

Long-Term Safety and Efficacy of Risankizumab Treatment in Patients with Crohn's Disease: Results from the Phase 2 Open-Label Extension Study

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Abstract

Background and Aims: Risankizumab, an interleukin-23 antibody, demonstrated efficacy and acceptable safety in a phase 2 study of patients with moderate-to-severe refractory Crohn's disease. This open-label extension investigated the long-term safety, pharmacokinetics, immunogenicity, and efficacy of risankizumab in responders to risankizumab in the parent phase 2 study.

Methods: Enrolled patients had achieved clinical response (decrease in Crohn's Disease Activity Index from baseline ≥ 100) without clinical remission (Crohn's Disease Activity Index < 150) at Week 26, or clinical response and/or remission at Week 52 in the parent phase 2 study and received open-label subcutaneous risankizumab 180 mg every 8 weeks.

Results: Sixty-five patients were enrolled, including 4 patients who had lost response in the parent study and were first reinduced with risankizumab 600 mg every 4 weeks (three infusions). Patients received risankizumab for a median of 33 months (total: 167.0 patient-years). The rate of serious adverse events was 24.6 events/100 patient-years; the majority were gastrointestinal in nature. Rates of serious infections, opportunistic infections, and fungal infections were 4.2, 1.8, and 6.6 events/100 patient-years, respectively. No deaths, malignancies, adjudicated major adverse cardiovascular events, latent/active tuberculosis, or herpes zoster were reported. Treatment-emergent anti-drug antibodies developed in 8 patients (12.3%); none were neutralising. Efficacy outcomes were maintained during the study,

including the proportions of patients (observed analysis) with clinical remission (>71%) and endoscopic remission (>42%).

Conclusions: Long-term maintenance treatment with subcutaneous risankizumab 180 mg every 8 weeks was well tolerated by patients with Crohn's disease, with no new safety signals.

Clinical trial registration number: NCT02513459

Key Words: Crohn's disease; long-term safety; open-label extension

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1. Introduction

Crohn's disease (CD) is an inflammatory bowel disease characterised by chronic relapsing inflammation in the gastrointestinal tract. Signs and symptoms of CD include abdominal pain, chronic diarrhoea, fever, weight loss, and fistula drainage, which represent a considerable systemic burden for patients.^{1,2} The reported worldwide incidence (0.0–29.3 per 100 000 person-years) and prevalence (0.9–322.0 per 100 000 persons) of CD vary greatly across geographical regions, with a prevalence of >0.3% in North America, Oceania, and many countries in Europe.³ While the incidence in newly industrialised countries in Africa, Asia, and South America is typically lower than in westernised countries, the incidence of CD is also rising in these countries.^{3,4}

Current treatments for CD include corticosteroids, thiopurines, methotrexate, tumour necrosis factor (TNF) antagonists, the integrin antagonist vedolizumab, and the interleukin (IL)-12/23 inhibitor ustekinumab.^{2,5} The European Crohn's and Colitis Organisation and the American College of Gastroenterology recommend using corticosteroids, TNF antagonists (adalimumab, infliximab, and certolizumab pegol), vedolizumab, and ustekinumab to induce remission in patients with moderate-to-severe CD; and thiopurines, methotrexate, TNF antagonists, vedolizumab, and ustekinumab for the maintenance of remission.^{2,5} However, approximately a third of patients do not respond to TNF antagonists or lose their response to TNF antagonists over time.¹

Risankizumab is a fully human immunoglobulin G monoclonal antibody that binds with high affinity to the p19 subunit of IL-23, which has been approved for the treatment of moderate-to-severe plaque psoriasis.^{6,7} Results from the phase 2 M15-993 study showed that risankizumab was effective and well tolerated through 52 weeks in patients with moderate-to-severe CD, the majority of whom had failed prior therapy with one or more TNF

antagonists.^{8,9} In the blinded induction period, a greater proportion of patients achieved clinical and endoscopic remission after 12 weeks of treatment with risankizumab 600 mg intravenous (IV) every 4 weeks (Q4W) compared with placebo. Risankizumab 600 mg IV treatment in the open-label reinduction period increased remission rates at Week 26, and remission was effectively maintained with risankizumab 180 mg subcutaneous (SC) through Week 52. Over 52 weeks, treatment-emergent anti-drug antibodies (ADAs) were observed in 8% of patients who received at least one dose of risankizumab; none were neutralising.⁹ Pooled phase 1 and 2 population pharmacokinetics data from patients with psoriasis or CD demonstrated that body weight had a modest effect on risankizumab exposure, while baseline serum albumin levels were statistically correlated with risankizumab clearance but had no clinically meaningful impact on serum concentrations of risankizumab.¹⁰

Patients who responded to risankizumab in the phase 2 study were eligible to enrol in the open-label extension (OLE) M15-989 study reported here. The objective of this OLE was to investigate the long-term safety, pharmacokinetics, immunogenicity, efficacy, and health-related quality of life (HRQoL) of risankizumab, in patients with moderate-to-severe active CD who achieved a clinical response or remission on previous treatment with risankizumab.

2. Methods

2.1. Study design and patients

Patients who successfully completed the phase 2 M15-993 study (NCT02031276) were eligible to enrol in this single-group OLE (M15-989; NCT02513459; US Clinical Trials Registry). Patients were included from 38 referral sites across Europe, Asia, and North America. All patients received maintenance therapy with open-label risankizumab 180 mg SC every 8 weeks (Q8W) up to 196 weeks (Figure 1). Successful completion of M15-993 was defined as achievement of clinical response (decrease in Crohn's Disease Activity Index

[CDAI] from baseline with ≥ 100 points) without clinical remission (CDAI < 150) at Week 26 or achievement of clinical response and/or remission at Week 52.⁹ Patients who had lost clinical remission at the end of the trial visit for the M15-993 study, or at screening for the M15-989 OLE, received open-label reinduction of risankizumab with three infusions of 600 mg IV Q4W, after which eligibility was reassessed. If clinical response or remission was achieved, patients were switched to maintenance treatment of risankizumab 180 mg SC Q8W from visit 5 for the remainder of the OLE. Patients who completed the M15-989 study could elect to enrol in the M16-000 sub-study 3, an ongoing phase 3 OLE (NCT03105102), in which they continue to receive open-label risankizumab 180 mg SC Q8W and are eligible to receive risankizumab rescue therapy. The M15-989 study was terminated by the sponsor to provide the option for patients to roll over for continuous open-label treatment within the ongoing phase 3 OLE.

Inclusion and exclusion criteria in the parent M15-993 study have been previously described.⁸ In brief, patients were adults (aged 18–75 years) with moderate-to-severe CD, defined as CDAI 220–450 and Crohn's Disease Endoscopic Index of Severity (CDEIS) ≥ 7 (or ≥ 4 for patients with isolated ileitis) with mucosal ulcers in the ileum and/or colon. Patients could have been biologic-naïve or previously treated with ≥ 1 TNF antagonists or vedolizumab, while patients who had received ustekinumab were ineligible for enrolment.

During the OLE, patients were permitted to continue oral corticosteroids (prednisone equivalent dose of ≤ 20 mg/day), oral 5-aminosalicylates, and immunosuppressive agents (azathioprine, 6-mercaptopurine, or methotrexate) if they had been on a stable dose for ≥ 4 weeks prior to visit 2. Patients who entered the OLE on concomitant treatments were required to continue on the stable dose throughout the OLE. Initiation of systemic antihistamines and

IV steroids was permitted in the case of infusion reactions during or after risankizumab infusion in accordance with the severity of the reaction and the local standard of care.

The M15-989 OLE was conducted in accordance with the International Conference on Harmonization guidelines, applicable regulations, and the Declaration of Helsinki. Study-related documents were approved by institutional ethics committees and review boards. All patients provided written, informed consent. An independent data monitoring committee was utilised to ensure that the welfare of patients participating in this study was maintained.

2.2. Outcomes

The primary objective was to assess long-term safety in patients with CD receiving maintenance risankizumab 180 mg SC Q8W. Adverse events (AEs), vital signs, and laboratory assessments were collected throughout the study and up to 20 weeks after the last dose of risankizumab for patients who prematurely discontinued the study. AEs were coded using the Medical Dictionary for Regulatory Activities version 21.1, and severity was graded based on the Rheumatology Common Toxicity Criteria version 4.0. Major cardiac, cerebrovascular, and thrombotic events were adjudicated by an independent cardiovascular adjudication committee.

Treatment-emergent AEs (TEAEs) were defined as events occurring or worsening either on or after the first dose of risankizumab in the M15-989 study; within 20 weeks after the last dose of risankizumab for patients who prematurely terminated the study drug in the M15-989 study; and before the first dose of risankizumab in the phase 3 OLE. Duration of risankizumab exposure was defined as the date of last risankizumab dose minus the date of first risankizumab dose in the M15-989 OLE plus 8 weeks. AEs are presented as the number

of patients (%) experiencing any event, the absolute number of events, and events per 100 patient-years (E/100 PY).

Secondary objectives included the assessment of pharmacokinetics, immunogenicity, efficacy, and HRQoL. Plasma samples were collected at scheduled visits, and were analysed at a later date using an enzyme-linked immunosorbent assay to measure risankizumab plasma concentration and an electrochemiluminescence assay with a three-tiered approach for the detection of ADAs.⁸ Due to sparse sampling, only trough plasma concentrations at the time relative to the first SC dose were summarised. Key efficacy outcomes included clinical remission (CDAI <150) and endoscopic remission (CDEIS ≤ 4 , or ≤ 2 for patients with isolated ileitis); HRQoL outcomes included Inflammatory Bowel Disease Questionnaire (IBDQ) response (increase from baseline in IBDQ total score ≥ 16) and remission (IBDQ total score ≥ 170); biomarker outcomes included median change from baseline in serum albumin, high-sensitivity C-reactive protein (hs-CRP), and faecal calprotectin. CDAI scores and hs-CRP levels were assessed at every visit; IBDQ scores and serum albumin concentrations were assessed every 24 weeks; faecal calprotectin was assessed at baseline, Week 24, and every 32 weeks thereafter; and ileocolonoscopies were performed yearly. Central scoring of endoscopy results was performed by independent, blinded reviewers for all endoscopic assessments.

2.3. Statistical analysis

Safety data were reported for patients who received at least one dose of risankizumab (safety analysis set). The pharmacokinetics and immunogenicity analysis set included all patients who had pharmacokinetics and ADA data. Efficacy and HRQoL data were reported for the intent-to-treat population with non-responder imputation (NRI) of missing data up to Week 128. This was because from that time point onwards patients could roll over to the phase 3

OLE, resulting in a decrease in the number of patients continuing in the current phase 2 OLE study towards its completion and prior to the roll over into the phase 3 OLE for further risankizumab treatment and follow-up. Therefore, only observed cases were reported beyond Week 128. Note that the final time point reported may vary for different efficacy outcomes according to the frequency of assessments described in the previous section, and that patients completed M15-989 at different time points to roll over into the phase 3 OLE. No sample size calculation or statistical comparisons were conducted; all analyses were summarised descriptively. Week 0 denotes the first dose of study drug in the M15-989 OLE. However, for baseline characteristics and changes from baseline, baseline was defined as being prior to the first dose of study drug in the parent M15-993 study.⁸

3. Results

3.1. Patient disposition

Of the 121 patients randomised in the M15-993 study,⁹ 65 rolled over to this OLE (all risankizumab group) from September 2015 onwards. This included patients who achieved clinical response (without clinical remission) at Week 26 ($n = 12$), patients who achieved clinical remission and/or response at Week 52 ($n = 49$), and 4 patients who had lost response at the end of the M15-993 study and were reinduced with risankizumab 600 mg IV Q4W at the beginning of the OLE (Figure 1). Forty-four patients (68%) completed the M15-989 study and transitioned into the phase 3 OLE, while 21 (32%) patients prematurely discontinued the current study. Seven patients discontinued the study due to AEs and 7 patients withdrew consent; all reasons for discontinuation are detailed in Figure 1. The M15-989 study concluded in June 2019; it was terminated by the sponsor to provide the option for patients to roll over to continuous open-label treatment within the ongoing phase 3 OLE.

Baseline characteristics and disease activity (i.e. at entry into the M15-993 study) of the OLE population are presented in Table 1. Median CD duration was 10.0 years (range: 2.0–38.0), and 92.3% of patients had been previously treated with at least one TNF antagonist.

3.2. Safety

In the all risankizumab group ($n = 65$), the treatment duration of risankizumab ranged from 114 to 1317 days, with a median of 1014 days (33 months) and a total of 167.0 PY. Forty patients (62%) received risankizumab for >924 days. All patients who required IV reinduction ($n = 4$) received the full reinduction with three infusions of 600 mg IV risankizumab Q4W (median duration: 84 days) and achieved clinical response by Week 8; then continued risankizumab 180 mg SC Q8W from Week 12 onwards.

Most patients experienced at least one TEAE (Table 2). The most common TEAEs were nasopharyngitis, gastroenteritis, and fatigue (Supplementary Table 1). Serious AEs (SAEs) were reported in 23 patients (35.4%; 24.6 E/100 PY). SAEs observed in more than 1 patient were worsening CD, intestinal stenosis, viral gastroenteritis, peritonitis, and post-procedural complications ($n = 2$ each). Six patients (9.2%; 4.2 E/100 PY) discontinued the study drug due to the following TEAEs: worsening CD ($n = 5$), including 1 patient with colon injury (intraluminal laceration of the colon with no perforation during an endoscopy), and ileal stenosis ($n = 1$). No deaths were reported.

Infections were reported in 48 patients (73.8%; 112.0 E/100 PY). The most common infections were nasopharyngitis, lower respiratory tract infection, oral herpes, and urinary tract infection. Serious infections were reported in 6 patients (9.2%; 4.2 E/100 PY); these included pelvic peritonitis secondary to anal dilatation and viral gastroenteritis (reported in

the same patient), peritonitis following ileocaecal resection surgery, *Campylobacter* infection, subcutaneous abscess, viral gastroenteritis, and perianal abscess. None of the serious infections led to discontinuation of risankizumab. Of the 6 patients with serious infections, 2 patients were receiving concomitant immunomodulators ($n = 1$) or corticosteroids ($n = 1$) throughout the OLE. Opportunistic infections were reported in 3 patients (4.6%; 1.8 E/100 PY) and included fungal oesophagitis and oral fungal infection; all were resolved during the study period. Fungal infections were reported in 7 patients (10.8%; 6.6 E/100 PY). Oral fungal infection and vulvovaginal mycotic infection were most frequently reported ($n = 2$ each). The remaining fungal infections were single events of *Blastocystis* infection, fungal infection of the hands and feet, fungal oesophagitis, fungal skin infection, tinea capitis, and vulvovaginal candidiasis. None of these were serious (all grade 1 or 2), and none led to treatment discontinuation. No events of tuberculosis or herpes zoster infections were reported.

Hypersensitivity reactions were reported in 16 patients (24.6%; 10.2 E/100 PY). The most frequently reported hypersensitivity reactions were rash ($n = 5$) and eczema ($n = 3$). Five events were considered to be related to the study drug according to the investigator, and no events led to discontinuation of risankizumab treatment. All hypersensitivity reactions were assessed as grade 1 or 2, except for one SAE, which was an anaphylactic reaction due to iron carboxymaltose (Ferinject[®]) infusion.

Hepatic events were reported in 6 patients (9.2%; 10.2 E/100 PY); 15 events involved increased liver enzymes. A single event of hepatic steatosis was observed in a patient with a body mass index $>30 \text{ kg/m}^2$. All hepatic events were assessed as grade 1, none were serious, and none led to discontinuation of risankizumab. Potentially clinically important increases in liver enzymes were rare (Supplementary Table 2), and increases in alanine aminotransferase

and aspartate aminotransferase returned to normal levels during the OLE. No patients met the criteria for Hy's Law.

No malignancies or adjudicated major adverse cardiovascular events were reported during this OLE study.

In general, changes in laboratory values were not considered clinically meaningful (Supplementary Table 2). There were few individual cases of $\geq$ grade 3 laboratory values and most of them were transient. Three patients had $\geq$ grade 3 decreases in lymphocytes, of whom 2 had $\geq$ grade 3 decreases only once during the study, and all decreases resolved without discontinuation. Six patients had $\geq$ grade 3 increases in creatine kinase, 5 of whom experienced increases only once during the study, and 3 of whom experienced increases during the follow-up period. All increases resolved without discontinuation. Most of these events were assessed by the investigator as temporary and not clinically meaningful. Five patients experienced $\geq$ grade 3 increases in triglycerides, 1 of whom had increased triglycerides prior to this study. No persistent trend was observed. All increases in triglycerides resolved, and no patients discontinued risankizumab due to increases in triglycerides.

Three pregnancies were reported during this OLE: two pregnancies occurred during maternal treatment with risankizumab 180 mg SC Q8W, and the third was the pregnancy of a patient's partner. Maternal use of risankizumab was discontinued after pregnancy was confirmed. One of the patients with maternal use of risankizumab pre-conception and during the first trimester (having received risankizumab treatment for 575 days in total) surgically terminated her pregnancy because of foetal defects (foetal cystic hygroma and hydrops fetalis) 78 days after risankizumab was discontinued; this was considered by the investigator as having a reasonable possibility of being related to risankizumab. This patient subsequently

had a second pregnancy outside the OLE reporting period (after discontinuation of risankizumab for >20 weeks and therefore not included as one of the three pregnancies that occurred during the OLE), which resulted in a miscarriage. The other two pregnancies concluded with live births without any reported complications or abnormalities.

3.3. Pharmacokinetics and immunogenicity

Steady-state plasma exposures of risankizumab were reached by Week 24 and were maintained throughout the study, with geometric mean trough concentrations ranging from 3.2 to 4.0 µg/mL (Figure 2).

At Week 0 (prior to first risankizumab dose in M15-989), pre-existing ADAs were detected in 2/65 patients (3%) who received at least one dose of risankizumab in the study, possibly due to prior exposure to risankizumab in the parent phase 2 study M15-993. Treatment-emergent ADAs developed in 8/65 patients (12%) during this OLE, none of whom developed neutralising antibodies. Four patients with treatment-emergent ADAs discontinued from the study for the following reasons: AE, pregnancy, withdrawal of consent, and lack of efficacy, respectively. ADA titres ranged from 1 to 64 with no apparent impact on risankizumab plasma exposure in all but 1 patient. Further pharmacokinetic and immunogenicity data will be collected and their correlations with safety and efficacy outcomes will be analysed in phase 3 studies.

3.4. Efficacy, HRQoL, and biomarkers

The proportions of patients in clinical remission and endoscopic remission were maintained with long-term risankizumab treatment throughout the duration of the study. Central reviewer scoring was used for all endoscopic efficacy assessments. Clinical remission was achieved in >71% of patients in the observed analysis and >64% of patients in the NRI analysis at any

given visit through Week 112 of OLE therapy (Figure 3A). Endoscopic remission was achieved in >42% of patients in the observed analysis and >41% of patients in the NRI analysis at any given visit through Week 104 (Figure 3B).

A high proportion of patients reported HRQoL improvements from baseline (prior to the first dose of risankizumab in the M15-993 study), assessed by IBDQ response (>88% of patients in the observed analysis and >70% of patients in the NRI analysis; Figure 3C) and IBDQ remission (>58% of patients in the observed analysis and >52% of patients in the NRI analysis; Figure 3D) at any given visit through Week 120. These improvements were observed across all four domains of IBDQ (bowel symptoms, systemic symptoms, social function, and emotional function).

Median reductions from baseline (prior to the first dose of risankizumab in the M15-993 study) in hs-CRP and faecal calprotectin observed at Week 0 of this OLE were generally maintained over the course of the OLE through Week 152 (Supplementary Figure 1A and 1B). Increased serum albumin levels at Week 0 were also generally maintained through Week 152 (Supplementary Figure 1C).

4. Discussion

In this OLE, risankizumab 180 mg SC Q8W maintenance treatment was well tolerated by patients with CD with over 3 years and 167 PY of treatment, and no new safety signals were observed. As secondary outcomes, the pharmacokinetics of risankizumab were consistent with previous observations,^{9,10} and efficacy was maintained during the study. Patients included in this study had treatment-refractory CD at M15-993 baseline and completed both the M15-993 and M15-989 studies before rolling over to the phase 3 OLE, suggesting that the safety and efficacy of risankizumab were compelling enough to warrant continued risankizumab.

The majority of SAEs were gastrointestinal in nature and may reflect underlying CD. Rates of serious infections, opportunistic infections, and fungal infections in the OLE (4.2, 1.8, and 6.6 E/100 PY, respectively) were similar to those reported in the parent phase 2 M15-993 study (4.6, 2.7, and 7.3 E/100 PY, respectively).⁹ Serious infections were predominantly driven by gastrointestinal events, and no cases of tuberculosis (including latent tuberculosis) or herpes zoster were reported. Hypersensitivity reactions were observed in about 25% of patients and occurred at a lower rate than that observed in the M15-993 study. There was one serious anaphylactic reaction to IV iron carboxymaltose administration that did not lead to drug discontinuation. No deaths, malignancies, or adjudicated cardiovascular events were reported.

Laboratory values $\geq$ grade 3 were infrequent and usually transient. The safety profile of risankizumab 180 mg in patients with CD was generally consistent with previous reports in psoriasis and psoriatic arthritis, despite the difference in risankizumab doses evaluated across indications (150 mg every 12 weeks for psoriasis and 150 mg every 4 or 12 weeks for psoriatic arthritis).^{11–13} The types of TEAEs reported with risankizumab in patients with CD were similar to those reported by studies of ustekinumab, an IL-12/23 inhibitor.^{14–16}

Of the three pregnancies reported during the OLE, two resulted in healthy births, while the third was surgically terminated due to foetal abnormalities. It is important to note that this OLE was not designed to evaluate the effects of risankizumab on pregnancies, as women of childbearing potential had agreed to use and remain on contraception from the date of screening until 20 weeks after the last dose of risankizumab treatment according to the protocol.

Steady-state plasma exposure was achieved by Week 24 following administration of risankizumab 180 mg SC Q8W. The development of largely low-titre, non-neutralising

ADAs in 8 patients was not expected to affect target binding sites on risankizumab and did not appear to have a clear impact on risankizumab plasma exposures. These results are consistent with previous studies of psoriasis, in which only high-titre ADAs (>128) for risankizumab had a meaningful impact on pharmacokinetics.^{17,18} Therefore, no marked impact on risankizumab exposure, and thus efficacy and safety, was expected given that the majority of the ADAs in this study were of low titre. However, these results should be interpreted with caution due to the small sample size of the study. Although 4 out of the 8 patients who developed treatment-emergent ADAs discontinued from the study, based on review of the time-course data for ADA titres, risankizumab exposure, and reasons for discontinuation there was no apparent correlation between immunogenicity and discontinuation.

The main limitation of this OLE was the relatively small sample size ($n = 65$). Another limitation was that this study was not powered for statistical comparisons. The open-label study design and lack of comparator or control treatment arms meant that the study was more likely to be subject to bias than a randomised controlled trial. In addition, interpretation of safety outcomes is more challenging without a control group. However, objective evaluations including endoscopy were performed prospectively. As all patients were required to remain on any concomitant treatments throughout the OLE, the achievement of steroid-free response or remission could not be assessed. While the small sample size of this study may limit the generalisability of the findings, safety and efficacy data will be confirmed by ongoing phase 3 studies with larger patient populations.

In this OLE, maintenance treatment with risankizumab 180 mg SC Q8W for up to 184 weeks was well tolerated by patients with moderate-to-severe refractory CD, and no new safety signals were observed. Results from ongoing phase 3 studies, including the phase 3 OLE, will further inform the efficacy and safety of risankizumab in patients with CD.

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Conflict of Interest

MF has received research grants from Amgen, Biogen, Janssen, Pfizer, and Takeda; consultancy fees from AbbVie, Boehringer Ingelheim, Celltrion, Janssen, Lilly, Medtronic, MSD, Pfizer, Sandoz, Takeda, and Thermo Fisher; and speakers' fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Falk, Ferring, Janssen, Lampro, MSD, Mylan, Pfizer, Sandoz, Takeda, and Truvion Healthcare.

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Authors' Contributions

MF, BGF, JP, FB, EL, OD, AK, WRD, YP, W-JL, DG, XL, KW, JK, and GRD contributed substantially to the conception and design of the work; the acquisition, analysis, and interpretation of data for the work; drafting the manuscript and revising it critically for important intellectual content; and reviewing and providing final approval of the version to be published, with the authors maintaining control over the final content.

Data Availability Statement

AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymised, individual and trial-level data (analysis data sets), as well as other information (e.g. protocols and clinical study reports), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications.

This clinical trial data can be requested by any qualified researchers who engage in rigorous, independent scientific research, and will be provided following review and approval of a research proposal and statistical analysis plan, and execution of a data sharing agreement. Data requests can be submitted at any time and the data will be accessible for 12 months, with possible extensions considered. For more information on the process, or to submit a request, visit the following link: <https://www.abbvie.com/our-science/clinical-trials/clinical-trials-data-and-information-sharing/data-and-information-sharing-with-qualified-researchers.html>.

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References

1. Gomollón F, Dignass A, Annesse V, *et al.* 3rd European evidence-based consensus on the diagnosis and management of Crohn's disease 2016: part 1: diagnosis and medical management. *J Crohns Colitis* 2017;**11**:3–25.
2. Lichtenstein GR, Loftus EV, Isaacs KL, Regueiro MD, Gerson LB, Sands BE. ACG clinical guideline: management of Crohn's disease in adults. *Am J Gastroenterol* 2018;**113**:481–517.
3. Ng SC, Shi HY, Hamidi N, *et al.* Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. *Lancet* 2018;**390**:2769–78.
4. Ng SC, Tang W, Ching JY, *et al.* Incidence and phenotype of inflammatory bowel disease based on results from the Asia-Pacific Crohn's and colitis epidemiology study. *Gastroenterology* 2013;**145**:158–65.e2.
5. Torres J, Bonovas S, Doherty G, *et al.* ECCO guidelines on therapeutics in Crohn's disease: medical treatment. *J Crohns Colitis* 2020;**14**:4–22.
6. AbbVie. Skyrizi (risankizumab) [package insert]. European Medicines Agency website. 13 July 2020. (Accessed 11 November 2020, at https://www.ema.europa.eu/en/documents/product-information/skyrizi-epar-product-information_en.pdf.)
7. AbbVie. Skyrizi (risankizumab) [package insert]. U.S. Food and Drug Administration website. 13 July 2020. (Accessed 11 November 2020, at https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/761105s000lbl.pdf.)
8. Feagan BG, Sandborn WJ, D'Haens G, *et al.* 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. *Lancet* 2017;**389**:1699–709.
9. Feagan BG, Panés J, Ferrante M, *et al.* Risankizumab in patients with moderate to severe Crohn's disease: an open-label extension study. *Lancet Gastroenterol Hepatol* 2018;**3**:671–80.

10. Suleiman AA, Khatri A, Minocha M, Othman AA. Population pharmacokinetics of the interleukin-23 inhibitor risankizumab in subjects with psoriasis and Crohn's disease: analyses of phase I and II trials. *Clin Pharmacokinet* 2019;**58**:375–87.
11. Gordon KB, Strober B, Lebwohl M, *et al.* Efficacy and safety of risankizumab in moderate-to-severe plaque psoriasis (UltIMMa-1 and UltIMMa-2): results from two double-blind, randomised, placebo-controlled and ustekinumab-controlled phase 3 trials. *Lancet* 2018;**392**:650–61.
12. Reich K, Gooderham M, Thaçi D, *et al.* Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. *Lancet* 2019;**394**:576–86.
13. Mease PJ, Kellner H, Morita A, *et al.* OP0307 Efficacy and safety of risankizumab, a selective il-23p19 inhibitor, in patients with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. *Ann Rheum Dis* 2018;**77**:200–1.
14. 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.
15. Sandborn WJ, Rutgeerts P, Gasink C, *et al.* Long-term efficacy and safety of ustekinumab for Crohn's disease through the second year of therapy. *Aliment Pharmacol Ther* 2018;**48**:65–77.
16. Ghosh S, Gensler LS, Yang Z, *et al.* Ustekinumab safety in psoriasis, psoriatic arthritis, and Crohn's disease: an integrated analysis of phase II/III clinical development programs. *Drug Saf* 2019;**42**:751–68.
17. Khatri A, Suleiman AA, Polepally AR, Othman AA. Exposure–response relationships for efficacy and safety of risankizumab in phase II and III trials in psoriasis patients. *Clin Pharmacol Ther* 2020;**107**:378–87.
18. Pang Y, Khatri A, Suleiman AA, Othman AA. Clinical pharmacokinetics and pharmacodynamics of risankizumab in psoriasis patients. *Clin Pharmacokinet* 2020;**59**:311–26.

Figure Legends

Figure 1. Study design and patient disposition. ^aPrimary reasons for discontinuation ^bOther reasons are as reported by the investigator (as free text) and have not been grouped to avoid inaccuracy in reporting ^cPatients rolled over to the ongoing phase 3 OLE (M16-000 sub-study 3) between Weeks 128 and 184 of M15-989
AE, adverse event; CD, Crohn's disease; IV, intravenous; OLE, open-label extension; Q4/8W, every 4/8 weeks; SC, subcutaneous.

Figure 2. Risankizumab trough plasma concentration over time in all patients. Analysis set included all patients with available pharmacokinetics and ADA data. Patients rolled over to the ongoing phase 3 OLE (M16-000 sub-study 3) between Weeks 128 and 184, and as a result had different last visit time points. ADA, anti-drug antibody; OLE, open-label extension; SC, subcutaneous; SD, standard deviation.

Figure 3. Proportions of patients achieving clinical remission (A), CDEIS remission (B), IBDQ response (C), and IBDQ remission (D) over time (intent-to-treat analysis set). From Week 128 onwards, patients could roll over to the ongoing phase 3 OLE (M16-000 sub-study 3). This resulted in a decrease in the number of patients continuing towards completion in the current phase 2 OLE study and prior to roll over into the phase 3 OLE for further risankizumab treatment and follow-up. Therefore, NRI for missing data was not presented after Week 128. Only observed cases were presented beyond Week 128. *n* denotes the number of responders and *N* denotes the number of patients at risk. CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; IBDQ, Inflammatory Bowel Disease Questionnaire; NRI, non-responder imputation; OLE, open-label extension.

Table 1. Patient characteristics at baseline^a and Week 0^b (intent-to-treat analysis set).

Patient characteristics at baseline ^a	All risankizumab (<i>n</i> = 65)		
Age, years, median (range)	34.0 (19–67)		
Female, <i>n</i> (%)	36 (55.4)		
Race, white, <i>n</i> (%)	55 (84.6)		
Weight, kg, median (range)	66.0 (41.0–123.9)		
Disease duration, years, median (range)	10.0 (2.0–38.0)		
CD location, <i>n</i> (%)			
Ileocolonic	37 (56.9)		
Colonic only	20 (30.8)		
Ileum only	8 (12.3)		
Prior TNF antagonist use, <i>n</i> (%)	60 (92.3)		
Prior use of one TNF antagonist	20 (30.8)		
Prior use of two TNF antagonists	32 (49.2)		
Prior use of three TNF antagonists	8 (12.3)		
Concomitant treatment, ^c <i>n</i> (%)			
Corticosteroid only	13 (20.0)		
IMM only	21 (32.3)		
Corticosteroid and IMM	9 (13.8)		
	Baseline, ^a median (range)	Baseline, ^a mean (SD)	Mean (SD) change from baseline at Week 0 ^b
CDAI	298.0 (109.0–477.6)	304.8 (78.0)	–198.5 (101.8)
CDEIS	11.9 (5.2–25.0)	13.3 (5.6)	–8.1 (6.0)
IBDQ	114.0 (52.0–182.0)	114.3 (34.4)	62.5 (38.8)
hs-CRP, mg/L	10.2 (0.2–109.0)	20.3 (23.2)	–14.6 (22.8)
Faecal calprotectin, mg/kg	1364.0 (40.0–25 252.0)	2436.5 (3707.0)	–1983.9 (3402.1)

^aBaseline is defined as prior to first dose of study drug in the parent M15-993 study ^bWeek 0is defined as first dose of study drug in the M15-989 OLE ^cPatients were permitted to

continue oral corticosteroids (prednisone equivalent dose of ≤ 20 mg/day) and immunomodulators (azathioprine, 6-mercaptopurine, or methotrexate) if they had been on a stable dose for at least 4 weeks prior to visit 2. Patients who entered the OLE on concomitant treatments were required to continue on a stable dose of this treatment throughout the M15-989 OLE. CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CDEIS, Crohn's Disease Endoscopic Index of Severity; hs-CRP, high-sensitivity C-reactive protein; IBDQ, Inflammatory Bowel Disease Questionnaire; IMM, immunomodulatory; OLE, open-label extension; SD, standard deviation; TNF, tumour necrosis factor.

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Table 2. Overview of TEAEs (safety analysis set).

	All risankizumab	
	(n = 65; PY = 167.0)	
	Number of patients (%)	E/100 PY
Any AE	60 (92.3)	408.4
AE possibly related to study drug ^a	26 (40.0)	49.7
Serious AE	23 (35.4)	24.6
Severe AE ^b	14 (21.5)	15.0
AE leading to discontinuation of study drug	6 (9.2)	4.2
All deaths	0	0
Infection	48 (73.8)	112.0
Serious infection	6 (9.2)	4.2
Opportunistic infection	3 (4.6) ^c	1.8
Fungal infection	7 (10.8) ^c	6.6
Tuberculosis	0	0
Herpes zoster	0	0
Malignancies excluding NMSC	0	0
Hypersensitivity	16 (24.6)	10.2
Anaphylactic reaction	1 ^d (1.5)	0.6
Hepatic event	6 (9.2)	10.2
Adjudicated MACE	0	0

^aAs assessed by the investigator ^bAEs with NCI toxicity $\geq$ grade 3 or unknown severity ^cOf all fungal infection cases, fungal oesophagitis (n = 2) and oral fungal infection (n = 1) were also coded as opportunistic infections ^dSerious anaphylactic reaction to intravenous iron carboxymaltose administration. AE, adverse event; E/100 PY, events per 100 patient-years; MACE, major adverse cardiovascular event; NCI, National Cancer Institute; NMSC, non-melanoma skin cancer; PY, patient-years; TEAE, treatment-emergent adverse event.

Figure 1

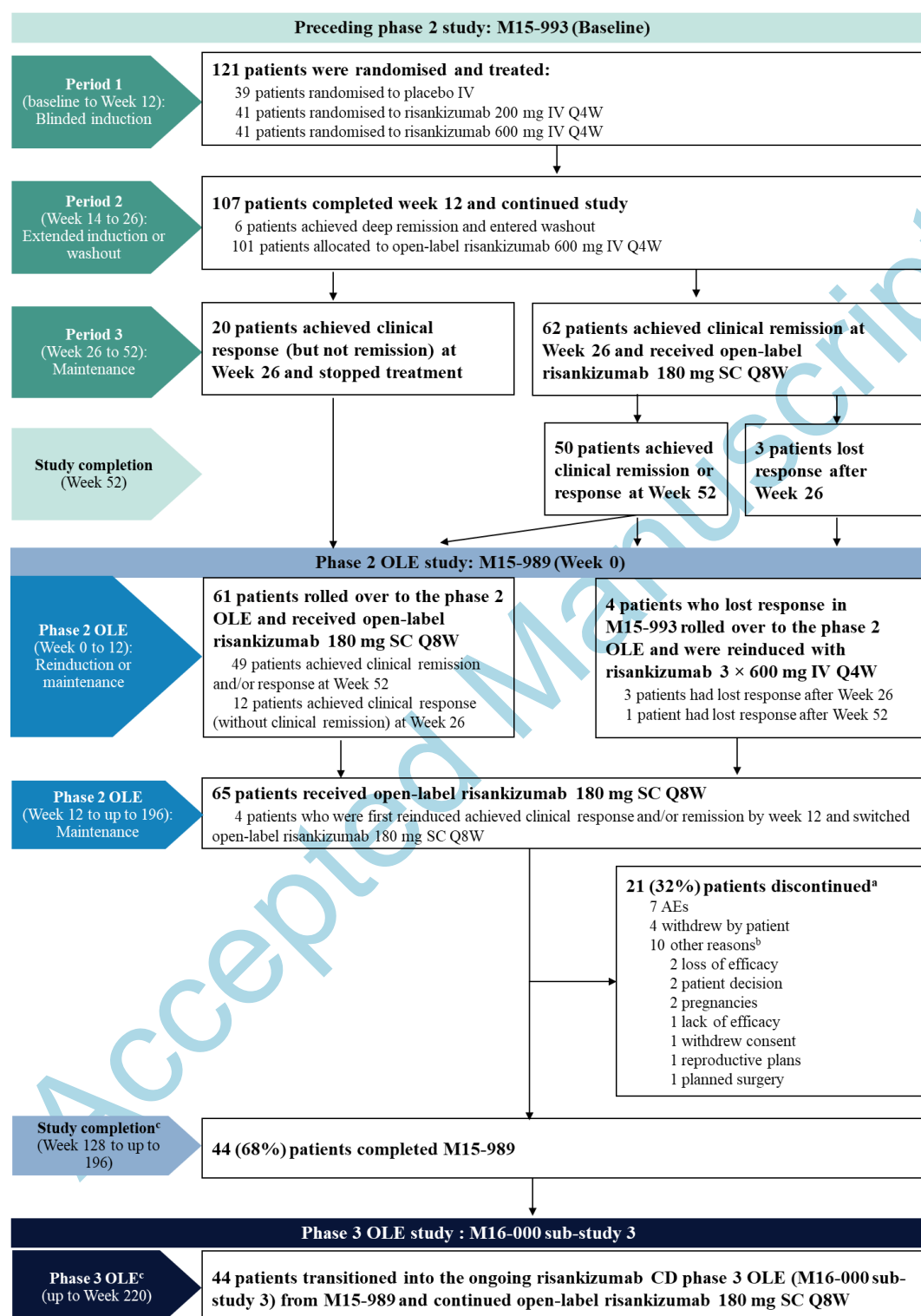


Figure 2

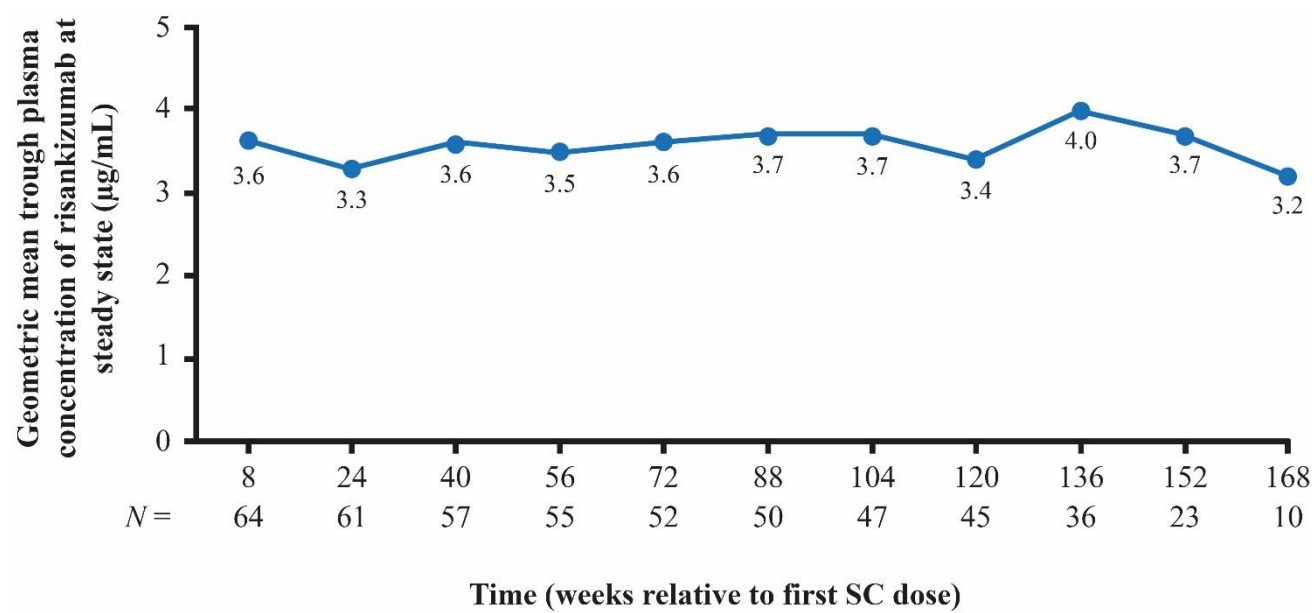
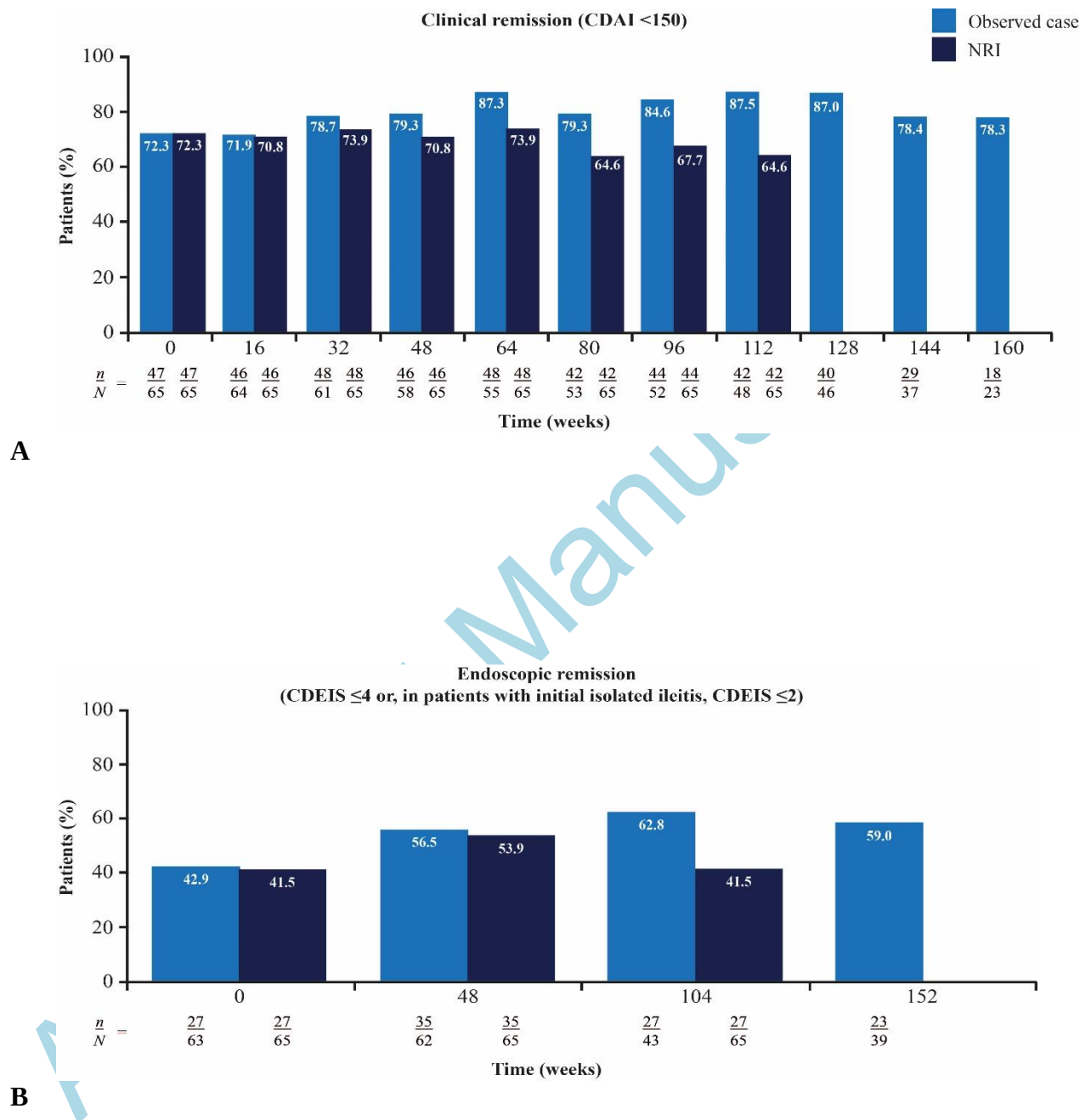
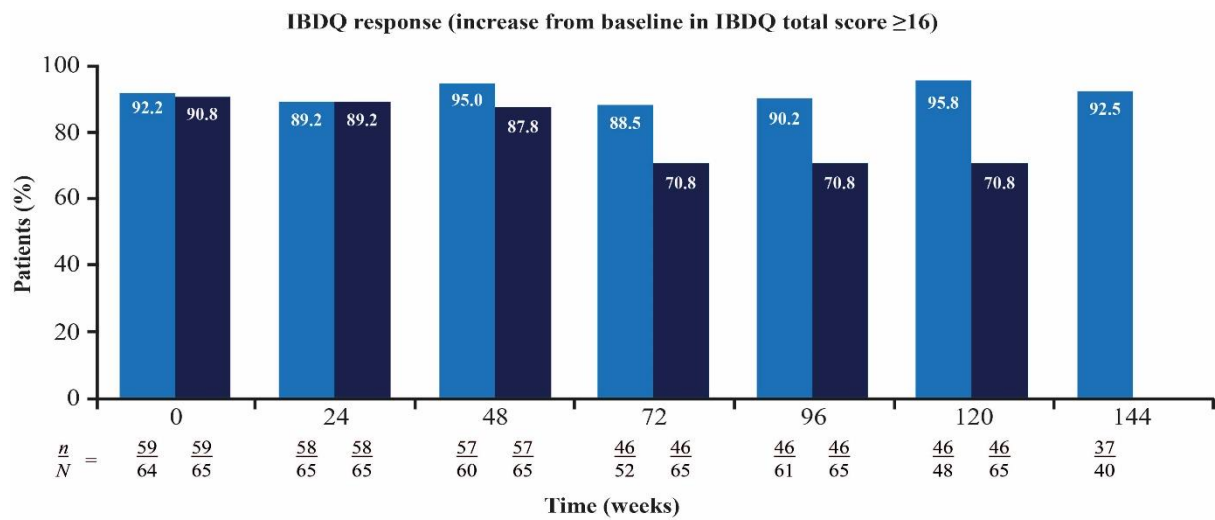


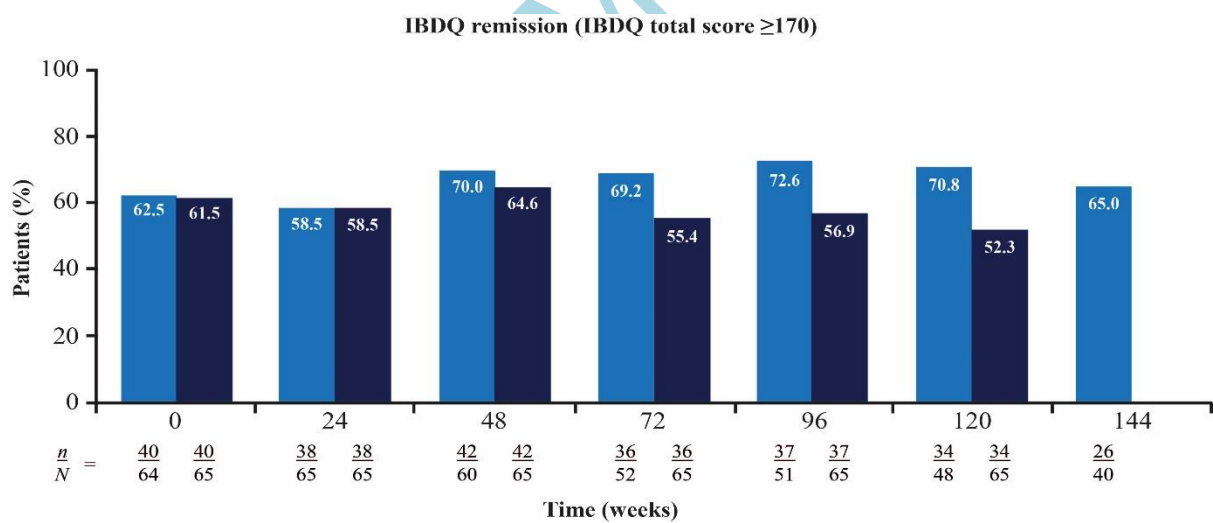
Figure 3





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