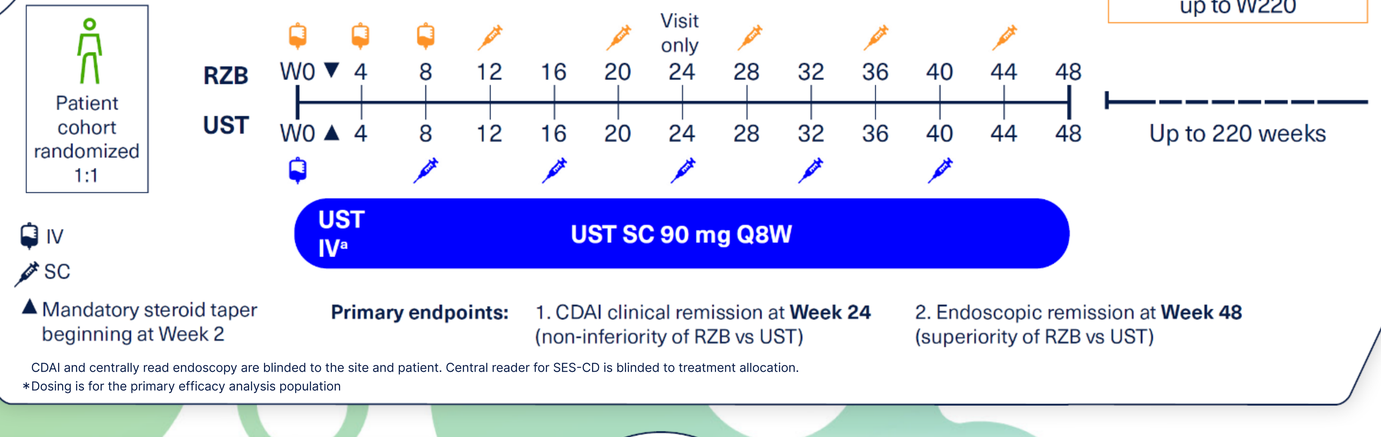
SEQUENCE

SEQUENCE is a head-to-head trial of risankizumab vs ustekinumab over 48 weeks in adults with moderately to severely active CD who have failed anti-TNF therapy

Study design[1,2]

A Phase IIIb, multicenter, randomized, efficacy assessor-blinded study



CDAI and centrally read endoscopy are blinded to the site and patient. Central reader for SES-CD is blinded to treatment allocation.
*Dosing is for the primary efficacy analysis population

Key eligibility criteria and study background

Inclusion criteria[1,2]

- Ages 18 years to 80 years (adult, older adult)
- Confirmed diagnosis of moderately to severely active CD at least 3 months prior to baseline
  - CDAI 220–450
  - Average daily SF ≥4 and/or APS ≥2
  - SES-CD ≥6 (≥4 for isolated ileitis), excluding the narrowing component
- Demonstrated intolerance or inadequate response to ≥1 anti-TNF therapies

Exclusion criteria[1,3]

- Current diagnosis of ulcerative colitis or indeterminate colitis
- Receipt of CD approved biologic agents prior to baseline (as detailed in protocol), or any investigational biologic or other agent or procedure prior to baseline (as detailed in protocol)
- Prior exposure to p19 and/or p40 inhibitors (e.g., RZB and UST)
- Prior exposure to vedolizumab
- Currently known complications of CD (strictures, short bowel, etc)

Stratification factors[2]

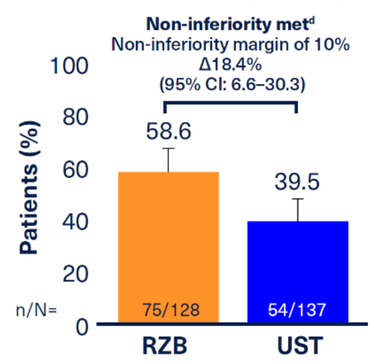
- Number of prior anti-TNF failures (1, >1)
- Corticosteroid use at baseline (yes or no)

Baseline demographics and disease characteristics[3]

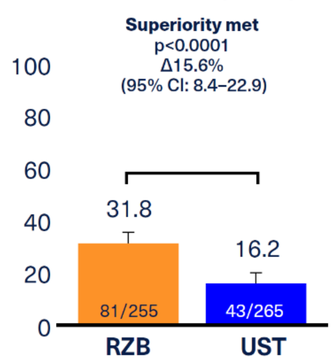
Variable (ITT1)[b]	RZB (N=255)	UST (N=265)
Age, years, mean (SD)	38.0 (13.1)	38.3 (13.8)
Female, n (%)	119 (46.7)	134 (50.6)
BMI, mean (SD)	23.8 (5.5)	24.8 (6.0)
Disease duration, years, mean (SD)	9.4 (7.8)	9.4 (8.7)
SES-CD, mean (SD)	13.5 (7.1)	14.1 (7.4)
Daily APS, n, mean (SD)	251,1.9 (0.5)	263, 1.9 (0.6)
Daily SF, n, mean (SD)	251, 5.5 (2.7)	263, 5.6 (2.5)
Immunomodulator use, n (%)	34 (13.3)	47 (17.7)
Corticosteroid use, n (%)	58 (22.7)	71 (26.8)
Baseline fecal calprotectin (mg/kg), n, median (min, max)	207, 1030 (30, 26,823)	215, 1515 (30, 26,361)
Baseline hsCRP (mg/L), n, median (min, max)	246, 8.20 (0.2, 287.1)	257, 9.40 (0.2, 196.6)
CDAI, n, mean (SD)	251, 309.4 (61.7)	263, 310.1 (62.6)
Failed >1 anti-TNFs, n (%)	59 (23.1)	61 (23.0)
Disease location, n (%)		
Ileal only	42 (16.5)	45 (17.0)
Colonic only	102 (40.0)	106 (40.0)
Ileal-colonic	111 (43.5)	114 (43.0)

Primary endpoints[2]

Clinical remission at Week 24 (ITT1H)[c]



Endoscopic remission at Week 48 (ITT1)[b]



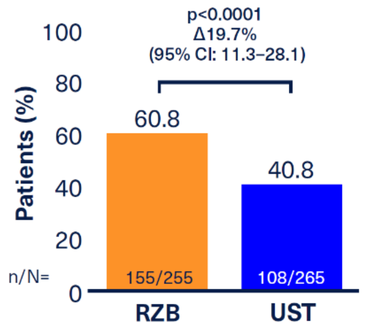
Nominal $P<0.01$ from a post hoc analysis testing for superiority[3]

RZB met both primary endpoints of non-inferiority to UST for clinical remission at Week 24 and superiority to UST for endoscopic remission at Week 48[2]

RZB was superior to UST for all ranked secondary endpoints

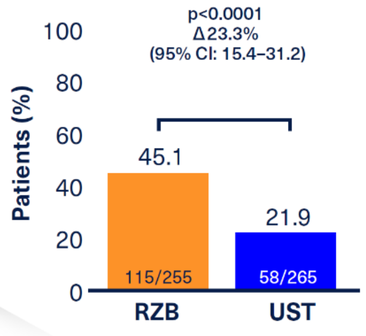
Ranked secondary endpoints[2]

Clinical remission
Week 48 (ITT1)[b]

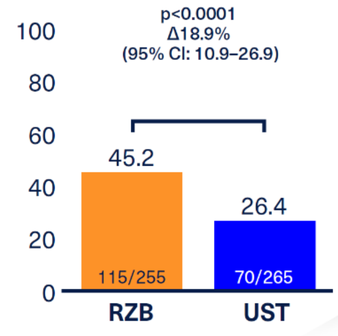


Endoscopic response

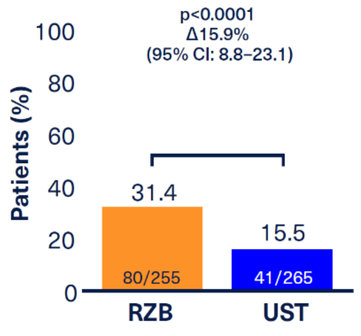
Week 48 (ITT1)[b]



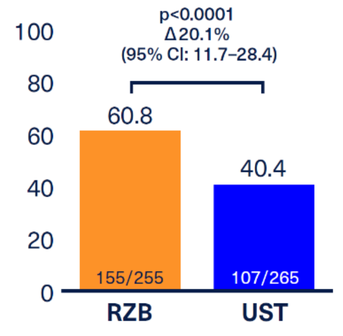
Week 24 (ITT1)[b]



Steroid-free endoscopic remission
Week 48 (ITT1)[b]



Steroid-free clinical remission
Week 48 (ITT1)[b]



Safety results[2]

The safety profiles of RZB and UST were consistent with previously published results

Rates of serious TEAEs and TEAEs leading to study drug discontinuation were numerically higher with UST than RZB[2]

TEAEs	RZB N=262 PYs=257.6 E/100PYs[e]	UST N=265 PYs=269.9 E/100PYs[e]
All TEAEs	879 (341.2)	763 (282.7)
Investigator defined drug-related AE[f,g]	167 (64.8)	111 (41.1)
Severe TEAEs	60 (23.3)	82 (30.4)
Serious TEAEs	36 (14.0)	64 (23.7)
TEAEs leading to discontinuation of study drug	10 (3.9)	14 (5.2)
Deaths	0	0

AESIs	RZB N=262 PYs=257.6 E/100PYs[e]	UST N=265 PYs=269.9 E/100PYs[e]
Adjudicated MACE/Extended MACE[h]	0	1 (0.4)
Serious infections	10 (3.9)	14 (5.2)
Active tuberculosis	0	0
Opportunistic infections excluding TB & herpes zoster	1 (0.4)[i]	0
Herpes zoster	1 (0.4)	1 (0.4)
Malignant tumors[j]	1 (0.4)	1 (0.4)
NMSC	1 (0.4)	0
Malignancies excluding NMSC	0	1 (0.4)
Hypersensitivity	37 (14.4)	32 (11.9)
Serious hypersensitivity	0	0
Adjudicated anaphylactic reaction	0	0
Hepatic events	26 (10.1)	23 (8.5)[k]
Injection site reactions	5 (1.9)	8 (3.0)

Summary[2]

In this head-to-head study of RZB vs UST over 48 weeks:

Efficacy

Both primary endpoints (non-inferiority of RZB to UST in achieving CDAI clinical remission at Week 24 and superiority of RZB to UST in achieving endoscopic remission at Week 48) were met.

All ranked secondary endpoints (superiority of RZB to UST) were met.

Safety

The overall incidence of TEAEs was similar with RZB vs UST, while the incidences of serious AEs and AEs leading to study drug discontinuation were numerically lower with RZB vs UST.

No new safety risks were identified; the safety profiles were consistent with the known safety profiles of RZB and UST.

Clinical remission: CDAI <150. **Endoscopic remission:** SES-CD ≤4 and at least a 2-point reduction vs BL and no subscore greater than 1 in any individual variable, as scored by a central reviewer. **Endoscopic response:** Decrease in SES-CD >50% from BL (or for patients with isolated ileal disease and a BL SES-CD of 4, at least a 2-point reduction from BL), as scored by central reviewer. **Steroid-free endoscopic remission:** SES-CD ≤4 and at least a 2-point reduction vs BL and no subscore greater than 1 in any individual component and not receiving steroids at the corresponding visit. **Steroid-free clinical remission:** CDAI clinical remission and not receiving steroids at the corresponding visit.

Categorical variables were analyzed using Cochran–Mantel–Haenszel (CMH) test. Non-responder imputation while incorporating multiple imputation to handle missing data (due to COVID-19 and geopolitical conflict) was used. Primary and secondary endpoints tested sequentially in the order specified using the CMH risk difference estimate test stratified by the number of failed anti-TNF therapies (≥1) and steroid use at baseline (yes, no).

[a]UST BL IV dose is a single weight-based dose. [b]ITT1 population included patients who were randomized to the UST or RZB selected dose and received at least one dose of study drug. [c]ITT1H population: A subset of ITT1 population which includes the first ~50% of ITT1 patients who have opportunity to reach Week 24 by the time of primary analysis of CDAI clinical remission at Week 24; non-inferiority of RZB vs UST. [d]Non-inferiority test: If the lower limit of 95% CI based on the CMH estimation for the risk difference between RZB and UST groups (RZB – UST) was greater than the negative of 10% non-inferiority margin, then non-inferiority was demonstrated for clinical remission at Week 24. If non-inferiority was demonstrated for clinical remission (CDAI) at Week 24, the superiority for the endoscopic remission at Week 48 was subsequentially tested at 2-sided significance level of 0.05 using the CMH test. [e]SA1 population: All patients who were randomized and received at least 1 dose of study drug in part 1 of the study. [f]As assessed by the investigator. [g]RZB related: Three patients with SAEs related to RZB (anal fistula, anal abscess, campylobacter, cystitis, localized infection, genital fistula); Eight patients with SAEs related to UST (abdominal pain, anal fistula, CD, ileal stenosis, vomiting). [h]Defined as cardiovascular death or death due to stroke, non-fatal myocardial infarction, and non-fatal stroke; extended MACE defined as MACE along with hospitalization for unstable angina and coronary revascularization procedures. [i]Opportunistic infection: esophageal candidiasis. [j]Malignant tumor: RZB, squamous cell carcinoma of skin; UST, anal squamous cell carcinoma. [k]One case of potential Hy's Law.

AE, adverse event; APS, abdominal pain score; BL, baseline; BMI, body mass index; CD, Crohn's disease; CDAI, Crohn's Disease Activity Index; CI, confidence interval; E/100PYs, events per 100 patient-years; hsCRP, high-sensitivity C-reactive protein; ITT, intent-to-treat; MACE, major adverse cardiovascular event; NMSC, non-melanoma skin cancer; Q8W, every 8 weeks; RZB, risankizumab; SA1, statistical area level 1; SAE, serious adverse event; SD, standard deviation; SES-CD, Simple Endoscopic Score for Crohn's Disease; SF, stool frequency; TEAE, treatment-emergent AE; TB, tuberculosis; TNF, tumor necrosis factor; UST, ustekinumab.

1. ClinicalTrials.gov. Study comparing intravenous (IV)/subcutaneous (SC) risankizumab to IV/SC ustekinumab to assess change in Crohn's Disease Activity Index (CDAI) in adult participants with moderate to severe Crohn's Disease (CD) (SEQUENCE) Available at: https://classic.clinicaltrials.gov/ct2/show/NCT04524611. Accessed: October 2023; 2. Peyrin-Biroulet L, et al. Presented at the United European Gastroenterology Week, 14–17 October 2023, Copenhagen, Denmark: Abstract LB01; 3. Peyrin-Biroulet L, et al. Presented at the United European Gastroenterology Week, 14–17 October 2023, Copenhagen, Denmark: Oral presentation LB01.

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