# Improvement in Fatigue With Mirikizumab Therapy Is Associated With Clinical Remission and Pain Improvements But Not With Endoscopic Response in Patients With Moderately to Severely Active Crohn's Disease

Miguel Regueiro (Presenter),[1] Monika Fischer,[2] David T. Rubin,[3] Toshifumi Hibi,[4] Peter Bossuyt,[5] Pascal Juillerat,[6] Paul Pollack,[7] Xian Zhou,[8] Marijana Protic,[7] Theresa Hunter Gibble,[7] Lai Shan Chan,[7] Hilde Carlier,[7] Pieter Hindryckx[9]

[1]Cleveland Clinic, Cleveland, USA; [2]Indiana University, Indianapolis, USA; [3]The University of Chicago Medical Center, Chicago, USA; [4]Kitasato Institute Hospital, Tokyo, Japan; [5]Imelda GI Clinical Research Centre, Bonheiden, Belgium; [6]Bern University Hospital, Bern, Switzerland; [7]Eli Lilly and Company, Indianapolis, USA; [8]Syneos Health, Morrisville, USA; [9]Ghent University Hospital, Ghent, Belgium
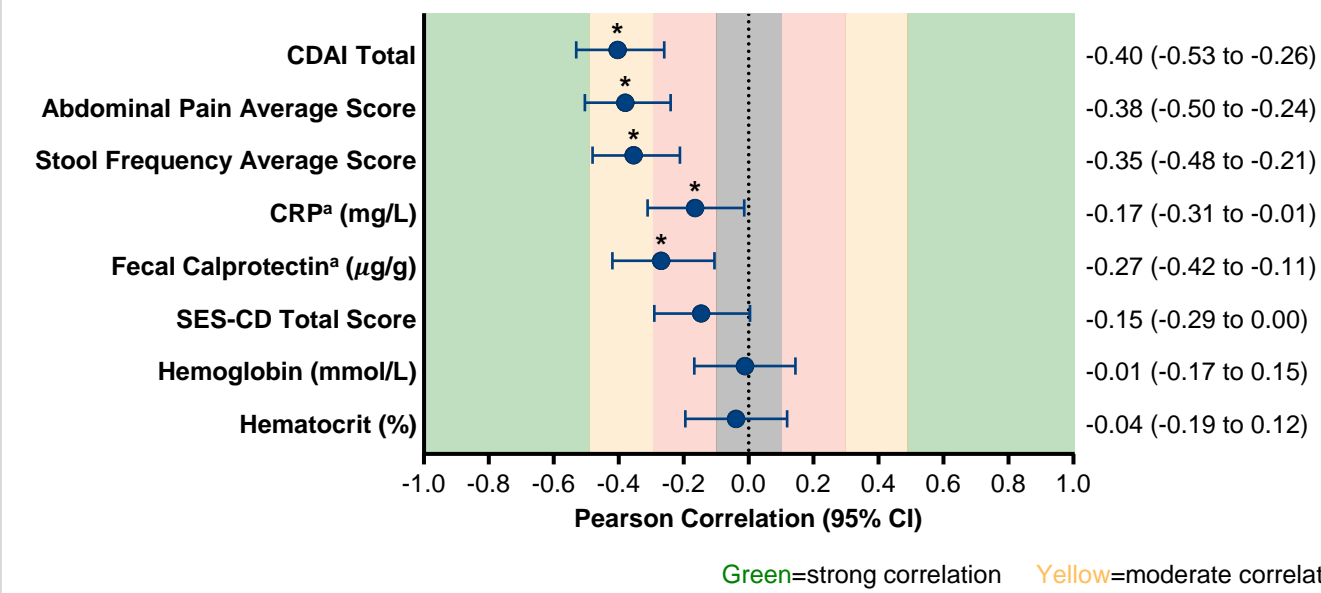
## BACKGROUND

- Fatigue is common in patients with Crohn's disease (CD) and negatively impacts quality of life[1]
- Mirikizumab is a humanized immunoglobulin G4 monoclonal antibody directed against the p19 subunit of interleukin-23[2]
  - In a Phase 2, randomized, double-blind, placebo-controlled clinical trial (AMAG; NCT02891226), mirikizumab was efficacious and well tolerated in patients with CD[2]
  - We previously reported that fatigue improved in patients with CD receiving all doses of mirikizumab in the AMAG study[3]

## OBJECTIVE

- To explore the association between changes in clinical and inflammatory markers and change in fatigue to better understand the mechanism of fatigue relief
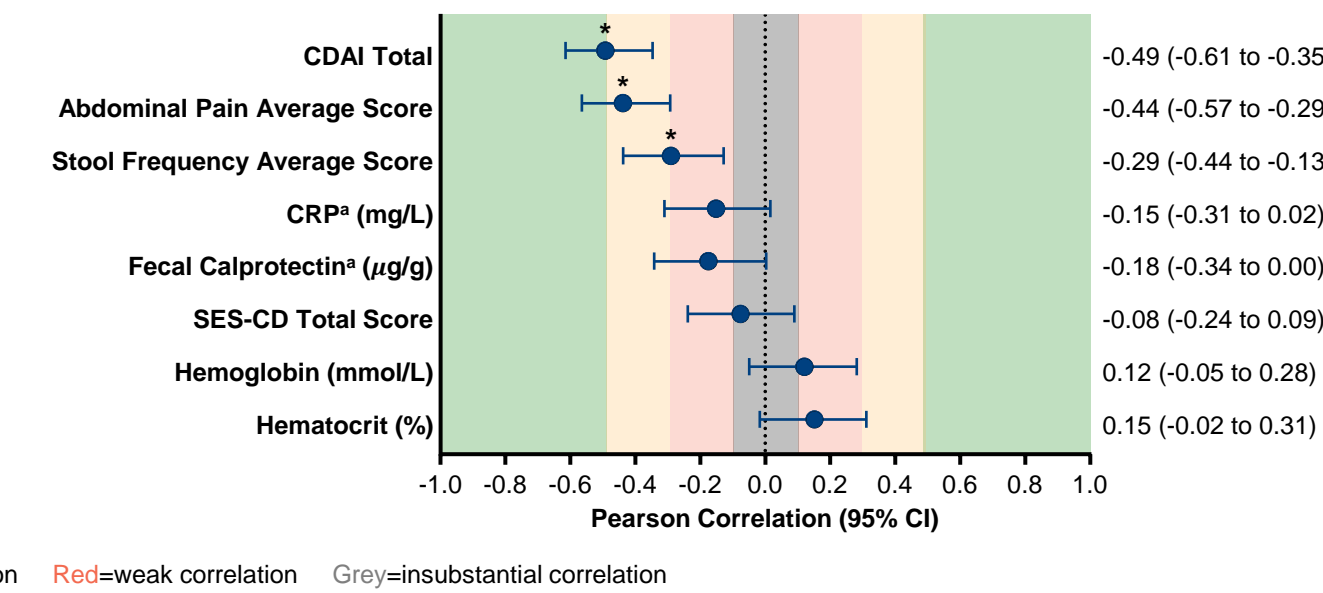
## KEY RESULTS

### Correlation of Change From Baseline in FACIT-F With Change in Clinical Measures at Week 12



| Clinical Measure | Value (95% CI) |
| --- | --- |
| CDAI Total | -0.40 (-0.53 to -0.26) |
| Abdominal Pain Average Score | -0.38 (-0.50 to -0.24) |
| Stool Frequency Average Score | -0.35 (-0.48 to -0.21) |
| CRP[a] (mg/L) | -0.17 (-0.31 to -0.01) |
| Fecal Calprotectin[a] (μg/g) | -0.27 (-0.42 to -0.11) |
| SES-CD Total Score | -0.15 (-0.29 to 0.00) |
| Hemoglobin (mmol/L) | -0.01 (-0.17 to 0.15) |
| Hematocrit (%) | -0.04 (-0.19 to 0.12) |

Pearson Correlation (95% CI)

Green=strong correlation    Yellow=moderate correlation    Red=weak correlation    Grey=insubstantial correlation

\* p<0.05
[a] Data are log-transformed

### Correlation of Change From Baseline in FACIT-F With Change in Clinical Measures at Week 52



| Clinical Measure | Value (95% CI) |
| --- | --- |
| CDAI Total | -0.49 (-0.61 to -0.35) |
| Abdominal Pain Average Score | -0.44 (-0.57 to -0.29) |
| Stool Frequency Average Score | -0.29 (-0.44 to -0.13) |
| CRP[a] (mg/L) | -0.15 (-0.31 to 0.02) |
| Fecal Calprotectin[a] (μg/g) | -0.18 (-0.34 to 0.00) |
| SES-CD Total Score | -0.08 (-0.24 to 0.09) |
| Hemoglobin (mmol/L) | 0.12 (-0.05 to 0.28) |
| Hematocrit (%) | 0.15 (-0.02 to 0.31) |

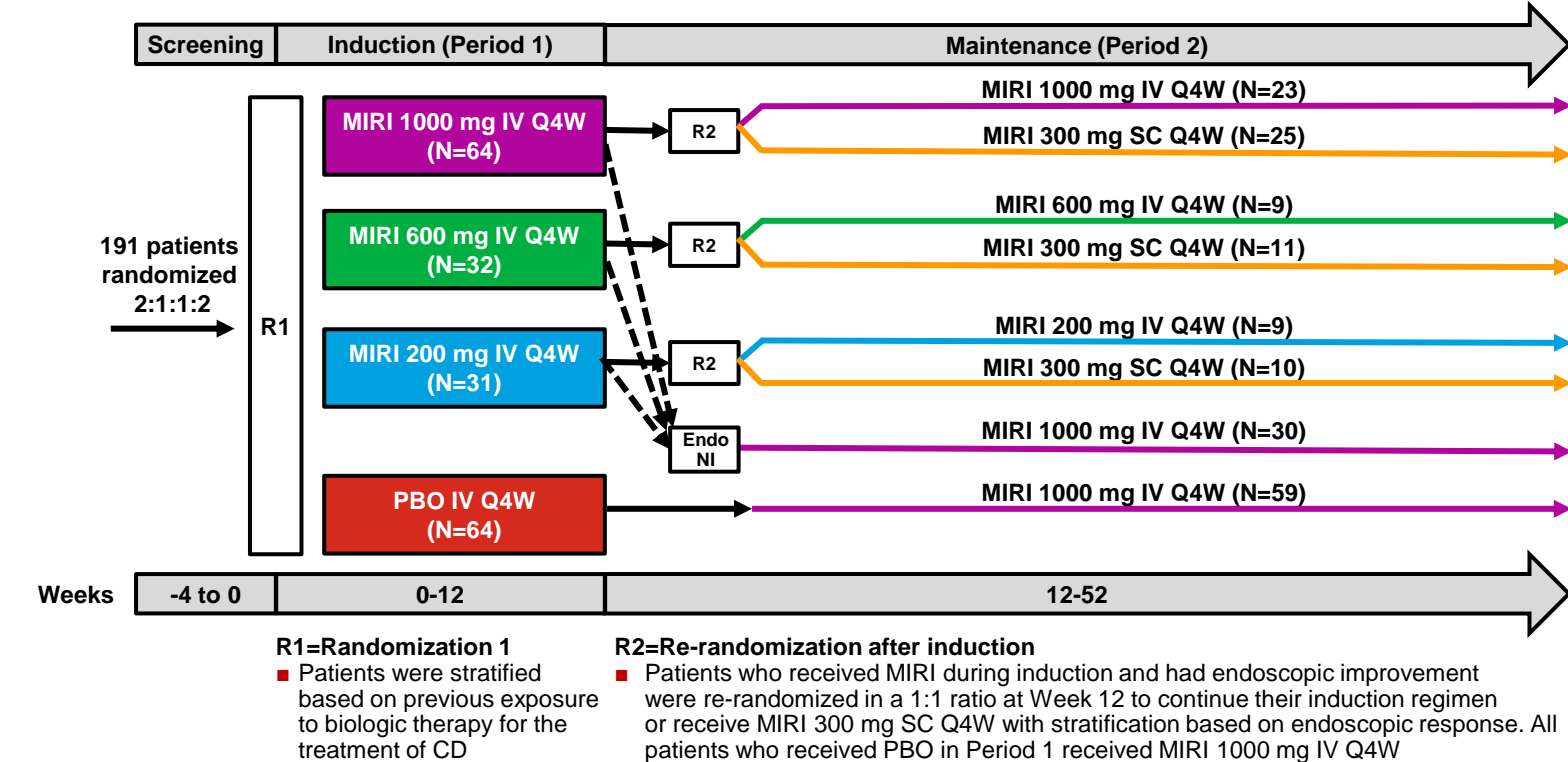Pearson Correlation (95% CI)

## CONCLUSIONS

- Improvements in fatigue were significantly correlated with improvements in Crohn's Disease Activity Index (CDAI), abdominal pain, and stool frequency in patients with CD at the end of induction and after 52 weeks of treatment
- Improvement in fatigue showed weak but significant correlation with inflammatory biomarkers at the end of the Induction Period and a trend toward weak correlation in the Maintenance Period
- An insubstantial correlation was observed between fatigue improvement and endoscopic score as well as improvement and resolution of anemia (change in hemoglobin and hematocrit levels)
- Although fatigue has been hypothesized to be mediated in part by inflammatory cytokines,[6] the data showed no consistent relationship between improvement in fatigue and changes in objective markers of disease activity, suggesting the possibility of alternative or additional mechanistic processes for fatigue in CD
- Symptoms of CD, including components of the CDAI, appeared to correlate with fatigue

### Limitations

- Post hoc analysis
- The design of this Phase 2 trial, such as small patient numbers per treatment group and no placebo data in the Maintenance Period to understand the lower side of changes in fatigue and clinical endpoints

## METHODS

### Study Design



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

R2=Re-randomization after induction
- Patients who received MIRI during induction and had endoscopic improvement were re-randomized in a 1:1 ratio at Week 12 to continue their induction regimen or receive MIRI 300 mg SC Q4W with stratification based on endoscopic response. All patients who received PBO in Period 1 received MIRI 1000 mg IV Q4W

Note: Endoscopic improvement defined as ≥1-point improvement in SES-CD. Endoscopic response defined as ≥50% reduction in SES-CD vs. baseline

- At baseline, patients with CD were randomized with a 2:1:1:2 allocation across 4 treatment arms (placebo and mirikizumab 200 mg, 600 mg, and 1000 mg intravenously [IV] every 4 weeks [Q4W])
- Patients who received mirikizumab and achieved ≥1-point improvement in Simplified Endoscopic Activity Score for Crohn's Disease (SES-CD) at Week 12 were re-randomized 1:1 to continue their induction regimen (IV/IV; N=41) or to receive mirikizumab 300 mg subcutaneously (SC) Q4W (IV/SC; N=46) until Week 52
- Patients who received mirikizumab and did not have SES-CD improvement at Week 12 (non-improver [NI]) and those who received placebo during induction received mirikizumab 1000 mg IV Q4W until Week 52 (NI/1000 mg, placebo/1000 mg)

### Key Eligibility Criteria

**Inclusion**
- Duration of active 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
  - SES-CD ≥7 for patients 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 ≥1 biologic agent for the treatment of CD

**Exclusion**
- Strictures, stenoses, or any other manifestation that 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)

### Assessments

- Fatigue was assessed using the FACIT-F questionnaire, validated for use in patients with inflammatory bowel disease[4]
  - Short, 13-item tool that measures an individual's level of fatigue during their usual daily activities over the past week
  - Level of fatigue is measured on a 5-point Likert scale (0=not at all fatigued to 4=very much fatigued), with score reversals
  - Higher FACIT-F scores mean better quality of life
- Endoscopic response was defined as ≥50% reduction from baseline in total SES-CD
- CDAI total

- Abdominal pain was assessed on a 4-point scale and calculated as an average over 7 days:
  - 0=None
  - 1=Mild
  - 2=Moderate
  - 3=Severe
- Stool frequency was calculated as an average of liquid or soft stools per day over 7 days
- Laboratory parameters were evaluated at each study visit:
  - Hematocrit
  - Hemoglobin
  - Fecal calprotectin
  - CRP

### Statistical Analyses

- Patients with baseline and post-baseline assessments were included
- Data were pooled for all treatment arms, including placebo
- For continuous variables, Pearson correlation coefficients, 95% confidence intervals, and p-values were calculated
- Cohen's conventions were used to assess the strength of correlations[5]
  - >0.5 is strong
  - 0.3 to ≤0.5 is moderate
  - 0.1 to <0.3 is weak
  - <0.1 is insubstantial

## RESULTS

### Baseline Demographic Characteristics

| | | Induction Treatment Groups | | |
| --- | --- | --- | --- | --- |
| | PBO IV (N=64) | MIRI 200 mg IV (N=31) | MIRI 600 mg IV (N=32) | MIRI 1000 mg IV (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, mg/L, median (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) |
| PROs | | | | |
| 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 (0-600) | 304.7 (93.1) | 348.3 (92.1) | 298.2 (103.7) | 304.5 (94.4) |
| FACIT-F (13 items, 0-52) | 21.9 (12.7) | 19.3 (10.4) | 28.2 (12.5) | 24.1 (12.1) |

Data are mean (standard deviation) unless stated otherwise

### Improvements in Fatigue Were Significantly Associated With Improvements in CDAI, Abdominal Pain, and Stool Frequency in Patients With CD at Weeks 12 and 52

| Correlation of Change From Baseline in FACIT-F With Change From Baseline in Clinical Measures | | | | | | |
| --- | --- | --- | --- | --- | --- | --- |
| | Week 12 (N=191) | | | Week 52 (N=176) | | |
| Clinical Measure | Pearson Correlation | 95% CI | p-Value | Pearson Correlation | 95% CI | p-Value |
| CDAI total | -0.404 | -0.530 to -0.259 | <0.0001 | -0.492 | -0.614 to -0.346 | <0.0001 |
| SES-CD total | -0.146 | -0.290 to 0.004 | 0.0572 | -0.076 | -0.238 to 0.090 | 0.3702 |
| Hematocrit, % | -0.039 | -0.194 to 0.119 | 0.6319 | 0.152 | -0.016 to 0.312 | 0.0756 |
| Hemoglobin, mmol/L | -0.011 | -0.167 to 0.145 | 0.8916 | 0.120 | -0.049 to 0.282 | 0.1638 |
| Fecal calprotectin, (μg/g), log | -0.269 | -0.419 to -0.105 | 0.0015 | -0.175 | -0.342 to 0.003 | 0.0544 |
| CRP (mg/mL), log | -0.165 | -0.310 to -0.013 | 0.0331 | -0.151 | -0.310 to 0.016 | 0.0756 |
| Abdominal pain average score | -0.380 | -0.504 to -0.240 | <0.0001 | -0.438 | -0.565 to -0.292 | <0.0001 |
| Stool frequency average score | -0.354 | -0.481 to -0.212 | <0.0001 | -0.290 | -0.437 to -0.128 | 0.0006 |

Yellow=moderate correlation
Red=weak correlation
Note: N=number of patients in the analysis (including patients with non-missing change scores)

### REFERENCES
1. D'Silva A, et al. Clin Gastroenterol Hepatol. 2022;20:995-1009.e7.
2. Sands BE, et al. Gastroenterology. 2022;162:495-508.
3. Regueiro MD, et al. Gastroenterology. 2021;160:S354-S355.
4. Tinsley A, et al. Aliment Pharmacol Ther. 2011;34:1328-1336.
5. Cohen J. Statistical Power Analysis for the Behavioral Sciences; 1988.
6. Patarca R. Ann N Y Acad Sci. 2001;933:185-200.