Efficacy and Safety of Mirikizumab After 52-Weeks Maintenance Treatment in Patients with Moderate-to-Severe Crohn's Disease

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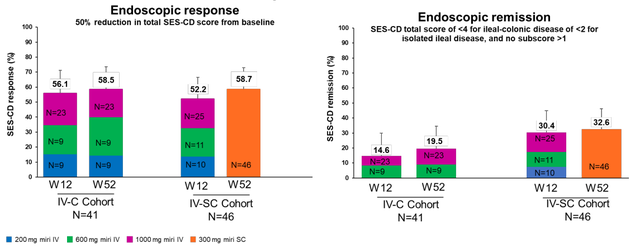
BACKGROUND

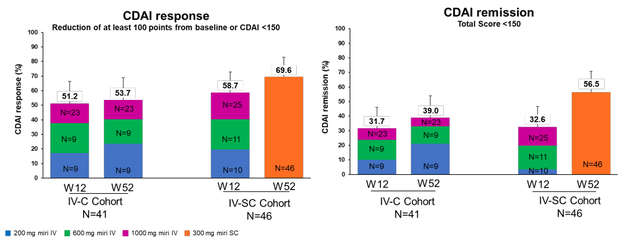
- The interleukin (IL)-23/Th17 pathway has a significant role in the pathogenesis of Crohn's disease (CD) with various anti-IL-23 antibodies having shown efficacy in treating CD
- Mirikizumab (miri) is a humanized immunoglobulin G4 (IgG4)–variant monoclonal antibody that binds to the p19 subunit of IL-23
- Phase 2 studies of miri have shown efficacy in treating ulcerative colitis[1], psoriasis[2], and Crohn's disease[3] leading to further development in ongoing Phase 3 studies in CD
- We previously reported the safety and efficacy of miri after 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 CD
- Maintenance Week 52 results are reported here

KEY RESULTS

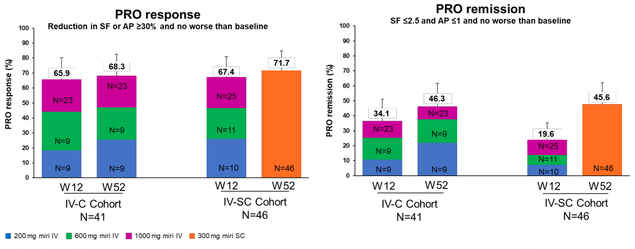
Endoscopic Response and Remission
Randomized Maintenance Group



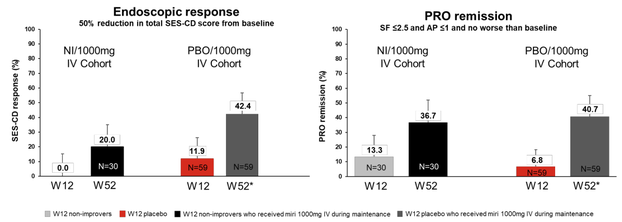
CDAI Response and Remission
Randomized Maintenance Group



PRO Response and Remission
Randomized Maintenance Group



Non-Improvers and Placebo
Non-Randomized Maintenance Group



Note: Total height of each bar represents the percentage of patients achieving each endpoint, error bars show upper limit 95% confidence interval. Bar partitions symbolize relative contributions by each dose. N in each partition represent the number of patients who were randomized to each treatment group. *40 Weeks of active drug administration.

CONCLUSIONS

- Miri treatment demonstrated durable endoscopic and symptomatic efficacy after 52 weeks in patients with Crohn's disease
  - The proportion of patients who had response/remission at Week 12 was maintained or improved at Week 52 across multiple parameters (endoscopic, PRO, CDAI)
  - Among patients who did not have endoscopic improvement after 12 weeks of miri treatment, continued treatment with miri led to additional patients achieving endoscopic response/remission at week 52.
- The safety profile of miri treatment was consistent with the anti-IL23 p19 class, with few discontinuations in the re-randomized maintenance group due to adverse events
- These Phase 2 data support continued characterization of miri efficacy and safety in the ongoing VIVID-1 Phase 3 program (NCT03926130)

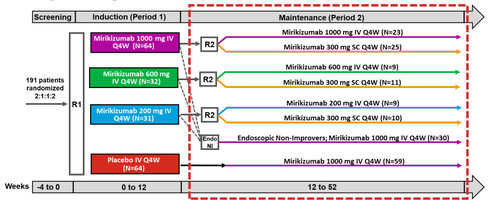
DISCLOSURES

- **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, Equilliurn, 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 Tillotts, 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. **V. Jairath** has received consulting fees from: AbbVie, Arena Pharmaceuticals, Celltrion, Eli Lilly and Company, GlaxoSmithKline, Genentech, Janssen, Merck, Pendopharm, Robarts Clinical Trials, Sandoz, Takeda, and Topivert, and is on the speakers bureau of: AbbVie, Ferring, Janssen, Pfizer, Shire, and Takeda. **G. D'Haens** has served as advisor for Abbvie, Ablynx, Allergan, Alphabiomics, Amakem, Amgen, AM Pharma, Arena Pharmaceuticals, AstraZeneca, Avaxia, Biogen, Bristol Meiers Squibb, Boehringer Ingelheim, Celgene/Receptos, Celltrion, Cosmo, Echo Pharmaceuticals, Eli Lilly, Engene, Ferring, DrFALK Pharma, Galapagos, Genentech/Roche, Gilead, Glaxo Smith Kline, Gossamerbio, Hospira/Pfizer, Immunic, Johnson and Johnson, Kintai Therapeutics, Lycera, Medimetrics, Millenium/Takeda, Medtronics, Mitsubishi Pharma, Merck Sharp Dome, Mundipharma, Nextbiotics, Novonordisk, Otsuka, Pfizer/Hospira, Photopill, Prodigest, Prometheus laboratories/Nestle, Progenity, Protagonist, RedHill; Robarts Clinical Trials, Salix, Samsung Bioepis, Sandoz, Seres/Nestle, Setpoint, Shire, Teva, Tigenix, Tillotts, Topivert, Versant and Vifor. **M. 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. **R. Belin, E. G. Valderas, D. Miller, A. Naegeli, V. Arora, J. Tuttle** are employees and stockholders of Eli Lilly and Company. **P. Pollack** was 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.
- The study was previously presented at United European Gastroenterology Week - 28th Annual Conference; Virtual; October 11 – 13, 2020.

METHODS

- Patients who entered maintenance (Period 2) are included in these analyses
- Due to small sample size, no formal statistical comparisons were made between treatment groups in the maintenance period, and summary data were presented for endoscopic improvers for all IV-C and IV-SC dosage groups combined
- Patients who discontinued study treatment prior to Week 52 or failed to have an adequate efficacy assessment were considered as not having met the respective endpoints at Week 52

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.

Objective and Endpoints

Maintenance Objective: the objective of this study was to evaluate the efficacy and safety of continued miri administration for up to 52 weeks

Efficacy Endpoints	Definition
Endoscopic Response	50% reduction from baseline in SES-CD score
Endoscopic Remission	SES-CD score <4 for ileal-colonic disease or <2 for isolated ileal disease, and no subscore >1
PRO Response	≥30% reduction in stool frequency and/or abdominal pain and neither worse than baseline
PRO Remission	Stool frequency ≤2.5 and abdominal pain ≤1 and no worse than baseline
CDAI Response	CDAI ≥100 or CDAI <150
CDAI Remission	CDAI score of <150
Durability of Response/Remission	Of patients with response/remission at W12, the percent of patients with response/remission at Week 52 (W52)

Note: Primary endpoint at week 12 has been reported previously – only secondary and exploratory endpoints are considered here.

Enrollment Criteria

Inclusion

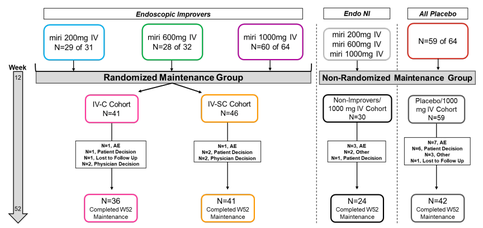
- Diagnosis of CD for ≥3 months before baseline (Week 0, randomization)
- Active CD defined as stool frequency ≥4 and/or abdominal pain ≥2 at baseline
- SES-CD ≥7 (centrally read) for subjects with ileal-colonic or ≥4 for subjects with isolated ileal disease
- Prior treatment for CD: failure/intolerance 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)

Note: Inclusion/Exclusion criteria to be eligible for the study assessed within the screening period (≤28 days prior to the start of study treatment).

Patient Disposition after W12 induction period



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RESULTS

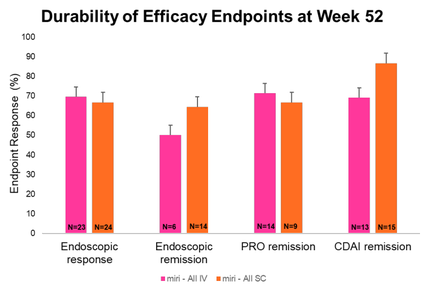
Baseline Demographics and Disease Characteristics
At screening (W-4 to 0)

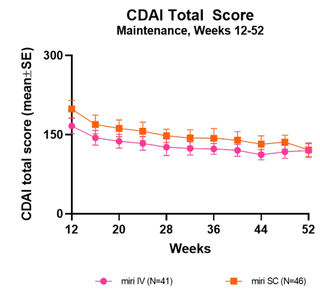
Mean (SD) unless otherwise specified	Randomized Maintenance Group		Non-Randomized Maintenance Group	
	IV-C Cohort (N=41)	IV-SC Cohort (N=46)	Non-Improvers/1000 mg IV Cohort (N=30)	Placebo/1000 mg IV Cohort (N=59)
Age, years	40 (13.2)	37.8 (11.9)	36.9 (12.9)	39.2 (13.0)
Male, *n (%)*	21 (51.2)	23 (50.0)	17 (56.7)	26 (44.1)
Disease Duration, years	8.7 (6.4)	8.8 (8.0)	10.1 (8.7)	10.0 (9.9)
Disease Location, *n (%)*				
Ileal	4 (10)	5 (11)	11 (37)	10 (17)
Colonic	18 (44)	17 (37)	11 (37)	22 (37)
Ileocolonic	19 (46)	24 (52)	8 (27)	27 (46)
CRP, *median mg/dL (range)*	6.0 (0-57)	6.3 (0-108)	4.9 (1-86)	6.6 (0-92)
SES-CD	14.9 (7.0)	14.1 (7.5)	11.3 (6.5)	12.0 (5.6)
PRO Scores				
Stool Frequency	6.3 (3.5)	7.3 (5.8)	6.0 (2.9)	6.2 (3.1)
Abdominal Pain	1.9 (0.5)	1.9 (0.6)	1.8 (0.7)	1.8 (0.6)
CDAI	303 (87.6)	327 (106.0)	293 (83.0)	298 (91.5)

Prior and Current Medications for CD
At screening (W-4 to 0)

Mean (SD) unless otherwise specified	Randomized Maintenance Group		Non-Randomized Maintenance Group	
	IV-C Cohort (N=41)	IV-SC Cohort (N=46)	Non-Improvers/1000 mg IV Cohort (N=30)	Placebo/1000 mg IV Cohort (N=59)
Prior biologic use, *n (%)*	25 (61)	27 (59)	20 (67)	39 (66)
Prior biologic failure, *n (%)*	19 (46)	21 (46)	18 (60)	32 (54)
Prior Vedolizumab use, *n (%)*	5 (12)	6 (13)	3 (10)	12 (20)
Prior anti-TNF use, *n (%)*				
0	19 (46)	19 (41)	11 (37)	24 (41)
1	13 (32)	15 (33)	11 (37)	15 (25)
2	8 (20)	8 (17)	8 (27)	19 (32)
3+	1 (2)	4 (9)	0	1 (2)
Oral corticosteroid use, *n (%)*	8 (20)	11 (24)	12 (40)	19 (32)
Immunosuppressant use, *n (%)*	12 (29)	15 (33)	13 (43)	18 (31)

Durability of Efficacy
Randomized Maintenance Group





Durability of an endpoint is defined as the percentage of patients who achieve that endpoint at Week 52 among those patients who had achieved the same endpoint at Week 12 (N). Error bars represent the upper limit 95% confidence interval.

Safety - week 52

	Randomized Maintenance Group		Non-Randomized Maintenance Group	
	IV-C Cohort (N=41)	IV-SC Cohort (N=46)	Non-Improvers/1000 mg IV Cohort (N=30)	Placebo/1000 mg IV Cohort (N=59)
TEAE, *n (%)*	31 (75.6)	35 (76.1)	21 (70.0)	45 (76.3)
SAE*, *n (%)*	0	2 (4.3)	3 (10.0)	8 (13.6)
Discontinuations due to AE, *n (%)*	1 (2.4)	1 (2.2)	3 (10.0)	7 (11.9)
Most common TEAEs, *n (%)* (≥3% in total study population)				
Nasopharyngitis	2 (4.9)	6 (13.0)	3 (10.0)	4 (6.8)
Headache	3 (7.3)	4 (8.7)	3 (10.0)	4 (6.8)
Arthralgia	3 (7.3)	6 (13.0)	1 (3.3)	3 (5.1)
Anaemia	2 (4.9)	2 (4.3)	2 (6.7)	5 (8.5)
Injection site pain	2 (4.9)	4 (8.7)	1 (3.3)	3 (5.1)
Upper respiratory tract infection	2 (4.9)	3 (6.5)	2 (6.7)	3 (5.1)
Abdominal pain	3 (7.3)	3 (6.5)	0	3 (5.1)
Crohn's disease	1 (2.4)	3 (6.5)	1 (3.3)	2 (3.4)
Weight increased	2 (4.9)	2 (4.3)	1 (3.3)	2 (3.4)
Fatigue	1 (2.4)	1 (2.2)	0	4 (6.8)
Pyrexia	1 (2.4)	2 (4.3)	2 (6.7)	1 (1.7)
Vulvovaginal mycotic infection	1 (2.4)	0	0	2 (6.1)

Note: *SAEs observed were: Crohn's disease, Ileal perforation, Intestinal obstruction, Clostridium difficile infection, Peritonitis, Pneumonia, Pyelonephritis, Anaphylactic reaction, Hypersensitivity, Non-cardiac chest pain, Dehydration, Hypokalaemia, Osteoarthritis, Abortion spontaneous, Maternal exposure during pregnancy. No serious infections, malignancies, or deaths were reported in any dose group.

ABBREVIATIONS

AE = adverse event; CDAI = Crohn's Disease Activity Index; CI = confidence interval; CRP = C-reactive protein; IV = intravenous; IV-C = intravenous administration in Induction Period continued in Maintenance Period; IV-SC = IV administration in Induction Period and SC administration in Maintenance Period; N = Number of patients achieving endpoint at Week 12; NI = non-improver; PBO = placebo; PRO = patient-reported outcomes; Q4W = treatment assignment every 4 weeks; SAE = serious adverse event; SC = subcutaneous; SE = standard error; SES-CD = Simple Endoscopic Score for Crohn's Disease; TEAE = treatment-emergent adverse event; TNF = tumor necrosis factor; W = week

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