Mirikizumab Treatment Improves Bowel Movement Urgency in Patients with Moderately to Severely Active Ulcerative Colitis

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BACKGROUND

- Interleukin (IL)-23 is a key cytokine in the pathogenesis of inflammatory bowel disease[1]
- Mirikizumab, a p19-directed IL-23 antibody, demonstrated efficacy and was well tolerated during 12 weeks of induction followed by an additional 40 weeks of maintenance treatment in a Phase 2, randomized clinical trial (NCT02589665) in patients with moderately to severely active ulcerative colitis (UC)[2,3]
- Bowel movement urgency is one of the most bothersome and important symptoms experienced by patients with UC and an often-overlooked aspect of their quality of life (QoL)[4]

OBJECTIVE

- To evaluate the effect of mirikizumab on patient-reported bowel movement urgency

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2. Sandborn WJ, et al. *Gastroenterology.* 2019;[Epub ahead of print].
3. D'Haens GGR, et al. *J Crohn's Colitis.* 2019;13:S26-S27.
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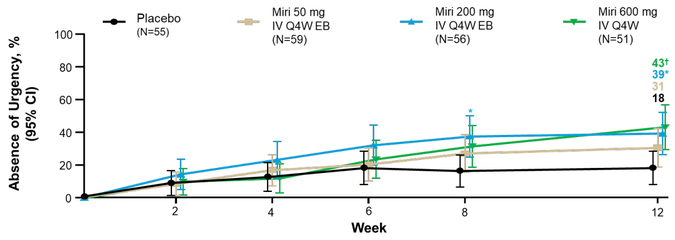
ABBREVIATIONS

ASA=aminosalicylic acid; CI=confidence interval; EB=exposure-based; IBDQ=Inflammatory Bowel Disease Questionnaire; IV=intravenous; Miri=mirikizumab; Q4W=every 4 weeks; Q12W=every 12 weeks; R=randomization; SC=subcutaneous

KEY RESULTS

Absence of Bowel Movement Urgency Induction Period

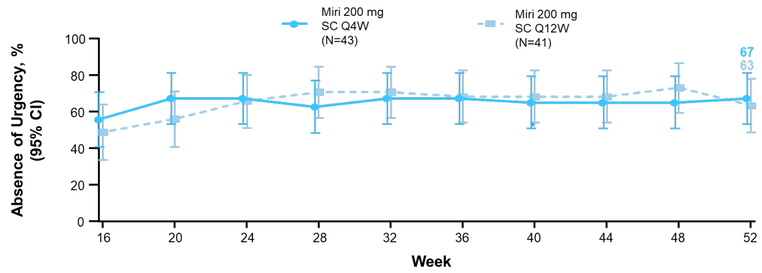
- All mirikizumab-treated patients with bowel movement urgency at baseline had improvement in bowel movement urgency at Week 12; improvements were significant versus placebo for the mirikizumab 200-mg and 600-mg groups
- Numerical differences in treatment effect were observed as early as Week 4; difference versus placebo was statistically significant at Week 8 in the mirikizumab 200-mg group



* p<0.05, † p<0.01 vs placebo by logistic regression analysis

Sustained Absence of Bowel Movement Urgency in Clinical Responders Maintenance Period

- Patients who had urgency at baseline and were clinical responders in the Induction Period sustained improvement in bowel movement urgency with minimal variation in response in the Maintenance Period



CONCLUSIONS

- In patients who reported bowel movement urgency at baseline, mirikizumab treatment resulted in significantly higher proportions of patients with absence of bowel movement urgency compared to placebo at Week 12
  - Numerical improvements in bowel movement urgency were observed as early as Week 4 and statistically significant improvements were observed by Week 8
- The improvement in bowel movement urgency was sustained through Week 52
- To the authors' knowledge, this is the first study to assess the effects of IL-23 on bowel movement urgency
- Reduction in bowel movement urgency is consistent with improvements in the signs and symptoms of UC and QoL following treatment with mirikizumab in the Phase 2 AMAC clinical trial[2,3,5]

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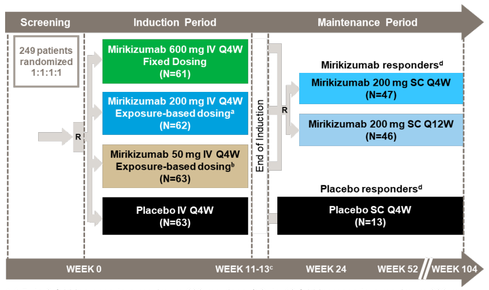
METHODS

Study Design, AMAC



[a] 1.5- to 3-fold increase to a maximum 600-mg dose; [b] 2- to 12-fold increase to a maximum 600-mg dose; [c] Patients who responded to mirikizumab at Week 12 were stratified according to their clinical remission status and re-randomized at a 1:1 ratio to receive mirikizumab 200 mg SC Q4W or Q12W through Week 52. Clinical response was defined as a Week 12 decrease in 9-point Mayo subscore (rectal bleeding, stool frequency, and endoscopy) inclusive of ≥2 points and ≥35% from baseline with a decrease of rectal bleeding subscore of ≥1 or a rectal bleeding subscore of 0 or 1; [d] Patients who did not meet clinical response criteria at Week 12 had the option to continue in an unblinded study extension period or to discontinue from the study

Key Eligibility Criteria

Inclusion Criteria

- Male or female, ≥18 and ≤75 years of age
- Moderately to severely active UC:
  - Mayo score 6-12 and endoscopic subscore ≥2 within 14 days before the first dose of study treatment[a]
- UC extending beyond the rectum (≥15 cm of involved colon)
- Treatment history:
  - Inadequate response, loss of response, or intolerance to current treatment with corticosteroids or immunomodulators, or a history of corticosteroid dependence

  OR
  - Inadequate response, loss of response, or intolerance to treatment with ≥1 biologic agent

[a] Partial Mayo score of ≥4 and other eligibility criteria must have been met before endoscopy was performed as a study procedure

Bowel Urgency Definitions and Analyses

- Patients used a paper diary to report daily symptoms, including presence or absence of bowel movement urgency each day
  - Data were collected throughout the 52-week trial
- **Instruction to patients:** "Please indicate the presence or absence of bowel urgency today"
- **Possible patient responses:** Urgency was present; urgency was absent
- **Analyses:** "Absence of urgency" defined as 3 consecutive days of patient-reported "absence of bowel urgency today" prior to each scheduled visit, excluding day of procedure (endoscopy) and day(s) subject took bowel preparation

Urgency Variable Assignment

Binary Variable = Absence of urgency (Yes/No)

	3 Days Prior to Visit	2 Days Prior to Visit	1 Day Prior to Visit	Absence of Urgency (Yes/No)
Response	Urgency was absent	Urgency was absent	Urgency was absent	Yes
Response	Anything other than "Urgency was absent"			No

Statistical Analyses

- Analyses were based on the Intent-to-Treat population with patient-reported bowel movement urgency at baseline
- Logistic regression analysis was conducted to evaluate the treatment differences in absence of urgency among patients with urgency present at baseline for the first 12 weeks
- The proportion of patients with absence of urgency was calculated for the maintenance period among patients with urgency present at baseline and reached clinical response at Week 12, irrespective of urgency status at Week 12
- Patients who had missing urgency data were imputed as having experienced urgency, irrespective of treatment assignment
  - Missing data were imputed using non-responder imputation

RESULTS

Baseline Demographics and Characteristics Induction Period Population

	Placebo (N=63)	Miri 50 mg IV Q4W EB (N=63)	Miri 200 mg IV Q4W EB (N=62)	Miri 600 mg IV Q4W (N=61)
Age, years	42.6 (13.5)	41.8 (14.1)	43.4 (14.7)	42.4 (13.4)
Female, n (%)	27 (42.9)	25 (39.7)	25 (40.3)	23 (37.7)
Weight, kg	74.1 (16.9)	77.0 (17.2)	75.6 (17.3)	73.0 (15.1)
Disease duration, years	9.5 (9.6)	8.2 (7.2)	9.0 (9.0)	6.0 (5.7)
Concomitant therapies at baseline, n (%)				
5-ASA use	47 (74.6)	42 (66.7)	56 (90.3)	39 (63.9)
Corticosteroids	33 (52.4)	29 (46.0)	25 (40.3)	35 (57.4)
Thiopurines	25 (39.7)	15 (23.8)	18 (29.0)	11 (18.0)
Number of unique prior biologic therapies, n (%)				
0	25 (39.7)	26 (41.3)	22 (35.5)	23 (37.7)
1	17 (27.0)	15 (23.8)	27 (43.5)	15 (24.6)
2	15 (23.8)	16 (25.4)	7 (11.3)	14 (23.0)
≥3	6 (9.5)	6 (9.5)	6 (9.7)	9 (14.8)
Stool Frequency Mayo subscore	2.4 (0.7)	2.4 (0.8)	2.3 (0.8)	2.6 (0.6)
Rectal Bleeding Mayo subscore	1.4 (0.7)	1.3 (0.9)	1.5 (0.8)	1.3 (0.8)
Bowel movement urgency present, n (%)[a]	55 (87.3)	59 (93.7)	56 (90.3)	51 (83.6)
IBDQ	124.1 (29.8)	122.5 (29.2)	133.0 (34.7)	125.5 (33.9)

Data are mean (standard deviation) unless otherwise indicated
[a] Absence of urgency defined as 3 consecutive days prior to baseline

Baseline[a] Demographics and Characteristics Maintenance Period Population

	Maintenance Period	
	Miri 200 mg SC Q4W (N=47)	Miri 200 mg SC Q12W (N=46)
Age, years	41.3 (14.1)	38.9 (12.4)
Female, n (%)	20 (42.6)	24 (52.2)
Weight, kg	74.6 (17.3)	72.5 (18.0)
Disease duration, years	9.2 (6.7)	6.0 (4.4)
Concomitant therapies at baseline, n (%)		
5-ASA use	37 (78.7)	40 (87.0)
Corticosteroids	22 (46.8)	19 (41.3)
Thiopurines	15 (31.9)	9 (19.6)
Number of unique prior biologic therapies, n (%)		
0	21 (44.7)	23 (50.0)
1	12 (25.5)	17 (37.0)
2	10 (21.3)	5 (10.9)
≥3	4 (8.5)	1 (2.2)
Stool Frequency Mayo subscore	2.4 (0.8)	2.3 (0.8)
Rectal Bleeding Mayo subscore	1.5 (0.9)	1.6 (0.8)
Bowel movement urgency present, n (%)[b]	43 (91.5)	41 (89.1)
IBDQ	120.9 (28.3)	127.2 (32.9)

Data are mean (standard deviation) unless otherwise indicated
[a] Baseline defined as Week 0
[b] Absence of urgency defined as 3 consecutive days prior to baseline, irrespective of urgency status at Week 12

DISCLOSURES

- **M. Dubinsky** has received consultancy fees from: AbbVie, Arena Pharmaceuticals, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Genentech, Janssen, Pfizer, Prometheus Laboratories, Takeda, and is a co-founder of Cornerstones Health; **S. Lee** has received grant/research support from: Abbvie, AbGenomics, Arena Pharmaceuticals, Celgene, GlaxoSmithKline, Janssen, Salix Pharmaceuticals, Shield Therapeutics, Takeda, Tetherex Pharmaceuticals, UCB Pharma; has received consultancy/advisory board fees from: Applied Molecular Transport, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Cornerstones Health, Eli Lilly and Company, Janssen, KCRN Research, and UCB Pharma; **R. Panaccione** has received fees for serving as a consultant, paid speaker, and/or advisory board member, and/or received educational/research support from Abbott, AbbVie, ActoGeniX, AGI Therapeutics, Alba Therapeutics, Albireo, Alfa Wasserman, Amgen, AM-Pharma BV, Anaphore, Aptalis, Astellas, Athersys, Atlantic Healthcare, AstraZeneca, Baxter, BioBalance, Biogen Idec, Boehringer Ingelheim, Bristol-Myers Squibb, Celek, Celgene, Cellerix, Cerimon, ChemoCentryx, CoMentis, Coronado Biosciences, Cosmo Technologies, Cubist, Cytokine Pharmasciences, Eagle, Eisai, Elan, Eli Lilly and Company, EnGene, Enteromedics, Exagen Diagnostics, Ferring, Flexion Therapeutics, Funxional Therapeutics, Genentech, Genzyme, Gilead, Given Imaging, GlaxoSmithKline, Hospira, Human Genome Sciences, Ironwood, Janssen, KaloBios, Lexicon, Lycera, Meda, Merck & Co., Merck Research Laboratories, MerckSerono, Millennium, Nisshin Kyorin, Novartis, Novo Nordisk, NPS Pharmaceuticals, Optimer, Orexigen, PDL Biopharma, Pfizer, Procter and Gamble, Prometheus Laboratories, ProtAb, Purgenesis Technologies, Receptos, Relypsa, Salient, Salix, Santarus, Shire Pharmaceuticals, Sigmoid Pharma, Sirtris, S.L.A. Pharma, Takeda, Targacept, Teva, Therakos, Tillotts, TxCell SA, UCB Pharma, Vascular Biogenics, Viamet, and Warner Chilcott; **M. T. Abreu** has received consultancy fees from: Boehringer Ingelheim, Eli Lilly and Company, Focus Medical Communications, Gilead, and Landos Biopharma; has received research funding from: Pfizer, Prometheus Laboratories, and Takeda; **S. Vermeire** has received grant/research support from: Abbvie, Janssen, MSD, Pfizer, and Takeda; has received consultancy fees/honoraria from: AbbVie, Arena, Celgene, Eli Lilly and Company, Ferring, Galapagos, Genentech/Roche, Gilead, Hospira, Janssen, Mundipharma, MSD, Pfizer, Progenity, Second Genome, Shire, and Takeda; and is on the speakers bureau of: AbbVie, Ferring, Hospira, Janssen, MSD, Pfizer, Takeda, and Tillots; **T. Lissoos**, **N. Morris**, **V. Arora**, **Y. Dong**, and **A. N. Naegeli** are current employees and shareholders of Eli Lilly and Company; **B. E. Sands** has received consultancy fees from: 4D Pharma, AbbVie, Allergan Sales, Amgen, Arena Pharmaceuticals, Boehringer Ingelheim, Capella Biosciences, Celgene, Eli Lilly and Company, EnGene, Ferring, Gilead, Janssen, Lyndra, MedImmune, Oppilan Pharma, Otsuka, Palatin Technologies, Pfizer, Progenity, Rheos Medicines, Seres Therapeutics, Synergy Pharmaceuticals, Takeda, Target PharmaSolutions, Theravance Biopharma R&D, TiGenix, Vivelix Pharmaceuticals, and WebMD; and has received research funding from Celgene, Janssen, Pfizer, and Takeda
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