Efficacy and safety of the oral selective sphingosine-1-phosphate-1 receptor modulator VTX002 in moderately to severely active ulcerative colitis: results from a randomised, double-blind, placebo-controlled, phase 2 trial (OP03)

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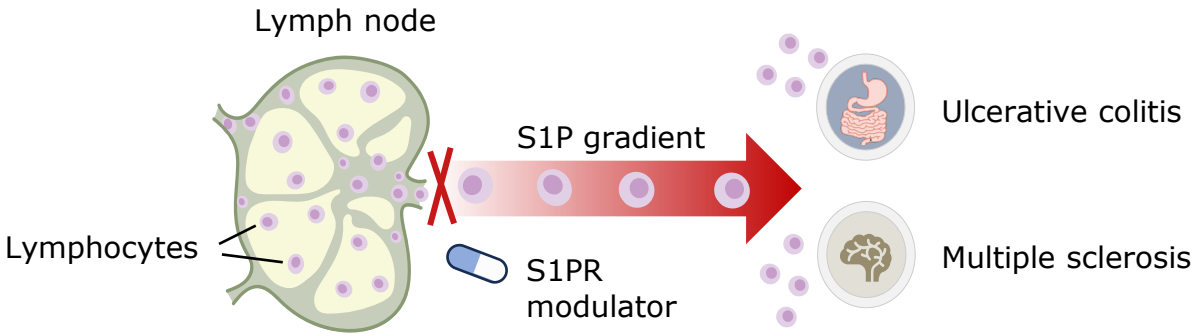
Potential Conflicts of Interest

- Consulting fees from AbbVie, Alimentiv , Amgen, Arena Pharmaceuticals, Artugen Therapeutics, Astra Zeneca, Boehringer Ingelheim, Boston Pharmaceuticals, Calibr, Celgene, Celltrion, ClostraBio, Equillium, Enthera, Evommune, Fresenius Kabi, Galapagos, Genentech (Roche), Gilead Sciences, GlaxoSmithKline, Gossamer Bio, Index Pharmaceuticals, Innovation Pharmaceuticals, Inotrem, Kaleido, Kallyope, Merck, Morphic Therapeutics, MRM Health, Progenity, Prometheus Biosciences, Prometheus Laboratories, Protagonist Therapeutics, Q32 Bio, Sun Pharma, Surrozen, Target RWE, Teva, TLL Pharmaceutical, Ventyx Biosciences; consulting and speaking fees from Abivax; consulting and speaking fees and other support from Lilly; research grants, consulting and speaking fees and other support from Bristol Myers Squibb, Janssen, Pfizer, Takeda; research grants and consulting fees from Theravance Biopharma; and stock options from Ventyx Biopharma

Background

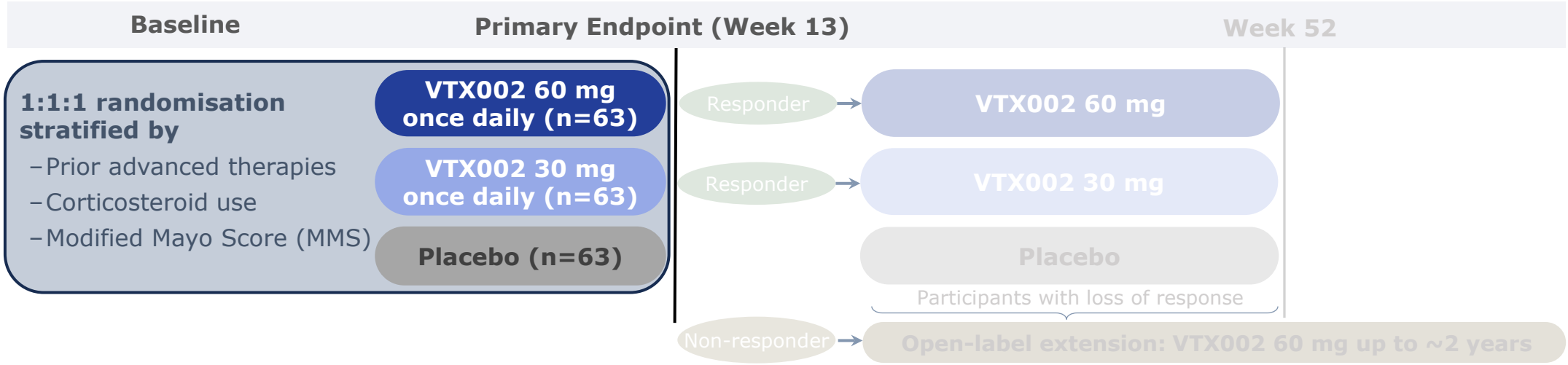
- Sphingosine-1-phosphate receptors (S1PR) are therapeutic targets in chronic inflammatory diseases
- S1PR modulators bind S1PR1 receptors on lymphocyte surfaces, leading to receptor internalization and sequestration of lymphocytes within lymph nodes
- Several S1PR modulators with varying receptor selectivity are approved for the treatment of multiple sclerosis (MS) and/or ulcerative colitis (UC)



S1PR modulator	Receptor selectivity	Indication
Fingolimod	S1PR1, S1PR3, S1PR4, S1PR5	MS
Siponimod	S1PR1 and S1PR5	MS
Ponesimod	S1PR1	MS
Ozanimod	S1PR1 and S1PR5	MS, UC
Etrasimod	S1PR1, S1PR4, S1PR5	UC
VTX002	S1PR1	UC

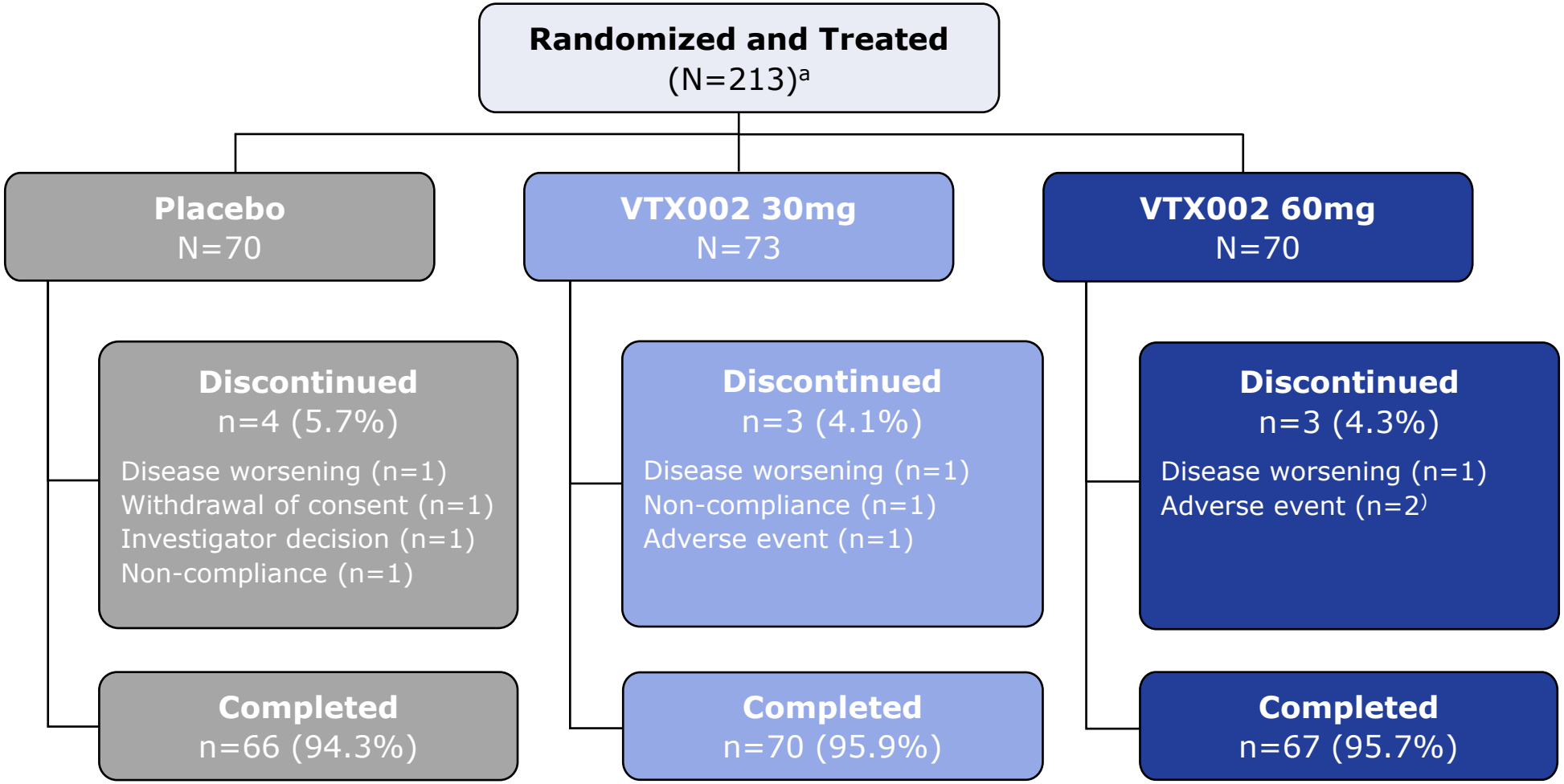
- VTX002 is a novel oral selective S1PR1 modulator in development for the treatment of UC
- The efficacy and safety of VTX002 in patients with UC was assessed in a phase 2, multicentre, randomised, double-blind, placebo-controlled study (NCT05156125)

Study Design



- **Key eligibility criteria**
  - Moderately to severely active UC (MMS 4-9)
  - No/insufficient response, loss of response, and/or intolerance to conventional or advanced therapies (≤ 2 biologics with different mechanisms of action or 1 biologic + a Janus kinase inhibitor)
- **Permitted concomitant medications**
  - Stable doses of oral 5-aminosalicylic acid
  - Stable doses of oral corticosteroids (prednisone ≤ 20 mg/day, budesonide ≤ 9 mg/day, or equivalent)
  - Immunosuppressants discontinued > 2 weeks prior to screening
- **Primary endpoint:** clinical remission (modified Mayo stool frequency ≤ 1, rectal bleeding = 0, and endoscopic subscore ≤ 1)
- **Sample size assumptions**: 28% VTX002 60 mg vs 8% placebo; 80% power at 5% significance level

Patient Disposition



[a]Four patients (VTX002 30 mg n=2 and VTX002 60 mg n=2) with baseline modified MMS=4 were excluded from the efficacy analysis population due to a protocol amendment limiting eligibility to patients with a baseline MMS of 5-9. These patients were included in the safety analysis population.

Baseline Demographics

	Placebo (N=70)	VTX002 30mg (N=73)	VTX002 60mg (N=70)
Age, mean (SD), years	40.1 (13.8)	42.3 (15.0)	39.4 (13.8)
Female, n (%)	32 (45.7)	26 (35.6)	39 (55.7)
Race, n (%)			
White	63 (90.0)	67 (91.8)	60 (85.7)
Asian	7 (10.0)	4 (5.5)	8 (11.4)
Other	0	2 (2.7)	2 (2.7)
Region, n (%)			
North America	10 (14.3)	16 (21.9)	10 (14.3)
Eastern Europe	48 (68.6)	46 (63.0)	47 (67.1)
Western Europe	6 (8.6)	7 (9.6)	6 (8.6)
Asia Pacific	6 (8.6)	4 (5.5)	7 (10.0)

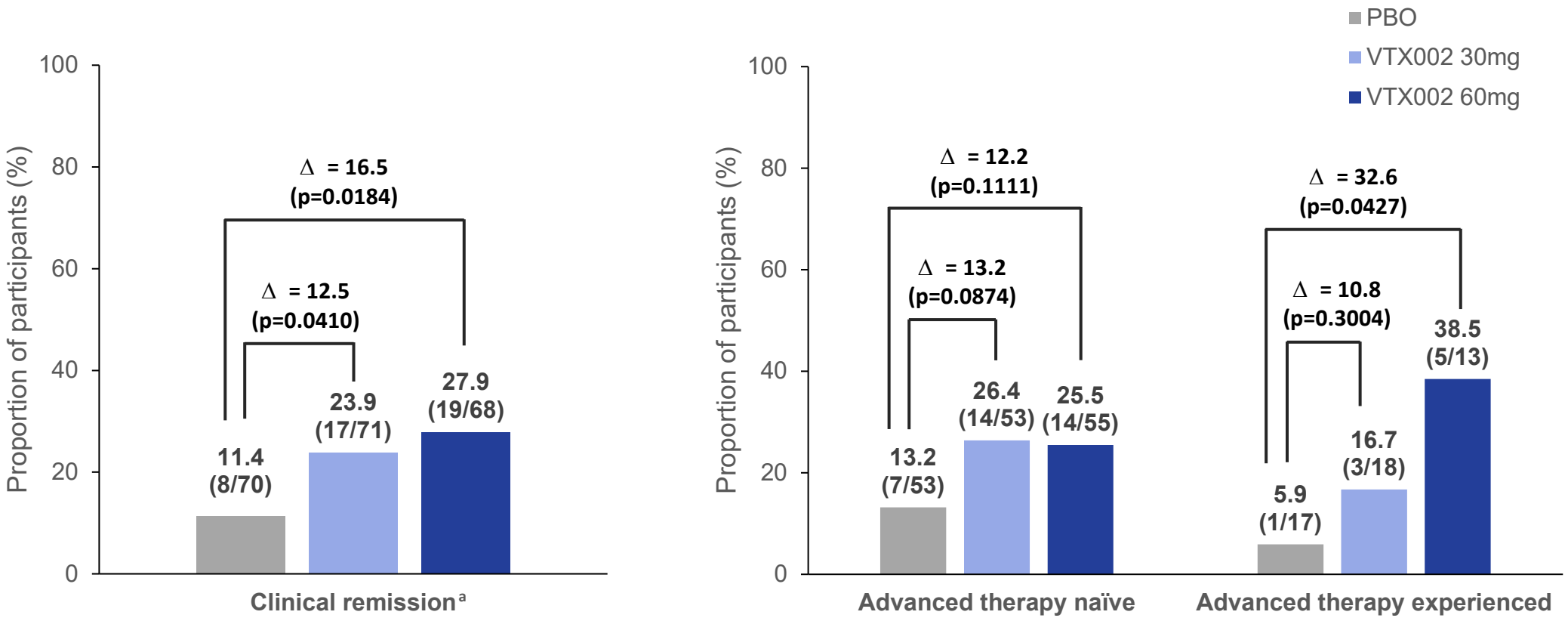
Baseline Disease Characteristics

	Placebo (N=70)	VTX002 30mg (N=73)	VTX002 60mg (N=70)
Duration of UC, mean (SD), years	6.9 (6.6)	6.5 (6.3)	6.8 (6.3)
Extent of UC, n (%)			
Proctitis	7 (10.0)	6 (8.2)	5 (7.1)
Proctosigmoiditis	26 (37.1)	30 (41.1)	31 (44.3)
Pancolitis	32 (45.7)	32 (43.8)	31 (44.3)
Left-sided colitis	5 (7.1)	5 (6.8)	3 (4.3)
Mayo endoscopy subscore, n (%)			
2	36 (51.4)	36 (49.3)	32 (45.7)
3	34 (48.6)	37 (50.7)	38 (54.3)
Corticosteroid use at baseline[a], n (%)	22 (31.4)	22 (30.1)	22 (31.4)
Prior use of advanced therapies[b], n (%)	17 (24.3)	18 (24.7)	14 (20.0)
1	10 (14.3)	11 (15.1)	8 (11.4)
2	6 (8.6)	6 (8.2)	6 (8.6)
3[c]	1 (1.4)	1 (1.4)	0 (0.0)

[a] At stable doses (prednisone ≤ 20 mg/day, budesonide ≤ 9 mg/day, or equivalent)
[b] ≤2 biologics with different mechanisms of action or 1 biologic + a Janus kinase inhibitor
[c] One patient treated with placebo had prior treatment with infliximab, tofacitinib, and vedolizumab; one patient treated with VTX002 30 mg had prior treatment with adalimumab, ustekinumab, and vedolizumab

Primary Endpoint: Clinical Remission at Week 13

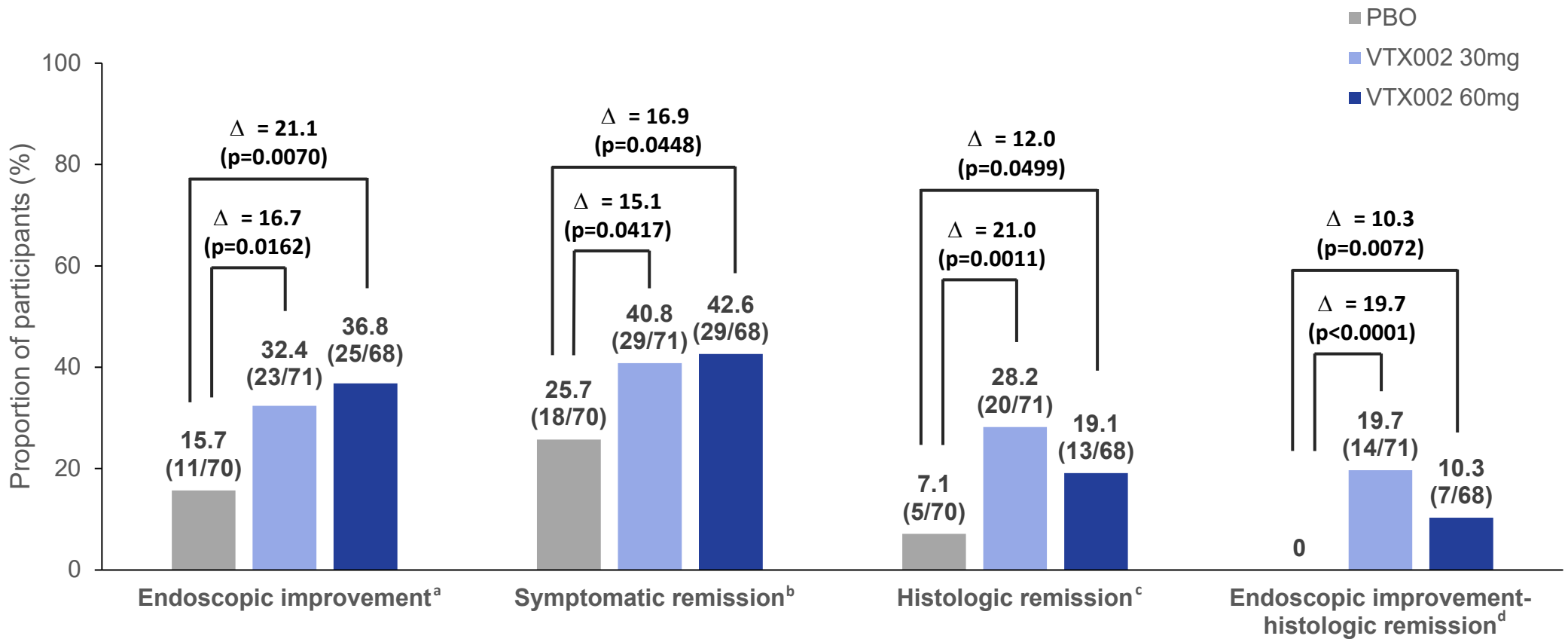
Baseline MMS 5 to 9 (N=209)



[a] **Clinical remission:** modified Mayo stool frequency (SF) subscore ≤ 1, rectal bleeding (RB) subscore = 0, endoscopic subscore (ES) ≤ 1

Key Secondary Endpoints at Week 13

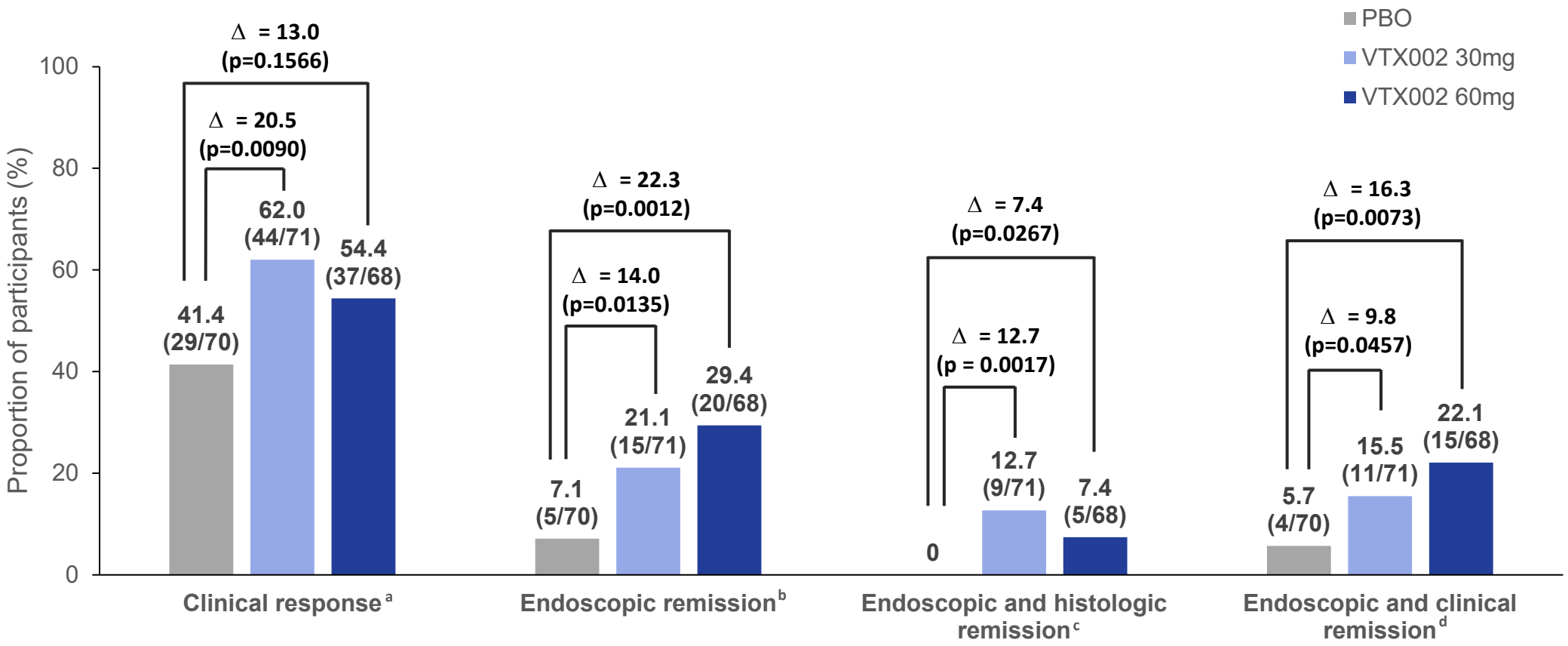
Baseline MMS 5 to 9 (N=209)



[a] **Endoscopic improvement:** modified Mayo ES ≤ 1
[b] **Symptomatic remission**: modified Mayo SF subscore ≤ 1 and RB subscore = 0
[c] **Histologic remission:** Geboes Index score < 2.0
[d] **Endoscopic improvement-histologic remission**: modified Mayo ES ≤ 1 and Geboes Index score < 2.0

Other Secondary Endpoints at Week 13

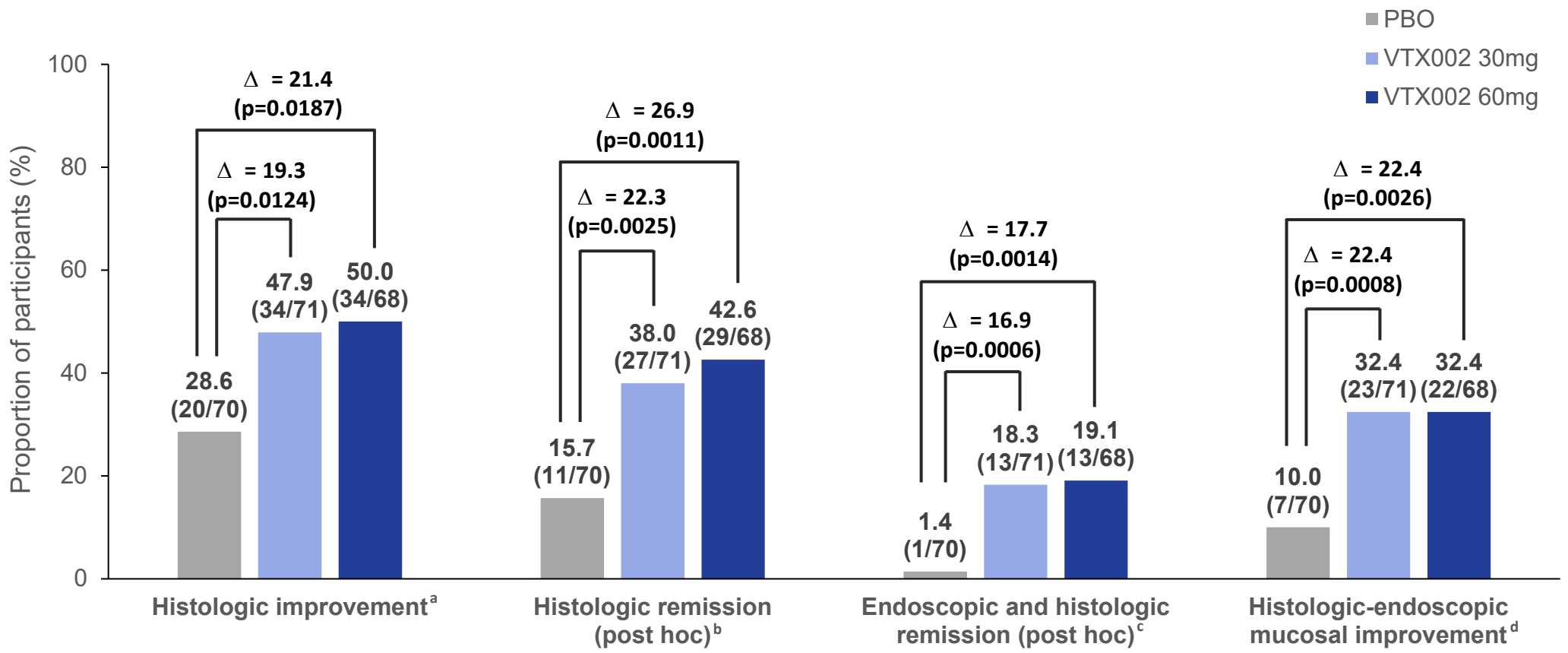
Baseline MMS 5 to 9 (N=209)



[a] **Clinical response:** ≥ 2-point and ≥ 30% decrease from baseline in MMS, and a ≥ 1-point decrease from baseline in RB or an absolute RB ≤ 1
[b] **Endoscopic remission**: modified Mayo ES = 0
[c] **Endoscopic and histologic remission:** modified Mayo ES = 0 and Geboes Index score < 2.0
[d] **Endoscopic and clinical remission**: modified Mayo SF subscore ≤ 1, RB subscore = 0, and ES = 0

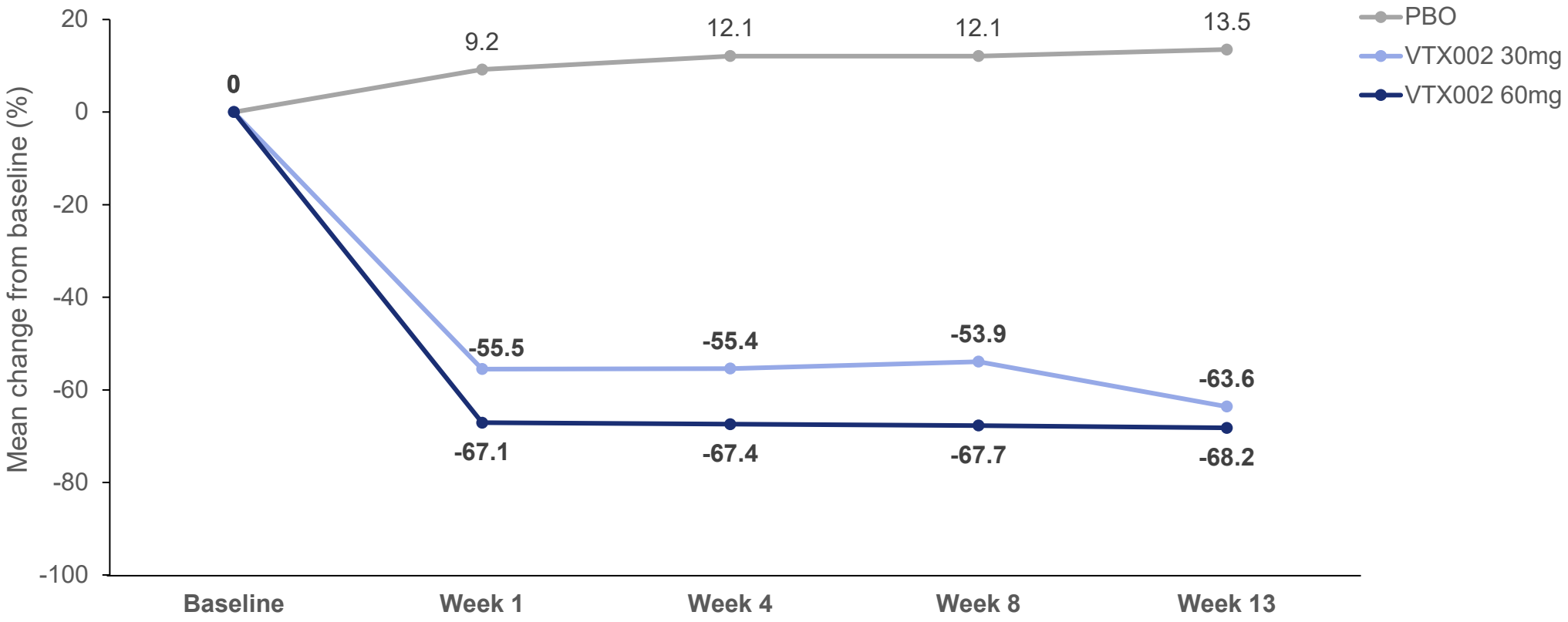
Endpoints with More Conventional and Less Stringent Histology Criteria

Baseline MMS 5 to 9 (N=209)



[a] **Histologic improvement (secondary endpoint):** Geboes Index score < 3.1
[b] **Histologic remission (post hoc)**: Geboes Index score ≤ 2.1
[c] **Endoscopic and histologic remission (post hoc):** modified Mayo ES = 0 and Geboes Index score ≤ 2.1
[d] **Histologic-endoscopic mucosal improvement (secondary endpoint)**: modified Mayo ES ≤ 1 and Geboes Index score < 3.1

Percent Change in Absolute Lymphocyte Count



Safety through Week 13

	Placebo (N=70)	VTX002 30mg (N=73)	VTX002 60mg (N=70)
Any adverse event (AE), n (%)	24 (34.3)	34 (46.6)	33 (47.1)
Serious AE, n (%)	0	2 (2.7)	3 (4.3)
AE Grade 3 or higher, n (%)	3 (4.3)	7 (9.6)	6 (8.6)
AE leading to study drug discontinuation[a], n (%)	1 (1.4)	1 (1.4)	3 (4.3)
Death, n (%)	0	0	0
Cardiovascular events, n (%)			
Hypertension	3 (4.3)	0	1 (1.4)
Infections and infestations[b], n (%)	8 (11.4)	10 (13.7)	12 (17.1)
Herpes zoster	0	1 (1.4)	0
Liver injury, n (%)			
Hepatic enzyme increased	0	0	2 (2.9)[c]
Alanine aminotransferase increased	1 (1.4)	0	0

[a] Oral candidiasis (placebo, Grade 2, related), decreased appetite and fatigue (VTX002 30 mg, Grade 2, unrelated), headache (VTX002 60 mg, Grade 2, related), exacerbation of UC (VTX002 60 mg, Grade 3, unrelated), restrictive pulmonary syndrome (VTX002 60 mg, Grade 1, related)
[b] All Grade 1 or Grade 2 in severity. No serious or opportunistic infections
[c] Grade 2 ALT elevation (4x ULN) resolved with study drug interruption/rechallenge and grade 1 ALT elevation remained < 3x ULN on study drug

Conclusion

- VTX002 was superior to placebo for induction of clinical, endoscopic, histologic, and symptomatic remission/response at week 13
  - Efficacy was consistent across subgroups regardless of prior history of treatment with advanced therapies
- VTX002 was well-tolerated through week 13
  - Most events were mild to moderate
  - No adverse events of bradycardia, atrioventricular block, serious infection, macular oedema, or death

Back-up Slides

Reductions in Absolute Lymphocyte Count in Randomised Controlled Trials of S1PR Antagonists

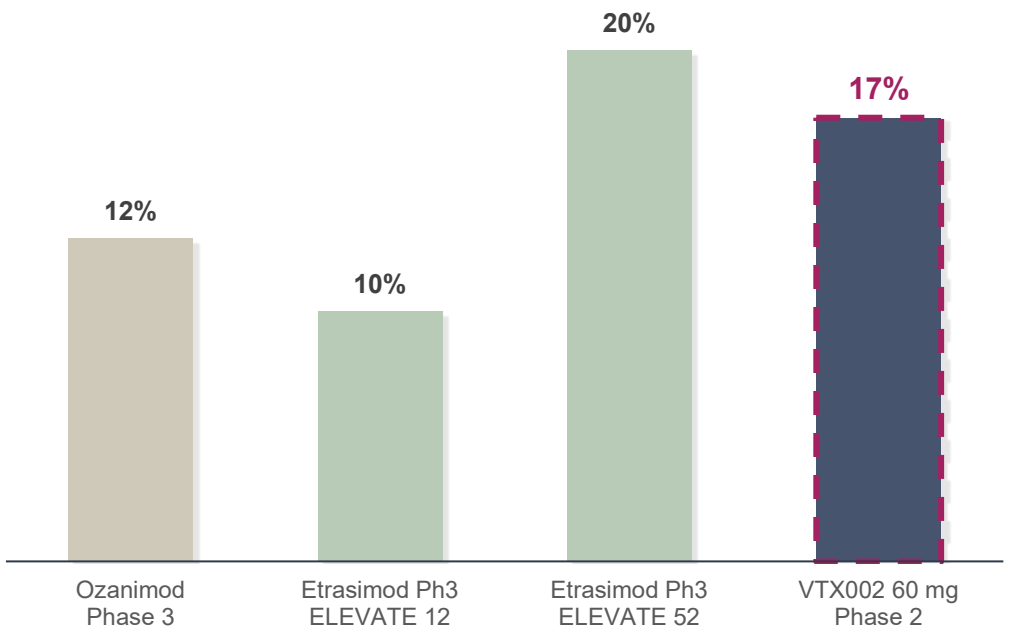
Agent	Dose	Timepoint for analysis	Percent reduction from baseline
Ozanimod[1]	0.5 mg	Week 8	32%
	1 mg	Week 8	49%
Etrasimod[2]	1 mg	Week 12	20%
	2 mg	Week 12	40%
VTX002	30 mg	Week 8	54%
	60 mg	Week 8	68%
	30 mg	Week 13	64%
	60 mg	Week 13	68%

[1] Sandborn et al. N Engl J Med 2016;374:1754-1762.
[2] Sandborn et al. Gastroenterology 2020;158:550-561.

Clinical and Endoscopic Remission Versus Ozanimod and Etrasimod

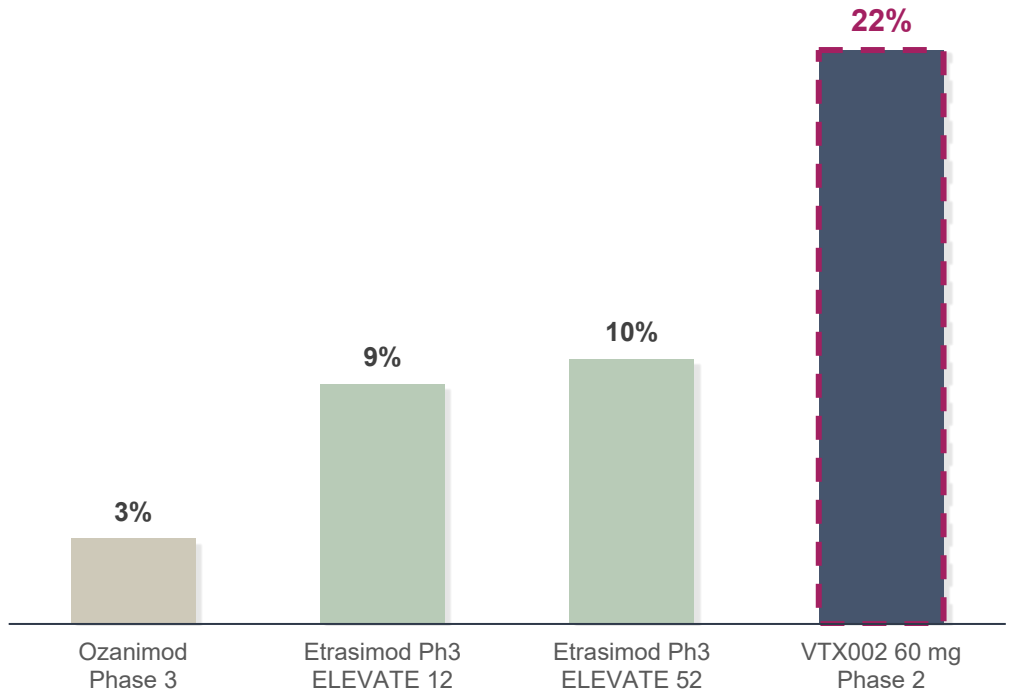
Placebo-adjusted Clinical Remission

Phase 2 and Phase 3 Trials – Induction Period



Placebo-adjusted Endoscopic Remission (ES=0)

Phase 2 and Phase 3 Trials – Induction Period



Note: Charts represent cross-trial comparisons and not results of head-to-head studies. Caution should be exercised when comparing across trials due to differences in trial design and patient characteristics.
Source: Sandborn et al. N Engl J Med 2021;385:1280-91. Sandborn et al. Lancet 2023;401:1159–71. Ventyx data on file