Association between absolute lymphocyte count and ozanimod efficacy and safety in patients with moderately to severely active ulcerative colitis: results from the phase 3 True North study

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Introduction

- Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator selectively targeting $S1P_1$ and $S1P_{1,5}$,[1] is approved in the United States and European Union for the treatment of adults with moderately to severely active ulcerative colitis (UC).[2,3]
- Binding with ozanimod results in internalization of $S1P_1$ receptors, which subsequently reduces the egress of lymphocyte subsets from lymphoid tissue into the circulation; this can be monitored by measurement of absolute lymphocyte count (ALC).[1,4]
- In True North, ozanimod treatment led to reductions in ALCs; these reductions were reversed upon treatment discontinuation, further establishing ALC as a good pharmacodynamic biomarker for ozanimod[5]

Objective

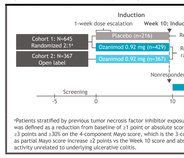
- This post hoc analysis assessed whether ALC was associated with disease activity or predictive of ozanimod efficacy or safety in patients with moderately to severely active UC during the induction and maintenance periods of the phase 3 True North trial

Methods

Study design[6]

- 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. [b]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.

Outcomes and endpoints

- The following clinical scores were assessed at baseline and at Weeks 10 and 52:
  - Total Mayo score, partial Mayo score, 9-point Mayo score, rectal bleeding subscore (RBS), stool frequency subscore (SFS), Physician's Global Assessment (PGA) subscore, and endoscopy subscore
- The following efficacy endpoints were assessed at Weeks 10 and 52:
  - Clinical remission, clinical response, endoscopic improvement, mucosal healing, and histologic remission
- Treatment-emergent adverse events (TEAEs) and ALCs were evaluated at baseline and at Weeks 5, 10, 18, 28, 40, and 52

Analyses

- Adjusted mean percent change from baseline in ALC was calculated for Weeks 5, 10, 18, 28, 40, and 52 in the total patient population and in subgroups of patients based on the occurrences of overall TEAEs and infection-related TEAEs
- Spearman's *rho* correlation coefficients were calculated to assess the relationship between:
  - Baseline ALC and baseline disease characteristics
  - Baseline ALC and change from baseline in clinical outcomes at Weeks 10 and 52
  - Change from baseline in ALC at Week 10 and change from baseline in clinical outcomes at Weeks 10 and 52
- The predictive and prognostic values of baseline ALC or changes in ALC for Weeks 10 and 52 efficacy endpoints were assessed using logistic regression
  - The model included treatment groups, baseline biomarkers or changes in biomarkers (continuous log2-transformed), 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 (ie, baseline biomarkers and baseline treatment by biomarker), and unadjusted *P*-values were determined

Results

Patients

- Baseline demographic and clinical characteristics, including baseline ALC, were similar between groups during the induction period (**Table 1**)

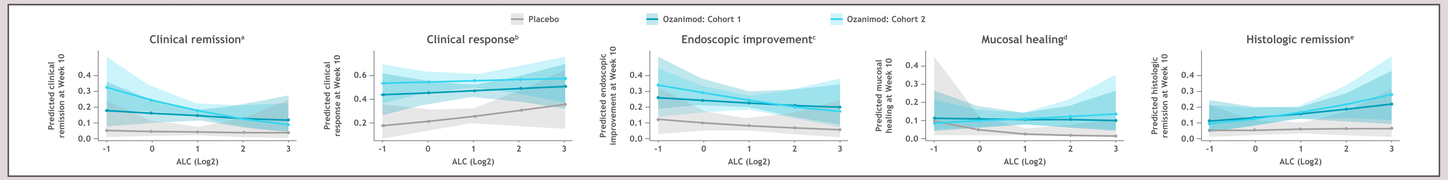
Table 1. Demographics and disease characteristics at baseline of the induction period

Characteristic	Cohort 1		Cohort 2
	Placebo (N=216)	Ozanimod (N=429)	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/m^2, 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
Fecal calprotectin, µg/g			
Median	1350	1080	1260
Interquartile range	345-3075	399-2532	421-2881
CRP, mg/liter			
Median	5.0	4.0	5.0
Interquartile range	2.0-12.0	1.0-9.0	2.0-11.0
ALC, 10^9/L, mean ± SD	1.9 ± 1.1	2.0 ± 0.9	1.9 ± 0.8
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)
Immunodilators	93 (43.1)	174 (40.6)	166 (45.2)
TNF inhibitor	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.
ALC, absolute lymphocyte count; CRP, C-reactive protein; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore; TNF, tumor necrosis factor; UC, ulcerative colitis.

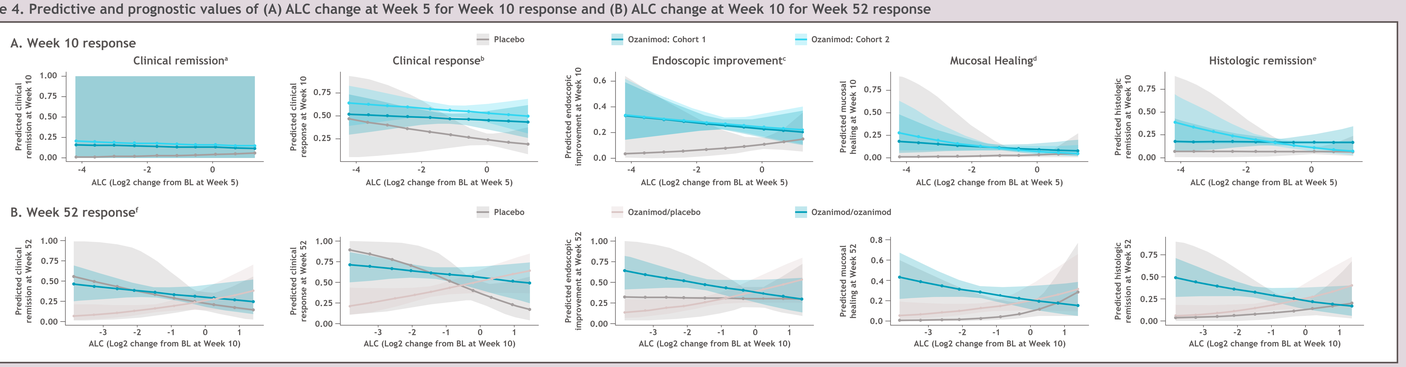
ALC was not predictive for ozanimod response or prognostic for disease activity

Figure 2. Predictive and prognostic values of baseline ALC for Week 10 response



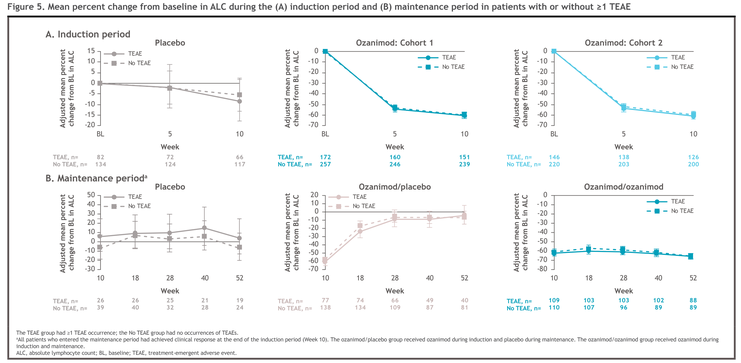
[a]Clinical remission is defined as RBS=0, SFS ≤1 (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1. [b]Clinical response is defined as reduction from baseline in the 9-point Mayo score (sum of the RBS, SFS, and endoscopy subscore) of ≥2 points and ≥35%, and a reduction from baseline in the RBS of ≥1 point or an absolute RBS of ≤1 point. [c]Endoscopic improvement is defined as endoscopy subscore of ≤1 point. [d]Mucosal healing is defined as endoscopy subscore ≤1 point and a Geboes index score <2.0. [e]Histologic remission is defined as a Geboes index score <2.0.
ALC, absolute lymphocyte count; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 4. Predictive and prognostic values of (A) ALC change at Week 5 for Week 10 response and (B) ALC change at Week 10 for Week 52 response



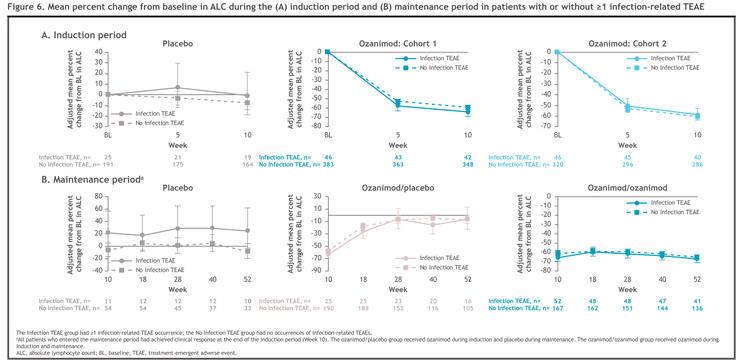
[a]Clinical remission is defined as RBS=0, SFS ≤1 (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1. [b]Clinical response is defined as reduction from baseline in the 9-point Mayo score (sum of the RBS, SFS, and endoscopy subscore) of ≥2 points and ≥35%, and a reduction from baseline in the RBS of ≥1 point or an absolute RBS of ≤1 point. [c]Endoscopic improvement is defined as endoscopy subscore of ≤1 point. [d]Mucosal healing is defined as endoscopy subscore ≤1 point and a Geboes index score <2.0. [e]Histologic remission is defined as a Geboes index score <2.0. [f]All placebo, ozanimod/placebo, and ozanimod/ozanimod patients were responders at Week 10.
ALC, absolute lymphocyte count; BL, baseline; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 5. Mean percent change from baseline in ALC during the (A) induction period and (B) maintenance period in patients with or without ≥1 TEAE



The TEAE group had ≥1 TEAE occurrence; the No TEAE group had no occurrences of TEAEs.
[a]All patients who entered the maintenance period had achieved clinical response at the end of the induction period (Week 10). The ozanimod/placebo group received ozanimod during induction and placebo during maintenance. The ozanimod/ozanimod group received ozanimod during induction and maintenance.
ALC, absolute lymphocyte count; BL, baseline; TEAE, treatment-emergent adverse event.

Figure 6. Mean percent change from baseline in ALC during the (A) induction period and (B) maintenance period in patients with or without ≥1 infection-related TEAE



The Infection TEAE group had ≥1 infection-related TEAE occurrence; the No Infection TEAE group had no occurrences of infection-related TEAEs.
[a]All patients who entered the maintenance period had achieved clinical response at the end of the induction period (Week 10). The ozanimod/placebo group received ozanimod during induction and placebo during maintenance. The ozanimod/ozanimod group received ozanimod during induction and maintenance.
ALC, absolute lymphocyte count; BL, baseline; TEAE, treatment-emergent adverse event.

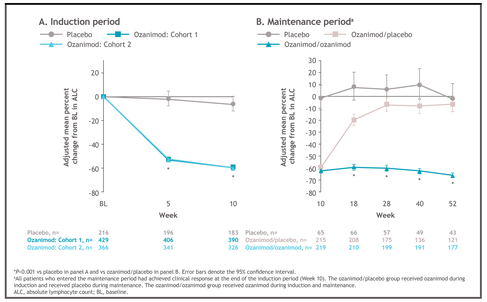
Baseline ALC

- Baseline ALC was very weakly correlated with baseline clinical scores (ie, Mayo scores, PGA subscore, and endoscopy subscore); Spearman's *rho* correlation coefficients were all ≤0.1
- Baseline ALC was not significantly correlated with clinical outcomes (ie, changes from baseline in Mayo score, RBS, SFS, PGA subscore, and endoscopy subscore) at Weeks 10 and 52 in patients receiving ozanimod or placebo
- Baseline ALC was not significantly predictive or prognostic for Week 10 (**Figure 2**) and Week 52 responses based on all efficacy endpoints assessed (*P*>0.05 for all efficacy endpoints)

Change in ALC

- Reductions from baseline in mean ALC occurred by Week 5 of the induction period with ozanimod and were significantly greater in patients who received ozanimod than placebo (**Figure 3A**)
- ALC reductions plateaued by Week 10 (end of induction and start of maintenance) and were maintained through Week 52 (end of maintenance) in patients on continuous ozanimod (**Figure 3A-B**)
- ALC returned to placebo levels by Week 52 in patients who switched to placebo for the maintenance period (**Figure 3B**)
- Change from baseline in ALC at Week 10 was generally not significantly correlated with change from baseline in clinical outcomes at Week 10 or Week 52
  - However, there was a weak significant correlation with change from baseline in RBS at Week 10 in patients who received ozanimod during induction (Spearman's *rho* correlation coefficient = 0.11; *P*<0.05)
- Based on all efficacy endpoints assessed, change from baseline in ALC at Week 5 was not significantly predictive of Week 10 response in patients treated with ozanimod (*P*>0.05 for all efficacy endpoints) (**Figure 4A**)
- Similarly, change from baseline in ALC at Week 10 was not significantly associated with Week 52 response in patients on continuous ozanimod (*P*>0.05 for all efficacy endpoints) (**Figure 4B**)
- Reductions from baseline in ALC at all weeks were similar in placebo- and ozanimod-treated patients with or without the occurrence of ≥1 TEAE (**Figure 5A-B**) and with or without the occurrence of infection-related TEAEs (**Figure 6A-B**)

Figure 3. Mean percent change from baseline in ALC



[a]*P*<0.001 vs placebo in panel A and vs ozanimod/placebo in panel B. Error bars denote the 95% confidence interval.
[b]All patients who entered the maintenance period had achieved clinical response at the end of the induction period (Week 10). The ozanimod/placebo group received ozanimod during induction and received placebo during maintenance. The ozanimod/ozanimod group received ozanimod during induction and maintenance.
ALC, absolute lymphocyte count; BL, baseline.

Conclusions

- ALC reductions occurring with ozanimod were reversed upon treatment discontinuation and were not associated with the occurrence of TEAEs
- Baseline ALC and ALC reductions were generally not correlated with clinical outcomes and were not predictive or prognostic for response
- These findings support the use of ALC as a pharmacodynamic biomarker but not as a prognostic biomarker for UC or as a predictive biomarker for ozanimod response

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SHa, CW, SHu, and AP: employees and/or shareholders of Bristol Myers Squibb. **RM:** employee of Bristol Myers Squibb.

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