Etrasimod 2 mg Once Daily as Treatment for Patients With Moderately to Severely Active Ulcerative Colitis: Topline and Subgroup Analysis From ELEVATE UC 52 and ELEVATE UC 12

D0381

Brian G. Feagan,[1]* Laurent Peyrin-Biroulet,[2]* William J. Sandborn,[3] Geert D'Haens,[4] Julian Panes,[5] Andres Yarur,[6] Douglas C. Wolf,[7] Timothy Ritter,[8] Stefan Schreiber,[9] Sheldon Sloan,[10] Fabio Cataldi,[10] Kevin Shan,[10] Christopher J. Rabbat,[10] Michael Chiorean,[11] Filip Baert,[12] Bruce E. Sands,[13] Marla C. Dubinsky,[14] Séverine Vermeire,[15] Martina Goetsch,[16] Silvio Danese[17]

*Dual first authors; [1]University of Western Ontario, London, ON, Canada; [2]Université de Lorraine, CHRU-Nancy, Department of Gastroenterology, F-54000 Nancy, France, and University of Lorraine, Inserm, NGERE, F-54000 Nancy, France; [3]University of California San Diego School of Medicine, La Jolla, CA; [4]University of Amsterdam, Amsterdam, the Netherlands; [5]Hospital Clínic de Barcelona, IDIBAPS. CIBERehd, Barcelona, Spain; [6]Cedars-Sinai Medical Center, Los Angeles, CA; [7]Atlanta Gastroenterology Associates, Atlanta, GA; [8]GI Alliance Research, Southlake, TX; [9] Department Internal Medicine I, University Hospital Schleswig-Holstein, Kiel University, Kiel, Germany; [10]Arena Pharmaceuticals, San Diego, CA, a wholly-owned subsidiary of Pfizer Inc, New York, NY; [11]IBD Center, Swedish Medical Center, Seattle, WA; [12]AZ Delta, Roeselare, Belgium; [13]Division of Gastroenterology, Icahn School of Medicine at Mount Sinai, New York, NY; [14]Feinstein IBD Center, Mount Sinai, New York, NY; [15]University Hospitals Leuven, Leuven, Flanders, Belgium; [16]Arena Pharmaceuticals Development GmbH, Zug, Switzerland, a wholly-owned subsidiary of Pfizer Inc New York, NY; [17]IRCCS Ospedale San Raffaele and University Vita-Salute San Raffaele Milan, Italy

BACKGROUND

- Etrasimod (APD334) is an investigational, once-daily, oral, selective sphingosine 1-phosphate receptor 1,4,5 modulator
- Here, we report data from ELEVATE UC 52 and ELEVATE UC 12, 2 randomized, double-blind, placebo-controlled, phase 3 trials that evaluated the efficacy and safety of etrasimod 2 mg/day in adults with ulcerative colitis (UC) as well as data from a predefined subgroup analyses which stratified patients by prior exposure to advanced therapy (biologic/Janus kinase inhibitors [JAKis])

LIMITATIONS

- The studies were not powered to assess efficacy vs placebo in the biologic/JAKi subgroups
- The long-term safety and efficacy data are limited to 52-weeks of follow up

CONCLUSIONS

- In both studies, treatment with etrasimod 2 mg/day resulted in clinically meaningful and statistically significant improvements in primary and key secondary outcomes measures
- Patients who were naïve to or received 1 prior biologic/JAKi therapy experienced similar benefit with etrasimod in both ELEVATE UC 52 and ELEVATE UC 12, whereas patients who had experience with multiple advanced therapies showed less consistent benefit
- The safety profile of etrasimod was favorable with that in previous studies

Disclosures

B. G. Feagan: consultant for AbbVie, AgomAb Therapeutics, Applied Molecular Transport, Arena Pharma, Boehringer-Ingelheim, Eli Lilly, Ferring, Galapagos, Atlantic, Genentech/Roche, Gilead, Gossamer Bio, GSK, F. Hoffmann-LaRoche, ImmuNext, Janssen, Morphic Therapeutics, Pandion Therapeutics, Pfizer, Prometheus, Progenity, Sanofi, Seres Therapeutics, Surrozen, Takeda, Theravance, TiGenix, Tillotts, and Zealand Pharma; speaker bureau fees from AbbVie, Janssen, and Takeda; scientific advisory board for AbbVie, Amgen, Boehringer-Ingelheim, Celgene/BMS, Genentech/Roche, Janssen, Novartis, Origo Biopharma, Pfizer, Prometheus, Takeda, Tillotts, Teva, Progenity, Index, and GSK; stockholder of Gossamer Bio.
L. Peyrin-Biroulet: personal fees from Galapagos, AbbVie, Janssen, Genentech, Alimentiv, Ferring, Tillotts, Celltrion, Takeda, Pfizer, Index Pharmaceuticals, Sandoz, Celgene, Biogen, Samsung Bioepis, Inotrem, Allergan, MSD, Roche, Arena, Gilead, Amgen, BMS, Vifor, Norgine, Mylan, Lilly, Fresenius Kabi, OSE Immunotherapeutics, Enthera, Theravance, Pandion Therapeutics, Gossamer Bio, Viatris, Thermo Fisher, and ONO Pharma; stockholder of CTMA.
W. J. Sandborn: research grants from AbbVie, Abivax, Arena, Boehringer Ingelheim, BMS, Genentech, Gilead Sciences, GSK, Janssen, Lilly, Pfizer, Prometheus Laboratories, Seres Therapeutics, Shire Pharmaceuticals, Takeda, and Theravance; consulting fees from AbbVie, Abivax, Alfasigma, Alimentiv (previously Robarts Clinical Trials, owned by Alimentiv Health Trust), Allakos, Amgen, Arena Pharmaceuticals, AstraZeneca, Atlantic Pharmaceuticals, BeiGene, Boehringer Ingelheim, BMS, Celltrion, ClostraBio, Forbion, Galapagos, Genentech/Roche, GSK, Gossamer Bio, Index Pharmaceuticals, Iota Biosciences, Janssen, Lilly, Morphic Therapeutics, Novartis, Oppilan Pharma (now Ventyx Biosciences), Pfizer, Pharm-Olam, Polpharm, Progenity, Prometheus Biosciences, Protagonist Therapeutics, PTM Therapeutics, Seres Therapeutics, Shoreline Biosciences, Sublimity Therapeutics, Surrozen, Takeda, Theravance Biopharma, Vedanta Biosciences, Ventyx Biosciences, Vimalan Biosciences, Vivreon Gastrosciences, Xencor, and Zealand Pharmaceuticals; stock or stock options in Allakos, BeiGene, Gossamer Bio, Oppilan Pharma (now Ventyx Biosciences), Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonists Therapeutics, Shoreline Biosciences, Ventyx Biosciences, Vimalan Biosciences, and Vivreon Gastrosciences; Chief Medical Officer of Ventyx Biosciences.
G. D'Haens: consultant for AbbVie, AgomAb, AstraZeneca, AM Pharma, AMT, Arena Pharmaceuticals, BMS, Boehringer Ingelheim, Celltrion, Eli Lilly, Exeliom Biosciences, Exo Biologics, Galapagos, Index Pharmaceuticals, Kaleido, Roche, Gilead, GSK, Gossamer Bio, Pfizer, Immunic, J&J, Origo, Polpharma, Procise Diagnostics, Prometheus Laboratories, Prometheus Biosciences, Progenity, and Protagonist; speakers bureau fees from AbbVie, Arena, Galapagos, Gilead, Pfizer, BMS, and Takeda.
J. Panes: consulting fees from AbbVie, Arena Pharmaceuticals, Athos, Atomwise, Boehringer Ingelheim, Celgene, Celltrion, Ferring, Galapagos, Genentech, GSK, Janssen, Mirum, Morphic, Nestle, Origo, Pandion, Pfizer, Progenity, Protagonist, Revolo, Robarts Clinical Trials, Roche, Takeda, Theravance, and Wassermann; speaker fees from AbbVie, Biogen, Ferring, Janssen, Pfizer, and Takeda; research funding from AbbVie and Pfizer.
A. Yarur: consulting fees from Takeda, Prometheus Labs, Arena pharmaceuticals, and BMS; speakers bureau fees from BMS.
D. C. Wolf: consulting and/or speaker honoraria from AbbVie, Arena, BMS, Janssen, Lilly, Pfizer, and Takeda.
T. Ritter: personal fees from Gilead, AbbVie, Arena Pharmaceuticals, Ferring, Genentech, Gossamer, Intercept, Janssen, Eli Lilly, Pfizer, Prometheus, and Takeda.
S. Schreiber: consultant for AbbVie, Amgen, Arena, BMS; Boehringer Ingelheim, Celltrion, Dr Falk Pharma, Ferring, Fresenius, Galapagos, Genentech, GSK, Gilead, I-Mab Biopharma, Janssen, Lilly, Merck, Novartis/Sandoz, Pfizer, Protagonist, Takeda, and Theravance.
S. Sloan, F. Cataldi, K. Shan, C. J. Rabbat, and **M. Goetsch:** employees and stockholders of Arena Pharmaceuticals, a wholly-owned subsidiary of Pfizer Inc.
M. Chiorean: speaker for AbbVie, Janssen, Medtronic, Pfizer, BMS, and Takeda; consultant for AbbVie, Arena, BMS, Medtronic, Pfizer, Prometheus, Lilly, and Takeda.
F. Baert: grant/research support from AbbVie, Amgen, Janssen, and Takeda; honoraria from AbbVie, Amgen, Arena, Celgene, Celltrion, Ferring, Fresenius Kabi, Janssen, MSD, Pfizer, Sandoz, and Takeda; speakers bureau fees from AbbVie, Arena, Ferring, Galapagos, Janssen, MSD, Pfizer, and Takeda.
B. E. Sands: consulting fees from Abivax, Amgen, Arena Pharmaceuticals, Artugen Therapeutics, AstraZeneca, Bacainn Therapeutics, Boehringer-Ingelheim, Boston Pharmaceuticals, BMS, Calibr, Celltrion Healthcare, ClostraBio, Entera, Evommune, Galapagos, Genentech, Gilead, GSK, Gossamer Bio, Index Pharmaceuticals, Inotrem, Innovation Therapeutics, Ironwood Pharmaceuticals, Janssen, Kaleido, Kallyope, Lilly, Miro Bio, Morphic Therapeutics, MRM Health, Pfizer, Progenity, Prometheus Biosciences, Protagonist Therapeutics, Q32 Bio, Surrozen, Takeda, Teva, TLL Pharmaceutical, USWM Enterprises, and Viela Bio; speakers bureau fees from Abivax, BMS, Janssen, Pfizer, and Takeda; grant/research support from Janssen.
M. C. Dubinsky: consulting fees from AbbVie, Arena, BMS, Celgene, Eli Lilly, Genentech, Gilead, Janssen, Pfizer, Prometheus Labs, and Takeda; founder and a shareholder of Trellus Health.
S. Vermeire: grants from AbbVie, J&J, Pfizer, Galapagos, and Takeda; consulting and/or speakers bureau fees from AbbVie, AbolerIS Pharma, AgomAb, Alimentiv, Arena Pharmaceuticals, AstraZeneca, Avaxia, BMS, Boehringer Ingelheim, Celgene, CVasThera, Dr Falk Pharma, Ferring, Galapagos, Genentech/Roche, Gilead, GSK, Hospira, IMIdomics, Janssen, J&J, Lilly, Materia Prima, MiroBio, Morphic, MrMHealth, Mundipharma, MSD, Pfizer, Prodigest, Progenity, Prometheus, Robarts Clinical Trials, Second Genome, Shire, Surrozen, Takeda, Theravance, Tillotts, and Zealand Pharma.
S. Danese: consultancy fees from AbbVie, Alimentiv, Allergan, Amgen, AstraZeneca, Athos Therapeutics, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Dr Falk Pharma, Eli Lilly, Enthera, Ferring, Gilead, Hospira, Inotrem, J&J, MSD, Mundipharma, Mylan, Pfizer, Roche, Sandoz, Sublimity Therapeutics, Takeda, TiGenix, UCB, and Vifor; payment for expert testimony from AbbVie, Amgen, Ferring, Gilead, Janssen, Mylan, Pfizer, and Takeda.

Ackowledgements

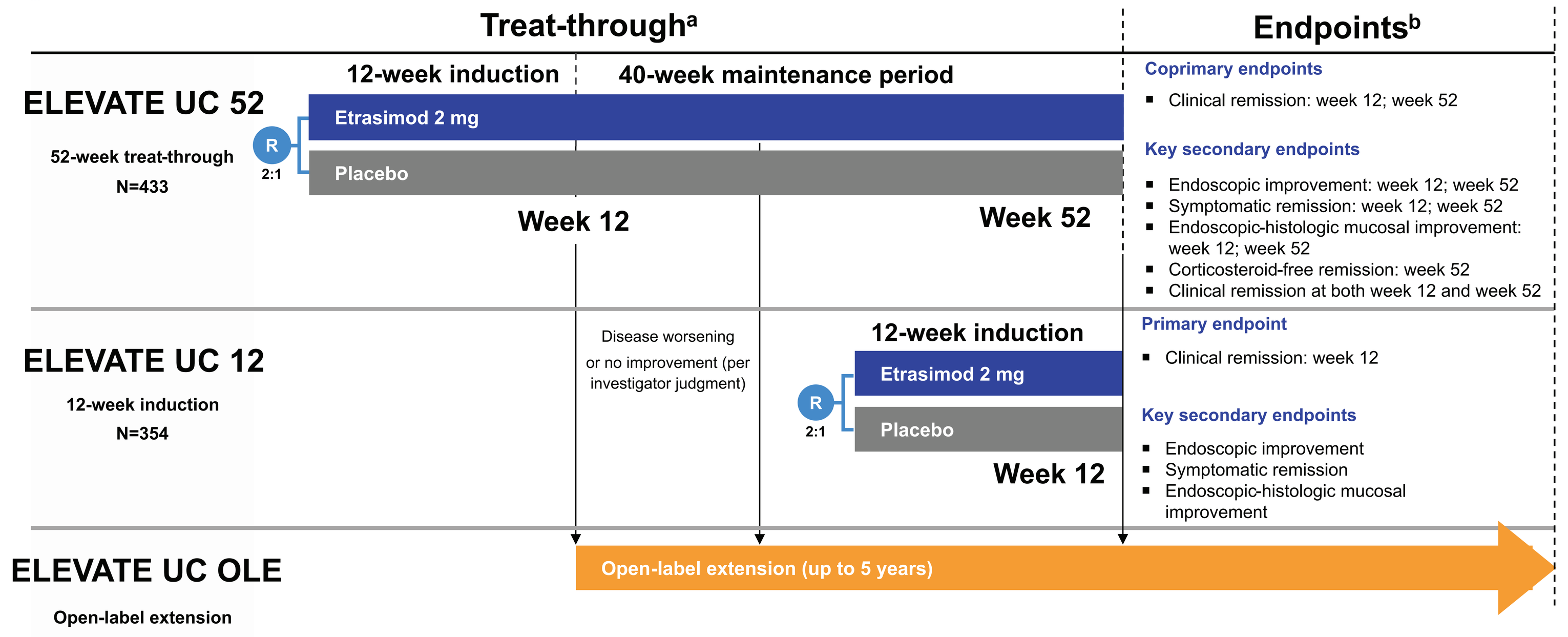
This study was sponsored by Arena, which was acquired by Pfizer in March 2022. Editorial/medical writing support was provided by Samantha O'Dwyer, PhD, at Health Interactions, Inc, and was funded by Arena, which was acquired by Pfizer in March 2022.

Presented at American College of Gastroenterology; October 21-26, 2022; Charlotte, North Carolina, and virtual.

METHODS

- ELEVATE UC 52 (NCT03945188) and ELEVATE UC 12 (NCT03996369) were 2 global, randomized, multicenter, double-blind, placebo-controlled, phase 3 trials with pre-established primary and key secondary endpoints; the primary analysis included patients with a modified Mayo Score (MMS) of 5-9 (**Figure 1**)
  - ELEVATE UC 52 used a treat-through design comprising a 12-week induction period followed by a 40-week maintenance period
  - ELEVATE UC 12 comprised a 12-week induction period only
- This subgroup analysis examined outcomes in patients naïve to, or with prior experience with 1 or >1 biologics/JAKi; the subgroup analysis included patients with an MMS of 4-9

Figure 1. ELEVATE UC 52 and ELEVATE UC 12 Trial Schematic


Treat-through[a]
Endpoints[b]
ELEVATE UC 52
52-week treat-through
N=433
12-week induction
40-week maintenance period
R
2:1
Etrasimod 2 mg
Placebo
Week 12
Week 52
Coprimary endpoints
Clinical remission: week 12; week 52
Key secondary endpoints
Endoscopic improvement: week 12; week 52
Symptomatic remission: week 12; week 52
Endoscopic-histologic mucosal improvement: week 12; week 52
Corticosteroid-free remission: week 52
Clinical remission at both week 12 and week 52
ELEVATE UC 12
12-week induction
N=354
Disease worsening or no improvement (per investigator judgment)
12-week induction
Etrasimod 2 mg
Placebo
Week 12
Primary endpoint
Clinical remission: week 12
Key secondary endpoints
Endoscopic improvement
Symptomatic remission
Endoscopic-histologic mucosal improvement
ELEVATE UC OLE
Open-label extension
Open-label extension (up to 5 years)

JAKi, Janus kinase inhibitor; OLE, open-label extension; R, randomization; UC, ulcerative colitis.
[a] Beginning at week 12, all patients could continue their randomized treatment into a 40-week maintenance period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue treatment and, if eligible, enroll in an OLE study (NCT03950232).
[b] Subgroup analyses included patients who had received prior biologic and JAKi treatments which included tumor necrosis factor antagonists (adalimumab, golimumab, infliximab, or biosimilars), anti-integrin antibodies (vedolizumab), anti–interleukin 12/23 antibodies (ustekinumab), and JAKis (tofacitinib).

RESULTS

Patient Demographics

- Among the prior biologic/JAKi-experienced patients, drug histories were similar across both treatment arms and included patients with exposure to tumor necrosis factor inhibitor (TNFi), anti-integrin, anti–interleukin (IL)-12/23, and JAKi therapy (**Table 1**)
- At baseline, prior biologic/JAKi–experienced patients had longer disease duration than patients naïve to biologic/JAKis

Table 1. Baseline Demographic and Clinical Characteristics

Characteristic	Population	ELEVATE UC 52		ELEVATE UC 12	
		Placebo Overall, N=144 Bio/JAKi naïve, n=99 1 bio/JAKi, n=25 >1 bio/JAKi, n=20	Etrasimod Overall, N=289 Bio/JAKi naïve, n=205 1 bio/JAKi, n=44 >1 bio/JAKi, n=40	Placebo Overall, N=116 Bio/JAKi naïve, n=77 1 bio/JAKi, n=20 >1 bio/JAKi, n=19	Etrasimod Overall, N=238 Bio/JAKi naïve, n=159 1 bio/JAKi, n=36 >1 bio/JAKi, n=43
Extent of UC (left-sided colitis/ proctosigmoiditis), n (%)	Overall	90 (62.5)	172 (59.5)	63 (54.3)	146 (61.3)
	Bio/JAKi naïve	68 (68.7)	128 (62.4)	43 (55.8)	105 (66.0)
	1 bio/JAKi	13 (52.0)	27 (61.4)	12 (60.0)	16 (44.4)
	>1 bio/JAKi	9 (45.0)	17 (42.5)	8 (42.1)	25 (58.1)
Duration of UC, mean (SD), years	Overall	5.9 (5.5)	7.5 (8.0)	7.7 (7.3)	7.3 (6.6)
	Bio/JAKi naïve	4.7 (4.6)	5.5 (6.3)	6.6 (6.7)	6.5 (6.6)
	1 bio/JAKi	8.3 (7.3)	12.9 (10.3)	8.2 (6.3)	8.2 (6.5)
	>1 bio/JAKi	8.8 (5.3)	11.5 (8.9)	11.4 (9.6)	9.3 (6.4)
MMS, mean (SD)[a]	Overall	6.7 (1.2)	6.7 (1.2)	6.6 (1.2)	6.6 (1.2)
	Bio/JAKi naïve	6.6 (1.2)	6.7 (1.2)	6.5 (1.2)	6.5 (1.2)
	1 bio/JAKi	6.8 (1.0)	6.8 (1.1)	7.2 (1.1)	6.7 (1.2)
	>1 bio/JAKi	6.8 (1.3)	6.8 (1.3)	6.6 (1.2)	6.6 (1.2)

Bio, biologic; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; UC, ulcerative colitis.
[a] The MMS is defined as the sum of the rectal bleeding subscore, stool frequency subscore, and endoscopy subscore (each subscore on a scale of 0-3). Overall scores range from 0 to 9, with higher scores indicating greater disease activity.

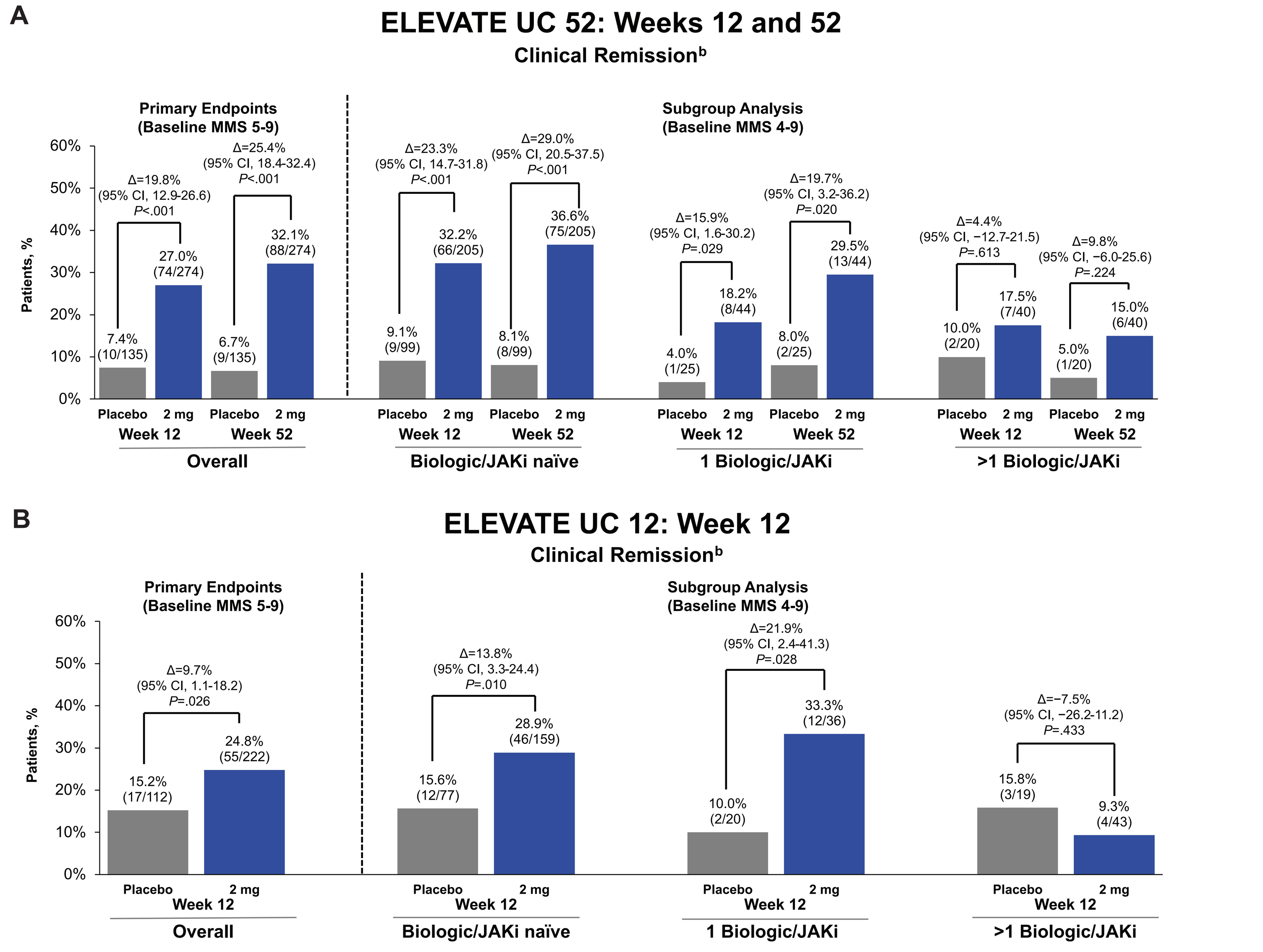
Clinical Remission in Overall Population (Primary Efficacy Endpoint) and Stratified by Prior Biologic/JAKi Exposure

- The primary efficacy endpoint of clinical remission was achieved with etrasimod vs placebo at both weeks 12 and 52 in ELEVATE UC 52 and week 12 in ELEVATE UC 12 (**Figure 2**)
- Clinical remission in ELEVATE UC 52 was achieved at both weeks 12 and 52 in biologic/JAKi-naïve patients treated with etrasimod vs placebo and responses were generally greater than in those with prior biologic/JAKi experience (**Figure 2A**)
  - Etrasimod-treated patients with 1 prior biologic/JAKi achieved significantly higher rates of clinical remission than placebo-treated patients at weeks 12 and 52
  - Patients who had prior experience with only 1 biologic/JAKi generally had higher responses rates with etrasimod than patients with prior experience with >1 biologic/JAKi
- Clinical remission in ELEVATE UC 12 was achieved at week 12 in biologic/JAKi-naïve patients treated with etrasimod vs placebo (**Figure 2B**)
  - Etrasimod-treated patients who had received 1 prior biologic/JAKi achieved significantly higher rates of clinical remission than placebo-treated patients at week 12

Achievement of Key Secondary Efficacy Endpoints (Overall Population)

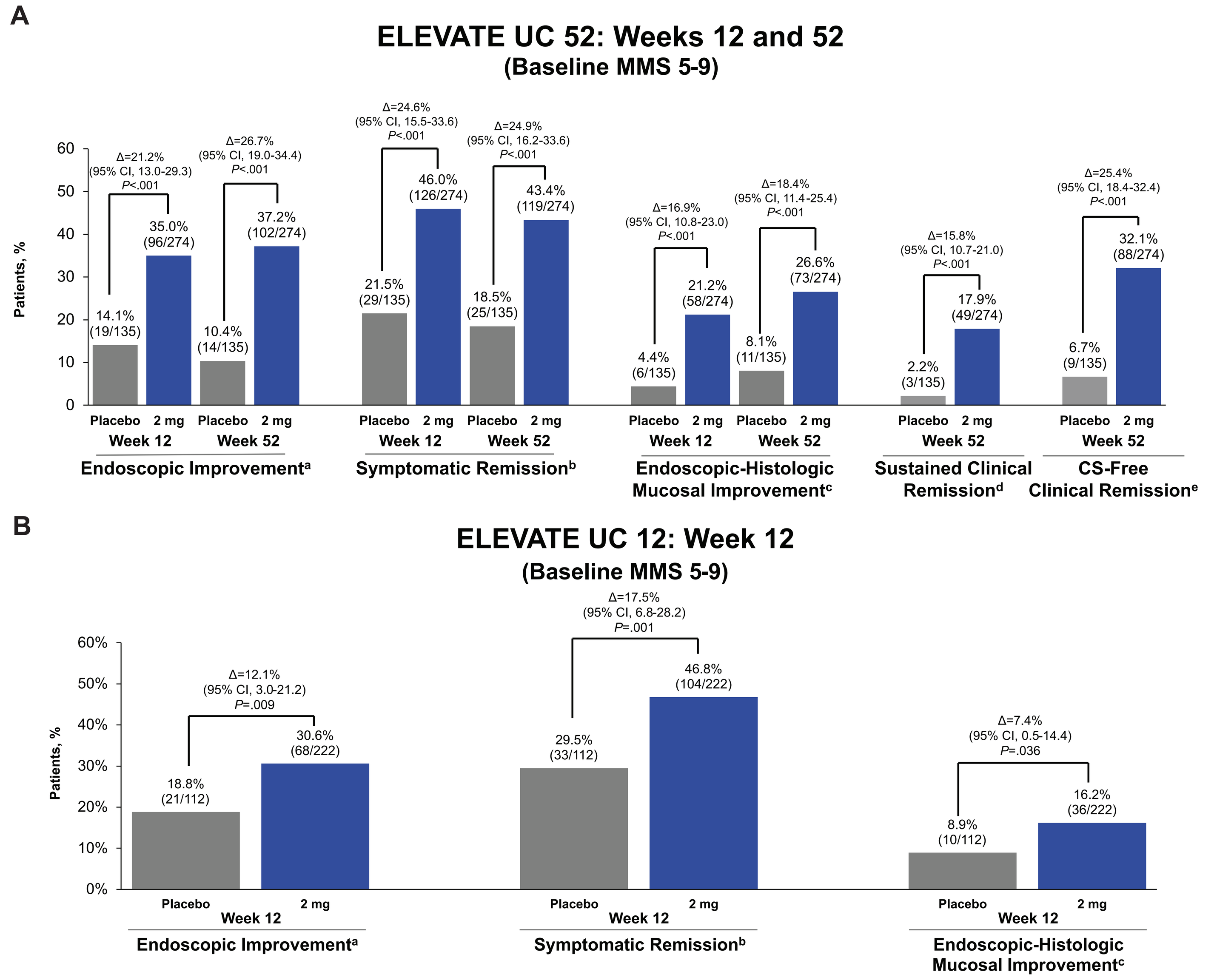
- In ELEVATE UC 52, significant improvements with etrasimod were observed in all key secondary endpoints at week 12 and week 52 (**Figure 3A**); similar findings were observed at week 12 in ELEVATE UC 12 (**Figure 3B**)

Figure 2. Achievement of Clinical Remission in (A) ELEVATE UC 52 and (B) ELEVATE UC 12 Overall Population (Primary Efficacy Endpoint) and Stratified by Prior Biologic/JAKi Exposure[a]


A
ELEVATE UC 52: Weeks 12 and 52
Clinical Remission[b]
Primary Endpoints (Baseline MMS 5-9)
Subgroup Analysis (Baseline MMS 4-9)
Patients, %
Placebo
2 mg
Week 12
Week 52
Overall
Biologic/JAKi naïve
1 Biologic/JAKi
>1 Biologic/JAKi
B
ELEVATE UC 12: Week 12
Clinical Remission[b]
Primary Endpoints (Baseline MMS 5-9)
Subgroup Analysis (Baseline MMS 4-9)
Patients, %
Placebo
2 mg
Week 12
Overall
Biologic/JAKi naïve
1 Biologic/JAKi
>1 Biologic/JAKi

ES, endoscopic subscore; JAKi, Janus kinase inhibitor; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
[a] The a priori defined analyses were based on Cochran-Mantel-Haenszel analysis of the full analysis set (all randomized patients who received ≥1 dose of study drug) and used the nonresponder imputation method with a baseline MMS of 5-9 in the primary analysis and a baseline MMS of 4-9 in the subgroup analysis. Significance for the subgroup analysis is represented using nominal 2-sided P values.
[b] SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1.

Figure 3. Achievement of Key Secondary Efficacy Outcomes in (A) ELEVATE UC 52 and (B) ELEVATE UC 12


A
ELEVATE UC 52: Weeks 12 and 52
(Baseline MMS 5-9)
Patients, %
Placebo
2 mg
Week 12
Week 52
Endoscopic Improvement[a]
Symptomatic Remission[b]
Endoscopic-Histologic Mucosal Improvement[c]
Sustained Clinical Remission[d]
CS-Free Clinical Remission[e]
B
ELEVATE UC 12: Week 12
(Baseline MMS 5-9)
Patients, %
Placebo
2 mg
Week 12
Endoscopic Improvement[a]
Symptomatic Remission[b]
Endoscopic-Histologic Mucosal Improvement[c]

ES, endoscopic subscore; MMS, modified Mayo Score; RB, rectal bleeding; SF, stool frequency.
[a] ES ≤1.
[b] SF subscore =0 (or =1 with a ≥1-point decrease from baseline) and RB subscore =0.
[c] ES ≤1 with histologic remission as measured by a Geboes Index score <2.0.
[d] Clinical remission at both weeks 12 and 52.
[e] Patients in remission at week 52 with no use of corticosteroids for at least the last 12 study weeks immediately before week 52.

Secondary Efficacy Endpoints (Subgroup Analysis)

- In both trials, significant improvements in endoscopic improvement, symptomatic remission, and endoscopic-histologic mucosal improvement were observed in biologic/JAKi–naïve patients treated with etrasimod vs placebo
- In ELEVATE UC 52, significant improvements in endoscopic improvement, symptomatic remission, and endoscopic-histologic mucosal improvement were observed in the subgroups with exposure to 1 prior biologic/JAKi; numerically greater improvements in ELEVATE UC 12 were observed in endoscopic improvement and endoscopic-histologic mucosal improvement with significant improvements experienced in symptomatic remission
- In patients with exposure to >1 prior biologic/JAKi, significant improvements were demonstrated at both weeks 12 and 52 in endoscopic-histologic mucosal improvement and at week 52 in endoscopic improvement in ELEVATE UC 52
- Overall, results from the subgroup analysis are consistent with data observed in the key secondary endpoints of the overall population

Etrasimod Safety and Tolerability

- Infections and serious infections were similar across treatment groups, including herpes zoster and opportunistic infections
- The majority of adverse events (AEs) were considered mild or moderate (**Table 2**)
  - No deaths occurred in either trial
  - 9 patients experienced bradycardia/sinus bradycardia with 8/9 occurring on day 1; 2/9 were symptomatic (dizziness) and 5/9 discontinued treatment
  - No serious/severe AEs of bradycardia or atrioventricular block were reported
  - 3 patients experienced AEs of atrioventricular block, all were asymptomatic and 2 of which discontinued treatment
  - In both studies, no malignancies or serious/severe hepatic injuries were reported in either treatment group

Table 2. Overall Safety Profile in ELEVATE UC 52 and ELEVATE UC 12

Participants, n (%)[a]	ELEVATE UC 52 Safety Set (N=433)		ELEVATE UC 12 Safety Set (N=354)	
	Placebo (n=144)	Etrasimod 2 mg (n=289)	Placebo (n=116)	Etrasimod 2 mg (n=238)
Any AEs	81 (56.3)	206 (71.3)	54 (46.6)	112 (47.1)
Any serious AEs	9 (6.3)	20 (6.9)	2 (1.7)	6 (2.5)
AEs leading to death	0	0	0	0
Overall infections and infestations	32 (22.2)	72 (24.9)	14 (12.1)	27 (11.3)
Most common AEs in etrasimod group				
Headache	7 (4.9)	24 (8.3)	2 (1.7)	11 (4.6)
Worsening of UC	13 (19.0)	22 (7.6)	1 (0.9)	9 (3.8)
COVID-19 infection	9 (6.3)	20 (6.9)	3 (2.6)	3 (1.3)

AE, adverse event; UC, ulcerative colitis.
[a] Safety set included all randomized patients who received ≥1 dose of study treatment. Data are not exposure adjusted.