Sustained Symptom Control With Mirikizumab in Patients With Moderately to Severely Active Ulcerative Colitis in the LUCENT-2 Maintenance Trial

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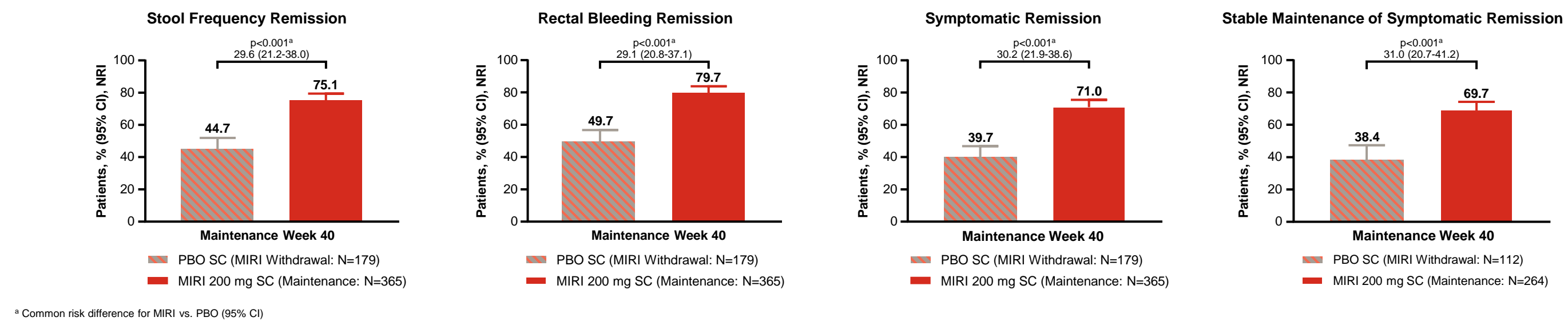
BACKGROUND

- Ulcerative colitis is a chronic inflammatory bowel disease associated with a relapsing-remitting disease course and symptoms of diarrhea, rectal bleeding, abdominal pain, and bowel urgency[1]
- Mirikizumab is a humanized IgG4–variant monoclonal antibody that specifically binds the p19 subunit of interleukin (IL)-23[2]
- In patients with moderately to severely active ulcerative colitis, treatment with mirikizumab was effective in induction of clinical remission at Week 12 (LUCENT-1; NCT03518086)[3] and in maintenance of clinical remission at Week 40, corresponding to 52 weeks of continuous treatment (LUCENT-2; NCT03524092)[4]

OBJECTIVE

- To assess sustained symptom control with mirikizumab during 40 weeks of maintenance treatment (52 weeks of continuous therapy; LUCENT-2) among patients who had a clinical response to mirikizumab during the induction study (LUCENT-1)

KEY RESULTS

Significantly Greater Rates of Stool Frequency Remission, Rectal Bleeding Remission, and Symptomatic Remission Were Observed With MIRI vs. PBO at 40 Weeks of Continuous Treatment

Stool Frequency Remission
p<0.001[a]; 29.6 (21.2-38.0)
PBO: 44.7; MIRI: 75.1
Maintenance Week 40
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

Rectal Bleeding Remission
p<0.001[a]; 29.1 (20.8-37.1)
PBO: 49.7; MIRI: 79.7
Maintenance Week 40
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

Symptomatic Remission
p<0.001[a]; 30.2 (21.9-38.6)
PBO: 39.7; MIRI: 71.0
Maintenance Week 40
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

Stable Maintenance of Symptomatic Remission
p<0.001[a]; 31.0 (20.7-41.2)
PBO: 38.4; MIRI: 69.7
Maintenance Week 40
PBO SC (MIRI Withdrawal): N=112
MIRI 200 mg SC (Maintenance): N=264
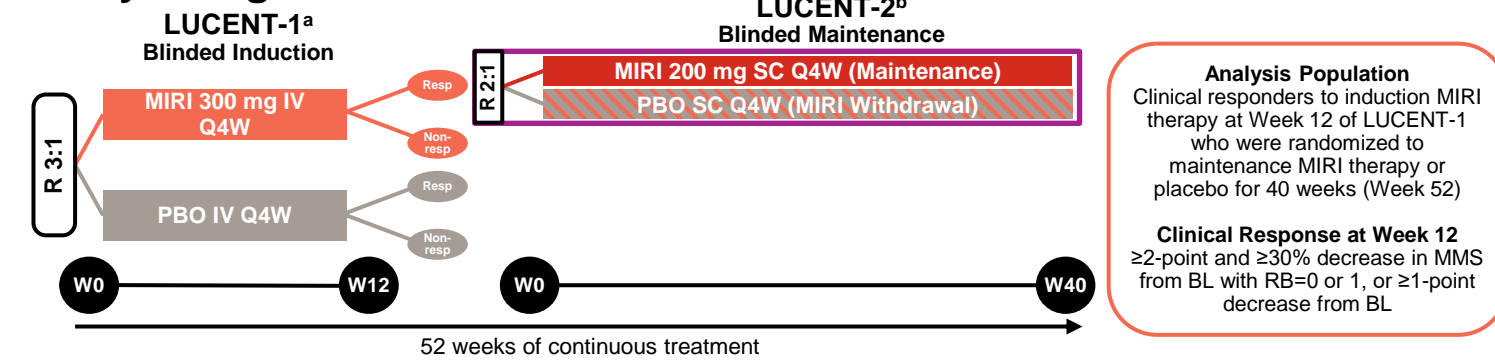
[a] Common risk difference for MIRI vs. PBO (95% CI)

CONCLUSIONS

- A greater proportion of mirikizumab-treated patients who were induction responders achieved stable maintenance of symptomatic remission compared with placebo through 40 weeks (ie, over 52 weeks of continuous treatment)
- Improvement in bowel urgency continued for patients who received mirikizumab treatment for 40 weeks, with patients accruing an additional 13.6-percentage point increase in bowel urgency remission during the first 8 weeks of maintenance therapy
- Sustained maintenance of remission of ulcerative colitis symptoms, including rectal bleeding, stool frequency, bowel urgency, and abdominal pain, was observed in mirikizumab-treated patients compared with placebo through 40 weeks (ie, over 52 weeks of continuous treatment)

METHODS

Study Design

LUCENT-1[a] Blinded Induction
R 3:1
MIRI 300 mg IV Q4W
PBO IV Q4W
W0 — W12

LUCENT-2[b] Blinded Maintenance
R 2:1
MIRI 200 mg SC Q4W (Maintenance)
PBO SC Q4W (MIRI Withdrawal)
W0 — W40

52 weeks of continuous treatment

Analysis Population
Clinical responders to induction MIRI therapy at Week 12 of LUCENT-1 who were randomized to maintenance MIRI therapy or placebo for 40 weeks (Week 52)
Clinical Response at Week 12
≥2-point and ≥30% decrease in MMS from BL with RB=0 or 1, or ≥1-point decrease from BL

[a] LUCENT-1 was a Phase 3, randomized, parallel-arm, double-blind, PBO-controlled induction trial of MIRI in patients with moderately to severely active ulcerative colitis; [b] LUCENT-2 was a Phase 3, double-blind, randomized, withdrawal maintenance study in patients who responded to MIRI induction therapy in LUCENT-1. Figure is not the full LUCENT-2 program; only the patient cohort who were MIRI responders during induction and randomized to maintenance treatment is presented here. Clinical responders to induction MIRI therapy at Week 12 of LUCENT-1 were randomized to receive maintenance MIRI therapy or PBO for 40 weeks (52 weeks of treatment). Randomization in LUCENT-2 was stratified by induction remission status, biologic failure status, baseline corticosteroid use, and region

Key Eligibility Criteria: LUCENT-1

- Age ≥18 and ≤80 years
- Moderately to severely active ulcerative colitis
  - Modified Mayo Score of 4-9, with an endoscopic subscore of 2-3
- Inadequate response, loss of response, or intolerance to:
  - Corticosteroids, immunomodulators, biologic therapy, or Janus kinase inhibitors for ulcerative colitis
- No previous exposure to anti–IL-12/23p40 or anti–IL-23p19 antibodies
- No previous failure of ≥3 different biologic therapies for ulcerative colitis, regardless of mechanism of action

Assessments

- Patient-reported outcomes were recorded daily in the patient eDiary and then averaged by week[a]:
  - Stool frequency Mayo subscore, from 0 (stools/day normal for the patient) to 3 (≥5 stools/day more than normal)
  - Rectal bleeding Mayo subscore, from 0 (no blood) to 3 (blood alone passed)
  - Bowel urgency severity (UNRS), from 0 (no urgency) to 10 (worst possible urgency)
  - Abdominal pain NRS, from 0 (none) to 10 (worst possible pain)
- Proportion of patients achieving:
  - Stool frequency remission: Stool frequency subscore 0, or 1 with ≥1-point decrease from induction BL
  - Rectal bleeding remission: Rectal bleeding subscore 0
  - Symptomatic remission: Stool frequency and rectal bleeding remission
  - Stable maintenance of symptomatic remission: Patients in symptomatic remission for ≥7 of 9 visits from Weeks 4-36 and at Week 40 among patients in symptomatic remission and with clinical response at the end of LUCENT-1
  - Abdominal pain improvement: NRS ≥30% reduction from BL in patients with abdominal pain NRS ≥3 at induction BL
  - Bowel urgency remission: Minimal to no bowel urgency (UNRS [0,1]) in patients with bowel urgency severity UNRS ≥3 at induction BL
  - Change in bowel urgency severity (UNRS) from induction BL

[a] For stool frequency and rectal bleeding, weekly assessments were calculated by averaging the 3 most recent available eDiary data in a 7-day period; for bowel urgency and abdominal pain, all available eDiary days in a 7-day period were averaged

Statistical Analysis

- Analyses were conducted using the modified Intent-to-Treat population (patients receiving ≥1 dose of mirikizumab or placebo)
  - Excludes patients impacted by an electronic clinical outcome assessment transcription error in Poland and Turkey
- Changes from baseline were compared between treatment arms using mixed-effects model of repeated measures, including treatment, baseline value, visit, interaction of baseline value-by-visit, interaction of treatment-by-visit, prior biologic or tofacitinib failure, corticosteroid use at baseline (LUCENT-1), global region, and clinical remission status at Week 12 (LUCENT-1)
- Response rates between treatment arms were compared using Cochran-Mantel-Haenszel test adjusted for prior biologic or tofacitinib failure, corticosteroid use at baseline (LUCENT-1), global region, and clinical remission status at Week 12 (LUCENT-1)
  - Common risk difference was the difference in proportions adjusted for stratification factors, with confidence intervals calculated using the Mantel-Haenszel-Sato method
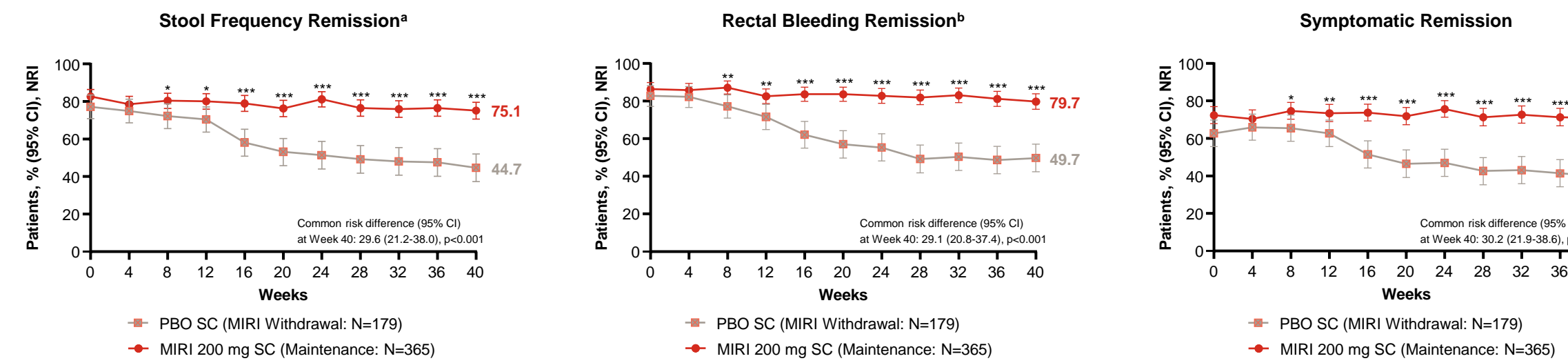 - Missing data were handled using non-responder imputation

RESULTS

Baseline[a] Demographics and Disease Characteristics

	MIRI Induction Responders	
	PBO SC (N=179)	MIRI 200 mg SC (N=365)
Age, years, mean (SD)	41.2 (12.8)	43.4 (14.2)
Male	104 (58.1)	214 (58.6)
Disease duration, years, mean (SD)	6.7 (5.6)	6.9 (7.1)
Disease location		
Left-sided colitis	119 (66.5)	234 (64.1)
Pancolitis	59 (33.0)	128 (35.1)
Modified Mayo Score, mean (SD)	6.6 (1.2)	6.5 (1.3)
Endoscopic Mayo subscore, moderate [score 2]	73 (40.8)	130 (35.6)
Endoscopic Mayo subscore, severe [score 3]	106 (59.2)	235 (64.4)
Bowel urgency severity, median (Q1, Q3)	6.0 (5.0, 8.0)	6.0 (5.0, 8.0)
Abdominal pain NRS, mean (SD)	5.3 (2.2)	4.9 (2.4)
Baseline corticosteroid use	68 (38.0)	135 (37.0)
Immunomodulator use	39 (21.8)	78 (21.4)
Prior biologic (or tofacitinib) failure	64 (35.8)	128 (35.1)
Prior anti-TNF failure	58 (32.4)	112 (30.7)
Prior vedolizumab failure	23 (12.8)	47 (12.9)
Prior tofacitinib failure	8 (4.5)	8 (2.2)
Number of failed biologics (or tofacitinib)		
0	115 (64.2)	237 (64.9)
1	35 (19.6)	77 (21.1)
≥2	29 (16.2)	51 (14.0)

Data are presented as n (%) unless stated otherwise
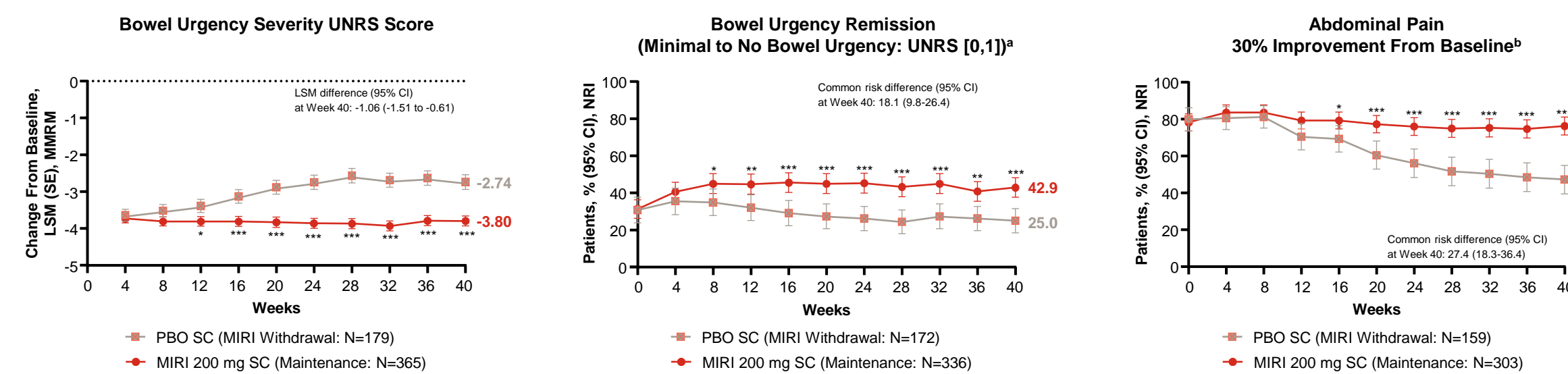[a] Refers to induction BL (Week 0 of LUCENT-1)

Remission Rates Were Sustained Through 40 Weeks of Continuous Treatment With MIRI vs. PBO

Stool Frequency Remission[a]
MIRI: 75.1; PBO: 44.7
Common risk difference (95% CI) at Week 40: 29.6 (21.2-38.0), p<0.001
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

Rectal Bleeding Remission[b]
MIRI: 79.7; PBO: 49.7
Common risk difference (95% CI) at Week 40: 29.1 (20.8-37.4), p<0.001
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

Symptomatic Remission
MIRI: 71.0; PBO: 39.7
Common risk difference (95% CI) at Week 40: 30.2 (21.9-38.6), p<0.001
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

*p<0.05; ** p<0.01; *** p<0.001 vs. PBO
[a] Mean (SD) stool frequency Mayo subscore at Week 0: 0.87 (0.77) for PBO SC, 0.81 (0.73) for MIRI 200 mg SC; [b] Mean (SD) rectal bleeding Mayo subscore at Week 0: 0.17 (0.38) for PBO SC, 0.13 (0.34) for MIRI 200 mg SC

Improvement in Bowel Urgency and Abdominal Pain Was Sustained Through 40 Weeks of Continuous Treatment With MIRI vs. PBO

Bowel Urgency Severity UNRS Score
MIRI: -3.80; PBO: -2.74
LSM difference (95% CI) at Week 40: -1.06 (-1.51 to -0.61)
PBO SC (MIRI Withdrawal): N=179
MIRI 200 mg SC (Maintenance): N=365

Bowel Urgency Remission (Minimal to No Bowel Urgency: UNRS [0,1])[a]
MIRI: 42.9; PBO: 25.0
Common risk difference (95% CI) at Week 40: 18.1 (9.8-26.4)
PBO SC (MIRI Withdrawal): N=172
MIRI 200 mg SC (Maintenance): N=336

Abdominal Pain 30% Improvement From Baseline[b]
MIRI: 76.2; PBO: 47.2
Common risk difference (95% CI) at Week 40: 27.4 (18.3-36.4)
PBO SC (MIRI Withdrawal): N=159
MIRI 200 mg SC (Maintenance): N=303

*p<0.05; ** p<0.01; *** p<0.001 vs. PBO
[a] In patients with Bowel urgency NRS ≥3 at BL (LUCENT-1); [b] In patients with Abdominal Pain NRS ≥3 at BL (LUCENT-1)

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4. Dubinsky MC, et al. Gastroenterology. 2022;162: S1393-S1394.