draining fistulas) predictive of week 52 clinical remission

or response (data not shown). After the step 0 of the intercept entered, no additional effects met the 0.05 significance level for entry into the model.

Risankizumab mean trough concentrations in patients who received intravenous 600 mg risankizumab during Period 2 (35.5 µg/mL) were similar to those observed in patients who received intravenous 600 mg risankizumab during Period 1 (34.2 µg/mL). As expected, consistent with the reduction in dose to 180 mg SC every 8 weeks in patients who rolled over to Period 3, risankizumab concentrations decreased considerably (from week 34) and approximately attained near steady-state levels by week 42 (~4 µg/mL). Among patients with pharmacokinetic data at week 50, risankizumab median trough plasma concentrations were not distinctly different between patients in clinical remission (3.53 µg/mL; n=37) and those who continued to experience active disease (3.27 µg/mL; n=9). Also at week 50, median trough plasma concentrations were similar between subjects who were also receiving a stable dose of immunomodulators (azathioprine, 6-mercaptopurine or methotrexate; median 3.7 µg/mL, N=23) versus those who were not receiving any other immunomodulator (median 2.9 µg/mL, N=29). Of those patients who entered the washout phase during Period 2, their median trough plasma concentrations (3.5 µg/mL, N=6) at week 50 were similar to those who had received 600 mg risankizumab during Period 2 (3.3 µg/mL, N=46).

Treatment-emergent anti-drug antibodies (ADAs) were observed in 8% of patients who received at least one dose of risankizumab (nine out of 108 patients with evaluable samples at baseline and post-treatment initiation). The time to ADA positivity ranged between 12 and 18 weeks post start of treatment and most were transient with low titre values. None of the ADA-positive patients had neutralising antibodies and no association was detected between the presence of ADA and risankizumab plasma concentrations.

Safety results for the double-blind, randomised treatment period (Period 1) have been reported previously.²¹ The frequencies of treatment-emergent adverse events per 100 patient-years of exposure to risankizumab for the individual periods are shown in table 3. No new safety signals were identified in Periods 2 and 3 compared with Period 1. Treatment-emergent adverse events most frequently experienced during treatment with risankizumab were: arthralgia (22%), headache (20%), abdominal pain (18%), nasopharyngitis (16%), nausea (16%), and pyrexia (13%). Most treatment-emergent adverse events were mild or moderate in severity and were considered by the investigator to be unrelated to study treatment. Discontinuation of risankizumab due to a treatment-emergent adverse event

occurred in one patient (1%) during Period 2 (“condition aggravated”) and two patients (3%) during Period 3 (both for worsening of Crohn’s disease, one of which was recorded as a serious adverse event). Serious adverse events were experienced by 11 patients (11%) in Period 2 and seven patients (11%) in Period 3; those occurring in two or more patients in either period were worsening of Crohn’s disease (three patients), intestinal obstruction (four patients), all in Period 2.

Serious infections were reported in five patients (4%) during treatment with risankizumab; each serious infection (anal abscess, appendicitis, incision site abscess, osteomyelitis, and pneumonia) was observed in individual patients (see appendix, p 5). Hepatic disorder or drug-induced liver injury adverse events were reported in seven patients (6%) treated with risankizumab; all adverse events were grade 1 or 2, and none met the criteria for Hy’s Law. No systemic/anaphylactic reactions, neoplasia or clinically meaningful changes in vital signs were observed in patients treated with risankizumab in any study period, and there were no consistent trends observed in clinical laboratory evaluations.

Discussion

As previously reported, the week 12 Period 1 induction results of this phase 2 study showed that blockade of interleukin-23 p19 with risankizumab was superior to placebo in achieving clinical remission and clinical response in patients with moderate-to-severe, treatment-refractory, Crohn’s disease.²¹ All efficacy outcomes at week 12 favoured the 600 mg risankizumab dose, suggesting that the higher dose is superior to the lower dose as induction therapy.²¹

For patients not in deep remission at week 12, the results at week 26 indicate that treatment with open-label intravenous 600 mg risankizumab was effective in achieving greater clinical remission rates than those observed at week 12. Switching from placebo to 600 mg risankizumab resulted in the clinical remission rate rising from 18% to 55%, confirming the efficacy results from the initial blinded induction period. Dose escalation from 200 mg in Period 1 to 600 mg risankizumab in Period 2 more than doubled the percentage of patients in clinical remission (from 21% at week 12 to 59% at week 26, not including the one patient who had been in deep remission at week 12), which is supportive of the dose-dependent efficacy noted in Period 1 (albeit Period 2 treatment was open-label). Even among patients

originally randomised to 600 mg risankizumab, extended treatment duration at the same dose was associated with a numerical increase in clinical remission rates (from 26% to 47%, not including the five patients who had been in deep remission at week 12), suggesting that some patients might benefit from extended 600 mg induction treatment or from a shorter induction duration with a higher dose than 600 mg intravenous risankizumab. Bearing in mind that most patients in this study had failed one or more TNF antagonists, this finding is consistent with other biological agents that suggest patients with extensive previous treatment with TNF antagonists may take longer to achieve remission.^{1,22} All patients in deep remission at week 12 who entered the washout phase and received no treatment in Period 2 were still in clinical remission at week 26. Larger phase 3 trials are ongoing, which will allow the evaluation of predictors of clinical remission.

Period 3 results suggest that open-label subcutaneous risankizumab 180 mg was an effective therapy to maintain clinical remission up to week 52 in patients who were in clinical remission at week 26, including those who had achieved deep remission at week 12 and were in washout during Period 2. The rate of deep remission was greater at the end of Period 3 than it was at week 12, supporting the hypothesis that endoscopic remission commonly follows clinical remission with increasing duration of treatment. The lack of correlation between risankizumab plasma levels and remission status in Period 3 could be attributed to the between-subject variability in sensitivity for the drug effect and the fact that a single maintenance dose level was evaluated in the study. Therefore, at the steady-state exposures with 180 mg SC maintenance dose, some patients may not sustain the response because of lower sensitivity to the drug compared with patients that sustain the response, while both categories have comparable plasma exposures. It remains to be seen whether higher maintenance doses can maintain remission in a larger proportion of patients. The highest rates of CDEIS remission, CDEIS response, and mucosal healing at week 52 were observed in patients who were assigned to risankizumab 600 mg during Period 1, suggesting that higher initial drug exposure increases the endoscopic resolution of disease activity.

Overall, risankizumab was well tolerated with no new safety signals detected during extended intravenous dosing nor during the subcutaneous treatment period. Serious adverse events reported in two or more patients treated with risankizumab were primarily gastrointestinal in nature and may reflect underlying disease.

The study had some limitations. First, a relatively small number of patients was evaluated, preventing robust sub-group analysis of clinically relevant populations. In particular, the limited number of TNF α antagonist-naïve patients studied precludes any comment on the relative efficacy of risankizumab to those with prior TNF α antagonist exposure. Second, the endoscopic outcomes used in the study have not been fully validated. However, this is a general limitation of studies in this field and the definitions used are consistent with expert panel recommendations.^{25,26} Third, during Periods 2 and 3, patients received open-label dosing which may have increased the perceived efficacy of risankizumab therapy for subjective endpoints such as the CDAI. Specifically, the lack of a control arm during these periods prevents us from drawing strong conclusions regarding the efficacy of risankizumab as a maintenance agent. Finally, a plateauing of the dose–response was not demonstrated during Period 1, suggesting that a dose higher than 600 mg may result in increased efficacy. Furthermore, no subcutaneous dose ranging was performed during Period 3, therefore the optimal dose for the maintenance of clinical remission was not identified.

In conclusion, these results suggest that extended treatment with intravenous risankizumab 600 mg in patients with moderate-to-severe, treatment-refractory Crohn's disease, who were not in deep remission at week 12, is effective in increasing clinical response and remission rates at week 26. The results also suggest that open-label subcutaneous risankizumab 180 mg is effective in the maintenance of clinical remission at week 52.

Contributors

The initial draft was prepared by professional medical writers under the direction of BGF. 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. BGF, JP, AK, GD'H, WJS, SJP, SV, DBH, and WOB contributed to the study design. BGF, JP, MF, AK, GD'H, WJS, EL, MFN, DF, OD, US, K-JK, and CS contributed to data collection. All authors contributed to data analysis, data interpretation, and writing and review of the manuscript.

Declaration of interests

BGF reports personal fees from Ablynx, ActoGeniX, Akros, Albireo Pharma, Allergan, Avaxia Biologics Inc, Avir Pharma, Atlantic Pharma, Baxter Healthcare Corporation, Biogen

Idec, Boehringer Ingelheim, Calypso Biotech, Celgene, Elan/Biogen, enGene, Ferring, Galapagos, Genentech/Roche, GiCare Pharma, Gilead, Given Imaging, GlaxoSmithKline, Inception IBD Inc., Ironwood, Japan Tobacco Company, Kyowa Hakko Kirin Co Ltd, Lexicon, Lilly, Lycera Biotech, Merck, Mesoblast Pharma, Millennium, Nestles, Novo Nordisk, Novartis, NextBiotix, Progenity, Prometheus Therapeutics & Diagnostics, Protagonist, Salix, Shire, Sigmoid Pharma, Synergy Pharma, Teva Pharma, TiGenix, Tillotts, UCB, Vertex, VHSquared, Vivelix Pharma, Wyeth, Zealand, and Zyngenia; grants from Sanofi; grants and personal fees from AbbVie, Amgen, Astra Zeneca, Bristol-Myers Squibb (BMS), Janssen Biotech/Centocor, Johnson and Johnson/Janssen, Pfizer, Receptos, and Takeda, outside the submitted work; and is a Senior Scientific Director for Robarts Clinical Trials Inc, Western University, London, Ontario, Canada.

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GD'H reports being an advisor for AbbVie, Ablynx, Amakem, Amgen, AM Pharma, Avaxia, Biogen, Bristol-Myers Squibb, Boehringer Ingelheim, Celgene/Receptos, Celltrion, Cosmo, Covidien/Medtronic, Ferring, Dr FALK Pharma, Eli Lilly, EnGene, Galapagos, Genentech/Roche, Gilead, GlaxoSmithKline, Immunic, Johnson and Johnson, Lycera, Medimetrics, Millennium/Takeda, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Nextbiotics, Novo Nordisk, Otsuka, Pfizer/Hospira, Prometheus laboratories/Nestle, Protagonist, Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, SetPoint, Shire, Teva, TiGenix, Tillotts, Topivert, Versant, and Vifor; and receiving speaker fees from AbbVie, Biogen, Ferring, Johnson and Johnson, Merck Sharp Dome, Mundipharma, Norgine, Pfizer, Samsung Bioepis, Shire, Millennium/Takeda, Tillotts, and Vifor; and is a Scientific Advisor for Robarts Clinical Trials Inc, Western University, London, Ontario, Canada.

WJS reports consulting fees from AbbVie, Akros Pharma, Allergan, Ambrx Inc., Amgen, Ardelyx, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Avaxia, Biogen, Boehringer Ingelheim, Bristol Meyers Squibb, Celgene, Conatus, Cosmo Technologies, Escalier Biosciences, Ferring, Ferring Research Institute, Forward Pharma, Galapagos, Genentech, Gilead Sciences, Immune Pharmaceuticals, Index Pharmaceuticals, Janssen, Kyowa Hakko Kirin Pharma, Lilly, Medimmune, Mesoblast, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Palatin, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Qu Biologics, Regeneron, Ritter Pharmaceuticals, Robarts Clinical Trials (owned by University of Western Ontario), Salix, Seattle Genetics, Seres Therapeutics, Shire, Sigmoid Biotechnologies, Takeda, Theradiag, Theravance, TiGenix, Tillotts Pharma, UCB Pharma, Vascular Biogenics, Vivelix; research grants from Atlantic Healthcare Limited, Amgen, Genentech, Gilead Sciences, AbbVie, Janssen, Takeda, Lilly, Celgene/Receptos; payments for lectures/speakers bureau from AbbVie, Janssen, Takeda; and holds stock/stock options in Escalier Biosciences, Oppilan Pharma, Precision IBD, Progenity, Ritter Pharmaceuticals; and is a Scientific Advisor for Robarts Clinical Trials Inc, Western University, London, Ontario, Canada.

EL reports research grants from Takeda and Pfizer; educational grants from AbbVie, MSD, and Takeda; speaker fees from Abbott, AbbVie, AstraZeneca, Ferring, MSD, Chiesi, Dr FALK Pharma, Takeda, Hospira, Janssen, Pfizer; and has provided consultancy to Abbott, AbbVie, Ferring, MSD, Mitsubishi Pharma, Takeda, Celltrion, Celgene, Hospira, and Janssen.

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CS reports receiving research grants from AbbVie, Takeda, and Warner Chilcott; has provided consultancy to AbbVie, Dr FALK Pharma, Janssen, Takeda, and Warner Chilcott; and receiving speaker fees from AbbVie, Dr FALK Pharma, Merck Sharp Dome, Takeda, and Warner Chilcott.

SJP, IH, AS, SV, DBH, and WOB report being employed by Boehringer Ingelheim. AMR, JZ, MM report being employed by AbbVie Inc; AAO and KW report being employed by

AbbVie Inc, and a shareholder of AbbVie Inc. In addition SJP, SV, and WOB also report a patent BI case 09-0645-US-4 pending. No other conflict of interest relevant to this article was reported.

DF, OD, and K-JK have nothing to disclose.

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Table 1: Summary baseline demographics and disease characteristics of patients who entered study Period 2 (grouped by originally randomised induction treatment)

	Placebo (n=33)	Risankizumab		All (N=107)
		200 mg (n=35)	600 mg (n=39)	
Age (years), mean \pm SD	36 \pm 14	39 \pm 13	40 \pm 13	39 \pm 13
Male sex, n (%)	14 (42)	15 (43)	16 (41)	45 (42)
Duration of disease (years), mean \pm SD	12 \pm 10	15 \pm 9	14 \pm 10	14 \pm 10
CDAI, median (IQR)	287 (246–365)	311 (258–374)	298 (246–330)	297 (246–358)
CDEIS, median (IQR)	11 (8–18)	12 (9–16)	12 (8–16)	12 (9–17)
CRP (mg/L), median (IQR)	10 (3–24)	10 (4–29)	8 (2–29)	10 (3–29)
Disease site, n (%)				
Ileum only	3 (9)	4 (11)	6 (15)	13 (12)
Ileum and colon	19 (58)	24 (69)	19 (49)	62 (58)
Colon only	11 (33)	7 (20)	14 (36)	32 (30)
Prior TNF antagonist use, n (%)				
1	9 (27)	8 (23)	9 (23)	26 (24)
2	16 (48)	18 (51)	22 (56)	56 (52)
≥ 3	6 (18)	7 (20)	5 (13)	18 (17)

CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; CRP, C-reactive protein; IQR, interquartile range; SD, standard deviation; TNF, tumour necrosis factor.

Table 2: Clinical (weeks 26 and 52) and endoscopic (week 52) endpoints for patients receiving treatment with open-label 600 mg IV risankizumab and open-label 180 mg SC risankizumab by original Period 1 treatment group and total

Week 26: Period 2 post open-label 600 mg IV risankizumab treatment*				
Original treatment allocation in Period 1, n (%)	Placebo (n=33)	Risankizumab		Total (N=101)
		200 mg (n=34)	600 mg (n=34)	
Clinical remission	18 (55)	20 (59)	16 (47)	54 (53)
Clinical response	24 (73)	26 (76)	24 (71)	74 (73)
Week 52: Period 3 post open-label 180 mg SC risankizumab treatment				
Original treatment allocation in Period 1, n (%)	Placebo (n=19 [†])	Risankizumab		Total (N=62)
		200 mg (n=22 [‡])	600 mg (n=21 [§])	
Clinical remission	15 (79)	13 (59)	16 (76)	44 (71)
Clinical response	16 (84)	17 (77)	17 (81)	50 (81)
Endoscopic remission	6 (32)	5 (23)	11 (52)	22 (35)
Endoscopic response	10 (53)	9 (41)	15 (71)	34 (55)
Deep remission	6 (32)	3 (14)	9 (43)	18 (29)
Mucosal healing	4 (21)	4 (18)	7 (33)	15 (24)

*Endoscopies were not conducted at week 26, thus only clinical endpoints are reported at this time point. [†]A protocol deviation resulted in one patient who was not in clinical remission at week 12 receiving a single SC treatment at the beginning of Period 3. [‡]Includes one patient who had been in washout during Period 2 after achieving deep remission at week 12, and one patient who had two CDAI measures at week 26: the value used for the efficacy calculation (CDAI of 166) differed from the value used to determine eligibility for entry into Period 3 (CDAI of 110). [§]Includes five patients who had been in washout during Period 2 after achieving deep remission at week 12.

Clinical endpoints at week 26 for patients (those not in deep remission at week 12) entering Period 2 treatment with 600 mg open-label IV risankizumab, and clinical and endoscopic endpoints at week 52 for patients in clinical remission entering Period 3 treatment with 180 mg open-label SC risankizumab are reported by original treatment randomisation. P2-treated and FAS-P3 were used for these analyses, using NRI for missing values. Clinical response is defined as a CDAI of <150 points or a CDAI reduction from baseline of ≥ 100 points. Clinical

remission is defined as a CDAI of <150 . Endoscopic response is defined as a $>50\%$ reduction in CDEIS from baseline to week 52. Endoscopic remission is a CDEIS of ≤ 4 at week 52 (for patients with baseline-isolated ileitis, CDEIS of ≤ 2). Deep remission is defined as clinical remission and endoscopic remission at week 52.

CDAI=Crohn's Disease Activity Index; CDEIS=Crohn's Disease Endoscopic Index of Severity; FAS=full analysis set; FAS-P3=FAS Period 3; IV=intravenous; NRI=non-response imputation; SC=subcutaneous.

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Table 3: Overview of treatment-emergent adverse events with risankizumab treatment per 100 PYs by treatment period, and all-exposure risankizumab safety population (Periods 1–3)

Events (events/100 PY)	Period 2 600 mg IV (P2-treated) N=101, PYs=28·8	Period 3 180 mg SC (FAS-P3) N=62, PYs=43·3	All-exposure risankizuma b safety population* N=115, PYs=109·1
Any adverse event	267 (927·1)	165 (381·1)	719 (659·0)
Severe	19 (66·0)	6 (13·9)	36 (33·0)
Possibly drug related [†]	28 (97·2)	23 (53·1)	81 (74·2)
Leading to discontinuation of drug	1 (3·5)	2 (4·6)	10 (9·2)
Leading to death	0	0	0
Serious adverse event	18 (62·5)	9 (20·8)	46 (42·2)
Infections	37 (128·5)	32 (73·9)	107 (98·1)
Serious	1 (3·5)	1 (2·3)	5 (4·6)
Opportunistic	0	0	3 (2·7)
Tuberculosis	0	0	1 (0·9)
Fungal	3 (10·4)	0	8 (7·3)
Malignancies	0	0	0
Infusion-related reaction	3 (10·4)	NA	4 (3·7)
Drug-induced liver injury or hepatic disorder [‡]	5 (17·4)	6 (13·9)	13 (11·9)
Cardiac arrhythmias	1 (3·5)	0	1 (0·9)
Systemic hypersensitivity/anaphylactic reactions	20 (69·4)	12 (27·7)	49 (44·9)
Depression, suicidal ideation, and behaviour	1 (3·5)	2 (4·6)	5 (4·6)

Treatment-emergent adverse events are defined as events that begin or worsen either on or after the first dose of the study drug, and within 105 days after the last dose of the study drug.

*Includes all patients who received at least one dose of risankizumab during Periods 1–3.

[†]Assessed by study investigator. [‡]All adverse events were grade 1 or 2, and none met the criteria for Hy's Law.

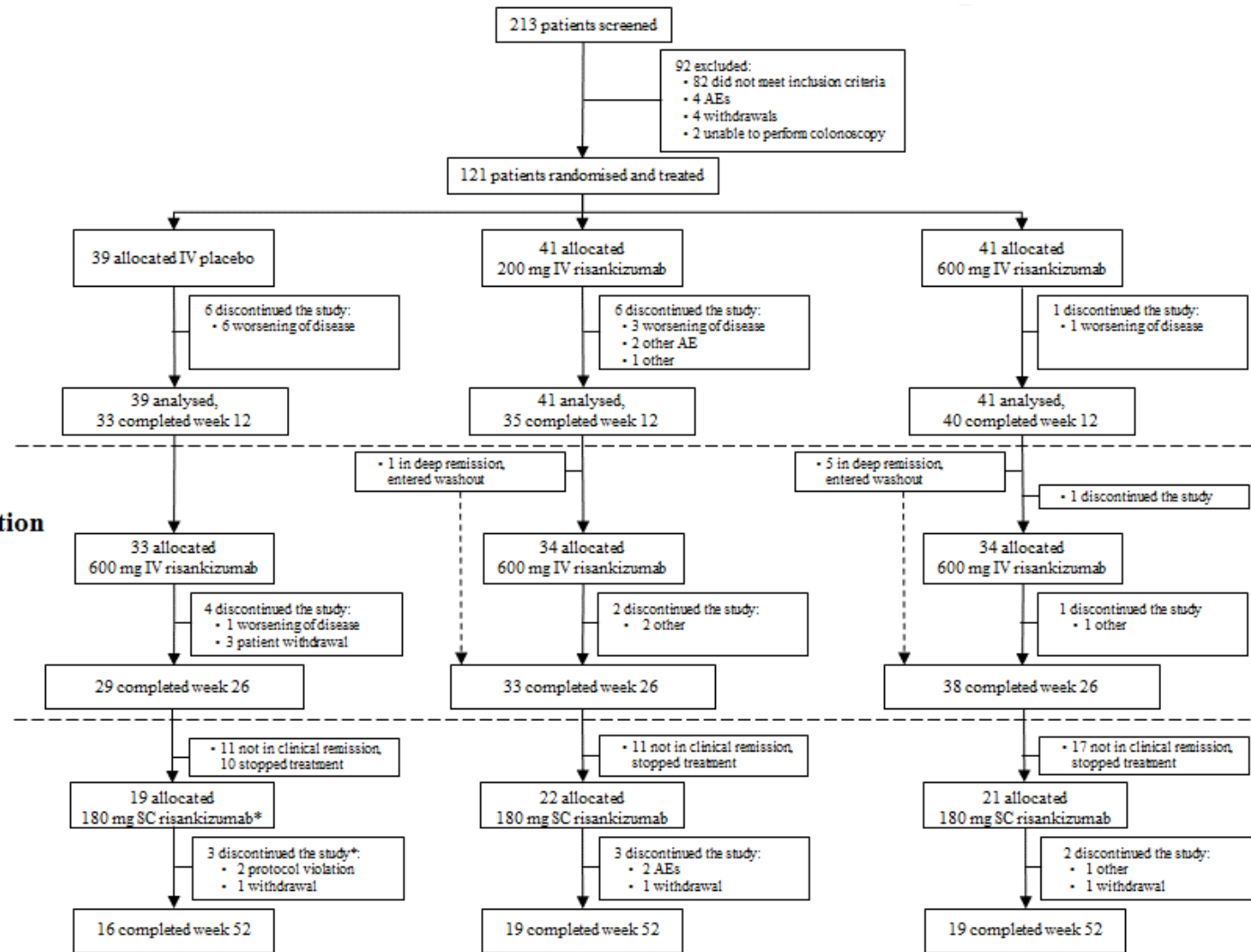
FAS=full analysis set; IV=intravenous; PY=patient-years; SC=subcutaneous.

Figure 1: Patient disposition

**Period 1:
Induction**

**Period 2:
Extended induction
or washout**

**Period 3:
Maintenance**



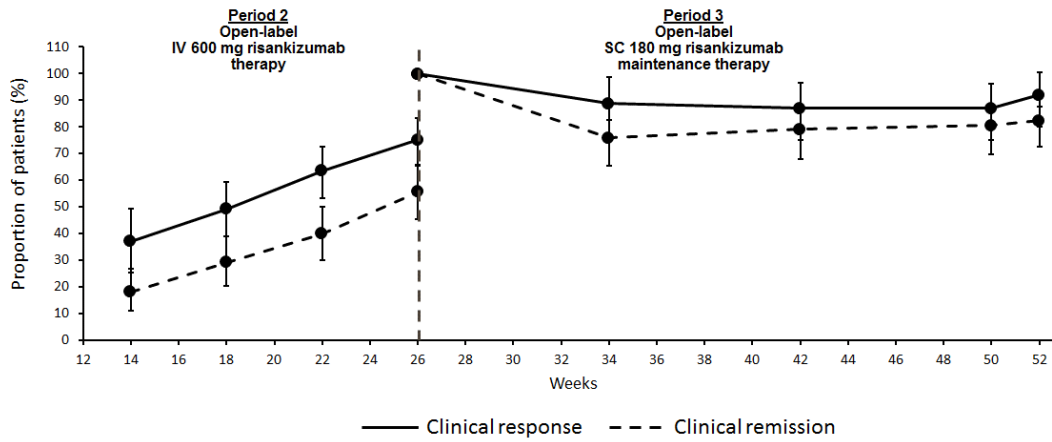
*One patient received open-label SC risankizumab in Period 3 despite not achieving clinical remission at the end of Period 2 (protocol violation); the patient discontinued risankizumab and is counted among the eight patients discontinuing treatment during Period 3. One additional subject had two CDAI values within the visit window for week 26; the value used for the efficacy calculation (CDAI of 166) differed from the value used to determine eligibility for entry into Period 3 (CDAI of 110).

AE=adverse event; IV=intravenous; SC=subcutaneous

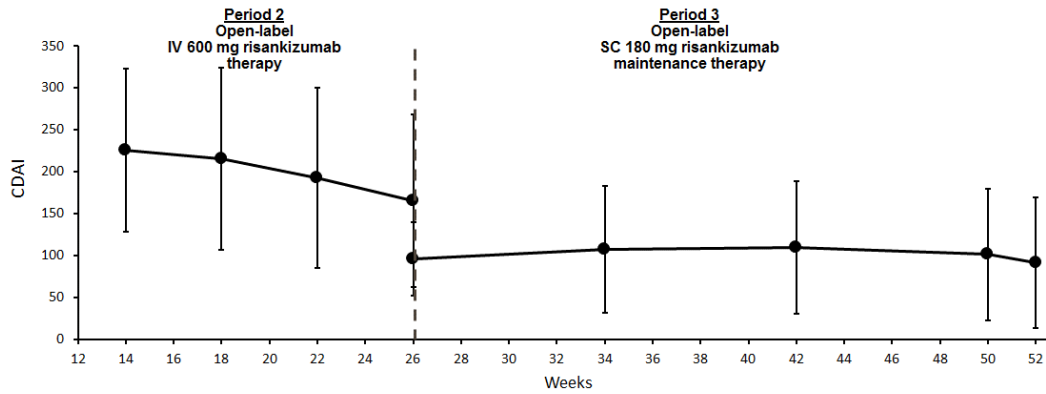
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Figure 2: Time course of clinical response, remission, and CDAI over time through Periods 2 (n=101)* and 3 (n=62)

A)



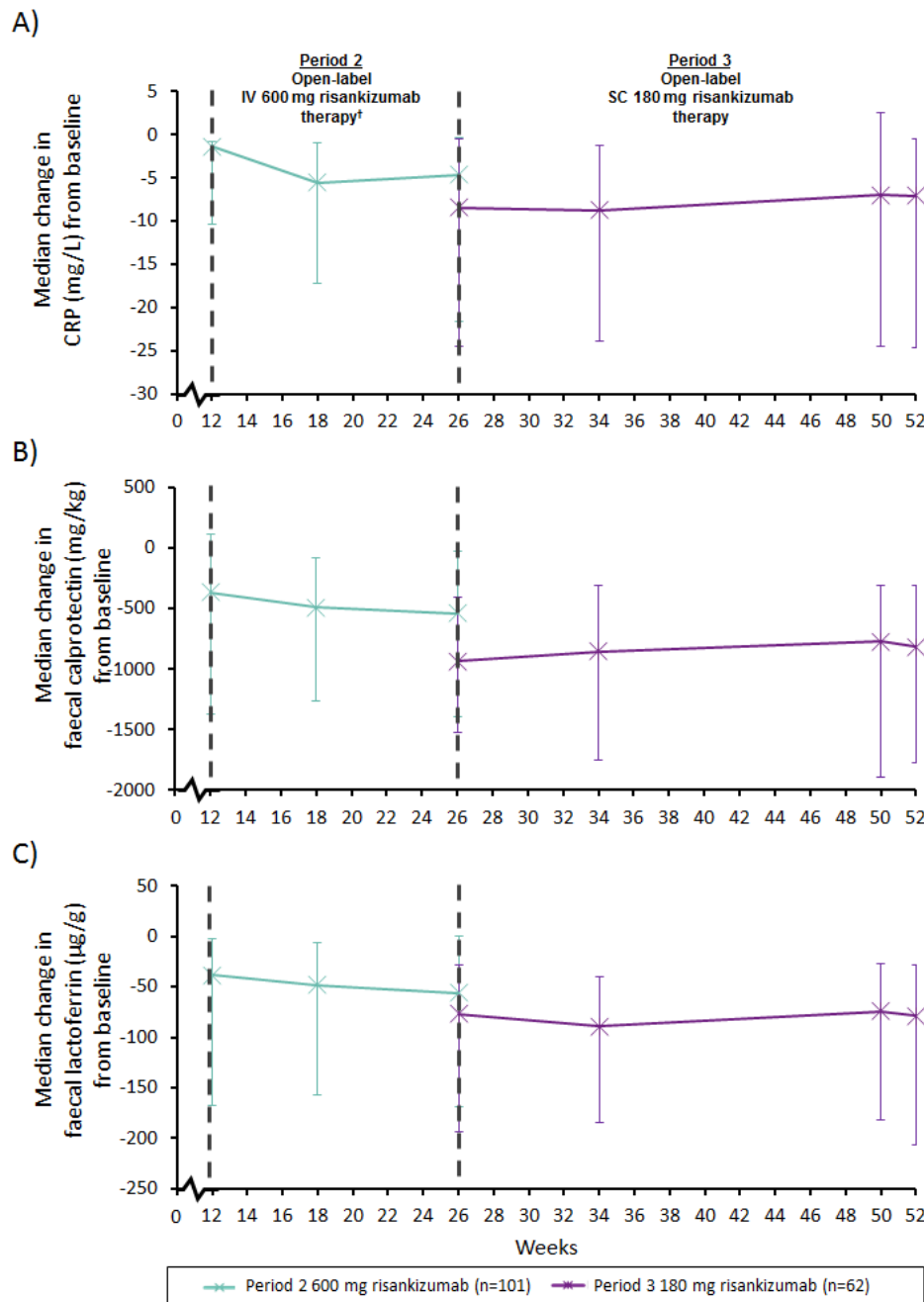
B)



*For Period 2, data shown do not include patients who were in deep remission at week 12 and who entered the washout period (N=6). FAS was used for this analysis, using LOCF for missing values and stratified Cochran–Mantel–Haenszel tests. For clinical response and remission percentage of patients $\pm 95\%$ CI are shown; for CDAI, mean \pm SD are shown.

CDAI=Crohn's Disease Activity Index; CI=confidence interval; FAS=full analysis set; IV=intravenous; LOCF=last observation carried forward; SC=subcutaneous; SD=standard deviation.

Figure 3: Median change in CRP, FCP, and LF over time through Periods 2 (n=101)* and 3 (n=62)



†For Period 2, data shown do not include patients who were in deep remission at week 12 and who entered the washout period (N=6). FAS was used for this analysis, using LOCF for missing values and stratified Cochran–Mantel–Haenszel tests. Median change from Period 1 baseline values and interquartile range are reported. FAS=full analysis set; hs-CRP=high sensitivity C-reactive protein; IV=intravenous; LOCF= last observation carried forward; SC=subcutaneous.

Appendix

Title: Open-label extension of a phase 2 trial of risankizumab in patients with moderate-to-severe Crohn's disease Corresponding author: Brian G. Feagan

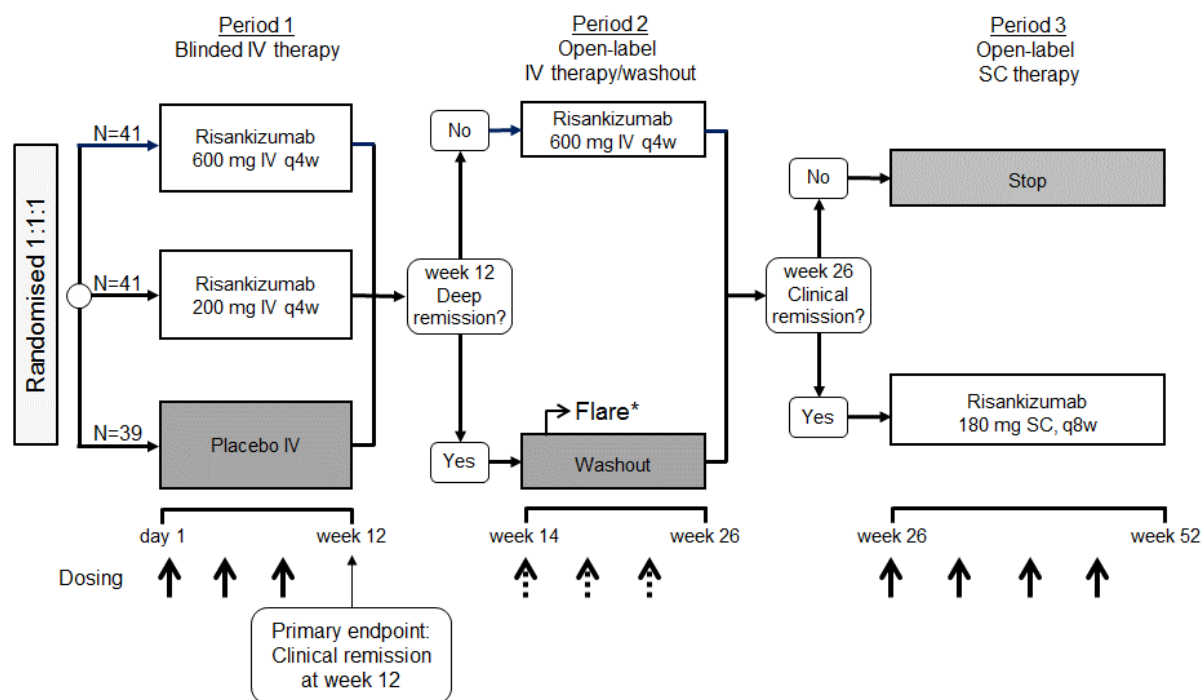
Table of contents	Page
Principal investigators and participating study sites	2
Figure S1: Study design	3
Figure S2: Clinical remission at week 26 by induction treatment outcome at week 12	4
Figure S3: CDAI over time (to week 52) in patients with deep remission at week 12	5
Table S1: Description of serious infections	6

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Principal investigators and participating study sites

Investigator	Study Site	Patients recruited
Prof. Dr Edouard Louis	University Hospital CHU of Liège, Liège, Belgium	9
Prof. Dr Julián Panés	Hospital Clínic de Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain	9
Prof. Dr Marc Ferrante	UZ Leuven, Leuven, Belgium	9
Prof. Dr Denis Franchimont	Hôpital Universitaire Erasme, Brussels, Belgium	7
Prof. Dr Arthur Kaser	University of Cambridge, Addenbrooke's Hospital, Cambridge, UK	6
Prof. Dr Geert D'Haens	Academic Medical Center, Amsterdam, Netherlands	6
Prof. Olivier Dewit	Cliniques Universitaires Saint-Luc, Brussels, Belgium	6
Prof. Dr Ursula Seidler	Medizinische Hochschule Hannover, Hannover, Germany	6
Prof. Dr Byung Ik Jang	Yeungnam University Medical Center, Daegu, South Korea	4
Dr Ronald Fogel	Clinical Research Institute of Michigan, Chesterfield, MI, USA	4
Dr Philip Ginsburg	Medical Research Center of Connecticut, Hamden, CT, USA	4
Dr Robert Petryka	ViVamed, Warsaw, Poland	4
Dr Filip Baert	AZ Delta, Roeselare, Belgium	3
Dr Peter Bossuyt	Imelda vzw, Bonheiden, Belgium	3
Dr Young-Ho Kim	Samsung Medical Center, Seoul, South Korea	3
Dr Satish Keshav	Oxford University Hospitals NHS Foundation Trust, Oxford, UK	3
Prof. Dr Kyung-Jo Kim	Asan Medical Center, Seoul, South Korea	3
Dr John Mansfield	Newcastle upon Tyne Hospitals NHS Foundation Trust, Newcastle, UK	3
Prof. Dr Dong Il Park	Kangbuk Samsung Hospital, Seoul, South Korea	3
Dr Christian Selinger	Leeds Teaching Hospitals NHS Trust, Leeds, UK	3
Prof. Dr Gerd Bouma	VU University Medical Center, Amsterdam, Netherlands	2
Dr Jae Hee Cheon	Severance Hospital, Seoul, South Korea	2
Dr Javier Pérez Gisbert	Hospital Universitario de La Princesa, Madrid, Spain	2
Dr Jordi Guardiola	Hospital Universitario de Bellvitge, Barcelona, Spain	2
Prof. Dr med. Markus F. Neurath	Universitätsklinikum Erlangen, Erlangen, Germany	2
Prof. Dr Marieke Pierik	Maastricht Universitair Medisch Centrum, Maastricht, the Netherlands	2
Dr William J. Sandborn	UC San Diego Medical Center, San Diego, CA, USA	2
Dr Brian G. Feagan	London Health Sciences Centre, London, ON, Canada	1
Dr Robert Hardi	MGG Group Co./Chevy Chase Clinical Research, Chevy Chase, MD, USA	1
Dr Peter Hasselblatt	Universitätsklinikum Freiburg, Freiburg, Germany	1
Dr Ammar Hmaidan	Advanced Medical Research Center, Port Orange, FL, USA	1
Dr Robert Herring	Quality Medical Research, Nashville, TN, USA	1
Dr Peter Irving	Guy's and St Thomas' Hospitals NHS Foundation Trust, London, UK	1
Dr John K Marshall	McMaster University Medical Centre, Hamilton, ON, Canada	1
Dr Jerzy Rozciecha	LexMedica, Wroclaw, Poland	1
Dr Wouter Van Moerkercke	AZ Groeninge, Kortrijk, Belgium	1

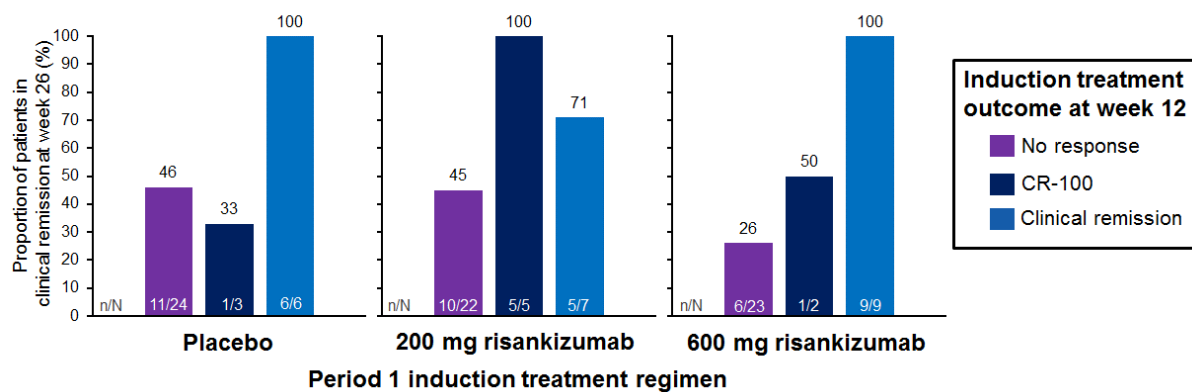
Figure S1: Study design



*If CDEIS >4 (CDEIS >2 for patients with baseline-isolated ileitis), patients to receive open-label IV therapy (600 mg risankizumab \times 3 q4w, dotted arrows).

IV=intravenous; q4w=every 4 weeks; q8w=every 8 weeks; SC=subcutaneous

Figure S2: Clinical remission at week 26 by induction treatment outcome at week 12*



*Only patients receiving treatment during Period 2 (P2-treated: n=101) were used for this analysis; the six patients with deep remission at week 12 were not included. The analysis used non-response imputation for missing values.

CR-100 is defined as a decrease in CDAI of ≥ 100 points compared with baseline in patients not in clinical remission.

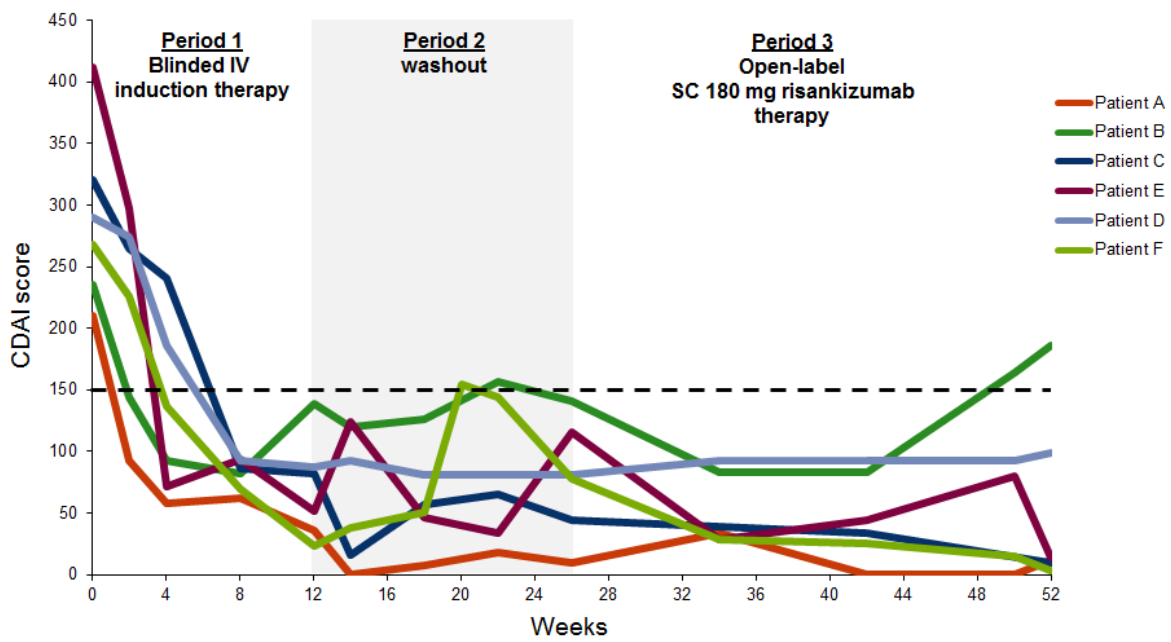
Figure S3: CDAI over time (to week 52) in patients with deep remission at week 1

Table S1: Description of serious infections

Serious infection	Description
Anal abscess	Age: 31 years, Sex: Male, Race: Asian, Weight: 61.2 kg Treatment in Period 1: risankizumab 600 mg IV Onset: Day 62, Lasting: 3 days Toxicity grade: Grade 1 Relationship to study drug: No reasonable possibility Actions taken with study treatment: Dose not changed Outcome: Recovered/Resolved Concomitant or additional treatment given: Yes
Appendicitis	Age: 26 years, Sex: Male, Race: White, Weight: 76.2 kg Treatment in Period 1: Placebo Onset: Day 235; Lasting: 2 days Toxicity grade: Grade 2 Relationship to study drug: No reasonable possibility Actions taken with study treatment: Dose not changed Outcome: Recovered/Resolved Concomitant or additional treatment given: Yes
abscess surgical site infection	Age: 34 years, Sex: Female, Race: White, Weight: 80.0 kg Treatment in Period 1: risankizumab 200 mg IV Onset: Day 157; Lasting: 18 days Toxicity grade: Grade 2 Relationship to study drug: Reasonable possibility Actions taken with study treatment: Dose not changed Outcome: Recovered/Resolved Concomitant or additional treatment given: Yes
Osteomyelitis	Age: 64 years, Sex: Female, Race: White, Weight: 59.1 kg Treatment in Period 1: risankizumab 600 mg IV Onset: Day 45; Lasting: 36 days Toxicity grade: Grade 3 Relationship to study drug: Reasonable possibility Actions taken with study treatment: Dose not changed Outcome: Recovered/Resolved Concomitant or additional treatment given: Yes
Pneumonia	Age: 23 years, Sex: Male, Race: Asian, Weight: 63.3 kg Treatment in Period 1: risankizumab 200 mg IV Onset: Day 51; Lasting: 8 days Toxicity grade: Grade 3 Relationship to study drug: No reasonable possibility Actions taken with study treatment: Dose not changed Outcome: Recovered/Resolved Concomitant or additional treatment given: Yes