ORIGINAL RESEARCH—CLINICAL

Early Endoscopic Outcomes After Risankizumab Are Associated With Fewer Hospitalizations and Surgeries in Crohn's Disease

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BACKGROUND AND AIMS: We evaluated the association between endoscopic outcomes following risankizumab induction and subsequent rates of hospitalization and surgery through 52 weeks of risankizumab (both doses) maintenance therapy in patients with Crohn's disease (CD). **METHODS:** Patients with moderately to severely active CD and clinical response to 12-week risankizumab induction were rerandomized to continued therapy or drug withdrawal in the phase 3 FORTIFY maintenance trial. Incidence rates (events/100 person-years) of CD-related hospitalization and surgery, and the composite of both, through 52 weeks of maintenance were compared between patients achieving vs not achieving predefined endoscopic outcomes following induction. **RESULTS:** Patients who achieved vs did not achieve endoscopic response or remission, or absence of ulcers (ulcer-free endoscopy) after induction had reduced rates of CD-related hospitalization through 52 weeks of risankizumab maintenance (endoscopic response, 1.7 vs 7.9/100 person-years; endoscopic remission, 1.2 vs 6.9/100 person-years; ulcer-free endoscopy, 1.5 vs 6.4/100 person-years; all $P < .05$). No CD-related surgeries were observed through 52 weeks of risankizumab maintenance among patients who achieved vs did not achieve endoscopic outcomes following induction (endoscopic response, 0 vs 3.2/100 person-years; endoscopic remission, 0 vs 2.6/100 person-years; ulcer-free endoscopy, 0 vs 2.4/100 person-years; all $P = .025$). In contrast, patients who received placebo during maintenance had statistically similar rates of CD-related hospitalizations and surgeries regardless of achievement of endoscopic outcomes after induction. **CONCLUSION:** Patients achieving endoscopic outcomes following risankizumab induction experienced less CD-related hospitalizations and surgeries through 52 weeks of maintenance when continuing active therapy. Early treatment success may predict favorable long-term outcomes of disease. **CLINICAL REGISTERATION NUMBER:** ADVANCE (NCT03105128); MOTIVATE (NCT03104413) and FORTIFY (NCT03105102).

Keywords: Clinical trials; Crohn's Disease; Endoscopy; Surgery

Introduction

Crohn's disease (CD) is a chronic inflammatory disorder of the gastrointestinal tract that frequently causes abdominal pain, diarrhea, weight loss, and extraintestinal complications.[1] Left uncontrolled, CD often results in complications of both luminal obstruction and abscess formation, resulting in increased morbidity and the need for hospitalization and surgery.[2,3] Rates of hospitalization and surgery are, therefore, credible markers for failure of medical management and may be useful to indirectly evaluate therapeutic effectiveness.[4,5] Indeed, decreased rates of hospitalization and surgery over the past 3 decades coincide with the availability of several advanced therapies and overall improvement in medical management.[6–10] Furthermore, from a patient perspective, hospitalization and surgery are undesired outcomes. Although surgery may be an invaluable management tool in specific scenarios, it is not curative and is associated with short- and long-term complications.[4,11] Hospitalization for acute flares, administering intravenous (IV) corticosteroids or rescue treatment with biologics, hyperalimentation, or treating infectious complications disrupt patients' lives.

Given these considerations, research has focused on defining short-term treatment targets that may result in improved quality of life and reduced rates of hospitalization and surgery. The STRIDE-I and II consensus recommendations

Abbreviations used in this paper: **APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; ITT, intention to treat; IV, intravenous; SC, subcutaneous; SD, standard deviation; SES-CD, Simple Endoscopic Score for CD; SF, stool frequency; SPIRIT, Selecting Endpoints for Disease-Modification Trials.**

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identified endoscopic remission as an important treatment target.[12,13] Subsequently, treatment goals identified by the Selecting Endpoints for Disease-Modification Trials (SPIRIT) consensus included preventing complications, like CD-related surgery and hospitalizations, and monitoring transmural healing.[14] These recommendations were based upon observational data of variable quality, and there is an absence of randomized controlled trials demonstrating that treating to an endoscopic target is superior to using the symptom- or biomarker-based targets validated in the REACT 1 and CALM trials, respectively.[8,15] Post hoc analysis of the REACT-2 trial suggests a potential benefit to treating to target ulcer-healing versus symptom-driven care in patients with objective evidence of inflammation at baseline by C-reactive protein (CRP); additional studies are warranted to validate these findings.[16] Risankizumab, an interleukin-23 inhibitor, was effective and well tolerated as induction therapy and maintenance of remission in patients with moderately to severely active CD.[17–19] The risankizumab Phase 3 trials were the first in CD to use SPIRIT recommended coprimary endpoints of clinical remission and endoscopic response. The extensive endoscopic data from this trial provided an opportunity to assess the potential value of endoscopy as a treatment target. This post hoc analysis evaluated the association between achievement of endoscopic outcomes after induction and subsequent hospitalization and surgery rates up to 1 year in patients with CD treated with risankizumab.

Materials and Methods

Study Design and Participants

To further understand the holistic benefits of endoscopy as a treatment target, this analysis compared the rates of hospitalization and surgery outcomes through 52 weeks of risankizumab maintenance treatment (FORTIFY) among patients who achieved or did not achieve prespecified endoscopic outcomes at the end of risankizumab IV induction treatment (in ADVANCE or MOTIVATE). Full details on ADVANCE, MOTIVATE, and FORTIFY, including study design, patient selection, and primary results were previously reported and briefly described below.[17,18]

This was a post hoc analysis of data from FORTIFY (NCT03105102), a rerandomized, double-blind, placebo-controlled phase 3 maintenance trial. Patients in FORTIFY had achieved a clinical response in either the ADVANCE (NCT03105128) or MOTIVATE (NCT03104413) induction trials. Clinical response was defined at Week 12 (end of induction) as a $\geq$30% decrease in average daily stool frequency (SF) and/or $\geq$30% decrease in average daily abdominal pain score (APS) from baseline and both not worse than baseline of the induction study.

Briefly, in ADVANCE and MOTIVATE, patients aged $\geq$16 to $\leq$80 years, with a confirmed diagnosis of moderately to severely active CD, who had previously demonstrated intolerance and/or inadequate response to conventional and/or biologic therapies were randomly assigned to receive risankizumab IV 600 mg or 1200 mg every 4 weeks, or placebo for 12 weeks. In FORTIFY, patients were rerandomized 1:1:1 to receive 180 mg or 360 mg risankizumab subcutaneous (SC) maintenance therapy or placebo every 8 weeks for up to 52 weeks.

Post hoc analysis population and cohorts. The primary analysis was performed on the intention to treat 1A population in FORTIFY, defined as randomized patients who received IV risankizumab during the 12-week induction period and had baseline eligible Simple Endoscopic Score for CD (SES-CD) of $\geq$6 (or $\geq$4 for those with isolated ileal disease). Patients who received active risankizumab (combined 180 or 360 mg SC) or withdrawal placebo in FORTIFY were analysed separately. Patients were stratified into two cohorts by achievement (yes/no) of prespecified endoscopic outcomes (defined below) at the end of induction (Week 0 of maintenance). Study design is shown in Figure 1.

Endoscopic outcome definitions. All endoscopic definitions used to stratify the population by those who achieved vs did not achieve each outcome at the end of induction were prespecified in the protocol. For all three studies, the SES-CD score was determined centrally by trained central readers unaware of the treatment assignment or visit sequence.

The SES-CD is a validated instrument for the assessment of endoscopic disease activity in CD.[20] The score can be used as a continuous variable for comparing differences in mean values between treatment groups or, more commonly, as a binary measure according to the following definitions: 1) *endoscopic response*, defined as a decrease in SES-CD >50% from baseline of the induction study (or for patients with isolated ileal disease and a SES-CD of 4 at baseline of the induction study, at least a 2-point reduction from baseline of the induction study); 2) *endoscopic remission*, defined as SES-CD $\leq$4 and at least a 2-point reduction from baseline of the induction study and no subscore >1 in any individual variable; and 3) *ulcer-free endoscopy* (absence of ulceration), defined as SES-CD ulcerated surface subscore of 0 in subjects with SES-CD ulcerated surface subscore $\geq$1 at baseline of the induction study.

In addition to the endoscopic outcomes described above, secondary analyses evaluated the relationships between the achievement of the composite target of "*deep remission*" (ie, symptomatic and endoscopic remission) at the end of induction and the subsequent outcomes of hospitalization and surgery. Deep remission was based on two different symptom-based remission definitions: achievement of Crohn's disease activity index (CDAI) clinical remission (CDAI <150) and endoscopic remission or achievement of SF/APS clinical remission (average daily SF $\leq$ 2.8 and not worse than baseline and average daily APS $\leq$1 and not worse than baseline) and endoscopic remission.

Outcomes

Exposure-adjusted occurrences (per 100 person-years) of the following outcomes were evaluated from the beginning of maintenance to Week 52 and analyzed based on incidence rates: CD-related hospitalization, CD-related surgery, and a composite of CD-related hospitalizations or surgeries. CD-related surgery included procedures due to adverse events or complications related to CD, for example, bowel resection, ostomy, and abscess drainage; but excluding examination under anaesthesia. For the purposes of this analysis, surgeries were considered minor based on the follow definition: a surgical procedure was defined as a medical procedure involving incision of the body, especially with instruments; this included "minor surgeries" such as incision and drainage of perianal

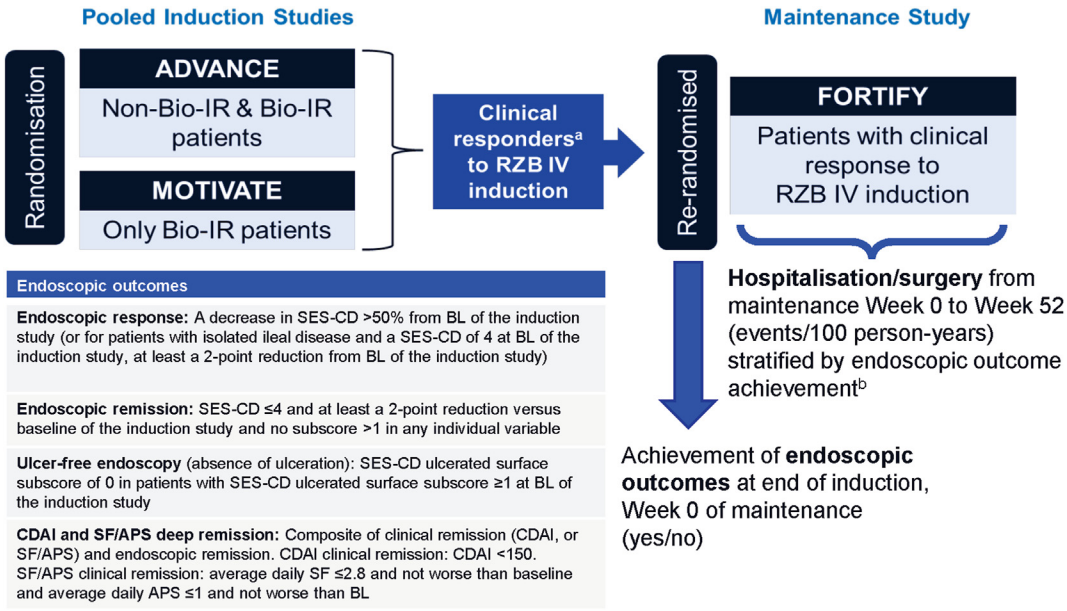

Figure 1. Study design. [a]Clinical response: ≥30% decrease in average daily SF and/or ≥30% decrease in average daily APS. Enhanced clinical response: decrease in average daily SF ≥ 60% and/or decrease in average daily APS ≥35% and both not worse than baseline of the induction study. SF/APS clinical remission: average daily SF ≤ 2.8 and average daily APS ≤1 and both not worse than baseline of the induction study. CDAI clinical remission: CDAI <150. [b]The primary analysis focused on patients who received risankizumab (n = 298) and the same analyses were conducted separately in the placebo withdrawal arm (n = 164). APS, abdominal pain score; BL, baseline; CDAI, Crohn's disease activity index; SES-CD, Simple Endoscopic Score for CD; SF, stool frequency.

abscess and simple perianal fistulectomy or fistulotomy; seton removal would not be considered a minor surgery. This may have included surgical procedures in an outpatient facility identified by review of serious adverse events. CD-related hospitalizations or surgeries were recorded during the clinical trials by investigators. The relationship of whether hospitalization or surgery events were attributable to CD was recorded by the investigators. The occurrences of CD-related hospitalizations or surgeries, or the composite of both outcomes, during the maintenance trial were reported among patients who achieved or did not achieve endoscopic outcomes following the 12-week induction therapy.

Statistical Analyses

Incidence rates for CD-related hospitalization and surgery outcomes were calculated as the number of patients with the respective event divided by the time at risk from the beginning of maintenance (Week 0) to Week 52 of the maintenance phase and reported as events/100 person-years. Event rates during the maintenance phase were compared between patients who achieved endoscopic outcomes at the end of induction (Week 0 of FORTIFY) and those who did not (yes/no). Incidence rate differences between cohorts (ie, those who achieved vs did not achieve endoscopic outcomes) are presented with 95% confidence interval (CI) and *P* values were based on the normal approximation to Poisson distribution. The primary analysis was conducted among patients who received either 180 mg or 360 mg SC risankizumab during FORTIFY, with both doses combined. The same analyses were performed separately for patients who were clinical responders to induction therapy and received withdrawal placebo SC during maintenance. No statistical comparisons were made between risankizumab and withdrawal placebo treatment arms, as this was outside of the objective of the analysis. Analyses were also conducted for all-cause hospitalizations and surgeries, with incidence rates and 95% CIs reported. Subgroup analyses were conducted for CD-related events stratified by prior biologic failure status and endoscopic outcome achievement (yes/no). Baseline characteristics were reported with descriptive statistics and compared between those who achieved or did not achieve endoscopic outcomes at the end of induction.

All authors had access to the study data and reviewed and approved the final manuscript.

Ethical Requirements

All three randomized controlled trials were conducted in compliance with the protocol, International Conference on Harmonisation guidelines, and the ethical principles of the Declaration of Helsinki. As per Good Clinical Practice, the study protocol, informed consent forms, and all other explanatory materials were approved by the relevant ethics committees or institutional review board at all study sites. All patients provided informed consent before study participation.

Results

Study Population

A total of 298 patients who had a clinical response at the end of induction with risankizumab and continued to receive active risankizumab maintenance therapy for 52 weeks, were included in the primary analysis. The mean age, sex, and weight were similar for patients who achieved

endoscopic response, endoscopic remission, and ulcer-free endoscopy compared to those who did not achieve these outcomes following induction. Disease duration was balanced across those achieving and not achieving endoscopic response and endoscopic remission, but higher (10.7 years ± standard deviation 9.5, vs 8.2years ± 8.5, Table) in those not achieving ulcer-free endoscopy versus those achieving ulcer-free endoscopy following risankizumab induction therapy (Week 0 of maintenance). There was a general trend of lower CDAI, SES-CD, average SF, fecal calprotectin, and CRP in patients who achieved versus those who did not achieve endoscopic improvement at end of induction (Week 0 of maintenance). Similar trends were observed for rates of deep remission (Table A1).

An additional 164 patients, who were randomized to receive withdrawal placebo during the maintenance period, were included in a separate secondary analysis.

Endoscopic Response, Remission, and Ulcer-free Endoscopy Achievement Status and Impact on Hospitalization and Surgery Rates

Patients who achieved endoscopic response at the end of induction and continued on active risankizumab therapy during maintenance had significantly lower incidence rates of CD-related hospitalizations by 52 weeks compared with those who did not achieve endoscopic response (1.7 vs 7.9 per 100 person years, $P = .016$; Figure 2A). Similar results through 52 weeks were observed in patients who achieved endoscopic remission relative to those who did not by the end of induction (1.2 vs 6.9 per 100 person years, $P = .012$; Figure 2B), as well as in those who achieved ulcer-free endoscopy versus those who did not (1.5 vs 6.4 per 100 person years, $P = .031$; Figure 2C). In addition, among patients who continued active risankizumab maintenance therapy, no CD-related surgeries occurred by 52 weeks among those who achieved endoscopic response, endoscopic remission, or ulcer-free endoscopy at the end of induction (Week 0 of maintenance) compared with those who did not achieve these outcomes (endoscopic response: 0 vs 3.2 per 100 person years, $P = .025$; endoscopic remission: 0 vs 2.6 per 100 person years, $P = .025$; ulcer-free endoscopy: 0 vs 2.4 per 100 person years, $P = .025$). There was also a similar trend of significantly lower incidence rates of the composite outcome of CD-related hospitalizations or CD-related surgeries by 52 weeks for those who achieved endoscopic outcomes at end of induction compared with those who did not, demonstrating the incremental benefit of these endoscopic outcomes in addition to achieving clinical response after induction therapy (Figure 2A–C) when active therapy is continued.

Deep Remission Status and Impact on Subsequent Hospitalization and Surgery Rates

Numerically lower incidence rates of CD-related hospitalizations and the composite of CD-related hospitalizations or surgeries, from the beginning of maintenance through 52 weeks of risankizumab treatment, were seen with patients

Table. Maintenance Baseline Characteristics by Endoscopic Response, Endoscopic Remission, and Ulcer-free Endoscopy Status at End of Induction (End of 12-Wk Active IV Treatment)

Baseline characteristic	Endoscopic response at end of induction		Endoscopic remission at end of induction		Ulcer-free endoscopy at end of induction	
	Yes (n = 121)	No (n = 177)	Yes (n = 83)	No (n = 215)	Yes (n = 70)	No (n = 228)
Age (years), mean ± SD	37.9 ± 13.2	38.7 ± 14.3	39.3 ± 13.3	38.0 ± 14.1	37.9 ± 13.4	38.5 ± 14.0
Female, n (%)	64 (52.9)	85 (48.0)	46 (55.4)	103 (47.9)	39 (55.7)	110 (48.2)
Weight (kg), mean ± SD	70.6 ± 16.4	69.2 ± 17.1	71.3 ± 15.5	69.2 ± 17.3	70.4 ± 16.0	69.6 ± 17.1
Disease duration (years), mean ± SD	9.6 ± 9.5	10.4 ± 9.1	10.1 ± 10.1	10.1 ± 9.0	8.2 ± 8.5[a]	10.7 ± 9.5[a]
CDAI, mean ± SD	119.7 ± 75.3[a]	145.3 ± 67.9[a]	124.2 ± 75.1	139.0 ± 70.6	127.8 ± 75.8	137.0 ± 70.9
SES-CD, mean ± SD	2.9 ± 3.1[a]	12.0 ± 6.3[a]	1.2 ± 1.5[a]	11.0 ± 6.1[a]	0.9 ± 1.8[a]	10.5 ± 6.2[a]
Average daily SF, mean ± SD	1.7 ± 1.6[a]	2.4 ± 2.0[a]	1.7 ± 1.6[a]	2.3 ± 2.0[a]	1.8 ± 1.7[a]	2.2 ± 1.9[a]
Average daily APS, mean ± SD	0.7 ± 0.6	0.7 ± 0.6	0.8 ± 0.6	0.7 ± 0.6	0.8 ± 0.6	0.7 ± 0.6
Fecal calprotectin ± mg/kg, mean ± SD	502.4 ± 686.2[a]	1511.5 ± 2862.5[a]	366.2 ± 607.8[a]	1388.2 ± 2629.0[a]	486.6 ± 902.5[a]	1281.3 ± 2541.3[a]
CRP ± mg/liter, mean ± SD	4.6 ± 6.8[a]	10.9 ± 23.7[a]	4.4 ± 7.5[a]	9.9 ± 21.7[a]	4.3 ± 6.5[a]	9.6 ± 21.3[a]

Age, gender, weight, and disease duration are based on their information collected at induction baseline; others are based on maintenance baseline of FORTIFY.
APS, abdominal pain score; CD, Crohn's disease; CDAI, Crohn's disease activity index; CRP, C-reactive protein; SD, standard deviation; SES-CD, Simple Endoscopic Score for CD; SF, stool frequency.
[a]$P \leq .05$ between patients who achieved versus who did not achieve endoscopic outcomes.

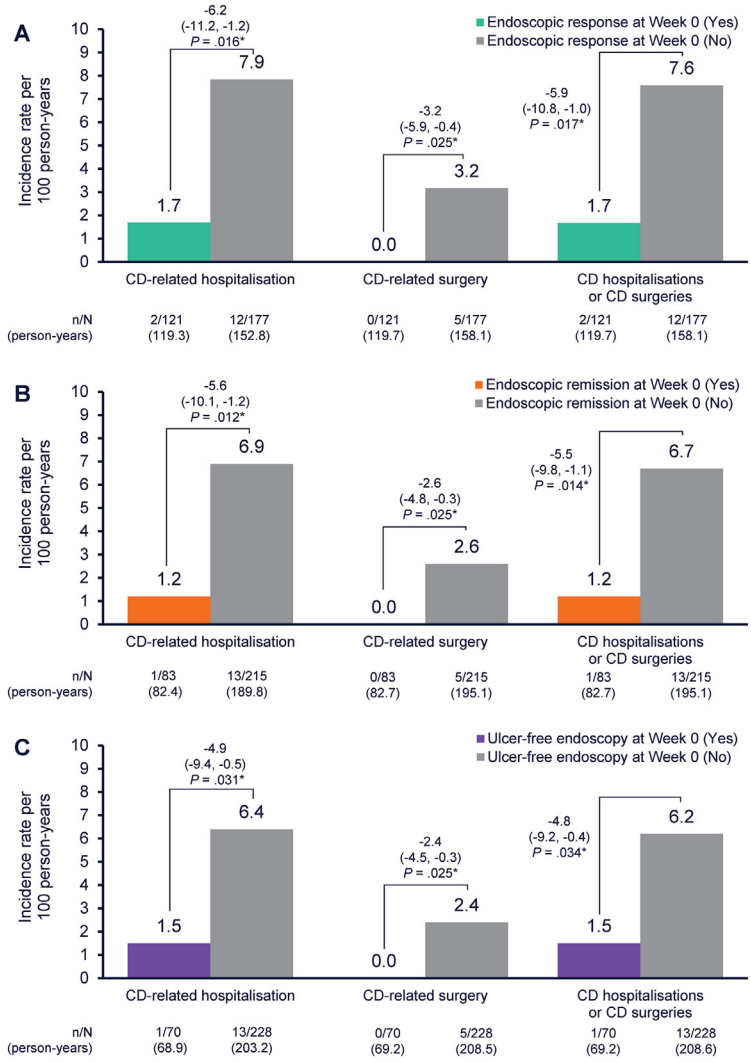

Figure 2. Incidence rate of hospitalization and surgery through Week 52 by endoscopic response (A), endoscopic remission (B) and ulcer-free endoscopy (absence of ulceration) (C) status (achieved [yes] vs did not achieve [no]) at end of 12-week active induction treatment (Week 0 of maintenance phase) among patients who received risankizumab (180 mg and 360 mg combined) during the maintenance period. Data are incidence rate difference with 95% CI presented in parentheses. *$P < .05$ between patients who achieved versus who did not achieve endoscopic outcomes. APS, abdominal pain score BL, baseline; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; SF, stool frequency.

who achieved CDAI deep remission (composite of clinical remission [CDAI <150] and endoscopic remission) at the end of induction compared with those who did not (2.0 vs 5.9 per 100 person years, $P = .121$ and 1.9 vs 5.7 per 100 person years, $P = .129$, respectively; Figure 3A). A similar finding was observed for SF/APS deep remission (composite of clinical remission [average daily SF $\leq$ 2.8 and APS $\leq$1 and not worse than baseline] and endoscopic remission) (hospitalizations: 2.0 vs 5.9, $P = .125$; composite: 1.9 vs 5.7 per 100 person years, $P = .133$; in those who achieved vs did not achieve deep remission, respectively; Figure 3B). No CD-related surgeries occurred through 52 weeks of active risankizumab maintenance in patients who achieved CDAI, or SF/APS deep remission compared to those who did not (0 vs 2.2 per 100 person years, $P = .025$, Figure 3A and B).

CD-related Events by Prior Biologic Failure Status

Consistent with the primary analysis, patients with prior biologic failure who achieved predefined endoscopic responses (endoscopic response, endoscopic remission, or ulcer-free endoscopy) with risankizumab induction treatment compared to those who did not achieve such a response also experienced significantly reduced CD-related hospitalization and surgery rates ($P < .05$, Table A2) through 52 weeks of maintenance therapy with risankizumab. The highest rates of CD-related hospitalizations or surgeries through 52 weeks were observed among patients who had previously failed a biologic and did not achieve a response after induction (eg, patients not achieving endoscopic response; hospitalization rate: 10.2 per 100 person years). The sample size in the nonbiologic failure population was small, limiting interpretations and conclusions.

All-cause Hospitalizations and Surgeries

Lower incidence rates of all-cause hospitalization and surgeries were observed through Week 52 of risankizumab maintenance therapy in patients who achieved any of the predefined endoscopic outcomes at the end of induction, compared to those who did not, with many of these outcomes reaching statistical significance ($P < .05$; Figure A1A–E).

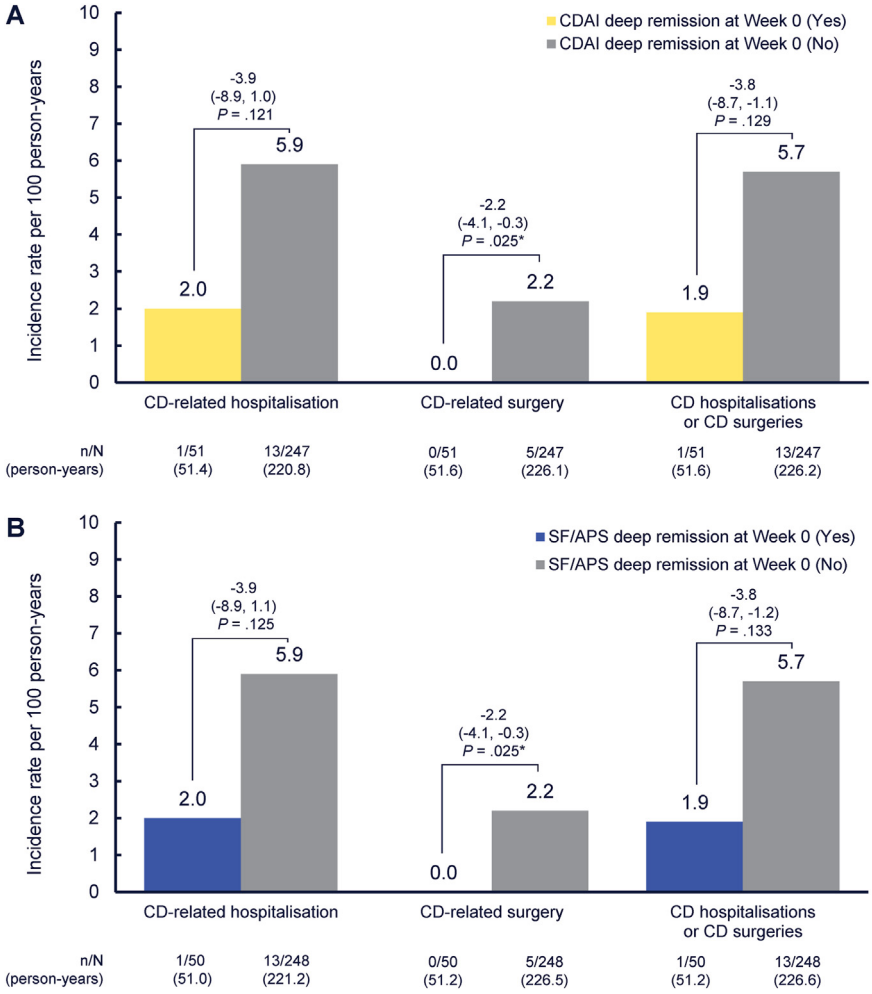

Figure 3. Incidence rate of hospitalization and surgery through Week 52 by CDAI deep remission (A), and SF/APS deep remission (B) status (achieved [yes] vs did not achieve [no]) at end of 12-week active induction treatment (Week 0 of maintenance phase) among patients who received risankizumab (180 mg and 360 mg combined) during the maintenance period. Data are incidence rate difference with 95% CI presented in parentheses. Deep remission defined as a composite of clinical remission ([A] CDAI; [B] SF/APS) and endoscopic remission. CDAI clinical remission: CDAI <150. SF/APS clinical remission: average daily SF $\leq$ 2.8 and not worse than BL and average daily APS $\leq$1 and not worse than BL. *$P < .05$ between patients who achieved versus who did not achieve endoscopic outcomes. APS, abdominal pain score BL, baseline; CD, Crohn's disease; CDAI, Crohn's disease activity index; CI, confidence interval; SF, stool frequency.

Hospitalization and Surgery Rates Among Patients Who Received Withdrawal Placebo during Maintenance

Among induction clinical responders who received withdrawal placebo SC during 52 weeks of maintenance (n = 164), incidence rates of CD-related hospitalizations and/or surgeries were statistically similar (endoscopic response: 7.3 vs 4.3/100 person years; similar trends for all outcomes; all $P > .05$) between those who additionally achieved endoscopic outcomes and those who did not achieve endoscopic outcomes at the end of induction (Figure A2A–E). These results may be expected given that no active treatment was received during the maintenance period. These results contrast with the primary analysis, in which patients who continued active treatment and achieved endoscopic outcomes following induction had reduced rates of CD-related hospitalizations and surgery events relative to those who did not achieve endoscopic outcomes. Additionally, when descriptively comparing the findings among patients who received placebo to the findings in Figures 2 and 3, the event rates were generally numerically higher among patients who received placebo during maintenance compared to those who received risankizumab, even among patients who were responders to endoscopic outcomes following induction therapy. For example, the rate per 100 person years of CD-related hospitalizations was 1.7 in patients who achieved endoscopic response following induction and continued to receive risankizumab through 52 weeks of maintenance and 7.4/100 person years in patients who also achieved endoscopic response following induction but received withdrawal placebo during maintenance.

Discussion

Achieving improvement in the endoscopic appearance in CD has been proposed as a long-term treatment target in the STRIDE II consensus.[13] Our results show that *early* achievement of endoscopic improvement after 12-week risankizumab induction therapy is associated with significant reductions in the rates of CD-related hospitalizations and surgeries among patients receiving risankizumab (combined 180 or 360 mg SC) maintenance therapy for 52 weeks. This observation was consistent regardless of the definition of endoscopic improvement, which included endoscopic response, endoscopic remission, and ulcer-free

endoscopy (absence of ulceration), highlighting the importance of achieving improvement in endoscopic appearance early in the course of disease management. Given that all patients in FORTIFY were also symptomatic responders to induction therapy, these data further demonstrate the incremental long-term benefit of additionally achieving endoscopic outcomes.

In contrast, patients assigned to placebo (ie, withdrawal from active treatment) after induction with risankizumab had similar rates of hospitalization and surgery regardless of achievement of endoscopic outcomes at the end of induction, although they had achieved symptomatic improvement which was required for continued participation in the maintenance trial; this highlights the importance of continued active therapy through maintenance. These findings indicate that the beneficial effects demonstrated are not likely due to the "carryover effect" of active induction therapy that is frequently observed in rerandomized withdrawal trials,[21] but rather the substantial value of continued maintenance treatment with active drug once an induction symptomatic and endoscopic response has occurred.

Although previous studies have evaluated the relationship between endoscopic healing and hospitalization or surgery, the majority of the data, which have been summarized in meta-analyses, are from observational studies.[22,23] While rates of CD-related surgeries in patients who have achieved versus those who did not achieve endoscopic healing have also been shown to be reduced, evidence from randomized controlled trials is limited by low event rates and imprecise estimates of the strength of association.[24] In the CHARM trial, adalimumab-treated patients with CD who achieved deep remission at Week 12 had fewer hospitalizations and CD-related surgeries relative to patients not achieving this outcome.[25] Follow-up data from the CALM trial showed that induction of deep remission was associated with decreased risk of major adverse outcomes (including hospitalization or surgery for CD) over a median time of 3 years.[26] Unlike clinical remission, which has not been shown to improve the natural course of CD, targeting endoscopic outcomes may provide a way to modify CD early in its disease course and improve outcomes.[24,27] Post hoc analysis of the REACT-2 trial also suggest benefits associated with treating to target ulcer healing rather than focusing on symptom-driven care, including reduced levels of CD-related complications.[16] Our study builds upon this existing literature to provide additional evidence supporting endoscopic outcomes as potentially viable treatment targets to improve the natural course of CD.

Lastly, although the cost drivers of CD management have shifted away from the provision of inpatient to outpatient care and biologic drugs, hospitalization and surgery remain costly interventions.[28–30] Indeed, inpatient care and surgery are the most expensive services provided to patients with CD in most jurisdictions.[29,31] In addition, patients with CD report productivity losses through work-related absence and diminished health-related quality of life, which contribute to the economic burden.[32] Slowing disease progression may reduce the costs to health care systems through reduced hospitalization and surgery rates and improved quality of life. Indeed, our study showed that endoscopic improvement is associated with reduced rates of hospitalization and surgery, and this finding is supported by other evidence suggesting that improvement in endoscopic outcomes can slow disease progression in CD.[24,26]

Notwithstanding the promise of endoscopy as a treatment target, it must be noted that important barriers exist to implementing such a strategy. First, the data available regarding the effects of current advanced therapies on endoscopic outcomes are relatively sparse, and direct comparisons between agents are largely unavailable.[33] Second, although the STRIDE-II and SPIRIT guidelines endorse endoscopy as a treatment target,[13] many health care providers, policy makers, and payers continue to support symptom-based care. The reasons for this situation are complex, however, ileocolonoscopy is an expensive and invasive procedure with a well-defined risk of serious complications. Finally, definitive data demonstrating that treating to an endoscopic target with any current advanced therapies is superior to symptom- or biomarker-based management is lacking. Additional evidence is needed for clinicians and payers to endorse endoscopic outcomes as the basis of their decision-making.

Notably, regulatory agencies, including the US Food and Drug Administration and the European Medicines Agency, include endoscopic improvement as a coprimary endpoint, along with symptom control, in the registrational trials for CD.[34,35] The ADVANCE and MOTIVATE studies are the first Phase 3 induction trials completed in CD to include the coprimary endpoints of clinical remission and endoscopic response. Our study included multiple predefined endoscopic outcomes to robustly evaluate their relationship at the end of the induction period with subsequent incidence rates of CD-related hospitalization and surgeries in the maintenance period. While we did not compare surgery or hospitalization events by randomization arm, the controlled clinical trial settings ensured adherence and close monitoring for a significant amount of time. In addition, the determination of disease-related hospitalization and surgeries were verified with clinical input.

There are limitations to this study. One example is the post hoc trial design; although this trial was not designed to answer the research question asked, it has provided a good data source to prevent selection bias in the real-world (eg, patients who underwent endoscopy were patients who had more severe CD). In addition, the results may not be generalizable beyond the study population of patients with moderate to severe CD. In some of the analyses presented, such as deep remission and the number of hospitalization and surgery events, results should be interpreted with caution as sample size in the subgroup was small. Furthermore, there was a relatively low number of events observed overall. Also, data beyond Week 52 will be important to further depict the long-term benefit associated with achievement of endoscopic outcomes early in the course of disease management. Furthermore, in this study, patients who achieved endoscopic outcomes, compared to those who did not, had lower average values in CDAI, SES-CD, daily SF, fecal calprotectin, and CRP

following induction. We did not adjust for these clinical outcomes given that they are probable mediators, rather than confounders, in the causal relationship between endoscopic improvement and hospitalization/surgery (ie, achievement of endoscopic improvement may inherently lead to improvement in clinical symptoms and biomarkers). Therefore, adjusting for these covariates may lead to biased estimates of the association between endoscopic improvement and hospitalization/surgery. Prior biologic failure is considered an effect modifier and not a confounder, so the results were described by stratifying patients with prior failure to biologic at induction baseline (Table A2). The results and trends were consistent among patients with prior biologic failure; however, small sample size in the nonbiologic failure population was too few and limited the ability to draw conclusions. Future prospective studies with larger sample sizes might allow for more sophisticated analyses.

In summary, early improvement of endoscopic outcomes after 12-week induction therapy with risankizumab was associated with significant reductions in CD-related hospitalizations and surgeries through 52 weeks for patients receiving risankizumab maintenance therapy. The observed association between early endoscopic response after induction and long-lasting disease modification with active maintenance therapy underscores the importance of continued maintenance therapy even in patients who have a symptomatic response to induction treatment.

Supplementary Materials

Material associated with this article can be found in the online version at https://doi.org/10.1016/j.gastha.2024.08.022.

References

1. Veauthier B, Hornecker JR. Crohn's disease: diagnosis and management. Am Fam Physician 2018;98:661–669.
2. Dretzke J, Edlin R, Round J, et al. A systematic review and economic evaluation of the use of tumour necrosis factor-alpha (TNF-α) inhibitors, adalimumab and infliximab, for Crohn's disease. Health Technol Assess 2011;15:1–244.
3. Golovics PA, Lakatos L, Mandel MD, et al. Prevalence and predictors of hospitalization in Crohn's disease in a prospective population-based inception cohort from 2000-2012. World J Gastroenterol 2015;21:7272–7280.
4. Cushing K, Higgins PDR. Management of Crohn disease: a review. JAMA 2021;325:69–80.
5. Opstelten JL, Vaartjes I, Bots ML, et al. Mortality after first hospital admission for inflammatory bowel disease: a nationwide registry linkage study. Inflamm Bowel Dis 2019;25:1692–1699.
6. Colombel JF, Sandborn WJ, Rutgeerts P, et al. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007;132:52–65.
7. Feagan BG, Panaccione R, Sandborn WJ, et al. Effects of adalimumab therapy on incidence of hospitalization and surgery in Crohn's disease: results from the CHARM study. Gastroenterology 2008;135:1493–1499.
8. Khanna R, Bressler B, Levesque BG, et al. Early combined immunosuppression for the management of Crohn's disease (REACT): a cluster randomised controlled trial. Lancet 2015;386:1825–1834.
9. Panaccione R, Colombel JF, Sandborn WJ, et al. Adalimumab maintains remission of Crohn's disease after up to 4 years of treatment: data from CHARM and ADHERE. Aliment Pharmacol Ther 2013;38:1236–1247.
10. Singh S, Stitt LW, Zou G, et al. Early combined immunosuppression may be effective and safe in older patients with Crohn's disease: post hoc analysis of REACT. Aliment Pharmacol Ther 2019;49:1188–1194.
11. Waterland P, Athanasiou T, Patel H. Post-operative abdominal complications in Crohn's disease in the biological era: systematic review and meta-analysis. World J Gastrointest Surg 2016;8:274–283.
12. Peyrin-Biroulet L, Sandborn W, Sands BE, et al. Selecting therapeutic targets in inflammatory bowel disease (STRIDE): determining therapeutic goals for treat-to-target. Am J Gastroenterol 2015;110:1324–1338.
13. Turner D, Ricciuto A, Lewis A, et al. STRIDE-II: an uUpdate on the selecting therapeutic targets in inflammatory bowel disease (STRIDE) Initiative of the International Organization for the study of IBD (IOIBD): determining therapeutic goals for treat-to-target strategies in IBD. Gastroenterology 2021;160:1570–1583.
14. Le Berre C, Peyrin-Biroulet L. Selecting end points for disease-modification trials in inflammatory bowel disease: the SPIRIT consensus from the IOIBD. Gastroenterology 2021;160:1452–1460.e21.
15. Panaccione R, Colombel JF, Travis SPL, et al. Tight control for Crohn's disease with adalimumab-based treatment is cost-effective: an economic assessment of the CALM trial. Gut 2020;69:658–664.
16. Jairath V, Khanna R, Guizzetti L, et al. OP110 a cluster-randomised controlled trial of an enhanced treatment algorithm for the management of Crohn's disease: REACT-2 [abstract]. United European Gastroenterol J 2022;10(Suppl 8):1088–1089.
17. D'Haens G, Panaccione R, Baert F, et al. Risankizumab as induction therapy for Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE induction trials. Lancet 2022;399:2015–2030.
18. Ferrante M, Panaccione R, Baert F, et al. Risankizumab as maintenance therapy for moderately to severely active Crohn's disease: results from the multicentre, randomised, double-blind, placebo-controlled, withdrawal phase 3 FORTIFY maintenance trial. Lancet 2022;399:2031–2046.
19. Schreiber SW, Ferrante M, Panaccione R, et al. OP26 Risankizumab induces early clinical remission and response in patients with moderate-to-severe Crohn's disease: results from the phase 3 ADVANCE and MOTIVATE studies. J Crohn's Colitis 2021;15:S026–S027.
20. Daperno M, D'Haens G, Van Assche G, et al. Development and validation of a new, simplified endoscopic activity score for Crohn's disease: the SES-CD. Gastrointest Endosc 2004;60:505–512.
21. Sands BE, Sandborn WJ, Panaccione R, et al. Ustekinumab as induction and maintenance therapy for ulcerative colitis. New Engl J Med 2019;381:1201–1214.

22. Neurath MF, Travis SP. Mucosal healing in inflammatory bowel diseases: a systematic review. Gut 2012;61:1619–1635.
23. Reinink AR, Lee TC, Higgins PD. Endoscopic mucosal healing predicts favorable clinical outcomes in inflammatory bowel disease: a meta-analysis. Inflamm Bowel Dis 2016;22:1859–1869.
24. Shah SC, Colombel JF, Sands BE, et al. Systematic review with meta-analysis: mucosal healing is associated with improved long-term outcomes in Crohn's disease. Aliment Pharmacol Ther 2016;43:317–333.
25. Colombel JF, Rutgeerts PJ, Sandborn WJ, et al. Adalimumab induces deep remission in patients with Crohn's disease. Clin Gastroenterol Hepatol 2014;12:414–422.e5.
26. Ungaro RC, Yzet C, Bossuyt P, et al. Deep remission at 1 year prevents progression of early Crohn's disease. Gastroenterology 2020;159:139–147.
27. Peyrin-Biroulet L, Loftus EV Jr, Colombel JF, et al. The natural history of adult Crohn's disease in population-based cohorts. Am J Gastroenterol 2010;105:289–297.
28. Boschetti G, Nancey S, Daniel F, et al. Costs of Crohn's disease according to severity states in France: a prospective observational study and statistical modeling over 10 years. Inflamm Bowel Dis 2016;22:2924–2932.
29. Pillai N, Dusheiko M, Maillard MH, et al. The evolution of health care utilisation and costs for inflammatory bowel disease over ten years. J Crohns Colitis 2019;13:744–754.
30. Singh S, Qian AS, Nguyen NH, et al. Trends in U.S. health care spending on inflammatory bowel diseases, 1996-2016. Inflamm Bowel Dis 2022;28:364–372.
31. Wylezinski LS, Gray JD, Polk JB, et al. Illuminating an invisible epidemic: a systemic review of the clinical and economic benefits of early diagnosis and treatment in inflammatory disease and related syndromes. J Clin Med 2019;8:493.
32. Ganz ML, Sugarman R, Wang R, et al. The economic and health-related impact of Crohn's disease in the United States: evidence from a nationally representative survey. Inflamm Bowel Dis 2016;22:1032–1041.
33. Bertani L. Treatment and management of chronic inflammatory bowel diseases: optimizing present and future therapeutic choices. J Clin Med 2022;11:5267.
34. FDA. Crohn's disease: developing drugs for treatment guidance for industry. DRAFT April 2022. US Department of Health and Human Services and Food and Drug Administration, 2022. Draft guidance. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/crohns-disease-developing-drugs-treatment. Accessed September 30, 2024.
35. EMA. Guideline on the development of new medicinal products for the treatment of Crohn's Disease. Committee for Medicinal Products for Human Use, 2018.

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Ethical Statement:
All three randomized controlled trials were conducted in compliance with the protocol, International Conference on Harmonization guidelines, and the ethical principles of the Declaration of Helsinki. As per Good Clinical Practice, the study protocol, informed consent forms, and all other explanatory materials were approved by the relevant ethics committees or institutional review board at all study sites. All patients provided informed consent before study participation.

Data Transparency Statement:
Part of this work was presented at the 17th Congress of the European Crohn's and Colitis Organization (ECCO 2022), February 16–19, 2022, virtual. AbbVie is committed to responsible data sharing regarding the clinical trials we sponsor. This includes access to anonymized, individual, and trial-level data (analysis data sets), as well as other information (eg, protocols, clinical study reports, or analysis plans), as long as the trials are not part of an ongoing or planned regulatory submission. This includes requests for clinical trial data for unlicensed products and indications. These clinical trial data can be requested by any qualified researchers who engage in rigorous, independent, scientific research, and will be provided following review and approval of a research proposal, Statistical Analysis Plan (SAP), and execution of a Data Sharing Agreement (DSA). Data requests can be submitted at any time after approval in the US and Europe and after acceptance of this manuscript for publication. 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://vivli.org/ourmember/abbvie/ then select "Home".

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