The impact of etrasimod on neutrophils in the ELEVATE UC clinical programme

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Introduction

- Neutrophils are thought to play a role in the pathogenesis of UC; they are believed to be the principal source of faecal calprotectin and are a histological marker of disease activity in mucosal biopsies[1,2]
- Etrasimod is an oral, once-daily, selective $S1P_{1,4,5}$ receptor modulator for the treatment of moderately to severely active UC

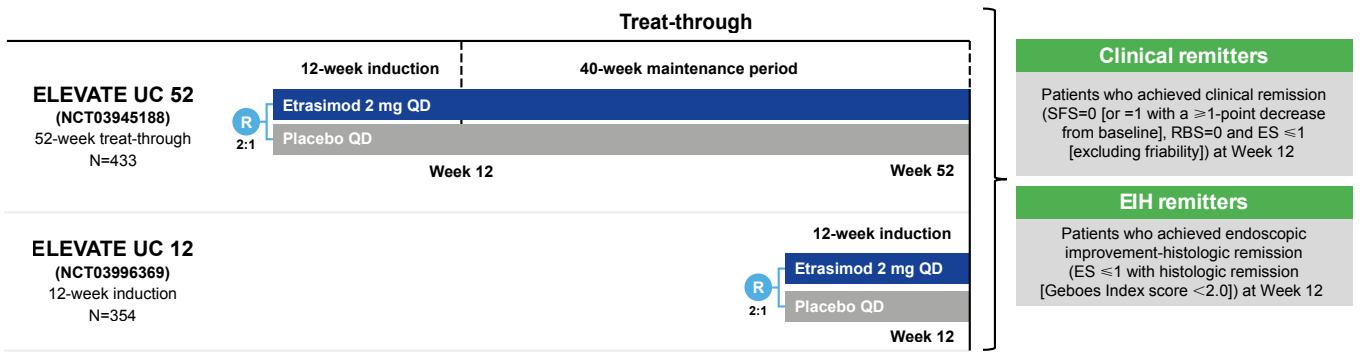
Objective

- To evaluate neutrophils in patients receiving etrasimod or placebo in a post hoc analysis of the ELEVATE UC clinical programme

Methods

- We assessed percentage changes from baseline in blood absolute neutrophil count (ANC) throughout ELEVATE UC 52 and ELEVATE UC 12 (**Figure 1**)
  - Patients were also stratified based on those who did/did not achieve clinical remission or EIHR at Week 12

Figure 1. ELEVATE UC clinical programme trial design and patient subgroups according to remission status



- Colonic biopsies were collected into RNAlater and frozen until RNA-seq analysis
- Transcriptional characterisation followed by gut cell-type deconvolution analysis from bulk RNA-seq (CytoReason) was performed on colonic biopsies to assess for neutrophils in Week 12 clinical remitters vs nonremitters receiving either etrasimod or placebo
- Incidence of neutropenia and potential associated infections were assessed

Results

Patients

- Analysis populations are shown in **Table 1**

Table 1. Key patient populations assessed in the ELEVATE UC programme

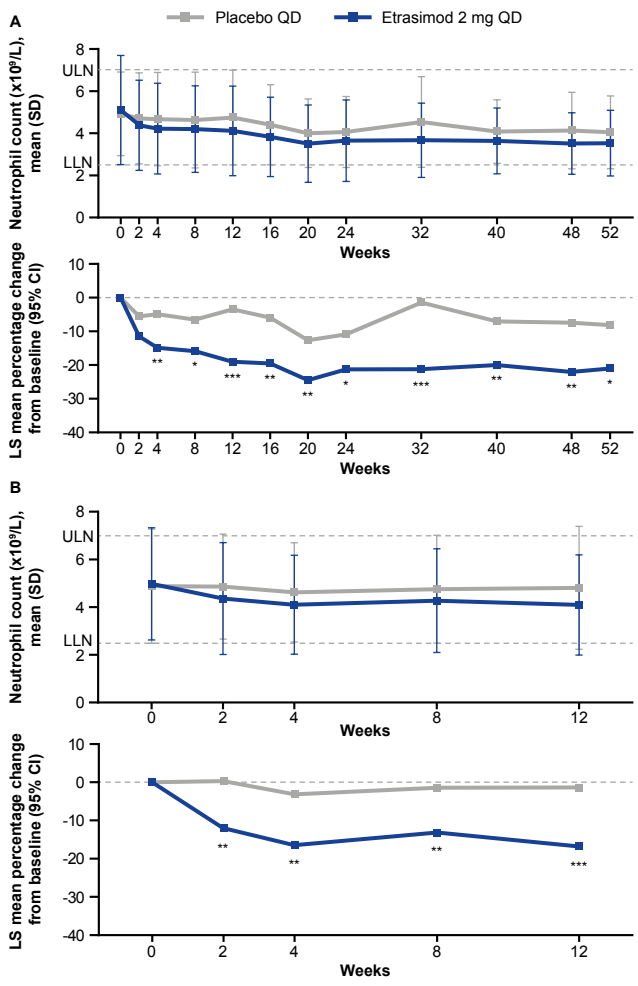
	ELEVATE UC 52		ELEVATE UC 12	
	Placebo QD (N=144)	Etrasimod 2 mg QD (N=289)	Placebo QD (N=116)	Etrasimod 2 mg QD (N=238)
Blood samples,[a] n	144	288	115	238
Tissue samples,[a] n	107	233	83	166

[a]At baseline.

Changes in circulating neutrophils

- Patients receiving etrasimod vs placebo had significant percentage decreases from baseline in ANC from Week 4 (ELEVATE UC 52) and Week 2 (ELEVATE UC 12; **Figure 2**)
- Week 12 clinical remitters vs nonremitters receiving etrasimod had a significantly greater percentage decrease in ANC from baseline at most time points (**Figure 3**)
- A similar trend was seen for EIH remitters vs nonremitters at Week 12 in ELEVATE UC 52
  - Nadir was reached for EIH remitters receiving etrasimod at Week 8 (LS mean of -31.7% [95% CI, -38.0, -24.6]) in ELEVATE UC 52

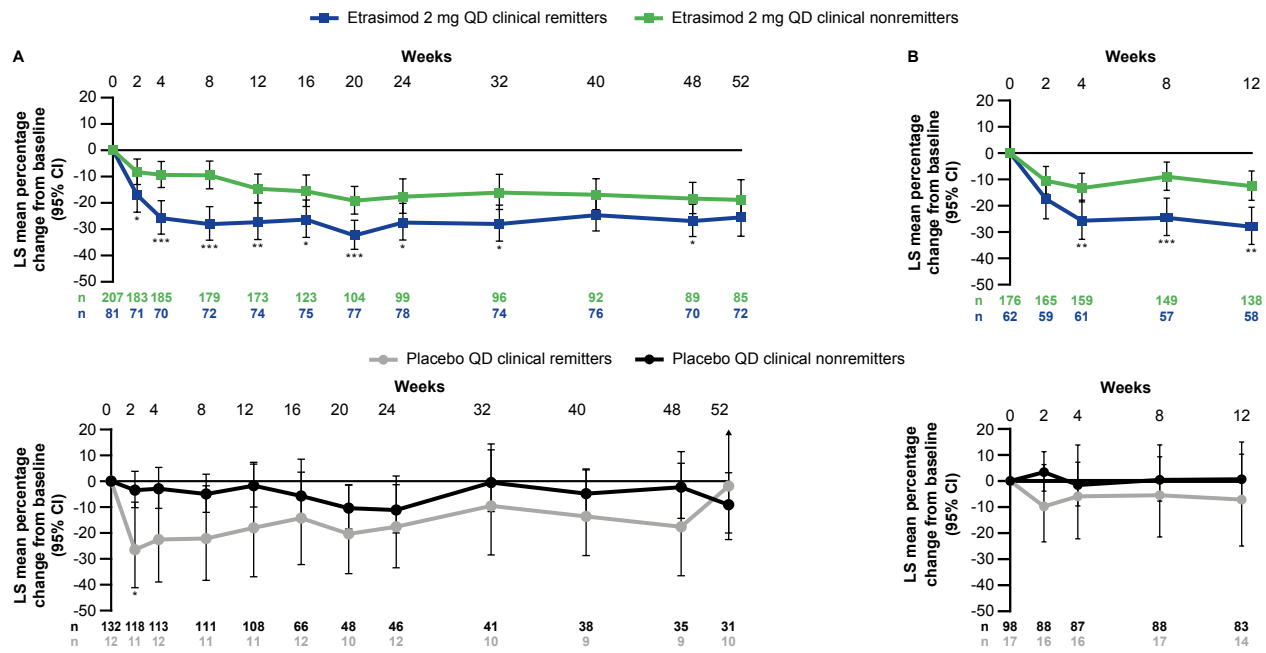
Figure 2. Absolute mean (SD) and LS mean percentage change from baseline in ANC in A) ELEVATE UC 52 and B) ELEVATE UC 12



*p<0.05, **p<0.01, ***p<0.001.

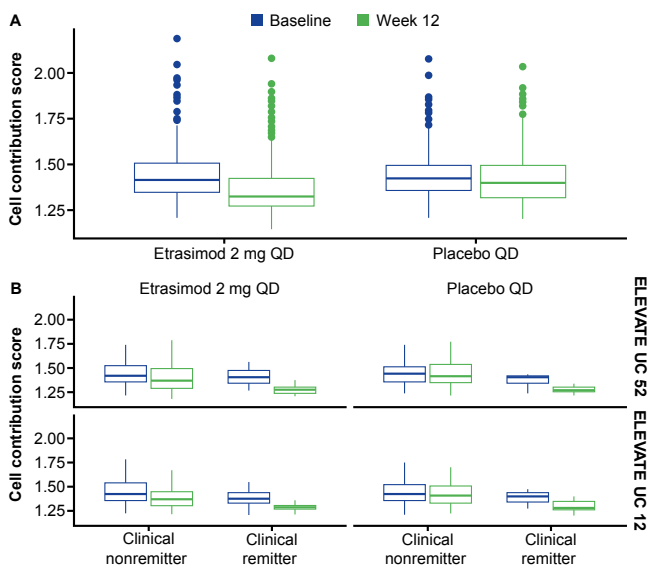
Estimates are from an MMRM model for log2FC with covariates of reported prior biologic/JAKi therapy at study entry (yes vs no), baseline corticosteroid use (yes vs no), and baseline disease activity (MMS 4–6 vs 7–9), treatment, visit, treatment by visit interaction and log2-transformed baseline value. Unstructured variance–covariance matrix was used. Baseline was the last measurement taken prior to the first dose of study treatment. *P* value was not adjusted to multiple comparisons.

Figure 3. LS mean percentage change from baseline in ANC based on clinical remitter status at Week 12 in A) ELEVATE UC 52 and B) ELEVATE UC 12



*p<0.05, **p<0.01, ***p<0.001. LS mean percentage change from baseline estimates in neutrophil count were from an MMRM on log2FC (log2 transformation of ANC at post-baseline visit divided by ANC at baseline) with covariates of reported prior biologic/JAKi therapy at study entry (yes vs no), baseline corticosteroid use (yes vs no) and baseline disease activity (MMS 4–6 vs 7–9), clinical remission at Week 12, visit and clinical remission at Week 12 by visit interaction and log2-transformed baseline value. Unstructured covariance matrix was used. LS mean percentage change values were obtained by back-transforming the LS mean log2FC values. *P* value was not adjusted to multiple comparisons.

Figure 4. Neutrophil levels in colonic biopsy tissue samples[a] by A) treatment and B) clinical remitter status



[a]Levels estimated via gut cell-type deconvolution analyses of RNA-seq data from colonic biopsies.

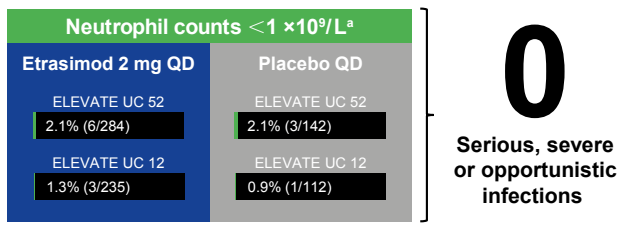
Changes in colonic neutrophils

- Colonic neutrophils were significantly decreased at Week 12 vs baseline for patients receiving etrasimod but not placebo (**Figure 4A**), and for clinical remitters vs nonremitters receiving etrasimod (**Figure 4B**)

Safety

- Across both trials, few patients had neutrophil counts $<1\times10^9$/L (Grade 3 or higher neutropenia) at any post-baseline assessment (**Figure 5**)
  - No patients reported serious, severe or opportunistic infections within 60 days following neutropenia
  - One patient receiving etrasimod experienced a **nonserious** viral respiratory tract infection ⩽60 days after reported neutropenia

Figure 5. Neutropenia and associated infection



Bracketed values indicate n/N, with N representing the number of patients in the analysis set with data at the specified timepoint. [a]At any post-baseline assessment.

Limitations

- Data are as observed with no imputations for missing values
- Further analyses are needed to contextualise findings to additional inflammatory markers

Conclusions

- **Etrasimod resulted in a modest decrease in circulating neutrophils with no increased risk of serious, severe or opportunistic infection**
- **Our data support a relationship between decreased circulating and mucosal neutrophil levels and clinical and endoscopic improvement with etrasimod treatment in patients with UC**

Electronic poster

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Abbreviations

ANC, absolute neutrophil count; **CI**, confidence interval; **EIH**, endoscopic improvement-histologic; **EIHR**, endoscopic improvement-histologic remission; **ES**, endoscopic subscore; **JAKi**, Janus kinase inhibitor; **LLN**, lower limit of normal; **log2FC**, log2 of fold change; **LS**, least squares; **MMRM**, mixed model for repeated measures; **MMS**, modified Mayo score; **N**, number of patients; **n**, number of patients in group; **S1P**, sphingosine 1-phosphate; **SD**, standard deviation; **SFS**, stool frequency subscore; **QD**, once daily; **R**, randomisation; **RBS**, rectal bleeding subscore; **RNA**, ribonucleic acid; **UC**, ulcerative colitis; **ULN**, upper limit of normal.

References

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2. Bjarnason I. Gastroenterol Hepatol (N Y) 2017; 13: 53–56.
3. DeTora LM et al. Ann Intern Med 2022; 175: 1298–1304.

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Disclosure of interests

MA has received lecture/speaker fees from and is a consultant for Pfizer Inc. **BV** has received research support, speaker fees and consultancy fees from Pfizer Inc. **CMC**, **RDR** and **JW** are employees and shareholders of Pfizer Inc. **MF**, **EK** and **KL** are employees of Pfizer AG and shareholders of Pfizer Inc. **ABD** is an employee of Pfizer Inc. **KW** is an employee and shareholder of Pfizer Canada Inc. **BS** has received lecture fees from and is a consultant for Pfizer Inc.

Poster presented at the 20th Congress of the European Crohn's and Colitis Organisation; 19–22 February 2025; Berlin, Germany

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Etrasimod verursachte eine reversible Verringerung der Neutrophilenzahl; der Anteil an mit Etrasimod behandelten Patient*innen, bei denen eine Verringerung der Neutrophilenzahl auf weniger als 0,5 x 10^9/l beobachtet wurde, lag in ELEVATE UC52 & UC12 bei 0,2 %. Diese Ereignisse führten nicht zu einem Behandlungsabbruch.

Nach Lymphopenie (11%) zählen Kopfschmerzen, Infektionen der Harnwege und der unteren Atemwege, Neutropenie, Hypercholesterinämie, Bradykardie, Schwindelgefühl, Sehverschlechterung, Hypertonie und erhöhte Leberenzyme zu den häufigsten Nebenwirkungen (⩾ 1/100 bis < 1/10).

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