Efficacy of ozanimod in vedolizumab-exposed patients with ulcerative colitis: a phase 3 True North post hoc analysis

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Introduction

- Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator selectively targeting $S1P_1$ and $S1P_5$, regulates lymphocyte migration from lymphoid tissues through S1P receptor internalization[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]
- Vedolizumab, an integrin receptor antagonist that interferes with lymphocyte trafficking to the gut,[5] is a treatment option for patients with moderately to severely active UC[6]
- The efficacy of ozanimod in patients who have been previously exposed to therapies that target lymphocyte trafficking, such as vedolizumab, has not yet been described

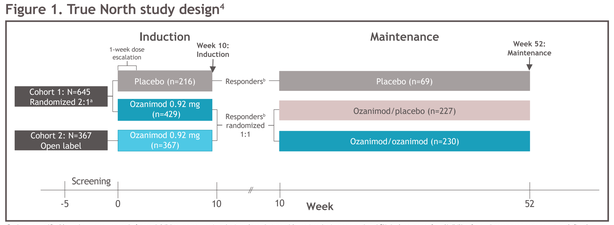
Objective

- This post hoc analysis of the True North study examined ozanimod efficacy in patients with moderately to severely active UC who were previously exposed to vedolizumab

Methods

- True North was a 52-week, randomized, double-blind, placebo-controlled phase 3 trial (**Figure 1**)
- This post hoc analysis of True North included patients who were previously exposed to vedolizumab (ie, primary and secondary nonresponders), either as the only advanced therapy or among other advanced therapies
  - Primary nonresponders had an ineffective treatment response to the initial biologic[7]
  - Secondary nonresponders had an initial effective treatment response, but the effect diminished over time[7]
- Ozanimod efficacy in the vedolizumab-exposed subgroup was assessed at the end of the induction period (Week 10) and maintenance period (Week 52)
- Differences in proportions between ozanimod and placebo at Week 10 were based on the Cochran-Mantel-Haenszel (CMH) test, and were stratified by corticosteroid use at screening and by prior anti-tumor necrosis factor (TNF) medication use
- Efficacy differences between the ozanimod/ozanimod and ozanimod/placebo arms at the end of the maintenance period (Week 52) were based on the CMH test, and were stratified by remission status and corticosteroid use at Week 10

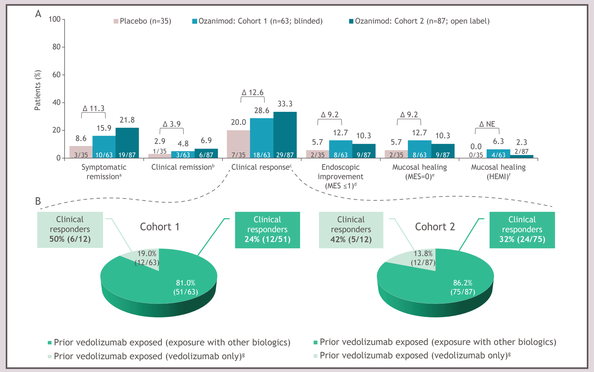
Figure 1. True North study design[4]



[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.

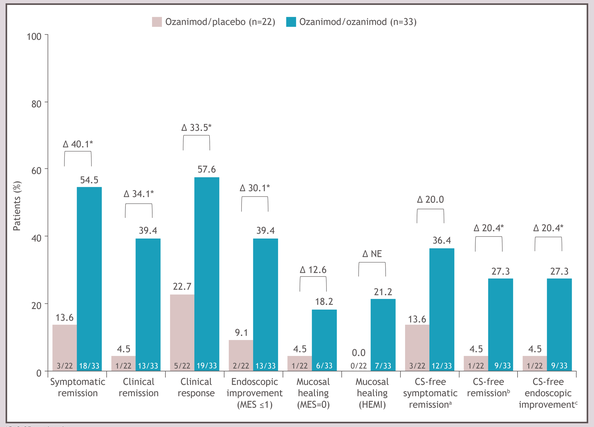
Ozanimod was effective in patients with moderate to severe UC who were previously exposed to vedolizumab therapy

Figure 3. Ozanimod efficacy of (A) all vedolizumab-exposed patients and (B) clinical responders with exposure to vedolizumab only or vedolizumab and other biologics in the induction period (Week 10)



Two different definitions of mucosal healing were assessed (MES=0 and HEMI).
[a]Symptomatic remission is defined as RBS=0 point and SFS ≤1 point, and a decrease of ≥1 point from the baseline SFS. [b]Clinical remission is defined as RBS=0 point and SFS ≤1 point, a decrease of ≥1 point from the baseline SFS, and endoscopy subscore ≤1 point. [c]Clinical response is defined as a reduction from baseline of ≥1 point or absolute score of ≤1 point in RBS, plus a reduction of ≥2 points and ≥35% on the 3-component Mayo score. [d]Endoscopic improvement is defined as endoscopy subscore of ≤1 point. [e]Mucosal healing is defined as an alternative definition of an endoscopy score of 0. [f]Mucosal healing is defined as endoscopy score of ≤1 point and Geboes index score <2.0. [g]Patients with prior vedolizumab-only exposure are a subset of the overall vedolizumab-exposed patient subgroup. There were very few patients with prior vedolizumab-only exposure in the True North study, which did not allow their evaluation during maintenance or at other objective endpoints.
Δ, difference in proportions; HEMI, histologic endoscopic mucosal improvement; MES, Mayo endoscopy score; NE, not estimable; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 4. Ozanimod efficacy of vedolizumab-exposed patients in the maintenance period (Week 52)

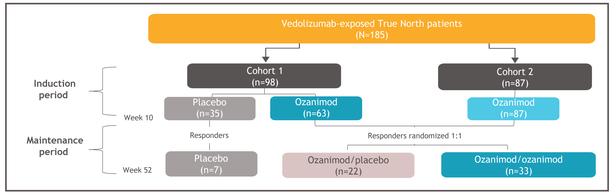


*P<0.05 vs placebo.
Note: Two different definitions of mucosal healing were assessed (ie, MES=0 and HEMI).
[a]CS-free symptomatic remission is defined as symptomatic remission at Week 52 while off CS for ≥12 weeks. [b]CS-free remission is defined as clinical remission at 52 weeks while off CS for ≥12 weeks. [c]CS-free endoscopic improvement is defined as endoscopy score of ≤1 point at Week 52 while off CS for ≥12 weeks.
Δ, difference in proportions; *, statistically significant; CS, corticosteroid; HEMI, histologic endoscopic mucosal improvement; MES, Mayo endoscopic score; NE, not estimable.

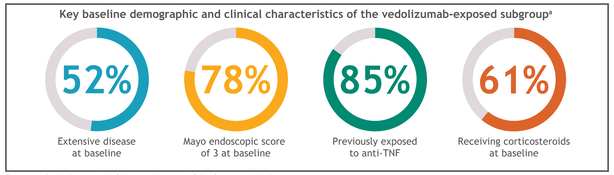
Results

- Of the 1012 total patients in True North, 185 were previously exposed to vedolizumab (**Figure 2**)

Figure 2. Disposition of vedolizumab-exposed patients in True North



- Among vedolizumab-exposed patients, baseline demographics and clinical characteristics were balanced across all treatment groups (**Table 1**)



[a]Percentages for placebo, ozanimod (Cohort 1), and ozanimod (Cohort 2) groups combined.

Table 1. Baseline demographics and clinical characteristics of vedolizumab-exposed patients in the induction period

Characteristic	Cohort 1		Cohort 2
	Placebo (n=35)	Ozanimod 0.92 mg (n=63)	Ozanimod 0.92 mg (n=87)
Age, y, mean (SD)	40.5 (14.6)	39.3 (13.7)	39.7 (12.8)
Male, n (%)	25 (71.4)	35 (55.6)	50 (57.5)
Body mass index, kg/m², mean (SD)	24.1 (3.8)	25.1 (5.6)	25.5 (7.4)
Years since UC diagnosis, mean (SD)	8.6 (7.0)	8.8 (6.5)	8.8 (6.5)
Extensive UC disease, n (%)	18 (51.4)	35 (55.6)	44 (50.6)
Corticosteroid use at screening,[a] n (%)	22 (62.9)	37 (58.7)	54 (62.1)
Prior therapies, n (%)			
5-aminosalicylic acid	33 (94.3)	60 (95.2)	84 (96.6)
Corticosteroid	33 (94.3)	62 (98.4)	84 (96.6)
Immunomodulator	27 (77.1)	46 (73.0)	71 (81.6)
Anti-TNF[b]	28 (80.0)	53 (84.1)	77 (88.5)
Disease activity			
Complete Mayo score, mean (SD)	9.6 (1.2)	9.1 (1.3)	9.6 (1.4)
9-point Mayo score, mean (SD)	7.1 (0.9)	6.8 (1.1)	7.0 (1.2)
Mayo endoscopic score, n (%)			
2	6 (17.1)	17 (27.0)	18 (20.7)
3	29 (82.9)	46 (73.0)	69 (79.3)
Biochemical markers			
C-reactive protein, mg/L, median (Q1-Q3)	5.0 (1.0-11.0)	6.0 (2.0-12.0)	5.0 (3.0-16.0)
Fecal calprotectin, mg/kg, median (Q1-Q3)	2525 (775.5-4235)	1579 (595.1-3531)	1332 (516.4-3321)

[a]Based on interactive response technology data. [b]Based on case report form data.
Q, quartile; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.

- At Week 10, ozanimod efficacy (Cohort 1) was numerically higher than placebo for all endpoints in vedolizumab-exposed patients (**Figure 3A**)
  - In patients previously exposed to vedolizumab only (ie, vedolizumab as a first-line advanced therapy), clinical response at Week 10 was achieved in 50% and 42% of ozanimod patients in Cohorts 1 and 2, respectively (**Figure 3B**)
  - In patients previously exposed to vedolizumab and other biologics, clinical response at Week 10 was achieved in 24% and 32% of ozanimod patients in Cohorts 1 and 2, respectively
- At Week 52, a higher proportion of vedolizumab-exposed patients on continuous ozanimod achieved all efficacy endpoints compared with those in the ozanimod/placebo group, with significant differences shown for symptomatic remission, clinical remission, clinical response, endoscopic improvement, corticosteroid-free remission, and corticosteroid-free endoscopic improvement (**Figure 4**)

Conclusions

- This post hoc analysis of the phase 3 True North study found that ozanimod was effective in patients with moderately to severely active UC who were previously exposed to vedolizumab, including those who failed vedolizumab alone, or following other advanced therapies
- After 52 weeks, a significantly higher proportion of vedolizumab-exposed patients who were rerandomized to ozanimod achieved symptomatic remission, clinical response, clinical remission, corticosteroid-free remission, and endoscopic improvement compared with those rerandomized to placebo
- Taken together, these data suggest that ozanimod is efficacious in patients who were previously exposed to vedolizumab
- Further studies evaluating the efficacy of ozanimod in larger cohorts of vedolizumab-exposed patients are warranted

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