Impact of Prior Biologic Exposure on Patient Response to Ozanimod for Moderate-to-Severe Ulcerative Colitis in the Phase 3 True North Study

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Introduction and Objective

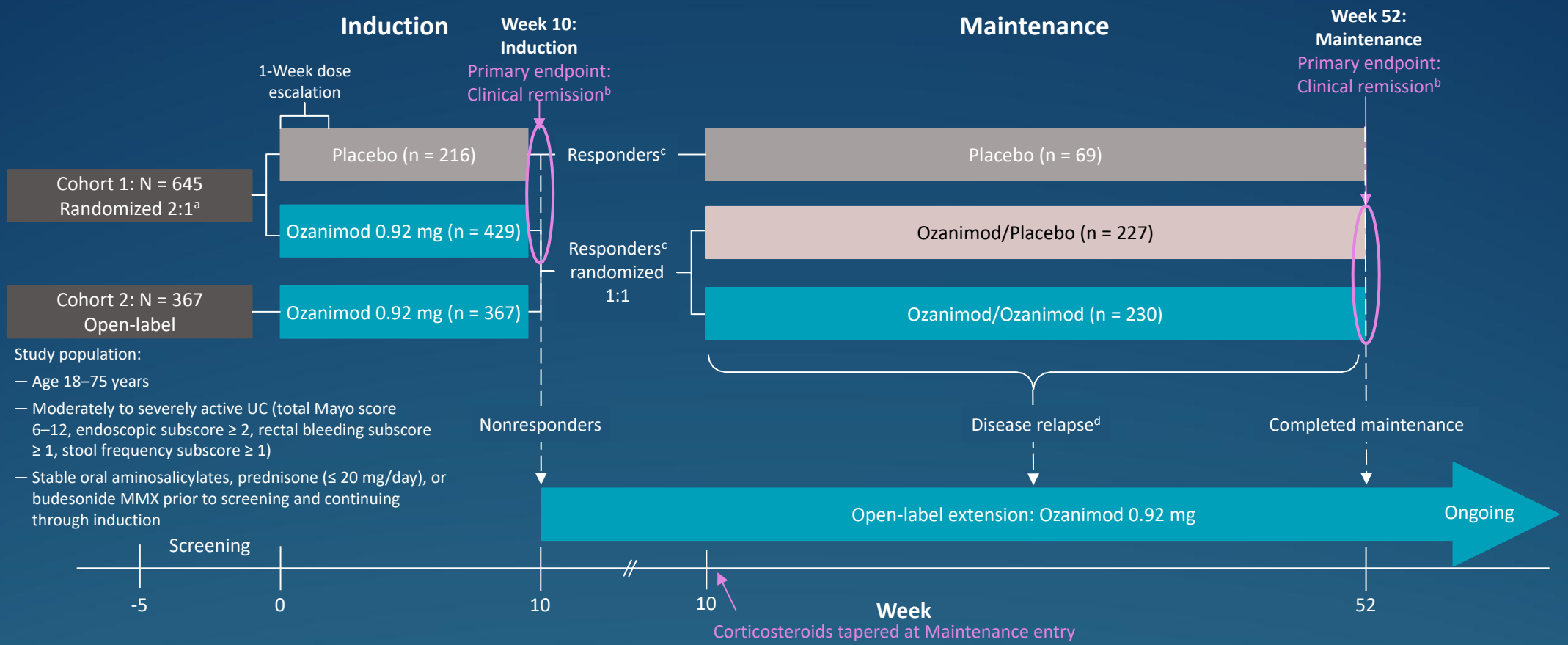
- Ozanimod is an oral S1P receptor modulator selectively targeting $S1P_1$ and $S1P_5$[1]
- Ozanimod has been approved by the EMA and US FDA for the treatment of RMS in adults and by the US FDA for the treatment of moderately to severely active UC in adults[2,3]
- Ozanimod demonstrated superior efficacy and safety vs PBO up to Week 52 in adults with moderately to severely active UC in the Phase 3 True North trial (NCT02435992)[4,5]
- True North included patients who were naive to biologics and patients with prior exposure to biologics
  - Patients previously treated with a biologic agent may be less likely to respond to another advanced treatment[6]

Objective: To evaluate the impact of prior biologic exposure on response to ozanimod

EMA, European Medicines Agency; S1P, sphingosine-1-phosphate; PBO, placebo; RMS, relapsing multiple sclerosis; UC, ulcerative colitis; US FDA, United States Food and Drug Association.

1. Scott FL et al. *Br J Pharmacol* 2016;173:1778-1792; 2. Zeposia® (ozanimod) EU SmPC; 3. Zeposia® (ozanimod) prescribing information, May 2021. 4. Sandborn WJ et al. Presentation no. LB02 at UEGW 2020. 5. Danese S et al. Presentation no. LB10 at UEGW 2020. 6. Sandborn WJ et al. *N Engl J Med* 2013;369(8):711-721.

True North Trial Study Design



- In this post-hoc analysis, outcomes based on prior biologic exposure (biologic-naive, 1 biologic, and 2+ biologics) were analyzed for clinical remission, clinical response, endoscopic improvement, and mucosal healing
- Patients exposed to only a JAK inhibitor were not included in this analysis

JAK, Janus kinase; UC, ulcerative colitis.
[a]Patients stratified by prior tumor necrosis factor inhibitor exposure (yes/no) and corticosteroid use (yes/no) at screening.
[b]Clinical remission based on 3-component Mayo score (RBS = 0, SFS ≤ 1 and decrease ≥ 1 from baseline, and MES ≤ 1 without friability).
[c]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 ≥ 35% on the 3-component Mayo score (partial Mayo), or ≥ 3 points and ≥ 30% on the 4-component Mayo score, which is the 3-component Mayo score with the addition of the Physician Global Assessment subscore.
[d]Disease relapse was defined as partial Mayo score increase ≥ 2 points versus 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.

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Demographic and Clinical Characteristics at Baseline During Induction

Characteristic	Biologic Exposure Status	Cohort 1		Cohort 2
		Placebo	Ozanimod	Ozanimod
		Naive, n = 137 1 Biologic, n = 36 2+ Biologics, n = 40	Naive, n = 287 1 Biologic, n = 58 2+ Biologics, n = 81	Naive, n = 192 1 Biologic, n = 68 2+ Biologics, n = 93
Age – mean±SD, yr	Biologic-naive	42.7±13.8	41.8±13.3	44.0±13.9
	1 Biologic	41.0±13.2	44.9±14.2	40.8±13.4
	2+ Biologics	41.0±13.8	37.7±13.4	39.9±12.6
Male Sex – n (%)	Biologic-naive	90 (65.7)	164 (57.1)	118 (61.5)
	1 Biologic	22 (61.1)	30 (51.7)	31 (45.6)
	2+ Biologics	29 (72.5)	50 (61.7)	56 (60.2)
Years Since UC Symptom Onset, mean±SD	Biologic-naive	7.0±7.4	6.7±6.3	7.6±8.0
	1 Biologic	8.6±5.9	10.8±9.7	9.1±7.2
	2+ Biologics	8.6±7.2	10.0±7.3	10.6±7.6
Extent of Disease – Left-sided/Extensive – n (%)	Biologic-naive	90 (65.7)/47 (34.3)	194 (67.6)/93 (32.4)	139 (72.4)/53 (27.6)
	1 Biologic	21 (58.3)/15 (41.7)	32 (55.2)/26 (44.8)	44 (64.7)/24 (35.3)
	2+ Biologics	23 (57.5)/17 (42.5)	41 (50.6)/40 (49.4)	50 (53.8)/43 (46.2)
Complete Mayo Score[a] – mean±SD	Biologic-naive	8.7±1.37	8.8±1.43	8.8±1.48
	1 Biologic	9.0±1.25	9.1±1.68	9.1±1.56
	2+ Biologics	9.4±1.22	9.0±1.46	9.6±1.27

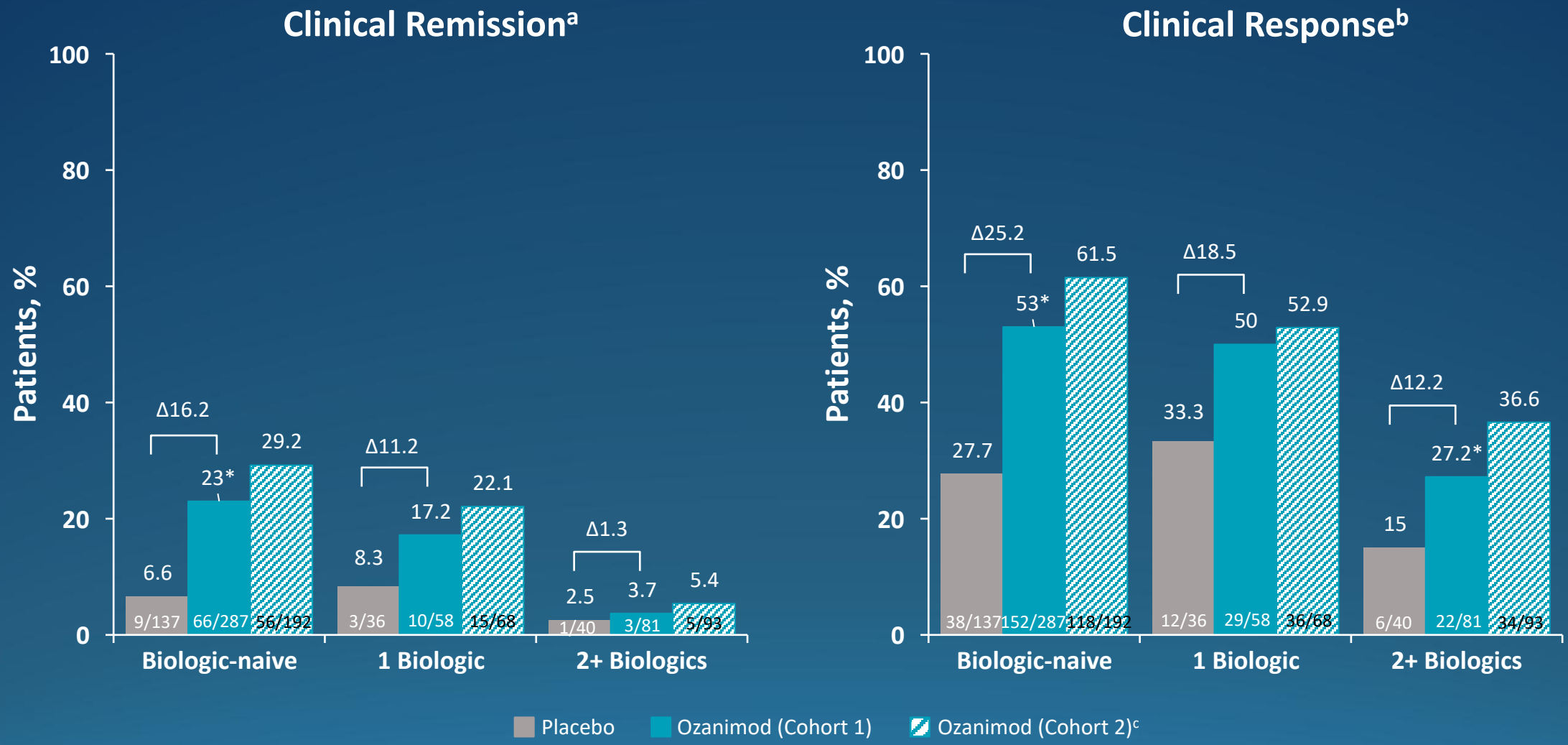
[a]Sum of the Rectal Bleeding subscore, Stool Frequency subscore, Physician Global Assessment subscore, and the Endoscopy subscore. Each subscore has a range of 0–3 points and the complete Mayo score has a range of 0–12 points.
SD, standard deviation; UC, ulcerative colitis.

Medication Use at Baseline During Induction

Characteristic	Biologic Exposure Status	Cohort 1		Cohort 2
		Placebo Naive, n = 137 1 Biologic, n = 36 2+ Biologics, n = 40	Ozanimod Naive, n = 287 1 Biologic, n = 58 2+ Biologics, n = 81	Ozanimod Naive, n = 192 1 Biologic, n = 68 2+ Biologics, n = 93
Corticosteroid Use at Screening, n (%)	Biologic-naive 1 Biologic 2+ Biologics	37 (27.0) 8 (22.2) 25 (62.5)	71 (24.7) 23 (39.7) 49 (60.5)	53 (27.6) 26 (38.2) 55 (59.1)
Prior Corticosteroid Use, n (%)	Biologic-naive 1 Biologic 2+ Biologics	89 (65.0) 31 (86.1) 39 (97.5)	188 (65.5) 52 (89.7) 79 (97.5)	123 (64.1) 59 (86.8) 90 (96.8)
Prior Biologic Use, n/N (%)	Anti-TNF[a]	63/213 (29.6)	126/426 (29.6)	141/353 (39.9)
	Anti-integrin[b]	40/213 (18.8)	77/426 (18.1)	91/353 (25.8)
	Ustekinumab	2/213 (0.9)	1/426 (0.2)	5/353 (1.4)
	S1PR (etrasimod)	0	0	1/353 (0.3)
	Other[c]	0	2/426 (0.5)	1/353 (0.3)

[a]Includes adalimumab, certolizumab, golimumab, infliximab, OPRX-106. [b]Includes abrilumab, anti-madcam, etrolizumab, SHP647, and vedolizumab. [c]Includes AG011, andecalixim, and vizilizumab.
SD, standard deviation; TNF, tumor necrosis factor.

Induction Efficacy Outcomes by Prior Biologic Use



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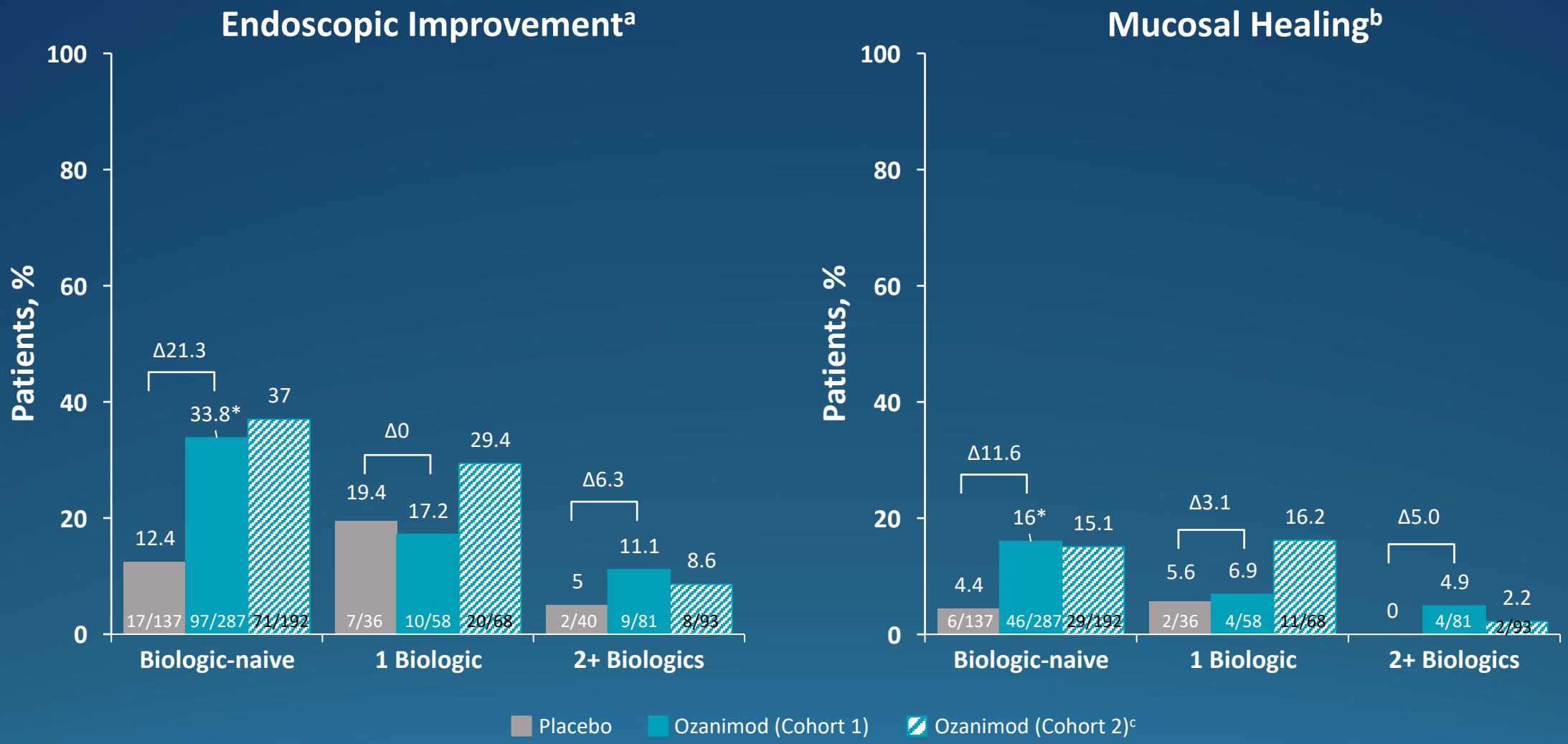
*Significant vs placebo.
[a]Defined as RBS = 0, SFS ≤ 1 (plus ≥ 1-point reduction from baseline), and MES ≤ 1 without friability. [b]Defined as reduction in 3-component Mayo score of ≥ 2 points and ≥ 35%, and reduction in RBS of ≥ 1 point or absolute RBS of ≤ 1 point. [c]Cohort 2 received open-label ozanimod, so a statistical analysis for comparison to placebo was not conducted.
MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Induction Efficacy Outcomes by Prior Biologic Use (cont'd)



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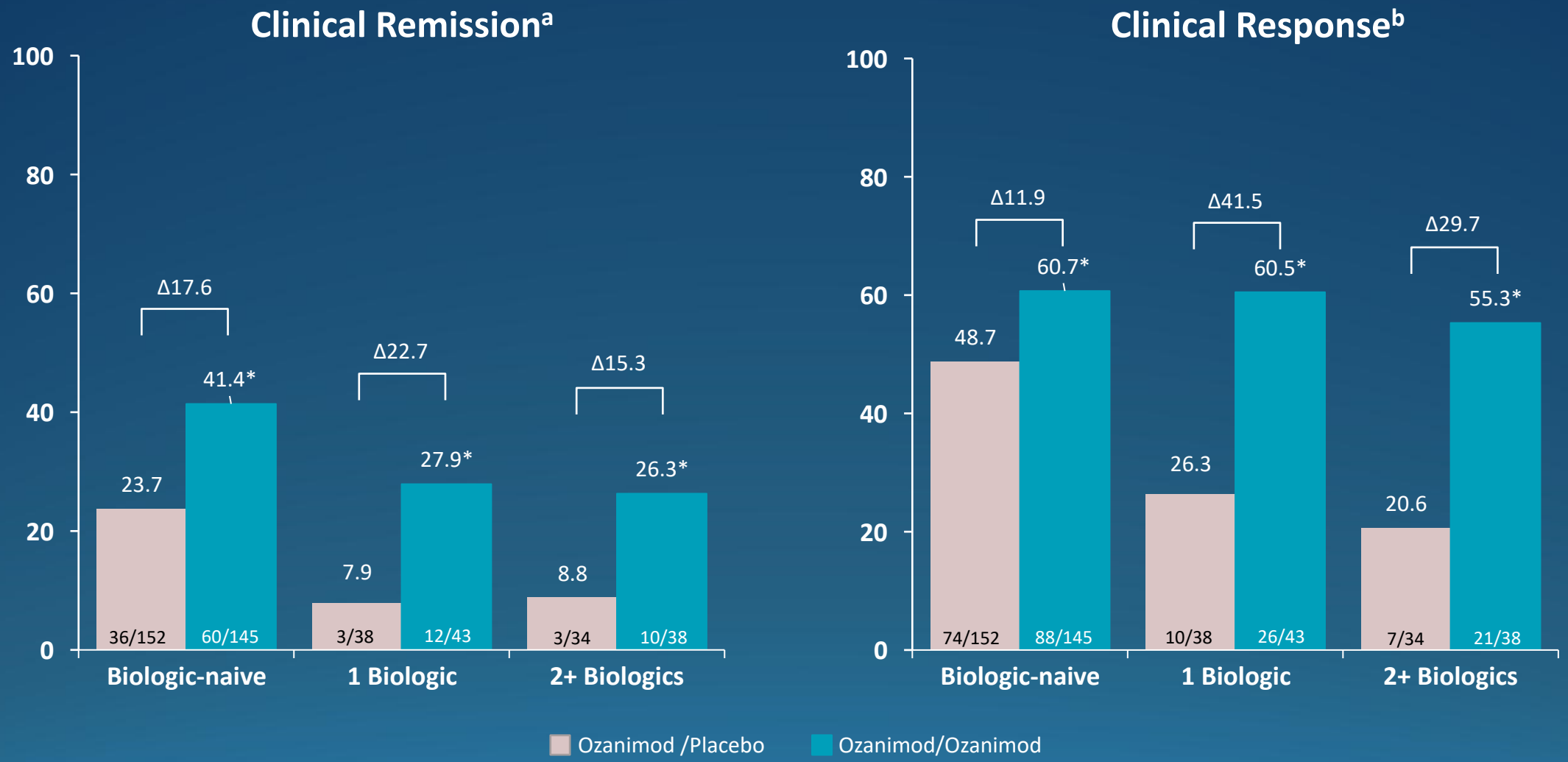
*Significant vs placebo.
[a]Defined as MES ≤ 1 without friability. [b]Defined as endoscopic improvement plus histologic remission (Geboes index score < 2.0 and absence of neutrophils in the epithelial crypts or lamina propria and no increase in eosinophils, no crypt destruction, and no erosions, ulcerations, or granulation tissue in the same patient). [c]Cohort 2 received open-label ozanimod, so a statistical analysis for comparison to placebo was not conducted.
MES, mucosal endoscopy subscore.

Maintenance Efficacy Outcomes by Prior Biologic Use



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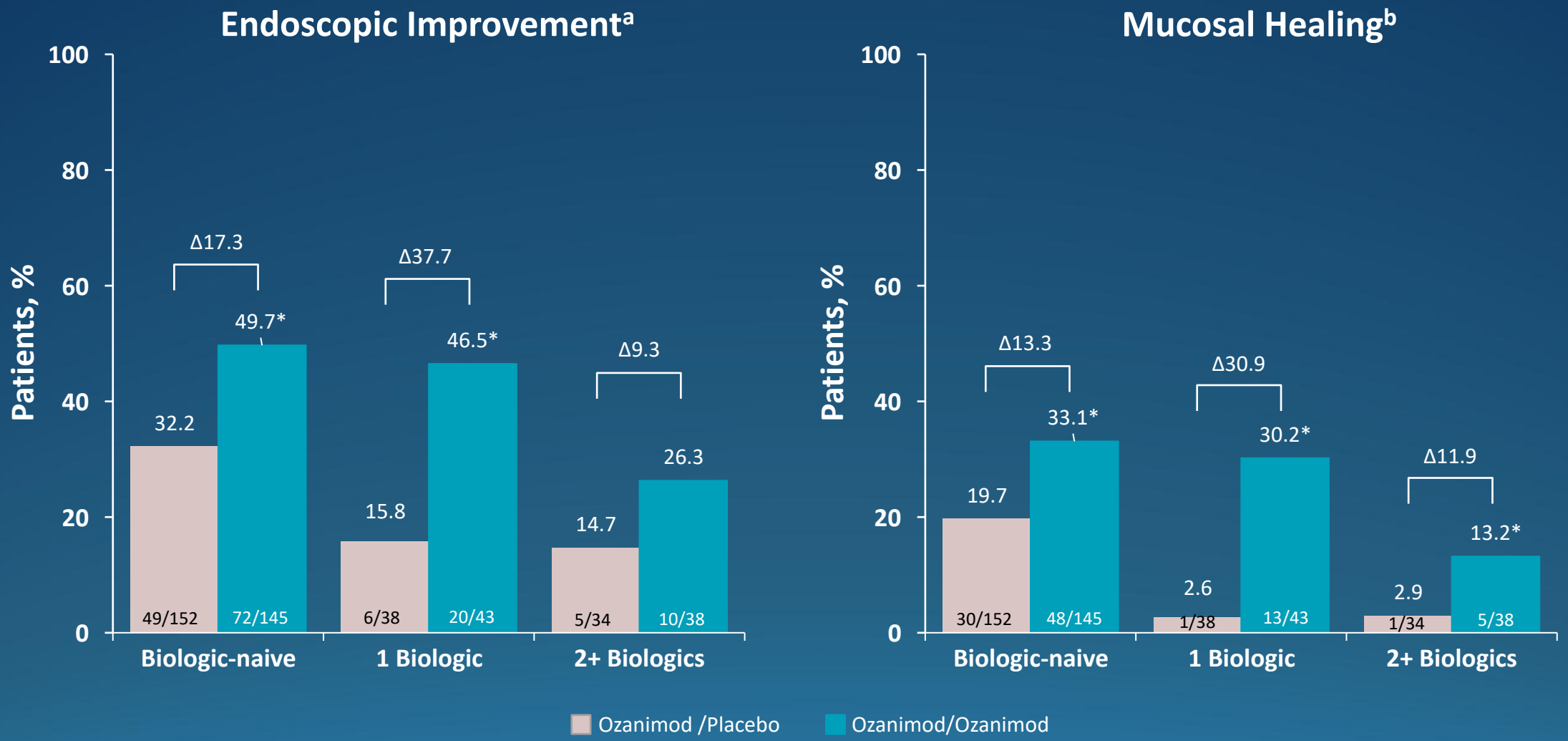
*Significant vs placebo.
[a]Defined as RBS = 0, SFS ≤ 1 (plus ≥ 1-point reduction from baseline), and MES ≤ 1 without friability. [b]Defined as reduction in 3-component Mayo score of ≥ 2 points and ≥ 35%, and reduction in RBS of ≥ 1 point or absolute RBS of ≤ 1 point.
MES, mucosal endoscopy subscore; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Maintenance Efficacy Outcomes by Prior Biologic Use (cont'd)



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*Significant vs placebo.
[a]Defined as MES ≤ 1 without friability. [b]Defined as endoscopic improvement plus histologic remission (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).
MES, mucosal endoscopy subscore.

True North Safety

	Induction Period (Week 10)		Maintenance Period (Week 52)	
	Placebo (n = 216)	Ozanimod (n = 429)	Ozanimod/Placebo (n = 227)	Ozanimod/Ozanimod (n = 230)
Any TEAE	82 (38.0)	172 (40.1)	83 (36.6)	113 (49.1)
Common TEAEs (≥ 3% in any group)				
Anemia	12 (5.6)	18 (4.2)	4 (1.8)	3 (1.3)
Nasopharyngitis	3 (1.4)	15 (3.5)	4 (1.8)	7 (3.0)
Headache	4 (1.9)	14 (3.3)	1 (0.4)	8 (3.5)
Alanine aminotransferase increased	0	11 (2.6)	1 (0.4)	11 (4.8)
Arthralgia	3 (1.4)	10 (2.3)	6 (2.6)	7 (3.0)
Gamma glutamyl transferase increased	0	5 (1.2)	1 (0.4)	7 (3.0)
Serious TEAEs	7 (3.2)	17 (4.0)	18 (7.9)	12 (5.2)
UC exacerbation[a]	4 (1.9)	6 (1.4)	9 (4.0)	1 (0.4)
Anemia[a]	0	4 (0.9)	0	1 (0.4)
Appendicitis/complicated appendicitis[a]	0	1 (0.2)	3 (1.2)	0
Severe TEAEs	4 (1.9)	14 (3.3)	9 (4.0)	9 (3.9)
TEAEs leading to treatment discontinuation	7 (3.2)	14 (3.3)	6 (2.6)	3 (1.3)

[a]Occurring in ≥2 patients in any group.
TEAE, treatment-emergent adverse event; UC, ulcerative colitis.
Sandborn WJ et al. Presented at ACG 2020. Oral presentation LB05.

Summary and Clinical Relevance

- Ozanimod treatment for up to 52 weeks in patients with moderate-to-severe UC improved clinical symptoms, mucosal ulcerations, and reduced cellular inflammation in both biologic-exposed and -naive patients
- Greater efficacy was observed in biologic-naive patients, followed by patients with prior exposure to 1 biologic, at Induction; however, all groups had benefits at end of Maintenance
  - Patients with prior biologic use may require additional time to respond to treatment
- Safety profile consistent with known profile for ozanimod; no new safety signals identified
- Limitations:
  - Post-hoc analysis; study not powered to detect differences between biologic-naive and biologic-exposed groups
  - Differences in baseline characteristics (ie, corticosteroid use at study entry and prior corticosteroid use, extent of disease, disease duration)

Acknowledgments

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