Efficacy and Safety of Mirikizumab (LY3074828) After 12 Weeks Induction Treatment in a Phase 2 Study of Patients with Crohn's Disease

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BACKGROUND

- The interleukin (IL)-23/Th17 pathway has a significant role in the pathogenesis of Crohn's disease (CD) with various anti-IL-23 antibodies having shown efficacy in CD.
- Mirikizumab (miri) is a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of IL-23.
- Phase 2 studies of mirikizumab have shown efficacy in treating ulcerative colitis[1], psoriasis[2], and Crohn's disease[3] leading to further development in ongoing Phase 3 studies.
- We assessed safety and efficacy of miri after a 12-Week induction treatment in a Phase 2, multi-center, randomized, parallel-arm, double-blind, placebo (PBO)-controlled trial (NCT02891226) in patients with moderate-to-severely active Crohn's disease.

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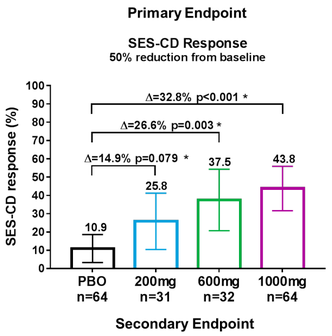
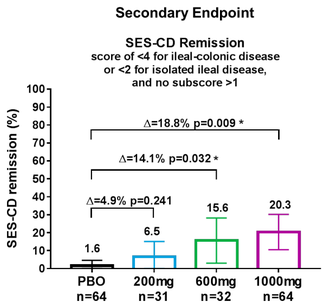
3. Sands BE, Sandborn WJ, Peyrin-Biroulet L, at al. OP-108 Efficacy and Safety of Mirikizumab After 52-Weeks Maintenance Treatment in Patients with Moderate-to-Severe Crohn's Disease. United European Gastroenterology Journal 2020; 8 (Supplement 1)

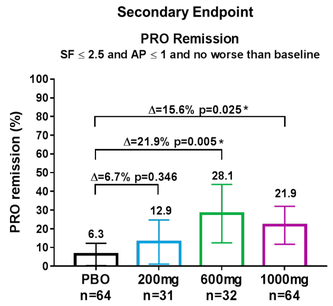
KEY RESULTS

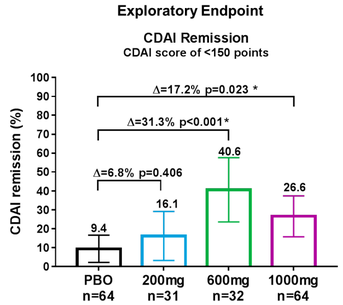
Endoscopic Response and Remission



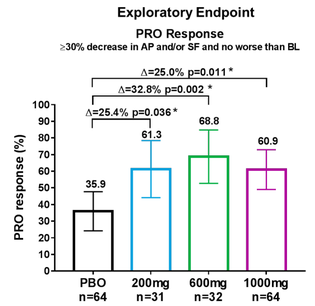


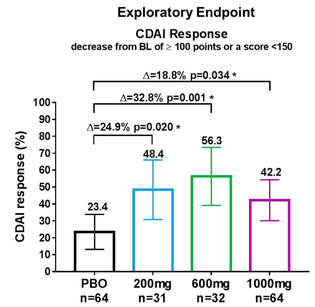
PRO and CDAI Remission





PRO and CDAI Response





* Statistically significant by pre-specified two-sided alpha level of 0.1

CONCLUSIONS

- Mirikizumab treatment results in
  - Significant improvement in endoscopic findings
  - Significant improvement in patient report outcomes (PRO) and CDAI
  - Demonstrates few SAEs or discontinuations due to AEs with induction treatment up to 1000 mg
    - Safety profile overall consistent with that of miri treatment of ulcerative colitis
- Mirikizumab induces meaningful improvements in clinical and endoscopic outcomes at Week 12 in patients with moderately to severely active Crohn's disease
- These data support the further development of mirikizumab in Crohn's disease

DISCLOSURES

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. **W. Sandborn** reports: research grants from Abbvie, Abivax, Arena Pharmaceuticals, Boehringer Ingelheim, Celgene, Genentech, Gilead Sciences, Glaxo Smith Kline, Janssen, Lilly, Pfizer, Prometheus Biosciences, Seres Therapeutics, Shire, Takeda, Theravance Biopharma; consulting fees from Abbvie, Abivax, Admirx, Alfasigma, Alimentiv (previously Robarts Clinical Trials, owned by Alimentiv Health Trust), Alivio Therapeutics, Allakos, Amgen, Applied Molecular Transport, Arena Pharmaceuticals, Bausch Health (Salix), Beigene, Bellatrix Pharmaceuticals, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Meyers Squibb, Celgene, Celltrion, Cellularity, Cosmo Pharmaceuticals, Escalier Biosciences, Equillium, Forbion, Genentech/Roche, Gilead Sciences, Glenmark Pharmaceuticals, Gossamer Bio, Immunic (Vital Therapies), Index Pharmaceuticals, Intact Therapeutics, Janssen, Kyverna Therapeutics, Landos Biopharma, Lilly, Oppilan Pharma, Otsuka, Pandion Therapeutics, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonists Therapeutics, Provention Bio, Reistone Biopharma, Seres Therapeutics, Shanghai Pharma Biotherapeutics, Shire, Shoreline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Thetis Pharmaceuticals, Tillotts Pharma, UCB, Vendata Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivelix Pharmaceuticals, Vivreon Biosciences, Zealand Pharma; stock or stock options from Allakos, BeiGene, Gossamer Bio, Oppilan Pharma, Prometheus Biosciences, Prometheus Laboratories Progenity, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Biosciences; and employee at Shoreline Biosciences. **L. Peyrin-Biroulet** has received honoraria from: AbbVie, Allergan, Alma, Amgen, Arena, Sterna, Biogen, Boerhinger Ingelheim, Celgene, Celltrion, Enterome, Ferring, Genentech, Gilead, Hikma, Index Pharmaceuticals, Janssen, MSD, Nestle, Pfizer, Pharmacosmos, Roche, Samsung Bioepis, Sandoz, Takeda, and Tillots, grants from: AbbVie, MSD, and Takeda, and stock options from CTMA. **P. Higgins** has received consultancy and/or advisory board fees from: AbbVie, Eli Lilly and Company, and Takeda, and honoraria from Takeda. **F. Hirai** has nothing to disclose. **R. Belin, E. G. Valderas, D. Miller, M. Morgan-Cox, A. Naegeli** and **J. Tuttle** are employees and stockholders at Eli Lilly and Company. **P. Pollack** is a former employee of Eli Lilly and Company. **T. Hibi** has received Advisory/consultancy fees from: AbbVie, Bristol-Myers Squibb, Celltrion, EA Pharma, Eli Lilly and Company, Gilead Sciences, Janssen, Kyorin, Mitsubishi-Tanabe Pharma, Nichi-Iko Pharmaceutical, Pfizer, Takeda Pharmaceutical, Zeria Pharmaceutical, and research grants from: AbbVie, EA Pharma, JIMRO, Otsuka Holdings, and Zeria Pharmaceuticals.

This study was previously presented at Digestive Disease Week, May 18 – 21, 2019.

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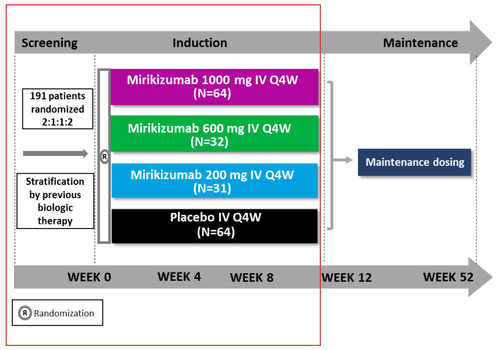
STUDY DESIGN

AMAG Study Design and Objectives at Week 12



Primary Objective

- Endoscopic response: 50% reduction from baseline in Simple Endoscopic Score for Crohn's disease (SES-CD)

Secondary Objectives

- Endoscopic remission: SES-CD <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1
- Clinical remission by Patient Reported Outcomes (PRO remission): SF ≤2.5 and AP ≤1 and no worse than baseline
- Safety and Tolerability

Exploratory Objectives

- Crohn's Disease Activity Index (CDAI) response: decrease from baseline in CDAI ≥100 points or CDAI <150
- CDAI remission: CDAI <150 points
- PRO response: ≥30% decrease in AP and/or SF and neither worse than baseline

Methods

- Endoscopy
  - Endoscopy score determined with central reading
- Statistics
  - Treatment comparisons of categorical efficacy variables conducted using a 2-sided alpha level of 0.10 and logistic regression analysis: treatment, geographic region, and prior biologic therapy use included in the model
    - All p values based on statistical testing without multiplicity control
  - Non-responder imputation (NRI): All patients who discontinued from study prior to Week 12 for any reason or failed to have an adequate Week 12 efficacy assessment considered non-responders at Week 12

Enrollment Criteria

- Inclusion
  - Crohn's disease ≥3 months active
  - Stool frequency ≥4 and/or abdominal pain ≥2 at baseline
  - SES-CD ≥7 (centrally read) for subjects with ileal-colonic or ≥4 for subjects with isolated ileal disease
  - Prior treatment for Crohn's disease: failure/intolerance to conventional treatment and/or treatment with ≥1 biologic agents
- Exclusion
  - Strictures, stenoses, 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 IL-23 p19
    - After an amendment, a single prior induction dose of UST was allowed (US only)

RESULTS

Baseline Demographics and Disease Characteristics

Mean (SD) unless otherwise specified	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)
Ileocolonic	28 (43.8)	11 (35.5)	17 (53.1)	27 (42.2)
C-reactive protein, median mg/L (range)	6.8 (0-92)	7.4 (0-94)	6.8 (0-78)	4.5 (0-108)
Simple endoscopic score for Crohn's disease (SES-CD)	11.9 (5.6)	14.4 (7.9)	15.2 (7.4)	13.1 (6.8)
PRO scores Stool frequency	6.4 (3.1)	7.4 (3.0)	6.4 (3.8)	6.6 (5.5)
PRO scores Abdominal pain	1.9 (0.6)	2.0 (0.6)	1.7 (0.7)	1.9 (0.6)
Crohn's Disease Activity Index (CDAI)	304.7 (93.1)	348.3 (92.1)	298.2 (103.7)	304.5 (94.4)

Current and Prior CD Medications

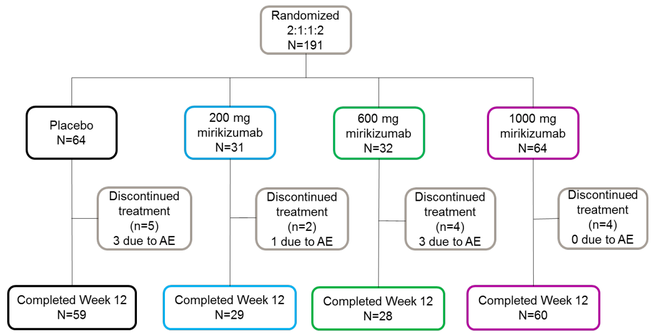
	Placebo (N=64)	Miri 200 mg (N=31)	Miri 600 mg (N=32)	Miri 1000 mg (N=64)
Previous biologic use*, n (%)	43 (67.2)	19 (61.3)	19 (59.4)	39 (60.9)
Previous biologic failure**, n (%)	36 (56.3)	15 (48.4)	16 (50.0)	31 (48.4)
Prior vedolizumab use, n (%)	14 (21.9)	5 (16.1)	5 (15.6)	6 (9.4)
Prior anti-TNF exposure, n (%) 0	25 (39.1)	14 (45.2)	14 (43.8)	26 (40.6)
1	16 (25.0)	10 (32.3)	9 (28.1)	22 (34.4)
2	22 (34.4)	7 (22.6)	5 (15.6)	14 (21.9)
3+	1 (1.6)	0	4 (12.5)	2 (3.1)
Oral corticosteroid use, n (%)	21 (32.8)	14 (45.2)	7 (21.9)	15 (23.4)
Immunosuppressant use, n (%)	19 (29.7)	12 (38.7)	10 (31.3)	21 (32.8)

* Although prior induction dosing of ustekinumab (UST) use was allowed, no patients had prior UST treatment

** Inadequate response, loss of response, or intolerance to medication

Patients with prior biologic exposure that were not biologic failures discontinued treatment for the following reasons: cannot afford, treatment availability, subject decision, completed treatment, and other

Patient Disposition



Safety at Week 12

	Placebo (N=64)	Miri 200 mg (N=31)	Miri 600 mg (N=32)	Miri 1000 mg (N=64)
TEAE, n (%)	45 (70.3)	18 (58.1)	21 (65.6)	42 (65.6)
SAE*, n (%)	7 (10.9)	0	3 (9.4)	2 (3.1)
Discontinuations due to AE, n (%)	3 (4.7)	1 (3.2)	3 (9.4)	0
Most common TEAEs, n (%) (≥3% in total study population, decreasing frequency)				
Headache	2 (3.1)	2 (6.5)	2 (6.3)	7 (10.9)
Crohn's disease	9 (14.1)	0	1 (3.1)	0
Arthralgia	3 (4.7)	1 (3.2)	1 (3.1)	3 (4.7)
Nasopharyngitis	1 (1.6)	0	2 (6.3)	4 (6.3)
Anaemia	1 (1.6)	2 (6.5)	1 (3.1)	2 (3.1)
Nausea	2 (3.1)	0	2 (6.3)	2 (3.1)
Pyrexia	2 (3.1)	0	3 (9.4)	1 (1.6)
Vomiting	3 (4.7)	0	0	3 (4.7)
Weight increased	0	1 (3.2)	2 (6.3)	3 (4.7)

SAEs observed were: Abdominal pain, Crohn's disease, Large intestinal stenosis, Large intestine perforation, Pneumatosis intestinalis, Chest pain, Malaise, Pyrexia, Back pain, and Blood potassium decreased. No serious infections, malignancies, or deaths were reported in any dose group

TEAE=Treatment-Emergent Adverse Event; SAE=Serious Adverse Event

Gastroenterology/Hepatology Advanced Practice Providers (GHAPP); Las Vegas, USA/Virtual; 9-11 September 2021

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