Supplementary Materials

Supplementary Table 1. Summary of treatment assignment and duration under early and late protocol amendments

Protocol amendment	DB study group	OLE treatment assignment	Treatment duration
Early protocol amendment (amendment 2[a])	Responders[b] who received etrasimod 1 mg or etrasimod 2 mg	Randomised 1:1 to receive etrasimod 2 mg or placebo (blinded)	52 weeks total or until experiencing a flare; then may convert to OL etrasimod 2 mg or discontinue study
	Responders[b] who received placebo	Placebo (blinded)	52 weeks total or until experiencing a flare; then may convert to OL etrasimod 2 mg or discontinue study
	Non-responders	OL etrasimod 2 mg	52 weeks total
Late protocol amendment (amendments 3 and 4)[c]	All DB completers	OL etrasimod 2 mg	46 weeks total

[a]The first patient enrolled under amendment 2.

[b]Response was defined as 3-component Mayo Clinic score (endoscopy findings, rectal bleeding,

or stool frequency) of ≥2 points and ≥30% with either a decrease of rectal bleeding of ≥1 or rectal bleeding score of ≤1 at Week 12 vs DB baseline.

[c]There were no differences in OLE treatment assignment or treatment duration between amendments 3 and 4, but amendment 4 used modified language to describe the DB patient groups.

DB, double-blind; OL, open-label; OLE, open-label extension.

Supplementary Table 2. Treatment-emergent adverse events reported by ≥2 patients in any treatment group (safety population)[a]

Treatment in OLE:	**Etrasimod 2 mg**				**Placebo**
Treatment in DB study:	**Placebo (n = 42)**	**Etrasimod 1 mg (n = 38)**	**Etrasimod 2 mg (n = 32)**	**Overall (n = 112)**	**Total (n = 6)[b]**
TEAEs reported by ≥2 patients in any treatment group, n (%) [no. of events][c,d]					
Gastrointestinal disorders					
Abdominal pain upper	1 (2.4)	1 (2.6)	0	2 (1.8)	0
Ulcerative colitis—worsening[e]	5 (11.9) [7]	8 (21.1)	8 (25.0) [9]	21 (18.8) [24]	1 (16.7)
Nausea	2 (4.8)	3 (7.9)	0	5 (4.5)	1 (16.7)
Pancreatitis	1 (2.4)	0	1 (3.1)	2 (1.8)	0
Gastroesophageal reflux disease	1 (2.4)	0	1 (3.1)	2 (1.8)	0
Infections and infestations					
Cystitis	2 (4.8) [3]	0	0	2 (1.8) [3]	0
Gastroenteritis	3 (7.1) [4]	1 (2.6)	0	4 (3.6) [5]	0
Nasopharyngitis	3 (7.1)	2 (5.3)	1 (3.1) [3]	6 (5.4) [8]	2 (33.3)
Sinusitis	0	2 (5.3)	0	2 (1.8)	0

Upper respiratory tract infection	2 (4.8) [3]	4 (10.5)	1 (3.1)	7 (6.3) [8]	0
Urinary tract infection	1 (2.4)	1 (2.6)	0	2 (1.8)	0
Blood and lymphatic system disorders					
Anaemia[f]	2 (4.8)	4 (10.5) [5]	6 (18.8) [7]	12 (10.7) [14]	0
Neutropenia	0	2 (5.3)	1 (3.1)	3 (2.7)	0
Nervous system disorders					
Headache	4 (9.5)	0	1 (3.1)	5 (4.5)	0
Migraine	1 (2.4)	0	1 (3.1)	2 (1.8)	0
Musculoskeletal disorders					
Back pain	2 (4.8)	1 (2.6)	1 (3.1)	4 (3.6)	2 (33.3)
Metabolism and nutrition disorders					
Decreased appetite	2 (4.8)	0	0	2 (1.8)	0
Dehydration	0	1 (2.6)	1 (3.1)	2 (1.8)	0
Iron deficiency	2 (4.8)	0	0	2 (1.8)	0
General disorders and administration site conditions					
Asthenia	1 (2.4)	0	1 (3.1)	2 (1.8)	0
Fatigue	1 (2.4)	1 (2.6)	0	2 (1.8)	0
Pyrexia	0	2 (5.3)	0	2 (1.8)	0
Skin and subcutaneous tissue disorders					

Dermatitis	2 (4.8) [3]	0	0	2 (1.8) [3]	0
Night sweats	1 (2.4)	1 (2.6)	0	2 (1.8)	0
Vascular disorders					
Hypertension	1 (2.4) [2]	1 (2.6)	0	2 (1.8) [3]	0
Psychiatric disorders					
Anxiety	0	0	2 (6.3)	2 (1.8)	0

[a]TEAEs were defined as any AE that occurred after the first dose of study medication in the OLE, including any AEs that started in the DB study and were ongoing, worsened, or ended in the OLE. Events were coded using the Medical Dictionary for Regulatory Activities, version 20.1.

[b]Of the 6 patients who received placebo in the OLE, in the DB study 2 received placebo, 1 received etrasimod 1 mg, and 3 received etrasimod 2 mg.

[c]At each level of patient summarisation, a patient was counted once if the patient reported one or more events. Unless otherwise indicated, the number of events = the number of patients.

[d]Laboratory investigations were not included as TEAEs.

[e]Includes “colitis”, “colitis ulcerative”, and “proctitis ulcerative”.

[f]Includes “anaemia” and “iron-deficiency anaemia”.

AE, adverse event; DB, double-blind; OLE, open-label extension; TEAE, treatment-emergent AE.

Supplementary Table 3. Summary of treatment-emergent adverse events, excluding patients with worsening UC (safety population)[a,b]

Treatment in OLE:	**Etrasimod 2 mg**				**Placebo**
Treatment in DB study:	**Placebo (n =37)**	**Etrasimod 1 mg (n = 30)**	**Etrasimod 2 mg (n = 24)**	**Overall (n = 91)**	**Total (n = 5)**
Patients with ≥1 TEAE, n (%)	20 (54.1)	17 (56.7)	9 (37.5)	46 (50.5)	4 (80.0)
Number of TEAEs	82	57	27	166	21
Patients with TEAEs leading to death, n	0	0	0	0	0
Patients with TEAEs leading to study discontinuation, n (%)	2 (5.4)	0	0	2 (2.2)	0
Atrial fibrillation	1 (2.7)	0	0	1 (1.1)	0
Headache	1 (2.7)	0	0	1 (1.1)	0
Patients with serious TEAEs, n (%)	2 (5.4)	0	1 (4.2)	3 (3.3)	0
Anaemia[c]	0	0	1 (4.2)	1 (1.1)	0
Atrial fibrillation	1 (2.7)	0	0	1 (1.1)	0
Fine motor skill dysfunction	1 (2.7)	0	0	1 (1.1)	0
Patients with TEAEs reported by ≥2 patients in any treatment group, n (%)[d]					

Gastrointestinal disorders					
Abdominal pain upper	1 (2.7)	1 (3.3)	0	2 (2.2)	0
Nausea	2 (5.4)	2 (6.7)	0	4 (4.4)	1 (20.0)
Infections and infestations					
Gastroenteritis	2 (5.4)	1 (3.3)	0	3 (3.3)	0
Nasopharyngitis	3 (8.1)	1 (3.3)	1 (4.2)	5 (5.5)	2 (40.0)
Sinusitis	0	2 (6.7)	0	2 (2.2)	0
Upper respiratory tract infection	2 (5.4)	3 (10.0)	1 (4.2)	6 (6.6)	0
Blood and lymphatic system disorders					
Anaemia[c]	2 (5.4)	2 (6.7)	2 (8.3)	6 (6.6)	0
Neutropenia	0	2 (6.7)	1 (4.2)	3 (3.3)	0
Nervous system disorders					
Headache	3 (8.1)	0	0	3 (3.3)	0
Musculoskeletal disorders					
Back pain	2 (5.4)	1 (3.3)	1 (4.2)	4 (4.4)	2 (40.0)
Metabolism and nutrition disorders					
Decreased appetite	2 (5.4)	0	0	2 (2.2)	0
Iron deficiency	2 (5.4)	0	0	2 (2.2)	0
General disorders and administration site conditions					

Asthenia	1 (2.7)	0	1 (4.2)	2 (2.2)	0
Fatigue	1 (2.7)	1 (3.3)	0	2 (2.2)	0

The overall group includes patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period.

[a]TEAEs were defined as any AE that occurred after the first dose of study medication in the OLE, including any AEs that started in the DB study and were ongoing, worsened, or ended in the OLE. Events were coded using the Medical Dictionary for Regulatory Activities, version 20.1.

[b]"Worsening UC" includes "colitis ulcerative" and "colitis."

[c]Includes "anaemia" and "iron-deficiency anaemia."

[d]Laboratory investigations were not included as TEAEs.

AE, adverse event; DB, double-blind; OLE, open-label extension; TEAE, treatment-emergent AE.

Supplementary Table 4. Adverse events of special interest

Adverse Event	Additional details
1	One patient who received placebo in the DB study and switched to open-label etrasimod 2 mg had a reported AE of first-degree AV block (Grade 1 severity) that was considered study-drug related by the investigator. The first-degree AV block was recorded by ECG on Day 1 at 2, 3, 4, 5, and 6 hours after dosing, but was not present on Day 2 and was considered resolved with no change in dose.
2	One patient who received placebo in the DB study and switched to open-label etrasimod 2 mg had a reported, asymptomatic AE of heart rate lowering (Grade 1) that was not considered study-drug related by the investigator. The heart rate lowering occurred about 1.5 hours after the first dose (Day 1), with the recorded nadir of 48 beats per minute (bpm) at approximately 1 hour 42 minutes and 1 hour 43 minutes after dosing, which corresponded to the last ECG-recorded heart rates before discharge from the clinic. The AE was considered resolved on Day 29 without a change in dose.
3	One patient, who received placebo in the DB study and under protocol amendment 2 also initially received placebo in the OLE, switched to open-label etrasimod 2 mg on OLE Day 191 after experiencing an ulcerative colitis flare (per protocol amendment 2). A first-degree AV block was recorded on Day 191 at 7 hours after dosing with etrasimod 2 mg with a heart rate of 62 bpm. At 8 hours after dosing, no first-degree AV block was reported, and the patient's heart rate was 62 bpm. The first-degree AV block was considered not clinically significant by the investigator and was not reported as an

	AE. The AV block was recorded in 1 of a series of 11 ECGs taken on that day. Findings of poor precordial R-wave progression were recorded for the same ECG and for most of the other ECGs taken on that day. Upon review of the Holter monitoring report, occurrences of AV block Mobitz I were noted at about 2 and 3.5 hours post-dosing on Day 191 with a heart rate nadir during these episodes of 44 bpm. By about 6 hours post-dose, the Holter report recorded a normal sinus rhythm. The findings were assessed by the site investigator as not clinically significant. On Day 192 (1 day after starting open-label etrasimod 2 mg), the patient reported AEs of chest pain, dyspnea, and headache (Grade 2 severity) that were considered not related to the study drug by the investigator. The AEs were reported as resolved on Day 198. On Day 197 (6 days after starting open-label etrasimod 2 mg), the patient reported an AE of atrial fibrillation (Grade 3 severity) that was considered not related to the study drug by the investigator. The AE was reported as resolved on Day 198. The patient was discontinued from the study.
4	One patient who received etrasimod 2 mg in the DB study and open-label etrasimod 2 mg during the OLE had a reported AE of supraventricular extra systoles (Grade 2 severity) that was considered not related to the study drug by the investigator. The AE was reported based on post-dose (Day 2) Holter findings and was reported as recovering/resolving without a change in dose.

Patients who transitioned into the OLE were monitored from 24 hours before through 24 hours after the first dose of open-label etrasimod 2 mg with a Holter monitor and remained in the clinic after the first dose of etrasimod 2 mg for >6 hours and received hourly ECG measurements. "Day 1" refers to OLE Study Day 1.

AE, adverse event; AV, atrioventricular; DB, double-blind; ECG, electrocardiogram; OLE, open-label extension.

Supplementary Table 5. Key efficacy endpoints by treatment in the DB study using "as observed" analyses

		Etrasimod	Etrasimod			Etrasimod	Etrasimod	
	Placebo	1 mg	2 mg	Overall	Placebo	1 mg	2 mg	Overall
Efficacy outcome	**Week 12**				**EOT**			
Patients with clinical response								
Evaluable cohort[a]								
N	33	33	28	94	33	33	28	94
n (%)	9 (27.3)	13 (39.4)	16 (57.1)	38 (40.4)	23 (69.7)	25 (75.8)	18 (64.3)	66 (70.2)
90% CI	15.0, 42.8	25.1, 55.2	40.0, 73.1	31.9, 49.4	54.0, 82.5	60.5, 87.3	47.0, 79.2	61.5, 77.9
Completer evaluable cohort[b]								
N	31	31	22	84	31	31	22	84
n (%)	9 (29.0)	13 (41.9)	14 (63.6)	36 (42.9)	23 (74.2)	25 (80.6)	18 (81.8)	66 (78.6)
90% CI	16.1, 45.2	26.9, 58.2	43.9, 80.4	33.7, 52.4	58.2, 86.5	65.3, 91.2	63.1, 93.5	69.9, 85.7

Patients with clinical remission								
Evaluable cohort[a]								
N	33	33	28	94	33	33	28	94
n (%)	3 (9.1)	3 (9.1)	14 (50.0)	20 (21.3)	11 (33.3)	11 (33.3)	11 (39.3)	33 (35.1)
90% CI	2.5, 21.9	2.5, 21.9	33.3, 66.7	14.6, 29.4	19.9, 49.1	19.9, 49.1	23.8, 56.5	26.9, 44.0
Completer evaluable cohort[b]								
N	31	31	22	84	31	31	22	84
n (%)	3 (9.7)	3 (9.7)	12 (54.5)	18 (21.4)	11 (35.5)	11 (35.5)	11 (50.0)	33 (39.3)
90% CI	2.7, 23.2	2.7, 23.2	35.3, 72.9	14.3, 30.1	21.3, 51.8	21.3, 51.8	31.1, 68.9	30.3, 48.8
Patients with endoscopic improvement								
Evaluable cohort[a]								
N	33	34	29	96	33	34	29	96
n (%)	5 (15.2)	5 (14.7)	15 (51.7)	25 (26.0)	14 (42.4)	17 (50.0)	12 (41.4)	43 (44.8)

90% CI	6.2, 29.3	6.0, 28.5	35.2, 68.0	18.8, 34.4	27.8, 58.1	34.9, 65.1	25.9, 58.3	36.1, 53.7
Completer evaluable cohort[b]								
N	31	32	22	85	31	32	22	85
n (%)	5 (16.1)	5 (15.6)	13 (59.1)	23 (27.1)	14 (45.2)	17 (53.1)	12 (54.5)	43 (50.6)
90% CI	6.6, 31.0	6.4, 30.1	39.5, 76.7	19.3, 36.1	29.7, 61.3	37.3, 68.5	35.3, 72.9	41.2, 60.0

All patients received etrasimod 2 mg during the OLE. Groups are based on treatment during the DB period. The overall group includes patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period. Week 12 was the end of the DB period. In the "as observed" analyses only patients with non-missing assessments were included, and no missing data were imputed.

90% CI are exact CI for the % of patients who met the given endpoint.

[a]The evaluable cohort included patients who received any etrasimod 2 mg during the OLE and had the same treatment assignment throughout the OLE.

[b]The completer evaluable cohort included patients who received any etrasimod 2 mg during the OLE, had the same treatment throughout the OLE, and completed the study.

CI, confidence interval; DB, double-blind; EOT, end of treatment; N of patients in the population; n, number of patients with observation; OLE, open-label extension.

Supplementary Table 6. Improvement from DB baseline in mMCS by DB treatment using "as observed" analyses

	Placebo	Etrasimod 1 mg	Etrasimod 2 mg	Overall	Placebo	Etrasimod 1 mg	Etrasimod 2 mg	Overall
Efficacy outcome	**Week 12**				**EOT**			
Improvement in mMCS								
Evaluable cohort[a]								
N	32	33	28	93	33	33	28	94
mean ± SD	1.5 ± 1.9	1.7 ± 1.8	3.3 ± 2.5	2.1 ± 2.2	3.4 ± 2.4	3.4 ± 2.1	3.4 ± 2.6	3.4 ± 2.3
Completer evaluable cohort[b]								
N	30	31	22	83	31	31	22	84
mean ± SD	1.6 ± 1.9	1.7 ± 1.8	3.7 ± 2.2	2.2 ± 2.1	3.6 ± 2.3	3.6 ± 1.9	4.1 ± 2.2	3.8 ± 2.1

All patients received etrasimod 2 mg during the OLE. Groups are based on treatment during the DB period. The overall group includes patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period. Week 12 was the end of the DB period. In the "as observed" analyses only patients with non-missing assessments were included, and no missing data were imputed.

[a]The evaluable cohort included patients who received any etrasimod 2 mg during the OLE and had the same treatment assignment throughout the OLE.

[b]The completer evaluable cohort included patients who received any etrasimod 2 mg during the OLE, had the same treatment throughout the OLE, and completed the study.

DB, double-blind; EOT, end of treatment; mMCS, modified Mayo Clinic score; N, number of patients in the cohort; OLE, open-label extension; SD, standard deviation.

Supplementary Table 7. Clinical remission at EOT in patients who were steroid-free at EOT by DB treatment using "as observed" analyses

	Placebo	Etrasimod 1 mg	Etrasimod 2 mg	Overall
Patients with steroid-free clinical remission at EOT				
Evaluable cohort[a]				
N	21	24	21	66
n (%)	5 (23.8)	9 (37.5)	10 (47.6)	24 (36.4)
90% CI	9.9, 43.7	21.2, 56.3	28.6, 67.2	26.5, 47.2
Completer evaluable cohort[b]				
N	19	23	18	60
n (%)	5 (26.3)	9 (39.1)	10 (55.6)	24 (40.0)
90% CI	11.0, 47.6	22.2, 58.3	34.1, 75.6	29.3, 51.4

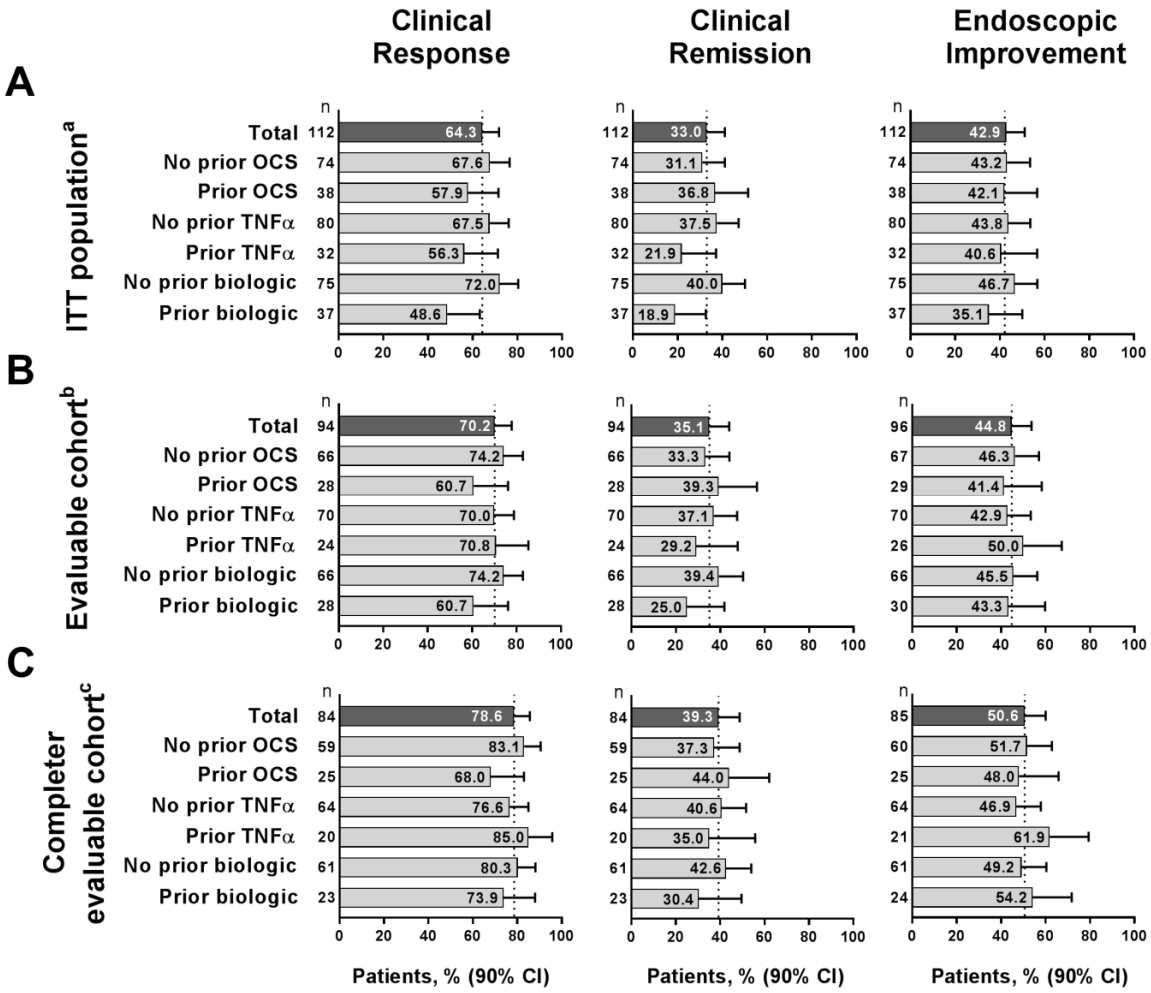
All patients received etrasimod 2 mg during the OLE. Groups are based on treatment during the DB period. The overall group includes patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB period. Week 12 was the end of the DB period. Patients were considered to have steroid-free clinical remission at EOT if they either did not use oral corticosteroids at any point during the OLE or were corticosteroid-free for at least 12 weeks prior to EOT. In the "as observed" analyses only patients with non-missing assessments were included, and no missing data were imputed.

[a]The evaluable cohort included patients who received any etrasimod 2 mg during the OLE and had the same treatment assignment throughout the OLE.

[b]The completer evaluable cohort included patients who received any etrasimod 2 mg during the OLE, had the same treatment throughout the OLE, and completed the study.

CI, confidence interval; DB, double-blind; EOT, end of treatment; N, number of patients who either did not use oral corticosteroids at any point during the OLE or were corticosteroid-free for at least 12 weeks prior to EOT; n, number of patients with observation; OLE, open-label extension.

Supplementary Figure 1. Proportion of patients with clinical response, clinical remission, or endoscopic improvement at EOT by prior UC treatment in the (A) ITT population, (B) evaluable cohort, and (C) completer evaluable cohort in patients who received etrasimod 2 mg in the OLE (overall group)



All patients received etrasimod 2 mg during the OLE. The overall group includes all patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB study. Biologic agents included anti-integrin and anti-TNFα agents. The vertical dotted lines indicate the percentage of patients with response in the total group.

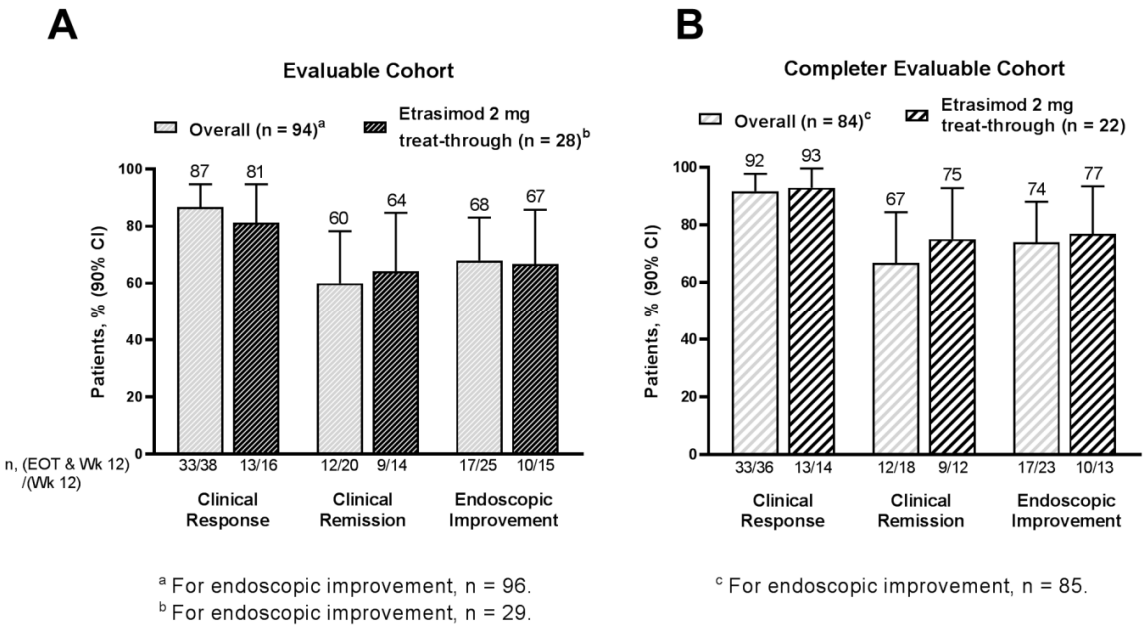
[a]The ITT population included all patients who received any etrasimod 2 mg during the OLE. In the NRI analysis data missing due to any reason, including study discontinuation, were imputed as non-response.

[b]The evaluable cohort included patients who received any etrasimod 2 mg during the OLE and had the same treatment assignment throughout the OLE.

[c]The completer evaluable cohort included patients who received any etrasimod 2 mg during the OLE, had the same treatment throughout the OLE, and completed the study.

CI, confidence interval; DB, double-blind; EOT, end of treatment; ITT, intention-to-treat; n, number of patients; NRI, non-responder imputation; OCS, oral corticosteroid; TNFα, tumour necrosis factor alpha; UC, ulcerative colitis.

Supplementary Figure 2. Proportion of patients with response at Week 12 that was sustained to EOT using "as observed" analyses



[a] For endoscopic improvement, n = 96.
[b] For endoscopic improvement, n = 29.
[c] For endoscopic improvement, n = 85.

All patients received etrasimod 2 mg during the OLE. The overall group includes patients who received any treatment (placebo, etrasimod 1 mg, or etrasimod 2 mg) during the DB study. The etrasimod 2 mg treat-through group received etrasimod 2 mg during both the DB study and OLE.

CI, confidence interval; DB, double-blind; EOT, end of treatment; n, number of patients; OLE, open-label extension; Wk, week.