Impact of ozanimod on fecal calprotectin levels and the association with efficacy in patients with moderately to severely active ulcerative colitis: results from the phase 3 True North study

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Introduction

- Ozanimod is an oral sphingosine 1-phosphate (S1P) receptor modulator selectively targeting $S1P_1$ and $S1P_5$[1]
  - Binding with ozanimod results in internalization of $S1P_1$ receptors, thus reducing the egress of lymphocytes into inflamed tissue
- Ozanimod is approved in the United States and European Union for the treatment of moderately to severely active ulcerative colitis (UC)[2,3]
- The infiltration of neutrophils into intestinal mucosa contributes to inflammation in inflammatory bowel diseases[4]
- Calprotectin, a neutrophilic activity marker that indicates the number of neutrophils contributing to inflammation, is useful for monitoring disease activity in UC[5,6]

Objective

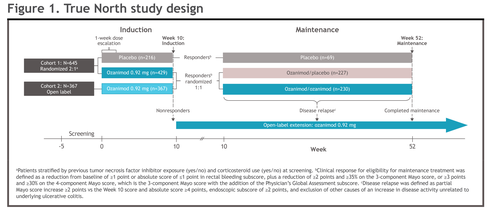
- This post hoc analysis assessed the effect of ozanimod on fecal calprotectin (FCP) levels and evaluated the association of FCP levels with disease activity and ozanimod efficacy in patients with moderately to severely active UC during the induction and maintenance periods of the phase 3 True North trial

Methods

Study design[7]

- True North was a 52-week, randomized, double-blind, placebo-controlled phase 3 trial (**Figure 1**)

Figure 1. True North study design



[a]Patients stratified by previous tumor necrosis factor inhibitor exposure (yes/no) and corticosteroid use (yes/no) at screening. [b]Clinical response for eligibility for maintenance treatment was defined as a reduction from baseline of ≥1 point or absolute score of ≤1 point in rectal bleeding subscore, plus a reduction of ≥2 points and ≥35% on the 3-component Mayo score, or ≥3 points and ≥30% on the 4-component Mayo score, which is the 3-component Mayo score with the addition of the Physician's Global Assessment subscore. [c]Disease relapse was defined as partial Mayo score increase ≥2 points vs the Week 10 score and absolute score >4 points, endoscopic subscore of ≥2 points, and exclusion of other causes of an increase in disease activity unrelated to underlying ulcerative colitis.

Endpoints

- Efficacy endpoints (ie, clinical remission, clinical response, endoscopic improvement, mucosal healing, and histologic remission) were assessed at Weeks 10 and 52
- FCP levels were assessed at baseline and at Weeks 10 and 52

Analyses

- Adjusted mean percent changes from baseline in FCP levels were calculated for Weeks 10 and 52 in the total patient population, as well as in subgroups of patients based on Week 10 or Week 52 clinical response status, prior biologic exposure status, and prior tumor necrosis factor inhibitor (TNFi) exposure status
- The predictive and prognostic values of baseline FCP levels or changes in FCP levels for Week 10 or Week 52 efficacy endpoints were assessed using logistic regression
  - The model included treatment groups, baseline biomarkers or changes (continuous log2-transformed) in biomarkers, and biomarker-by-treatment group interaction, with adjustment for covariates of baseline Mayo score, age, gender, and stratification factors
  - Interaction-effect plots for continuous biomarkers, model estimates (eg, baseline biomarkers, baseline treatment by biomarker), and unadjusted *P*-values were determined

Patients

- Baseline demographic and clinical characteristics, including baseline FCP levels, were similar in patients receiving ozanimod or placebo during the induction period (**Table 1**)

Table 1. Demographics and disease characteristics at baseline of the induction period

Characteristic	Cohort 1 Placebo (N=216)	Cohort 1 Ozanimod (N=429)	Cohort 2 Ozanimod (N=367)
Male, n (%)	143 (66.2)	245 (57.1)	214 (58.3)
Age, y, mean ± SD	41.9 ± 13.6	41.4 ± 13.5	42.1 ± 13.7
Body mass index, kg/m², mean ± SD	25.1 ± 4.5	25.4 ± 5.5	25.9 ± 5.8
Time since UC diagnosis, y, mean ± SD	6.8 ± 7.0	6.9 ± 6.6	7.9 ± 7.4
Extent of UC disease, n (%)			
Left-sided	134 (62.0)	268 (62.5)	237 (64.6)
Extensive	82 (38.0)	161 (37.5)	130 (35.4)
Mayo score, mean ± SD			
Total score[a]	8.9 ± 1.4	8.9 ± 1.5	9.1 ± 1.5
3-component score[b]	6.6 ± 1.2	6.6 ± 1.2	6.8 ± 1.3
FCP levels, µg/g			
Median	1350	1080	1260
Interquartile range	345-3075	399-2532	421-2881
C-reactive protein, mg/L			
Median	5.0	4.0	5.0
Interquartile range	2.0-12.0	1.0-9.0	2.0-11.0
Corticosteroid use at screening, n (%)	70 (32.4)	119 (27.7)	124 (33.8)
Prior medication use, n (%)			
Corticosteroids	162 (75.0)	322 (75.1)	286 (77.9)
Immunomodulators	93 (43.1)	174 (40.6)	166 (45.2)
TNF inhibitors	65 (30.1)	130 (30.3)	159 (43.3)

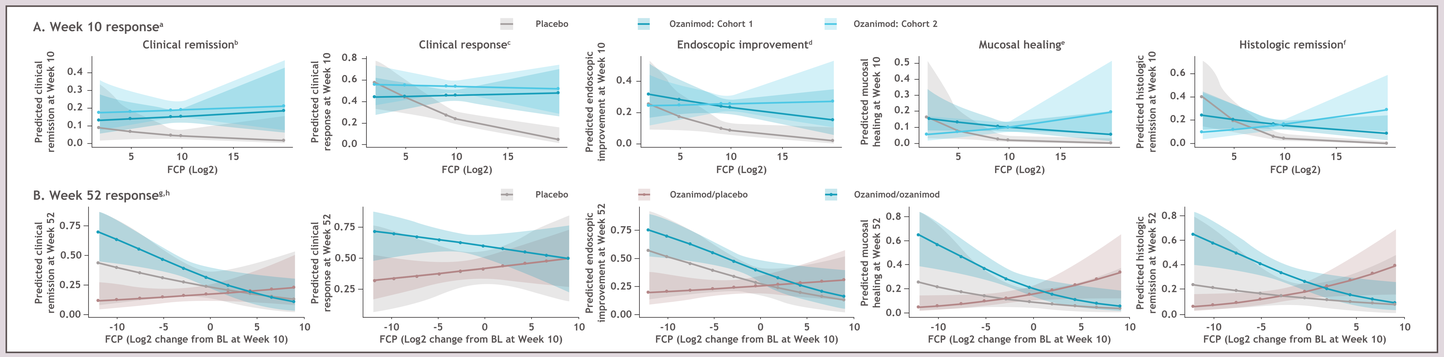
[a]The total Mayo score is defined as the sum of the RBS, SFS, Physician's Global Assessment subscore, and endoscopy subscore. Overall scores range from 0 to 12 (with each subscore on a scale from 0 to 3), with higher scores indicating greater activity. Scores were assessed by a central reader. [b]The 3-component Mayo score is defined as the sum of the RBS, SFS, and endoscopy subscore. Overall scores range from 0 to 9 (with each subscore on a scale from 0 to 3), with higher scores indicating greater activity. Scores were assessed by a central reader.
FCP, fecal calprotectin; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore; TNF, tumor necrosis factor; UC, ulcerative colitis.

Changes in FCP levels from baseline to Week 10

- Patients receiving ozanimod demonstrated a significant reduction from baseline in FCP levels compared with those receiving placebo (**Figure 2**)
- Reductions from baseline in FCP levels were significantly greater in patients with versus without clinical response at Week 10 in all treatment groups (**Figure 3**)

FCP levels were predictive for ozanimod response and prognostic for disease activity

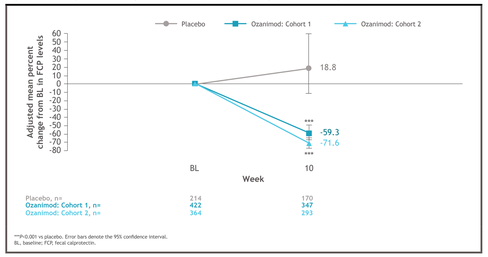
Figure 8. Predictive and prognostic values of (A) BL FCP levels for Week 10 response and (B) changes in FCP levels at Week 10 for Week 52 response



[a]Predictive effects were significant for ozanimod clinical response (Cohort 1, *P*<0.01; Cohort 2, *P*=0.03), mucosal healing (Cohort 2, *P*=0.01), and histologic remission (Cohort 1, *P*=0.02; Cohort 2, *P*<0.001). [b]Clinical remission is defined as RBS=0, SFS ≤1 (and a decrease of ≥1 point from BL SFS), and endoscopy subscore ≤1. [c]Clinical response is defined as reduction from BL in the 9-point Mayo score (sum of the RBS, SFS, and endoscopy subscore) of ≥2 points and ≥35%, and a reduction from BL in the RBS of ≥1 point or an absolute RBS of ≤1 point. [d]Endoscopic improvement is defined as endoscopy subscore of ≤1 point. [e]Mucosal healing is defined as endoscopy subscore ≤1 point and a Geboes index score <2.0. [f]Histologic remission is defined as Geboes index score <2.0. [g]All placebo, ozanimod/placebo, and ozanimod/ozanimod patients were responders at Week 10. [h]Predictive effects were significant for ozanimod clinical remission (*P*=0.02), endoscopic improvement (*P*=0.02), mucosal healing (*P*<0.001), and histologic remission (*P*<0.001). Prognostic effects were significant for clinical remission (*P*=0.01), endoscopic improvement (*P*=0.01), mucosal healing (*P*=0.004), and histologic remission (*P*=0.01).
BL, baseline; FCP, fecal calprotectin; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

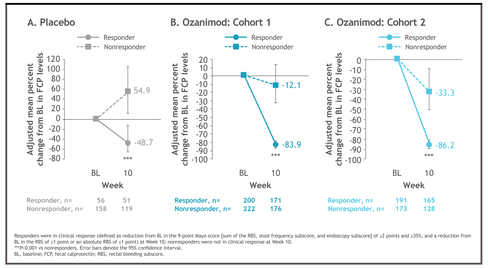
- Significantly greater reductions from baseline in FCP levels occurred with ozanimod compared with placebo, regardless of prior biologic exposure status (**Figure 4A-B**) or prior TNFi exposure status (**Figure 4C-D**)

Figure 2. Mean percent change from BL in FCP levels during the induction period



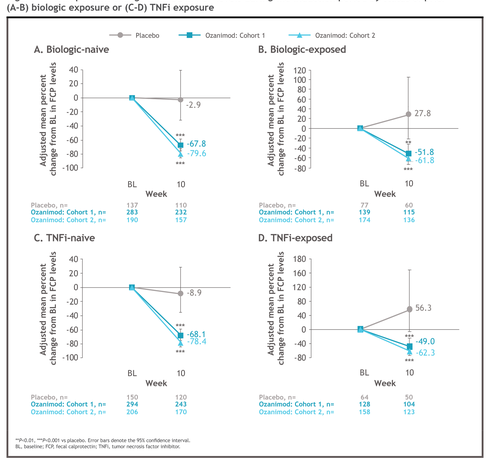
***P<0.001 vs placebo. Error bars denote the 95% confidence interval.
BL, baseline; FCP, fecal calprotectin.

Figure 3. Mean percent change from BL in FCP levels during the induction period by Week 10 clinical response status for patients receiving (A) placebo, (B) double-blind ozanimod, and (C) open-label ozanimod



Responders were in clinical response (defined as reduction from BL in the 9-point Mayo score [sum of the RBS, stool frequency subscore, and endoscopy subscore] of ≥2 points and ≥35%, and a reduction from BL in the RBS of ≥1 point or an absolute RBS of ≤1 point) at Week 10; nonresponders were not in clinical response at Week 10.
***P<0.001 vs nonresponders. Error bars denote the 95% confidence interval.
BL, baseline; FCP, fecal calprotectin; RBS, rectal bleeding subscore.

Figure 4. Mean percent change from BL in FCP levels during the induction period by status of prior (A-B) biologic exposure or (C-D) TNFi exposure

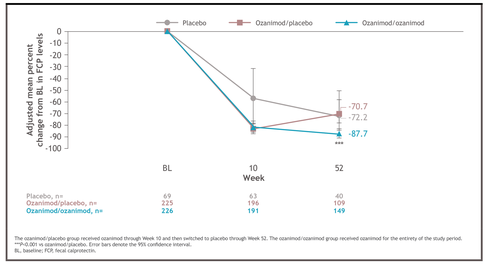


**P<0.01, ***P<0.001 vs placebo. Error bars denote the 95% confidence interval.
BL, baseline; FCP, fecal calprotectin; TNFi, tumor necrosis factor inhibitor.

Changes in FCP levels from baseline to Week 52

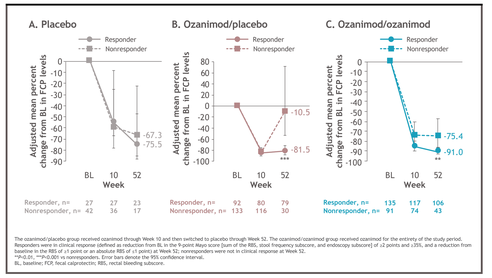
- Reductions from baseline in FCP levels were maintained through Week 52 of the maintenance period; patients who continued ozanimod had significantly greater reductions from baseline in FCP levels at Week 52 compared with patients who switched to placebo (**Figure 5**)
- Reductions from baseline in FCP levels were significantly greater in patients with versus without clinical response at Week 52 in those who continued ozanimod and in those who switched to placebo (**Figure 6**)
- Significantly greater reductions from baseline in FCP levels occurred in patients who continued ozanimod compared with those who switched to placebo, regardless of prior biologic-exposure status (**Figure 7A-B**) or prior TNFi-exposure status (**Figure 7C-D**)

Figure 5. Mean percent change from BL in FCP levels during the maintenance period



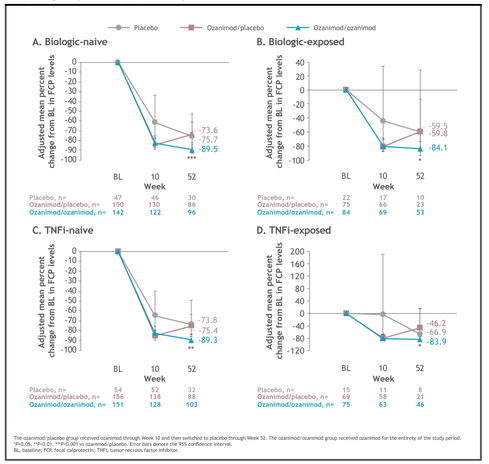
The ozanimod/placebo group received ozanimod through Week 10 and then switched to placebo through Week 52. The ozanimod/ozanimod group received ozanimod for the entirety of the study period.
***P<0.001 vs ozanimod/placebo. Error bars denote the 95% confidence interval.
BL, baseline; FCP, fecal calprotectin.

Figure 6. Mean percent change from BL in FCP levels during the maintenance period by Week 52 clinical response status for patients receiving (A) placebo, (B) ozanimod to Week 10 then placebo, and (C) continuous ozanimod



The ozanimod/placebo group received ozanimod through Week 10 and then switched to placebo through Week 52. The ozanimod/ozanimod group received ozanimod for the entirety of the study period. Responders were in clinical response (defined as reduction from BL in the 9-point Mayo score [sum of the RBS, stool frequency subscore, and endoscopy subscore] of ≥2 points and ≥35%, and a reduction from baseline in the RBS of ≥1 point or an absolute RBS of ≤1 point) at Week 52; nonresponders were not in clinical response at Week 52.
*P<0.05, **P<0.01, ***P<0.001 vs nonresponders. Error bars denote the 95% confidence interval.
BL, baseline; FCP, fecal calprotectin; RBS, rectal bleeding subscore.

Figure 7. Mean percent change from BL in FCP levels during the maintenance period by status of prior (A-B) biologic exposure or (C-D) TNFi exposure



The ozanimod/placebo group received ozanimod through Week 10 and then switched to placebo through Week 52. The ozanimod/ozanimod group received ozanimod for the entirety of the study period.
*P<0.05, **P<0.01, ***P<0.001 vs ozanimod/placebo. Error bars denote the 95% confidence interval.
BL, baseline; FCP, fecal calprotectin; TNFi, tumor necrosis factor inhibitor.

Predictive and prognostic value of FCP levels

- Baseline FCP levels were predictive for clinical response, mucosal healing, and histologic remission at Week 10 (**Figure 8A**)
- Reductions from baseline in FCP levels at Week 10 were predictive and prognostic for all endpoints except clinical response at Week 52 (**Figure 8B**)

Conclusions

- Ozanimod led to significant reductions in FCP levels, which were indicative of decreases in intestinal neutrophil levels
  - Reductions in FCP levels were greater in patients who achieved clinical response than in those who did not
  - Reductions in FCP levels occurred with ozanimod regardless of whether patients had prior biologic or TNFi exposure
- Baseline FCP levels were predictive for ozanimod response at Week 10
- Reductions in FCP levels at Week 10 were predictive and prognostic for response at Week 52
- These findings may help support the use of FCP levels as a predictive biomarker for ozanimod response and as a prognostic biomarker in UC

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Disclosures

SHa, SHu, CW, and AP: employees and/or shareholders of Bristol Myers Squibb. **RM:** employee of Bristol Myers Squibb. **YL:** employee of Parexel International and consultant for Bristol Myers Squibb.

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