Fecal Calprotectin and C-Reactive Protein Levels Are Correlated With Long Term Clinical and Endoscopic Outcomes: Analysis of the OASIS Open Label Extension Trial of Etrasimod for Ulcerative Colitis

Andres Yarur,[1] Michael Chiorean,[2] Jinkun Zhang,[3] Walter Reinisch,[4] Séverine Vermeire,[5] Julián Panés,[6] Laurent Peyrin-Biroulet,[7] Bruce E. Sands,[8] Christopher H. Cabell,[3] Snehal U. Naik,[3] William J. Sandborn[9]

[1]Medical College of Wisconsin, Milwaukee, WI, USA; [2]Virginia Mason Medical Center, Seattle, WA, USA; [3]Arena Pharmaceuticals, Inc., San Diego, CA, USA; [4]Medical University of Vienna, Vienna, Austria; [5]University Hospitals Leuven, Leuven, Flanders, Belgium; [6]Hospital Clinic of Barcelona, IDIBAPS, CIBERehd, Barcelona, Spain; [7]Department of Gastroenterology, INSERM U954, Lorraine University, Vandoeuvre-lès-Nancy, France; [8]Icahn School of Medicine at Mount Sinai, New York, NY, USA; [9]University of California San Diego, La Jolla, CA, USA

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INTRODUCTION

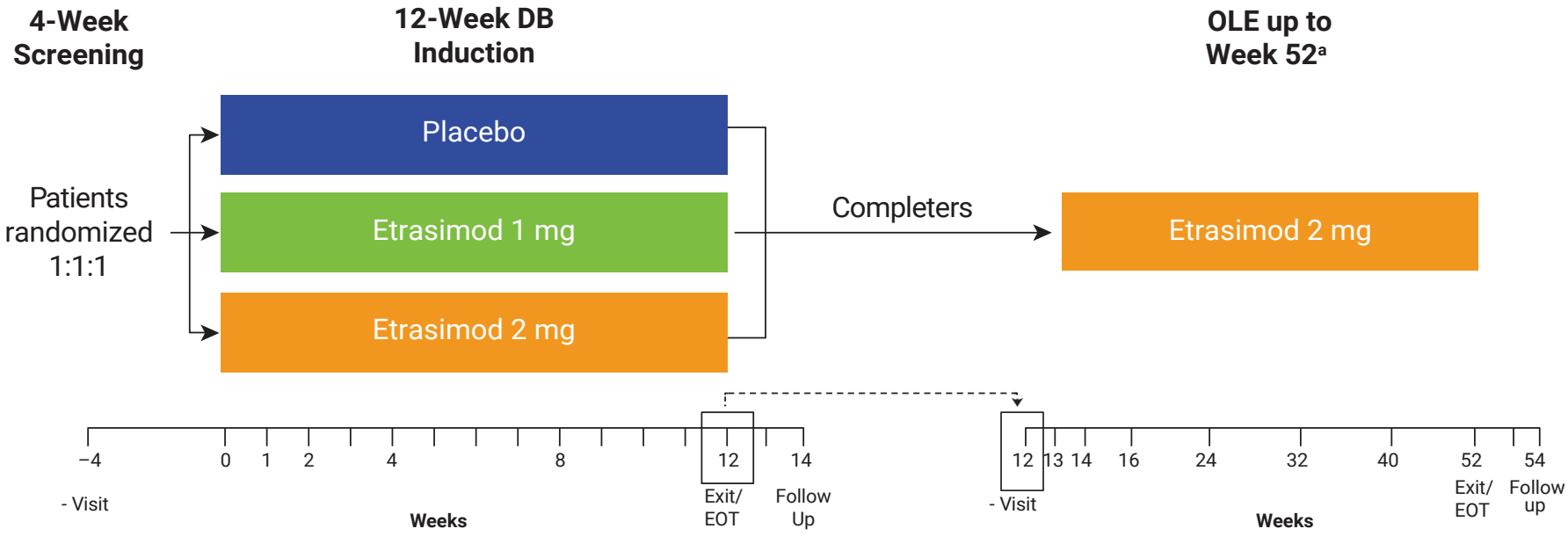
- Surrogate biomarkers of disease activity in ulcerative colitis are used to assess responses to treatment
- Etrasimod (APD334) is a once-daily, oral, selective sphingosine 1-phosphate receptor modulator with efficacy in patients with moderately to severely active ulcerative colitis (UC) in the 12-week, randomized, double-blind (DB), placebo-controlled, multicenter phase 2 OASIS study (NCT02447302)[1] and the open-label extension (OLE) study (NCT02536404)[2]
- The biomarkers fecal calprotectin (FC) and C-reactive protein (CRP) previously were shown to be useful in evaluating efficacy in the OASIS DB study[3]
- In the present post hoc analysis of the OLE, we evaluated the utility of FC and CRP as surrogate biomarkers for assessing sustained efficacy in patients with UC receiving etrasimod

METHODS

STUDY DESIGN

- During the DB study, adult patients who met the inclusion criteria of a modified Mayo Clinic Score (mMCS) of 4–9 with endoscopic subscore ≥2, and rectal bleeding subscore ≥1 were treated once daily with etrasimod 1 mg, etrasimod 2 mg, or placebo[1]
- Patients who completed the DB study were eligible to enroll in the OLE and receive etrasimod 2 mg once daily for up to an additional 40 weeks (52 weeks total) irrespective of their response or treatment in the DB study (**Figure 1**)

Figure 1. Study Design



EOT, end of treatment
[a]For patients enrolled under later protocol amendments, treatment ended at 46 weeks

- End of treatment was defined as the last treatment visit, occurring at Week 46, Week 52, or earlier for patients with early treatment discontinuation
- FC from stool was measured at baseline and Weeks 4, 8, and 12 during the DB study and at Weeks 32 and EOT in the OLE
- CRP from blood was measured at baseline and Weeks 1, 2, 4, 8, and 12 during the DB study and Weeks 16, 24, 32 and EOT in the OLE

METHODS (Cont'd)

- Clinical and endoscopic outcomes were evaluated at baseline and Week 12 in the DB study and at EOT in the OLE
  - mMCS (range 0—9) included endoscopic, rectal bleeding (RB), and stool frequency (SF) subscores
  - Clinical remission was defined as an endoscopic subscore ≤1 (with absence of friability), RB and SF scores ≤1, and a SF decrease from baseline of ≥1
  - Clinical response was defined as clinical remission or decrease in mMCS of ≥2 and a ≥30% decrease from DB baseline, with either a RB decrease of ≥1 or RB score of ≤1

STATISTICAL ANALYSES

- Analyses were performed using the evaluable cohort modified intention-to-treat population (mITT), which included patients who received etrasimod 2 mg throughout the OLE period and who had all required assessments
- Comparisons between FC and CRP levels versus baseline (pre-specified) and between patients who achieved remission and those who did not (post hoc) by study week were made using a Wilcoxon rank-sum test (2-sided *P* values)
- Comparisons between patients with normalization of FC and CRP versus baseline (post hoc) used a paired Student *t*-test on response values (no = 0, yes = 1)
- Analysis of correlation between mMCS, endoscopic subscore, CRP, and FC (post hoc) was performed using the Spearman's rank coefficient

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 during the OLE
  - 105 patients (evaluable cohort) received etrasimod 2 mg throughout the OLE
  - 92/112 (82.1%) patients in the etrasimod safety population completed the OLE
- Mean (standard deviation [SD]) study drug exposure was 45 (9) weeks from the start of the DB study and 33 (9) weeks in the OLE
- Patients within the etrasimod safety population had the following demographic and baseline characteristics:
  - Mean (SD) age of 43.7 (13.3) years at the start of the OLE; 60.7% of patients were male, and 93.8% were white
  - Mean (SD) duration of UC of 6.9 (6.1) years at the start of the DB study with a mean (SD) mMCS of 4.4 (2.4) at the start of the OLE
  - Median (range) values for FC and CRP of 850.5 (30–22,716) mg/kg and 4.5 (0.2–119.0) mg/L, respectively, at the start of the OLE

RESULTS (Cont'd)

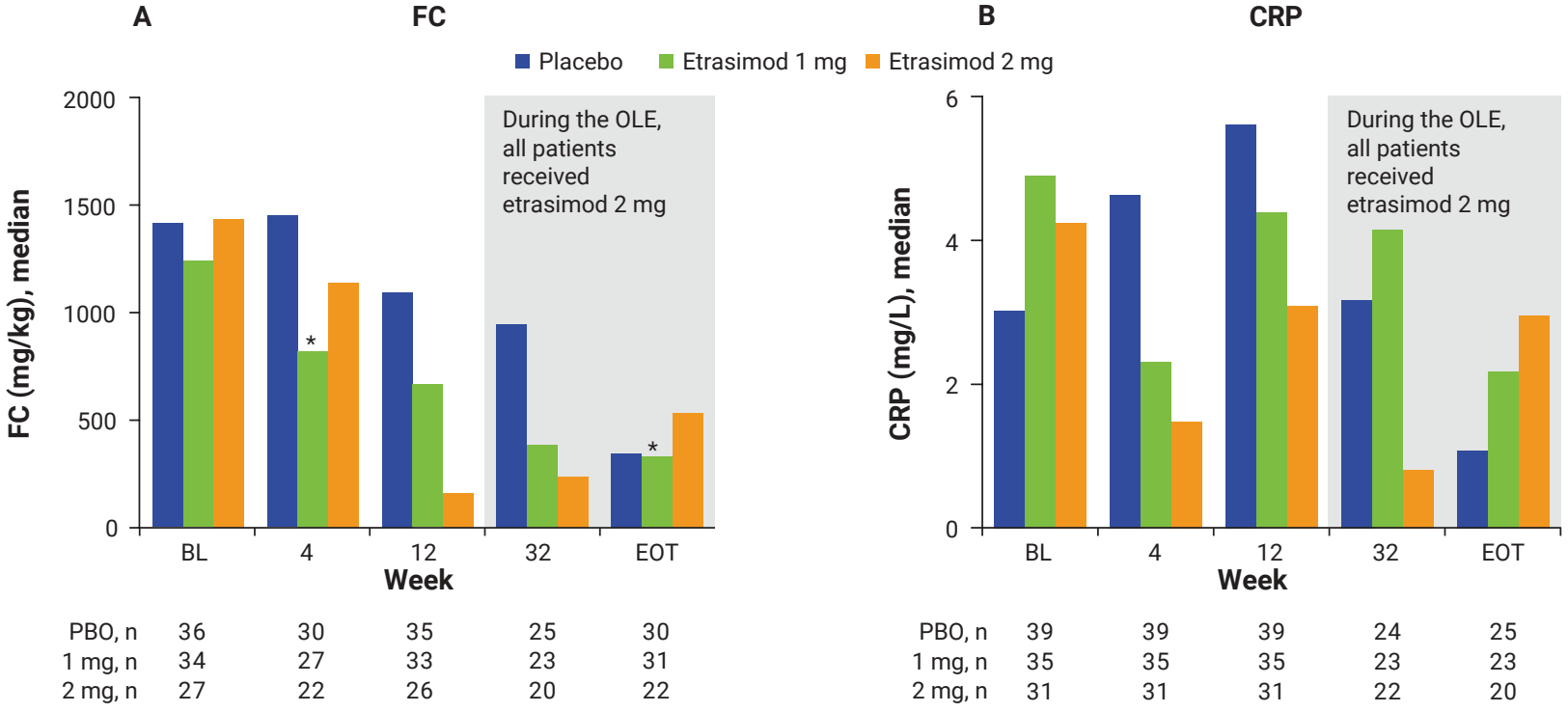
EFFICACY

- At EOT, 70% of patients overall had a clinical response, 35% were in clinical remission, and 45% had endoscopic improvement[2]
- Among evaluable patients that completed the OLE, clinical response, clinical remission, or endoscopic improvement was sustained from DB study Week 12 to OLE EOT in 92%, 67%, and 74% of patients, respectively. In the group that received etrasimod 2 mg throughout both studies the proportions were 93%, 75%, and 77%, respectively.[2]

BIOMARKER ANALYSES

- Overall, patients in the mITT evaluable cohort had a median decrease in FC of 601.1 mg/kg (P = 0.003) at EOT compared with DB baseline (**Figure 2A**)
  - For each treatment group, CRP trended toward a decrease from baseline (**Figure 2B**)

Figure 2. FC and CRP Levels Over Time by DB Treatment Group



	BL	4	12	32	EOT
PBO, n	36	30	35	25	30
1 mg, n	34	27	33	23	31
2 mg, n	27	22	26	20	22

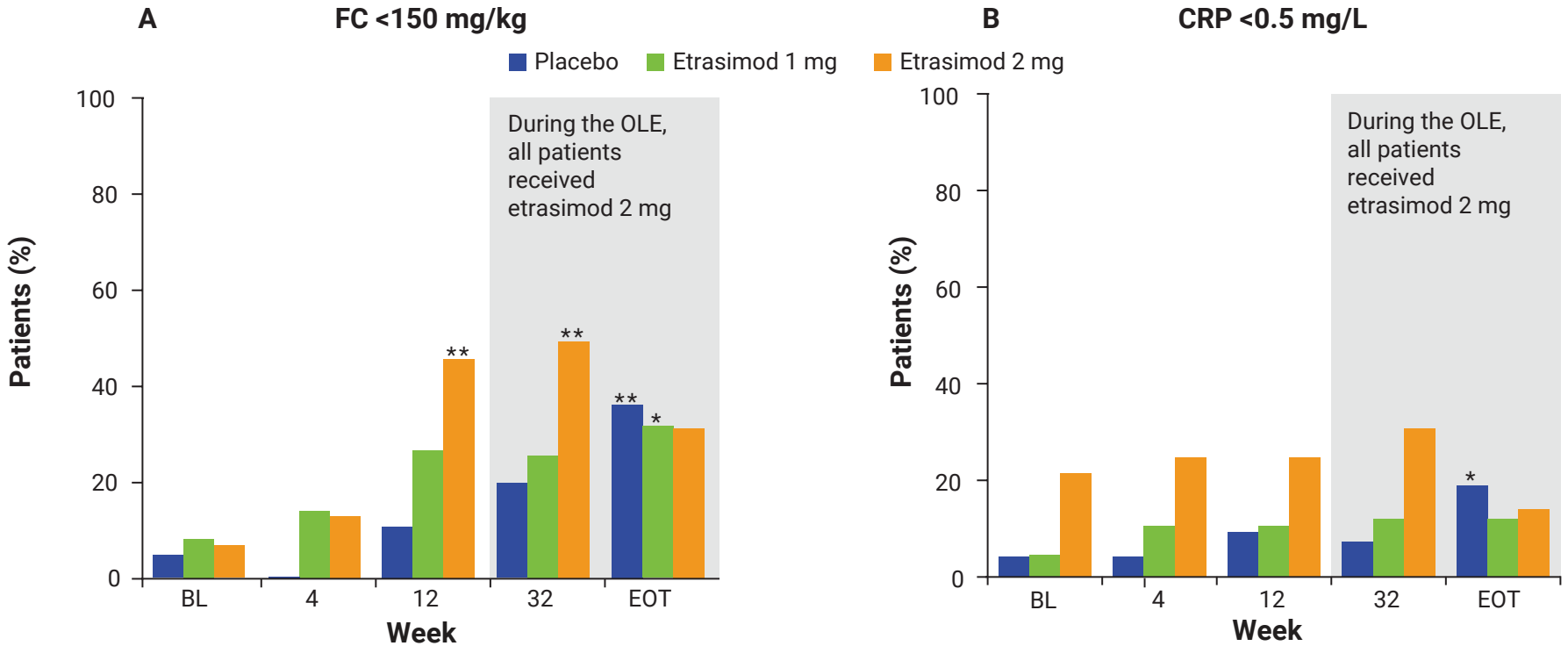
	BL	4	12	32	EOT
PBO, n	39	39	39	24	25
1 mg, n	35	35	35	23	23
2 mg, n	31	31	31	22	20

BL, double-blind baseline; PBO, placebo
*P < 0.05; P value indicates within-subject pair comparison at visit vs BL

RESULTS (Cont'd)

- The percentage of patients with normalized FC (<150 mg/kg) progressively increased after receiving etrasimod 2 mg (**Figure 3A**)
  - By EOT approximately 34% of patients in the mITT evaluable cohort had normalized FC levels, irrespective of DB treatment
  - The percentage of patients with normalized CRP (<0.5 mg/L) trended toward an increase for each treatment group compared with DB baseline (**Figure 3B**)

Figure 3. Percentage of Patients With Normalization of (A) FC (<150 mg/kg) and (B) CRP (<0.5 mg/L) by DB Treatment Group



	BL	4	12	32	EOT
PBO, n	36	30	35	25	30
1 mg, n	34	27	33	23	31
2 mg, n	27	22	26	20	22

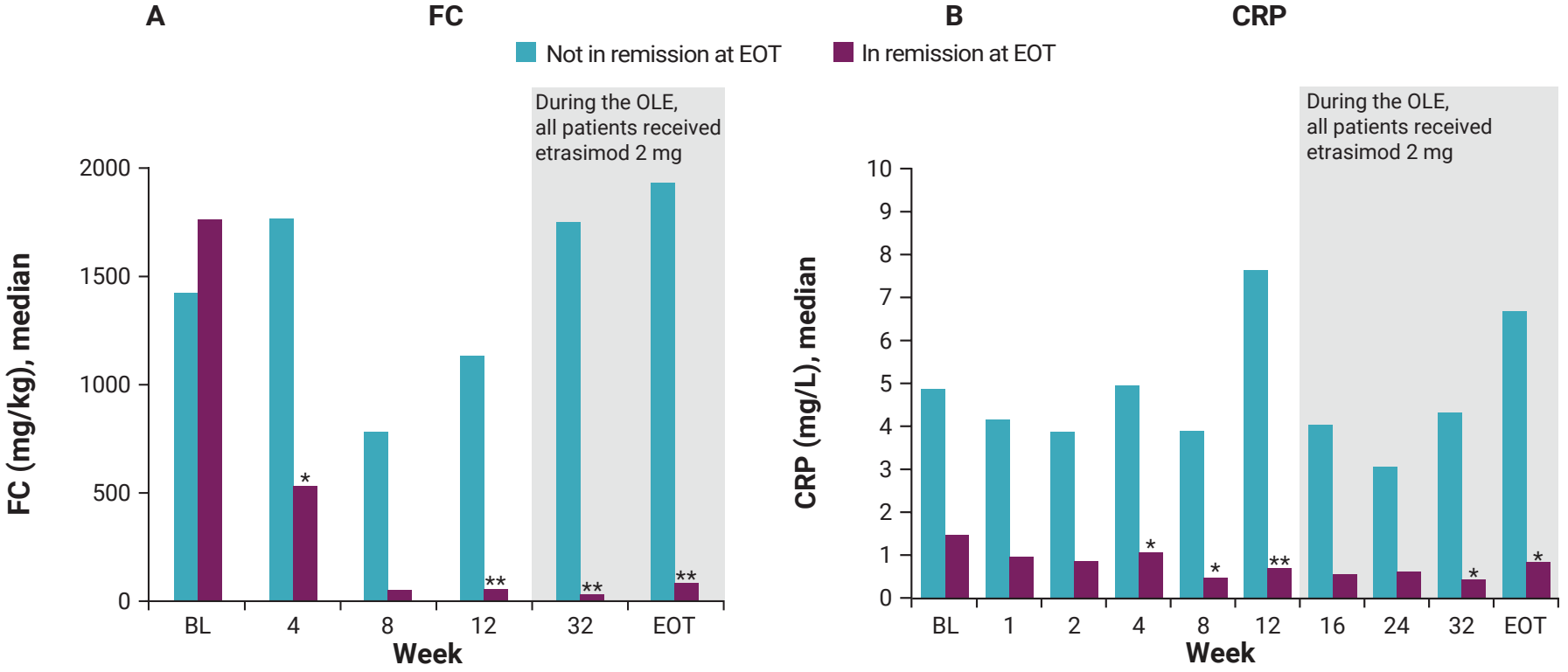
	BL	4	12	32	EOT
PBO, n	39	39	39	24	25
1 mg, n	35	35	35	23	23
2 mg, n	31	31	31	22	20

*P < 0.05 vs baseline; **P < 0.01 vs baseline

RESULTS (Cont'd)

- Patients who received etrasimod 2 mg throughout the DB study and OLE and were in clinical remission by EOT had significantly lower levels of FC (**Figure 4A**) and CRP (**Figure 4B**) at Weeks 4, 12, 32, and EOT compared with patients who were not in remission
  - CRP was also significantly lower at Week 8 in patients who were in remission at EOT (**Figure 4B**)

Figure 4. (A) FC and (B) CRP Levels Over Time in Patients Treated With Etrasimod 2 mg Throughout the DB Study and OLE by Clinical Remission Status at EOT



	BL	4	8	12	32	EOT
Non-remitters, n	17	13	16	16	12	12
Remitters, n	10	9	9	10	8	10

	BL	1	2	4	8	12	16	24	32	EOT
Non-remitters, n	20	20	20	20	20	20	14	14	13	9
Remitters, n	11	11	11	11	11	11	9	9	9	11

*$P < 0.05$ vs non-remitters; **$P < 0.01$ vs non-remitters

RESULTS (Cont'd)

- Strong (>0.5) correlations were observed between mMCS and FC and between endoscopic outcomes and FC; moderate (0.3 to ≤0.5) correlations were observed between mMCS and CRP and between endoscopic outcomes and CRP (**Table 1**)
  - There was a moderate correlation between FC and CRP in patients receiving etrasimod 2 mg during the OLE and a strong correlation between FC and CRP in patients receiving etrasimod 2 mg throughout the DB study and OLE

Table 1. Correlation Analysis of Clinical and Endoscopic Disease Activity, FC Level, and CRP Level at EOT

Variables Compared	DB Study: Etrasimod 2 mg OLE: Etrasimod 2 mg	DB Study: Any treatment OLE: Etrasimod 2 mg
mMCS vs FC Spearman coefficient	n = 20 0.77 *P* < 0.0001	n = 79 0.61 *P* < 0.0001
Endoscopic subscore vs FC Spearman coefficient	n = 21 0.76 *P* < 0.0001	n = 81 0.59 *P* < 0.0001
mMCS vs CRP Spearman coefficient	n = 20 0.45 *P* = 0.047	n = 68 0.39 *P* = 0.001
Endoscopic subscore vs CRP Spearman coefficient	n = 20 0.18 *P* = 0.45	n = 68 0.26 *P* = 0.034
CRP vs FC Spearman coefficient	n = 17 0.55 *P* = 0.022	n = 63 0.38 *P* = 0.002

CONCLUSIONS

- Patients with UC who received etrasimod 2 mg throughout the OLE exhibited statistically significant decreases in FC throughout the study; FC levels strongly correlated with long-term clinical and endoscopic outcomes
- FC and (to a lesser extent) CRP were useful biomarkers associated with response to therapy in patients with UC treated with etrasimod in this study

REFERENCES: 1. Sandborn WJ et al. *Gastroenterology*. 2020;158:550–561. **2.** Vermeire S et al. United European *Gastroenterol J.* 2019;7(8_supplement):352. **3.** Yarur AJ et al. *Gastroenterology.* 2019; 156(6, Supplement 1):S-1108–S-1109.

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