Effect of Etrasimod on Circulating Lymphocytes in Patients With Moderately to Severely Active Ulcerative Colitis: Data From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials

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BACKGROUND

- Etrasimod (APD334) is an investigational, once-daily, oral, selective sphingosine 1-phosphate receptor (S1P) 1,4,5 modulator
- Etrasimod demonstrated efficacy in adults with moderately to severely active ulcerative colitis (UC) in the phase 2 OASIS trial (NCT02447302) and the phase 3 ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) trials[1,2]
- Etrasimod reversibly sequesters specific lymphocyte subsets in lymph nodes, reducing circulating lymphocytes and resulting in fewer immune cells available to traffic to the gastrointestinal tract[3,4]
- Previous reports in healthy volunteers demonstrated selective effects of etrasimod on adaptive immune cell subsets and negligible effects on innate cells, such as natural killer cells[5]; however, the impact is unknown in patients with UC
- In this per-protocol exploratory analysis of data from the ELEVATE UC 52 and ELEVATE UC 12 studies, we report the effect of etrasimod on circulating immune cells (T cells, B cells, natural killer cells, and monocytes) in adults with moderately to severely active UC

LIMITATIONS

- There is inherent variability in the assessment of circulating lymphocyte subsets due to the changing course of disease
- Additionally, variations in the time of day at which samples were collected and in site-specific processing of samples may impact measurements

CONCLUSIONS

- This per-protocol exploratory analysis demonstrated that etrasimod had a rapid and differential effect on the frequency of circulating immune cell subsets in peripheral blood in patients with moderately to severely active UC through sequestration of lymphocytes in lymph nodes
- Consistent with the proposed mechanism of action of S1P receptor modulators, as well as previous reports in healthy subjects and those with atopic dermatitis,[5,6] etrasimod reduced adaptive immune cells (T and B cells) in the periphery, with a greater impact on $CD4^+$ T cells than on $CD8^+$ T cells
- Reductions in T and B cell subsets paralleled reductions in absolute lymphocyte counts
- Conversely, etrasimod had no notable impact on innate immune cells (natural killer cells and monocytes) that are important components of immune surveillance

Disclosures

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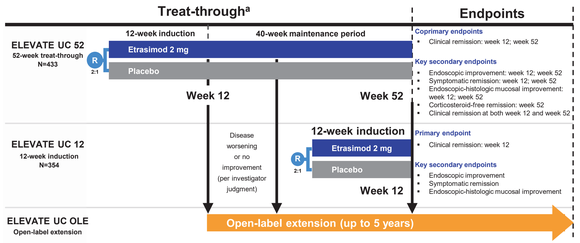
METHODS

Patient Population and Trial Design

- ELEVATE UC 52 and ELEVATE UC 12 were phase 3, global, randomized, double-blind, placebo-controlled trials (**Figure 1**)
  - In both trials, adults (aged 16-80 years) with moderately to severely active UC (based on a modified Mayo Score [MMS] of 4-9 with a centrally read endoscopic subscore of ≥2 and a rectal bleeding subscore of ≥1) and a documented history of inadequate response, loss of response, or intolerance of ≥1 treatment for UC were randomized 2:1 to once-daily treatment with etrasimod 2 mg or placebo
  - Patients were stratified by prior exposure to biologic/Janus kinase inhibitor (JAKi) therapy, concomitant corticosteroid use, and baseline disease activity (MMS 4-6 or 7-9)
- The biomarker analysis set comprised all randomized subjects who received ≥1 dose of study treatment and had a baseline MMS of 5 to 9

Figure 1. ELEVATE UC 52 and ELEVATE UC 12 Trial Schematic



OLE, open-label extension; R, randomization; UC, ulcerative colitis.
[a] Beginning at week 12, all patients could continue their randomized treatment into a 40-week maintenance period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue, and if eligible, enroll in an OLE study (NCT03950232).

Assessments and Data Analysis

- In this per-protocol exploratory analysis, whole blood was collected at weeks 2, 4, 8, 12, 16, 20, 24, 32, 40, 48, and 52 in ELEVATE UC 52 and weeks 2, 4, 8, and 12 in ELEVATE UC 12 for assessment of absolute lymphocyte counts and immunophenotyping
- Absolute lymphocyte counts were determined through complete blood count with differential
- Flow cytometry of fresh samples was used to characterize the following immune cell subsets:
  - Total T cells ($CD3^+$)
  - T helper cells ($CD3^+CD4^+$)
  - Cytotoxic T cells ($CD3^+CD8^+$)
  - B cells ($CD3^-CD19^+$)
  - Natural killer cells ($CD3^-CD56^+CD16^+$)
  - Monocytes ($CD14^+$)
- Mean (SE) percent change from baseline (in cells/μL) at each time point was compared between etrasimod 2 mg and placebo using 2-sided *t* tests
  - Patients with missing baseline samples were not included in the immunophenotyping analysis; such missing sample collections were noted as minor protocol deviations

RESULTS

Patient Demographics

- Immunophenotyping analysis was performed on whole blood from 419 patients in ELEVATE UC 52 (etrasimod 2 mg, n=274; placebo, n=135) and 333 patients in ELEVATE UC 12 (etrasimod 2 mg, n=221; placebo, n=112) who had a baseline sample collection
- Baseline characteristics were similar between treatment arms and across both trial populations[2] (**Table 1**)

Table 1. Summary of Subject Baseline Demographic Characteristics[a]

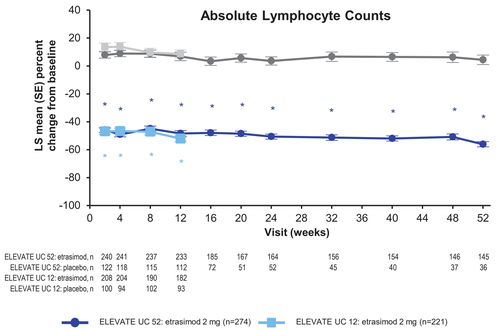
	ELEVATE UC 52		ELEVATE UC 12	
Characteristic	Etrasimod 2 mg (n=274)	Placebo (n=135)	Etrasimod 2 mg (n=221)	Placebo (n=112)
Age, mean (SD), years	41.6 (14.0)	38.6 (14.0)	40.4 (13.7)	40.7 (13.2)
Male, n (%)	144 (52.6)	80 (59.3)	124 (56.1)	70 (62.5)
Ethnicity, n (%)				
Hispanic or Latino	12 (4.4)	7 (5.2)	9 (4.1)	9 (8.0)
Non–Hispanic or Latino	260 (94.9)	127 (94.1)	210 (95.0)	103 (92.0)
Extent of disease, n (%)				
Left-sided colitis/ proctosigmoiditis	161 (58.8)	81 (60.0)	134 (60.6)	61 (54.5)
Pancolitis	92 (33.6)	47 (34.8)	75 (33.9)	40 (35.7)
Proctitis	19 (6.9)	6 (4.4)	12 (5.4)	11 (9.8)
Prior biologic/JAKi naive, n (%)	194 (70.8)	93 (68.9)	148 (67.0)	74 (66.1)
Concomitant CS use, n (%)	93 (33.9)	43 (31.9)	63 (28.5)	34 (30.4)
Concomitant 5-ASA use, n (%)	213 (77.7)	102 (75.6)	187 (84.6)	91 (81.3)
Baseline MMS, mean (SD)	6.88 (1.04)	6.84 (0.95)	6.74 (1.06)	6.71 (1.13)
Duration of UC, mean (SD), years	7.6 (8.1)	6.0 (5.6)	7.2 (6.5)	7.9 (7.4)

5-ASA, 5-aminosalicylic acid; CS, corticosteroid; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; UC, ulcerative colitis.
[a] Data are derived from the safety analysis set and include all subjects who received ≥1 dose of study treatment and had a baseline MMS of 5 to 9.

Etrasimod Effect on Absolute Lymphocyte Counts

- Subjects treated with etrasimod demonstrated nearly nadir absolute lymphocyte counts by week 2; counts were maintained during the treatment period through week 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12 (**Figure 2**)

Figure 2. LS Mean (SE) Percent Change From Baseline in Absolute Lymphocyte Counts Over Time (MMS 5-9)[a]

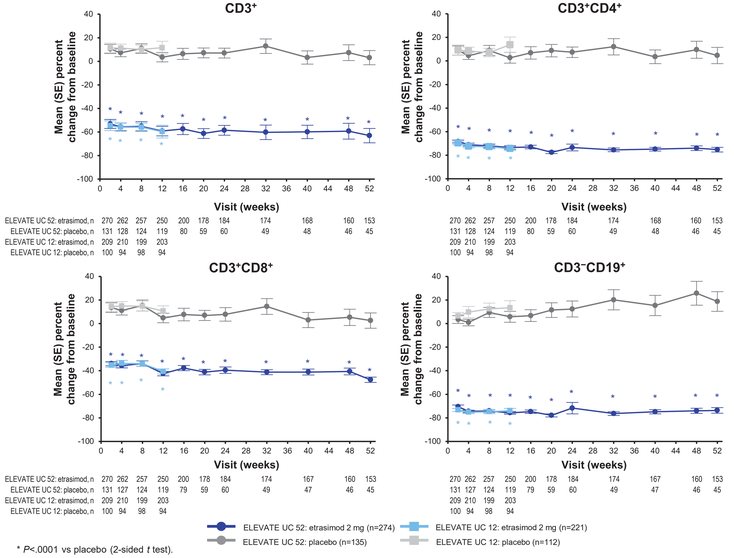


JAKi, Janus kinase inhibitor; LS, least squares; MMRM, mixed model of repeated measures; MMS, modified Mayo Score.
[a] Only subjects with a baseline MMS between 5 and 9 are included. Estimates are from an MMRM model of percent change from baseline, with a covariate for baseline score and factors for naivety to biologic/JAKi therapy at study entry, baseline corticosteroid use, baseline disease activity (MMS, 4-6 or 7-9), treatment, visit, and treatment-by-visit interaction.
* $P<.001$ vs placebo (2-sided *t* test).

Etrasimod Effect on Circulating Lymphocyte Subsets

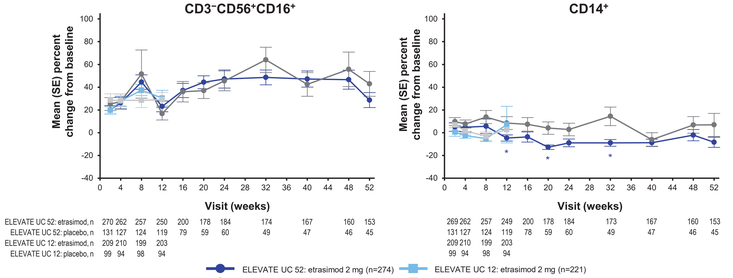
- Treatment with etrasimod 2 mg resulted in rapid mean percent reductions from baseline to week 2, with nadir and near nadir changes from baseline reached by week 4 in ELEVATE UC 52 and ELEVATE UC 12, respectively, for total T cells ($CD3^+$: −55.6% [1.50] and −55.9% [1.65]), T helper cells ($CD3^+CD4^+$: −71.1% [1.33] and −72.5% [1.30]), cytotoxic T cells ($CD3^+CD8^+$: −35.7% [1.94] and −33.8% [2.60]), and B cells ($CD3^-CD19^+$: −74.5% [1.05] and −75.2% [1.18])
- Reductions were maintained through week 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12 (**Figure 3**)
- No clinically significant changes in natural killer cell ($CD3^-CD56^+CD16^+$) or monocyte ($CD14^+$) levels were found during the treatment period of either study (**Figure 4**)

Figure 3. Mean (SE) Percent Change From Baseline in Circulating Adaptive Immune Cell Subsets (cells/μL) Over Time (MMS 5-9; safety set)



* $P<.0001$ vs placebo (2-sided *t* test).

Figure 4. Mean (SE) Percent Change From Baseline in Circulating Innate Immune Cell Subsets (cells/μL) Over Time (MMS 5-9; safety set)



* $P<.05$ vs placebo (2-sided *t* test).