Ozanimod is an efficacious oral therapy after 5-ASA failure in immunomodulator- and biologic-naive patients with ulcerative colitis: post hoc analysis from True North

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Background

- Conventional therapies for ulcerative colitis (UC) are oral 5-aminosalicylates (5-ASA), corticosteroids (CS), and immunomodulators (steroid-sparing agents); patients who do not respond to these agents move on to advanced therapies (eg, biologics)[1-3]
- Ozanimod, an oral sphingosine 1-phosphate receptor modulator that reduces lymphocyte migration to inflamed tissues, is approved for the treatment of moderately to severely active UC in the United States and European Union[4,5]
- The pivotal True North phase 3 trial demonstrated that ozanimod was effective and tolerable in patients with moderately to severely active UC[6]

Objectives

- This post hoc analysis from True North evaluated the efficacy of ozanimod at Week 10 (end of induction) with or without concomitant CS in immunomodulator- and biologic-naive, 5-ASA–exposed patients with moderately to severely active UC

Methods

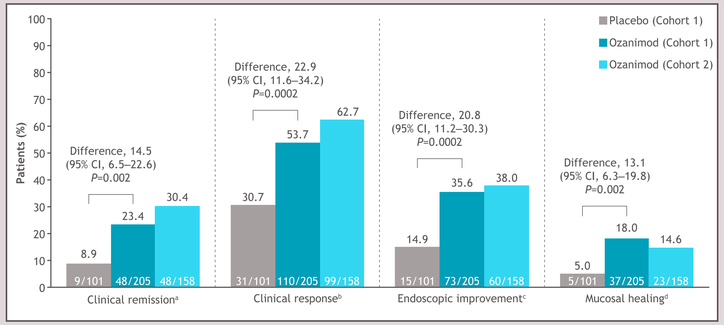
- True North (NCT02435992) was a phase 3 trial that evaluated ozanimod in patients with moderately to severely active UC[6]
- Patients entered a 10-week induction period after the screening period
  - In Cohort 1, patients were randomized to ozanimod 0.92 mg (equivalent to ozanimod hydrochloride 1 mg) or placebo
  - In Cohort 2, patients received open-label ozanimod 0.92 mg
- Clinical responders to ozanimod at Week 10 were rerandomized to ozanimod or placebo through Week 52 during the maintenance period
- Patients were required to have received stable doses of oral 5-ASA and/or CS for ≥2 weeks before screening and to continue receiving the same dose throughout the induction period[6]
- The True North exclusion criteria consisted of patients who[6]:
  - Received a biologic within 8 weeks or 5 elimination half-lives of that biologic (whichever was less) prior to randomization
  - Received treatment with cyclosporine or tacrolimus within 16 weeks of screening or tofacitinib within 2 weeks of screening
  - Planned on concurrent treatment with immunosuppressive agents (ie, azathioprine, 6-mercaptopurine, or methotrexate)
- Efficacy endpoints were clinical remission, clinical response, endoscopic improvement, and mucosal healing at Week 10[6]

Results

- The baseline characteristics of patients by CS use at baseline were similar between treatment groups (**Table 1**)
- Compared with those who received placebo, a higher proportion of ozanimod-treated patients achieved efficacy for all endpoints at Week 10 (**Figure 1**)
- A greater proportion of patients receiving ozanimod compared with placebo achieved all efficacy endpoints regardless of CS use at baseline (**Figure 2**)
- The incidences of treatment-emergent adverse events (TEAEs) by CS use in immunomodulator- and biologic-naive, 5-ASA–exposed patients during the induction period are shown in **Table 2**
- The most common TEAEs were anemia, nasopharyngitis, increased alanine aminotransferase, and hypertension
- The incidences of serious TEAEs were similar, regardless of CS use

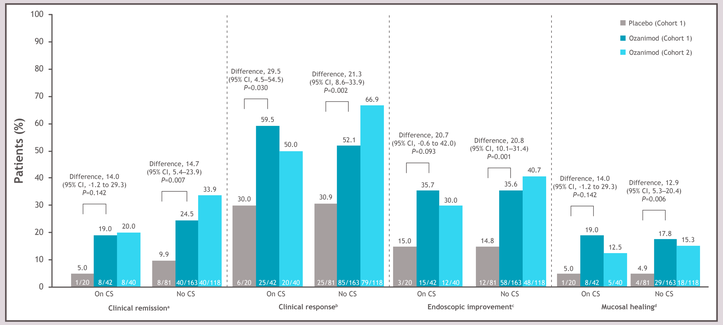
Ozanimod is efficacious in immunomodulator- and biologic-naive, 5-ASA–exposed patients with UC during induction

Figure 1. Efficacy of ozanimod vs placebo in immunomodulator- and biologic-naive, 5-ASA–exposed patients at Week 10 (IP) in the True North post hoc analysis



Differences in proportions, 95% Wald CIs, and *P*-values for comparison were based on the 2-sided Cochran-Mantel-Haenszel test and stratified by corticosteroid use at baseline (yes/no).
[a]Defined as RBS=0, SFS ≤1 (plus ≥1 point reduction from baseline), and MES ≤1 without friability. [b]Defined as reduction in 3-component Mayo score of ≥2 points and ≥35%, and reduction in RBS of ≥1 point or absolute RBS of ≤1 point. [c]Defined as MES ≤1 without friability. [d]Defined as endoscopic improvement plus histologic remission; histologic remission is defined as Geboes index score <2.0 and absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue in the same patient.
5-ASA, 5-aminosalicylates; IP, induction period; MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Figure 2. Efficacy of ozanimod vs placebo in immunomodulator- and biologic-naive, 5-ASA–exposed patients at Week 10 (IP) by CS use at baseline in the True North post hoc analysis



Differences in proportions, 95% Wald CIs, and *P*-values for comparison were based on the 2-sided chi-squared test.
[a]Defined as RBS=0, SFS ≤1 (plus ≥1 point reduction from baseline), and MES ≤1 without friability. [b]Defined as reduction in 3-component Mayo score of ≥2 points and ≥35%, and reduction in RBS of ≥1 point or absolute RBS of ≤1 point. [c]Defined as MES ≤1 without friability. [d]Defined as endoscopic improvement plus histologic remission; histologic remission is defined as Geboes index score <2.0 and absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue in the same patient.
5-ASA, 5-aminosalicylates; CS, corticosteroids; IP, induction period; MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Table 1. Baseline demographic and clinical characteristics of immunomodulator- and biologic-naive, 5-ASA–exposed patients by CS use at baseline

	Cohort 1				Cohort 2	
	Placebo (n=101)		Ozanimod 0.92 mg (n=205)		Ozanimod 0.92 mg (n=158)	
Characteristic	CS use (n=20)	No CS use (n=81)	CS use (n=42)	No CS use (n=163)	CS use (n=40)	No CS use (n=118)
Age at diagnosis of UC, y, mean (SD)	34.2 (11.8)	37.2 (14.0)	36.9 (12.0)	37.1 (13.5)	35.0 (13.0)	38.2 (13.3)
Time since diagnosis of UC, y, mean (SD)	5.2 (5.1)	6.4 (8.0)	5.6 (6.0)	5.0 (5.5)	6.1 (8.3)	6.2 (7.8)
Extent of UC disease, n (%)						
Left-sided	14 (70.0)	56 (69.1)	30 (71.4)	112 (68.7)	27 (67.5)	93 (78.8)
Extensive	6 (30.0)	25 (30.9)	12 (28.6)	51 (31.3)	13 (32.5)	25 (21.2)
Fecal calprotectin, µg/g						
Median (interquartile range)	350.3 (128.1–2071)	1244 (284.3–3031)	1168 (446.3–2726)	897.4 (277.2–2068)	1624 (397.9–4649)	992.1 (272.7–2288)
C-reactive protein, mg/L						
Median (interquartile range)	3.5 (1.0–7.5)	5.0 (2.0–13.0)	2.0 (1.0–8.0)	3.0 (1.0–8.0)	3.0 (1.0–7.0)	4.0 (2.0–12.0)
Rectal bleeding, n (%)						
No blood seen	0	0	0	1 (0.6)	0	1 (0.8)
Streaks of blood with stool less than half the time	8 (40.0)	36 (44.4)	16 (38.1)	60 (36.8)	9 (22.5)	45 (38.1)
Obvious blood with stool most of the time	9 (45.0)	42 (51.9)	24 (57.1)	90 (55.2)	27 (67.5)	68 (57.6)
Blood alone passes	3 (15.0)	3 (3.7)	2 (4.8)	12 (7.4)	4 (10.0)	4 (3.4)
Stool frequency, n (%)						
1–2 stools more than normal	1 (5.0)	13 (16.0)	6 (14.3)	29 (17.8)	6 (15.0)	21 (17.8)
3–4 stools more than normal	7 (35.0)	36 (44.4)	14 (33.3)	58 (35.6)	8 (20.0)	43 (36.4)
≥5 stools more than normal	12 (60.0)	32 (39.5)	22 (52.4)	76 (46.6)	26 (65.0)	54 (45.8)
Mucosal appearance from endoscopy, n (%)						
Moderate disease (Mayo endoscopic score = 2)	11 (55.0)	36 (44.4)	18 (42.9)	90 (55.2)	22 (55.0)	60 (50.8)
Severe disease (Mayo endoscopic score = 3)	9 (45.0)	45 (55.6)	24 (57.1)	73 (44.8)	18 (45.0)	58 (49.2)
Total Mayo score,[a] mean (SD)	9.0 (1.1)	8.6 (1.4)	8.8 (1.5)	8.6 (1.4)	8.9 (1.4)	8.6 (1.4)

[a]Derived from the rectal bleeding, stool frequency, Physician's Global Assessment, and endoscopy subscores.
5-ASA, 5-aminosalicylates; CS, corticosteroids; UC, ulcerative colitis.

Table 2. TEAEs of interest by CS use in immunomodulator- and biologic-naive, 5-ASA–exposed patients (IP)

	Cohort 1				Cohort 2	
	Placebo (n=101)		Ozanimod 0.92 mg (n=205)		Ozanimod 0.92 mg (n=158)	
TEAE, n (%)	CS use (n=20)	No CS use (n=81)	CS use (n=42)	No CS use (n=163)	CS use (n=40)	No CS use (n=118)
≥1 TEAE	6 (30.0)	23 (28.4)	20 (47.6)	51 (31.3)	15 (37.5)	40 (33.9)
≥1 serious TEAE	0	1 (1.2)	1 (2.4)	3 (1.8)	3 (7.5)	6 (5.1)
≥1 TEAE leading to discontinuation of study drug	0	2 (2.5)	3 (7.1)	5 (3.1)	1 (2.5)	2 (1.7)
Infections of interest						
Nasopharyngitis	0	0	2 (4.8)	3 (1.8)	1 (2.5)	5 (4.2)
Influenza	0	1 (1.2)	1 (2.4)	0	1 (2.5)	0
Upper respiratory tract infection	0	0	1 (2.4)	2 (1.2)	1 (2.5)	4 (3.4)
Sinusitis	1 (5.0)	0	1 (2.4)	1 (0.6)	0	0
Herpes zoster	0	0	0	1 (0.6)	0	0
Cardiovascular disorders of interest						
Hypertension	0	0	2 (4.8)	3 (1.8)	0	5 (4.2)
Hypertensive crisis	0	0	1 (2.4)	0	0	0
Bradycardia	0	0	1 (2.4)	0	0	1 (0.8)
Elevated hepatic enzymes of interest						
Alanine aminotransferase increased	0	0	3 (7.1)	4 (2.5)	0	4 (3.4)
Aspartate aminotransferase increased	0	0	2 (4.8)	2 (1.2)	0	0
Gamma-glutamyl transferase increased	0	0	1 (2.4)	2 (1.2)	0	3 (2.5)
Other common TEAEs						
Dizziness	0	1 (1.2)	2 (4.8)	1 (0.6)	1 (2.5)	0
Anemia	1 (5.0)	8 (9.9)	2 (4.8)	5 (3.1)	3 (7.5)	2 (1.7)
UC	0	1 (1.2)	0	1 (0.6)	2 (5.0)	0

5-ASA, 5-aminosalicylates; CS, corticosteroids; TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

Conclusions

- Ozanimod demonstrated efficacy during induction in immunomodulator- and biologic-naive, 5-ASA–exposed patients with moderately to severely active UC, regardless of CS use at baseline
- Safety data were similar between placebo and ozanimod cohorts, regardless of prior CS exposure
- Our data suggest that ozanimod may be effective for steroid-free induction in patients with moderately to severely active UC who are naive to immunomodulators and biologics

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Acknowledgments

- This study was supported by Bristol Myers Squibb (Princeton, NJ, USA)
- All authors contributed to and approved this poster. 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

BES: received research grants from Janssen, Pfizer, Takeda, and Theravance Biopharma R&D; received consulting fees from 4D Pharma, Abivax, AbbVie, Alimentiv, Allergan, Amgen, Arena, AstraZeneca, Bacainn Therapeutics, Boehringer Ingelheim, Boston Pharmaceuticals, Bristol Myers Squibb, Calibr, Capella Bioscience, Celgene, Celltrion, ClostraBio, Eli Lilly, Enthera, Ferring, Galapagos, Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Immunic, InDex Pharmaceuticals, Innovation Pharmaceuticals, Ironwood Pharmaceuticals, Janssen, Kaleido, Kallyope, MiroBio, Morphic Therapeutic, Oppilan Pharma, OSE Immunotherapeutics, Otsuka Pharmaceutical, Palatin Technologies, Pfizer, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, RedHill Biopharma, Rheos Medicines, Roche, Salix Pharmaceuticals, Seres Therapeutics, Shire, Sienna Biopharmaceuticals, Sun Pharmaceutical Industries, Surrozen, Takeda, Target PharmaSolutions, Teva Branded Pharmaceutical Products R&D, Thelium Therapeutics, Theravance Biopharma R&D, TLL Pharmaceutical, USWM Enterprises, Ventyx Biosciences, Viela Bio, Vivante Health, and Vivelix Pharmaceuticals; received stock from Vivante Health and Ventyx Biosciences.

AD: received fees for participation in clinical trials, review activities (eg, data monitoring boards), statistical analysis, and endpoint committees from AbbVie, Celgene/Bristol Myers Squibb, Falk Foundation, Gilead Sciences, Janssen, and Pfizer; received consulting fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene/Bristol Myers Squibb, Eli Lilly, Falk Foundation, Ferring, Fresenius Kabi, Galapagos, Gilead Sciences, Janssen, MSD, Pharmacosmos, Pfizer, Roche/Genentech, Sandoz/Hexal, Takeda, Tillotts, and Vifor Pharma; received payment for lectures, including service on speaker bureaus, from AbbVie, Eli Lilly, Falk Foundation, Ferring, Gilead Sciences/Galapagos, Janssen, MSD, Pfizer, Takeda, Tillotts, and Vifor Pharma; received payment for development of educational presentations from Ferring and Tillotts.

PI: received lecture fees from AbbVie, Bristol Myers Squibb, Celgene, Celltrion, Falk Foundation, Ferring, Galapagos, Gilead Sciences, Janssen, MSD, Pfizer, Sandoz, Sapphire Medical Clinics, 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 Sciences, Hospira, Janssen, MSD, Pfizer, Pharmacosmos, Prometheus Biosciences, Roche, Sandoz, Samsung Bioepis, Takeda, Topivert, Viator Health Limited, Vifor Pharma, and Warner Chilcott.

MC: reported advisory/consulting roles with AbbVie, Arena, Bristol Myers Squibb, Eli Lilly, Janssen, Medtronic, and Pfizer; reported speaker role with AbbVie, Bristol Myers Squibb, Janssen, Medtronic, and Pfizer; received research funding from Fuji, Gilead, Janssen, Novartis, Pfizer, and Takeda.

ML: consulted for AbbVie, Bristol Myers Squibb, Calibr, Eli Lilly, Genentech, Janssen, Pfizer, Prometheus Biosciences, Roche, Salix Pharmaceuticals, Takeda, Target PharmaSolutions, Theravance, and Valeant.

HAA, MTO, AP, and AE: employees and/or shareholders of Bristol Myers Squibb.

TR: reported nothing to disclose.

SD: received honoraria as a speaker, consultant, and/or advisory board member from AbbVie, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Eli Lilly, Enthera, Ferring, Gilead Sciences, Hospira, Inotrem, Janssen, Johnson & Johnson, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB, and Vifor Pharma.

Presented at American College of Gastroenterology (ACG) 2022; October 21-26; 2022; Charlotte, NC, USA, and Virtual.
Previously presented at European Crohn's and Colitis Organisation (ECCO) 2022; February 16-19, 2022; Virtual.

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