Absence of Bowel Urgency is Associated with Significantly Improved Inflammatory Bowel Disease Related Quality of Life in a Phase 2 Trial of Mirikizumab in Patients with Ulcerative Colitis

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BACKGROUND

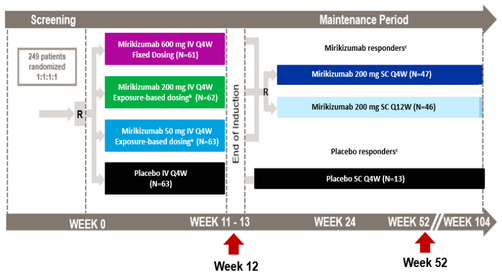
- Bowel urgency is one of the most common symptoms experienced by patients with ulcerative colitis (UC) and may impact health-related quality of life (HRQoL)[1]
- Mirikizumab is a humanized monoclonal antibody directed against the p19 subunit of IL-23
- Mirikizumab demonstrated efficacy[2], was well-tolerated, and significantly reduced bowel urgency[3] in a phase 2 52-week randomized clinical trial in patients with UC (NCT02589665)
- Inflammatory bowel disease questionnaire (IBDQ) scores are indicators of patient health; higher IBDQ scores indicate higher HRQoL

OBJECTIVE

- To explore the relationship between patient-reported bowel urgency and IBDQ scores in a pooled sample of patients participating in a phase 2 clinical trial for UC

METHODS

Figure 1. Study Design

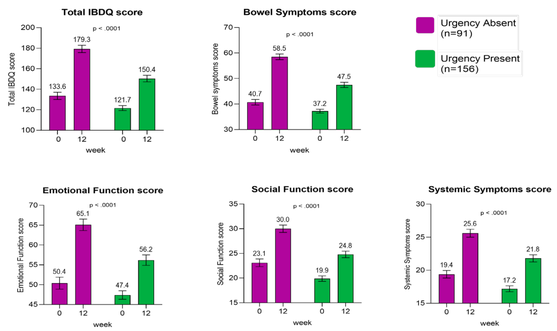


[a] 2-12 fold increase to a maximum 600 mg dose; [b] 1.5-3 fold increase to a maximum 600 mg dose; [c] Clinical response defined at Week 12 as a decrease in 9-point Mayo subscore (rectal bleeding, stool frequency, and endoscopy) inclusive of ≥2 points and ≥35% from baseline, with either a decrease of rectal bleeding subscore of ≥1, or a rectal bleeding subscore of 0 or 1.

IV=intravenous; Q4W=every 4 weeks; Q12W=every 12 weeks; R=randomization; SC=subcutaneous

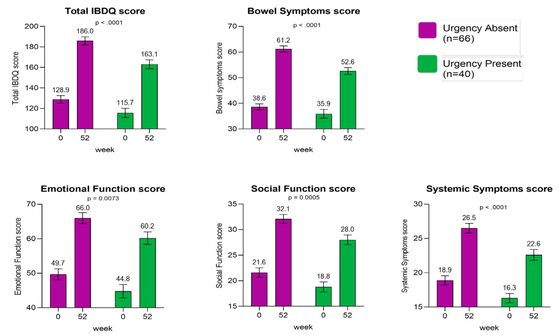
KEY RESULTS

Figure 2. Change in IBDQ total score and domain subscores from baseline in patients stratified by bowel urgency absence or presence at week 12



P value is for a comparison of change from baseline to week 12 between patients reporting urgency absent vs present. Data are mean ± standard error.

Figure 3. Change in IBDQ total score and domain subscores from baseline in patients stratified by bowel urgency absence or presence at week 52



P value is for a comparison of change from baseline to week 52 between patients reporting urgency absent vs present. Data are mean ± standard error.

CONCLUSIONS

- Absence of urgency is associated with improvements in HrQoL as measured by IBDQ total score and domain subscores
- These findings suggest that bowel urgency is a distinct symptom that may be a useful surrogate marker of disease activity
- Bowel urgency is an important symptom to discuss with patients with UC along with Stool frequency and Rectal bleeding

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Key Eligibility Criteria

Inclusion criteria

- Moderate to severely active UC:
  - Mayo score 6-12 and endoscopic subscore ≥2 within 14 days before the first dose of study treatment[a]
- Up-to-date colorectal cancer surveillance for subjects with family history of colorectal cancer, personal history of increased colorectal cancer risk, age >50 years, or other known risk factor
- Treatment history:
  - Naïve to biologic therapy and have inadequate response or intolerance to current treatment with corticosteroids or immunomodulators, or a history of corticosteroid dependence
    OR
  - Documented history of failure to respond to or tolerate biologic treatment ≥1 biologic agent

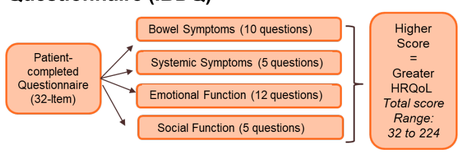
Exclusion criteria

- Diagnosed with indeterminate colitis, proctitis, or crohn's disease

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

Clinical Outcome Measures

Figure 4. Inflammatory Bowel Disease Questionnaire (IBDQ)



Domains: Each graded on a 7-point Likert scale
IBDQ total score improvement ≥16 (clinically meaningful improvement), IBDQ score ≥170 (remission)
HRQoL = Health related quality of life

Statistical Analysis

- Absence of bowel urgency was defined as reporting three consecutive days of no bowel urgency prior to the week 12 and 52 visit dates. Missing bowel urgency data were imputed as having bowel urgency present at that visit.
- HrQoL outcomes were assessed at week 12 by pooling the Intent-to-Treat population across treatment groups. Week 52 outcomes were assessed by pooling a subset of the Intent-to-Treat population that demonstrated clinical response at week 12.
- Mean change from baseline was assessed using analysis of covariance (ANCOVA) models. Each ANCOVA model included absence of urgency status, geographic region, prior biologic experience, age, gender, and baseline value of the IBDQ score.
- Multivariable linear models were fitted to compare the coefficient of partial determination (R^2) between absence of urgency, stool frequency, rectal bleeding, and endoscopic score. Each linear model included the Week 12 Mayo stool frequency score, rectal bleeding score, endoscopy score, absence of bowel urgency status, geographic region, prior biologic experience, age, gender, and baseline value of the IBDQ score
- Modified baseline observation carried forward was used to impute missing Mayo score components and IBDQ values at weeks 12 or 52.

Abbreviations

UC= Ulcerative Colitis; IBDQ=Inflammatory Bowel Disease Questionnaire; IV=intravenous;; Q4W=every 4 weeks; Q12W=every 12 weeks; R=randomization; SC=subcutaneous; HRQOL= Health related quality of life; ASA=aminosalicylic acid; ANCOVA=Analysis of covariance

References

1. Petryszyn PW, et al. Adv Clin Exp Med. 2018;27(6):813-818
2. Sandborn WJ, et. al. Gastroenterology, 158(3);537–549.e10
3. Dubinsky M, et al. Gastroenterology, 158(3);S17-8

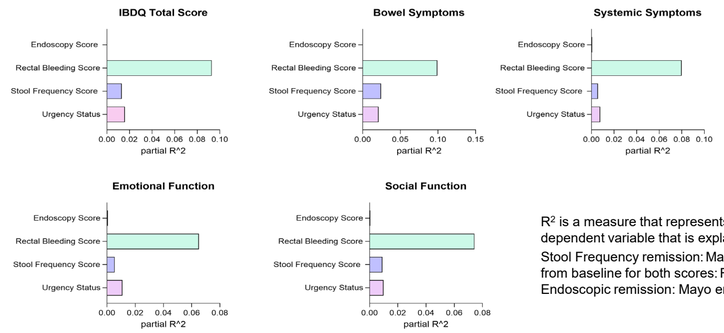
Acknowledgments

The authors would like to thank Ciara O Neill for their writing and editorial contributions.

RESULTS

- Patients with absence of bowel urgency at weeks 12 and 52 achieved higher IBDQ total and domain subscores compared to those with presence of bowel urgency **(Figure 2 & 3)**
- Patients with absence of bowel urgency at weeks 12 and 52 also achieved a greater change from baseline in IBDQ total and domain subscores compared to those with presence of bowel urgency **(Figure 2 & 3)**
- A patient's rectal bleeding score was seen to have the greatest association with IBDQ total and domain subscores. Bowel urgency had similar magnitudes of association with change in IBDQ total score and domain subscores as stool frequency **(Figure 5)**

Figure 5. Magnitude of the partial correlation (R^2) for Urgency status, Stool frequency, Rectal Bleeding, and Endoscopy for the IBDQ total score and domain subscores at week 12



R^2 is a measure that represents the proportion of the variance for a dependent variable that is explained by an independent variable.
Stool Frequency remission: Mayo SF = 0 or 1, and a ≥ 1point decrease from baseline for both scores: Rectal bleeding remission: Mayo RB = 0; Endoscopic remission: Mayo endoscopy = 0 or 1

Table 1. Baseline Demographics and Characteristics

	Bowel urgency status at week 12		Bowel urgency status at week 52	
Baseline Variables	Bowel urgency Absent (N=91)	Bowel urgency Present(N=158)	Bowel urgency Absent (N=66)	Bowel urgency Present (N=40)
Age, years	41.1 (13.26)	43.4 (14.15)	39.6 (12.84)	41.6 (15.00)
Gender: Female, n (%)	36 (39.56)	64 (40.51)	31 (46.97)	18 (45.00)
Male, n (%)	55 (60.44)	94 (59.49)	35 (53.03)	22 (55.00)
Weight, kg	73.6 (16.68)	75.7 (16.66)	71.3 (16.61)	78.7 (18.54)
Disease duration, years	6.9 (5.71)	9.0 (9.12)	8.3 (6.81)	6.9 (6.57)
Number of unique prior biologic therapies, n (%)	0.8 (1.04)	1.2 (1.06)	0.7 (0.84)	1.0 (1.13)
Concomitant therapies at baseline, n (%): 5-ASA use	66 (72.53)	118 (74.68)	54 (81.82)	31 (77.50)
Corticosteroids	44 (48.35)	78 (49.37)	28 (42.42)	20 (50.00)
Thiopurines	23 (25.27)	46 (29.11)	20 (30.30)	9 (22.50)
Total Mayo score n (%)	8.5 (1.42)	8.9 (1.46)	8.8 (1.47)	8.6 (1.60)
9-point modified Mayo score	6.3 (1.34)	6.7 (1.26)	6.7 (1.40)	6.4 (1.41)
Endoscopy Mayo subscore	2.7 (0.46)	2.8 (0.43)	2.7 (0.45)	2.7 (0.45)
Stool Frequency Mayo subscore	2.2 (0.80)	2.5 (0.68)	2.4 (0.76)	2.3 (0.84)
Rectal Bleeding Mayo subscore	1.4 (0.86)	1.4 (0.78)	1.6 (0.84)	1.4 (0.81)
IBDQ Total	133.6 (33.65)	121.5 (30.16)	128.9 (30.30)	115.7 (28.01)
IBDQ bowel domain	40.7 (10.35)	37.2 (9.27)	38.6 (9.49)	35.9 (10.72)
IBDQ emotional domain	50.4 (14.45)	47.3 (13.22)	49.7 (12.85)	44.8 (12.29)
IBDQ social domain	23.1 (7.33)	19.8 (6.79)	21.6 (7.48)	18.8 (6.15)
IBDQ systemic domain	19.4 (5.46)	17.2 (5.43)	18.9 (5.44)	16.3 (4.23)

Data are mean (standard deviation) unless otherwise indicated
ASA=aminosalicylic acid; IBDQ = Inflammatory Bowel Disease Questionnaire .

DISCLOSURES

M. Dubinsky has received consultancy fees from: Abbvie, Arena Pharmaceuticals, Bristol-Myers Squibb, Celgene, Eli Lilly and Company, Genentech, Janssen, Pfizer, Prometheus Labs, Takeda, and is a co-founder of Cornerstones Health, Co-Founder And share holder Trellus Health, Co-Founder MiTest 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, 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, Celgene, Celek, Cellerix, Cerimon, ChemoCentryx, CoMentis, Cosmo Technologies, Coronado Biosciences, Cubist, Cytokine Pharmasciences, Eagle, Eisai, Elan, EnGene, Eli Lilly and Company, 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, Vascular Biogenics, Viamet and Warner Chilcott; **M. Abreu** has received consultancy fees from: Boehringer Ingelheim, Eli Lilly and Company, Focus Medical Communications, Gilead, Landos Biopharma, research funding from: Pfizer, Prometheus and Takeda; **S. Vermeire** has received grant/research support from: Abbvie, Janssen, MSD, Pfizer, Takeda, 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, Takeda, and is on the speakers bureau of: Abbvie, Ferring, Hospira, Janssen, MSD, Pfizer, Takeda, and Tillots; **T. Lissoos**, **N. Morris**, **V. Arora**, **M. Shan**, 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, WebMD, and research funding from Celgene, Janssen, Pfizer, and Takeda

This study was previously presented at United European Gastroenterology Week (UEGW); Virtual; Dates (11-13 October 2020)

Study was sponsored by Eli Lilly and Company