Effect of Etrasimod on Immune Cell Subsets in Colonic Tissue of Patients With Ulcerative Colitis: Immunophenotyping Analysis of Colon Biopsy Samples From the Phase 3 ELEVATE UC 52 and ELEVATE UC 12 Trials

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Background

- Etrasimod is an investigational, once-daily, oral, selective sphingosine 1-phosphate receptor 1,4,5 (S1P1,4,5) modulator for the treatment of moderately to severely active ulcerative colitis (UC)
- Etrasimod reversibly sequesters specific lymphocyte subsets in lymph nodes, reducing circulating lymphocytes and resulting in fewer immune cells available to traffic to the gastrointestinal tract1-3
- Previous data support differential effects of etrasimod on peripheral immune cell subsets2-4; however, robust assessments of the ability of etrasimod to reduce the infiltration and accumulation of immune cells associated with inflammation in the intestines have not been conducted
- In the phase 3 ELEVATE UC programme, both ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) included per-protocol, exploratory biomarker substudies to better characterize the efficacy and mechanism of action of etrasimod and its impact on immunological pathways

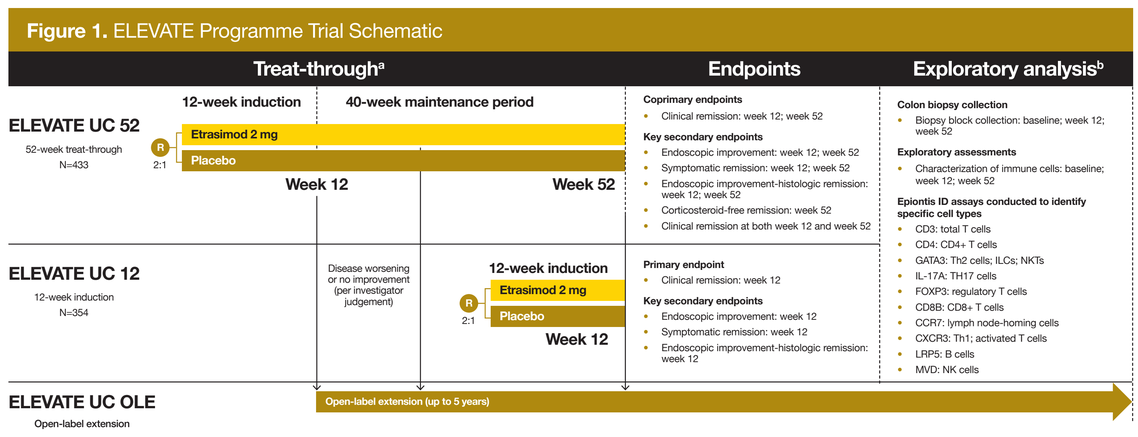
Objective

- To better understand how etrasimod reduces inflammation in UC, the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials included a per-protocol exploratory immunophenotyping biomarker analysis in fixed-formalin paraffin-embedded colon biopsies

Methods

- ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) were phase 3, global, randomised, double-blind, placebo-controlled trials (**Figure 1**)
  - ELEVATE UC 52 comprised a 12-week induction period followed by a 40-week maintenance period with a treat-through design
  - ELEVATE UC 12 comprised a 12-week induction period only
- In both trials, subjects (aged 16-80 years) with moderately to severely active UC and a history of inadequate response, loss of response, or intolerance of ≥1 approved treatment for UC were randomised 2:1 to once-daily treatment with etrasimod 2 mg or placebo with no titration regimen
- Biopsy blocks were the primary histopathology assessment samples collected at baseline and week 12 in both ELEVATE UC 12 and ELEVATE UC 52, and at week 52 in ELEVATE UC 52, and were analysed by Epiontis ID5, an epigenetic immune-monitoring method (**Figure 1**)
- Biomarker levels for each lymphocyte subset were evaluated between responders vs nonresponders at weeks 12 and 52, defined by achievement of clinical efficacy criteria in each treatment group, using t tests and nominal P values (**Table 1**)

Figure 1. ELEVATE Programme Trial Schematic



FOXP3, forkhead box P3; GATA3, GATA binding protein 3; IL17A; interleukin 17A; ILC, innate lymphoid cell; LRP5, low-density lipoprotein receptor-related protein 5; MVD, mevalonate diphosphate decarboxylase; NK, natural killer; OLE, open-label extension; R, randomisation; UC, ulcerative colitis.
[a] Beginning at week 12, all patients could continue their randomised treatment into a 40-week treatment period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue and enrol in an OLE study (NCT03950232).
[b] Analyses at Week 52 were only conducted in ELEVATE UC 52.

Table 1. Efficacy Outcome Response Definitions

Response Outcome	Definition
Clinical remission	SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability)
Clinical response	≥2-point and ≥30% decrease from baseline in MMS and ≥1-point decrease from baseline in RB subscore or an absolute RB subscore ≤1
Endoscopic improvement	Score ≤1 (excluding friability)
Endoscopic improvement-histologic remission	ES ≤1 (excluding friability) with histologic remission measured by a Geboes Index score <2
HEMI	ES ≤1 (excluding friability) with histologic improvement measured by a Geboes Index score ≤3.1
Histologic remission (Geboes)	Geboes Index score <2.0
Histologic remission (RHI)	RHI score ≤3 with scores of 0 for both Geboes grade 2B (lamina propria neutrophils) and grade 3 (neutrophils in epithelium)
Histologic remission (Nancy)	Nancy histologic index score ≤1

ES, endoscopic subscore; HEMI, histologic-endoscopic mucosal improvement; MMS, modified Mayo score; RB, rectal bleeding; RHI, Robarts Histopathology Index; SF, stool frequency

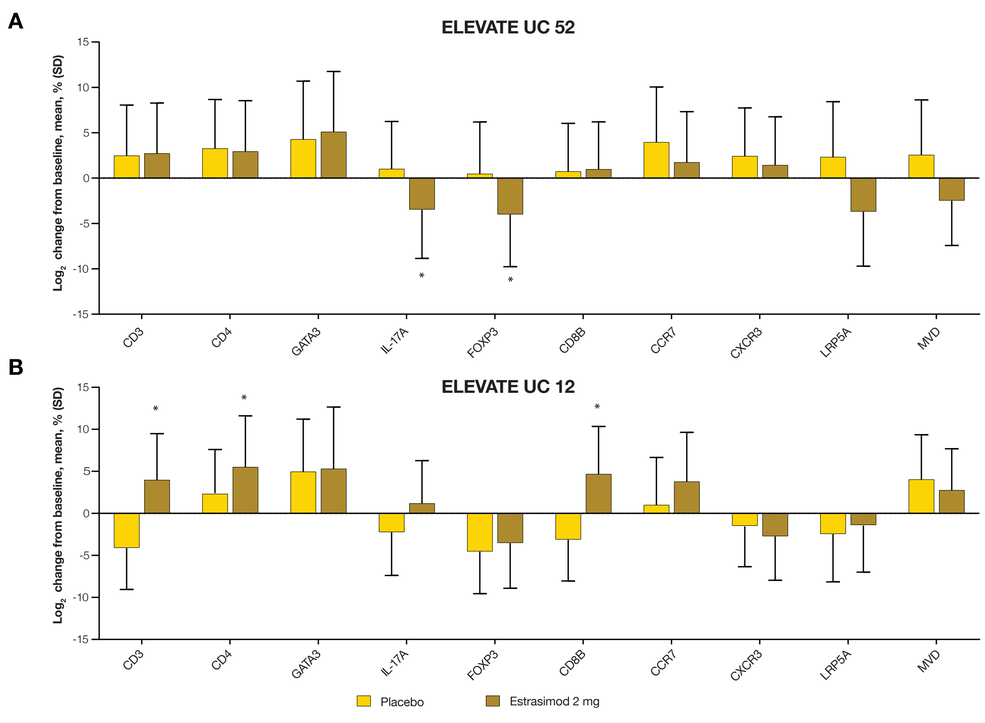
Results

- There were no meaningful differences in baseline demographics and clinical characteristics between subjects treated with etrasimod or placebo in both ELEVATE UC 52 and ELEVATE UC 12
- Of the total subjects included in the exploratory analyses, 276 in ELEVATE UC 52 (179 etrasimod; 97 placebo) and 150 in ELEVATE UC 12 (97 etrasimod; 53 placebo) had colon biopsies collected and analysed

Changes in Colonic Tissue Immune Cell Subsets Following Etrasimod Treatment

- Etrasimod induced significant changes from baseline (nominal P value <.05) in colonic T- and B-cell subsets at week 12 in ELEVATE UC 52 and ELEVATE UC 12; these changes were maintained through week 52 in ELEVATE UC 52 (**data not shown**)
- Significant differences between etrasimod- and placebo-induced changes from baseline for select inflammatory immune cell subsets were seen at week 12 in ELEVATE UC 52 (**Figure 2A**) and ELEVATE UC 12 (**Figure 2B**)

Figure 2. Mean Percentage Change From Baseline to Week 12 in (A) ELEVATE UC 52 and (B) ELEVATE UC 12 in FFPE Colon Biopsy Immune Cell Subsets (Epiontis ID)[a]



FFPE, fixed-formalin paraffin-embedded; FOXP3, forkhead box protein P3; GATA3, GATA-binding factor 3; IL-17A; interleukin 17A; LRP5A, low-density lipoprotein receptor-related protein 5A; MVD, mevalonate diphosphate decarboxylase;UC, ulcerative colitis.
* P<.05 vs placebo.
[a] Log2 transformation of absolute values was done for all mean percent change from baseline values, and a constant value of 1 was added to each data point to adjust for negative values. The number of samples varied for each immune cell subset assay and treatment group, with 73 to 81 and 15 to 17 samples from placebo-treated subjects and 120 to 151 and 33 to 38 from etrasimod-treated subjects from ELEVATE UC 52 and ELEVATE UC 12, respectively, included in this analysis.

Analysis of Responders vs Nonresponders

- At week 12, etrasimod induced significant reductions from baseline (nominal P value <.05) in colonic T- and B-cell subsets expressing IL-17A, FOXP3, CCR7, CXCR3, and LRP5A in responders vs nonresponders (**Table 2**)
- At week 12, etrasimod, but not placebo, induced significant reductions from baseline (nominal P value <.05) in colonic CD8B-expressing T cells in responders vs nonresponders in ELEVATE UC 52; these trends were maintained through week 52
- Significant effects on CXCR3, FOXP3 and LRP5A were observed in responders vs nonresponders in ELEVATE UC 12

Table 2. Summary of Differences in Percent Change From Baseline in FFPE Colon Biopsy Immune Cell Subsets Between Responders and Nonresponders Treated With Etrasimod (Epiontis ID)

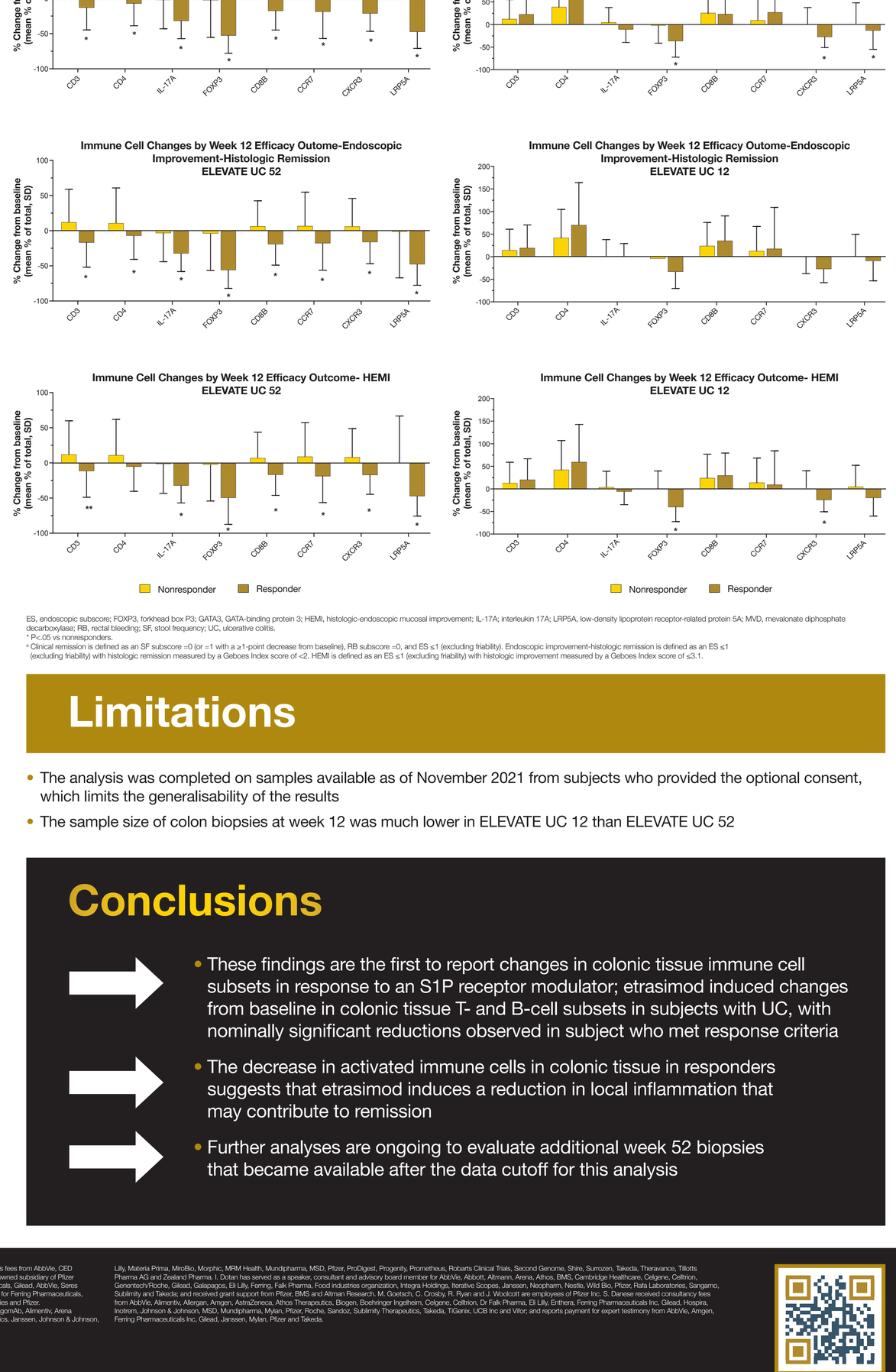
ELEVATE UC 52 (week 12)									
Response Outcome	**CD3**	**CD4**	**IL-17A**	**FOXP3**	**CD8B**	**CCR7**	**CXCR3**	**LRP5A**	**MVD**
Clinical remission[a]	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*	NS
Clinical response[b]	NS	NS	NS	↓*	NS	↓*	↓*	↓*	NS
Endoscopic improvement[c]	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*	NS
Endoscopic improvement-histologic remission[d]	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*	NS
HEMI[e]	↓*	↓*	↓*	↓*	↓*	↓*	↓*	↓*	NS
Histologic remission (Geboes)[f]	↓*	↓*	↓*	↓*	NS	↓*	↓*	↓*	NS
Histologic remission (RHI)[g]	NS	NS	↓*	↓*	NS	↓*	↓*	↓*	NS
Histologic remission (Nancy)[h]	NS	NS	↓*	↓*	NS	↓*	↓*	↓*	NS

ELEVATE UC 12 (week 12)									
Response Outcome	**CD3**	**CD4**	**IL-17A**	**FOXP3**	**CD8B**	**CCR7**	**CXCR3**	**LRP5A**	**MVD**
Clinical remission[a]	NS	NS	NS	↓*	NS	NS	↓*	NS	↓*
Clinical response[b]	NS	NS	NS	NS	NS	NS	NS	NS	NS
Endoscopic improvement[c]	NS	NS	NS	↓*	NS	NS	NS	NS	NS
Endoscopic improvement-histologic remission[d]	NS	NS	NS	NS	NS	NS	NS	NS	NS
HEMI[e]	NS	NS	NS	↓*	NS	NS	↓*	NS	NS
Histologic remission (Geboes)[f]	NS	NS	NS	NS	NS	NS	↓*	NS	NS
Histologic remission (RHI)[g]	NS	NS	NS	↓*	NS	NS	↓*	↓*	NS
Histologic remission (Nancy)[h]	NS	NS	NS	↓*	NS	NS	↓*	↓*	NS

ES, endoscopic subscore; FFPE, fixed-formalin paraffin-embedded; FOXP3, forkhead box P3; HEMI, histologic-endoscopic mucosal improvement; IL-17A; interleukin 17A; LRP5A, low-density lipoprotein receptor-related protein 5A; MMS, modified Mayo score; MVD, mevalonate diphosphate decarboxylase; NS, not significant; RB, rectal bleeding; RHI, Robarts Histopathology Index; SF, stool frequency; UC, ulcerative colitis.
* P<.05 vs nonresponders (↓= significant decrease in responders vs nonresponders). [a] Clinical remission is defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability). [b] Clinical response is defined as a ≥2-point and ≥30% decrease from baseline in MMS and a ≥1-point decrease from baseline in RB subscore or an absolute RB subscore of ≤1. [c] Endoscopic improvement is defined as a score of ≤1 (excluding friability). [d] Endoscopic improvement-histologic remission is defined as an ES ≤1 (excluding friability) with histologic remission measured by a Geboes Index score of <2. [e] HEMI is defined as an ES ≤1 (excluding friability) with histologic improvement measured by a Geboes Index score of ≤3.1. [f] Histologic remission (Geboes) is defined as a Geboes Index score of <2.0. [g] Histologic remission (RHI) is defined as an RHI score of ≤3 with scores for Geboes grade 2B (lamina propria neutrophils) and grade 3 (neutrophils in epithelium) both =0. [h] Histologic remission (Nancy) is defined as a Nancy Histologic Index score of ≤1.

- In ELEVATE UC 52, etrasimod treatment led to significant decreases in CD3, CD4, IL-17A, FOXP3, CD8, CCR7, CXCR3 and LRP5A in responders who achieved clinical remission, endoscopic improvement-histologic remission and HEMI compared with nonresponders at week 12 (**Figure 3A**)
- Similar significant reductions were seen in FOXP3, CXCR3 and MVD in responders vs nonresponders who achieved these key outcomes at week 12 in ELEVATE UC 12 (**Figure 3B**)

Figure 3. Immune Cell Subset Changes Amongst Efficacy Outcomes by Responders and Nonresponders Treated With Etrasimod at Week 12 in (A) ELEVATE UC 52 and (B) ELEVATE UC 12[a]



ES, endoscopic subscore; FOXP3, forkhead box P3; GATA3, GATA-binding protein 3; HEMI, histologic-endoscopic mucosal improvement; IL-17A; interleukin 17A; LRP5A, low-density lipoprotein receptor-related protein 5A; MVD, mevalonate diphosphate decarboxylase; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.
* P<.05 vs nonresponders.
[a] Clinical remission is defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability). Endoscopic improvement-histologic remission is defined as an ES ≤1 (excluding friability) with histologic remission measured by a Geboes Index score of <2. HEMI is defined as an ES ≤1 (excluding friability) with histologic improvement measured by a Geboes Index score of ≤3.1.

Limitations

- The analysis was completed on samples available as of November 2021 from subjects who provided the optional consent, which limits the generalisability of the results
- The sample size of colon biopsies at week 12 was much lower in ELEVATE UC 12 than ELEVATE UC 52

Conclusions

- These findings are the first to report changes in colonic tissue immune cell subsets in response to an S1P receptor modulator; etrasimod induced changes from baseline in colonic tissue T- and B-cell subsets in subjects with UC, with nominally significant reductions observed in subject who met response criteria
- The decrease in activated immune cells in colonic tissue in responders suggests that etrasimod induces a reduction in local inflammation that may contribute to remission
- Further analyses are ongoing to evaluate additional week 52 biopsies that became available after the data cutoff for this analysis

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