Ozanimod is an effective oral treatment for patients with ulcerative colitis regardless of moderate or severe endoscopic disease activity at baseline: a post hoc analysis of the phase 3 True North study

C0387

Douglas C. Wolf,[1] Remo Panaccione,[2] Irina Blumenstein,[3] Millie Long,[4] Bincy Abraham,[5] Anjali Jain,[6] Arteid Memaj,[6] Chun Wu,[6] Vanessa Hobbs,[6] Sarah Harris,[6] James Canavan,[6] Laurent Peyrin-Biroulet[7]

[1]Atlanta Gastroenterology Associates LLC, Atlanta, GA, USA; [2]Inflammatory Bowel Disease Clinic, Calgary, Alberta, Canada; [3]Goethe University Hospital, Frankfurt, Germany; [4]UNC Chapel Hill, Chapel Hill, NC, USA; [5]Houston Methodist Academic Institute, Houston, TX, USA; [6]Bristol Myers Squibb, Princeton, NJ, USA; [7]Nancy University Hospital, Nancy, France

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 high inflammatory burden may be more challenging to treat, so disease-related factors (eg, disease extent, inflammation severity) and patient-related factors (eg, preferences, cost, comorbidities) are considered when selecting therapies for patients with UC[5,6]

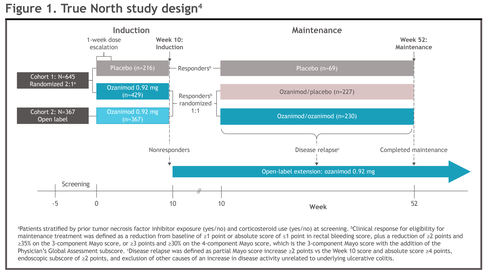
Objective

- This post hoc analysis from the phase 3 True North trial assessed the impact of baseline endoscopic disease activity on clinical outcomes with ozanimod treatment in patients with moderately to severely active UC

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 score, plus a reduction of ≥2 points and ≥25% 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.

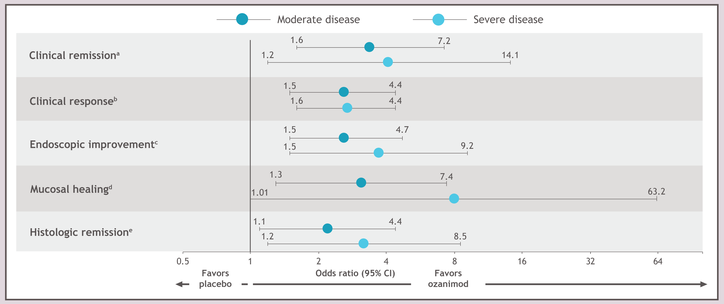
- This post hoc analysis from True North evaluated ozanimod efficacy at Weeks 10 and 52 in 2 subgroups of patients based on baseline endoscopic disease activity (Mayo endoscopic score = 2 [moderate disease] vs Mayo endoscopic score = 3 [severe disease])
- Multiple clinical efficacy endpoints were evaluated 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 prior anti-tumor necrosis factor use
  - 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 proportion of patients had severe disease (n=609, 60.2%) than moderate disease (n=403, 39.8%) at baseline
- Baseline demographic and disease characteristics in patients with moderate and severe disease are shown in **Table 1**
  - Disease duration was similar in both subgroups
  - Endoscopically severe disease at baseline was associated with greater proportions of prior medication use, endoscopically extensive disease at baseline, and higher Mayo scores at baseline than endoscopically moderate disease at baseline
  - Endoscopically severe disease at baseline was associated with higher C-reactive protein and fecal calprotectin (FCP) levels at baseline than endoscopically moderate disease at baseline

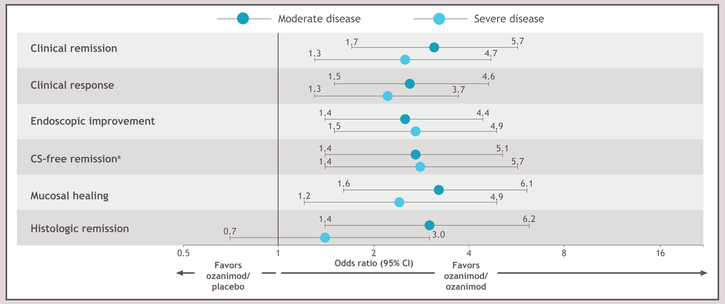
Ozanimod is efficacious regardless of baseline endoscopic disease activity

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



[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 (sum of the RBS, SFS, and endoscopy subscore) of ≥2 points and ≥35%, and a reduction from baseline in the RBS ≥1 point or an absolute RBS ≤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.
RBS, rectal bleeding subscore; SFS, stool frequency subscore.

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



[a]CS-free remission is defined as clinical remission at Week 52 while off CS for ≥12 weeks.
CS, corticosteroids.

- The treatment effects of ozanimod were similar for all evaluated efficacy endpoints at Week 10 in patients with UC with moderate and severe disease (**Figure 2**)
- At Week 52, the treatment effects of continuous ozanimod were similar for most evaluated efficacy endpoints in patients with UC with moderate and severe disease (**Figure 3**)

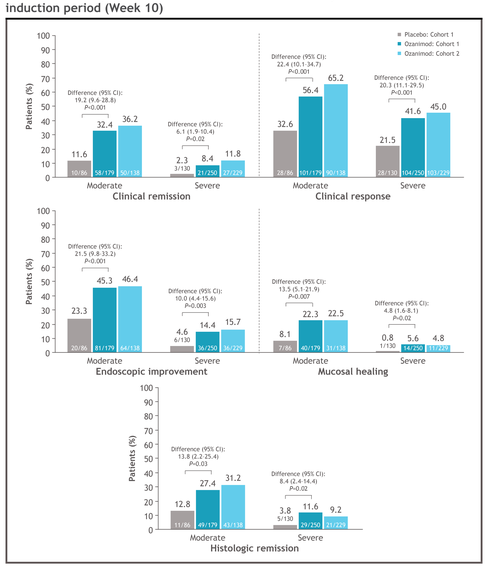
Table 1. Baseline demographic and disease characteristics by disease activity

Characteristic	Patients with moderate disease (n=403)	Patients with severe disease (n=609)
Age, y, median (Q1, Q3)	40 (30.0, 53.0)	40 (31.0, 52.0)
Male, n (%)	221 (54.8)	381 (62.6)
Race, n (%)		
White	375 (93.1)	523 (85.9)
Asian	11 (2.7)	54 (8.9)
Black or African American	11 (2.7)	17 (2.8)
Other	6 (1.5)	15 (2.5)
Age at diagnosis, y, median (Q1, Q3)	33.0 (25.0, 44.0)	32.0 (25.0, 44.0)
Years since diagnosis, median (Q1, Q3)	4.7 (1.7, 9.9)	5.3 (2.3, 10.5)
Extent of UC disease, n (%)		
Left-sided	279 (69.2)	360 (59.1)
Extensive	124 (30.8)	249 (40.9)
Mayo score		
9-point Mayo score[a] (mean ± SD)	5.8 ± 1.1	7.3 ± 0.91
Total Mayo score[b] >9, n (%)	32 (7.9)	355 (58.3)
Partial Mayo score[c] (mean ± SD)	5.9 ± 1.2	6.7 ± 1.2
Fecal calprotectin, mg/kg, median (Q1, Q3)	859.0 (273.7, 2031.1)	1452.9 (516.4, 3334.3)
C-reactive protein, mg/L, median (Q1, Q3)	3.0 (1.0, 7.0)	5.0 (2.0, 12.0)
Concomitant medication use, n (%)		
Systemic corticosteroids	99 (24.6)	214 (35.1)
Oral aminosalicylates	359 (89.1)	512 (84.1)
Prior medication use, n (%)		
Prior anti-TNFs (based on IRT)	97 (24.1)	257 (42.2)
Prior immunomodulators	134 (33.3)	299 (49.1)
Prior biologics[d]	52 (12.9)	178 (29.2)

[a]Sum of RBS, SFS, and endoscopy subscore. [b]Sum of RBS, SFS, endoscopy subscore, and Physician's Global Assessment subscore. [c]Sum of RBS, SFS, and Physician's Global Assessment subscore. [d]Includes all biologics that are not anti-TNF biologics.
IRT, interactive response technology; Q, quartile; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore; TNF, tumor necrosis factor.

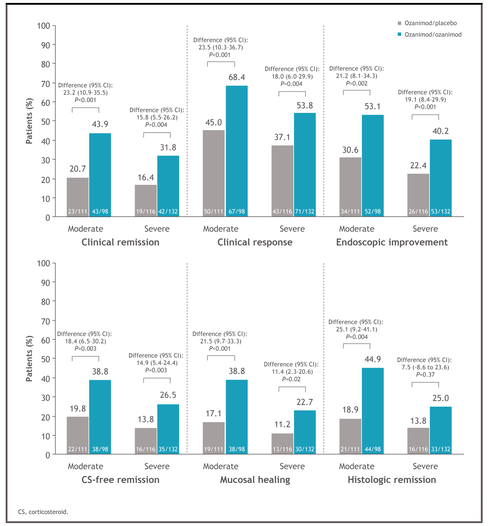
- At Week 10, ozanimod was more effective than placebo for all evaluated efficacy endpoints in patients with UC with moderate and severe disease (**Figure 4**)

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



- 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 both the moderate and severe disease subgroups (**Figure 5**)

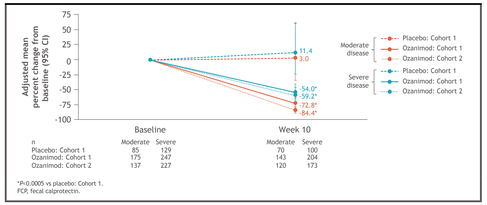
Figure 5. Efficacy by baseline endoscopic disease activity in the True North maintenance period (Week 52)



CS, corticosteroid.

- Reductions from baseline in FCP levels were significantly greater in patients receiving ozanimod compared with placebo in both the moderate and severe disease subgroups at Week 10 (**Figure 6**)

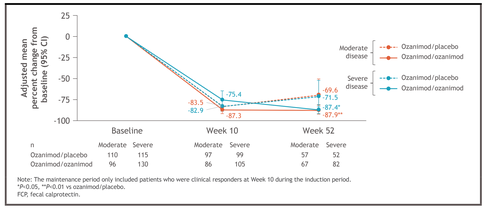
Figure 6. Mean percent changes from baseline in FCP levels by endoscopic disease activity (induction period)



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

- In the moderate and severe disease subgroups, Week 10 responders who were rerandomized to ozanimod had significantly greater reductions from baseline in FCP levels at Week 52 compared with those who were rerandomized to placebo (**Figure 7**)

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



Note: The maintenance period only included patients who were clinical responders at Week 10 during the induction period.
*P<0.05, **P<0.01 vs ozanimod/placebo.
FCP, fecal calprotectin.

Conclusions

- Compared with placebo, ozanimod demonstrated significantly superior efficacy in most clinical outcomes in patients with moderate and severe endoscopic disease
- Regardless of baseline moderate or severe disease activity, ozanimod efficacy was demonstrated by the objective endpoint of significant reductions in FCP levels at Weeks 10 and 52
- Ozanimod is efficacious regardless of baseline endoscopic disease activity

References

1. Scott FI et al. *Br J Pharmacol*. 2016;173:1778-1792. **2.** Zeposia (ozanimod) [package insert]. Princeton, NJ: Bristol Myers Squibb; April 2022. **3.** Zeposia (ozanimod) [summary of product characteristics]. Utrecht, Netherlands: Celgene Distribution B.V.; December 2021. **4.** Sandborn WJ et al. *N Engl J Med*. 2021;385:1280-1291. **5.** Kayal M, Shah S. *J Clin Med*. 2019;9:94. **6.** Armuzzi A et al. *PLoS ONE*. 2020;15:e0227914.

Acknowledgments

- This clinical trial was sponsored by Bristol Myers Squibb
- Writing and editorial assistance was provided by Anny Wu, PharmD, of Peloton Advantage, LLC, an OPEN Health company, and was funded by Bristol Myers Squibb

Disclosures

DCW: received research funding from AbbVie, Bristol Myers Squibb, Genentech, Janssen, Pfizer (Arena), and Takeda; consulted for AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Pfizer, and Takeda; received speaker fees from AbbVie, Bristol Myers Squibb, Janssen, and Takeda. **RP:** received consulting fees from AbbVie, Abbott, Alimentiv, Amgen, Arena, AstraZeneca, Bristol Myers Squibb, Boehringer Ingelheim, Celgene, Celltrion, Cosmos Pharmaceuticals, Eisai, Elan, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Eli Lilly, Merck, Mylan, Oppilan Pharma, Pandion Therapeutics, Pfizer, Progenity, Protagonist Therapeutics, Roche, Sandoz, Satisfai Health, Schering-Plough, Shire, Sublimity Therapeutics, Theravance, UCB, and Takeda; received speaker fees from AbbVie, Arena, Celgene, Eli Lilly, Ferring, Gilead Sciences, Janssen, Merck, Pfizer, Roche, Sandoz, Shire, and Takeda; received research/educational support from AbbVie, Ferring, Janssen, Pfizer, and Takeda; served on an advisory board for AbbVie, Amgen, Arena, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Ferring, Galapagos, Genentech, Gilead Sciences, GlaxoSmithKline, Janssen, Merck, Mylan, Oppilan Pharma, Pandion Pharma, Pfizer, Sandoz, Shire, Sublimity Therapeutics, Takeda, and Theravance. **IB:** received consulting fees from AbbVie, Amgen, Arena, Biogen, Bristol Myers Squibb, Celltrion, Ferring, Galapagos, Janssen, Pfizer, Shire, and Takeda; received speaker fees from AbbVie, Amgen, Arena, Biogen, Bristol Myers Squibb, Celgene, Celltrion, Ferring, Galapagos, Janssen, Mylan, Pfizer, Shire, and Takeda. **ML:** received research funding from Pfizer and Takeda; consulted for AbbVie, Bristol Myers Squibb, Calibr, Eli Lilly, Genentech, Janssen, Pfizer, Prometheus, Roche, Salix, Takeda, Target Pharmasolutions, and Theravance. **BA:** received research funding from Takeda; consulted for AbbVie, Bristol Myers Squibb, Eli Lilly, Janssen, Medtronic, Pfizer, Samsung Bioepis, and Takeda; lectured for AbbVie, Bristol Myers Squibb, Janssen, Pfizer, Takeda, and Eli Lilly. **AJ, AM, CW, VH, SH, and JC:** employees and/or shareholders of Bristol Myers Squibb. **LPB:** served as a speaker, consultant, and advisory board member for AbbVie, Amgen, Biogaran, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Ferring, Forward Pharma, Genentech, H.A.C. Pharma, Hospira/Pfizer, Index Pharmaceuticals, Janssen, Lycera, Merck, Mitsubishi, Norgine, Samsung Bioepis, Sandoz, Takeda, Theravance, Tillotts, and Vifor.

Presented at American College of Gastroenterology (ACG) 2022; October 21-26; 2022; Charlotte, NC, USA, and Virtual.
Previously presented at United European Gastroenterology (UEG) Week 2022; October 8-11, 2022; Vienna, Austria, and Virtual.

Email: m4desk@aol.com