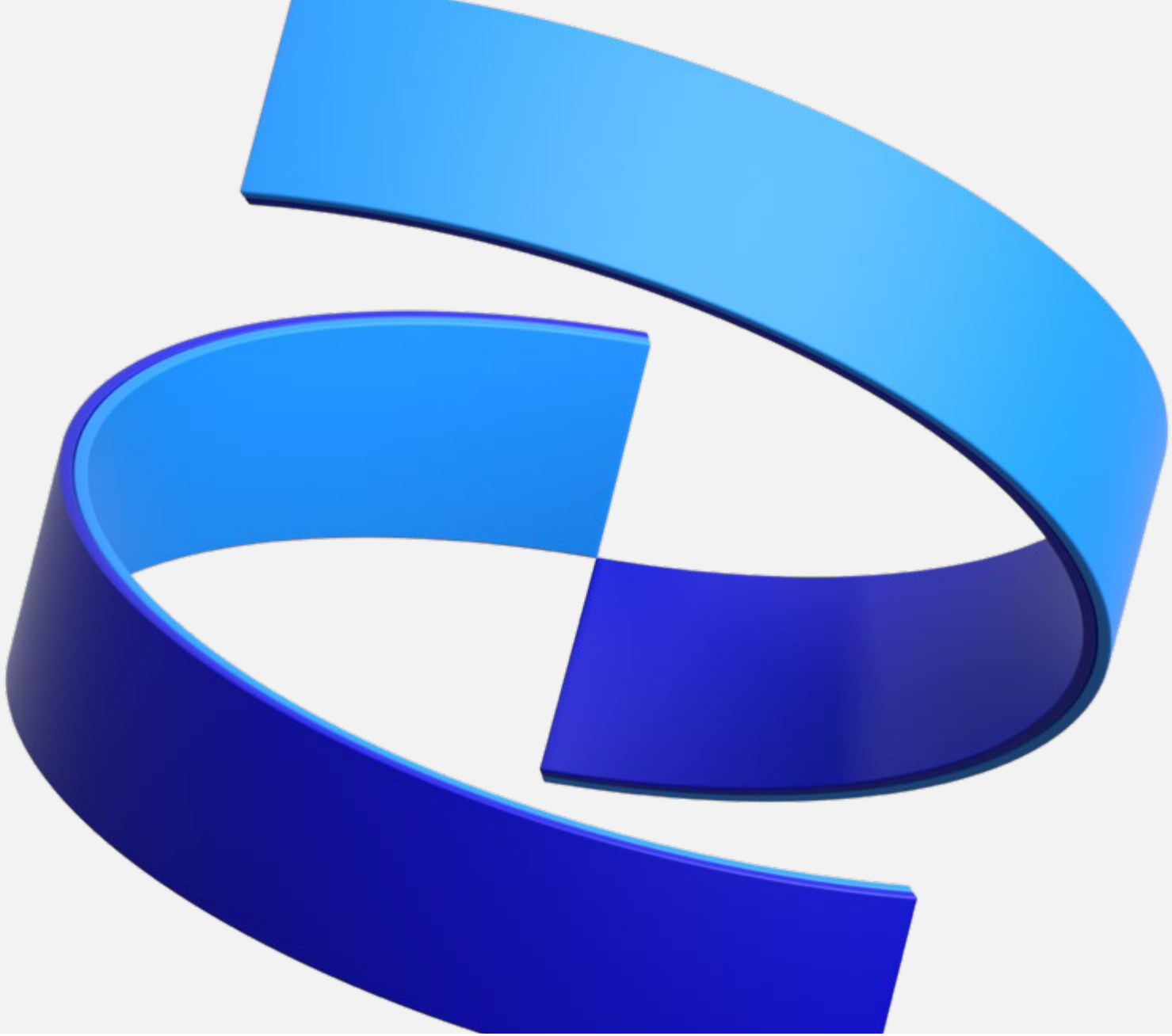
Isolated Proctitis: Unmet Needs and Therapeutic Approaches



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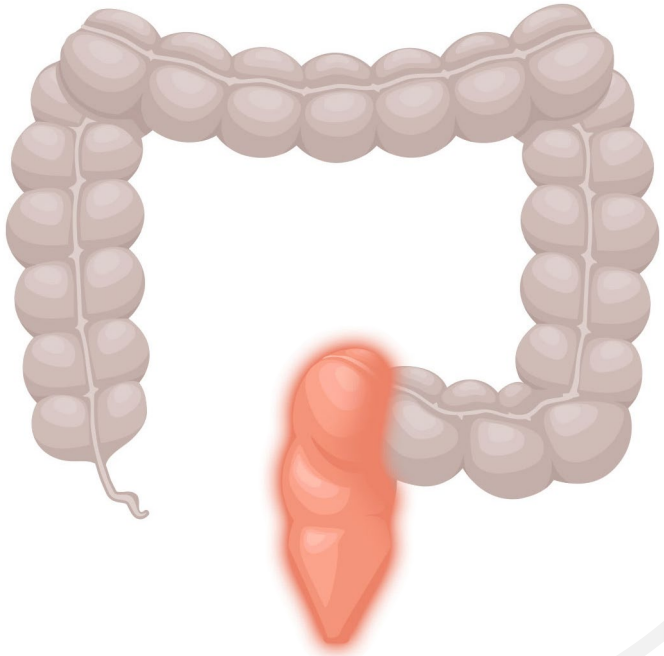
Isolated Proctitis (IP): Unmet Needs and Therapeutic Approaches



- **Isolated Proctitis Is Associated With High Symptomatic Burden[1]**
- **Isolated Proctitis Should Not Be Considered as a Minor Form of Disease[2]**
- **Poorly Controlled Isolated Proctitis May Lead to Proximal Disease Extension[3]**
- **More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis[4]**
- **Clinical Data of Etrasimod in Patients with Isolated Proctitis**

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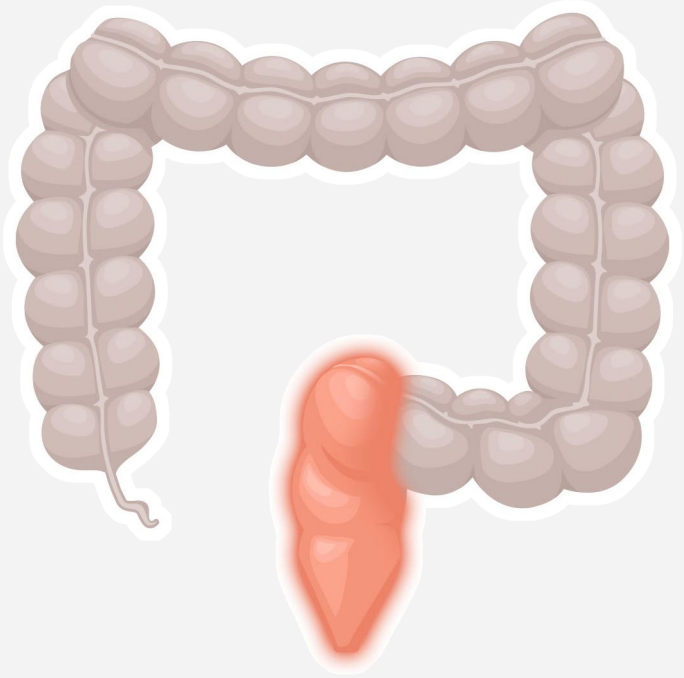
References: **1.** Caron B, et al. *Gut*. 2021;70(7):1203-1209; **2.** Hochart A, et al. *Gut*. 2017;66(11):1912-1917; **3.** Meucci G, et al. *Am J Gastroenterol*. 2000;95(2):469-473; **4.** Dubois E, et al. *United European Gastroenterol J*. 2020;8(8):933-941; **5.** Peyrin-Biroulet L, et al. Presented at: 18th Congress of European Crohn's and Colitis Organisation; March 1-4, 2023; Copenhagen, Denmark. Poster P407.

Isolated Proctitis Is Associated With High Symptomatic Burden

Isolated proctitis[1,2]

Inflammation limited to the rectum



~30% of patients with UC initially present with isolated proctitis[3,a]

IP symptoms include[3]:

- Rectal bleeding
- Tenesmus
- Urgency
- Diarrhea (variable)
- Fecal leakage
- Fecal incontinence
- Delayed transit and constipation (20-30% patients)

IP=isolated proctitis; QoL=quality of life; UC=ulcerative colitis.

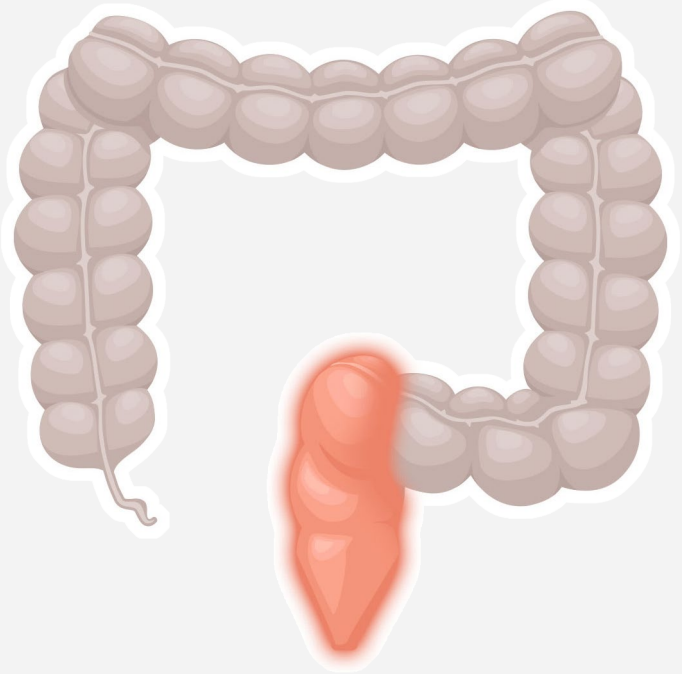
[a] LIMITATIONS: Systematic literature reviews include different trial designs and types, different practice types and regions (some ex-US), different definitions for and severity of ulcerative proctitis across the trials studied, and some missing trials during the selection process.[3]

References: **1.** Ungaro R, et al. *Lancet*. 2017;389(10080):1756-1770. **2.** Satsangi J, et al. *Gut*. 2006;55(6):749-753. **3.** Caron B, et al. *Gut*. 2021;70(7):1203-1209.

Isolated Proctitis Is Associated With High Symptomatic Burden

Isolated proctitis

Inflammation limited to the rectum



Symptoms may differ from more extensive forms of UC[1]. **Current scoring systems exclude common symptoms of proctitis, such as fecal incontinence, urgency and constipation.**[2]

Recommendations for the management of isolated proctitis are mostly based on **extrapolation of data from treatment of more extensive disease.**[3]

Within ~7.5 years of diagnosis, **24% of patients** with isolated proctitis will **progress to left-sided colitis**, and **14% will progress to extensive colitis.**[4]

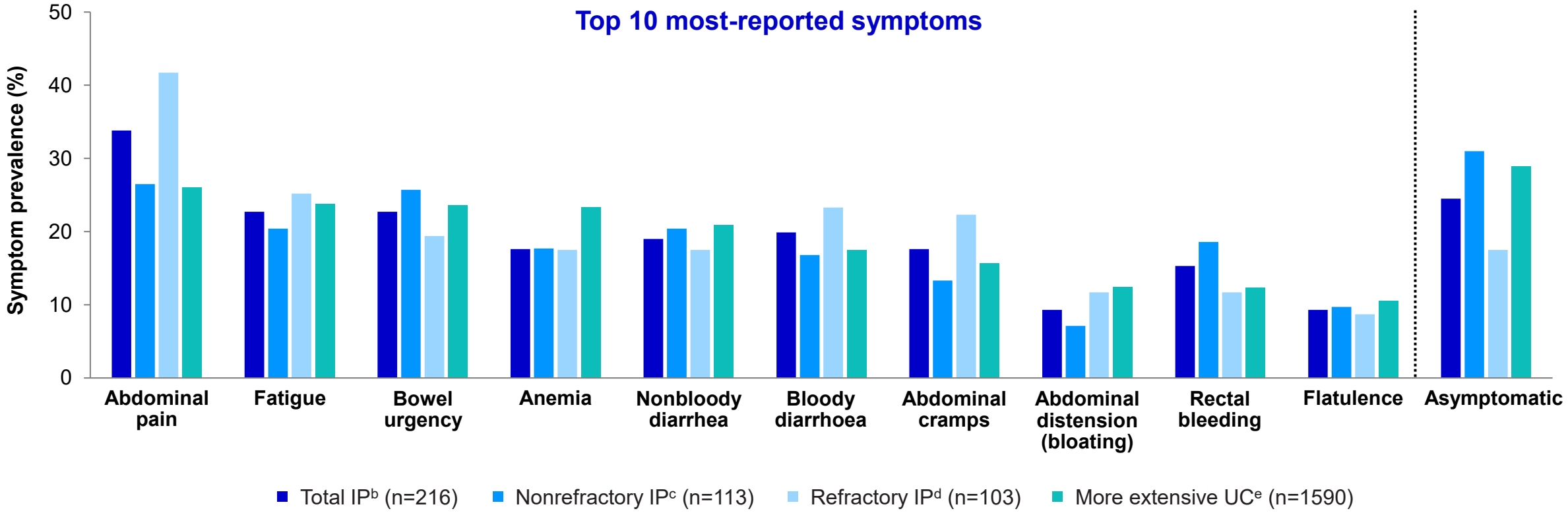
There is a tendency to consider isolated proctitis as a minor form of UC, but **disease extent and severity are not mutually** exclusive.[5-7]

UC=ulcerative colitis.

References: **1.** Ungaro R, et al. *Lancet*. 2017;389:1756-1770. **2.** Kyriacou M, et al. *BMJ Open Gastroenterol*. 2023;10:e001139. doi:10.1136/bmjgast-2023-001139. **3.** Caron B, et al. *Gut*. 2021;70:1203-1209. **4.** Burisch J, et al. *J Crohns Colitis*. 2017;11:1200-1204. **5.** Hochart A, et al. *Gut*. 2017;66:1912-1917. **6.** Meucci G, et al. *Am J Gastroenterol*. 2000;95:469-473. **7.** Peyrin-Biroulet L, et al. *Clin Gastroenterol Hepatol*. 2016;14:348-354.

Isolated Proctitis Is Associated With High Symptomatic Burden

Patients with IP experience a similar symptom burden to patients with more extensive disease[a]



[a]Patients (N=1828) from the US, France, Germany, Italy, Spain, and UK were included. At the time of consultation, 32.6% of total IP, 69.9% of refractory IP, and 66.2% of MEUC cohorts were receiving advanced therapies.
[b]Total IP group includes patients with IP at diagnosis and consultation.
[c]Nonrefractory IP group includes patients with IP who only received 5-ASAs and/or steroids.
[d]Refractory IP group includes patients with IP who received an immunomodulator (IM) and/or advanced therapy (AT; specifically, infliximab, adalimumab, golimumab). Receipt of IM/AT was considered a proxy for failing oral steroids combined with oral and rectal 5-ASA therapy.
[e]More extensive UC group includes patients whose disease extended beyond IP at both diagnosis and consultation.

5-ASA=5-aminosalicylic; IP=isolated proctitis; MEUC=More extensive ulcerative colitis; UC=ulcerative colitis.

Reference: Armuzzi A, et al. Presented at: 19th Congress of European Crohn's and Colitis Organisation; February 21-24, 2024; Stockholm, Sweden. Poster P931.

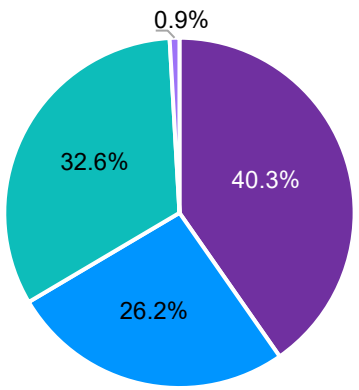
Isolated Proctitis Should Not Be Considered as a Minor Form of Disease

Patients with IP have significant disease activity, similarly to patients with more extensive UC[a]

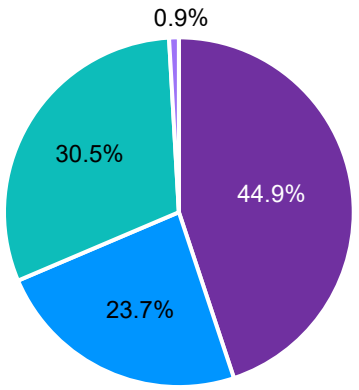
Disease activity at consultation (defined by Mayo score[a])

Isolated proctitis

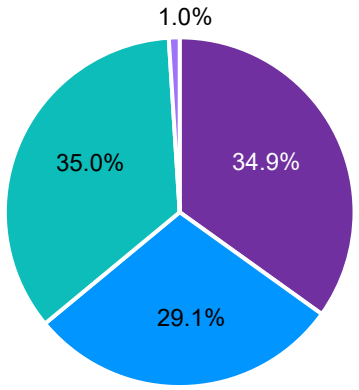
Total IP (n=221)



Nonrefractory IP (n=118)

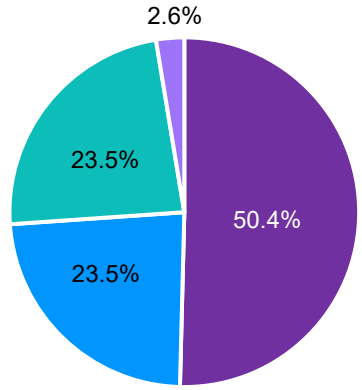


Refractory IP (n=103)



More extensive ulcerative colitis

(n=1607)



Remission: 0-2 **Mild: 3-5** **Moderate: 6-10** **Severe: 11-12**

[a]Based on derived Mayo scores.

IP=isolated proctitis; UC=ulcerative colitis.

Reference: Armuzzi A, et al. Presented at: 19th Congress of European Crohn's and Colitis Organisation; February 21-24, 2024; Stockholm, Sweden. Poster P931.

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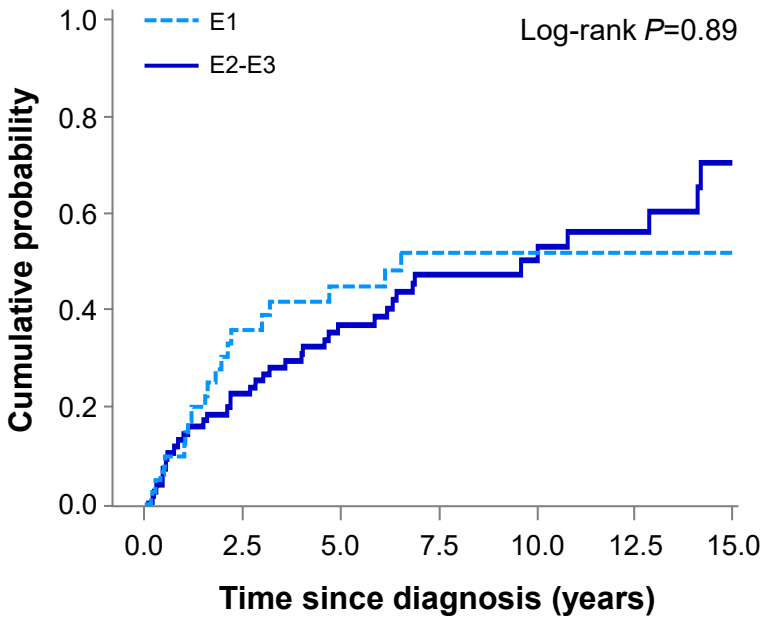
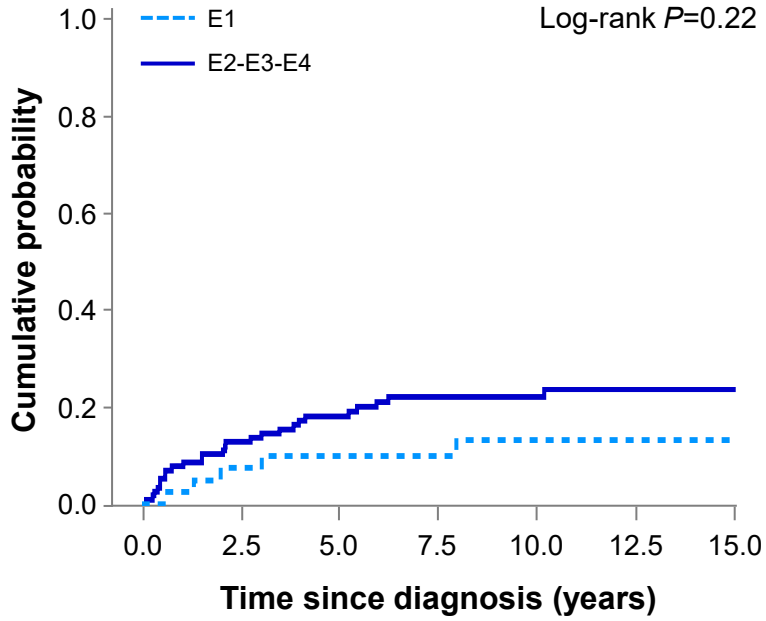
Isolated Proctitis Should Not Be Considered as a Minor Form of Disease

Compared with more extensive disease, patients with IP are at similar risk for:

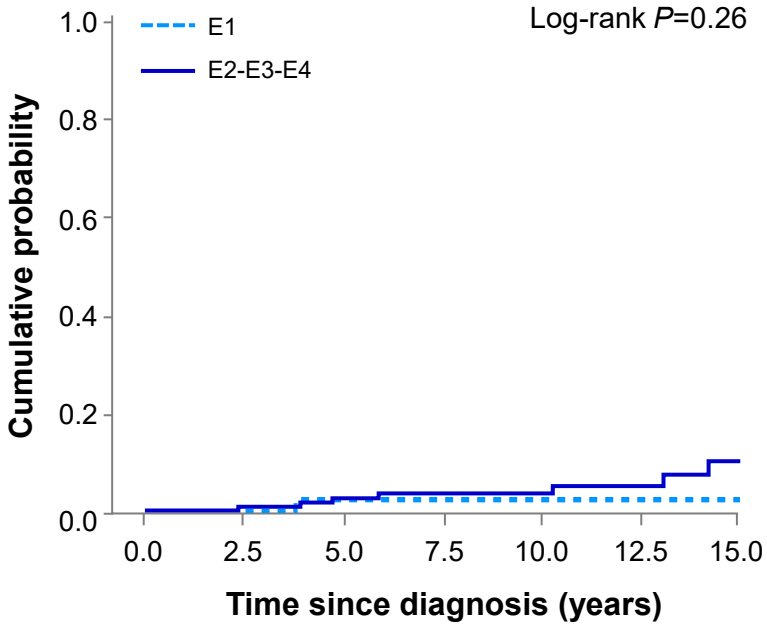
Disease extension[a]



Colectomy[a]



Anti-TNF therapy[a]



E1=IP group (n=40)

E2-E3-E4=extensive locations group[b] (n=118)

[a]Results from 158 patients with pediatric-onset UC and a median age at diagnosis of 14.5 years (IQR 11.4–16.1).

[b]The extensive locations group are inclusive of left-sided colitis defined as colonic involvement limited from the distal colorectum to splenic flexure (E2); extensive colitis defined as a colonic involvement from the colorectum distal to hepatic flexure (E3); and pancolitis defined as a colonic involvement proximal to hepatic flexure (E4).

IP=isolated proctitis; IQR=interquartile range; TNF=tumor necrosis factor; UC=ulcerative colitis.

References: Hochart A, et al. *Gut.* 2017;66(11):1912-1917.

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Poorly Controlled Isolated Proctitis May Lead to Proximal Disease Extension

Patients with isolated proctitis or left-sided colitis are at risk of progression to more extensive disease

Proximal extension observed in[1,a]

17.8%
(95% CI, 12.3-25.1 [*P*<0.001])
at 5 years

31.0%
(95% CI 23.5-39.7 [*P*<0.001])
at 10 years

In a 2024 study of patients with isolated proctitis (N=344) at diagnosis[2,b]

Disease extension occurred within 1 year in:

9.5%
To left-sided colitis

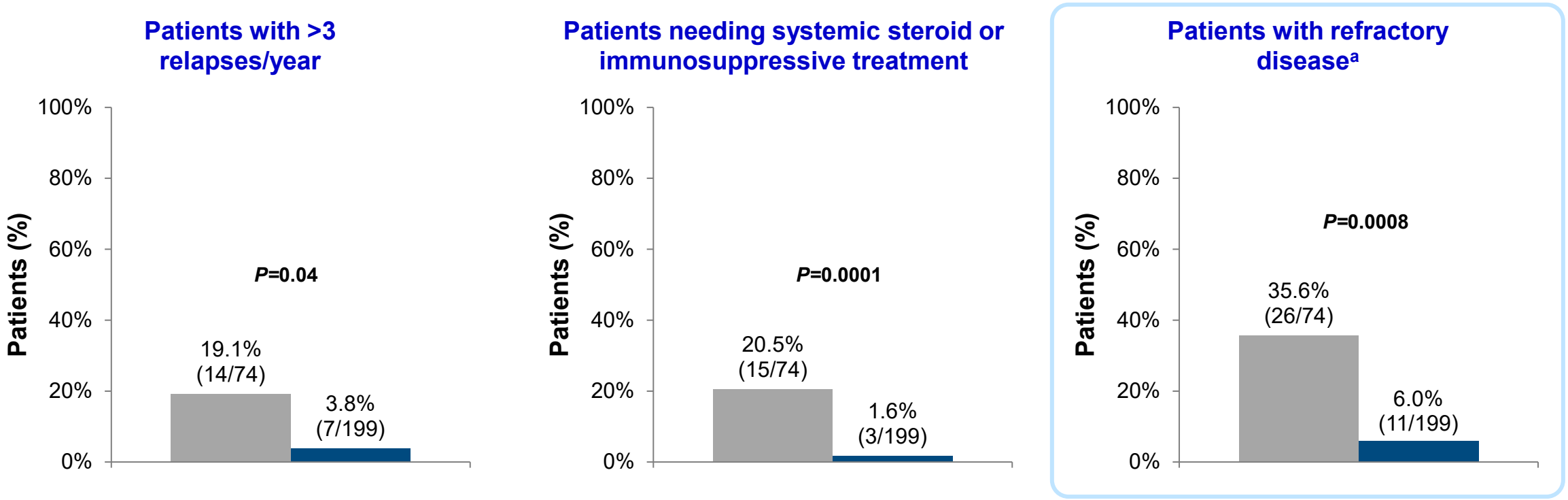
14.3%
To extensive colitis

[a]The systematic review involved 41 studies. Twenty-four studies were from Europe, 7 from North America, 7 from Asia, and 1 from Africa. The accrual periods reported in 38 studies, ranged from 1953 to 2016. Eleven studies lacked sufficient information for inclusion in the meta-analysis. Finally, 30 studies were used for the meta-analysis.
[b]Number of patients who underwent colonoscopy=431 (49.1% of study patients).
CI=confidence interval; UC=ulcerative colitis.

References: **1.** Roda G, et al. *Aliment Pharmacol Ther*. 2017;45:1481-1492. **2.** Strande V, et al. *Aliment Pharmacol Ther*. 2024;60(3):357-368. doi:10.1111/apt.18097

Poorly Controlled Isolated Proctitis May Lead to Proximal Disease Extension

Prognostic factors for proximal extension of IP (univariate analysis):



A multivariate analysis of 273 patients with IP identified refractory disease[a] as a predictor of proximal extension

[a]Proctitis was classified as refractory if the patient exhibited one of the following features: >3 relapses per year, chronic disease activity despite continuous medical therapy, or need for systemic steroids or immunosuppressants.

IP=isolated proctitis.

Reference: Meucci G, et al. *Am J Gastroenterol.* 2000;95:469-473.

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More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Survey-based consensus opinion on patient preference in refractory IP

A 3-round Delphi study based in the UK (round 1 n=29, round 2 n=21, round 3 n=21) conducted between January-June 2022 established 14 consensus statements on refractory IP based on insights from both healthcare experts and patients living with IP

In the treatment of refractory **IP,** many patients **prefer oral or systemic therapies** rather than topical therapy

Level of agreement
Whole group **70%**; Medical professionals **66%**;
Nurse practitioners **80%**; Patients **78%**

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IP=isolated proctitis.

Reference: Kyriacou M, et al. *BMJ Open Gastroenterol*. 2023;10:e001139. doi:10.1136/bmjgast-2023-001139.

More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Topical treatments are recommended for proctitis, but may be poorly accepted

ECCO Guidelines[1]

Treatment	Induction	Maintenance	Recommendation	Evidence
Topical (rectal) 5-ASA[a]	✓		Strong	Low quality
Topical (rectal) 5-ASA[b]		✓	Weak	Very low quality
Topical (rectal) steroids[c]	✓		Strong	Very low quality

ACG Guidelines[2]

Treatment	Induction	Maintenance	Recommendation	Evidence
Topical (rectal) 5-ASA[d]	✓		Strong	High quality
Topical (rectal) 5-ASA[e]		✓	Strong	Moderate quality

Topical therapies are more likely to be associated with **nonadherence** than oral therapy[3]

~70% of patients discontinued topical 5-ASA (most common treatment) during the first month of treatment[4,f]

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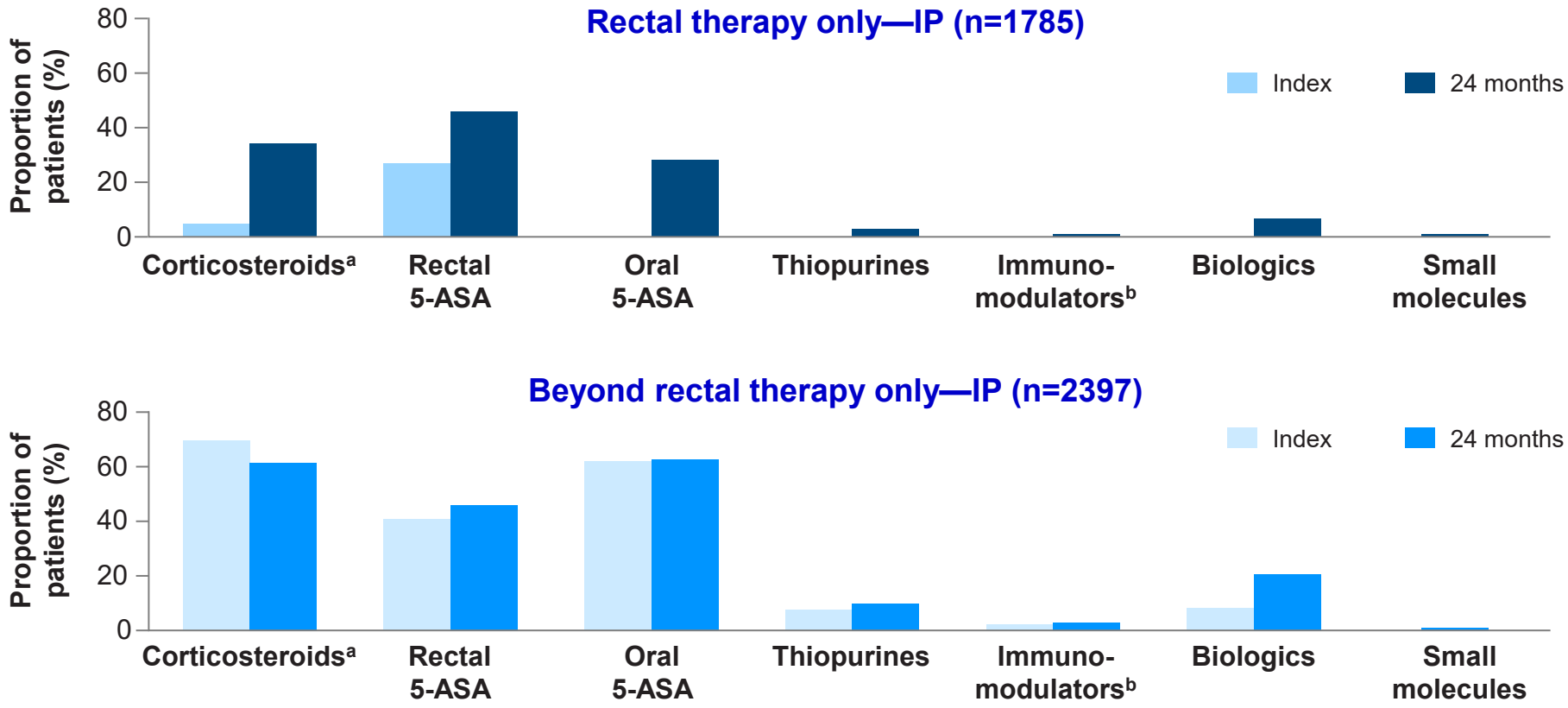
[a]For patients with mild to moderately active UC; [b]For patients with distal UC; [c]For patients with active distal colitis; [d]In patients with mildly active isolated proctitis; [e]In patients with mildly active isolated proctitis; [f]A retrospective study in 636 new-onset isolated proctitis patients

5-ASA=5-aminosalicylic acid; ACG=American College of Gastroenterology; ECCO=European Crohn's and Colitis Organisation; UC=Ulcerative colitis.

References: **1.** Raine T, et al. *J Crohns Colitis*. 2022;16:2-17. **2.** Rubin DT, et al. *Am J Gastroenterol*. 2019;114(3):384-413. **3.** De Deo D, et al. *Expert Opin Biol Ther*. 2024;24(6):443-453. **4.** Richter JM, et al. *Aliment Pharmacol Ther*. 2012;36:248-256.

More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Medication use from rectal to systemic therapies at index and 24-month follow-up



A substantial proportion of isolated proctitis patients required treatment intensification over 24 months

[a]Corticosteroids included oral, rectal, and injectable/intravenous.
[b]Immunomodulator medications included methotrexate, cyclosporine, tacrolimus, and mycophenolate.
5-ASA=5-aminosalicylic; IP=isolated proctitis; UC=ulcerative colitis.

Reference: Chiorean MV, et al. Presented at: Digestive Disease Week; May 18-21, 2024; Washington, DC. USA. Poster Mo1807.

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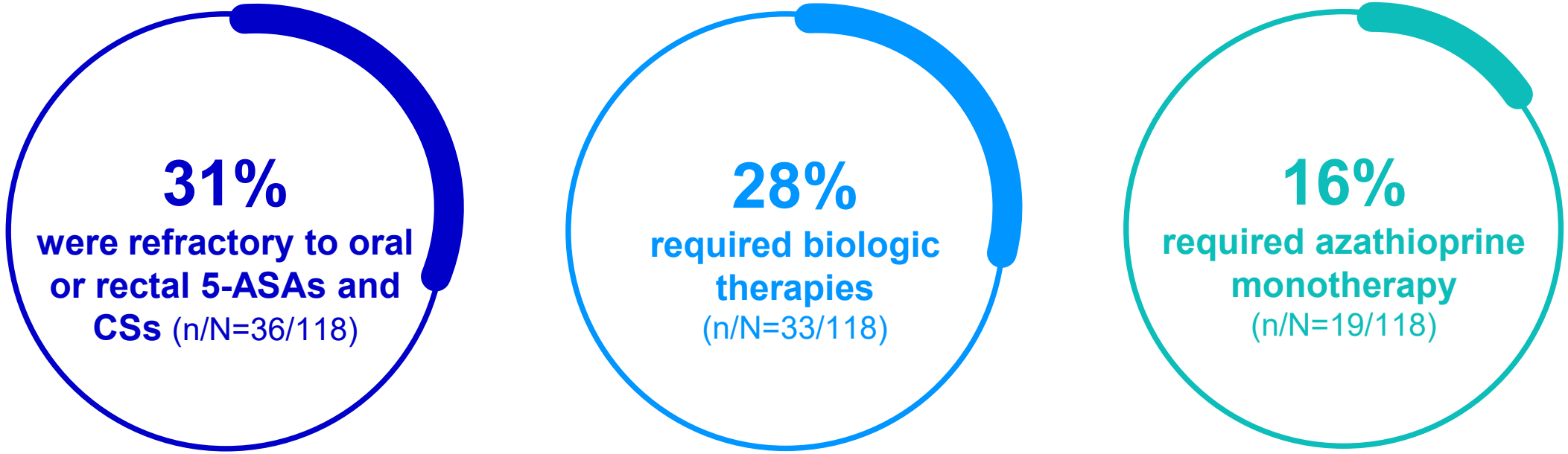
More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Patients with refractory IP may require additional therapies



See what fraction of patients with IP were refractory to conventional therapies

See how patients with refractory IP benefited from treatment with biologics

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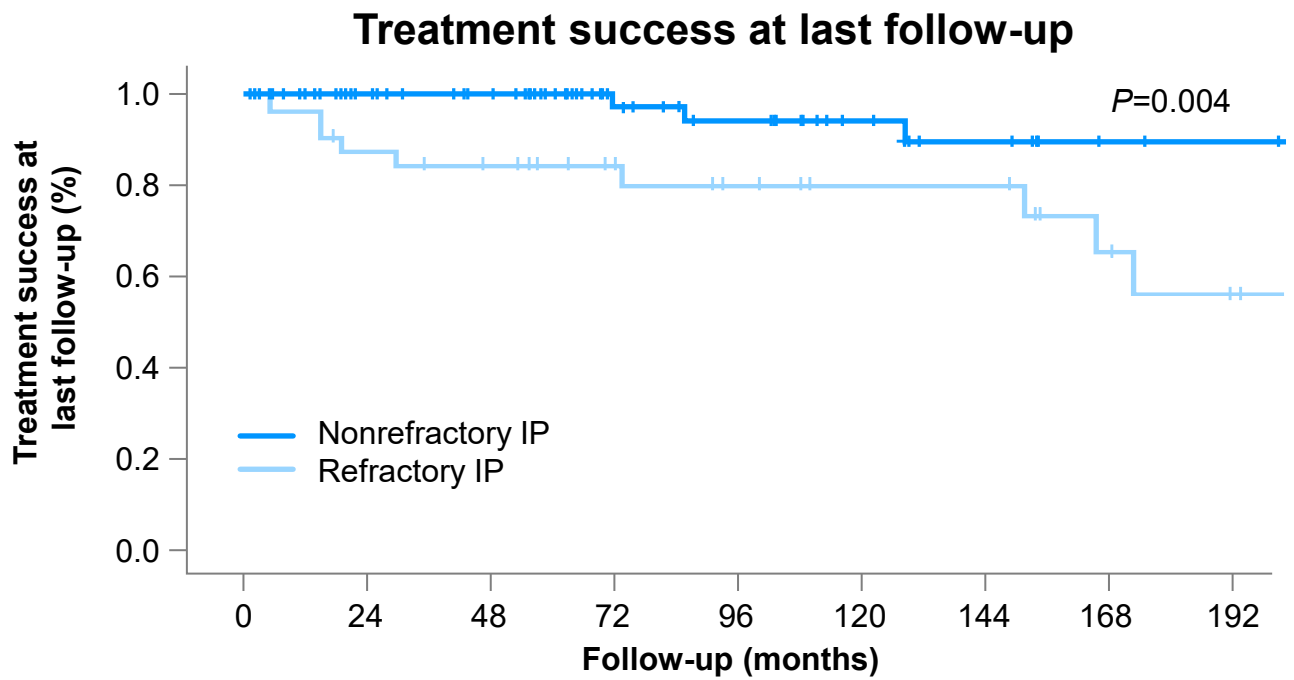
Single center cohort, Retrospective study involving 118 patients with IP.
5-ASA=5-aminosalicylate; CS=corticosteroid.

Reference: Dubois E, et al. *United European Gastroenterol J*. 2020;8:933-941.

More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Approximately one-third of patients with IP were refractory to conventional treatment with 5-ASAs and steroids



Number at risk:

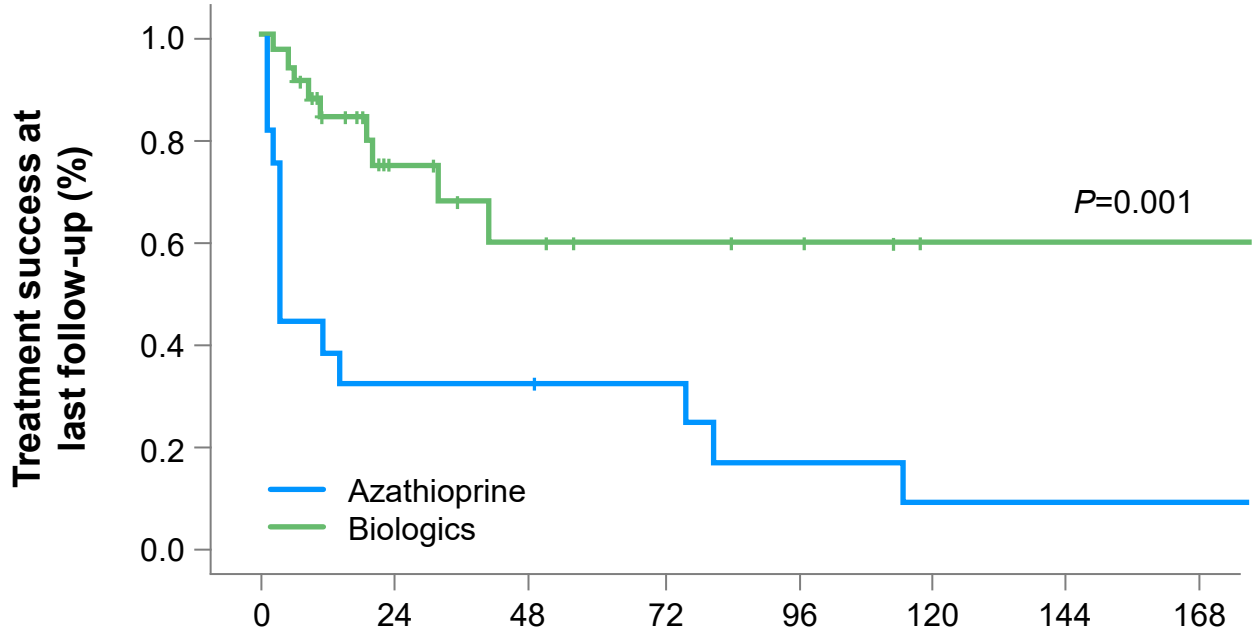
Nonrefractory IP	97	72	65	47	38	28	22	16	15
Refractory IP	36	28	25	19	16	13	13	8	5

Retrospective study involving 118 patients with IP.
5-ASA=5-aminosalicylic acid; IP=isolated proctitis.
Reference: Dubois E, et al. *United European Gastroenterol J*. 2020;8(8):933-941.

5-ASA=5-aminosalicylate; CS=corticosteroid.
Reference: Dubois E, et al. *United European Gastroenterol J*. 2020;8:933-941.

More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Patients with refractory IP can benefit from treatment with biologics



Number at risk:

Biologicals	33	11	7	5	4	1	1	1
Azathioprine	19	5	5	4	2	1	1	1

IP=isolated proctitis.

Reference: Dubois E, et al. *United European Gastroenterol J*. 2020;8(8):933-941.

Clinical response rates were significantly higher for patients with refractory proctitis treated with biologics than with azathioprine

5-ASA=5-aminosalicylate; CS=corticosteroid.

Reference: Dubois E, et al. *United European Gastroenterol J*. 2020;8:933-941.

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More Treatment Options Are Needed for Patients With Refractory Isolated Proctitis

Limited evidence is available for therapies in patients with isolated proctitis as they were largely excluded from pivotal trials for advanced therapies[1-3]

Patients with IP were included in trials for the following therapies:

- **Topical and oral 5-ASAs**
- **Topical steroids**

Patients with IP were excluded from the following trials for advanced therapies[a]:

- **ULTRA[4]**
- **PURSUIT-SC[5]**
- **ACT[6]**
- **GEMINI[7]**
- **UNIFI[8]**
- **SELECTION[9]**
- **U-ACHIEVE[10]**
- **OCTAVE[11]**
- **True North[12]**
- **INSPIRE & COMMAND[13]**

5-ASA=5-aminosalicylic acid IP=isolated proctitis.

[a] Exclusion of IP was not specifically mentioned in the following studies: Rutgeerts P, et al. *N Engl J Med.* 2005, Feagan BG, et al. *N Engl J Med.* 2013, Sands BE, et al. *N Engl J Med.* 2019, Sandborn W, et al. *N Engl J Med.* 2021, and Louis E, et al. *JAMA*. 2024

References: **1.** Caron B, et al. *J Crohns Colitis*. 2022;16;922-930. **2.** Kyriacou M, et al. *BMJ Open Gastroenterol.* 2023;10:e001139. doi:10.1136/bmjgast-2023-001139. **3.** Aruljothy A, et al. *Aliment Pharmacol Ther.* 2023. doi: 10.1111/apt.17666 **4.** Reinisch W, et al. *Gut.* 2011;60:780–787. **5.** Sandborn W, et al. *Gastroenterology.* 2014;146:85-95. **6.** Rutgeerts P, et al. *N Engl J Med.* 2005;353:2462–2476. **7.** Feagan BG, et al. *N Engl J Med.* 2013;369:699-710. Supplemental appendix. **8.** Sands BE, et al. *N Engl J Med.* 2019;381:1201–1214. Supplemental appendix. **9.** Feagan BG, et al. *Lancet.* 2021;397:2372-2384. Supplemental appendix. **10.** Danese S, et al. *Lancet.* 2022;399:2113–2128. **11.** Sandborn W, et al. *N Engl J Med.* 2017;376:1723-1736. **12.** Sandborn W, et al. *N Engl J Med.* 2021;385:1280–1291. **13.** Louis E, et al. *JAMA*. Published online July 22, 2024. doi:10.1001/jama.2024.12414

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Background: UC patients with IP are commonly excluded from drug development trials for advanced UC treatments[1-3]

Patients with isolated proctitis (<10 cm rectal involvement) at baseline who met other eligibility criteria* could enroll in the ELEVATE UC clinical program, with enrolment capped at 15% of total patients. Adult patients with IP made up 8% of the ELEVATE UC study population[4]

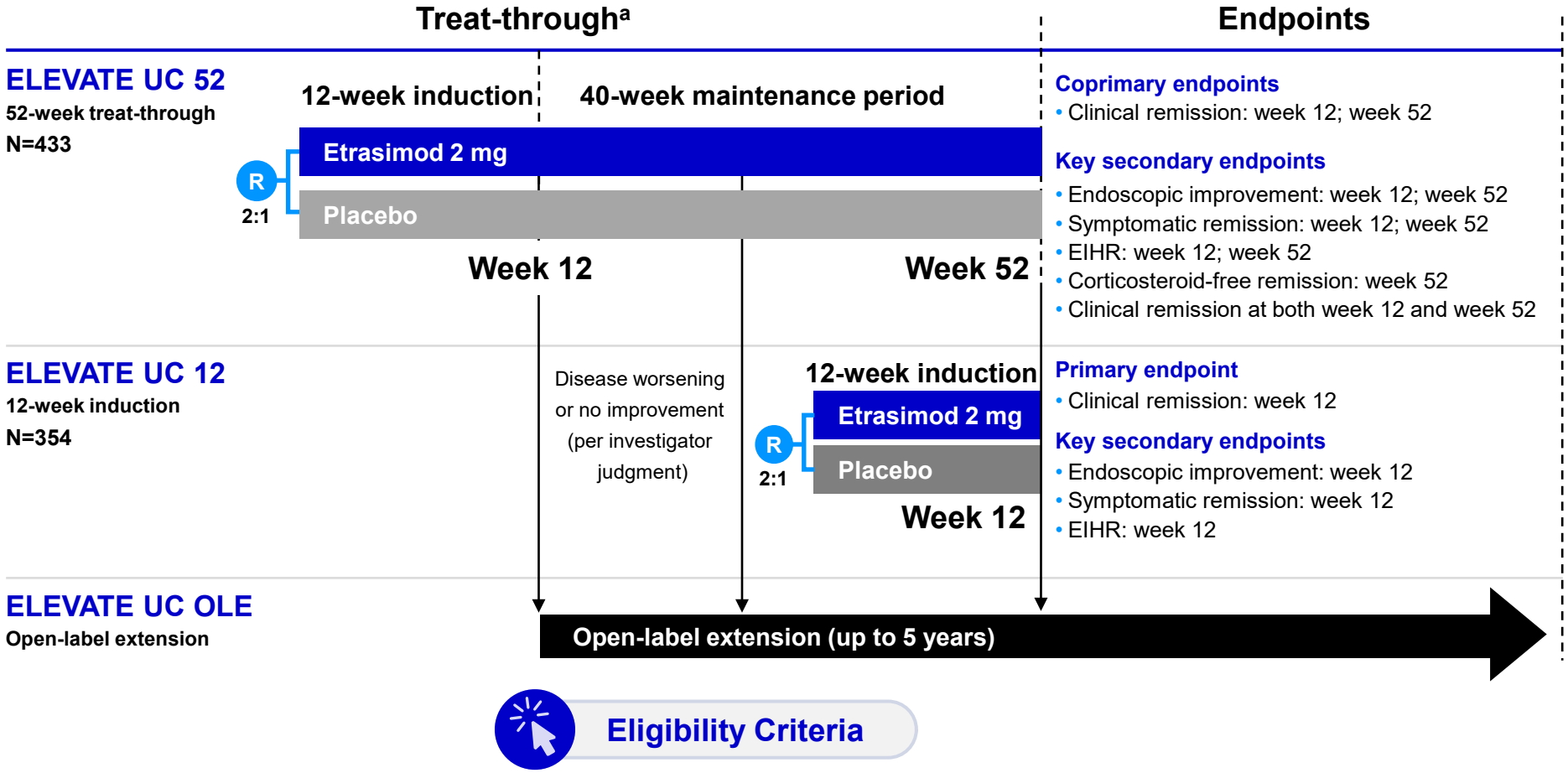
This is a **post hoc analysis** with a relatively small sample size and was not powered to determine statistical differences across the subgroup of patients with isolated proctitis. Therefore, efficacy conclusions cannot be drawn, and the data should be viewed cautiously[4]

IP=isolated proctitis; UC=ulcerative colitis. *based on an MMS of 4–9 with a centrally read endoscopic subscore ≥2 and rectal bleeding subscore ≥1

References: **1.** Caron B, et al. *Clin Gastroenterol Hepatol*. 2022;20(11):2619-2627.e1. **2.** Caron B, et al. *J Crohns Colitis*. 2022;16(6):922-930. **3.** Caron B, et al. *Gut*. 2021;70(7):1203-1209. **4.** Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Study design of the Etrasimod ELEVATE UC Program[1,2]



[a]Beginning at week 12, all subjects 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 judgment and, if objective disease worsening criteria were met) could discontinue and enroll in an OLE study (NCT03950232).[1,2]

EIHR=endoscopic improvement–histologic remission; OLE=open-label extension; UC=ulcerative colitis.

Reference: **1.** Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282. **2.** Sanborn WJ et al. *Lancet* 2023;401(10383):1159–71.

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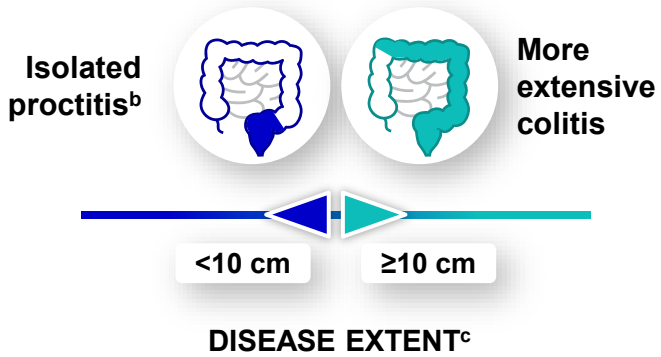
Patients With Isolated Proctitis Were Allowed to Enroll in ELEVATE UC 52 and UC 12, Provided They Met All Other Eligibility Criteria[1,2]

- 16-80 years of age
- Moderate to severe UC activity by mMS 4-9,[a] including:
  - Endoscopic subscore of ≥2 (centrally read)
  - Rectal bleeding subscore of ≥1



SELECT ELIGIBILITY CRITERIA

Baseline oral 5-ASA

Baseline oral steroids

(prednisone [≤20 mg/day], budesonide [≤9 mg/day], or equivalent)[d]

- 12-week induction period: continued at a stable dose
- 40-week maintenance period: tapered off (tapering was recommended, but not mandated, due to nonresponders continuing beyond week 12)[3]

Any per-rectum therapy including enemas

(eg, 5-ASA, corticosteroids)

- Prohibited during the study

[a]The modified Mayo score is defined as the sum of the rectal bleeding subscore, stool frequency subscore, and endoscopic subscore (each subscore on a scale of 0-3). Overall scores range from 0 to 9, with higher scores indicating greater disease activity.[2]

[b]Subpopulation of patients with IP was capped at 15% of total patients.

[c]UC confirmed by endoscopy and histopathology.[4]

[d]Provided that they were on a stable dose 2 weeks or 4 weeks before trial screening, respectively.

5-ASA=5-aminosalicylic acid; mMS=modified Mayo score; ; IP=isolated proctitis; UC=ulcerative colitis.

References: **1.** Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282. **2.** Sanborn WJ et al. *Lancet* 2023;401(10383):1159–71. **3**. Peyrin-Biroulet L, et al. Presented at: 18th Congress of European Crohn's and Colitis Organisation; March 1-4, 2023; Copenhagen, Denmark. Poster P407. **4.** Sanborn WJ et al. *Lancet* 2023;401(10383):1159–71. Supplementary appendix

[a] Beginning at Week 12, all subjects could continue their randomized treatment into a 40-week treatment period; those whose disease had not improved or had worsened vs baseline (based on investigator judgement) could discontinue and enroll in an OLE study (NCT03950232).

EIHR, endoscopic improvement–histologic remission; IP, isolated proctitis; OLE, open-label extension; UC, ulcerative colitis.

Peyrin-Biroulet L, et al. Presented at: 18th Congress of European Crohn's and Colitis Organisation; March 1-4, 2023; Copenhagen, Denmark. Poster P407.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Baseline Demographics and Clinical Characteristics[1] Post Hoc Analysis

	ELEVATE UC 52 + UC 12	
	Placebo (n=22)	Etrasimod 2 mg (n=42)
Age, mean (SD), years	41.4 (14.0)	38.6 (11.0)
Female, n (%)	10 (45.5)	22 (52.4)
BMI, mean (SD), kg/m^2	25.6 (4.3)	25.2 (6.0)
Duration of UC, mean (SD), years	6.9 (6.6)	7.4 (8.1)
Baseline mMS, mean (SD)[a]	5.8 (1.3)	6.0 (1.2)
Baseline ES=3, n (%)	6 (27.3)	13 (31.0)
Baseline corticosteroid use, n (%)	3 (13.6)	8 (19.0)
Naive to biologic/JAKi therapies, n (%)	20 (90.9)	31 (73.8)
Baseline urgency NRS score, mean (SD)	5.1 (2.7)	5.7 (2.6)
Baseline fecal calprotectin, mean (SD), mg/kg	733.3 (1181.5)	823.7 (1392.6)
Baseline fecal hsCRP, mean (SD), mg/L	1.9 (3.2)	3.0 (4.7)

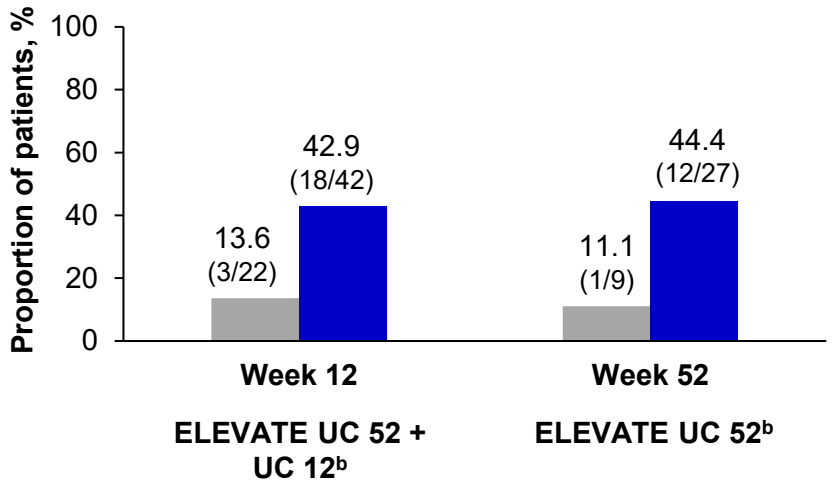
[a]The modified Mayo score is defined as the sum of the rectal bleeding subscore, stool frequency subscore, and endoscopic subscore (each subscore on a scale of 0-3). Overall scores range from 0 to 9, with higher scores indicating greater disease activity.[2]

BMI=body mass index; ES=endoscopic subscore; hsCRP=high-sensitivity C-reactive protein; JAKi=Janus kinase inhibitor; mMS=modified Mayo score; NRS=numeric rating scale; QD=once daily; SD; standard deviation; UC=ulcerative colitis.

Reference: **1.** Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282. **2.** Sanborn WJ et al. *Lancet* 2023;401(10383):1159–71.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Clinical Remission[a] in Patients with Isolated Proctitis Post Hoc Analysis



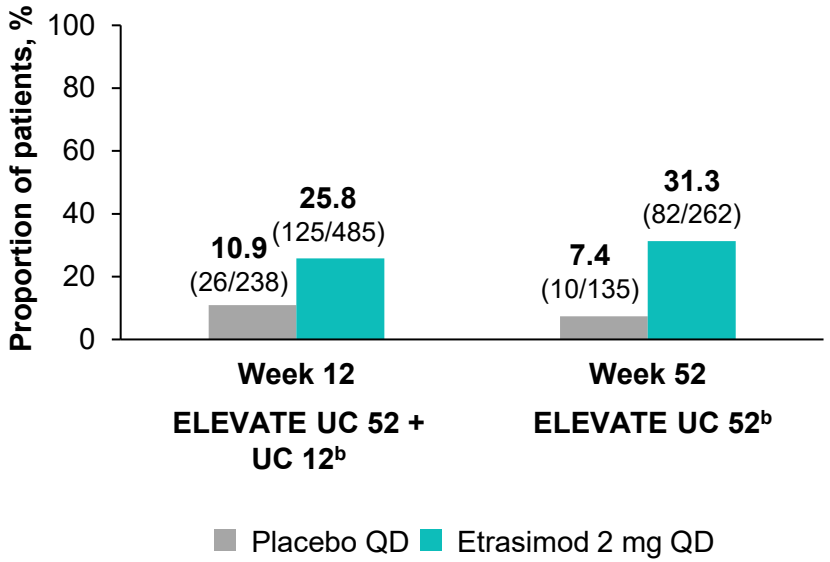
See data for patients with more extensive UC

[a]Clinical remission was defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability).
[b]Predefined endpoints were assessed at week 12 (pooled data from both trials) and week 52 (ELEVATE UC 52 only).
ES=endoscopic subscore; QD=once daily; RB=rectal bleeding; SF=stool frequency; UC=ulcerative colitis.

References: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Clinical Remission[a] in Patients With More Extensive Colitis Post Hoc Analysis



[a]Clinical remission was defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline), RB subscore =0, and ES ≤1 (excluding friability).
[b]Predefined endpoints were assessed at week 12 (pooled data from both trials) and week 52 (ELEVATE UC 52 only).
ES=endoscopic subscore; QD=once daily; RB=rectal bleeding; SF=stool frequency; UC=ulcerative colitis.
Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

[b] Predefined endpoints were assessed at week 12 (pooled data from both trials) and week 52 (ELEVATE UC 52 only).
ES, endoscopic subscore; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.
Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024:jjae038.

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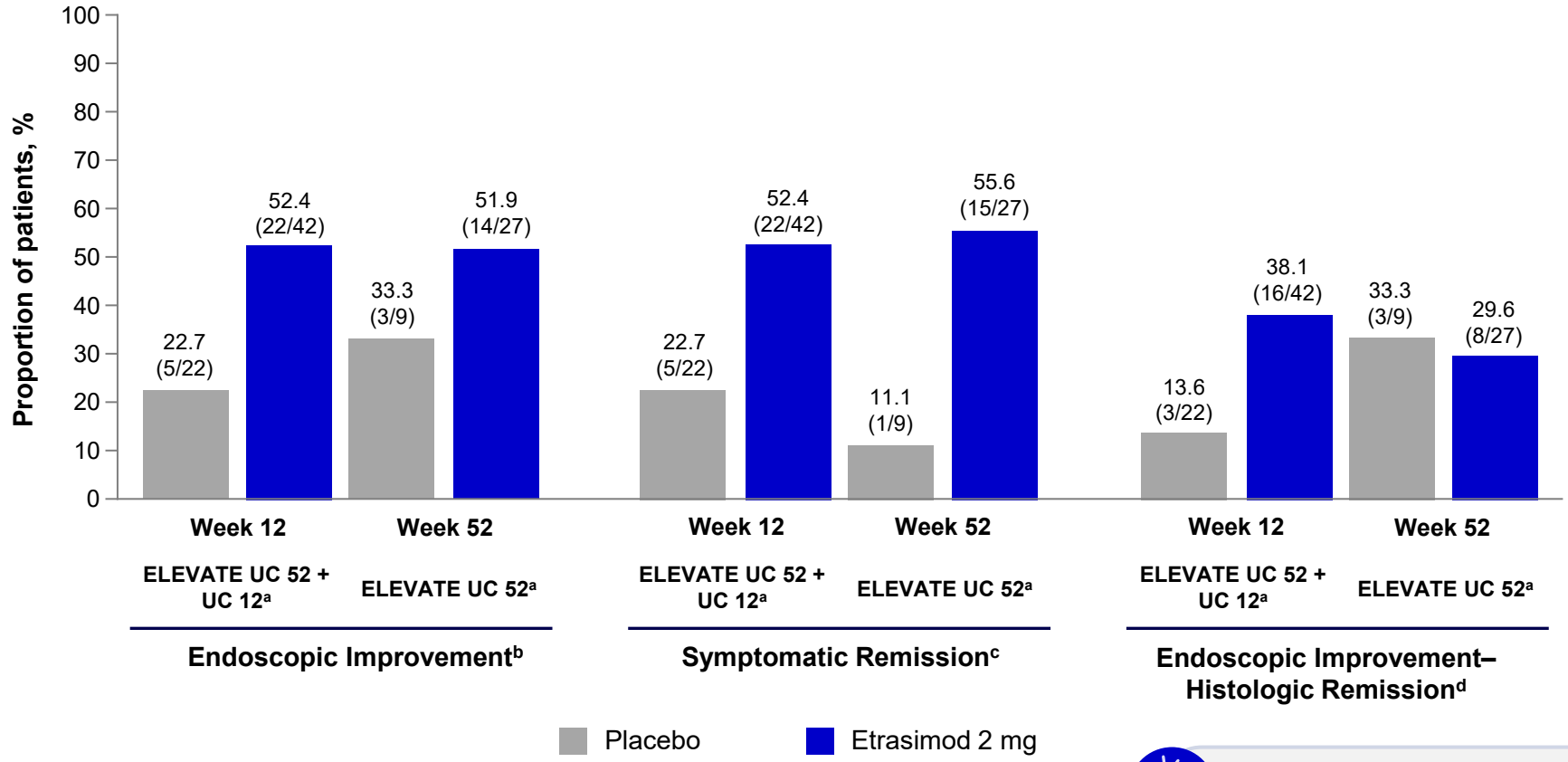
Clinical Data of Etrasimod in Patients With Isolated Proctitis

Key Secondary Endpoints in Patients with Isolated Proctitis Post Hoc Analysis

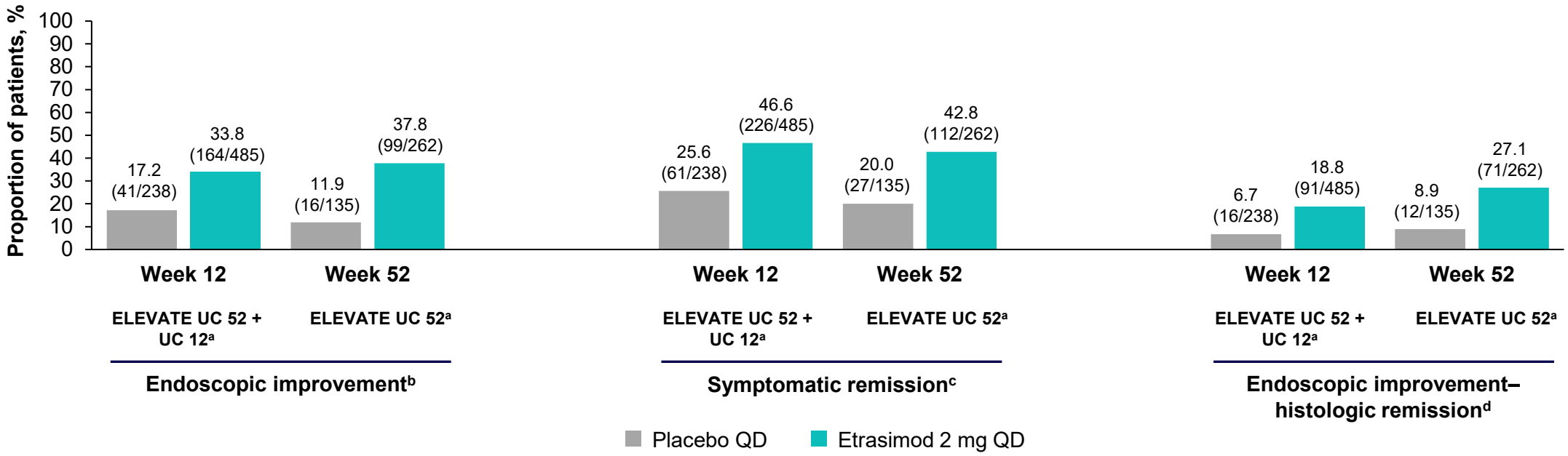


See data for patients with more extensive UC

[a]Predefined endpoints were assessed at week 12 (pooled data from both trials) and week 52 (ELEVATE UC 52 only).
[b]Endoscopic improvement was defined as a ES score of ≤1 (excluding friability).
[c]Symptomatic remission was defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline) and an RB subscore =0.
[d]Endoscopic improvement–histologic remission was defined as an ES ≤1 (excluding friability) with histologic remission as measured by a Geboes Index score <2.0.
ES=endoscopic subscore; QD=once daily; RB=rectal bleeding; SF=stool frequency; UC=ulcerative colitis.

References: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

Key Secondary Endpoints in Patients With More Extensive Colitis Post Hoc Analysis



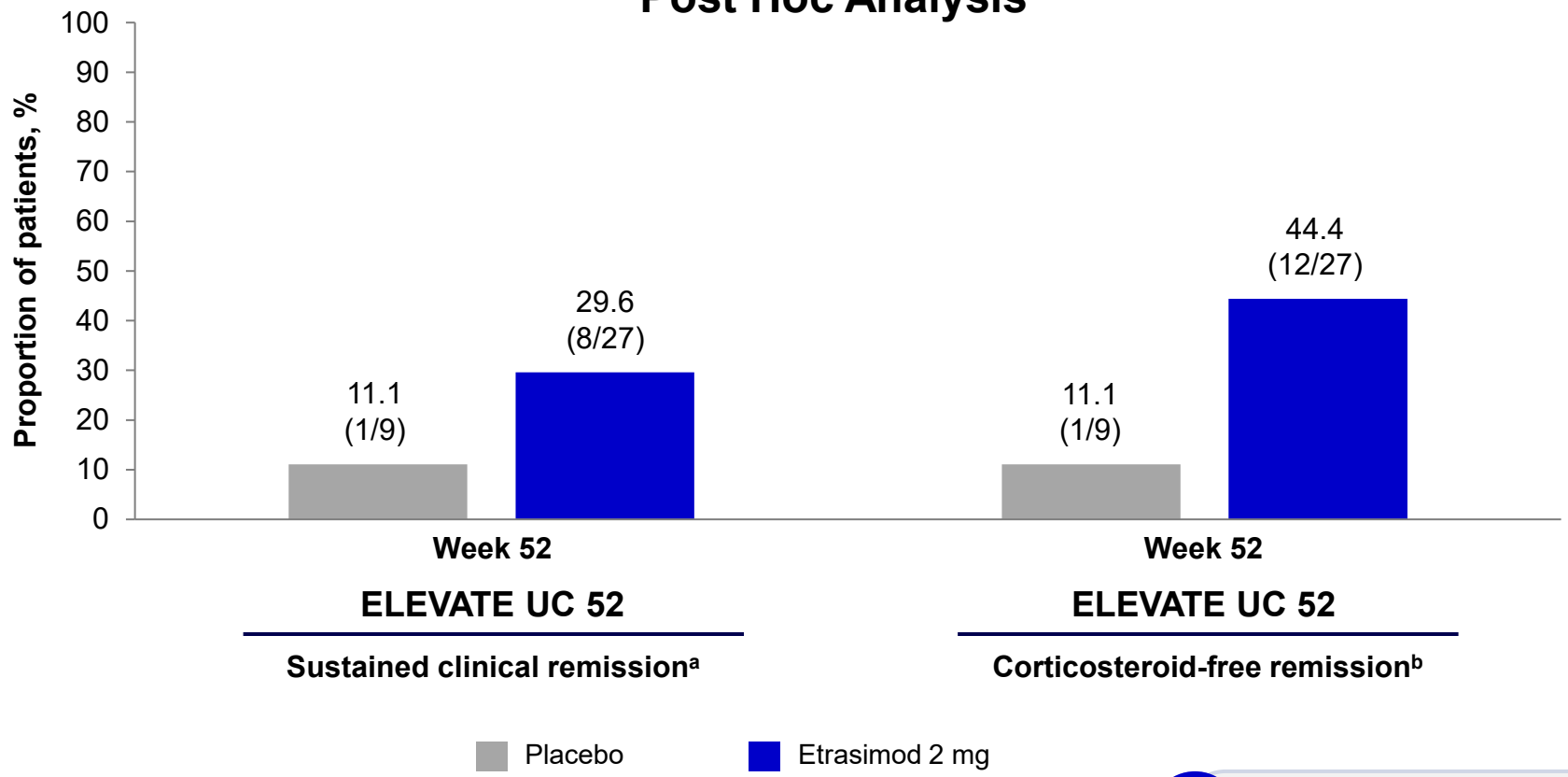
[a]Predefined endpoints were assessed at week 12 (pooled data from both trials) and week 52 (ELEVATE UC 52 only).
[b]Endoscopic improvement was defined as a ES score of ≤1 (excluding friability).
[c]Symptomatic remission was defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline) and an RB subscore =0.
[d]Endoscopic improvement–histologic remission was defined as an ES ≤1 (excluding friability) with histologic remission as measured by a Geboes Index score <2.0.
ES=endoscopic subscore; QD=once daily; RB=rectal bleeding; SF=stool frequency; UC=ulcerative colitis.

Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282. Supplementary data

ES, endoscopic subscore; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.
Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024:jjae038.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Sustained Clinical and Corticosteroid-free Remission in Patients with Isolated Proctitis Post Hoc Analysis



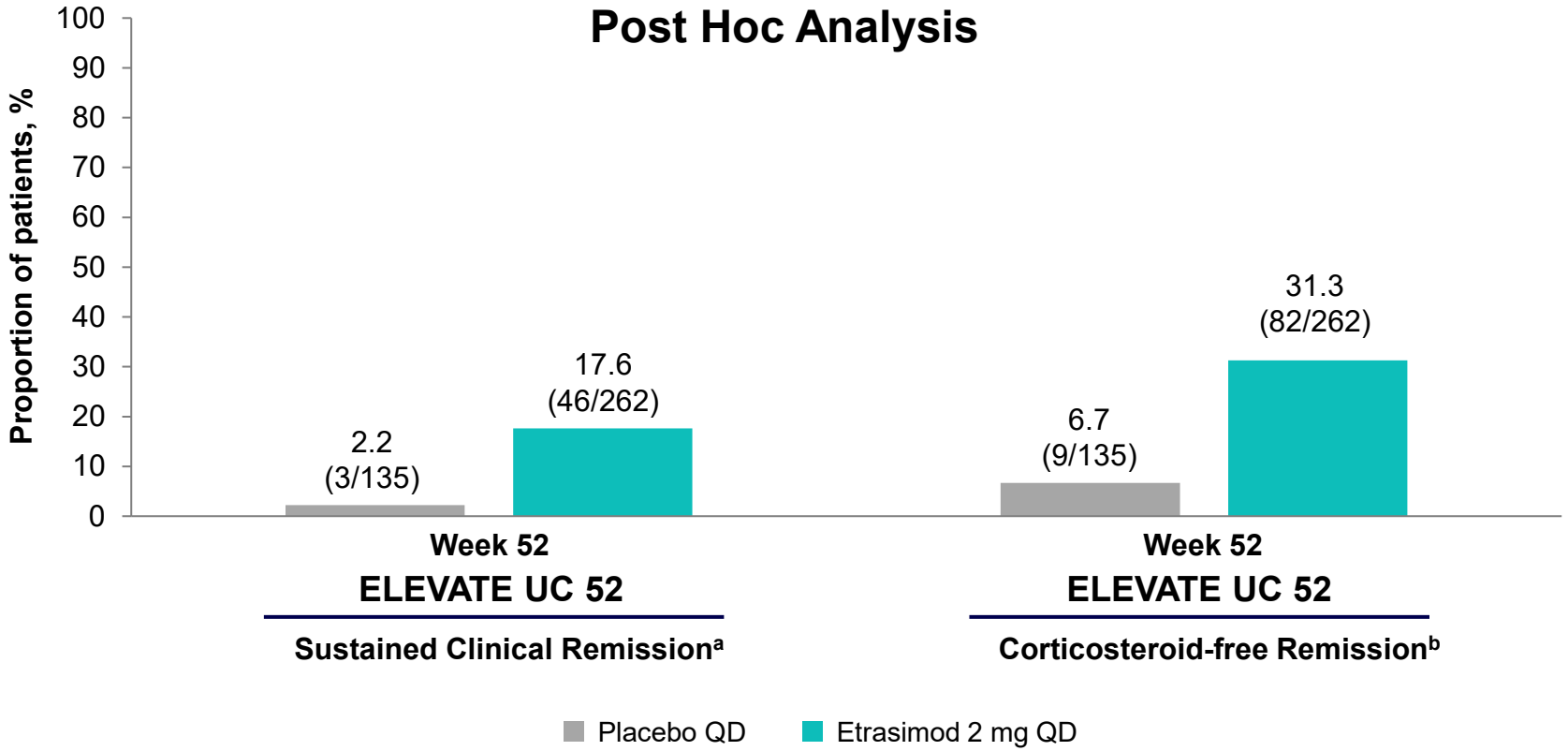
See data for patients with more extensive UC

Sustained clinical remission and corticosteroid-free remission were prespecified secondary endpoints.
[a]Sustained clinical remission was defined as clinical remission at both weeks 12 and 52.
[b]Corticosteroid-free remission was defined as clinical remission at week 52 with no use of corticosteroids for at least the last 12 study weeks immediately before Week 52.
QD=once daily; UC=ulcerative colitis.

Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Sustained Clinical and Corticosteroid-free Remission in Patients With More Extensive Colitis Post Hoc Analysis



[a]Sustained clinical remission was defined as clinical remission at both weeks 12 and 52.
[b]Corticosteroid-free remission was defined as clinical remission at week 52 with no use of corticosteroids for at least the last 12 study weeks immediately before week 52.
QD=once daily.
Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

[a] *Sustained clinical remission* was defined as clinical remission at both Weeks 12 and 52.
[b] *Corticosteroid-free remission* was defined as remission at Week 52 with no use of corticosteroids for at least the last 12 study weeks immediately before Week 52.
CS, corticosteroid; UC, ulcerative colitis.
Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024:jjae038.

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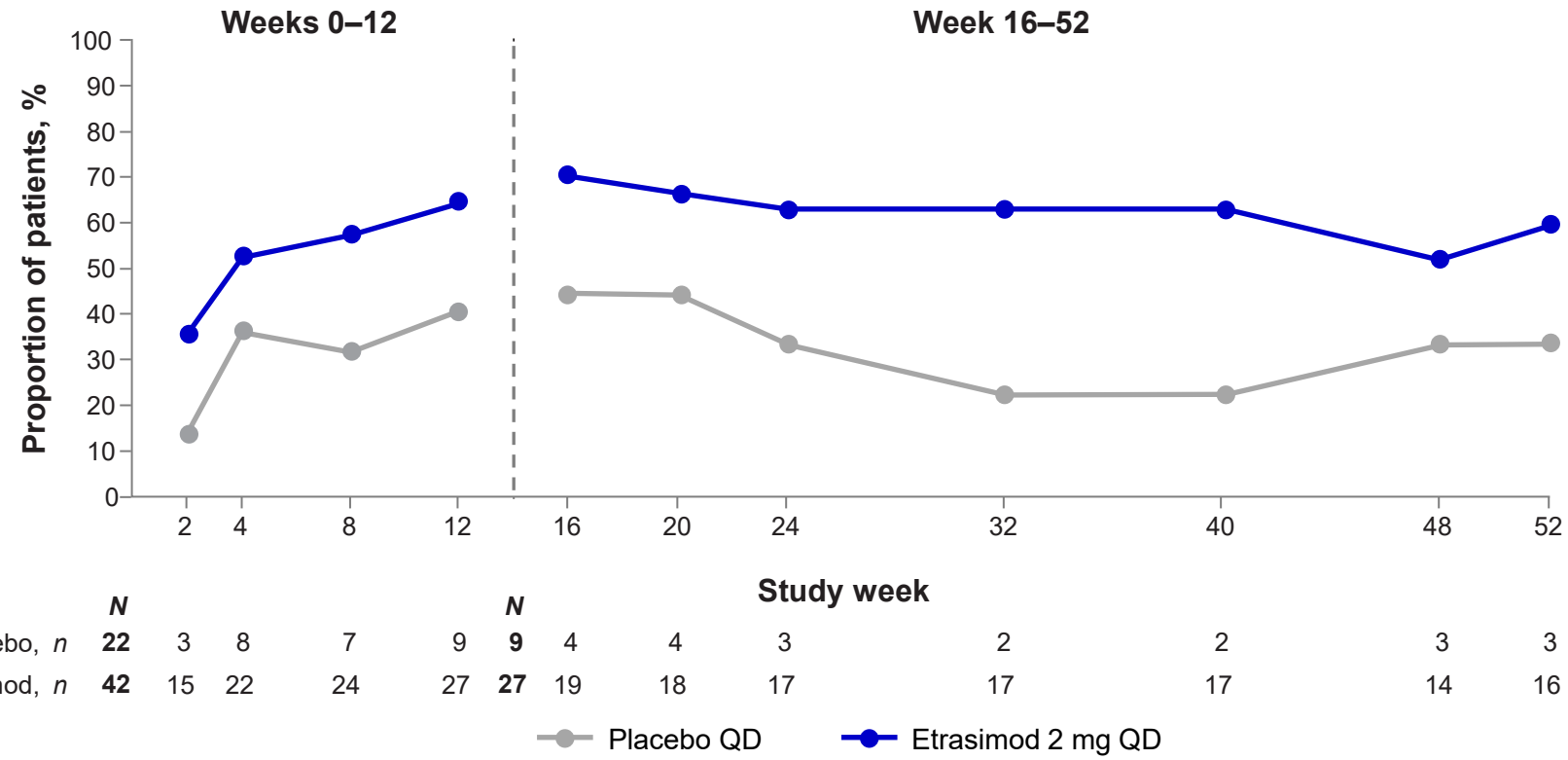
Clinical Data of Etrasimod in Patients With Isolated Proctitis

Cessation of Rectal Bleeding (RBS = 0)[a] Post Hoc Analysis



Higher proportion of patients receiving etrasimod had rectal bleeding cessation versus placebo from Week 2

[a]Missing responses are imputed as nonresponse.
QD=once daily; RBS=rectal bleeding subscore.

Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282. Supplementary data

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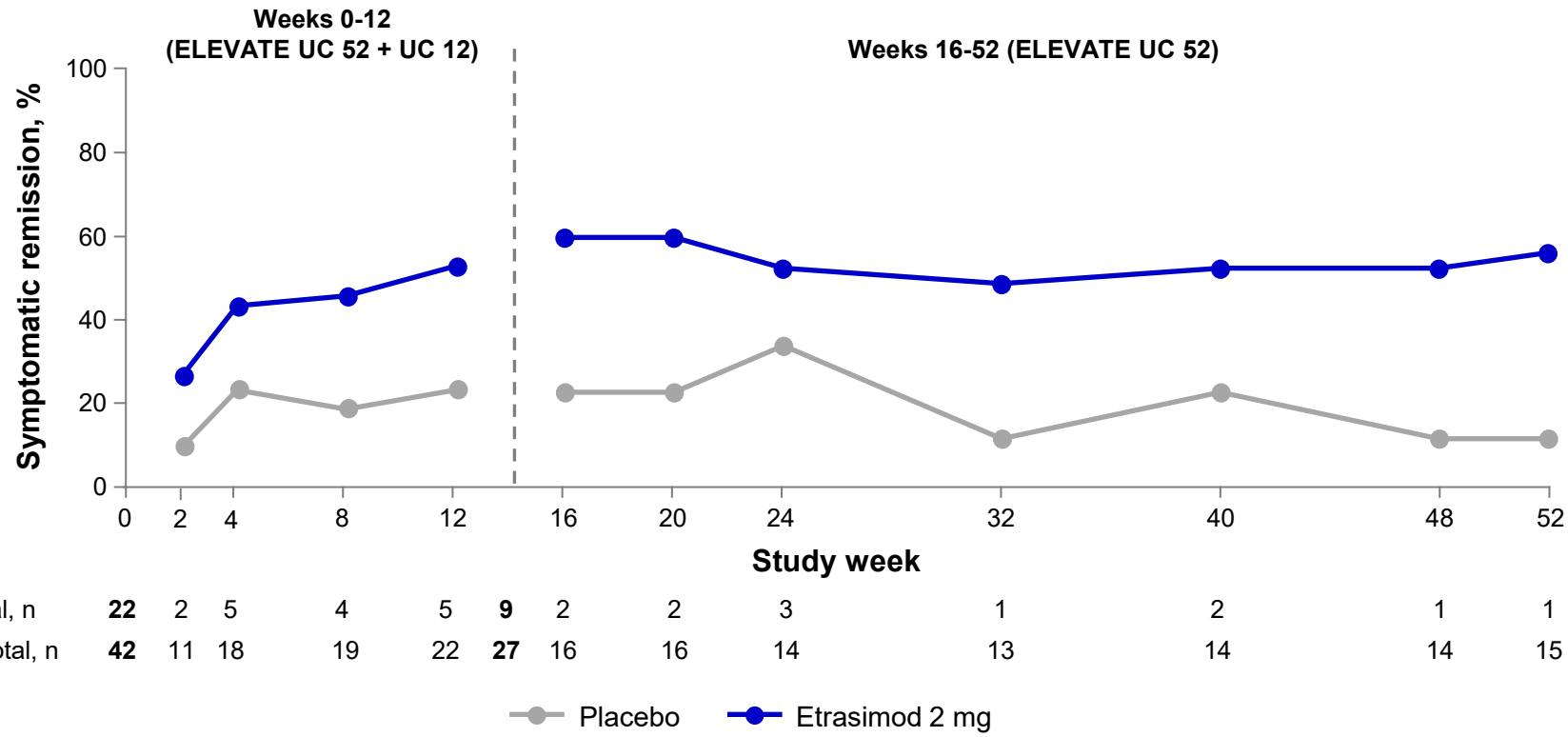
Clinical Data of Etrasimod in Patients With Isolated Proctitis

Achievement of Symptomatic Remission[a] Over Time Post Hoc Analysis



Higher proportions of patients treated with etrasimod achieved symptomatic remission by Week 4 vs. placebo, which was sustained through 52 weeks

[a]Symptomatic remission was defined as an SF subscore =0 (or =1 with a ≥1-point decrease from baseline) and an RB subscore =0. Missing responses are imputed as nonresponse.
RB=rectal bleeding; SF=stool frequency.

Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024;18(8):1270-1282.

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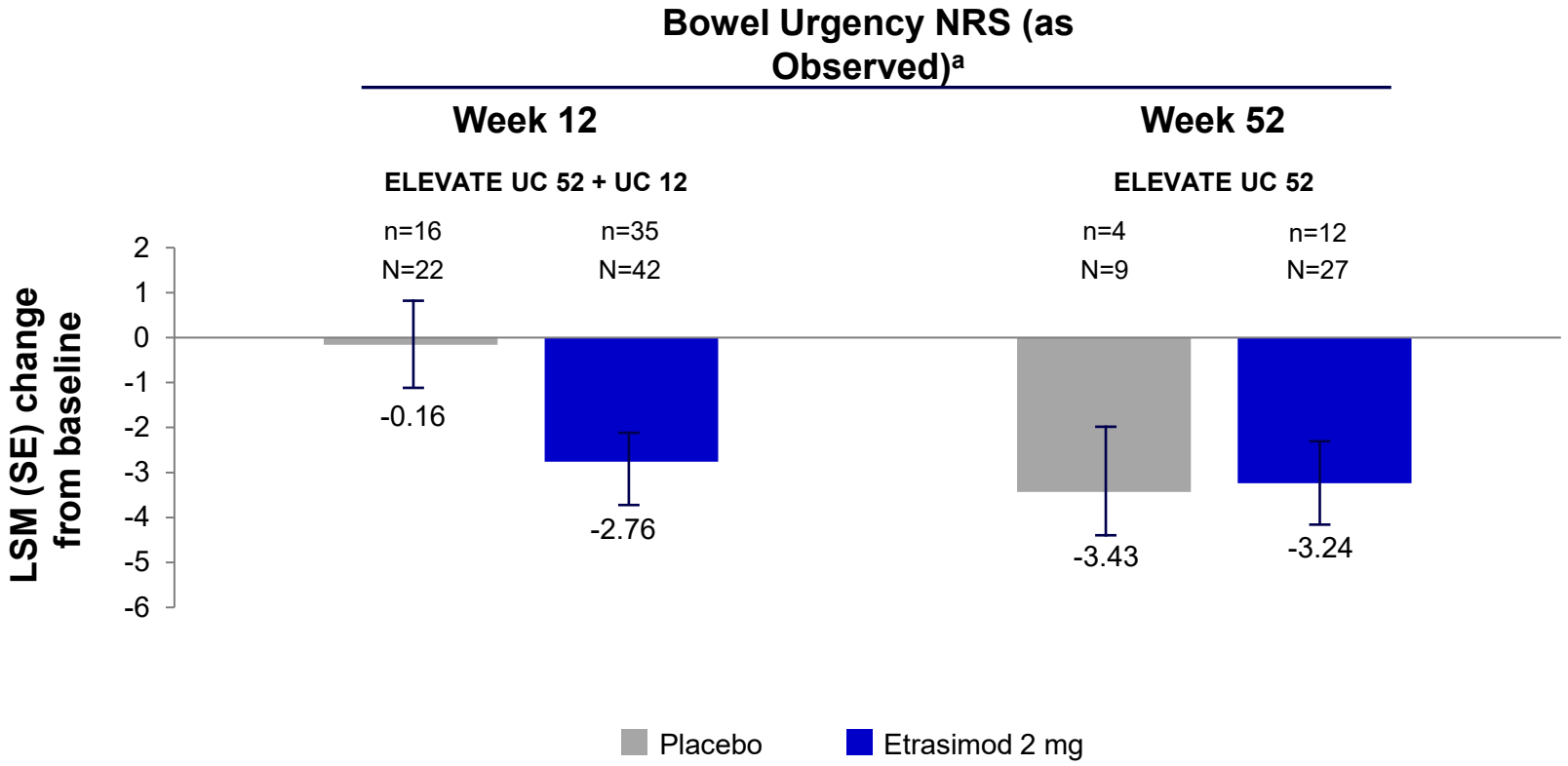
Clinical Data of Etrasimod in Patients With Isolated Proctitis

Change From Baseline in Bowel Urgency Post Hoc Analysis



Patients treated with etrasimod had improvements in bowel urgency at Week 12 vs placebo[1]

[a]A ≥3-point improvement in the Urgency NRS score was previously validated as a meaningful improvement in bowel urgency[2]; a 1- to 2-point change was previously reported as the minimal desired improvement.[3] Bowel urgency NRS score is a validated measure of urgency severity in patients with UC, with the patient's perception of bowel urgency severity over 24 hours assessed on an 11-point NRS ranging from 0 ("no urgency") to 10 ("worst possible urgency"). A 3-point improvement in the bowel urgency NRS score is considered meaningful, and most patients surveyed reported a 1- to 2-point change as the minimal desired improvement.[1]

LSM=least-squares mean; NRS=numeric rating scale; SE=standard error; UC=ulcerative colitis.

References: **1.** Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024 ;18(8):1270-1282. **2.** Dubinsky MC, et al. *J Patient Rep Outcomes*. 2022;6(1):114. **3.** Dubinsky MC, et al. *J Patient Rep Outcomes*. 2022;6(1):31.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Treatment-emergent adverse events

ELEVATE UC 52 + ELEVATE UC 12

AEs, n (%)	Patients With Isolated Proctitis		Patients With More Extensive Colitis	
	Etrasimod 2 mg (n=42)	Placebo (n=22)	Etrasimod 2 mg (n=485)	Placebo (n=238)
Most common TEAEs (≥4% patients)[a]				
Headache	4 (9.5)	0	31 (6.4)	9 (3.8)
Arthralgia	2 (4.8)	0	15 (3.1)	6 (2.5)
Blood creatine phosphokinase increased	2 (4.8)	0	6 (1.2)	2 (0.8)
Dizziness	2 (4.8)	0	16 (3.3)	1 (0.4)
Pyrexia	1 (2.4)	0	21 (4.3)	9 (3.8)
Ulcerative colitis[b]	0	0	29 (6.0)	12 (5.0)

Post Hoc Analysis Data should be interpreted with caution considering the relatively small sample

[a]The most common TEAEs included above are the most frequently occurring TEAEs among etrasimod-treated patients only, per the isolated proctitis subgroup. Common TEAEs were defined as those reported in >1% of patients (etrasimod group) and with higher IR (proportion) in the etrasimod group than in the placebo group, in the overall population.
[b]Ulcerative Colitis includes UC worsening/UC flares.
AE=adverse event; TEAE=treatment-emergent adverse event; UC=ulcerative colitis.
Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024 ;18(8):1270-1282.

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Clinical Data of Etrasimod in Patients With Isolated Proctitis

Serious AEs and AEs of Special Interest

ELEVATE UC 52 + ELEVATE UC 12

AEs, n (%)	Patients With Isolated Proctitis: Etrasimod 2 mg (n=42)	Patients With Isolated Proctitis: Placebo (n=22)	Patients With More Extensive Colitis: Etrasimod 2 mg (n=485)	Patients With More Extensive Colitis: Placebo (n=238)
Serious AE	2 (4.8)	0	24 (5.0)	11 (4.6)
Infections[a]	0	1 (4.6)	10 (2.1)	8 (3.4)
Severe infections[b]	0	0	3 (0.6)	5 (2.1)
Herpes simplex	0	0	1 (0.2)	0
Herpes zoster	0	0	2 (0.4)	2 (0.8)
Opportunistic infections[c,d]	0	1 (4.6)	1 (0.2)	0
Malignancies[a]	0	0	0	0
Macular edema[a,e]	0	0	1 (0.2)	0
Cardiovascular events[a]	1 (2.4)[f]	0	19 (3.9)	2 (0.8)

Post Hoc Analysis Data should be interpreted with caution considering the relatively small sample

[a]AESI (Adverse Events of Special Interest). AEs are AESI and met the review criteria.
[b]Severe infections were defined as those that met the Common Terminology Criteria for Adverse Events version 5.0, Grade ≥3.
[c]Opportunistic infections is based on the Standardized Medical Dictionary for Regulatory Activities query (version 24.1), narrow scope.
[d]Opportunistic infection was tuberculosis in a patient receiving placebo; the patient discontinued from the study; the event resolved with treatment.
[e]Two additional cases of macular edema were reported by study investigators; however, these did not meet the review criteria for AEs of special interest.
[f]Cardiovascular event was arterial hypertension unlikely related to study treatment; the patient recovered without change to study treatment.
AE=adverse event; TEAE=treatment-emergent adverse event; UC=ulcerative colitis.
Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024 ;18(8):1270-1282.

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Clinical Data of Etrasimod in Patients With Isolated Proctitis

Subgroup Analysis Limitations

Patient eligibility in this analysis was based on criteria from the ELEVATE clinical trials and, therefore, may not be representative of the overall UC population with isolated proctitis.

Mayo score was not designed to evaluate patients with isolated proctitis and may not be the most appropriate scoring system for this population

This was a **post hoc analysis** with a relatively small sample size and was not powered to determine statistical differences across the subgroup of patients with isolated proctitis. Therefore, efficacy conclusions cannot be drawn, and the data should be viewed cautiously.

Major efficacy endpoints were collected only at week 12 and week 52; therefore, transient effects at other time points cannot be assessed.

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NRS=Numeric Rating Scale; UC=ulcerative colitis.

Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024 ;18(8):1270-1282.

Clinical Data of Etrasimod in Patients With Isolated Proctitis

Conclusions

The outcomes of etrasimod in patients with isolated proctitis were consistent with those in the overall population of the ELEVATE UC program.

Etrasimod improved proctitis-related symptoms such as rectal bleeding from Week 2 and bowel urgency at Week 12 of treatment.

This analysis expands upon the clinical data of etrasimod in UC into a subpopulation of UC patients with isolated proctitis who are commonly excluded from drug development trials of advanced therapies.

RB=rectal bleeding; UC=ulcerative colitis.

Reference: Peyrin-Biroulet L, et al. *J Crohns Colitis*. 2024 ;18(8):1270-1282.