Evaluation of ozanimod efficacy and safety in older patients with ulcerative colitis: post hoc analysis from the phase 3 True North study

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Introduction

- Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator that selectively targets $S1P_1$ and $S1P_{1,5}$, reduces lymphocyte migration to the intestines through S1P receptor internalization[1]
- Ozanimod is approved in the United States and European Union for the treatment of moderately to severely active ulcerative colitis (UC)[2,3]
- Approximately 25%–30% of patients with inflammatory bowel disease (IBD) are aged >60 years; this number is likely to increase, as 10%–15% of new IBD diagnoses occur in patients aged >60 years[4]
- Older patients, who generally have more comorbidities than younger patients, represent an understudied population in IBD[4,5]

Objective

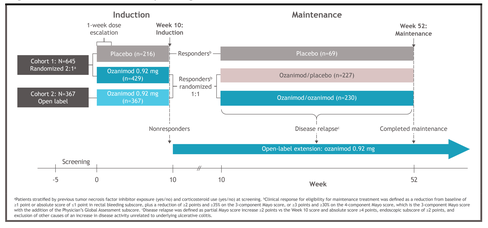
- This post hoc analysis from the phase 3 True North study (NCT02435992) examined the safety and efficacy of ozanimod in patients with moderately to severely active UC by age group: <60 years or ≥60 years

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. [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.

Analyses

- This analysis compared the safety and efficacy of ozanimod versus placebo in patients aged <60 years and aged ≥60 years
- Treatment-emergent adverse events (TEAEs) and adverse events of special interest (AESIs) were explored at Weeks 10 and 52
- Efficacy endpoints (ie, clinical remission, clinical response, endoscopic improvement, and mucosal healing) were also assessed by age cohort at Weeks 10 and 52
  - Adjusted treatment differences and *P*-values for comparison between the ozanimod and placebo groups were calculated using the Cochran-Mantel-Haenszel test, and were stratified by corticosteroid use at screening and prior anti-tumor necrosis factor use (Week 10 comparisons) or by Week 10 remission status and Week 10 corticosteroid use (Week 52 comparisons)

Results

Patients

- Baseline demographics and disease characteristics were generally well balanced across treatment and age groups (**Table 1**)
  - However, older patients had longer average disease duration, less extensive disease, lower baseline fecal calprotectin levels (ozanimod-treated patients only), and more polypharmacy
  - Older patients had more comorbidities than younger patients
  - Prior medication use was similar between the age groups

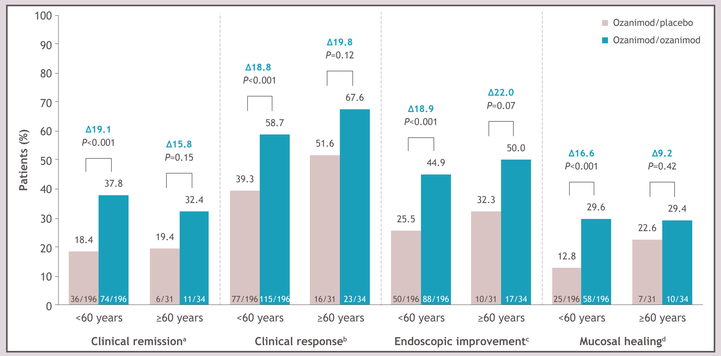
Ozanimod is a safe treatment option that resulted in numerically higher efficacy rates versus placebo for older patients with UC

Table 4. TEAEs occurring during the maintenance period in younger and older patients

Characteristic	Patients aged <60 years		Patients aged ≥60 years	
	Ozanimod/placebo (n=196)	Ozanimod/ozanimod (n=196)	Ozanimod/placebo (n=31)	Ozanimod/ozanimod (n=34)
≥1 TEAE, n (%)	71 (36.2)	94 (48.0)	12 (38.7)	19 (55.9)
≥1 serious TEAE, n (%)	17 (8.7)	11 (5.6)	1 (3.2)	1 (2.9)
≥1 TEAE leading to treatment discontinuation, n (%)	5 (2.6)	2 (1.0)	1 (3.2)	1 (2.9)
Most common TEAEs, n (%)[a]				
UC flare	10 (5.1)	1 (0.5)	0	0
Arthralgia	5 (2.6)	5 (2.6)	1 (3.2)	2 (5.9)
Back pain	3 (1.5)	2 (1.0)	0	2 (5.9)
Nasopharyngitis	3 (1.5)	5 (2.6)	1 (3.2)	2 (5.9)
Alopecia	2 (1.0)	1 (0.5)	0	2 (5.9)
Urinary tract infection	2 (1.0)	0	2 (6.5)	0
ALT increased	1 (0.5)	11 (5.6)	0	0
GGT increased	1 (0.5)	5 (2.6)	0	2 (5.9)
Herpes zoster[b]	1 (0.5)	3 (1.5)	0	2 (5.9)
Cataract	0	0	0	2 (5.9)
Dyspepsia	0	1 (0.5)	0	2 (5.9)
Peripheral edema	0	3 (1.5)	0	3 (8.8)

[a]The most common TEAEs were defined as those that occurred in ≥5% of the patients who received ozanimod or placebo during the maintenance period. [b]Patients were required to have documentation of positive VZV immunoglobulin G antibody status or complete VZV vaccination at least 30 days prior to randomization in True North.
ALT, alanine aminotransferase; GGT, gamma-glutamyl transferase; TEAE, treatment-emergent adverse event; UC, ulcerative colitis; VZV, varicella zoster virus.

Figure 3. Efficacy in the maintenance period by age group



Treatment differences (Δ) for comparison between ozanimod/ozanimod and ozanimod/placebo are model-based adjusted treatment differences calculated based on the Cochran-Mantel-Haenszel test, stratified by remission status at Week 10 (yes/no) and corticosteroid use at Week 10 (yes/no).
[a]RBS=0, SFS ≤1 point (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1 point. [b]Reduction from baseline in the 9-point Mayo score (sum of RBS, SFS, and endoscopy subscore) of ≥2 points and ≥35%, and reduction from baseline in the RBS of ≥1 point or an absolute RBS ≤1 point. [c]Endoscopy subscore ≤1 point. [d]Endoscopy subscore ≤1 point and Geboes index score <2.0.
RBS, rectal bleeding subscore; SFS, stool frequency subscore.

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

Characteristic	Patients aged <60 years			Patients aged ≥60 years		
	Cohort 1		Cohort 2	Cohort 1		Cohort 2
	Placebo (n=186)	Ozanimod (n=376)	Ozanimod (n=315)	Placebo (n=30)	Ozanimod (n=53)	Ozanimod (n=52)
Male, n (%)	124 (66.7)	216 (57.4)	184 (58.4)	19 (63.3)	29 (54.7)	30 (57.7)
Age, y, mean ± SD	38.3 ± 10.7	38.2 ± 11.1	38.4 ± 11.0	64.8 ± 4.3	64.2 ± 3.4	64.4 ± 3.4
Body mass index, kg/m², mean ± SD	24.8 ± 4.4	25.1 ± 5.5	25.6 ± 6.0	26.8 ± 4.5	27.6 ± 4.7	27.6 ± 4.1
Time since UC diagnosis, y, mean ± SD	6.4 ± 6.3	6.6 ± 6.0	7.4 ± 6.8	9.4 ± 10.3	9.3 ± 9.9	11.2 ± 9.8
Extent of UC disease, n (%)						
Left-sided	113 (60.8)	229 (60.9)	202 (64.1)	21 (70.0)	39 (73.6)	35 (67.3)
Extensive	73 (39.2)	147 (39.1)	113 (35.9)	9 (30.0)	14 (26.4)	17 (32.7)
Total Mayo score,* n (%)						
≤9	117 (62.9)	243 (64.6)	168 (53.3)	23 (76.7)	37 (69.8)	37 (71.2)
>9	69 (37.1)	133 (35.4)	147 (46.7)	7 (23.3)	16 (30.2)	15 (28.8)
Fecal calprotectin levels, µg/g						
Median	1326.6	1211.6	1381.1	1688.3	564.4	625.4
Interquartile range	332.7, 3053.6	445.9, 2726.3	464.7, 2971.0	496.9, 4410.7	145.1, 1215.3	226.4, 1753.3
C-reactive protein, mg/L						
Median	5.0	3.0	5.0	8.5	4.0	6.0
Interquartile range	1.0, 11.0	1.0, 9.0	2.0, 11.0	4.0, 13.0	2.0, 9.0	3.0, 14.0
Corticosteroid use at screening, n (%)	65 (34.9)	126 (33.5)	126 (40.0)	8 (26.7)	17 (32.1)	18 (34.6)
Prior medication use, n (%)						
Corticosteroids	142 (76.3)	286 (76.1)	245 (77.8)	20 (66.7)	36 (67.9)	41 (78.8)
Immunomodulators	83 (44.6)	154 (41.0)	145 (46.0)	10 (33.3)	20 (37.7)	21 (40.4)
Anti-TNF	57 (30.6)	114 (30.3)	143 (45.4)	8 (26.7)	16 (30.2)	16 (30.8)
Non-anti-TNF biologic	37 (19.9)	74 (19.7)	96 (30.5)	7 (23.3)	6 (11.3)	10 (19.2)
Oral 5-ASA	180 (96.8)	366 (97.3)	310 (98.4)	30 (100.0)	52 (98.1)	52 (100.0)
Polypharmacy use (≥5 medications), n (%)	93 (50.0)	220 (58.5)	194 (61.6)	17 (56.7)	33 (62.3)	37 (71.2)
Comorbidities, n (%)						
Diabetes	4 (2.2)	14 (3.7)	6 (1.9)	6 (20.0)	4 (7.5)	9 (17.3)
Hypertension	20 (10.8)	38 (10.1)	33 (10.5)	11 (36.7)	15 (28.3)	23 (44.2)
Hypercholesterolemia	3 (1.6)	5 (1.3)	4 (1.3)	0	2 (3.8)	1 (1.9)
Chronic obstructive pulmonary disease	1 (0.5)	1 (0.3)	0	0	1 (1.9)	1 (1.9)
Asthma	7 (3.8)	21 (5.6)	17 (5.4)	2 (6.7)	0	1 (1.9)
Any malignancy	1 (0.5)	3 (0.8)	0	1 (3.3)	3 (5.7)	2 (3.8)
Arthritis	6 (3.2)	11 (2.9)	13 (4.1)	5 (16.7)	5 (9.4)	6 (11.5)
Myocardial infarction	0	0	0	1 (3.3)	1 (1.9)	1 (1.9)
Stroke	0	0	0	0	0	3 (5.8)

*The total Mayo score is defined as the sum of the rectal bleeding, stool frequency, Physician's Global Assessment, and endoscopy subscores. Overall scores range from 0 to 12 (with each subscore on a scale of 0 to 3), with higher scores indicating greater activity. Scores were assessed by a central reader.
ASA, aminosalicylic acid; SD, standard deviation; TNF, tumor necrosis factor; UC, ulcerative colitis.

Safety

Induction period

- No new safety signals were identified during the induction period in the age-based subgroup analysis, and the overall rates of TEAEs were similar compared to the overall population[6]
- The incidences of TEAEs were similar with ozanimod and placebo in both age groups, with lower rates in older patients than younger patients on ozanimod (**Table 2**)
- Rates of serious TEAEs were similar in older and younger patients on ozanimod and were similar to those of patients in the younger group on placebo
- Rates of TEAEs leading to treatment discontinuation were similar between treatment and age groups

Table 2. TEAEs occurring during the induction period in younger and older patients

Characteristic	Patients aged <60 years			Patients aged ≥60 years		
	Cohort 1		Cohort 2	Cohort 1		Cohort 2
	Placebo (n=186)	Ozanimod (n=376)	Ozanimod (n=315)	Placebo (n=30)	Ozanimod (n=53)	Ozanimod (n=52)
≥1 TEAE, n (%)	72 (38.7)	153 (40.7)	130 (41.3)	10 (33.3)	19 (35.8)	16 (30.8)
≥1 serious TEAE, n (%)	7 (3.8)	14 (3.7)	21 (6.7)	0	3 (5.7)	2 (3.8)
≥1 TEAE leading to treatment discontinuation, n (%)	6 (3.2)	13 (3.5)	11 (3.5)	1 (3.3)	1 (1.9)	3 (5.8)
Most common TEAEs, n (%)[a]						
Anemia	11 (5.9)	18 (4.8)	15 (4.8)	1 (3.3)	0	1 (1.9)
Nausea	2 (1.1)	9 (2.4)	3 (1.0)	1 (3.3)	3 (5.7)	0
Diarrhea	1 (0.5)	3 (0.8)	0	1 (3.3)	3 (5.7)	0
Fatigue	1 (0.5)	4 (1.1)	1 (0.3)	0	3 (5.7)	0
Nasopharyngitis	1 (0.5)	14 (3.7)	9 (2.9)	2 (6.7)	1 (1.9)	1 (1.9)

[a]The most common TEAEs were defined as those that occurred in ≥5% of the patients who received ozanimod or placebo during the induction period.
TEAE, treatment-emergent adverse event.

- AESIs were generally low overall during the induction period (**Table 3**)
- One death from acute respiratory distress syndrome due to viral pneumonia occurred during the induction period in an older patient (aged 64 years) receiving ozanimod but was deemed unrelated to treatment

Table 3. AESIs[a] occurring during the induction period in younger and older patients

Characteristic	Patients aged <60 years			Patients aged ≥60 years		
	Cohort 1		Cohort 2	Cohort 1		Cohort 2
	Placebo (n=186)	Ozanimod (n=376)	Ozanimod (n=315)	Placebo (n=30)	Ozanimod (n=53)	Ozanimod (n=52)
Hepatic effects	0	5 (1.3)	1 (0.3)	0	0	0
Infection	0	2 (0.5)	1 (0.3)	0	0	0
Macular edema	0	1 (0.3)	0	0	0	0
Pulmonary effects	0	1 (0.3)	1 (0.3)	0	0	1 (1.9)
Cardiac events	0	0	1 (0.3)[b]	0	0	2 (3.8)[c]
Malignancy	0	0	2 (0.6)	0	0	0

[a]AESIs occurring in ≥1 patient on ozanimod. [b]1 patient had symptomatic bradycardia. [c]1 patient had bradycardia and 1 patient had 3 separate cardiac events of bradycardia due to bisoprolol use, sinus bradycardia, and bradycardia.
AESI, adverse event of special interest.

Maintenance period

- No new safety signals were identified during the maintenance period in the age-based subgroup analysis, and the overall rates of TEAEs were similar compared to the overall population[6]
- Rates of TEAEs were higher in patients on continuous ozanimod than in those who switched to placebo in both age groups, with TEAEs occurring slightly more frequently with continuous ozanimod treatment in older versus younger patients (**Table 4**)
- Rates of serious TEAEs were similar or slightly higher in patients who switched to placebo than those on continuous ozanimod, with less frequent occurrence in older versus younger patients
- Rates of TEAEs leading to treatment discontinuation were low and similar between treatment and age groups
- AESIs were low overall during the maintenance period (**Table 5**)
  - No cardiac events (eg, bradycardia) occurred during the maintenance period

Table 5. AESIs[a] occurring during the maintenance period in younger and older patients

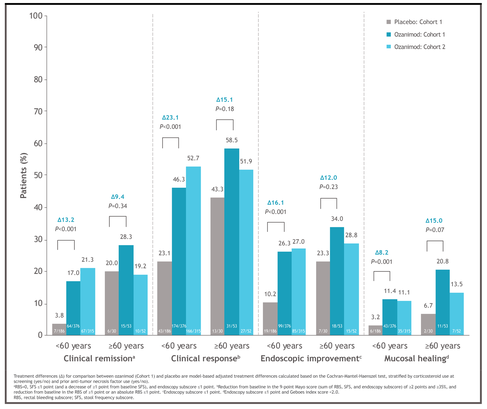
Characteristic	Patients aged <60 years		Patients aged ≥60 years	
	Ozanimod/placebo (n=196)	Ozanimod/ozanimod (n=196)	Ozanimod/placebo (n=31)	Ozanimod/ozanimod (n=34)
Infection	1 (0.5)	3 (1.5)	0	2 (5.9)
Hepatic effects	0	2 (1.0)	1 (3.2)	0
Malignancy	2 (1.0)	2 (1.0)	0	0
Pulmonary effects	0	1 (0.5)	0	0
Macular edema	0	0	0	1 (2.9)

[a]AESIs occurring in ≥1 patient on ozanimod.
AESI, adverse event of special interest.

Efficacy

- The proportions of patients who achieved clinical remission, clinical response, endoscopic improvement, and mucosal healing while on ozanimod were similar regardless of age group; adjusted treatment differences favored ozanimod versus placebo at Week 10 (**Figure 2**) and Week 52 (**Figure 3**)
- However, placebo response rates were higher in older compared to younger patients across all efficacy endpoints at Weeks 10 and 52; therefore, the adjusted treatment differences for ozanimod versus placebo for most endpoints were lower for the older age group and none achieved significance

Figure 2. Efficacy in the induction period by age group



Treatment differences (Δ) for comparison between ozanimod (Cohort 1) and placebo are model-based adjusted treatment differences calculated based on the Cochran-Mantel-Haenszel test, stratified by corticosteroid use at screening (yes/no) and prior anti-TNF use (yes/no).
[a]RBS=0, SFS ≤1 point (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1 point. [b]Reduction from baseline in the 9-point Mayo score (sum of RBS, SFS, and endoscopy subscore) of ≥2 points and ≥35%, and reduction from baseline in the RBS of ≥1 point or an absolute RBS ≤1 point. [c]Endoscopy subscore ≤1 point and Geboes index score <2.0. [d]Endoscopy subscore ≤1 point.
RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Conclusions

- Ozanimod treatment was not associated with any new safety signals nor with higher rates of serious adverse events in older patients
- Ozanimod resulted in numerically higher efficacy rates compared to placebo in older patients with UC
- Ozanimod is a safe and tolerable oral treatment option for older patients with UC
  - However, the study had relatively few participants aged ≥60 years, so larger real-world studies may be warranted

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Acknowledgments

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

Disclosures

NK: received research support from Pfizer, Samsung, and Takeda; received advisory fees from Pharmacosmos and Takeda. **PI:** received lecture fees from AbbVie, Bristol Myers Squibb, Celgene, Celltrion, Dr. Falk Pharma, Ferring, Galapagos, Gilead, MSD, Janssen, Pfizer, Sandoz, Sapphire Medical, Shire, Takeda, Tillotts, and Warner Chilcott; received financial support for research from Celltrion, MSD, Pfizer, and Takeda; received advisory fees from AbbVie, Arena, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Eli Lilly, Genentech, Gilead, Hospira, Janssen, MSD, Pfizer, Pharmacosmos, Prometheus Biosciences, Roche, Sandoz, Samsung Bioepis, Takeda, Topivert, VH2, Vifor, and Warner Chilcott. **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. **SH:** consulted for AbbVie, Janssen, and Takeda. **HA, GL, VH, AJ, and AM:** employees and/or shareholders of Bristol Myers Squibb.
ANA: received advisory fees from Iterative Scopes and Menten AI.

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.

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