Early and Durable Symptom Control in Patients With Moderately-to-Severely Active Ulcerative Colitis Treated With Etrasimod (APD334) in the Randomised, Double-blind, Placebo-controlled, Phase 2 OASIS Trial and Open-label Extension

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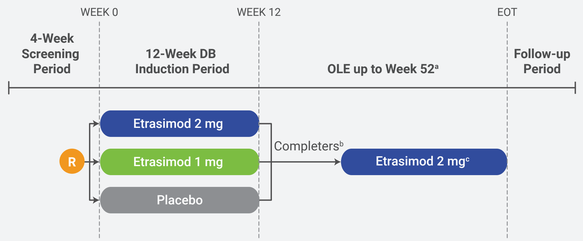
INTRODUCTION

- Etrasimod is an oral, sphingosine 1-phosphate (S1P) receptor modulator with specificity for $S1P_1$, $S1P_4$, and $S1P_5$[1]
- In the 12-week, randomised, double-blind (DB), placebo-controlled OASIS trial (NCT02447302) in adult patients with moderately-to-severely active ulcerative colitis (UC), once-daily etrasimod 2 mg demonstrated significant improvement in modified Mayo Clinic Score (mMCS) that included rectal bleeding (RB), stool frequency (SF), and endoscopic subscores[2,3]
- In the open-label extension (OLE; NCT02536404) of OASIS, etrasimod 2 mg demonstrated sustained benefit, with clinical response, clinical remission, and endoscopic improvement at end of treatment (EOT) in 93%, 75%, and 77% of patients with each respective status at Week 12 who received etrasimod 2 mg in the DB study and OLE and who completed the OLE[4]
- The aim of this analysis was to evaluate the association of improvement in RB and SF, which are key indicators of therapeutic success,[5] with clinical and endoscopic response at EOT in patients receiving once-daily etrasimod 2 mg

METHODS

- Patients who completed the DB study were eligible to enrol in the OLE and receive etrasimod 2 mg once daily for up to 52 weeks total (**Figure 1**)[4]

Figure 1. Study Design



DB, double blind; OLE, open label extension; R, randomisation.
[a]For patients enrolled under a later protocol amendment, treatment ended at Week 46.
[b]Patients who did not enrol in the OLE exited the study at Week 12 and had a follow-up visit at Week 14.
[c]A small number of patients (n = 6) received placebo during the OLE (not illustrated).

- Analyses used the modified intention-to-treat (mITT) population for each outcome, defined as patients who received ≥ 1 dose of the study drug during either the DB study or OLE and lacked missing assessments for the given outcome; missing values were not imputed
- Analyses of the OLE study period included evaluable patients who received etrasimod 2 mg throughout the DB study and whose only treatment assignment during the OLE was to etrasimod 2 mg (etrasimod 2 mg treat-through group [TTG])
- Study drug exposure was calculated for the safety population, which included patients who received any etrasimod 2 mg in the DB study or OLE
- Outcomes used Mayo Clinic subscores (range 0–3) defined as:
  - Clinical response: clinical remission or a decrease in mMCS of ≥ 2 and ≥ 30%, with either a RB score ≤ 1 or a ≥ 1 RB decrease
  - Clinical remission: endoscopic improvement, RB score ≤ 1, and SF score ≤ 1 with ≥ 1 point decrease from DB baseline
  - Endoscopic improvement: endoscopic subscore ≤ 1
- EOT occurred at Week 52 (or at Week 46 for patients enrolled under the later protocol amendment) or earlier for patients who terminated treatment before the scheduled end of therapy
- Analyses of RB or SF by clinical response, clinical remission, or endoscopic improvement status were post hoc

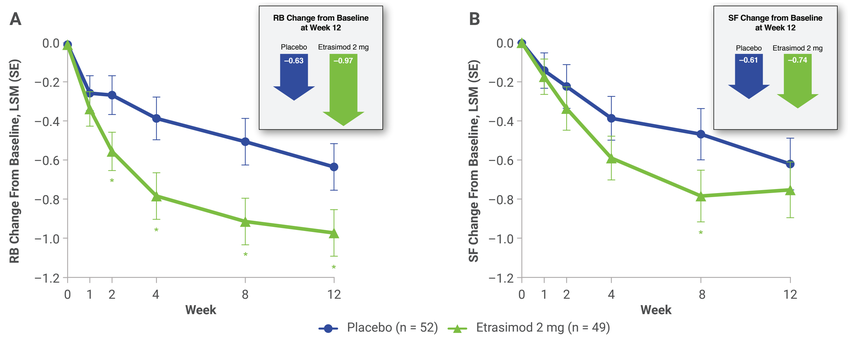
RESULTS

- The DB mITT population comprised 49 and 52 patients who received once-daily etrasimod 2 mg or placebo, respectively
- The OLE mITT population included a total of 31 evaluable patients who received once-daily etrasimod 2 mg throughout the DB study and OLE (etrasimod 2 mg TTG), of whom 23 completed the OLE
- Among patients who received any once-daily etrasimod 2 mg during both the DB or OLE period (safety population, n = 32), the median (range) of etrasimod 2 mg treatment was 46 weeks (20–56 weeks) from the start of the DB study

REDUCTIONS IN RB AND SF

- During the DB study, patients who received etrasimod 2 mg had a significant reduction in RB versus placebo at Week 2 that continued through Week 12 (**Figure 2A**)
- Compared with placebo, patients who received etrasimod 2 mg had a numerically greater reduction in SF as early as Week 2 that was statistically significant at Week 8 and continued to be numerically greater through Week 12 (**Figure 2B**)

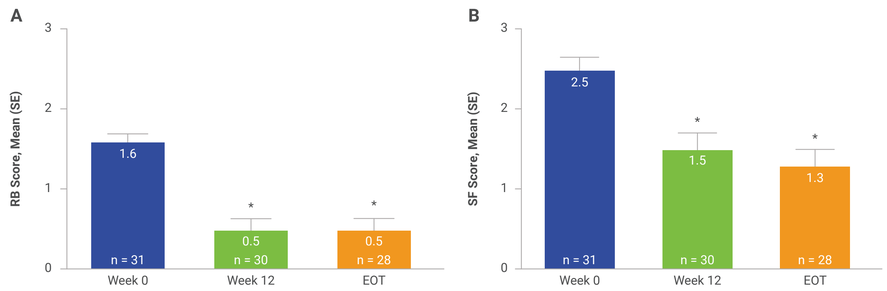
Figure 2. Change From Baseline in (A) RB and (B) SF During the DB Period by DB Treatment Group (DB mITT)



DB, double blind; LSM, least-squares mean; mITT, modified intention-to-treat population; RB, rectal bleeding; SE, standard error; SF, stool frequency.
Mixed model repeated measures analysis with current oral corticosteroid use, prior exposure to anti-TNFα agents, treatment, week, and treatment-by-week interaction as factors and baseline value as a covariate.
*P < 0.05 vs placebo (nominal P value from model for etrasimod 2 mg vs placebo).
Nominal P values for etrasimod 2 mg vs placebo at Week 12 for RB and SF were P = 0.025 and P = 0.237, respectively.

- Reductions in RB and SF observed at Week 12 were durable to EOT; patients in the etrasimod 2 mg TTG had no change in RB or SF at EOT compared with Week 12 (**Figure 3**)

Figure 3. (A) RB and (B) SF Scores at Week 0, Week 12, and EOT in Patients Receiving Etrasimod 2 mg Throughout the DB period and OLE (OLE mITT)

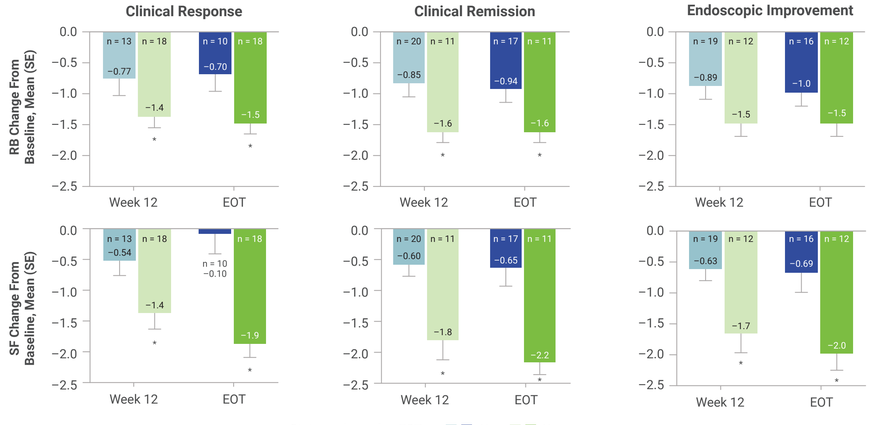


DB, double blind; EOT, end of treatment; mITT, modified intention-to-treat population; OLE, open label extension; RB, rectal bleeding; SE, standard error; SF, stool frequency.
*P < 0.05 vs Week 0 (nominal P value determined by t-test vs Week 0).
Nominal P values for the difference from Week 12 to EOT for RB and SF were P = 0.769 and P = 0.558, respectively.

ASSOCIATION OF RB AND SF WITH CLINICAL RESPONSE, CLINICAL REMISSION, AND ENDOSCOPIC IMPROVEMENT

- In the etrasimod 2 mg TTG, reductions in RB and SF were significantly greater (P < 0.05) at both Week 12 and EOT for patients who had clinical response or clinical remission at EOT versus patients who did not have a given outcome (**Figure 4**)
  - Reductions in SF were significantly greater at Week 12 and EOT in those with endoscopic improvement at EOT versus those without
  - Patients with endoscopic improvement at EOT had numerically greater reductions in RB at Week 12 and EOT than those without endoscopic improvement (Week 12, P = 0.051; EOT, P = 0.097)
- Reductions in RB and SF at Week 12 and EOT were qualitatively similar in magnitude among patients that had clinical response, clinical remission, or endoscopic improvement at EOT
- The correlations between improvements in RB and SF and clinical response, clinical remission, and endoscopic improvement status at EOT that occurred at Week 12 continued to EOT

Figure 4. Change in RB and SF Score by Efficacy Status at EOT in Patients Receiving Etrasimod 2 mg Throughout the DB period and OLE (OLE mITT)



DB, double blind; EOT, end of treatment; mITT, modified intention-to-treat population; OLE, open label extension; RB, rectal bleeding; SE, standard error; SF, stool frequency.
*P < 0.05 vs EOT status (nominal P value determined by t-test of EOT status [no vs yes]).

CONCLUSIONS

- Patients with UC who received etrasimod 2 mg in the OASIS clinical trial and its OLE had early and durable clinical improvements in RB and SF seen as soon as Week 2
- Patients with endoscopic improvement at EOT had long-term improvements in RB and SF that were comparable to the improvements observed in patients who had clinical response or clinical remission at EOT
- These data support the further investigation of etrasimod 2 mg in patients with moderately-to-severely active UC in the ongoing phase 3 ELEVATE studies

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REFERENCES: **1.** Al-Shamma H, et al. *J Pharmacol Exp Ther.* 2019;369:311–317. **2.** Sandborn WJ, et al. *United Eur Gastroent.* 2018;6(8S):A94. **3.** Sandborn WJ, et al. *Gastroenterology.* 2020;158:550–561. **4.** Vermeire S, et al. *United Euro Gastroent.* 2019;7(8_supplement):352. **5.** Peyrin-Biroulet L, et al. *Am J Gastroenterol.* 2015;110:1324–38.

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