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

Running title: Matching-Adjusted Indirect Comparison of Risankizumab and Ustekinumab

Authors: Marla Dubinsky[1], Christopher Ma[2], Jenny Griffith[3], Marjorie Crowell[4], Ezequiel Neimark[3], Kristina Kligys[3], Tom O'Connell[4]

Affiliations: [1]Department of Pediatrics, Susan and Leonard Feinstein IBD Center, Icahn School of Medicine, Mount Sinai, New York, NY, USA; [2]Division of Gastroenterology & Hepatology, Departments of Medicine & Community Health Sciences, University of Calgary, Calgary, AB, Canada; [3]AbbVie Inc., North Chicago, IL, USA; [4]Medicus Economics LLC, Boston, MA, USA.

Corresponding Author: Tom O'Connell
thomas.oconnell@medicuseconomics.com
Medicus Economics, LLC
2 Stonehill Lane, Milton, MA 02186

SUPPLEMENTARY MATERIAL

Appendix A: Treat-Through Analyses

In clinical practice, patients achieving a response to induction therapy may continue therapy during maintenance,[1] in alignment with the structure of the UST and RZB maintenance clinical-study designs. The benefit of a pharmacologic intervention such as UST or RZB may therefore be considered as the joint probability of inducing and maintaining a response.

To reflect the effectiveness of UST and RZB in inducing and maintaining a clinical response, a "treat-through" analysis was conducted, whereby the clinical response rate in induction was multiplied by the clinical remission rate in maintenance, to reflect the percentage of patients expected to achieve the desired clinical response to therapy across both induction and maintenance. The treat-through analysis was only conducted for the CCF+BF population, as the UST maintenance CDAI remission rate is not reported for other populations. Note that for RZB, eligibility for maintenance was based on induction clinical response at 12 weeks, defined as "≥ 30% decrease in average daily stool frequency (SF) and/or ≥ 30% decrease in average daily abdominal pain (AP) score and both not worse than baseline of the induction study". In UST studies, eligibility for maintenance was based on induction CDAI response at 8 weeks.

Treat-through analyses were conducted for both absolute and relative response rates. Interpretation of results based on absolute response rates may be most intuitive, reflecting the percentage of patients starting induction expected to reach maintenance CDAI remission. However, the analysis of absolute response rates may be subject to bias if imbalances in prognostic factors exist between the relevant RZB and UST studies compared. The treat-through analysis was therefore also conducted for relative response rates, which avoid potential bias from imbalanced prognostic factors, and were calculated as PBO-subtracted response rates:

$$(R_{IndInt} \times R_{MaintInt}) - (R_{IndPBO} \times R_{MaintPBO})$$

where "Int" indicates the intervention (RZB or UST), and:

- R_{IndInt} = CDAI response rate for the intervention in induction
- R_{IndPBO} = CDAI response rate for PBO in induction
- $R_{MaintInt}$ = CDAI remission rate for the intervention in maintenance
- $R_{MaintPBO}$ = CDAI remission rate for PBO in maintenance

Due to the potential for propagation of error in the multiplication of induction and maintenance response rates, 95% CIs for treat-through responses rates were calculated as Wilson score intervals,[2] to reduce risk of Type I error versus traditional Wald interval. Confidence intervals should be interpreted with caution and no formal statements around statistical significance of differences should be made.

Results of the treat-through analyses are presented by RZB maintenance dosing of 180 mg in **Supplementary Table 4** and 360 mg in **Supplementary Table 5**.

REFERENCES

1. Al Hashash J and Regueiro M. Overview of medical management of high-risk, adult patients with moderate to severe Crohn disease. In Kane SV and Robson KM (Ed.), UpToDate. September 7, 2021. URL: https://www.uptodate.com/contents/overview-of-medical-management-of-high-risk-adult-patients-with-moderate-to-severe-crohn-disease
2. Wallis S. Accurate confidence intervals on Binomial proportions, functions of proportions, algebraic formulae and effect sizes. University College London. 2021. URL: https://www.ucl.ac.uk/english-usage/staff/sean/resources/confidence-intervals.pdf.

Supplementary Table S1: Baseline Characteristics at Induction

		RZB 600 mg characteristics *before* matching				UST 6 mg/kg characteristics as reported in trial publications				RZB 600 mg characteristics *after* matching			
		CCF	BF	CCF+BF		CCF	BF	CCF + BF		CCF	BF	CCF+BF	
		CDAI	CDAI	CDAI	Endo	CDAI	CDAI	CDAI	Endo	CDAI	CDAI	CDAI	Endo
N / ESS		212	379	591	579	419	496	915	252	146	204	302	325
Demographics													
Age	*Mean age*	39.6	38.5	38.9	38.9	39.3	37.3	38.2	40.3	39.9	39.1	39.3	40.5
Sex	*Percent male*	56.1%	54.4%*	55.0%*	54.8%	45.1%	44.2%	44.6%	47.2%	58.5%*	55.1%	59.4%*	58.5%
Disease characteristics													
Duration (ind. BL)	*Mean time since diagnosis*	7.4	9.5	8.7	8.8	9.6	12.4	11.1	11.1	9.3	11.4	11.4	12.0
	Time since diagnosis <2 yrs	38.7%*	11.9%	21.5%*	21.6%	20.4%	11.9%	7.6%	16.8%	20.4%	11.9%	7.6%	16.8%
	Time since diagnosis ≥2 and <5 yrs	17.5%	21.6%*	20.1%*	19.7%*	19.8%	8.4%	9.3%	9.1%	19.8%	8.3%	9.3%	9.1%
	Time since diagnosis ≥5 and <15 yrs	26.9%*	47.2%	39.9%*	40.2%	39.5%	49.9%	56.2%	40.0%	39.5%	49.9%	56.2%	40.0%
	Time since diagnosis ≥15 yrs	17.0%	19.3%*	18.4%*	18.5%*	20.3%	29.9%	26.9%	34.1%	20.3%	29.9%	26.9%	34.1%
Extra-intestinal involved (ind. BL)	Yes vs. No	36.3%*	48.3%	44.0%*	N/A	56.3%	50.3%	53.1%	NR	34.1%*	49.7%	40.1%*	N/A
Location (ind. BL)	Ileum only	15.1%	15.8%	15.6%	15.5%	22.2%	13.3%	17.3%	19.1%	15.4%	17.7%	15.4%	16.0%
	Colon only	36.8%*	34.8%*	35.5%*	35.4%*	19.1%	18.0%	18.5%	17.9%	33.5%*	33.6%*	32.5%*	34.0%*
	Ileum + colon	48.1%	49.3%*	48.9%*	49.1%*	58.7%	68.8%	64.2%	63.0%	51.1%	48.7%*	52.1%*	50.0%*
Phenotype	Fistula(s) (current)	10.4%	14.5%	13.1%	13.2%	15.3%	20.2%	17.9%	15.1%	8.5%	11.0%*	10.1%*	10.6%

(ind. BL)	Fistula(s) (current or past)	NR	NR	NR	NR	36.0%	48.2%	42.6%	36.1%	NR	NR	NR	NR
	Stricturing / stenosis (current)	NR	NR	NR	NR	9.8%	8.7%	9.2%	7.1%	NR	NR	NR	NR
	Stricturing / stenosis (current or past)	20.3%*	23.0%*	22.0%*	21.6%*	31.5%	45.0%	38.8%	36.1%	31.5%	45.0%	38.8%	36.1%
Severity (ind. BL)	*Mean SES-CD*	N/A	N/A	N/A	13.8	NR	NR	NR	13.5	N/A	N/A	N/A	14.1
	CDAI >300	57.1%*	52.0%	53.8%	53.9%	42.1%	60.1%	51.8%	59.0%	42.1%	60.1%	51.9%	59.0%
Lab and immune markers													
CRP (ind. BL)	>0.5 mg/dL	54.3%*	68.3%	63.2%*	63.3%	67.0%	68.8%	74.3%	67.7%	67.0%	69.2%	74.5%	67.9%
	Median CRP	0.58	0.92	0.76	0.78	0.82	0.92	0.87	0.84	0.78	1.14	0.98	0.84
FCP (ind. BL)	*Median FCP*	710	1,124	923	N/A	469	523	498	NR	756	1,200	1,054	N/A
Prior / concomitant treatment													
Prior anti-TNF failure	Prior failure	0.0%	100.0%	64.1%*	63.7%*	0.0%	100.0%	54.2%	42.5%	0.0%	100.0%	54.2%	42.5%
	Non-response (primary or secondary)	0.0%	87.9%*	56.4%	N/A	0.0%	98.2%	53.2%	NR	0.0%	88.9%*	47.8%	N/A
	Intolerance ("unacceptable side effects")	0.0%	25.9% *	16.6%	N/A	0.0%	38.7%	21.0%	NR	0.0%	33.9%	17.6%	N/A
Prior biologics failed	One prior biologic failed	0.0%	72.8%*	46.7%*	N/A	0.0%	47.2%	25.6%	NR	0.0%	46.5%	25.2%	N/A
	2-3 prior biologics failed	0.0%	27.2%*	17.4%*	N/A	0.0%	52.8%	28.6%	NR	0.0%	53.5%	29.0%	N/A
Steroid use	*Used with active biologic therapy*	31.8%	30.8%*	31.2%*	31.1%	39.8%	44.1%	42.2%	40.8%	24.0%*	70.9%*	73.8%*	73.8%*
Immunomodulator	Used with active biologic therapy	30.7%	25.9%	27.6%	27.8%	34.6%	32.1%	33.2%	30.2%	29.1%	23.5%	26.3%	26.4%

RZB values exclude UST/VDZ exposed and/or COVID-19 impacted patients. Statistically significant differences of RZB vs. UST ($p \leq 0.05$) are reflected by an asterisk, based on two-sided Wald tests (percentages) and t-tests (continuous variables). Italicized variables (e.g., demographics, including age and sex) are included for context, but are not recognized to be effect-modifying factors. Significance testing of differences was not conducted for median CRP and median FCP, due to lack of consistent reporting of interquartile ranges. Endo, endoscopic; ESS, effective sample size; NA, not applicable; NR, not reported.

Supplementary Table S2: Baseline Characteristics at Induction: RZB 180 mg

		RZB characteristics *before* matching				UST characteristics as reported in trial publications				RZB characteristics *after* matching			
		RZB (180 mg)				UST (90mg/kg Q8W)		UST (90mg/kg Q12W)		RZB (180 mg)			
		CCF+BF against Q8W		CCF+BF against Q12W		CCF + BF		CCF + BF		CCF+BF against Q8W		CCF+BF against Q12W	
		CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo	CDAI	Endo
N / ESS		232	232	232	232	265	53	265	41	194	152	190	140
Patient characteristics													
Age	*Mean age*	38.4	38.4	38.4	38.4	39.1	41.1	38.7	38.6	39.1	39.5	39.4	38.2
Sex	*Percent male*	50.4%	50.4%	50.4%	50.4%	44.2%	37.7%	43.4%	51.2%	52.8%	54.2%	53.0%	53.5%
Disease characteristics													
Duration (ind. BL)	*Mean time since diagnosis*	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 yrs	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 yrs	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 yrs	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 yrs	23.3%	23.3%	23.3%	23.3%	23.2%	32.6%	18.5%	37.4%	21.1%	19.5%	21.5%	17.9%
Extra-intestinal involved (ind. BL)	Yes vs. No	N/A	N/A	N/A	N/A	NR	NR	NR	NR	N/A	N/A	N/A	N/A
Location (ind. BL)	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%
	Colon only	39.2%*	39.2%*	39.2%*	39.2%*	21.5%	20.8%	19.2%	17.1%	36.9%*	35.4%	35.8%*	39.4%*

	Ileum + colon	49.1%*	49.1%	49.1%*	49.1%*	64.2%	64.2%	63.8%	78.0%	48.8%*	49.5%	47.3%*	55.7%*
Phenotype (ind. BL)	Fistula(s) (current)	N/A	11.6%	N/A	11.6%	NR	7.5%	NR	14.6%	N/A	8.1%	N/A	8.7%
	Fistula(s) (current or past)	N/A	NR	N/A	NR	NR	32.1%	NR	34.1%	N/A	NR	N/A	NR
	Stricturing / stenosis (current)	N/A	NR	N/A	NR	NR	7.5%	NR	7.3%	N/A	NR	N/A	NR
	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%
Severity (ind. BL)	*Mean SES-CD*	N/A	14.2	N/A	14.2	NR	15.8	NR	15.0	N/A	13.8	N/A	14.7
	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%
Severity (CDAI maint. BL)	CDAI < 75	27.6%	N/A	27.6%*	N/A	18.9%	NR	15.8%	NR	28.7%	N/A	28.3%*	N/A
	CDAI ≥ 75 and < 150	35.3%	N/A	35.3%	N/A	42.5%	NR	41.9%	NR	31.5%	N/A	31.5%	N/A
	CDAI ≥ 150	37.1%	N/A	37.1%	N/A	38.6%	NR	42.3%	NR	39.8%	N/A	40.1%	N/A
Lab and immune markers													
CRP (ind. BL)	>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%
	Median CRP	0.82	0.82	0.82	0.82	0.94	0.94	0.92	1.17	0.82	0.80	0.82	0.80
FCP (ind. BL)	*Median FCP*	986	N/A	986	N/A	577	NR	562	NR	883	N/A	883	N/A
Prior / concomitant treatment													
Prior anti-TNF failure	Prior 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%
Immunomodulator	Used with active biologic therapy	27.2%	27.2%	27.2%	27.2%	34.3%	26.4%	37.4%	31.7%	27.1%	27.3%	26.7%	29.6%
Steroid use	*Used with active biologic therapy*	27.6%	27.6%	27.6%	27.6%	35.5%	41.5%	35.5%	39.0%	26.5%	25.6%	26.3%	26.3%
Response to induction (at end of ind. / maint. BL)	CDAI remission (<150pts)	56.0%	N/A	56.0%	N/A	61.4%	NR	57.7%	NR	53.1%	N/A	52.6%	N/A
	Endo. response (SES-CD reduction ≥3)	N/A	44.4%	N/A	44.4%	NR	55.5%	NR	50.4%	N/A	48.2%	N/A	51.2%
	CRP normalization (<0.3 mg/dL)	41.8%	N/A	41.8%	N/A	40.1%	NR	39.2%	NR	40.8%	N/A	41.0%	N/A

	FCP normalization (<250 mg/kg)	43.2%	N/A	43.2%	N/A	50.7%	NR	41.5%	NR	46.2%	N/A	45.9%	N/A

RZB values exclude UST/VDZ exposed and/or COVID-19 impacted patients. Statistically significant differences of RZB vs. UST ($p \leq 0.05$) are reflected by an asterisk, based on two-sided Wald tests (percentages) and t-tests (continuous variables). Italicized variables (e.g., demographics, including age and sex) are included for context, but are not recognized to be effect-modifying factors. Significance testing of differences was not conducted for median CRP and median FCP, due to lack of consistent reporting of interquartile ranges. Endo, endoscopic; ESS, effective sample size; NA, not applicable; NR, not reported.

Supplementary Table S3: Baseline Characteristics at Induction: RZB 360 mg

		RZB characteristics *before* matching				UST characteristics as reported in trial publications				RZB characteristics *after* matching			
		RZB (360 mg)				UST (90mg/kg Q8W)		UST (90mg/kg Q12W)		RZB (360 mg)			
		CCF+BF against Q8W		CCF+BF against Q12W		CCF + BF		CCF + BF		CCF+BF against Q8W		CCF+BF against 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
Patient characteristics													
Age	*Mean age*	38.0	38.0	38.0	38.0	39.1	41.1	38.7	38.6	38.3	38.5	38.2	38.5
Sex	*Percent male*	55.9%*	55.9%	55.9%*	55.9%	44.2%	37.7%	43.4%	51.2%	57.3%	58.8%	57.0%*	58.7%
Disease characteristics													
Duration (ind. BL)	*Mean time since diagnosis*	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 yrs	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 yrs	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 yrs	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 yrs	21.8%	21.8%	21.8%	21.8%	23.2%	32.6%	18.5%	37.4%	19.6%	18.3%	19.6%	18.2%
Extra-intestinal involved (ind. BL)	Yes vs. No	N/A	N/A	N/A	N/A	NR	NR	NR	NR	N/A	N/A	N/A	N/A
Location (ind. BL)	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%
	Colon only	35.9%*	35.9%	35.9%*	35.9% *	21.5%	20.8%	19.2%	17.1%	39.1%*	39.9%*	39.3%*	40.1%*
	Ileum + colon	50.0%*	50.0%	50.0%*	50.0%*	64.2%	64.2%	63.8%	78.0%	45.3%*	43.2%	45.2%*	43.0%*

Phenotype (ind. BL)	Fistula(s) (current)	N/A	11.8%	N/A	11.8%	NR	7.5%	NR	14.6%	N/A	9.7%	N/A	9.7%
	Fistula(s) (current or past)	N/A	NR	N/A	NR	NR	32.1%	NR	34.1%	N/A	NR	N/A	NR
	Stricturing / stenosis (current)	N/A	NR	N/A	NR	NR	7.5%	NR	7.3%	N/A	NR	N/A	NR
	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%
Severity (ind. BL)	*Mean SES-CD*	N/A	13.8	N/A	13.8	NR	15.8	NR	15.0	N/A	13.2	N/A	13.2
	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%
Severity (CDAI maint. BL)	CDAI < 75	25.9%	N/A	25.9%*	N/A	18.9%	NR	15.8%	NR	26.9%	N/A	26.7%	N/A
	CDAI ≥ 75 and < 150	36.4%	N/A	36.4%	N/A	42.5%	NR	41.9%	NR	34.3%	N/A	34.2%	N/A
	CDAI ≥ 150	37.7%	N/A	37.7%	N/A	38.6%	NR	42.3%	NR	38.8%	N/A	39.1%	N/A
Lab and immune markers													
CRP (ind. BL)	>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%
	Median CRP	0.82	0.82	0.82	0.82	0.94	0.94	0.92	1.17	0.82	0.80	0.82	0.80
FCP (ind. BL)	*Median FCP*	986	N/A	986	N/A	577	NR	562	NR	883	N/A	883	N/A
Prior / concomitant treatment													
Prior anti-TNF failure	Prior 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%
Immunomodulator	Used with active biologic therapy	29.1%	29.1%	29.1%	29.1%	34.3%	26.4%	37.4%	31.7%	29.8%	30.4%	29.8%	30.4%
Steroid use	*Used with active biologic therapy*	25.9%	25.9%	25.9%	25.9%	35.5%	41.5%	35.5%	39.0%	24.4%	23.2%	24.4%	23.2%
Response to induction (at end of ind. / maint. BL)	CDAI remission (<150pts)	56.8%	N/A	56.8%	N/A	61.4%	NR	57.7%	NR	55.5%	N/A	55.3%	N/A
	Endo. response (SES-CD reduction ≥3)	N/A	45.5%	N/A	45.5%	NR	55.5%	NR	50.4%	N/A	52.4%	N/A	52.5%
	CRP normalization (<0.3 mg/dL)	41.8%	N/A	41.8%	N/A	40.1%	NR	39.2%	NR	40.9%	N/A	41.0%	N/A
	FCP normalization (<250 mg/kg)	44.3%	N/A	44.3%	N/A	50.7%	NR	41.5%	NR	46.4%	N/A	46.3%	N/A

RZB values exclude UST/VDZ exposed and/or COVID-19 impacted patients. Statistically significant differences of RZB vs. UST ($p \leq 0.05$) are reflected by an asterisk, based on two-sided Wald tests (percentages) and t-tests (continuous variables). Italicized variables (e.g., demographics, including age and sex) are included for context, but are not recognized

to be effect-modifying factors. Significance testing of differences was not conducted for median CRP and median FCP, due to lack of consistent reporting of interquartile ranges.
Endo, endoscopic; ESS, effective sample size; NA, not applicable; NR, not reported.

Supplementary Table S4. Treat-through response rates in maintenance treatment, RZB 180 mg

		Induction				Maintenance		Treat-through response rate								
		N[a]		CDAI response (%)		CDAI remission (%)		Absolute response rate Intervention			Absolute response rate PBO			Relative response rate (PBO-subtracted)		
		INT	PBO	INT	PBO	INT	PBO	Mean	95% CI[b] Low	95% CI[b] High	Mean	95% CI[b] Low	95% CI[b] High	Mean	95% CI[c] Low	95% CI[c] High
RZB matched to:	UST Q8W	184	118	66.5%	36.3%	61.1%	47.8%	40.6%	33.8%	47.8%	17.4%	11.6%	25.2%	23.3%	12.9%	32.5%
	UST Q12W					60.2%	47.6%	40.0%	33.2%	47.2%	17.3%	11.5%	25.1%	22.8%	12.4%	32.0%
UST	Q8W	458	456	47.0%	25.7%	53.1%	35.9%	25.0%	21.2%	29.1%	9.2%	6.9%	12.2%	15.7%	10.9%	20.5%
	Q12W					48.8%	35.9%	22.9%	19.3%	27.0%	9.2%	6.9%	12.2%	13.7%	9.0%	18.4%
Difference[c]	RZB vs UST Q8W							15.7%	7.7%	23.8%				7.5%	−3.9%	18.0%
	RZB vs UST Q12W							17.1%	9.2%	25.2%				9.0%	−2.3%	19.4%

[a]N reflects the number of patients entering induction, among whom treat-through success (i.e., induction clinical response and maintenance clinical remission) could be observed. [b]Confidence interval calculated as Wilson score interval, to reduce risk of Type I error vs. traditional Wald interval. See equation (6) in Wallis (2021). [c]Confidence interval calculated as Newcombe-Wilson interval, reflecting the difference in independent proportions based on their Wilson score intervals. See equations (18) and (19) of Wallis (2021). CDAI, Crohn's Disease Activity Index; CI, confidence interval; INT, intervention; PBO, placebo; Q8W, every 8 weeks; Q12W, every 12 weeks; RZB, risankizumab; UST, ustekinumab.

Supplementary Table S5: Treat-through response rates in maintenance treatment, RZB 360 mg

		Induction				Maintenance		Treat-through response rate								
		N[a]		CDAI response (%)		CDAI remission (%)		Absolute response rate Intervention			Absolute response rate PBO			Relative response rate (PBO-subtracted)		
		INT	PBO	INT	PBO	INT	PBO	Mean	95% CI[b] Low	95% CI[b] High	Mean	95% CI[b] Low	95% CI[b] High	Mean	95% CI[c] Low	95% CI[c] High
RZB matched to:	UST Q8W	184	118	66.5%	36.3%	59.0%	46.7%	39.2%	32.5%	46.4%	17.0%	11.2%	24.7%	22.3%	12.0%	31.5%
	UST Q12W					58.9%	46.3%	39.2%	32.4%	46.4%	16.8%	11.1%	24.6%	22.4%	12.1%	31.5%
UST	Q8W	458	456	47.0%	25.7%	53.1%	35.9%	25.0%	21.2%	29.1%	9.2%	6.9%	12.2%	15.7%	10.9%	20.5%
	Q12W					48.8%	35.9%	22.9%	19.3%	27.0%	9.2%	6.9%	12.2%	13.7%	9.0%	18.4%
Difference[c]	RZB vs UST Q8W							14.3%	6.3%	22.4%				6.6%	–4.8%	16.9%
	RZB vs UST Q12W							16.2%	8.3%	24.3%				8.7%	–2.7%	19.0%

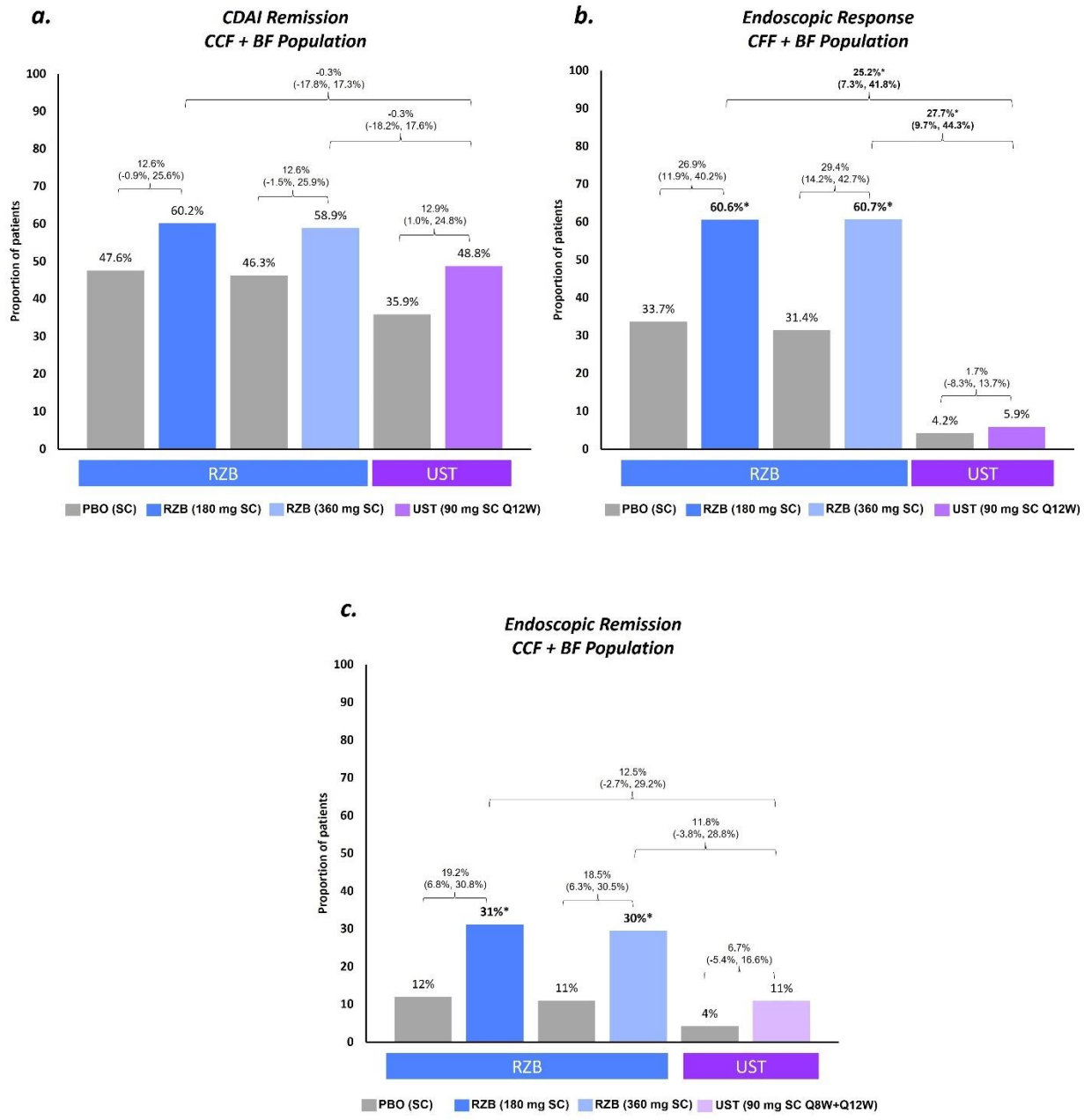
[a]N reflects the number of patients entering induction, among whom treat-through success (i.e., induction clinical response and maintenance clinical remission) could be observed. [b]Confidence interval calculated as Wilson score interval, to reduce risk of Type I error versus. traditional Wald interval. See equation (6) in Wallis (2021). [c]Confidence interval calculated as Newcombe-Wilson interval, reflecting the difference in independent proportions based on their Wilson score intervals. See equations (18) and (19) of Wallis (2021). CDAI, Crohn's Disease Activity Index; CI, confidence interval; INT, intervention; PBO, placebo; Q8W, every 8 weeks; Q12W, every 12 weeks; RZB, risankizumab; UST, ustekinumab.

Supplementary Table S6: Safety Outcomes by Clinical Trial[a]

Study	N	Any AE n (%)	Serious AEs n (%)	Serious Infections n (%)
ADVANCE				
PBO	186	105 (56)	28 (15)	7 (4)
RZB 600 mg	373	210 (56)	27 (7)	3 (1)
RZB 1200 mg	372	191 (51)	14 (4)	2 (1)
MOTIVATE				
PBO	137	137 (66)	26 (13)	5 (2)
RZB 600 mg	98	98 (48)	10 (5)	1 (<1)
RZB 1200 mg	121	121 (59)	9 (4)	2 (1)
FORTIFY				
PBO[b]	184	135 (75)	23 (13)	7 (4)
RZB 180 mg	179	128 (72)	22 (12)	5 (3)
RZB 360 mg	179	129 (72)	24 (13)	8 (4)
UNITI-1				
PBO	245	159 (65)	15 (6)	3 (1)
UST 6 mg/kg	249	164 (66)	18 (7)	7 (3)
UNITI-2				
PBO	208	113 (54)	12 (6)	3 (1)
UST 6 mg/kg	207	115 (56)	6 (2.9)	1 (<1)
IM-UNITI				
PBO	133	111 (84)	20 (15)	3 (2)
UST 90 mg/kg Q8W	131	107 (82)	13 (10)	3 (2)
UST 90 mg/kg Q12W	132	106 (80)	16 (12)	7 (5)

[a]Outcomes reported are limited to that which was published for both studies. [b]In this study, PBO was a RZB withdrawal group. PBO, placebo; RZB, risankizumab; UST, ustekinumab.

Supplementary Figure S1: Rates of Response and Remission in Maintenance Therapy with RZB (180 mg or 360 mg) and UST (90 mg Q12W)



*$p \leq 0.05$ 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 therapy failure; CDAI, Crohn's disease Activity Index; PBO, placebo; Q8W, every 8 weeks; Q12W, every 12 weeks; RZB, risankizumab; SC, subcutaneous; UST, ustekinumab.