Mirikizumab Therapy is Associated with Improved Fatigue in Patients with Moderately to Severely Active Crohn's Disease

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BACKGROUND

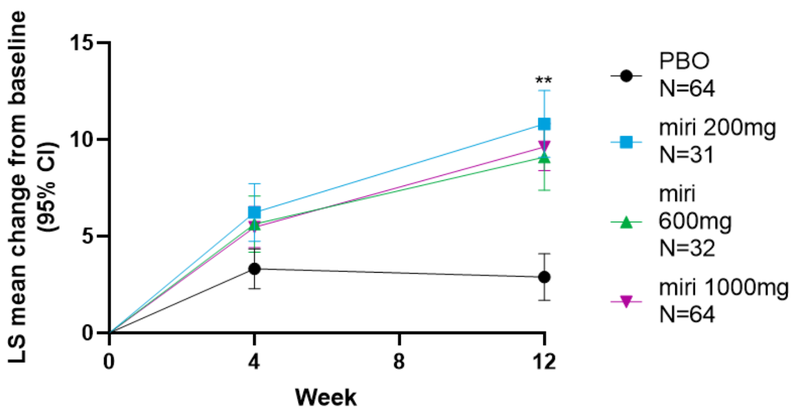
- Mirikizumab (miri) is a humanized monoclonal antibody directed against the p19 subunit of IL-23. and has previously demonstrated efficacy in treating ulcerative colitis (UC) and moderate to severely active CD.[1]
- Crohn's disease (CD) is an inflammatory bowel disease (IBD), characterized by inflammation of the digestive tract.[2]
- IL-23 has been shown to play a key role in driving immune responses in patients with Crohn's disease.[3]
- Fatigue is a common symptom experienced by patients with CD which can adversely affect patient quality of life (QoL).[4]

OBJECTIVE

- Evaluate the impact of miri treatment on fatigue in patients with moderately to severely active CD.

KEY RESULTS

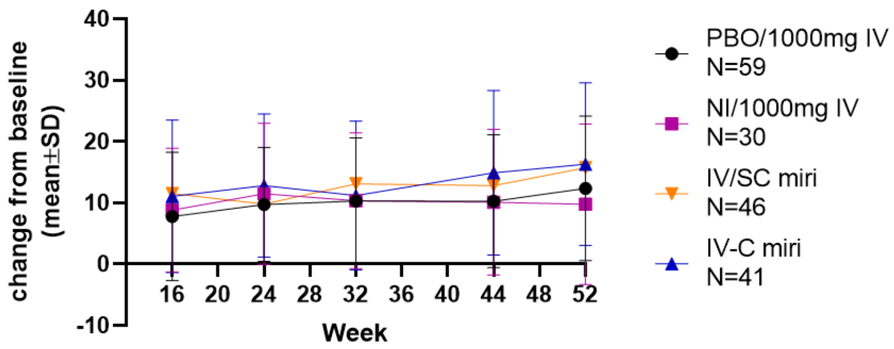
Figure 1. Change from baseline in Induction period (Weeks 0-12)



** Week 12: miri 200mg p<0.001, miri 600mg p=0.004, miri 1000mg p<0.001

- In comparison to the PBO group, those in the miri treatment arms had higher least squares mean change on the FACIT–Fatigue scale at week 12.

Figure 2. Change from baseline in FACIT-Fatigue from Weeks 12-52 (Maintenance)



- Observed changes from baseline on the FACIT–Fatigue scale were maintained from Weeks 12-52 for those in the miri treatment arms.

CONCLUSIONS

- Miri treatment was associated with improved FACIT–fatigue scores compared to PBO during induction (Weeks 0-12). This change was sustained until week 52.
- During the maintenance period (Weeks 12-52), a high proportion of patients in all miri groups achieved the minimum clinically important difference on the FACIT–Fatigue scale (miri 200mg: 77.4%; miri 600mg: 56.3% miri 1000mg: 64.1%; PBO: 37.5%).
- These results show that miri improves fatigue in patients with moderately to severely active CD.

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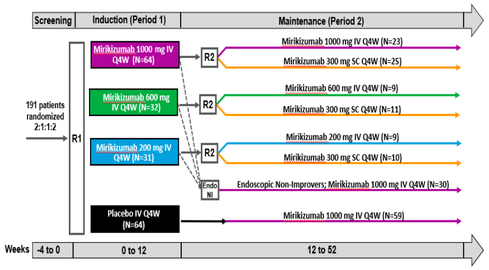
METHODS

Figure 3. Study Design



R1 = Randomization 1 Patients were and stratified based on previous exposure to biologic therapy for treatment of CD.

R2 = Randomization 2. Patients who received miri during induction and had endoscopic improvement (≥1-point improvement in SES-CD score) were randomized in a 1:1 ratio and stratified based on endoscopic response at Week 12 (W12) (a ≥ 50% reduction in SES-CD score vs baseline). All patients who received placebo in Period 1 received miri 1000 mg IV Q4W.

Study Methodology

Study Design

- This study was a Phase 2, randomized, double-blind, placebo-controlled trial (NCT02891226).
- At baseline patients with CD were randomized with a 2:1:1:2 allocation across 4 treatment arms (placebo (PBO) and 200mg, 600mg, and 1000mg miri).
- Patients who received miri and achieved ≥1 point improvement by Week (W) 12 in Simple Endoscopic Score for Crohn's Disease (SES-CD) were re-randomized 1:1 into double-blind maintenance to continue the same IV treatment assignment Q4W (IV/IV; N=41) or to 300mg miri SC Q4W (IV/SC; N=46) until W52. Patients who received miri and did not have SES-CD improvement at W12 and those who received PBO during induction received 1000mg miri IV Q4W until W52 (NI/1000mg, PBO/1000mg).

Key Eligibility Criteria

Inclusion criteria

- Duration of active Crohn's disease (CD) ≥3 months since diagnosis
- Moderately to severely active disease:
  - Stool frequency ≥4 per day (loose and watery stools defined as Bristol Stool Scale Category 6 or 7) AND/OR abdominal pain ≥2 (on a 4-point scale) at baseline
  - Simple Endoscopic Score (centrally read) for Crohn's Disease (SES-CD) score ≥7 for subjects with ileal-colonic disease or ≥4 for patients with isolated ileal disease
- Treatment history:
  - Inadequate response or intolerance to ≥1 conventional treatment or prior exposure to biologics for the treatment of CD

Exclusion criteria

- Strictures, stenoses, or any other manifestation, which might require surgery
- Bowel resection, diversion, or placement of a stoma within 6 months; other intra-abdominal surgery within 3 months
- Previous exposure to any biologic therapy targeting the IL-23 p19 subunit, either licensed or investigational
  - After an amendment, a single prior induction dose of ustekinumab was allowed (USA only)

Analysis of fatigue

- Fatigue was measured using the FACIT–fatigue scale, a validated 13-item questionnaire which assesses the impact of fatigue on daily activities.[5]

Endpoints

- Change from baseline to Week 12 and Week 52 in FACIT-fatigue were calculated. Randomized patients with baseline and at least 1 post baseline observation are included for evaluation.
- The number of patients who achieved the MCID on the FACIT–fatigue scale (increase from BL ≥3.56 points in FACIT-fatigue score) at Week 12 and during maintenance (Weeks 12-52) between miri treatment arms and PBO. Patients with missing data was considered as non-responders in this analysis.

Abbreviations: *IV = intravenous; NI = non-improver; Q4W = treatment assignment every 4 weeks; SC = subcutaneous; SES-CD = Simple Endoscopic Score for Crohn's Disease; W = week; CDAI = Crohn's Disease Activity Index; CRP = C-reactive protein; IBDQ = Inflammatory Bowel Disease Questionnaire; Miri = mirikizumab; n = number of patients with non-missing values*

Statistical analysis

- Change in FACIT-fatigue from baseline to week 12 was compared between treatment groups using a mixed model for repeated measures (MMRM). The model included treatment, geographic region, prior CD biologic therapy, visit, and visit by treatment interactions. An unstructured covariance structure was used. The change from baseline to week 52 in the FACIT-fatigue are presented descriptively.
- The proportion of patients treated with miri who achieved MCID on the FACIT–fatigue scale at Week 12 (increase from baseline ≥3.56 points in FACIT-F score) was compared to the PBO group using a logistic regression model that included the same covariates as the week 12 analysis

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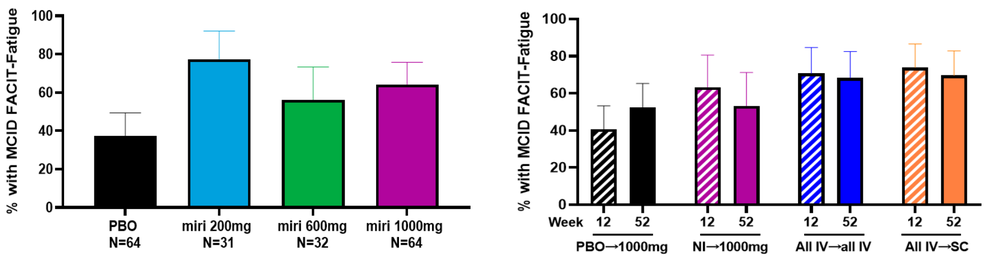
RESULTS

Figure 4. Percentage of patients achieving MCID on the FACIT–fatigue scale for Weeks 0-12 (A) and Weeks 12-52 (B).



At W12 higher rates of patients achieved MCID FACIT-Fatigue (miri 200mg: 77.4%; miri 600mg: 56.3% miri 1000mg 64.1%; PBO: 37.5%). These improvements were sustained through Week 52 in patients who received miri during induction, with 68.3% and 69.6% of patients in the IV/IV and IV/SC groups and 53.3% of NI/1000mg group, respectively, having MCID FACIT-Fatigue at W52.

Table 1. Baseline demographic characteristics of each trial arm

	Induction Treatment Groups			
	Placebo (N=64)	Miri 200 mg (N=31)	Miri 600 mg (N=32)	Miri 1000 mg (N=64)
Age, years	39.0 (13.0)	38.1 (11.8)	40.4 (13.3)	37.7 (13.1)
Male, n (%)	28 (43.8)	17 (54.8)	14 (43.8)	34 (53.1)
Disease duration, years	10.2 (9.8)	8.9 (7.4)	10.8 (9.7)	8.6 (6.7)
Disease location, n (%)				
Ileal	11 (17.2)	6 (19.4)	5 (15.6)	11 (17.2)
Colonic	25 (39.1)	14 (45.2)	10 (31.3)	26 (40.6)
Ileal-colonic	28 (43.8)	11 (35.5)	17 (53.1)	27 (42.2)
CRP, median mg/L (range)	6.8 (0-92)	7.4 (0-94)	6.8 (0-78)	4.5 (0-108)
SES-CD	11.9 (5.6)	14.4 (7.9)	15.2 (7.4)	13.1 (6.8)
Patient-reported outcomes				
Stool frequency	6.4 (3.1)	7.4 (3.0)	6.4 (3.8)	6.6 (5.5)
Abdominal pain	1.9 (0.6)	2.0 (0.6)	1.7 (0.7)	1.9 (0.6)
CDAI	304.7 (93.1)	348.3 (92.1)	298.1 (103.7)	304.5 (94.4)
IBDQ	113.9 (37.1)	104.8 (34.3)	127.0 (35.5)	120.3 (32.4)

Data are mean (standard deviation) unless stated otherwise

DISCLOSURES

- **Miguel Regueiro:** Unrestricted Educational Grants from AbbVie, Janssen, UCB, Pfizer, Takeda, Celgene, Genentech, Gilead. Advisory Boards and Consultant for AbbVie, Janssen, UCB, Takeda, Pfizer, Miraca Labs, Amgen, Celgene, Seres, Allergan, Genentech, Gilead, Salix, Prometheus, Lilly, TARGET Pharma Solutions, ALFASIGMA, S.p.A., Bristol Meyer Squibb (BMS), CME Companies: CME Outfitters, Imedex, GI Health Foundation (GiHF), Cornerstones, Remedy, MJH life sciences Royalties: Wolters Kluwer Health as Author/Editor of Up To Date. **Monika Fischer:** consultant to Finch Therapeutics Group and DSMB member for Rebiotix. **David T. Rubin:** Research grants from AbbVie, Abgenomics, Allergan, Arena Pharmaceuticals, Biomica, Bristol-Myers Squibb, Dizal Pharmaceuticals, Eli Lilly and Company, Ferring Pharmaceuticals, Genentech/Hoffmann-La Roche, Janssen Research & Development, Mahana Therapeutics, Medtronic, Merck, Napo Pharmaceuticals, Pfizer, Prometheus Laboratories, Shire, Takeda, and Target Pharma Solutions. **Pieter Hindryckx:** University Hospital of Ghent, Ghent, Belgium; consulting fees from AbbVie and Takeda; and speakers fees from Ferring, Falk Pharma, Vifor Pharma, Tillotts Pharma, Chiesi, Takeda and AbbVie.
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