



Matching-Adjusted Indirect Comparison Between Risankizumab and Ustekinumab for Induction and Maintenance Treatment of Moderately to Severely Active Crohn's Disease

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ABSTRACT

Introduction: Risankizumab (RZB) and ustekinumab (UST), interleukin (IL)-23 and IL-12/23 inhibitors, respectively, are approved treatments for moderately to severely active Crohn's disease (CD); direct comparison between the two is ongoing. We indirectly compared efficacy of RZB versus UST using data from phase 3 trials (RZB: NCT03104413; NCT03105128; NCT03105102; UST: NCT01369329; NCT01369342; NCT01369355).

Methods: Matching-adjusted indirect comparison was conducted using individual patient-level data from RZB trials and published

aggregated data from UST trials. During induction, patients received RZB 600 mg intravenous (IV) at weeks 0, 4, and 8 or a single dose of UST 6 mg/kg IV at week 0. During maintenance, patients received RZB 180 or 360 mg subcutaneous (SC) or UST 90 mg SC every 8 or 12 weeks to 52 weeks. Outcomes included proportion of patients achieving Crohn's Disease Activity Index (CDAI) response (decrease of ≥ 100 points or total score < 150) or remission (CDAI ≤ 150) and endoscopic improvement (measured by the Simple Endoscopic Score in CD [SES-CD]; response, $\geq 50\%$ reduction from baseline; remission, SES-CD ≤ 2) following induction/baseline.

Results: Higher proportions of patients achieved clinical and endoscopic outcomes with RZB vs. UST induction treatment, resulting in significantly ($p \leq 0.05$) greater percent differences (95% confidence intervals) between groups for CDAI remission (15% [5%, 25%]) and endoscopic response (26% [13%, 40%]) and remission (9% [0%, 19%]). Following maintenance, rates of CDAI remission were similar (range -0.3% to -5.0%) for RZB vs. UST. Differences for endoscopic response and remission ranged from 9.3% to 27.7% and 11.6% to 12.5%, respectively; differences were significant ($p < 0.05$) for endoscopic response for both doses of RZB compared to UST 12-week dosing. **Conclusions:** This indirect comparison demonstrated higher rates of clinical and endoscopic outcomes during induction for RZB

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compared to UST; CDAI remission following maintenance was comparable. Direct comparisons of RZB and UST are warranted to validate these findings.

PLAIN LANGUAGE SUMMARY

Using individual patient-level data from risankizumab and aggregated data from ustekinumab phase 3 Crohn's disease trials, we indirectly compared efficacy of risankizumab and ustekinumab to determine whether rates of improvement in disease symptoms (clinical) and endoscopic outcomes differed between treatments. Findings showed that clinical and endoscopic outcomes were more frequently achieved for patients receiving risankizumab versus ustekinumab after induction, while most maintenance outcomes were comparable.

Keywords: CDAI; Crohn's disease; Endoscopic improvement; Matching-adjusted indirect comparison; Risankizumab; Ustekinumab

Key Summary Points

Why carry out this study?

Risankizumab (RZB), a targeted interleukin (IL)-23 inhibitor, was recently approved for use in patients with moderately to severely active Crohn's disease (CD); direct comparisons to ustekinumab in CD is currently being conducted (NCT04524611)

This study indirectly compared efficacy of RZB with ustekinumab (UST), an IL-12/23 inhibitor, using phase 3 clinical trial data; outcomes assessed were CD Activity Index (CDAI) response and remission, as well as endoscopic response and remission as measured by Simple Endoscopic Score in CD (SES-CD)

What was learned from the study?

Using matching-adjusted indirect comparison analyses, this study showed that greater proportions of patients receiving RZB versus UST treatment achieved CDAI and endoscopic outcomes after induction, while maintenance treatment was generally comparable

The findings of this study, which characterized the comparative effectiveness of RZB versus UST, may assist in clinical decision-making, ensuring that appropriate treatments are selected for the patient, thereby increasing the likelihood of achieving treatment targets

INTRODUCTION

Crohn's disease (CD) is a chronic, progressive inflammatory disease of the gastrointestinal tract, characterized by abdominal pain, diarrhea, fatigue, and weight loss [1–3]. Management of CD involves induction and maintenance therapy with the overall goal of improving patient symptoms. Clinical recommendations for treatment of CD, as described in the recent Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) II initiative of the International Organization for the Study of Inflammatory Bowel Diseases (IOIBD), have identified short-term, intermediate, and long-term targets [3]. Induction therapy is intended to improve symptoms and normalize C-reactive protein levels in the short term, after which maintenance therapy is employed to normalize calprotectin levels as an intermediate target [4]. Long-term targets include normalization of patient quality of life, absence of disability, and endoscopic healing [4]. The Crohn's Disease Activity Index (CDAI) is a measure commonly used to assess patient outcomes and captures symptoms such as abdominal pain, stool frequency, body weight, and extraintestinal complications [5, 6]. In recent years, endoscopy, an objective measure of disease activity, has been used to provide assurance

that changes in clinical symptoms align with mucosal improvements [5, 7]. Indeed, STRIDE II recommendations have deemed endoscopic healing as a primary long-term target of treatment, with endoscopic response suitable as a short-term target [4]. Recent guidelines from the US Food and Drug Administration recommend endoscopic outcomes be included in clinical trials for CD, with endoscopic response defined as a 50% reduction in Simple Endoscopic Score for Crohn's Disease (SES-CD) and remission defined as an SES-CD of 0–2 [8].

Biologics have been shown to be effective in induction of clinical response and clinical remission as measured by CDAI scores [9, 10]. Inhibitors of tumor necrosis factor (TNF) are effective in the treatment of moderately to severely active CD that has failed to respond to conventional therapy [3, 11]. However, approximately a third of patients treated with anti-TNF therapies do not have an initial response to therapy [12]. A relatively recently approved (2016) biologic ustekinumab (UST), an anti-interleukin (IL)-12/23, has emerged as an alternative option that targets a different inflammatory pathway [3, 12–14]. Risankizumab (RZB), the first specific IL-23 inhibitor, is the newest biologic therapy on the market after receiving approval for treatment of adults with moderately to severely active CD in the USA, Canada, and the European Union in 2022 [15–17]. In two induction trials and one maintenance trial, RZB demonstrated significant improvements compared to placebo (PBO) in both clinical (CDAI) and endoscopic outcomes (measured by SES-CD) [18, 19].

Considering that both UST and RZB have demonstrated efficacy in patients with CD who had previously failed conventional care (CCF) or biologic therapies (BF), evidence characterizing the comparative effectiveness of RZB versus UST is needed to assist in clinical decision-making in the treatment of CD [3, 18, 19]. Moreover, while they have similar mechanisms of action (i.e., IL-23 inhibition), RZB is the first CD therapy to demonstrate endoscopic improvement as a ranked co-primary endpoint [18, 19]. Given the very recent approval of RZB, no direct comparisons to UST in CD have been published. However, indirect treatment

comparison (ITC) methods can be used to assess the comparative effectiveness of different treatments [20, 21].

Network meta-analysis (NMA) is a common form of ITC which uses multiple aggregate relative effect measures to synthesize different studies. However, traditional NMA assumes that population characteristics that may influence the outcome of treatment do not differ between studies [20]. To address this limitation, we used matching-adjusted indirect comparison (MAIC) to compare the effectiveness of the two therapies. In MAIC, propensity score weighting of individual patient data (IPD) from one of the studies is used to balance population characteristics that may influence outcomes [21]. While phase 3 studies of RZB and UST were similar in eligibility criteria and study design, key differences may exist between the populations. For example, BF patients in RZB studies may have previous exposure to UST and/or vedolizumab (VDZ), which was exclusionary in UST studies. This study conducted MAICs comparing the effectiveness of RZB versus UST as induction and maintenance therapy for treatment of moderately to severely active CD in adults (CCF and/or BF), focusing on CDAI response and remission, as well as endoscopic response and endoscopic remission. It aims to provide an objective comparison so that clinicians may form their own opinions on when to use UST or RZB given their specific patient's needs.

METHODS

Study Design and Participants

This study used IPD available from the RZB clinical studies ADVANCE, MOTIVATE, and FORTIFY (NCT03104413; NCT03105128; NCT03105102) [18, 19]. Aggregated population characteristics and outcomes data for UST studies were extracted from the UNITI-1, UNITI-2, and IM-UNITI publications (NCT01369329; NCT01369342; NCT01369355) [6, 22]. Outcome definitions in the RZB IPD were modified to match the definitions used in the UST studies to ensure comparability. These definitions

differed marginally from the reported phase 3 RZB clinical program for CDAI response and endoscopic outcomes.

MAICs comparing RZB to UST adjusting for between-study population differences in effect modifiers were conducted for all combinations of outcomes, populations, and relevant maintenance dosing variations of RZB and UST based on data availability.

RZB patients included in the analysis were adults diagnosed with CD who were either CCF or BF prior to induction therapy. RZB patients with previous exposure to UST or VDZ were excluded to match the inclusion criteria used in the UST phase 3 program. Additionally, those RZB-treated patients who missed an efficacy measurement or discontinued treatment as a result of COVID-19 were excluded. The following dose groups were included for RZB: 600 mg intravenous (IV) induction at weeks 0/4/8 and 180 or 360 mg subcutaneous (SC) every 8 weeks for maintenance. For UST only published data for the single 6 mg/kg IV loading dose (approved dosing) along with 90 mg SC administered every 8 or 12 weeks for maintenance (Q8W and Q12W, respectively) were included. The UST 6 mg/kg induction dose approximates dosing by weight range (i.e., less than 55 kg, 260 mg; 55–85 kg, 390 mg; greater than 85 kg, 520 mg).

Clinical Outcomes

Analyses for this study included anchored MAICs comparing RZB versus UST for CDAI response, CDAI remission, endoscopic response, and endoscopic remission at induction and maintenance among the different populations (CCF only, BF only, and CCF + BF) and dosing variations when relevant.

Outcome definitions from the UST trials were used. In RZB studies, outcomes were defined as the following: CDAI response, at least a 100-point decrease in CDAI from baseline; endoscopic response, at least 50% decrease in SES-CD from baseline or at least 2-point reduction from baseline for patients with isolated ileal disease and a baseline SES-CD of 4; endoscopic remission, SES-CD ≤ 4 and at least a

2-point reduction from baseline and no subscore greater than 1 in any individual variable. For this analysis, outcome variables in the RZB IPD were recoded on the basis of the underlying CDAI and SES-CD data and the UST definitions. As such, CDAI response was defined as a decrease from baseline of at least 100 points or CDAI < 150 (CDAI remission was defined as a CDAI < 150 in both RZB and UST studies). An endoscopic response was defined as a 50% or greater reduction from baseline in SES-CD score, and endoscopic remission as a total SES-CD score ≤ 2 . As a result of limitations of the data reported for UST studies, induction and maintenance MAICs of endoscopic outcomes could only be reported for the CCF + BF population; likewise, there was also no ability to evaluate CDAI response for the maintenance MAICs as it was not reported in UST studies.

Statistical Analysis of Data

The feasibility of conducting the planned analyses was assessed on the basis of review of similarity in design of the RZB and UST studies; inclusion of a common comparator in the studies assessed (allowing for anchored analysis); and completeness of the reported UST data required for the analyses. In the induction studies, the IV PBO arms were considered sufficiently similar to act as an anchor/common comparator; for maintenance studies, the active treatment withdrawal PBO groups were considered the anchor/common comparator.

MAICs were conducted adjusting for differences in treatment effect-modifying variables between the RZB and UST study populations using a structured process that identified matching variables following recommendations from the National Institute for Health Care Excellence (NICE) guidance on MAIC methodology [21]. This process included a targeted literature review to identify factors predictive of the treatment effect of biologic therapies in CD, clinical input, and review of UST pivotal publications [7, 22] and RZB IPD for availability of data on effect-modifying factors. Where effect modifier distributions or values were available, tests of statistical significance of differences

between the UST and RZB populations were conducted. RZB patients were weighted such that their mean baseline characteristics matched those reported for the published UST trials for effect-modifying variables. Weights were obtained on the basis of a logistic regression model for the propensity of enrollment in the RZB trial versus the UST trial (weights estimated as the inverse of the propensity), with matched baseline characteristics identified from the structured process described above using a method-of-moments-based matching approach. Treatment effect-modifying variables ultimately used in the matching included duration of disease categories, disease severity (induction baseline CDAI > 300, induction baseline CRP > 0.5 mg/dL), disease phenotype (stenosis current or past), previous biologic failure, and prior number of failed biologics.

Baseline characteristics before and after matching were compared between RZB and UST cohorts using two-sided Wald tests for categorical variables and *t* tests for continuous variables. The log-odds ratio of RZB versus PBO was estimated along with its 95% confidence interval (CI) and then back-transformed to estimate absolute probabilities of response [21]. Of note, as described in MAIC methodological guidance, estimates of absolute outcomes may be biased if there is substantial imbalance of prognostic factors across the populations, as only effect-modifying factors are adjusted for in anchored MAIC [21].

The relative effect measure of RZB compared to UST was calculated as the difference in the PBO-subtracted response rates for RZB and UST; statistically significant differences ($p \leq 0.05$) were assessed using a two-sample test of binomial proportions. Differences in the absolute effect measure were assessed on the basis of comparison of the 95% CI estimated in the MAIC for RZB, and the Wald 95% CI calculated for UST.

To assess the effectiveness of RZB and UST in inducing and maintaining clinical outcomes, a “treat-through” sensitivity analysis was also conducted in the combined CCF + BF population wherein the clinical response rate during induction was multiplied by the clinical remission rate during maintenance. This analysis

estimates the expected proportion of patients achieving clinical remission across both induction and maintenance; a full description of this analysis is in Appendix A (Supplementary Material). The PBO-subtracted relative response rates of achieving clinical remission (95% CIs) for RZB- versus UST-treated patients are reported.

Ethical Statement

This study, and each clinical trial included in the analysis, was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice, Good Epidemiology Practices, and applicable regulatory requirements [7, 18, 19, 22]. This analysis utilized de-identified data from published clinical trial data; thus, no ethics committee approval was required. However, each individual trial included in this analysis was approved by independent ethics committees or institutional review boards at each study site and all patients (or parents/legal guardians for adolescent patients) provided written informed consent before enrolling in each clinical trial [7, 18, 19, 22].

RESULTS

Patient Demographics

Baseline characteristics before and after matching for effect modifiers among patients receiving RZB or UST induction are presented in Table 1 for induction and Tables 2 and 3 for maintenance analyses. A full list of patient demographics and clinical characteristics prior to and after matching is provided in Supplementary Materials (Tables S1–S3). Briefly, after matching, the RZB groups closely aligned with the UST groups, with similar disease durations, similar rates of ileal disease involvement, CDAI severity, and prior failure of TNF inhibitors. The effective sample size for the RZB-treated groups ranged from 146 to 325 in induction and

Table 1 Baseline demographic and clinical characteristics of patients in induction studies, before and after matching (RZB 600 mg)

	RZB 600 mg IV ^a before matching			UST 6 mg/kg IV			RZB 600 mg IV ^a after matching			
	CCF	BF	CDAI	CCF	BF	CDAI	CCF	BF	CDAI	
N/ESS	212	379	591	419	496	915	252	204	302	325
Disease characteristics										
Time since diagnosis (years), mean	7.4	7.4	8.7	8.8	12.4	11.1	11.1	11.4	11.4	12.0
Time since diagnosis < 2 years, %	38.7%*	38.7%*	21.5%*	21.6%	11.9%	7.6%	16.8%	20.4%	11.9%	16.8%
Time since diagnosis ≥ 2 and < 5 years, %	17.5%	17.5%	20.1%*	19.7%*	8.4%	9.3%	9.1%	19.8%	8.3%	9.1%
Time since diagnosis ≥ 5 and < 15 years, %	26.9%*	26.9%*	39.9%*	40.2%	49.9%	56.2%	40.0%	39.5%	49.9%	40.0%
Time since diagnosis ≥ 15 years, %	17.0%	17.0%	18.4%*	18.5%*	29.9%	26.9%	34.1%	20.3%	29.9%	34.1%
Location, %										
Ileum only	15.1%	15.8%	15.6%	15.5%	13.3%	17.3%	19.1%	15.4%	17.7%	16.0%
Phenotype, %										
Stricturing/stenosis (current or past)	20.3%*	23.0%*	22.0%*	21.6%*	45.0%	38.8%	36.1%	31.5%	45.0%	36.1%
Disease severity										
CDAI > 300, %	57.1%*	52.0%	53.8%	53.9%	60.1%	51.8%	59.0%	42.1%	60.1%	59.0%
Lab and immune markers										
CRP > 0.5 mg/dL, %	54.3%*	68.3%	63.2%*	63.3%	68.8%	74.3%	67.7%	67.0%	69.2%	67.9%
Treatment history										
Prior anti-TNF failure, %	0.0%	100.0%	64.1%*	63.7%*	100.0%	54.2%	42.5%	0.0%	100.0%	42.5%
Prior failure	0.0%	100.0%	64.1%*	63.7%*	100.0%	54.2%	42.5%	0.0%	100.0%	42.5%
Prior anti-TNFs failed, %	0.0%	72.8%*	46.7%*	N/A	0.0%	25.6%	NR	0.0%	6.5%	25.2%
One prior failed	0.0%	72.8%*	46.7%*	N/A	0.0%	47.2%	NR	0.0%	6.5%	25.2%
One prior failed	0.0%	72.8%*	46.7%*	N/A	0.0%	47.2%	NR	0.0%	6.5%	25.2%

Table 1 continued

	RZB 600 mg IV ^a before matching			UST 6 mg/kg IV			RZB 600 mg IV ^a after matching					
	CCF	BF	CCF + BF	CCF	BF	CCF + BF	CCF	BF	CCF + BF			
	CDAI	CDAI	Endo	CDAI	CDAI	Endo	CDAI	CDAI	Endo			
2–3 prior failed	0.0%	27.2%*	17.4%*	N/A	0.0%	52.8%	28.6%	NR	0.0%	53.5%	29.0%	N/A

BF biologic failure, CCF conventional care failure, CDAI Crohn's disease Activity Index, CRP c-reactive protein, Endo endoscopic, ESS effective sample size, NA not applicable, NR not reported, RZB risankizumab, SC subcutaneous, UST ustekinumab

* $p \leq 0.05$ for RZB versus UST based on two-sided test of binomial proportions (percentages) and t tests (continuous variables)

^aRZB values exclude UST/VDZ-exposed and/or COVID-19-impacted patients

138–194 in maintenance, with the largest impact on the BF population because patients with prior UST/VDZ were excluded.

Rates of Response and Remission Following Induction Therapy

Following induction therapy with RZB or UST, a higher proportion of patients, in all populations and active treatment groups, achieved CDAI and endoscopic outcomes as compared to PBO (Fig. 1). Among CCF, BF, and CCF + BF populations, absolute and relative (i.e., PBO-adjusted) effect measures for CDAI response and remission favored RZB (Fig. 1a–c).

Among the CCF population, the absolute proportion of RZB-treated patients achieving clinical remission was significantly greater than UST-treated patients (56.3% vs. 40.2%; $p \leq 0.05$; Fig. 1a). More RZB-treated BF patients achieved clinical response (64.0% vs. 37.8%; $p \leq 0.05$) and remission (46.8% vs. 20.9%; $p \leq 0.05$) compared with UST-treated patients (Fig. 1b). Likewise, a greater proportion of CCF + BF patients achieved clinical response (66.5% vs. 47.0%, $p \leq 0.05$) and clinical remission (53.9% vs. 29.7%; $p \leq 0.05$), endoscopic response (45.5% vs. 21.7%, $p \leq 0.05$), and endoscopic remission (19.4% vs. 8.4%; $p \leq 0.05$) versus UST-treated patients (Fig. 1c, d).

Although numeric differences favored RZB for all clinical outcomes in the analyses, the relative differences reached statistical significance only in the CCF + BF population for clinical remission with 14.6% (95% CI 4.6%, 24.5%; $p \leq 0.05$; Fig. 1c) more RZB patients achieving this outcome compared with UST. Likewise, relative effect measures were statistically significant in CCF + BF RZB- vs. UST-treated patients for endoscopic response (26.3% [13.0%, 39.6%]; $p \leq 0.05$) and endoscopic remission (9.3% [0.0%, 18.6%]; $p \leq 0.05$; Fig. 1d).

Rates of Response and Remission Following Maintenance Therapy

Available data from UST trials only assessed maintenance outcomes among the CCF + BF

Table 2 Baseline demographic and clinical characteristics of patients in maintenance studies, before and after matching (RZB 180 mg)

	RZB (180 mg SC) ^a before matching				UST				RZB (180 mg SC) ^a after matching			
	CCF + BF vs. Q8W		CCF + BF vs. Q12W		UST (90 mg/kg Q8W)		UST (90 mg/kg Q12W)		CCF + BF vs. Q8W		CCF + BF vs. Q12W	
	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI
N/ESS	232	232	232	232	265	53	265	41	194	152	190	140
Disease characteristics												
Time since diagnosis (years), mean	9.5	9.5	9.5	9.5	10.1	10.7	10.5	11.6	9.0	8.6	9.1	8.0
Time since diagnosis < 2 years, %	22.8%	22.8%	22.8%	22.8%	18.8%	18.7%	17.6%	18.5%	28.4%	32.4%	28.3%	32.8%
Time since diagnosis ≥ 2 and < 5 years, %	19.4%	19.4%	19.4%	19.4%	15.9%	9.5%	17.0%	8.4%	16.7%	14.8%	16.3%	15.6%
Time since diagnosis ≥ 5 and < 15 years, %	34.5%	34.5%	34.5%*	34.5%	42.0%	39.3%	46.9%	35.7%	33.8%	33.2%	33.9%*	33.8%
Time since diagnosis ≥ 15 years, %	23.3%	23.3%	23.3%	23.3%	23.2%	32.6%	18.5%	37.4%	21.1%	19.5%	21.5%	17.9%
Location, %												
Ileum only	11.6%	11.6%	11.6%	11.6%	14.3%	15.1%	17.0%	4.9%	14.3%	15.1%	17.0%	4.9%
Phenotype, %												
Stricturing/stenosis (current or past)	N/A	19.4%	N/A	19.4%	NR	32.1%	NR	34.1%	N/A	19.9%	N/A	18.6%
Disease severity												
CDAI > 300, %	51.7%	51.7%	51.7%	51.7%	60.6%	63.7%	62.2%	64.6%	60.6%	63.7%	62.2%	64.6%
Lab and immune markers												
CRP > 0.5 mg/dL, %	N/A	66.5%	N/A	66.5%	NR	73.9%	NR	76.6%	N/A	65.3%	N/A	66.1%
Treatment history												
Prior anti-TNF failure, %	63.8%*	63.8%*	63.8%*	63.8%*	44.9%	32.1%	45.3%	31.7%	44.9%	32.1%	45.3%	31.7%

BF biologic failure, CCF conventional care failure, CDAI Crohn's disease Activity Index, CRP c-reactive protein, Endo endoscopic, ESS effective sample size, NA not applicable, NR not reported, RZB risankizumab, SC subcutaneous, UST ustekinumab

* $p \leq 0.05$ for RZB versus UST based on two-sided test of binomial proportions (percentages) and t tests (continuous variables)

^aRZB values exclude UST/VDZ-exposed and/or COVID-19-impacted patients

Table 3 Baseline demographic and clinical characteristics of patients in maintenance studies, before and after matching (RZB 360 mg)

	RZB (360 mg SC) ^a before matching				UST		RZB (360 mg SC) ^a after matching					
	CCF + BF vs. Q8W		CCF + BF vs. Q12W		UST (90 mg/kg Q8W)		UST (90 mg/kg Q12W)		CCF + BF vs. Q8W		CCF + BF vs. Q12W	
	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo
N/ESS	220	220	220	220	265	53	265	41	180	141	178	138
Disease characteristics												
Time since diagnosis (years), mean	9.0	9.0	9.0	9.0	10.1	10.7	10.5	11.6	8.3	7.8	8.2	7.8
Time since diagnosis < 2 years, %	22.7%	22.7%	22.7%	22.7%	18.8%	18.7%	17.6%	18.5%	29.3%	33.7%	29.3%*	33.9%
Time since diagnosis ≥ 2 and < 5 years, %	19.6%	19.6%	19.6%	19.6%	15.9%	9.5%	17.0%	8.4%	17.8%	16.7%	17.7%	16.6%
Time since diagnosis ≥ 5 and < 15 years, %	35.9%	35.9%	35.9%	35.9%	42.0%	39.3%	46.9%	35.7%	33.3%	31.3%	33.4%*	31.3%
Time since diagnosis ≥ 15 years, %	21.8%	21.8%	21.8%	21.8%	23.2%	32.6%	18.5%	37.4%	19.6%	18.3%	19.6%	18.2%
Location, %												
Ileum only	14.1%	14.1%	14.1%	14.1%	14.3%	15.1%	17.0%	4.9%	15.6%	16.9%	15.5%	16.9%
Phenotype, %												
Stricturing/stenosis (current or past)	N/A	20.5%	N/A	20.5%	NR	32.1%	NR	34.1%	N/A	20.9%	N/A	20.9%
Disease severity												
CDAI > 300, %	47.7%*	47.7%	47.7%*	47.7%	60.6%	63.7%	62.2%	64.6%	60.6%	63.7%	62.2%	64.6%
Lab and immune markers												
CRP > 0.5 mg/dL, %	N/A	66.4%	N/A	66.4%	NR	73.9%	NR	76.6%	N/A	66.4%	N/A	66.5%
Treatment history												
Prior anti-TNF failure, %	64.1%*	64.1%*	64.1%*	64.1%*	44.9%	32.1%	45.3%	31.7%	44.9%	32.1%	45.3%	31.7%

BF biologic failure, CCF conventional care failure, CDAI Crohn's disease Activity Index, CRP c-reactive protein, Endo endoscopic, ESS effective sample size, NA not applicable, NR not reported, RZB risankizumab, SC subcutaneous, UST ustekinumab

*p ≤ 0.05 for RZB versus UST based on two-sided test of binomial proportions (percentages) and t tests (continuous variables)

^aRZB values exclude UST/VDZ-exposed and/or COVID-19-impacted patients

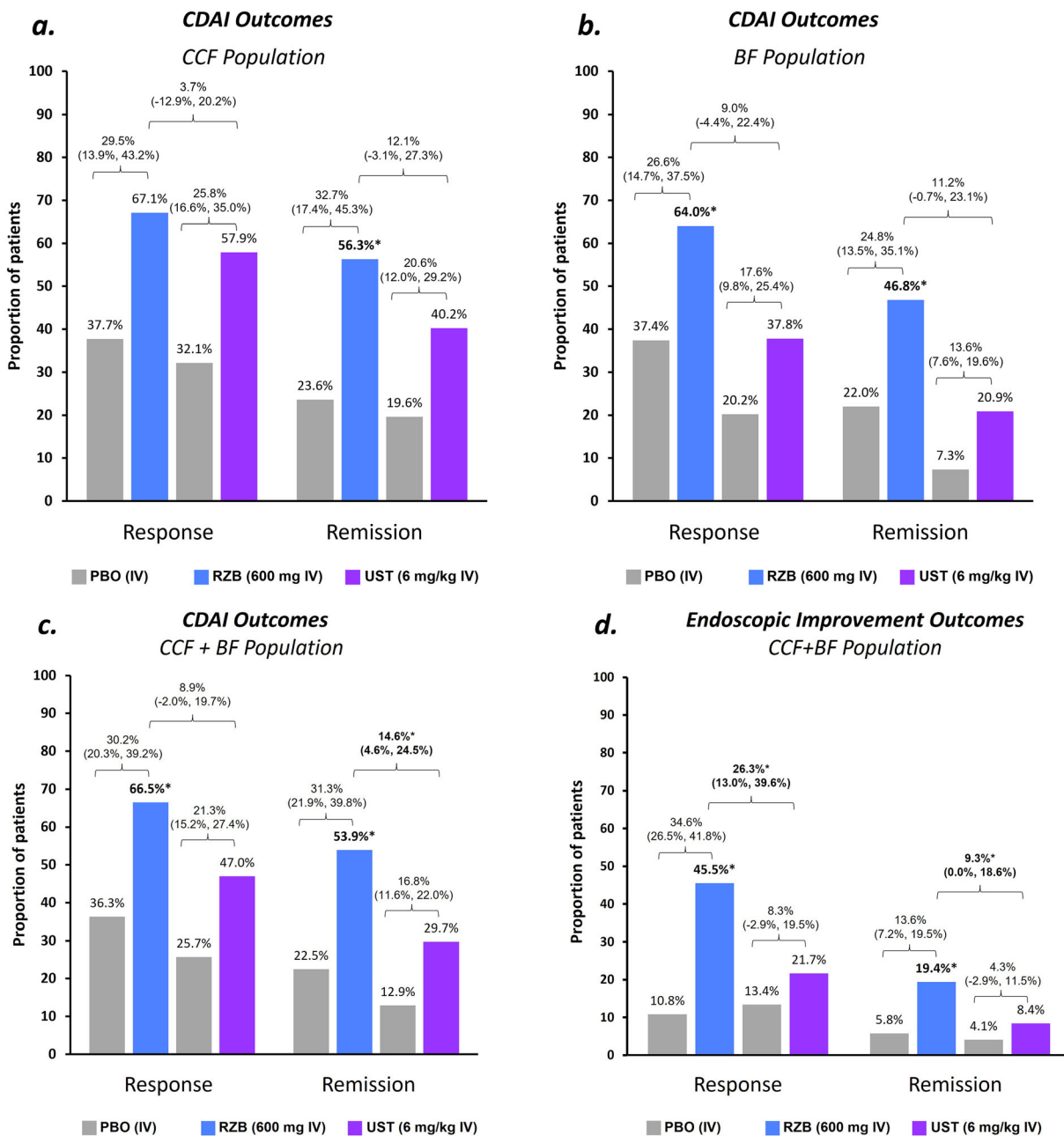


Fig. 1 Rates of response and remission following induction therapy with RZB (600 mg) or UST (6 mg/kg). * $p \leq 0.05$ for RZB versus UST. Relative effect measures are shown as the percent difference between treatment groups; absolute effect measures are the proportions of

patients achieving each outcome in each treatment group. *BF* biologic failure, *CCF* conventional care failure, *CDAI* Crohn’s Disease Activity Index, *IV* intravenous, *PBO* placebo, *RZB* risankizumab, *UST* ustekinumab

population. As such, all maintenance results reported for RZB trials included in the analysis are from the CCF + BF population and stratified

by UST maintenance dose that the RZB population was matched to (UST 90 mg Q8W: Fig. 2; UST 90 mg Q12W: Fig. S1). However, published

rates of endoscopic remission among UST-treated patients were reported as the aggregate of both the 90 mg Q8W and 90 mg Q12W groups and thus are reported in the same manner herein [7].

Overall, there were no statistically significant differences in CDAI remission rates (either absolute or relative) between RZB or UST at any dosage (Fig. 2a; Fig. S1a). The placebo-adjusted treatment difference for RZB compared to UST in CDAI remission rates ranged from -0.3% to -5.0% for any of the comparisons. Relative effect measures were numerically higher for endoscopic response (treatment difference range $9.3\text{--}27.7\%$) and endoscopic remission (treatment difference range $11.6\text{--}12.5\%$) for RZB compared with UST, regardless of dose (Fig. 2b; Fig. S1b). Likewise, absolute rates for endoscopic response and remission were also higher for RZB-treated patients (Fig. 2b,c; Fig. S1b).

Treat-Through Analyses of Relative Response Rates for CDAI Clinical Remission

Patients receiving maintenance RZB 180 mg had placebo-adjusted treat-through clinical remission (induction CDAI response, maintenance CDAI remission) rates 7.5% (95% CI -3.9% , 18.0%) and 9.0% (95% CI -2.3% , 19.4%) greater at the end of maintenance than patients receiving UST Q8W or Q12W, respectively (Table S4). Similarly, those receiving maintenance RZB 360 mg had placebo-adjusted treat-through clinical remission rates 6.6% (95% CI -4.8% , 16.9%) and 8.7% (-2.7% , 19.0%) higher than patients receiving UST Q8W or Q12W, respectively (Table S5).

DISCUSSION

Both RZB and UST are now approved for the treatment of moderately-to-severely active CD, although there is limited comparative efficacy data to inform clinical decision-making and the relative positioning of these agents. Furthermore, the trial populations entering the respective phase 3 development programs for

RZB and UST were substantively different. To address these limitations, we used MAIC analyses to compare the relative clinical and endoscopic effectiveness of RZB versus UST as induction and maintenance treatments of moderately to severely active CD. There are several important findings from this analysis. First, despite adjustments for differences in effect-modifying characteristics between the RZB and UST populations, clinical outcomes remained similar in the majority of MAICs. However, RZB was relatively more effective in inducing CDAI remission in the combined trial population compared to UST. Second, for endoscopic outcomes, the MAIC analyses favored RZB with significantly more patients achieving endoscopic response and remission at the end of induction in the combined population of CCF + BF patients. Likewise, during maintenance, significantly more patients in both RZB 180 mg and 360 mg groups achieved endoscopic response and remission more frequently than UST.

Similar clinical outcomes, with improved endoscopic outcomes for RZB and UST, may be expected on the basis of the unadjusted absolute clinical trial data informing the MAICs [7, 18, 19, 22]. Indeed, at least 30% of patients in RZB and UST induction and maintenance trials achieved clinical remission and up to 25% achieved endoscopic remission [7, 18, 19, 22]. However, there were key differences in the populations of patients included in these studies, with RZB trials enrolling patients who failed conventional therapies and/or biologic therapies (including UST and vedolizumab) and UST trials focused on those who failed anti-TNF therapies or immunosuppressants [7, 18, 19, 22]. In this analysis, when matching populations that failed anti-TNF therapies, there were marked differences among the two treatments in the proportion of patients in the CCF + BF population that achieved clinical remission, endoscopic response, and endoscopic remission after induction, and endoscopic outcomes after maintenance therapy, which favored RZB compared to UST. The marked differences in improvement during induction therapy are especially important, as achieving clinical

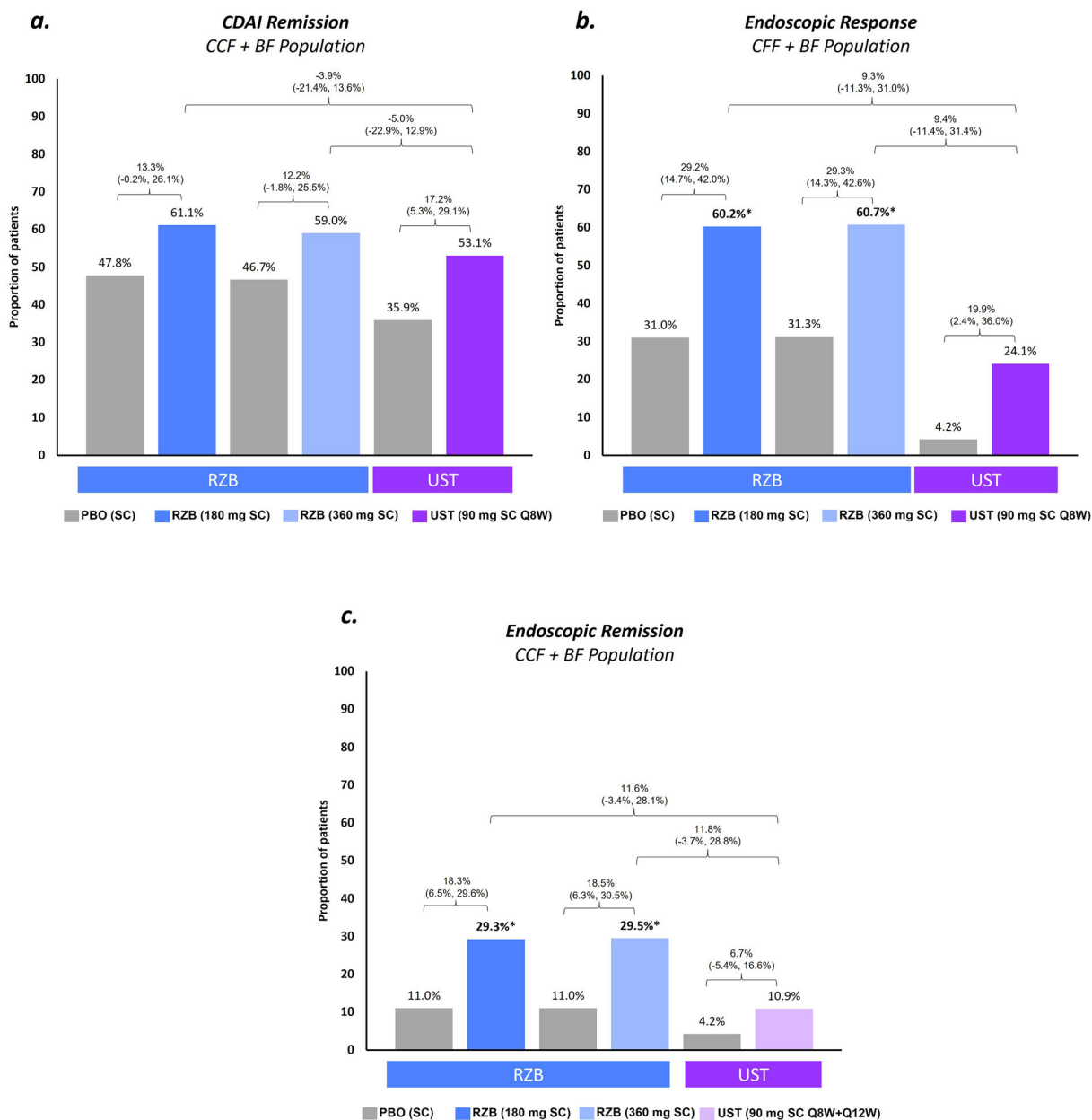


Fig. 2 Rates of response and remission following maintenance therapy with RZB (180 mg or 360 mg) or UST (90 mg Q8W). * $p \leq 0.05$ for RZB versus UST. Relative effect measures are shown as the percent difference between treatment groups; absolute effect measures are

the proportions of patients achieving each outcome in each treatment group. *BF* biologic failure, *CCF* conventional care failure, *CDAI* Crohn’s Disease Activity Index, *PBO* placebo, *Q8W* every 8 weeks, *Q12W* every 12 weeks, *RZB* risankizumab, *SC* subcutaneous, *UST* ustekinumab

improvements early in the treatment course is important and relevant to patients.

The assessment of endoscopic response to therapy has become a key measure in treatment of CD, such that endoscopic healing is now considered a long-term treatment target

[4, 5, 7]. ADVANCE, MOTIVATE, and FORTIFY are the first trials to use endoscopic response as a co-primary endpoint rather than secondary or exploratory endpoints, highlighting the growing importance of endoscopic measures. This study showed that a greater proportion of RZB-

treated patients achieved endoscopic response, with an overall trend toward endoscopic remission, than UST-treated patients. It is important to note that, in interpreting the results of the endoscopic maintenance analyses, baseline characteristics indicate there was an imbalance in the proportion of patients with prior anti-TNF failure. For example, prior anti-TNF failure was higher in the RZB 360 mg maintenance population (64.1%) than in the endoscopic substudy of UST maintenance (32.1% for Q8W, 31.7% for Q12W). Evidence in CD suggests that prior anti-TNF failure is associated with failure of a second anti-TNF therapy and, a meta-analysis showed that, among patients switching to a second anti-TNF therapy, remission rates depended significantly on the cause for switching [23, 24]. Indeed, remission rates were higher for patients with previous anti-TNF intolerance (61%) than those with primary (30%) or secondary (45%) failure of their previous anti-TNF therapy [24]. The MAIC of maintenance outcomes in CCF + BF patients in this study suggest that the negative association of previous anti-TNF failure with subsequent treatment response may extend to IL-12/23 and/or IL-23 inhibitors. Nonetheless, the results from this study favored RZB over UST in most outcomes.

Strengths of this study include the breadth of populations (CCF, BF, and CCF + BF), outcomes (CDAI response and remission; endoscopic response and remission), and treatment phases (induction and maintenance) that were assessed. Further, to inform the population characteristics adjusted in the analyses, a rigorous process was applied to identify effect-modifying variables, including structured literature review and clinical input from experts, in alignment with methodological guidance [21]. While adjustments to balance population characteristics of the RZB and UST studies required exclusion or lesser weighting of certain subgroups and associated reductions to effective sample size (ESS) of the analytical population, reasonably large samples of patients from the RZB studies were retained in all analyses. The inclusion of endoscopic response and remission as outcomes for comparison in this study may be of particular interest to healthcare providers.

Recent consensus clinical recommendations for treatment of CD, as described in the recent STRIDE II initiative of IOIBD, recognize endoscopic healing as the primary long-term target of treatment, and that endoscopic response is a suitable short-term target [4]. While endoscopic measures are recognized as objective assessments, until recently they have been less commonly reported in the evidence base, perhaps because of the relative recency of clinical recommendations for their use and/or heterogeneity in definitions [5, 7, 8]. In this study, we addressed the differences in definitions of endoscopic outcomes between RZB and UST studies by recoding RZB patient-level data according to UST outcome definitions. Despite limited sample sizes and corresponding uncertainty in the UST endoscopic substudy, important numeric (and in certain cases statistically significant) differences in responses rates for endoscopic outcomes were observed. RZB versus PBO endoscopic outcomes consistently improved when matching to UST population characteristics, driven by the higher proportion of the RZB population with prior biologic failure (approximately 60–65% in RZB studies vs. 30–40% in UST studies).

Certain limitations of the analysis include differences in the designs of the studies compared, which might introduce heterogeneity that could not be adjusted for. First, owing to differences in study designs, outcomes compared in the analysis were measured at 8 and 44 weeks in UST induction and maintenance studies, respectively, as compared to measurement at 12 and 52 weeks in RZB studies. Second, enrollment in the maintenance studies of induction responders may also introduce heterogeneity. The MAICs adjusted for imbalances between the populations in potentially “effect-modifying” characteristics, as recommended in methodological guidance, but not for prognostic factors that might affect PBO response rates across trials. Relative effect measures were calculated by subtracting PBO response rates from those for the interventions; any systematic difference between the PBO arms may therefore bias comparison, which could arise from “carryover” influences from induction to the withdrawal PBO arms in

maintenance. For example, different response rates in induction or elimination half-lives across therapies may yield a systematic bias in the withdrawal PBO response rates in maintenance. Third, after balancing on matching variables, ESS was reduced; however, across all the MAICs, the ESS reduction for the RZB population did not exceed 50% compared to the population that excluded prior UST/VDZ exposure and COVID-impacted patients, maintaining statistical power for the analysis. As expected, the induction analyses for the BF population had the largest reduction in sample size due to adjustment as the prior UST/VDZ-exposed patients were concentrated in this population. The lowest ESS for RZB-treated patients was 93 in induction analyses, 61 in maintenance RZB 360 mg analyses, and 68 in maintenance RZB 180 mg analyses. Fourth, in maintenance analyses, for both treatments, the PBO groups were actually active drug withdrawal and not a true PBO, which may impact outcomes. Fifth, while this study found some significant differences in endoscopic response and/or remission rates between RZB- and UST-treated patients in the maintenance studies, it is important to note that these results may not be generalizable given the small sample size. Finally, this analysis was limited to indirect comparisons of treatment effectiveness due to potential heterogeneity in adverse event reporting. Both efficacy and safety are important considerations for a benefit/risk assessment in making treatment decisions. Given the limited frequency of safety events, and that matching variables may differ for safety vs. efficacy outcomes, safety outcomes were not compared. However, for reference, safety outcomes for each trial included in this analysis are summarized in Table S6. Head-to-head comparisons of RZB and UST are needed to confirm the results of this analysis and better compare safety outcomes. The Study Comparing Intravenous/Subcutaneous Risankizumab to IV/SC Ustekinumab to Assess Change in Crohn's Disease Activity Index in Adult Participants With Moderate to Severe Crohn's Disease (SEQUENCE; NCT04524611) is ongoing and findings from this study may help to differentiate the two treatments in the future.

CONCLUSION

Anchored MAICs comparing RZB and UST phase 3 clinical studies, adjusting for differences in effect-modifying population characteristics, demonstrated comparative clinical effectiveness (i.e., CDAI remission) and endoscopic effectiveness of RZB versus UST favored RZB. Endoscopic outcomes comparing RZB to PBO consistently improved when analyses were matched to UST population characteristics, driven by the higher proportion of the BF population in the original phase 3 RZB trial.

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Compliance with Ethics Guidelines. This study, and each clinical trial included in the analysis, was conducted in accordance with the ethical principles that have their origin in the current Declaration of Helsinki and was consistent with International Conference on Harmonization Good Clinical Practice, Good Epidemiology Practices, and applicable regulatory requirements [7, 18, 19, 22]. This analysis utilized de-identified data from published clinical trial data; thus, no ethics committee approval was required. However, each individual trial included in this analysis was approved by independent ethics committees or institutional review boards at each study site and all patients (or parents/legal guardians for adolescent patients) provided written informed consent before enrolling in each clinical trial [7, 18, 19, 22].

Data Availability. The data sets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

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