Efficacy and safety of 2 years of continuous ozanimod treatment: interim analysis of the True North open-label extension study

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Introduction

- Ozanimod, an oral sphingosine 1-phosphate (S1P) receptor modulator that selectively targets $S1P_1$ and $S1P_5$, reduces lymphocyte migration from lymphoid tissues through $S1P_1$ 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]
- The phase 3 True North study (NCT02435992) demonstrated the efficacy and safety of ozanimod treatment for up to 52 weeks in patients with moderately to severely active UC[4]
- The ongoing True North open-label extension (OLE) study is exploring the long-term efficacy and safety of ozanimod in the treatment of UC

Objective

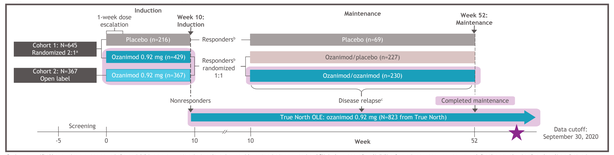
- This interim analysis of the True North OLE evaluated the efficacy and safety of ozanimod in patients who received 98 weeks of continuous ozanimod treatment

Methods

Study design[4]

- True North was a 52-week, randomized, double-blind, placebo-controlled phase 3 trial in patients with moderately to severely active UC (**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.
OLE, open-label extension.

Analyses

- This analysis assessed the efficacy and safety of ozanimod in patients who entered the True North OLE upon achieving clinical response after 52 weeks of continuous ozanimod treatment in the induction and maintenance periods
  - Efficacy was also assessed in subgroups of these patients who entered the OLE in clinical remission or in clinical response only
- The data cutoff was September 30, 2020
- Efficacy endpoints (ie, clinical remission, clinical response, endoscopic improvement, and corticosteroid-free remission) were assessed at OLE Week 46 using observed case (OC) and nonresponder imputation (NRI) analyses
- Treatment-emergent adverse events (TEAEs), adverse events of special interest, and clinical laboratory measures were also examined during the OLE

Results

Patients

- Of the 131 patients who entered the OLE in clinical response after 52 weeks of continuous ozanimod treatment, 63% had achieved clinical remission and 37% had achieved clinical response only at Week 52
  - 73% of the 131 patients entering the OLE in clinical response or clinical remission (69% of the 83 patients entering the OLE in clinical remission and 79% of the 48 patients entering the OLE in clinical response only) completed OLE Week 46 (ie, Week 98 of continuous ozanimod therapy) at the time of data cutoff when outcomes were measured
- Baseline demographic and clinical characteristics were generally similar for patients who were continuously treated with ozanimod and entered the OLE in clinical remission or clinical response only (**Table 1**)
  - However, more patients with clinical response only at OLE entry had prior exposure to tumor necrosis factor inhibitors than patients in clinical remission at OLE entry; these patients also had slightly higher exposure to prior immunomodulators
- Disease activity at baseline was similar between patient groups and improved from baseline to OLE entry after 52 weeks of continuous ozanimod treatment (**Table 2**)

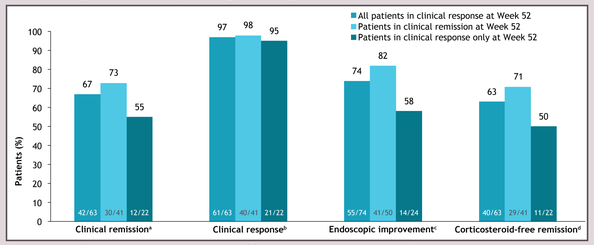
Table 1. Baseline demographic and clinical characteristics of patients treated with continuous ozanimod in clinical response at maintenance period Week 52 (OLE entry)

Characteristic	All patients in clinical response[a] at Week 52 (n=131)	Patients in clinical remission[b] at Week 52 (n=83)	Patients in clinical response only at Week 52 (n=48)
Age, y, mean (SD)	44.3 (13.6)	44.2 (12.5)	44.4 (15.5)
Males, n (%)	63 (48.1)	38 (45.8)	25 (52.1)
Body mass index, kg/m^2, mean (SD)	25.9 (5.8)	25.9 (5.6)	25.8 (6.2)
Years since UC diagnosis, mean (SD)	8.5 (7.3)	9.1 (7.0)	7.6 (7.7)
Extent of UC disease, n (%)			
Left-sided	89 (67.9)	55 (66.3)	34 (70.8)
Extensive	42 (32.1)	28 (33.7)	14 (29.2)
Corticosteroid use at screening, n (%)	31 (23.7)	19 (22.9)	12 (25.0)
Prior therapies, n (%)			
5-ASA	129 (98.5)	81 (97.6)	48 (100.0)
Corticosteroid	90 (68.7)	57 (68.7)	33 (68.8)
Immunomodulator	46 (35.1)	27 (32.5)	19 (39.6)
TNFi	42 (32.1)	21 (25.3)	21 (43.8)
Non-TNFi biologic	26 (19.8)	17 (20.5)	9 (18.8)

[a]Clinical response is defined as a reduction from baseline in the 9-point Mayo score (sum of RBS, SFS, and endoscopy subscores) of ≥2 points and ≥35% and reduction from baseline in the RBS of ≥1 point or an absolute RBS of ≤1 point. [b]Clinical remission is defined as RBS=0, SFS ≤1 (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1. 'Met criteria for clinical response but not clinical remission.
ASA, 5-aminosalicylate; OLE, open-label extension; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore; TNFi, tumor necrosis factor inhibitor; UC, ulcerative colitis.

Patients with UC who achieved clinical response or clinical remission after 1 year of ozanimod treatment had a high rate of sustained efficacy for another year, with no new safety signals identified

Figure 2. Ozanimod efficacy at OLE Week 46 by clinical response and clinical remission status at maintenance period Week 52 (OLE entry): OC analysis



Note: Denominators for the OC analysis were based on the numbers of patients who completed OLE Week 46 and on the data that were available for the endpoints in question.
[a]Clinical remission is defined as RBS=0 points, SFS ≤1 point (and a decrease of ≥1 point from the baseline SFS), and endoscopy subscore ≤1 point. [b]Clinical response is defined as a reduction from baseline in 9-point Mayo score of ≥2 points and ≥35%, and a reduction from baseline in RBS of ≥1 point or an absolute RBS of ≤1 point. [c]Endoscopic improvement is defined as an endoscopy subscore of ≤1 point. [d]Corticosteroid-free remission is defined as clinical remission while off corticosteroids for ≥12 weeks. Corticosteroid doses were kept stable during the True North induction period and tapered during the True North maintenance period; for patients who could not tolerate the taper without recurrence of clinical symptoms or steroid withdrawal, the corticosteroid dose could be increased and tapering resumed within 2 weeks.
OC, observed case; OLE, open-label extension; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

Table 3. Overall safety during the True North OLE for all patients and for patients treated with continuous ozanimod in clinical response at maintenance period Week 52 (OLE entry)

Characteristic	All patients in the OLE (N=823) Total PY[a] = 1540.4 n (%)	All patients in the OLE (N=823) Total PY[a] = 1540.4 EAIR per 100 PY[b]	Patients treated with continuous ozanimod in clinical response at Week 52 (OLE entry) (n=131) Total PY[a] = 316.8 n (%)	Patients treated with continuous ozanimod in clinical response at Week 52 (OLE entry) (n=131) Total PY[a] = 316.8 EAIR per 100 PY[b]
TEAEs	620 (75.3)	102.64	101 (77.1)	83.54
Serious TEAEs	105 (12.8)	7.33	16 (12.2)	5.53
TEAEs leading to treatment discontinuation	39 (4.7)	2.55	5 (3.8)	1.59
Most frequent TEAEs (occurring in ≥5% of patients)[c]				
Lymphopenia	108 (13.1)	7.70	17 (13.0)	5.81
Arthralgia	53 (6.4)	3.64	14 (10.7)	4.81
Headache	53 (6.4)	3.62	13 (9.9)	4.37
Hypertension	37 (4.5)	2.47	13 (9.9)	4.35
Lymphocyte count decreased[d]	68 (8.3)	4.66	11 (8.4)	3.63
Alanine aminotransferase increased[d]	64 (7.8)	4.43	11 (8.4)	3.70
Nasopharyngitis	73 (8.9)	5.10	10 (7.6)	3.33
Anemia	71 (8.6)	4.92	10 (7.6)	3.35
Gamma-glutamyl transferase increased[d]	38 (4.6)	2.57	10 (7.6)	3.35
Sinusitis	23 (2.8)	1.53	9 (6.9)	2.95
Back pain	27 (3.3)	1.80	7 (5.3)	2.27
Herpes zoster infection	26 (3.2)	1.72	7 (5.3)	2.26
Upper respiratory tract infection	49 (6.0)	3.33	6 (4.6)	1.95

Data cutoff: September 30, 2020. One sudden death occurred during the OLE in a 57-year-old patient who entered the OLE in clinical response only, but the death was deemed unlikely to be related to ozanimod; the patient had a history of myocarditis, but the cause and circumstances of the death are unknown.
[a]Total PY was defined as the sum of the number of years on study contributed by each patient from time of first dose per treatment group to last date on study per treatment group. [b]EAIRs were calculated as number of patients/PY × 100. [c]The most frequent events were defined as those that occurred in ≥5% of patients who received ozanimod in the total OLE group or in subgroups of patients in clinical response at Week 52. [d]Laboratory values were flagged by the central laboratory if they fell outside the standard reference range; investigators decided whether laboratory values qualified as adverse events.
EAIR, exposure-adjusted incidence rate; OLE, open-label extension; PY, patient-years; TEAE, treatment-emergent adverse event.

Table 2. Disease activity at baseline and maintenance period Week 52 in patients treated with continuous ozanimod in clinical response at maintenance period Week 52 (OLE entry)

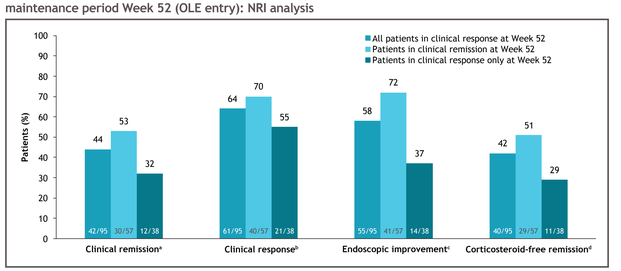
Characteristic	All patients in clinical response[a] at Week 52 (n=131) Baseline[c]	All patients in clinical response[a] at Week 52 (n=131) Week 52[c]	Patients in clinical remission[b] at Week 52 (n=83) Baseline[c]	Patients in clinical remission[b] at Week 52 (n=83) Week 52[c]	Patients in clinical response only at Week 52 (n=48) Baseline[c]	Patients in clinical response only at Week 52 (n=48) Week 52[c]
Total Mayo score,[d] mean (SD)	8.7 (1.5)	1.9 (1.7)	8.7 (1.5)	1.0 (0.9)	8.6 (1.6)	3.5 (1.5)
9-point Mayo score,[e] mean (SD)	6.5 (1.3)	1.5 (1.3)	6.5 (1.3)	0.7 (0.7)	6.5 (1.4)	2.8 (1.0)
Partial Mayo score,[e] mean (SD)	6.2 (1.3)	0.9 (1.1)	6.2 (1.3)	0.5 (0.7)	6.1 (1.3)	1.7 (1.3)
Endoscopy subscore, mean (SD)	2.5 (0.5)	1.0 (0.91)	2.5 (0.5)	0.5 (0.5)	2.5 (0.5)	1.8 (0.81)
Endoscopy subscore, n (%)						
0	0	50 (38.2)	0	45 (54.2)	0	5 (10.4)
1	0	43 (32.8)	0	38 (45.8)	0	5 (10.4)
2	64 (48.9)	31 (23.7)	41 (49.4)	0	23 (47.9)	31 (64.6)
3	67 (51.1)	7 (5.3)	42 (50.6)	0	25 (52.1)	7 (14.6)
CRP, mg/L, median (IQR)	3.0 (1.0-7.0)	2.0 (1.0-4.0)	3.0 (1.0-8.0)	2.0 (1.0-4.0)	2.0 (1.0-5.5)	2.0 (1.0-6.0)
Fecal calprotectin, ug/g, median (IQR)	1201 (337.9-2639.0)	44.1 (18.1-252.5)	1307 (359.3-3008.0)	22.7 (14.2-92.9)	976.8 (234.8-1675.0)	228.1 (67.9-1126.0)

[a]Clinical response is defined as a reduction from baseline in the 9-point Mayo score (sum of RBS, SFS, and endoscopy subscores) of ≥2 points and ≥35% and reduction from baseline in the RBS of ≥1 point or an absolute RBS of ≤1 point. [b]Clinical remission is defined as RBS=0, SFS ≤1 (and a decrease of ≥1 point from baseline SFS), and endoscopy subscore ≤1. [c]Baseline of the induction period. [d]End of the maintenance period OLE entry. [e]Sum of the RBS, SFS, PGA subscore, and endoscopy subscore.
CRP, C-reactive protein; IQR, interquartile range; OLE, open-label extension; PGA, Physician's Global Assessment; RBS, rectal bleeding subscore; SD, standard deviation; SFS, stool frequency subscore.

Efficacy

- A high proportion of patients treated with continuous ozanimod who entered the OLE in clinical response sustained clinical remission, clinical response, endoscopic improvement, and corticosteroid-free remission on ozanimod at OLE Week 46 in both OC (**Figure 2**) and NRI (**Figure 3**) analyses
  - 97% of all patients sustained clinical response over 98 weeks (OC analysis)
  - Of the patients in clinical response only at OLE entry, 55% achieved clinical remission after another year of ozanimod treatment (by OLE Week 46, OC analysis)

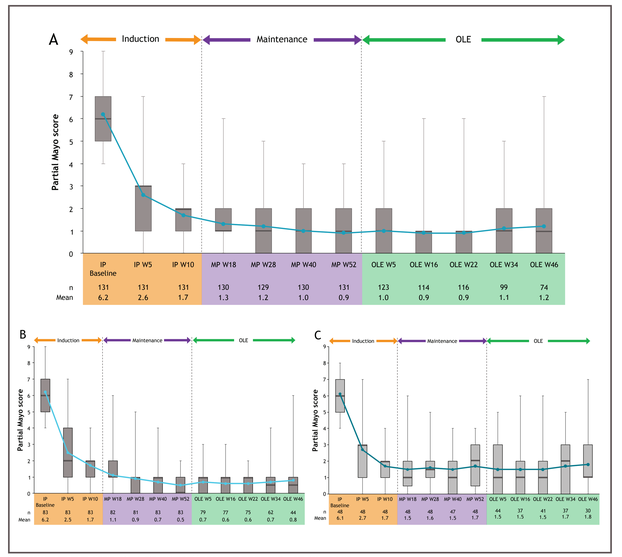
Figure 3. Ozanimod efficacy at OLE Week 46 by clinical response and clinical remission status at maintenance period Week 52 (OLE entry): NRI analysis



Note: Denominators for the NRI analysis were based on the numbers of patients who completed OLE Week 46 and who withdrew before OLE Week 46 but would have reached it if they had stayed.
[a]Clinical remission is defined as RBS=0 points, SFS ≤1 point (and a decrease of ≥1 point from the baseline SFS), and endoscopy subscore ≤1 point. [b]Clinical response is defined as a reduction from baseline in 9-point Mayo score of ≥2 points and ≥35%, and a reduction from baseline in RBS of ≥1 point or an absolute RBS of ≤1 point. [c]Endoscopic improvement is defined as an endoscopy subscore of ≤1 point. [d]Corticosteroid-free remission is defined as clinical remission while off corticosteroids for ≥12 weeks. Corticosteroid doses were kept stable during the True North induction period and tapered during the True North maintenance period; for patients who could not tolerate the taper without recurrence of clinical symptoms or steroid withdrawal, the corticosteroid dose could be increased and tapering could be resumed within 2 weeks.
NRI, nonresponder imputation; OLE, open-label extension; RBS, rectal bleeding subscore; SFS, stool frequency subscore.

- The mean partial Mayo score remained consistently low after the induction period in patients treated with continuous ozanimod who entered the OLE in clinical response (**Figure 4A**)
- The mean partial Mayo score was slightly lower in patients in clinical remission at OLE entry than those in clinical response only (**Figure 4B-C**)

Figure 4. Partial Mayo score[a] over time in patients treated with continuous ozanimod in (A) clinical response, (B) clinical remission, and (C) clinical response only at maintenance period Week 52 (OLE entry)



The box plot shows medians and interquartile ranges (error bars represent the minimum and maximum values). Means are shown in blue.
[a]Sum of the rectal bleeding, stool frequency, and Physician's Global Assessment subscores.
IP, induction period; MP, maintenance period; OLE, open-label extension; W, week.

Safety

- Safety data were generally similar between the total OLE population and patients treated with continuous ozanimod who entered the OLE in clinical response (**Table 3** and **Table 4**)
  - However, patients who entered the OLE in clinical response had lower incidence rates for TEAEs, serious TEAEs, and TEAEs leading to treatment discontinuation than those in the total OLE population

Table 4. Additional safety findings during the True North OLE for all patients and for patients treated with continuous ozanimod in clinical response at maintenance period Week 52 (OLE entry)

Characteristic	All patients in the OLE (N=823) Total PY[a] = 1540.4 n (%)	All patients in the OLE (N=823) Total PY[a] = 1540.4 EAIR per 100 PY[b]	Patients treated with continuous ozanimod in clinical response at Week 52 (OLE entry) (n=131) Total PY[a] = 316.8 n (%)	Patients treated with continuous ozanimod in clinical response at Week 52 (OLE entry) (n=131) Total PY[a] = 316.8 EAIR per 100 PY[b]
Infection TEAEs (occurring in ≥3% of subjects)[c]	288 (35.0)	25.76	53 (40.5)	24.49
Serious infection	22 (2.7)	1.45	5 (3.8)	1.63
Nasopharyngitis	73 (8.9)	5.10	10 (7.6)	3.33
Upper respiratory tract infection	49 (6.0)	3.33	6 (4.6)	1.95
Herpes zoster infection	26 (3.2)	1.72	7 (5.3)	2.26
Sinusitis	23 (2.8)	1.53	9 (6.9)	2.95
Bronchitis	23 (2.8)	1.53	6 (4.6)	1.93
Gastroenteritis	9 (1.1)	0.59	4 (3.1)	1.29
Influenza	19 (2.3)	1.25	4 (3.1)	1.28
Malignancy TEAEs	8 (1.0)	0.52	2 (1.5)	0.64
Basal cell carcinoma	4 (0.5)	0.26	1 (0.8)	0.32
Rectal adenocarcinoma	1 (0.1)	0.06	0	0
Lung neoplasm malignant	1 (0.1)	0.06	1 (0.8)	0.32
Breast cancer	1 (0.1)	0.06	0	0
Adverse events of special interest				
Bradycardia	9 (1.1)	0.59	4 (3.1)	1.30
Hypertension	37 (4.5)	2.47	13 (9.9)	4.35
Macular edema	3 (0.4)	0.19	1 (0.8)	0.32
Laboratory assessments[d]	n/N (%)		n/N (%)	
Alanine aminotransferase				
≥2 × ULN	120/817 (14.7)	NR	8/131 (6.1)	NR
≥3 × ULN	45/817 (5.5)	NR	8/131 (6.1)	NR
≥5 × ULN	14/817 (1.7)	NR	2/131 (1.5)	NR
Absolute lymphocyte count				
<200 cells/mm^3	31/805 (3.9)	NR	7/131 (5.3)	NR
<500 cells/mm^3	400/805 (49.7)	NR	7/131 (5.3)	NR

[a]Total PY was defined as the sum of the number of years on study contributed by each patient from time of first dose per treatment group to last date on study per treatment group. [b]EAIRs were calculated as number of patients/PY × 100. [c]Infectious TEAEs that occurred in ≥3% of patients who received ozanimod in the total OLE group or in subgroups of patients in clinical response at Week 52. [d]Patients were included if their laboratory values met these cutoffs at any point in the study; the denominator shows the number of evaluable subjects.
EAIR, exposure-adjusted incidence rate; NR, not reported; OLE, open-label extension; PY, patient-years; TEAE, treatment-emergent adverse event; ULN, upper limit of normal.

Conclusions

- This interim analysis of the True North OLE demonstrated that most patients who achieved clinical response or clinical remission after 52 weeks of ozanimod treatment sustained clinical remission, clinical response, and endoscopic improvement for another year with ongoing ozanimod treatment
- Patients in clinical response but not in clinical remission after 52 weeks of ozanimod treatment could achieve clinical remission with continued ozanimod therapy during the OLE
  - Patients in clinical response only after 52 weeks were more likely to have been exposed to TNF inhibitors than those who were in clinical remission
- No new safety signals were observed with long-term ozanimod use

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MTA: consulted and/or served on an advisory board for AbbVie, Arena Pharmaceuticals, Bristol Myers Squibb, Celsius Therapeutics, Eli Lilly, Gilead, Janssen, Microba, Pfizer, Prometheus Biosciences, UCB Biopharma, and WebMD Global; served as a teacher, lecturer, or speaker for Alimentiv, Intellisphere (HCP Live Institutional Perspectives in GI), Janssen, Prime CME, and Takeda; received grants/research support from Alimentiv, Bristol Myers Squibb, and Takeda. **PD:** received research support from Pfizer and Takeda; consulted for Bristol Myers Squibb, Eli Lilly, Gilead, Janssen, Novartis, Pfizer, and Takeda; shareholder of Digbi Health; received licensing royalties from Prenciklag. **AD:** received fees for participation in clinical trials and review activities (ie, data monitoring boards, statistical analysis, and endpoint committees) from AbbVie, Abivax, Celgene/Bristol Myers Squibb, Falk Foundation, Gilead, Janssen, and Pfizer; received consultancy fees from AbbVie, Amgen, Biogen, Boehringer Ingelheim, Celgene/Bristol Myers Squibb, Eli Lilly, Falk, Ferring, Fresenius Kabi, Galapagos, Gilead, Janssen, MSD, Pfizer, Pharmacosmos, Roche/Genentech, Sandoz/Hexal, Takeda, Tillotts, and Vifor; received payment for lectures, including service on speaker bureaus, from AbbVie, Eli Lilly, Falk Foundation, Ferring, Gilead/Galapagos, Janssen, MSD, Pfizer, Takeda, Tillotts, and Vifor; received payment for development of educational presentations from Ferring and Tillotts. **ES:** served as speaker for AbbVie, Alfasigma, AG Pharma, EG Stada Group, Fresenius Kabi, Grifols, Janssen, Innovamedica, Malesci, Pfizer, Reckitt Benckiser, Sandoz, SILA, Sofar, Takeda, and Unifarco; served as consultant for Alfasigma, Amgen, Biogen, Bristol Myers Squibb, Celltrion, Diadema Farmaceutici, Falk, Fresenius Kabi, Janssen, Merck, Reckitt Benckiser, Regeneron, Sanofi, Shire, SILA, Sofar, Synformulas GmbH, Takeda, and Unifarco; received research support from Reckitt Benckiser, SILA, Sofar, and Unifarco. **DH:** consulted for AbbVie, Bristol Myers Squibb, Janssen, Pfizer, and Takeda; received research support from Janssen and Pfizer. **AA:** served as consultant for AbbVie, Bristol Myers Squibb, DiaSorin, Eli Lilly, Gilead, Janssen, Pfizer, Takeda, and TLL Pharmaceuticals; and received speaker fees from AbbVie, Bristol Myers Squibb, Janssen, Pfizer, and Takeda. **VJ:** served as speaker for AbbVie, Ferring, Galapagos, Janssen, Pfizer, and Takeda; served as investigator, consultant, and advisory board member for AbbVie, Alimentiv (formerly Robarts Clinical Trials), Amgen, Applied Strategic, Arena, Asahi Kasei Pharma, Asieris, AstraZeneca, BioJamp, Celgene/Bristol Myers Squibb, Celltrion, Eli Lilly, Ferring, F. Hoffmann-La Roche Ltd., Flagship Pioneering, Fresenius Kabi, Galapagos, Genentech, Gilead, GlaxoSmithKline, Janssen, Organon (Merck), Landos Biopharma, Mylan, Pandion, Pendopharm, Pfizer, Protagonist Therapeutics, Reistone Biopharma, Roche, Sandoz, Second Genome, Takeda, Teva, Topivert, Ventyx Biosciences, and Vividion Therapeutics; employee and shareholder of Western University. **MO, LA, WJL, AM, AP, AJ, and JBC:** employees and/or shareholders of Bristol Myers Squibb. **SV:** received grant support from AbbVie, Johnson & Johnson, Pfizer, and Takeda; received consultancy fees from AbbVie, Arena, Celgene, Eli Lilly, Ferring, Galapagos, Genentech/Roche, Gilead, Hospira, Janssen, MSD, Mundipharma, Pfizer, Progenity, Second Genome, Shire, and Takeda.

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