Improving patient outcomes in moderate-to-severe ulcerative colitis

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What is the significance of the disease burden of ulcerative colitis when assessing patients?

Prof. Ailsa Hart

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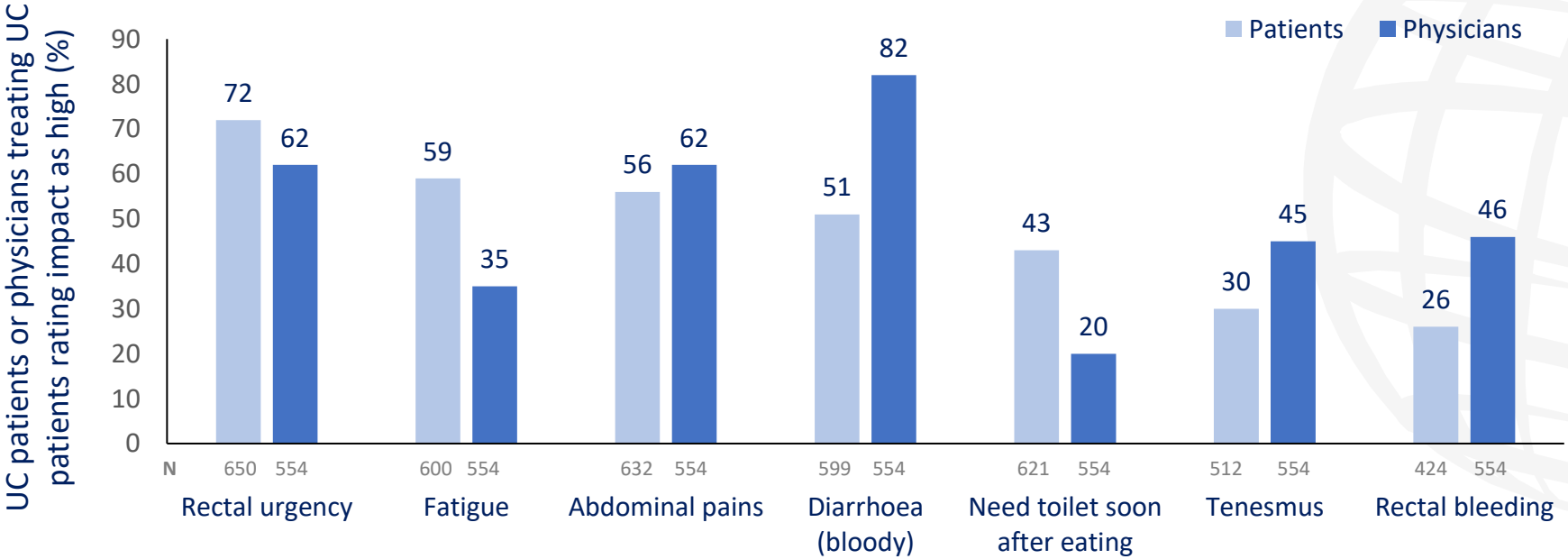
Patient- and physician-reported symptoms with the greatest impact on quality of life in ulcerative colitis



UC, ulcerative colitis.

Figure reproduced with permission from Rubin D, et al. *Inflamm Bowel Dis.* 2021;27:1942–53.

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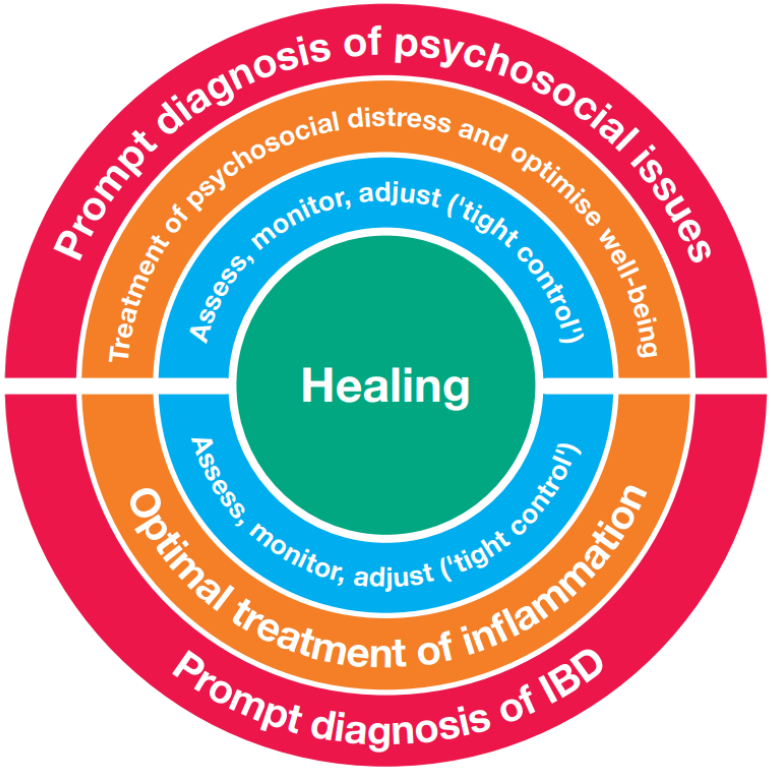
Integrated approach for holistic, patient-centred IBD care



IBD, inflammatory bowel disease.
Figure reproduced with permission from Keefer L, et al. *Gastroenterology.* 2022;162:1439–51.

BOOST: Living well with fatigue, pain and urgency in IBD[1,2]

A programme designed to give patients the tools, skills and support to better manage symptoms in addition to routine medical care

30-minute telephone call with an IBD nurse

12 online sessions
(one per week recommended)

IBD-BOOST Trial:
A randomized controlled trial of an interactive online symptom management programme with nurse support in addition to routine medical care vs routine medical care alone
(www.kcl.ac.uk/research/ibd-boost)

IBD, inflammatory bowel disease.
1. BOOST homepage. Available at: www.ibd-boost.org/ (accessed 25 January 2022); 2. Norton C, et al. *Trials.* 2021;22:516.

Burden of current treatment options for patients with ulcerative colitis

Clinical concerns

Treatment side effects[1,2]

Hospital visits for infusions[2,3]

Drug monitoring procedures and appointments[2]

Psychosocial concerns

Unpredictable disease course, relapse and treatment failures[2]

Fear of surgical procedures and surgery outcomes[2]

Embarrassment and lifestyle changes following colectomy[2]

1. Quezada S, et al. *Expert Rev Gastroenterol Hepatol.* 2018;12:1183–91; 2. Rapport F, et al. *BMC Gastroenterol.* 2019;19:166; 3. Buisson A, et al. *Inflamm Bowel Dis*. 2013;19:2464–7.

The importance of timely diagnosis and early treatment in ulcerative colitis: Why does it matter?

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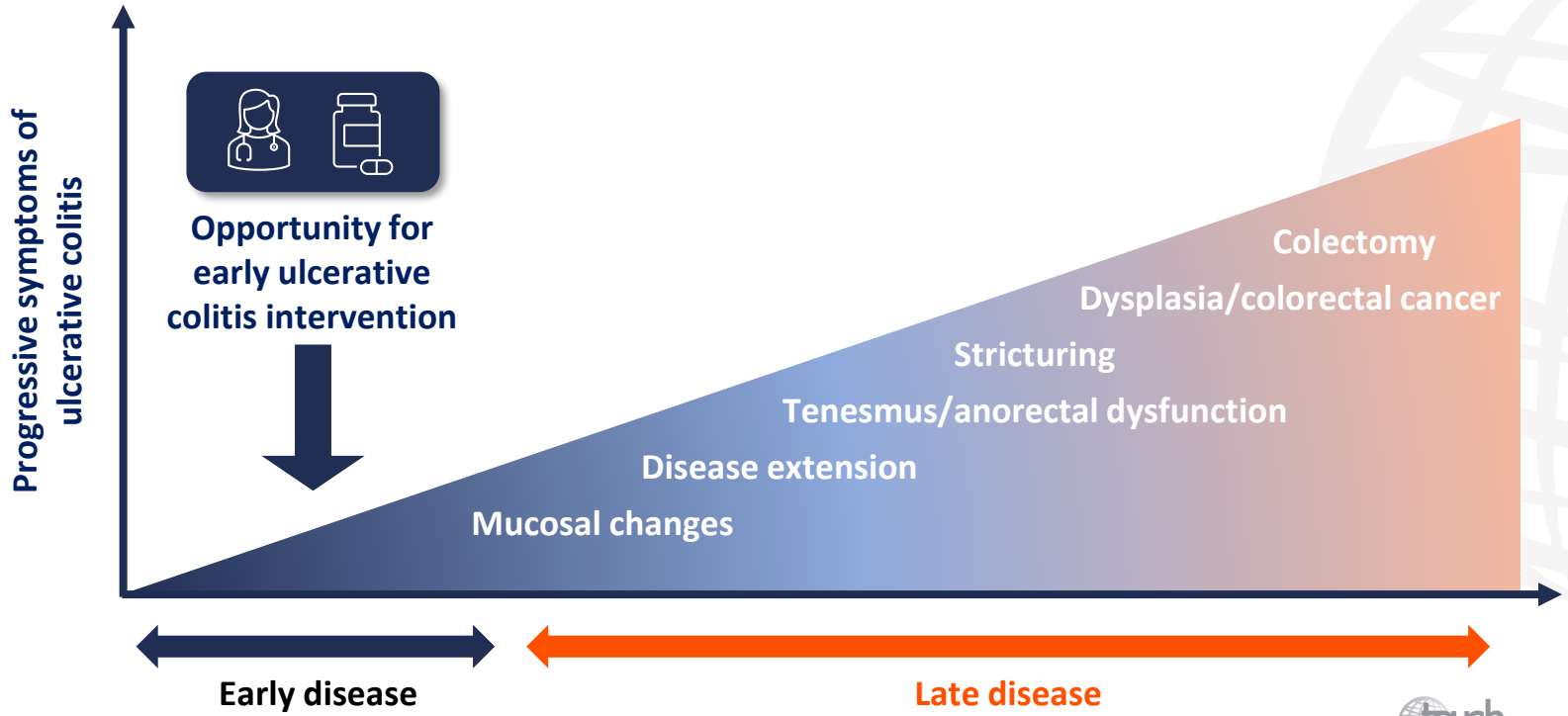
Similar to Crohn's disease, ulcerative colitis may have a progressive disease course



Solitano V, et al. *J Clin Med.* 2020;9:2646.

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Identifying patients at a high risk for developing ulcerative colitis

Clinical features associated with severe disease[1]

- Extensive disease
- Deep ulcers
- Extra-intestinal manifestations

Biomarkers to identify severe disease[1,2]

- Elevated serum inflammatory markers
- Faecal calprotectin or lactoferrin

Patient history and demographics[1,2]

- Family history of IBD
- Young age (<40 years)
- History of gastroenteritis
- Oral contraceptives, HRT, NSAIDs

Environmental factors[2,3]

- Former smoker
- High perceived stress or stressful life events associated with IBD

HRT, hormone replacement therapy; IBD, inflammatory bowel disease; IBD, inflammatory bowel disease; NSAID, non-steroidal anti-inflammatory drug.

1. Ko CW, et al. *Gastroenterology.* 2019;156:748–64; 2. Ungaro R, et al. *Lancet.* 2017;389:1756–70; 3. van der Sloot K, et al. *J Crohns Colitis*. 2020;14:1662–71.

Approved treatments for ulcerative colitis

Mild-to-moderate disease[1]

- Oral/rectal 5-ASA are the mainstay of treatment
  - Sulfasalazine
  - Mesalamine
  - Diazo-bonded 5-ASA
- In patients with 5-ASA refractory disease, the addition of either oral prednisone or budesonide MMX is suggested

Moderate-to-severe disease[2]

- A number of drug classes are approved
  - Biologic agents:
    - TNF-α antagonists (infliximab, adalimumab, golimumab)
    - Anti-IL-12/IL-23 (ustekinumab)
    - Anti-integrin (vedolizumab*)
  - Immunomodulators (thiopurines, methotrexate)
  - Small molecules
    - JAK inhibitor (tofacitinib†)
    - S1P receptor inhibitor (ozanimod[3])

*Currently approved for intravenous administration by the EMA and FDA; a subcutaneous formulation is also approved by the EMA.[2,4]
†In biologic-naive patients with moderate-to-severe ulcerative colitis, tofacitinab is currently only recommended for use in the setting of a clinical or registry study.[2]
5-ASA, 5-aminosalicylates; EMA, European Medicines Agency; FDA, US Food and Drug Administration; IL, interleukin; JAK, Janus kinase; MMX, Multi-Matrix System; PI, prescribing information; S1P, sphingosine 1 phosphate; SmPC, summary of product characteristics; TNF-α, tumour necrosis factor alpha.
1. Ko C, et al. *Gastroenterology.* 2019;156:748–64; 2. Feuerstein J, et al. *Gastroenterology.* 2020;158:1450–61; 3. FDA. Ozanimod PI. Revised 2021; 4. EMA. Vedolizumab SmPC. Revised 2022.
PI and SmPC available via the FDA and EMA, respectively at: www.accessdata.fda.gov/scripts/cder/daf/ and www.ema.europa.eu/en/medicines (accessed 9 March 2022).

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Therapeutic drug monitoring for a personalized medicine approach in ulcerative colitis

Therapeutic drug monitoring

Blood concentrations[1]

- Active metabolites
- Anti-TNF-α drug
- Anti-drug antibodies

E.g. Higher serum induction/trough concentrations of infliximab and adalimumab are associated with endoscopic healing and clinical remission[1]

Dose optimization, to improve response rates and prevent secondary loss of response, by targeting drug concentrations that are considered to be in the optimal therapeutic range[2]

TNF-α, tumour necrosis factor alpha.

1. Ungaro R, et al. *Lancet.* 2017;389:1756–70; 2. Papamichael K, Cheifetz A. *Curr Opin Gastroenterol.* 2019;35:302–10.

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How might emerging therapy options in UC impact current clinical practice?

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Considerations for the development of new therapies in moderate-to-severe UC

Effectiveness of current therapies

- Approximately a third of patients with IBD do not respond to biologic therapy[1]
- A substantial proportion of responders to biologic agents lose response over time[1]

Safety issues with current therapies

- Biologics are associated with an increased risk of serious infections[1]
- Carcinogenic risk with azathioprine[2]

Drug delivery

- Parenteral delivery is burdensome for patients and may result in decreased persistence with therapy[1]
- Small molecules can be administered orally;[1] however, non-adherence to oral therapies can be an issue in IBD[3]

Cost

- Substantial treatment costs associated with biologic agents (direct and indirect)[1]

IBD, inflammatory bowel disease; UC, ulcerative colitis.

1. Ma C, et al. *Drugs*. 2019;79:e1321–35; 2. Greuter T, et al. *Digestion*. 2020;101(Suppl. 1):136–45; 3. Chan W, et al. *Intest Res*. 2017;15:434–45.

Emerging therapies in UC[1]

Drug class	Agent	Target	Delivery	Stage of clinical development
JAK inhibitor	**Tofacitinib** **Filgotinib** Upadacitinib	**JAK1/JAK3** **JAK1** JAK1	**Oral** **Oral** Oral	**FDA approved** **EMA approved[2]*** Phase III recruiting
S1P receptor modulator	**Ozanimod** Etrasimod	**S1PR1 and S1PR5** S1PR1, S1PR4 and S1PR5	**Oral** Oral	**FDA[3] and EMA[4†] approved** Phase III recruiting
Anti-trafficking therapy	**Vedolizumab** Etrolizumab AJM300	**α4β7 integrin** α4β7 and αEβ7 integrins α4 integrin	**SC** SC Oral	**EMA approved[5†]** Phase III completed Phase III recruiting
IL-23 inhibitor	Risankizumab Mirikizumab Guselkumab	IL-23/p19 subunit IL-23/p19 subunit IL-23/p19 subunit	IV, SC IV, SC IV, SC	Phase III enrolling by invitation Phase III recruiting Phase II/III recruiting

Table adapted from Al-Bawardy B, et al. 2021.[1] Agents approved for UC or in current phase III development included.
*Approved for patients with moderate-to-severe ulcerative colitis who have had an inadequate response, lost response or were intolerant to conventional or biologic therapy.[2]
†In patients with moderate to severely active disease who have failed on, or are intolerant to, standard treatments or biological agents.
EMA, European Medicines Agency; FDA, Food and Drug Administration; IL, interleukin; IV, intravenous; JAK, Janus kinase; PI, prescribing information; S1P, sphingosine 1-phosphate; S1PR, sphingosine 1-phosphate receptor; SC, subcutaneous; SmPC, summary of product characteristics; UC, ulcerative colitis.
1. Al-Bawardy B, et al. *Front Pharmacol*. 2021;12:651415; 2. EMA. Filgotinib SmPC. Revised 2021; 3. FDA. Ozanimod PI. Revised 2021; 4. EMA. Ozanimod SmPC. Revised 2021. 5. EMA. Vedolizumab SmPC. Revised 2022. PI and SmPC available via the FDA and EMA, respectively at: www.accessdata.fda.gov/scripts/cder/daf/ and www.ema.europa.eu/en/medicines (accessed 9 March 2022).

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JAK inhibitors in moderate-to-severe UC

Broad spectrum immunosuppressants: Optimal dosing needed to minimize immunosuppression and achieve efficacy[1]

Tofacitinib[2]*

Three phase III trials in moderate-to-severe UC:

- OCTAVE Induction 1 (N=598)
- OCTAVE Induction 2 (N=541)
- OCTAVE Sustain (N=593)

18.5% 8-week remission vs **8.2%** with placebo; p=0.007 (OCTAVE Induction 1)

16.6% 8-week remission vs **3.6%** with placebo; p<0.001 (OCTAVE Induction 2)

40.6% 52-week remission vs **11.1%** with placebo; p<0.001 (OCTAVE Sustain)

Safety (tofacitinib vs placebo)[2]

- Higher rates of overall infections, non-melanoma skin cancer, and cardiovascular events reported
- Increased lipid levels

↑ risk of cancers and MACE with tofacitinib in RA[3]†

*Data presented for the 10-mg approved dose.
†Vs tumour necrosis factor inhibitors.[3]
JAK, Janus kinase; MACE, major adverse cardiovascular events; RA, rheumatoid arthritis; UC, ulcerative colitis.
1. Nash P, et al. *Ann Rheum Dis.* 2021;80:71–87; 2. Sandborn W, et al. *N Engl J Med.* 2017;376:1723–36; 3.Ytterberg S, et al. *N Engl J Med* 2022;386:316–26.

JAK inhibitors in moderate-to-severe UC

Broad spectrum immunosuppressants: Optimal dosing needed to minimize immunosuppression and achieve efficacy[1]

Upadacitinib[2]

Phase IIb trial in moderate-to-severe UC*:

- N=250
- 1° endpoint: % of patients in remission at week 8†

8.5%	7.5 mg vs **0.0%** with placebo; p=0.052
14.3%	15 mg vs **0.0%** with placebo; p=0.013
13.5%	30 mg vs **0.0%** with placebo; p=0.011
19.6%	45 mg vs **0.0%** with placebo; p=0.002

Safety

- Upadacitinib was well tolerated
- Frequency of AEs of special interest was generally low (<5%) in the upadacitinib groups with the exception of anaemia, hepatic disorder and creatine phosphokinase elevation

Phase III, long-term safety and efficacy trial currently enrolling patients (NCT03006068)

*In patients with an inadequate response, loss of response, or intolerance to corticosteroids, immunosuppressive agents, and/or biologic therapies.
†Clinical remission according to the adapted Mayo score.
AE, adverse event; JAK, Janus kinase; UC, ulcerative colitis.
1. Nash P, et al. *Ann Rheum Dis.* 2021;80:71–87; 2. Sandborn W, et al. *Gastroenterology.* 2020;158:2139–49.

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JAK inhibitors in moderate-to-severe UC

Broad spectrum immunosuppressants: Optimal dosing needed to minimize immunosuppression and achieve efficacy[1]

Filgotinib[2]

Phase IIb/III trial in moderate-to-severe UC:

- SELECTION (N=659)

23.8% 58-week remission with 100-mg dose vs **13.5%** with placebo; p=0.0420*

26.1% 10-week remission with 200-mg dose vs **15.3%** with placebo; p=0.0157 (induction A; biologic-naive)

11.5% 10-week remission with 200-mg dose vs **4.2%** with placebo; p=0.0103 (induction B; biologic-experienced)

Safety

- Filgotinib was well tolerated, with incidence of SAEs and AEs of interest similar between treatment groups

*Clinical remission: filgotinib 100 mg vs placebo, week 10, not significantly different.
AE, adverse event; JAK, Janus kinase; SAE, serious adverse event; UC, ulcerative colitis.
1. Nash P, et al. *Ann Rheum Dis.* 2021;80:71–87; 2. Feagen B, et al. *Lancet.* 2021;397:2372–84.

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S1PR modulators in moderate-to-severe UC

Target lymphocyte recirculation through blockade of lymphocyte egress from lymph nodes[1]

Ozanimod

Trials in moderate-to-severe UC:

- Phase II TOUCHSTONE (N=197)[2]
- Phase III TRUE NORTH (N=1,012)[3]

18.4% 10-week remission vs **6.0%** with placebo; p<0.001 (induction)[3]

37.0% 52-week remission vs **18.5%** with placebo; p<0.001 (maintenance)[3]

Safety[3]

- Incidence of infection was similar to placebo during induction and higher than placebo during maintenance
- Elevated liver aminotransferase levels more common with ozanimod

FDA and EMA approved based on pivotal TRUE NORTH trial[4,5]

Cases of PML with S1PR modulators in MS have been reported, but the risk is considered extremely low[6]

EMA, European Medicines Agency; FDA, US Food and Drug Administration; MS, multiple sclerosis; PML, progressive multifocal leukoencephalopathy; S1PR, sphingosine 1-phosphate receptor; UC, ulcerative colitis.

1. Argollo M, et al. *Expert Opin Biol Ther*. 2020;20:413–20; 2. Sandborn W, et al. *N Engl J Med*. 2016;374:1754–62; 3. Sandborn W, et al. *N Engl J Med*. 2021;385:1280–91;
4. FDA. Ozanimod PI. Revised 2021; 5. EMA. Ozanimod SmPC. Revised 2021; 6. Sriwastava S, et al. *J Neurol*. 2022;269:1678–87.

PI and SmPC available via the FDA and EMA, respectively at: www.accessdata.fda.gov/scripts/cder/daf/ and www.ema.europa.eu/en/medicines (accessed 9 March 2022).

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S1PR modulators in moderate-to-severe UC

Target lymphocyte recirculation through blockade of lymphocyte egress from lymph nodes[1]

Etrasimod[2]

Trials in moderate-to-severe UC:

- Phase II (N=156)
- Phase III ELEVATE UC 12 (NCT03996369; N=354)

33.0%

12-week remission with 2-mg dose vs **8.1%** with placebo; p<0.001[2]

41.8%

12-week endoscopic improvement with 2-mg dose vs **17.8%** with placebo; p=0.003[2]

Safety[2]

- Most common AEs were worsening of UC, respiratory tract infections, nasopharyngitis and anaemia in all groups

Phase III trials of etrasimod in UC are currently ongoing or recruiting: ELEVATE UC 52 (NCT03945188), ELEVATE UC OLE (NCT03950232) and NCT04176588

AE, adverse event; S1PR, sphingosine 1-phosphate receptor; UC, ulcerative colitis.

1. Argollo M, et al. *Expert Opin Biol Ther*. 2020;20:413–20; 2. Sandborn W, et al. *Gastroenterology*. 2020;158:550–6.

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