Long-term Efficacy and Safety of Etrasimod for Ulcerative Colitis: Results from the Open-label Extension of the OASIS Study

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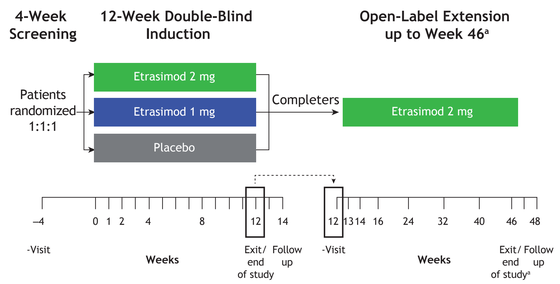
Introduction

- Etrasimod is an oral, selective, sphingosine 1-phosphate receptors 1, 4, and 5 ($S1P_1$, $S1P_4$, $S1P_5$) modulator in development for treatment of immune and inflammatory-mediated diseases[1]
- The efficacy of etrasimod as induction therapy in adult patients with moderately-to-severely active ulcerative colitis (UC) was previously demonstrated in the 12-week, phase 2, randomised, placebo-controlled, double-blind (DB) OASIS study (NCT02447302)[2]
- This open-label extension (OLE) study (NCT02536404) subsequently evaluated, for an additional 34 weeks, the safety and efficacy of etrasimod in achieving and maintaining clinical response and/or remission in patients who completed OASIS

Methods

- During the 12-week DB OASIS study, patients were treated once-daily with etrasimod 1 mg, etrasimod 2 mg, or placebo[2]
- Patients who completed the DB study were eligible to enrol in the OLE and receive etrasimod 2 mg once daily for up to an additional 34 weeks, irrespective of their response or treatment during the DB study (**Figure 1**)
  - A few patients (n = 6) received placebo during the OLE and were included in the safety, but not the efficacy, analyses
- Efficacy was summarized in the evaluable cohort, which included patients who received etrasimod 2 mg throughout the OLE
  - The modified intention-to-treat (mITT) population included patients with the required assessments
- Endpoints were:
  - Clinical remission (Mayo Clinic endoscopic score ≤ 1 [with absence of friability], rectal bleeding [RB] score ≤ 1, and stool frequency [SF] score ≤ 1 with ≥ 1-point decrease from DB baseline) at end of treatment (EOT),
  - Clinical response (clinical remission or decrease relative to DB baseline in 3-component Mayo Clinic score [endoscopy findings, RB, SF] of ≥ 2 points and ≥ 30% decrease, with either a decrease from DB baseline of RB of ≥ 1 or RB score of ≤ 1 at EOT, and
  - Endoscopic improvement, defined as Mayo Clinic endoscopic subscore ≤ 1 or maintenance of endoscopic improvement at EOT
- Safety was evaluated by treatment-emergent adverse events (TEAEs) and treatment-emergent serious adverse events (SAEs)
- All statistics are descriptive

Figure 1. Study Design



[a]22 (19.6%) patients treated with etrasimod 2 mg in the OLE continued treatment up to 52 weeks as per multiple protocol amendments.

Results

Patient Disposition and Characteristics

- 118 patients (84% of DB completers) entered the OLE
  - 112 patients (etrasimod safety population) received etrasimod 2 mg at any point in the OLE
  - 105 patients (evaluable cohort) received etrasimod 2 mg throughout the OLE
  - Of the 112 patients receiving etrasimod 2 mg in the OLE, 92 (82.1%) completed the study
- Mean (SD) study drug exposure in the OLE was 33 (9) weeks

Efficacy

- At EOT, overall 70% of patients had a clinical response, 35% were in clinical remission, and 45% had endoscopic improvement (**Table 1**)
- The greatest numerical improvements in all efficacy measures were seen among patients who initially received placebo or etrasimod 1 mg for 12 weeks in the DB period followed by 2 mg for up to 34 additional weeks in the OLE study (**Table 1**)

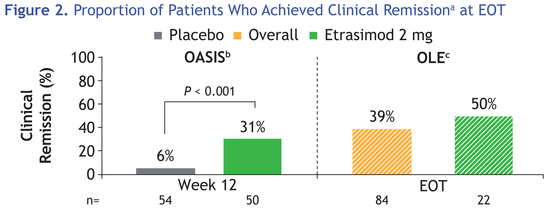
Table 1. Key Efficacy Endpoints (mITT Evaluable Cohort)

	Placebo (n = 39)	Etrasimod 1 mg (n = 35)	Etrasimod 2 mg (n = 31)	Overall (N = 105)
Patients with clinical response, %				
n	33	33	28	94
Week 12 (end of DB study)	27.3	39.4	57.1	40.4
End of treatment	69.7	75.8	64.3	70.2
Patients with clinical remission, %				
n	33	33	28	94
Week 12 (end of DB study)	9.1	9.1	50.0	21.3
End of treatment	33.3	33.3	39.3	35.1
Patients with endoscopic improvement, %				
n	33	34	29	96
Week 12 (end of DB study)	15.2	14.7	51.7	26.0
End of treatment	42.4	50.0	41.4	44.8

Groups are based on treatment during the DB period. The overall group is patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period.

- Among patients who completed the OLE study, the overall rate of clinical remission was 39%; for the etrasimod 2 mg group, the proportion of patients achieving clinical remission was 31% at end of week 12 in the DB period and 50% at EOT in the OLE study (**Figure 2**)

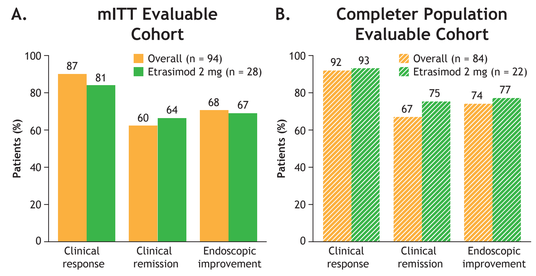
Figure 2. Proportion of Patients Who Achieved Clinical Remission[a] at EOT



Groups are based on treatment during the DB period. The overall group is patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period.
[a]Clinical Remission in **Figure 2** is defined as Mayo Clinic endoscopic score = 0 or 1, RB score = 0, and SF score = 0 or 1. [b]OASIS mITT population. [c]OLE completer population evaluable cohort.

- Among patients achieving clinical response, clinical remission, or endoscopic improvements at Week 12, treatment effects were maintained at EOT in the majority of patients (**Figure 3**)

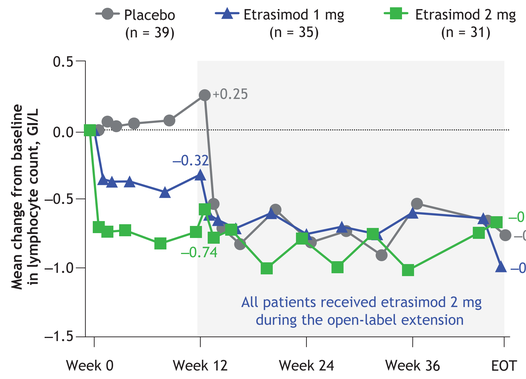
Figure 3. Proportion of Patients With Response at Week 12 With Sustained Response at EOT in the (A) mITT Evaluable Cohort and (B) Completer Population Evaluable Cohort



Groups are based on treatment during the DB period. The overall group is patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period.

- Mean lymphocyte reduction from the beginning of the DB study was 0.74 GI/L (43%) at Week 12 and 0.67 GI/L (38%) at EOT among patients receiving etrasimod 2 mg in both the DB study and the OLE (**Figure 4**)

Figure 4. Change from DB Baseline in Lymphocyte Count at Week 12 and EOT



Groups are based on treatment during the DB period.

Safety

- Occurrence of TEAEs was similar among groups, and most TEAEs (94%) were of mild or moderate severity (**Table 2**)
- Of 14 serious TEAEs reported in 7 patients, only 1 was considered treatment-related (worsening UC)
  - There were no treatment-related serious infections
- 10 (9%) patients discontinued study drug due to a TEAE (worsening UC, atrial fibrillation, or headache)
- The impact on heart rate and atrioventricular (AV) conduction was minimal, with no study discontinuations related to bradycardia or AV block

Table 2. Summary of Adverse Events During the OLE in Patients Receiving Etrasimod 2 mg in the OLE (Safety Population)

	Placebo (n = 42)	Etrasimod 1 mg (n = 38)	Etrasimod 2 mg (n = 32)	Overall (N = 112)
Patients with ≥ 1 TEAE, n (%)	25 (60)	25 (66)	17 (53)	67 (60)
Number of TEAEs	111	85	56	252
Patients with ≥ 1 SAE, n (%)	4 (10)	0	3 (9)	7 (6)
Number of SAEs	11	0	3	14
Patients discontinued due to TEAE, n (%)	4 (10)	2 (5)	4 (13)	10 (9)
Patients with TEAE of severity: mild/ moderate/severe (%)	43/48/12	45/61/3	31/38/16	40/49/10

Groups are based on treatment during the DB period. The overall group is patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period. The 6 patients who received placebo during the OLE are not shown.

Conclusions

- **Clinical response, clinical remission, or endoscopic improvement observed with etrasimod 2 mg at week 12 was sustained or improved up to week 46 in most patients participating in the OLE**
- **Etrasimod demonstrated a favourable safety profile, with most TEAEs of mild to moderate severity; no new safety findings were reported**

References

1. Al-Shamma H et al. *J Pharmacol Exp Ther*. 2019;369:311–17. 2. Sandborn WJ et al. *Am J Gastroenterol*. 2018;113:S327–28.

Acknowledgements

The study and analyses were supported by Arena Pharmaceuticals, Inc. (San Diego, CA, USA). Lisa Baker, PhD, on behalf of inScience Communications, Springer Healthcare (Philadelphia, PA, USA), provided medical writing support funded by Arena Pharmaceuticals, Inc.

Declaration of Conflicting Interests

SV has received grants from AbbVie, J&J, Pfizer, and Takeda; and has received consulting and/or speaking fees from AbbVie, Arena, Avaxia, Boehringer Ingelheim, Celgene, Dr Falk Pharma, Ferring, Galapagos, Genentech-Roche, Gilead, Hospira, Janssen, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Takeda, Theravance, and Tillots.

JP has received financial support for research from AbbVie and Merck Sharp & Dohme; lecture fees from AbbVie, Janssen, Merck Sharp & Dohme, Pfizer, Shire, and Takeda; and consultancy honoraria from AbbVie, Arena, Boehringer Ingelheim, Celgene, Genentech, Janssen, Merck Sharp & Dohme, Nestlé, Oppilan, Pfizer, Progenity, Roche, Shire, Takeda, Theravance, and TiGenix.

MC has received consulting and/or speaking fees from AbbVie, Arena Pharmaceuticals, Celgene, Janssen, Medtronic, Pfizer, Takeda, and UCB.

LP-B has received consulting and/or speaking fees from AbbVie, Alma, Amgen, Biogaran, Biogen, Boerhinger-Ingelheim, Celgene, Celltrion, Enterome, Ferring, Genentech, HAC-Pharma, Index Pharmaceuticals, Janssen, Lilly, Merck, Mylan, Nestlé, Pfizer, Pharmacosmos, Samsung Bioepis, Sandoz, Sterna, Takeda, Tillots, and Vifor.

BES has received consulting fees from Abbvie, Allergan, Amgen, Arena Pharmaceuticals, AstraZeneca, Boehringer-Ingelheim, Capella Bioscience, Celgene, Celltrion Healthcare, Ferring, Gilead, Hoffmann-La Roche, Ironwood Pharmaceuticals, Janssen, Lilly, Otsuka, Pfizer, Palatin Technologies, Prometheus Laboratories, Rheos Medicines, Salix Pharmaceuticals, Shire, Takeda, Target PharmaSolutions, and Theravance Biopharma R&D, Inc.; and has received grant/research support for his institution from Celgene and Theravance Biopharma.

WJS received consulting fees and medical writing support from Arena Pharmaceuticals relevant to the submitted work; has received grants from AbbVie, Amgen, Atlantic Pharmaceuticals, Boehringer Ingelheim, Celgene (Receptos), Genentech, Gilead Sciences, Janssen, Lilly, Nutrition Science Partners, Pfizer, Prometheus Laboratories, Robarts Clinical Trials, and Takeda; and has received personal fees from AbbVie, Akros Pharma, Allergan, Ambrx Inc, Amgen, Ardelyx, Arena Pharmaceuticals, Atlantic Pharmaceuticals, Avaxia, Biogen Idec, Boehringer Ingelheim, Bristol Myers Squibb, Celgene (Receptos), Conatus, Cosmo Technologies, Escalier Biosciences, Ferring Pharmaceuticals, Ferring Research Institute, Forward Pharma, Galapagos, Genentech, Gilead Sciences, Gossamer Biosciences, Immune Pharmaceuticals, Index Pharmaceuticals, Janssen, Kyowa Hakko Kirin Pharma, Lilly, Medimmune, Mesoblast, Miraca Life Sciences, Nivalis Therapeutics, Novartis, Nutrition Science Partners, Oppilan Pharma, Otsuka, Palatin, Paul Hastings, Pfizer, Precision IBD, Progenity, Prometheus Laboratories, Qu Biologics, Regeneron, Ritter Pharmaceuticals, Robarts Clinical Trials, Salix Pharmaceuticals, Seattle Genetics, Seres Therapeutics, Shire, Sigmoid Biotechnologies, Takeda, Theradiag, Theravance, Tigenix, Tillotts Pharma, UCB Pharma, Vascular Biogenics, and Vivelix; and has received stock options from Escalier Biosciences, Gossamer Biosciences, Oppilan Pharma, Precision IBD, Progenity, and Ritter Pharmaceuticals.

JZ, KL, CHC, SUN, and **PKK** are employed by Arena Pharmaceuticals.

Presented at United European Gastroenterology Week (UEGW), October 19—23, 2019, Barcelona, Spain