Ozanimod is an effective oral treatment for patients with ulcerative colitis regardless of baseline endoscopic disease distribution: a post hoc analysis of 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 $S1P_5$, prevents lymphocyte migration from lymphoid tissues; this results in decreased levels of circulating lymphocyte subsets[1-3]
- Ozanimod is approved in the United States and European Union for the treatment of moderately to severely active ulcerative colitis (UC)[2,3]
- The pivotal, phase 3 True North trial (NCT02435992) demonstrated ozanimod efficacy and tolerability over 52 weeks in patients with moderately to severely active UC[4]
- Patients with extensive colitis may have increased symptomatology and a higher risk of colectomy than patients with left-sided UC[5]

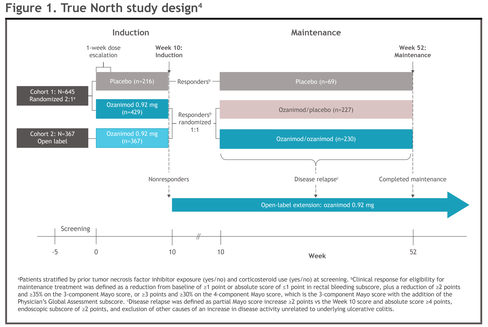
Objective

- This post hoc analysis from the phase 3 True North trial evaluated the association of baseline endoscopic disease distribution (left-sided colitis vs extensive colitis) on clinical outcomes in patients with moderately to severely active UC who were treated with ozanimod

Methods

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

Figure 1. True North study design[4]



[a]Patients stratified by prior 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.

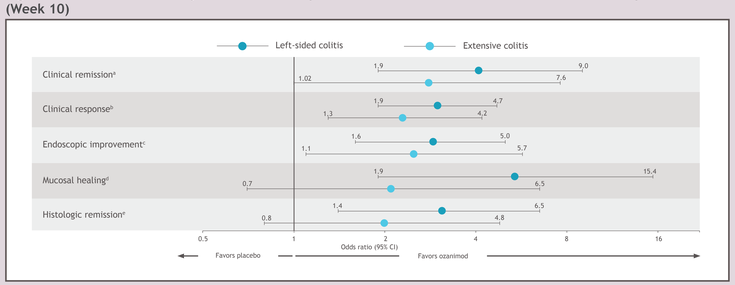
- This analysis from True North evaluated ozanimod efficacy at Weeks 10 and 52 in 2 subgroups of patients with moderately to severely active UC with left-sided vs extensive colitis at baseline
- Patients enrolled in True North completed an endoscopy at screening to confirm disease extent
- Multiple clinical efficacy endpoints were evaluated in this analysis
- Odds ratio (ozanimod/placebo), treatment difference, 2-sided 95% Wald CI, and *P*-value for comparison between the ozanimod and placebo groups were evaluated based on the Cochran-Mantel-Haenszel test
  - Induction phase: results were stratified by corticosteroid use at screening and by prior use of anti–tumor necrosis factor (TNF)
  - Maintenance phase: results were stratified by remission status at Week 10 and corticosteroid use at Week 10

Results

- Of the total True North population (N=1012), a higher percentage of patients had left-sided colitis (63.1%) than extensive colitis (36.9%) at baseline
- Overall, the demographics and disease characteristics were generally similar in patients with left-sided and extensive colitis at baseline (**Table 1**)
  - As expected, a higher percentage of patients with extensive colitis had prior exposure to anti-TNF agents, immunomodulators, or non–anti-TNF biologics than those with left-sided colitis

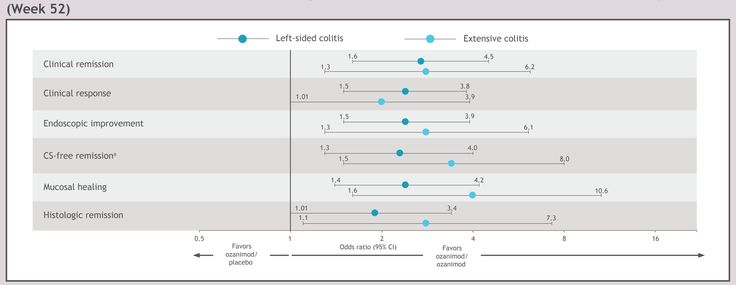
Ozanimod is similarly efficacious in patients with UC with left-sided and extensive colitis

Figure 2. Treatment effects by baseline endoscopic disease distribution in the True North induction period (Week 10)



Clinical remission and clinical response were based on the 3-component Mayo score.
[a]Clinical remission is defined as RBS–0 point, SFS ≤1 point (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1 point. [b]Clinical response is defined as a reduction from baseline in the 9-point Mayo score 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 an endoscopy subscore ≤1 point. [d]Mucosal healing is defined as an endoscopy subscore of ≤1 point and Geboes index score <2 points. [e]Histologic remission is defined as Geboes index score <2 points.
RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 3. Treatment effects by baseline endoscopic disease distribution in the True North maintenance period (Week 52)



Clinical remission and clinical response were based on the 3-component Mayo score.
[a]CS-free remission is defined as clinical remission at Week 52 while off CS for ≥12 weeks.
CS, corticosteroids.

Table 1. Demographics and disease characteristics at baseline

Parameter	Patients with left-sided colitis (n=639)	Patients with extensive colitis (n=373)
Age, y, median (Q1, Q3)	41.0 (31.0, 54.0)	38.0 (29.0, 50.0)
Male, n (%)	378 (59.2)	224 (60.1)
Race, n (%)		
White	578 (90.5)	320 (85.8)
Asian	37 (5.8)	28 (7.5)
Black or African American	17 (2.7)	11 (2.9)
Other	7 (1.1)	14 (3.8)
Age at UC diagnosis, y, median (Q1, Q3)	34.0 (26.0, 46.0)	30.0 (22.0, 41.0)
Years since UC diagnosis, median (Q1, Q3)	4.8 (1.9, 10.1)	5.3 (2.3, 10.6)
9-point Mayo score,* median (Q1, Q3)	7.0 (6.0, 8.0)	7.0 (6.0, 8.0)
Mayo endoscopic subscore, n (%)		
2 - Moderate disease	279 (43.7)	124 (33.2)
3 - Severe disease	360 (56.3)	249 (66.8)
Fecal calprotectin, mg/kg, median (Q1, Q3)	1062.5 (316.3, 2648.8)	1438.3 (525.6, 3137.2)
C-reactive protein, mg/L, median (Q1, Q3)	4.0 (1.0, 9.0)	5.0 (2.0, 13.0)
Concomitant medication use, n (%)		
Systemic corticosteroids	184 (28.8)	129 (34.6)
Oral aminosalicylates	567 (88.7)	304 (81.5)
Prior medication use, n (%)		
Prior anti-TNFs (based on IRT)	187 (29.3)	167 (44.8)
Prior immunomodulators	240 (37.6)	193 (51.7)
Prior biologics[b]	121 (18.9)	109 (29.2)

*Derived from baseline rectal bleeding, stool frequency, endoscopy, and Physician's Global Assessment subscores. [b]Includes all biologics that are not anti-TNF biologics.
IRT, interactive response technology; Q, quartile; TNF, tumor necrosis factor.

- Ozanimod treatment effects were generally similar in patients with left-sided and extensive colitis at Week 10 for most evaluated endpoints (**Figure 2**)
- The treatment effects of Week 10 responders who were rerandomized to ozanimod were generally similar for patients with left-sided and extensive colitis at Week 52 for all evaluated endpoints (**Figure 3**)
- Ozanimod was more effective than placebo in patients with left-sided and extensive colitis at Week 10 for all evaluated endpoints (**Figure 4**)
  - Among patients with left-sided colitis who achieved endoscopic improvement on ozanimod treatment (Cohorts 1 and 2 combined), 30.7% had a Mayo endoscopic subscore (MES) of 0 and 69.3% had an MES of 1
  - Among patients with extensive colitis who achieved endoscopic improvement on ozanimod treatment (Cohorts 1 and 2 combined), 17.2% had an MES of 0 and 82.8% had an MES of 1
- Week 10 clinical responders to ozanimod who were rerandomized to ozanimod in the maintenance period achieved greater efficacy at Week 52 for all evaluated endpoints than those who were rerandomized to placebo in patients with left-sided and extensive colitis (**Figure 5**)
  - Among patients with left-sided colitis who achieved endoscopic improvement on ozanimod (ozanimod/ozanimod group), 55.4% had an MES of 0 and 44.6% had an MES of 1
  - Among patients with extensive colitis who achieved endoscopic improvement on ozanimod (ozanimod/ozanimod group), 48.4% had an MES of 0 and 51.6% had an MES of 1
- At Week 10, reductions from baseline in fecal calprotectin (FCP) levels were significantly greater in ozanimod-treated patients compared with placebo in patients with left-sided and extensive colitis (**Figure 6**)
- At Week 52 in patients with left-sided and extensive colitis, the Week 10 responders who had been rerandomized to ozanimod had significantly greater reductions from baseline in FCP levels compared with those who had been rerandomized to placebo (**Figure 7**)

Figure 4. Efficacy by baseline endoscopic disease distribution in the True North induction period (Week 10)

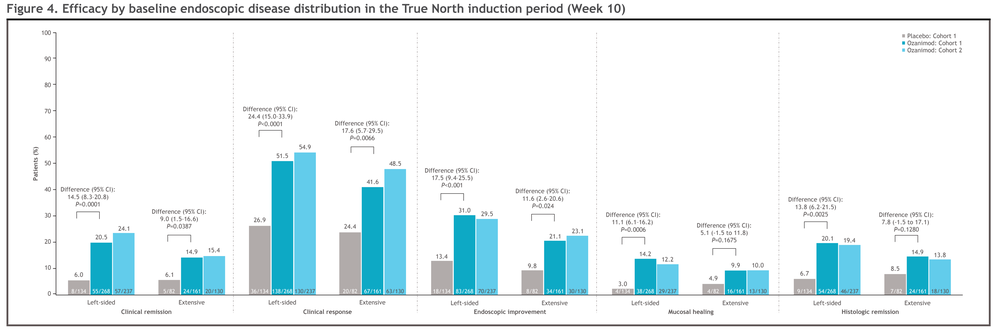
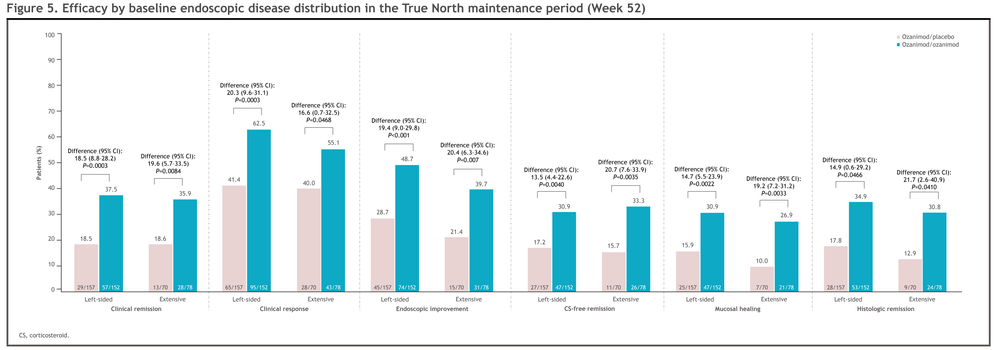
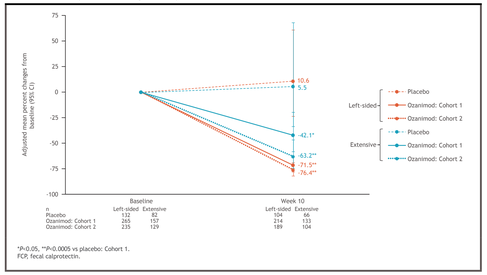


Figure 5. Efficacy by baseline endoscopic disease distribution in the True North maintenance period (Week 52)



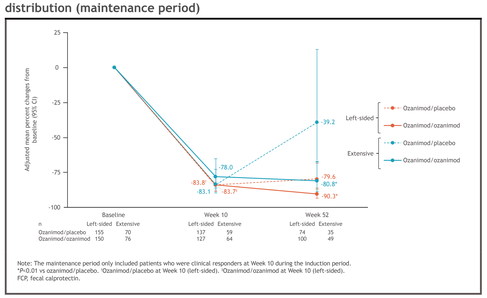
CS, corticosteroid.

Figure 6. Mean percent changes from baseline in FCP by endoscopic disease distribution (induction period)



*P<0.05, **P<0.0005 vs placebo: Cohort 1.
FCP, fecal calprotectin.

Figure 7. Mean percent changes from baseline in FCP by endoscopic disease distribution (maintenance period)



Note: The maintenance period only included patients who were clinical responders at Week 10 during the induction period.
*P<0.01 vs ozanimod/placebo. [a]Ozanimod/placebo at Week 10 (left-sided). [b]Ozanimod/ozanimod at Week 10 (left-sided).
FCP, fecal calprotectin.

Conclusions

- This analysis of True North demonstrated that ozanimod was more effective than placebo in patients with left-sided and extensive colitis at Weeks 10 and 52 for all evaluated endpoints
  - Patients with extensive disease at baseline may need a longer time to robustly achieve more stringent histologic endpoints, but these endpoints were achieved by Week 52
- Ozanimod led to reductions in FCP levels at Weeks 10 and 52 regardless of whether patients had left-sided or extensive colitis
- Ozanimod is similarly efficacious in left-sided and extensive colitis

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