Association of Ulcerative Colitis Bowel Urgency Improvement With Clinical Response and Remission

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BACKGROUND

- Bowel urgency is a common symptom of ulcerative colitis, and many patients with ulcerative colitis experience reduced quality of life due to their symptoms[1]
- Mirikizumab is a humanized immunoglobulin G4–variant monoclonal antibody that specifically binds the p19 subunit of interleukin (IL)-23[2]
- Bowel urgency with mirikizumab treatment has been assessed in patients with moderately to severely active ulcerative colitis in the 12-week induction study, LUCENT-1 (NCT03518086), and the 40-week maintenance study, LUCENT-2 (NCT03524092)

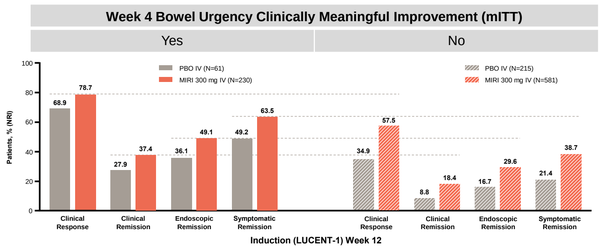
OBJECTIVE

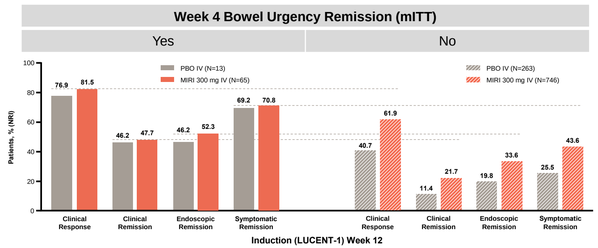
- To evaluate whether early improvement in bowel urgency is associated with later clinical endpoint improvements in patients treated with mirikizumab in the Phase 3 LUCENT-1 and LUCENT-2 studies

KEY RESULTS

Patients Experiencing Bowel Urgency CMI or Remission at Week 4 Were More Likely to Achieve Clinical Response and Clinical, Endoscopic, or Symptomatic Remission at Week 12

- Treatment (mirikizumab vs. placebo) and early bowel urgency improvement status (no improvement vs. bowel urgency clinically meaningful improvement (CMI) or bowel urgency remission at Week 4) were statistically significant main effects for clinical outcomes at Week 12 of induction treatment (p<0.001 and p<0.02, respectively)



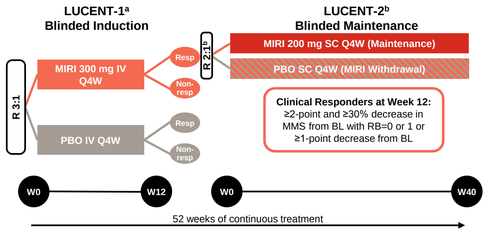


CONCLUSIONS

- Patients experiencing early bowel urgency improvement (either CMI or remission at Week 4) achieved better clinical outcomes at the end of induction (Week 12)
  - During induction treatment, patients experiencing bowel urgency CMI or remission at Week 4 were consistently more likely to achieve clinical response and clinical, endoscopic, or symptomatic remission at Week 12 for both mirikizumab and placebo groups
  - Maintenance treatment with mirikizumab was associated with better clinical outcomes at Week 40 compared with placebo, irrespective of urgency improvement status at end of induction (Week 12)
- These findings suggest that early bowel urgency improvement is associated with clinical outcomes during induction treatment
- Mirikizumab provided significantly better bowel urgency CMI and remission during induction and maintenance[3] compared with placebo
  - Bowel urgency can also represent a symptom that is independent from remission status

METHODS

Study Design



[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:
  - Conventional failed: ≥1 corticosteroid, immunomodulator for ulcerative colitis, or
  - Biologic failed: ≥1 biologic therapy or Janus kinase inhibitor (tofacitinib) for ulcerative colitis
- No previous exposure to anti–IL-12/23p40 or anti–IL-23p19 antibodies
- No previous failure of ≥3 different biologic therapies[a]

[a] Regardless of mechanism of action

Assessments

- Patient-reported outcomes were recorded daily in the patient eDiary and then averaged by week:
  - Bowel urgency severity (Urgency Numeric Rating Scale [UNRS]), from 0 (no urgency) to 10 (worst possible urgency)
  - Stool frequency Mayo subscore, from 0 (stools per day normal for the patient) to 3 (≥5 stools per day more than normal)
  - Rectal bleeding (RB) Mayo subscore, from 0 (no blood) to 3 (blood alone passed)
  - Endoscopic Mayo subscore (ES) from 0 (normal/inactive) to 3 (severe)
- Proportion of patients achieving:
  - Bowel urgency CMI: UNRS ≥3-point improvement in patients with bowel urgency UNRS ≥3 at baseline
  - Bowel urgency remission (no to minimal bowel urgency): UNRS (0,1) in patients with bowel urgency UNRS ≥3 at baseline
  - Symptomatic remission: Stool frequency remission (subscore 0, or 1 with ≥1-point decrease from induction baseline) and RB remission (RB subscore 0)
- Endoscopy:
  - Endoscopic remission: ES (0,1) excluding friability

Statistical Analyses

- Analyses were conducted using the modified Intent-to-Treat population (patients receiving ≥1 dose of mirikizumab or placebo)
- Association between early bowel urgency improvement (bowel urgency CMI or remission) and later clinical outcomes (clinical response and clinical, endoscopic, or symptomatic remission) was assessed using logistic regression[a,b]
  - Associations were assessed between bowel urgency CMI or remission at Week 4 and clinical outcomes at Week 12 of induction treatment (LUCENT-1)
  - Associations were assessed between bowel urgency CMI or remission at Week 12 of induction treatment and clinical outcomes at Week 40 (52 continuous weeks) of maintenance treatment (LUCENT-2)
- The Fisher exact test was used to compare treatments for clinical outcomes within urgency status groups
- Non-responder imputation was used for missing values

[a] Induction logistic regression analysis with treatment, subgroup, and treatment-by-subgroup interaction and prior biologic or tofacitinib failure (yes/no); baseline corticosteroid use (yes/no); baseline disease activity (MMS: 4-6 or 7-9); and region (North America/Europe/other) as factors; [b] Maintenance logistic regression analysis with treatment, subgroup, and treatment-by-subgroup interaction and prior biologic or tofacitinib failure (yes/no); baseline corticosteroid use (yes/no); region (North America/Europe/other); and clinical remission status (yes/no) at induction Week 12 as factors

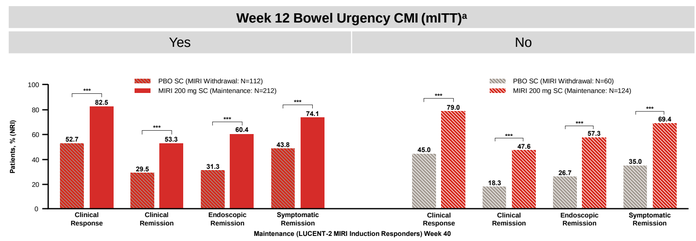
RESULTS

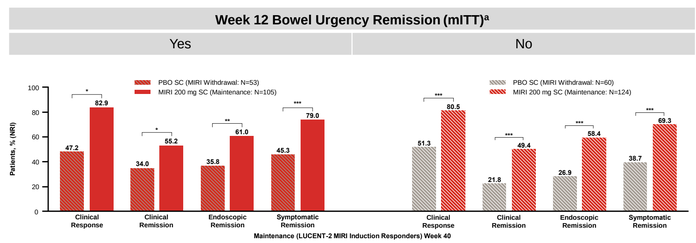
Demographics and Baseline Characteristics[a]

	LUCENT-1 (mITT)		LUCENT-2 (mITT MIRI Induction Responders)	
	PBO IV (N=294)	MIRI 300 mg IV (N=868)	PBO SC (MIRI Withdrawal) (N=179)	MIRI 200 mg SC (N=365)
Age, years, mean (SD)	41.3 (13.8)	42.9 (13.9)	41.2 (12.8)	43.4 (14.2)
Male	165 (56.1)	530 (61.1)	104 (58.1)	214 (58.6)
Disease duration, years, mean (SD)	6.9 (7.0)	7.2 (6.7)	6.7 (5.6)	6.9 (7.1)
Disease location				
Left-sided colitis	188 (64.2)	544 (62.7)	119 (66.5)	234 (64.1)
Pancolitis	103 (35.2)	318 (36.6)	59 (33.0)	128 (35.1)
MMS category				
Moderate [score 4-6]	138 (47.1)	404 (46.5)	77 (43.0)	181 (49.6)
Severe [score 7-9]	155 (52.9)	463 (53.3)	102 (57.0)	184 (50.4)
Endoscopic Mayo subscore, severe [score 3]	200 (68.3)	574 (66.1)	106 (59.2)	235 (64.4)
Bowel urgency severity (UNRS), mean (SD)	6.2 (2.2)	6.1 (2.2)	6.2 (1.9)	6.0 (2.2)
Baseline corticosteroid use	113 (38.4)	351 (40.4)	68 (38.0)	135 (37.0)
Baseline immunomodulator use	69 (23.5)	211 (24.3)	39 (21.8)	78 (21.4)
Prior biologic or tofacitinib failure	118 (40.1)	361 (41.6)	64 (35.8)	128 (35.1)

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

MIRI Achieved Higher Rates of Clinical Response and Clinical, Endoscopic, or Symptomatic Remission at End of Maintenance vs. PBO[a] Irrespective of Bowel Urgency Status at Week 12





* p<0.05; ** p<0.01; *** p<0.001 vs. PBO
[a] LUCENT-2 analysis population: Clinical responders to induction MIRI therapy at Week 12 of LUCENT-1 who were re-randomized to maintenance MIRI therapy or PBO for 40 weeks (52 weeks of continuous treatment)

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1. Nelson L, et al. *J Patient Rep Outcomes*. 2019;3:66.
2. Sandborn WJ, et al. *Gastroenterology*. 2020;158:537-549.e10.
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ABBREVIATIONS

BL=baseline; CMI=clinically meaningful improvement; ES=endoscopic subscore; IV=intravenous; MIRI=mirikizumab; mITT=modified Intent-to-Treat; MMS=Modified Mayo Score; Non-resp=non-responders; NRI=non-responder imputation; PBO=placebo; Q4W=every 4 weeks; R=randomization; RB=rectal bleeding; Resp=responders; SC=subcutaneous; SD=standard deviation; UNRS=Urgency Numeric Rating Scale; W=Week

DISCLOSURES

- **D. B. Clemow**, **C. Sapin**, and **T. Hunter Gibble** are employees and shareholders of Eli Lilly and Company; **T. Hibi** has received lecture fees from: AbbVie, Aspen Japan K.K., Ferring Pharmaceuticals, Gilead Sciences, Janssen, JIMRO, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Pfizer, and Takeda; has received honoraria as an advisory board member or consultant from: AbbVie, Apo Plus Station, Bristol Myers Squibb, Celltrion, EA Pharma, Eli Lilly and Company, Gilead Sciences, Janssen, Kyorin, Mitsubishi Tanabe Pharma, Nichi-iko Pharmaceutical, Pfizer, Takeda, and Zeria Pharmaceutical; has received pharmaceutical and research grants from: AbbVie, ActivAid, Alfresa Pharma, Bristol Myers Squibb, Eli Lilly Japan K.K., Ferring Pharmaceuticals, Gilead Sciences, Janssen Pharmaceutical K.K., JMDC, Mochida Pharmaceutical, Nippon Kayaku, Pfizer Japan, and Takeda; has received scholarship contributions from: Mitsubishi Tanabe Pharma, Nippon Kayaku, and Zeria Pharmaceutical; and has belonged to study groups sponsored by: AbbVie, Alfresa Pharma, EA Pharma, JIMRO, Kyorin, Mochida Pharmaceutical, MIYARISAN Pharmaceutical, Otsuka, and Zeria Pharmaceutical; **M. C. Dubinsky** has received honoraria as a consultant for: AbbVie, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Eli Lilly and Company, F. Hoffmann-La Roche, Genentech, Gilead Sciences, Janssen, Pfizer, Prometheus Therapeutics and Diagnostics, Takeda, and UCB Pharma; has been contracted for research by: AbbVie, Janssen, Pfizer, and Prometheus Biosciences; has stock interest in: Trellus Health; and has received licensing fees from: Takeda; **S. Vermeire** has received honoraria as a consultant for: AbbVie, Arena Pharmaceuticals, Avaxia Biologics, Boehringer Ingelheim, Celgene, Dr. Falk Pharma, Ferring Pharmaceuticals, Galapagos NV, GenentechRoche, Gilead Sciences, Hospira, Janssen, Mundipharma, Merck Sharp & Dohme, Pfizer, ProDigest, Progenity, Prometheus Therapeutics and Diagnostics, Robarts Clinical Trials, Second Genome, Shire, Takeda, Theravance Biopharma, and Tillotts Pharma AG; and has received lecture fees from: AbbVie, Dr. Falk Pharma, Ferring Pharmaceuticals, Galapagos NV, GenentechRoche, Gilead Sciences, Janssen, Pfizer, Robarts Clinical Trials, and Takeda; **S. Schreiber** has received personal fees and/or travel support from: AbbVie, Amgen, Arena Pharmaceuticals, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly and Company, Dr. Falk Pharma, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos NV, Gilead Sciences, I-MAB Biopharma, Janssen, Merck Sharp & Dohme, Mylan, Novartis, Pfizer, Protagonist Therapeutics, Provention Bio, Roche, Sandoz/Hexal, Shire, Takeda, Theravance Biopharma, and UCB Pharma; **L. Peyrin-Biroulet** has received grants or contracts from: AbbVie, Fresenius Kabi, Merck Sharp & Dohme, and Takeda; and has received honoraria as a consultant for: AbbVie, Alimentiv, Allergan, Amgen, Arena Pharmaceuticals, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly and Company, Enthera, Ferring Pharmaceuticals, Fresenius Kabi, Galapagos NV, Genentech, Gilead Sciences, Gossamer Bio, InDex Pharmaceuticals, Inotrem, Janssen, Merck Sharp & Dohme, Mylan, Norgine, Ono Pharmaceutical, OSE Immunotherapeutics, Pandion Therapeutics, Pfizer, Roche, Samsung Bioepis, Sandoz, Takeda, Theravance Biopharma, Thermo Fisher Scientific, Tillotts Pharma AG, Viatris, and Vifor Pharma; **M. Watanabe** has received grants or contracts from: AbbVie, Alfresa Pharma, EA Pharma, Kissei, Kyorin, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Nippon Kayaku, Takeda, and Zeria Pharmaceutical; has received honoraria as a consultant for: AbbVie, Boehringer Ingelheim, EA Pharma, Eli Lilly Japan K.K., Gilead Sciences, Nippon, and Takeda; and has received lecture fees from: EA Pharma, Eli Lilly Japan K.K., Gilead Sciences, Janssen, JIMRO, Kissei, Mitsubishi Tanabe Pharma, Mochida Pharmaceutical, Pfizer Japan, Takeda, and Zeria Pharmaceutical; **R. Panaccione** has received speaker fees and/or served as a consultant and/or advisory board member for: Abbott, AbbVie, Alimentiv, Amgen, Arena Pharmaceuticals, AstraZeneca, Biogen, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Cosmo Pharmaceuticals, Eisai, Elan Pharma, Eli Lilly and Company, Ferring Pharmaceuticals, Galapagos NV, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Mylan, Oppilan Pharma, Pandion Therapeutics, Pfizer, Progenity, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Shire, Sublimity Therapeutics, Takeda, Theravance Biopharma, and UCB Pharma; and has received research/educational support from: AbbVie, Ferring Pharmaceuticals, Janssen, Pfizer, and Takeda
- Medical writing assistance was provided by Linda Donnini, PhD, of ProScribe – Envision Pharma Group, and was funded by Eli Lilly and Company. This study was previously presented at the United European Gastroenterology Week (UEGW) 2022

Study was sponsored by Eli Lilly and Company