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REVIEW

# Sphingosine-1-phosphate receptor modulators in ulcerative colitis – a narrative review of current evidence and practical considerations

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## Abstract

Ulcerative colitis (UC) is a chronic inflammatory bowel disorder with a relapsing and remitting course often necessitating the use of advanced therapy to maintain disease control. Sphingosine-1-phosphate receptor modulators (S1PRMs) represent a new class of oral small molecules approved for the management of moderate-to-severe UC. Evidence from pivotal trials shows promising results for the induction and maintenance of remission in UC. This comprehensive review of S1PRMs explores their mechanism of action, key clinical trial data, real-world insights, and an overview of their safety, including considerations for special populations and comparative effectiveness. S1PRMs offer distinct advantages, including oral administration and a lack of immunogenicity, positioning them as valuable additions to the UC treatment landscape. However, future research will be required to understand their position in the evolving UC treatment paradigms.

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**Keywords:** etrasimod, inflammatory bowel disease, small molecules, sphingosine-1-phosphate, ulcerative colitis, ozanimod.

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# Introduction

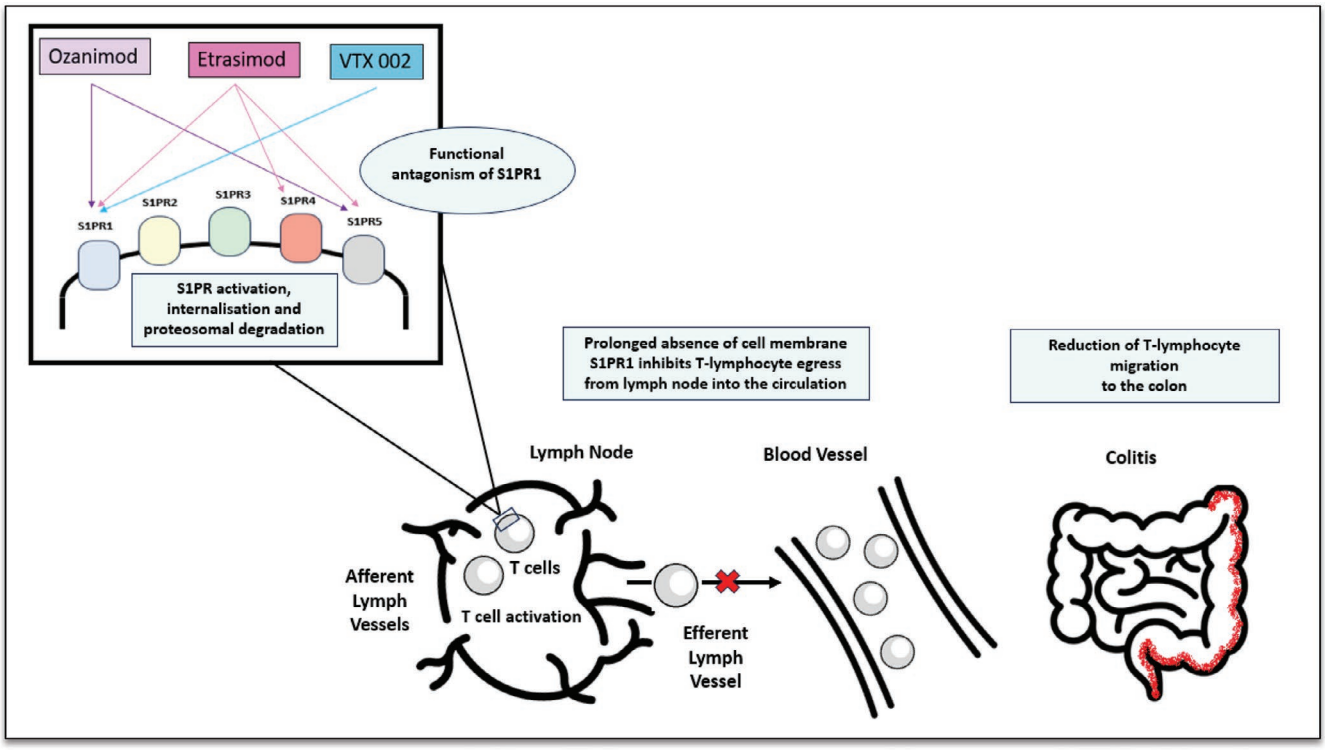
Ulcerative colitis (UC) is an immune-mediated, lifelong, chronic inflammatory bowel disorder affecting the mucosal layer, characterized by a relapsing-remitting course, with a global prevalence of approximately 5 million.[1]

The immunopathogenesis of UC is complex, involving an interplay of genetic and environmental factors, principally epithelial barrier dysfunction, dysregulated immune responses and dysbiosis. Our understanding in this area continues to evolve and is reflected in the development of several effective biologic therapies for patients with moderately to severely active UC, targeting distinct inflammatory pathways.[2]

The biologic era was spearheaded by antitumour necrosis factor (TNF) therapies, but newer molecules abrogating the immuno-inflammatory pathway are now available and widely used, namely anti-integrin agents (vedolizumab), IL-12/IL-23 inhibitors (ustekinumab) and IL-23 (P19) inhibitors.[3–5] In addition to biologics, newer small-molecule therapies have been developed, with the potential to target a myriad of cytokine targets. Janus kinase (JAK) inhibitors (JAKi) (tofacitinib, filgotinib and upadacitinib) targeting the JAK and S1 modulators targeting signal transducer and activator of transcription (STAT) pathways and have demonstrated efficacy in UC.[6]

Whilst biologic and small-molecule therapies have increased the treatment options for patients with

**Figure 1. Mechanism of action of sphingosine-1-phosphate receptor modulators. S1PR, sphingosine-1-phosphate receptor.**




UC, several limitations remain. A considerable number of patients still require alternative therapeutic approaches owing to primary non-response, loss of response, immunogenicity or intolerance of current therapeutic options.[7,8] Other considerations include associated economic costs of chronic parenteral drug administration, increased infection risk and longer-term risks, including malignancy.[9] As such, there remains a need for novel UC treatments that focus on novel targets, whilst mitigating adverse events (AEs). Sphingosine-1-phosphate (S1P) and its receptor (S1PR) are implicated in the pathogenesis of many immune-mediated inflammatory disorders, including inflammatory bowel disease. The use of S1PR modulators (S1PRMs) represents a novel treatment choice for patients with UC.

# Methods

## Aims of the article

This review aims to comprehensively summarize the current knowledge on the efficacy, safety and mechanism of action of S1PRMs in the treatment of UC. The review focuses on pivotal clinical trials, meta-analyses and real-world evidence to provide a consolidated overview for clinicians.

## Search strategy

A comprehensive literature search was conducted across Medline, EMBASE and PubMed up to June 25, 2025. The keywords used in the search strategy included: "inflammatory bowel disease", "ulcerative colitis", "S1P", "sphingosine -1-phosphate", "ozanimod" and "etrasimod".

# Review

## Mechanism of action of S1PRMs

S1P is a membrane-derived lysophospholipid signalling molecule involved in the immune-modulatory response. S1PRs are found on various immune cells across different organ systems.[10,11] The S1P–S1PR signalling pathway is activated when the extracellular S1PRs on the cell surface are activated. These are G protein-coupled receptors (S1PR1–S1PR5) with unique signalling properties and play a key role in various biological processes such as cell trafficking, proliferation, differentiation, vascular effects, and cerebral and cardiac function.[12] An S1P gradient exists, with lower concentrations present in tissues and lymph nodes and higher concentrations in the blood and lymph; this gradient is fundamental to the trafficking of B cells and T cells.[13]

S1PRMs can be selective or non-selective for S1PR subtypes; hence, their mechanism of action varies accord-

ing to S1PR sub-type and the cell type upon which it is expressed (Figure 1). S1PR1, S1PR2 and S1PR3 are expressed ubiquitously, particularly by immune cells but also in the cardiovascular and central nervous system. S1PR4 expression is mainly in lymphoid tissue, and S1PR5 is in the spleen and nervous system.[12] Agonistic activity on S1PR1 (widely expressed by immune cells and involved in lymphocyte trafficking) causes internalization and proteasomal degradation of the receptor. T cells subsequently become unresponsive to the S1P gradient, which in turn reversibly inhibits T lymphocyte egress from lymph nodes and migration to sites of inflammation (such as the gastrointestinal tract in patients with UC) (Figure 1).[13,14] Within this review, ozanimod and etrasimod are discussed in detail, as they are the currently licensed S1PRMs in the management of UC.

## Ozanimod

Ozanimod is a selective S1PRM that primarily binds to S1P1R and S1P5R sub-types. Its current indications include relapsing–remitting multiple sclerosis and UC.[15]

Its mechanism of action involves the inhibition of lymphocyte egress from lymphoid tissues, leading to a reduction in the number of circulating lymphocytes. This action is crucial in the context of UC, as it reduces the infiltration of these inflammatory cells into the gastrointestinal mucosa, thereby mitigating inflammation.[16] The binding of ozanimod to S1P1 receptors on lymphocytes triggers receptor internalization and subsequent degradation. This disrupts the S1P gradient necessary for lymphocyte egress from lymphoid organs, effectively trapping them in the lymph nodes.[17] This reduction in circulating lymphocytes helps decrease the immune-mediated damage in the colonic mucosa, which is a hallmark of UC. Importantly, ozanimod specifically reduces the capacity of lymphocytes to egress from lymphoid tissue, directly impacting the pathogenesis of inflammatory bowel disease (IBD), which involves lymphocyte migration from lymphoid tissues to the intestines.[17]

### Pharmacokinetics of ozanimod

Ozanimod is predominantly metabolized via multiple pathways, including alcohol and aldehyde dehydrogenase, cytochrome p450, and gut microflora, into two major active metabolites, CC112273 and CC1084037.

After multiple dosing, 94% of the circulating active components are composed of CC112273 (73%), CC1084037 (15%) and ozanimod (6%). Of note, food intake does not affect ozanimod absorption. The mean plasma half-life of ozanimod was approximately 21 hours with excretion mainly via urine and faeces in the form of inactive metabolites.

No adjustment is required for renal impairment or older age; however, a reduced dosing schedule is followed for mild-to-moderate hepatic impairment (Table 1). Severe hepatic impairment is a contraindication to the use of ozanimod.

### Therapeutic efficacy of ozanimod in UC

#### *Phase II study (TOUCHSTONE)*

The TOUCHSTONE study was a randomized, double-blind, placebo-controlled phase II trial that assessed the efficacy and safety of ozanimod in patients with moderately to severely active UC.[18] The study included 197 patients who were randomized in 1:1:1 ratio to receive ozanimod 0.5 mg, ozanimod 1 mg or placebo daily. The primary endpoint was the proportion of patients achieving clinical remission at week 8, defined as a Mayo Clinic Score (MCS) of ≤2 with no sub-score >1. Clinical remission was achieved by 16% of patients in the ozanimod 1 mg group compared with 6% in the placebo group ($p$=0.048). Significant improvements were also observed in clinical response (defined as reduction from baseline in MCS of ≥2 points and ≥30% and either a reduction in rectal bleeding score of ≥1 point or an absolute rectal bleeding score of ≤1 point) (57% *versus* 37%; $p$=0.02) and mucosal healing (34% *versus* 12%; $p$=0.002) in the ozanimod 1 mg group compared with placebo.

Patients who responded to ozanimod during the induction phase continued treatment in the maintenance phase, demonstrating higher rates of clinical remission (21% *versus* 6%; $p$=0.01) with ozanimod 1 mg daily at week 32 compared with placebo. Significant improvements were also observed with secondary endpoints of clinical response (51% *versus* 20%; $p$<0.001), mucosal healing (33% *versus* 12%; $p$=0.005) and histological remission (31% *versus* 8%; $p$<0.001) in ozanimod 1 mg group compared with placebo at week 32. The findings from TOUCHSTONE laid the groundwork for the subsequent phase III TRUE NORTH study, further validating ozanimod's therapeutic potential in this patient population.[19]

#### *OLE of TOUCHSTONE*

The open-label extension (OLE) phase assessed the long-term safety and efficacy of ozanimod 1 mg daily, with 170 patients entering this phase.[20] Long-term treatment with ozanimod demonstrated durable efficacy, with 71.2% of patients achieving partial Mayo clinical response and 54.7% achieving clinical remission at OLE week 56 (defined as per the phase II study). These benefits were maintained through OLE week 200, with 41.2% and 36.5% of patients maintaining clinical response and remission, respectively. The TOUCHSTONE study provided robust evidence of the efficacy and safety of ozanimod in the treatment of moderately to severely active

**Table 1. Key characteristics of etrasimod *versus* ozanimod.**

| Category | Etrasimod[65] | Ozanimod[15] |
|---|---|---|
| Indication | Patients with UC ≥16 years with moderately to severely active disease | Adult UC (≥18 years) with moderately to severely active disease |
| Mode of action | Binds S1P1, S1P4, S1P5 receptors (balanced agonist) | Binds S1P1, S1P5 receptors (selective modulator) |
| Dose regimen | Single-step 2 mg once daily; if interrupted ≥7 days, restart with food for three doses | 7-day titration: days 1–4: 0.23 mg; days 5–7: 0.46 mg; day 8+: 0.92 mg once daily |
| Special dosing considerations | If interrupted ≥7 days, resume with food for 3 days; no titration at treatment initiation beyond first-dose food | Mandatory 7-day titration; retitration after interruptions of ≥1 day in first 14 days, ≥7 days in days 15–28, or ≥14 days thereafter |
| Pharmacodynamics | Mean peripheral lymphocyte reduction to 43–55% of baseline over 52 weeks; transient bradycardia and AV conduction delays on initiation | Mean lymphocyte count reduction to ~45% of baseline; transient bradycardia on first dose, resolving with dose escalation |
| Pharmacokinetics | $T_{max}$ ~4 h; half-life ~30 h<br>Steady state by day 7<br>Metabolized via enzymes CYP2C8/2C9/3A4; 82% faecal, 4.9% renal excretion<br>Food can delay $T_{max}$ by about 2 h without affecting overall exposure | Steady state by day 7<br>Active metabolites terminal half-lives up to 3 months<br>Metabolized by CYP2C8/CYP3A4 pathways<br>No impact of food on absorption/exposure |
| Screening requirements | ECG pre-initiation<br>CBC, LFTs<br>Pregnancy test<br>Exclude active infections (e.g. TB, hepatitis) | ECG pre-initiation<br>CBC, LFTs<br>Pregnancy test<br>Exclude active infections<br>VZV immunity check |
| Cardiac monitoring | 4-h monitoring post-first dose for patients with HR <50 bpm, AV block or cardiac history<br>Repeat ECG at 4 h<br>Regular BP monitoring | 6-h monitoring post-first dose for HR <55 bpm, AV block or cardiac history<br>ECG at 6 h<br>Regular BP monitoring |
| Hepatic adjustment/ monitoring | Avoid in severe hepatic impairment (Child–Pugh C)<br>LFTs at 1, 3, 6, 9, 12 months and then periodically | Avoid in severe hepatic impairment (Child–Pugh C)<br>Mild to moderate: 0.92 mg every other day post-titration period<br>LFTs at 1, 3, 6, 9, 12 months and then periodically |
| Blood monitoring | Periodic CBC (interrupt if lymphocytes <0.2 x $10^9$/L until >0.5 x $10^9$/L) | Periodic CBC (interrupt if lymphocytes <0.2 x $10^9$/L until >0.5 x $10^9$/L) |
| Ophthalmical monitoring | Ophthalmological screening in patients at high risk (diabetes, uveitis, retinal disease)<br>Fundus exam within 3–4 months and for visual changes | Ophthalmological evaluation pre-treatment in patients at high risk (diabetes, uveitis)<br>Monitor for symptoms |
| Infection risks | Avoid live vaccines during and 2 weeks after treatment stopped<br>Monitor for PML, herpes infections | Avoid live vaccines during and 3 months after treatment stopped<br>VZV vaccination required if non-immune |
| Contraception | Required during treatment and 14 days post-discontinuation | Required during treatment and 3 months post-discontinuation |
| Pregnancy planning | Discontinue 14 days pre-conception | Discontinue 3 months pre-conception |

(*Continued*)

**Table 1. (Continued)**

| Category | Etrasimod[65] | Ozanimod[15] |
|---|---|---|
| Contraindications | Hypersensitivity to etrasimod or excipients<br>Immunodeficient state<br>Recent (last 6 months) MI, unstable angina, stroke, TIA, decompensated HF requiring hospitalization, NYHA III/IV HF<br>Mobitz type II second-degree or third-degree AV block, sick sinus syndrome, sino-atrial block (unless pacemaker)<br>Severe active or chronic infection (e.g. hepatitis, TB)<br>Active malignancy<br>Severe hepatic impairment<br>Pregnancy and women of childbearing potential not using effective contraception | Hypersensitivity to ozanimod or excipients<br>Immunodeficient state<br>Recent (last 6 months) MI, unstable angina, stroke, TIA, decompensated HF requiring hospitalization, NYHA III/IV HF<br>Mobitz II second-degree or third-degree AV block, sick sinus syndrome (unless pacemaker)<br>Severe active or chronic infection (e.g. hepatitis, TB)<br>Active malignancy<br>Severe hepatic impairment<br>Pregnancy and women of childbearing potential not using effective contraception |
| Key warnings | Bradycardia, infections, liver injury, macular oedema, hypertension, skin cancers | Bradycardia, PML, liver injury, macular oedema, hypertension, PRES, skin cancers |
| Drug interactions | Moderate to strong inhibitors of ≥2 CYP2C8, CYP2C9, CYP3A4 (e.g. fluconazole)<br>Moderate to strong inducers of ≥2 CYP2C8, CYP2C9, CYP3A4 (e.g. rifampicin, enzalutamide)<br>Caution with beta-blockers, calcium channel blockers, QT-prolonging drugs, class Ia/III antiarrhythmics (cardiologist advice needed)<br>Not recommended with other antineoplastic, immune-modulating or non-corticosteroid immunosuppressive therapies (risk of additive immunosuppression)<br>Live attenuated vaccines during and for at least 2 weeks after discontinuation | CYP2C8 inducers (e.g. rifampicin) not recommended<br>MAO inhibitors (e.g. selegiline, phenelzine) not recommended<br>Caution with strong CYP2C8 inhibitors (e.g. gemfibrozil, clopidogrel)<br>Caution with beta-blockers, calcium channel blockers, Class Ia/III antiarrhythmics (cardiologist advice needed)<br>Not recommended with other antineoplastic, immunomodulatory, or non-corticosteroid immunosuppressive therapies (risk of additive immunosuppression)<br>Live attenuated vaccines during and for 3 months after discontinuation |
| Special populations | Caution in elderly (>65 years) and severe respiratory disease | Caution in elderly and severe respiratory disease |

AV, atrioventricular; BP, blood pressure; CBC, complete blood count; CYP, cytochrome P450; ECG, electrocardiogram; HF, heart failure; HR, heart rate; LFTs, liver function tests; MAO, monoamine oxidase; MI, myocardial infarction; NYHA, New York Heart Association; PML, progressive multifocal leukoencephalopathy; PRES, posterior reversible encephalopathy syndrome; S1P1, sphingosine-1-phosphate receptor 1; TB, tuberculosis; TIA, transient ischemic attack; $T_{max}$, time to maximum concentration; UC, ulcerative colitis; VZV, varicella zoster virus.

UC, demonstrating significant improvements in clinical remission, endoscopic improvement and mucosal healing during both the induction and maintenance phases, with sustained efficacy and a favourable safety profile in long-term follow-up.

### *TRUE NORTH study: induction and maintenance outcomes*

The TRUE NORTH study, a pivotal phase III clinical trial, evaluated the efficacy and safety of ozanimod in patients with moderately to severely active UC.[19] This study comprised two parts: an induction phase and a maintenance phase, both of which demonstrated significant clinical benefits of ozanimod over placebo.

#### Induction phase

In the induction phase, 645 patients were randomized to receive ozanimod 0.92 mg daily or placebo for 10 weeks. The primary endpoint was the proportion of patients achieving clinical remission at week 10, defined as an MCS of ≤2 with no individual sub-score >1. In the ozanimod group, 18.4% of patients achieved clinical remission compared with 6.0% in the placebo group ($p$<0.001). Secondary endpoints, in-

cluding clinical response (47.8% *versus* 25.9%; $p<0.001$), endoscopic improvement (27.3% *versus* 11.6%; $p<0.001$) and mucosal healing (12.6% *versus* 3.7%; $p<0.001$), were also significantly higher in the ozanimod group.[19]

#### Maintenance phase

Patients who responded to ozanimod during the induction phase were rerandomized to continue with ozanimod 0.92 mg daily or switch to placebo for 52 weeks. The primary endpoint was the proportion of patients in clinical remission at week 52. Results indicated that 37.0% of patients receiving ozanimod maintained clinical remission at week 52 compared with 18.5% of those on placebo ($p<0.001$). Secondary endpoints, such as durable clinical response (60.0% *versus* 41.0%; $p<0.001$) and endoscopic improvement (45.7% *versus* 26.4%; $p<0.001$), further underscored ozanimod's efficacy.[19]

##### *TRUE NORTH OLE*

The TRUE NORTH OLE study assessed the long-term efficacy and safety of ozanimod in patients with moderately to severely active UC.[21] Amongst 131 week-52 clinical responders, high rates of sustained clinical response (91.4%) and remission (69.1%) were observed through OLE week 94 (approximately 3 years of continuous treatment). Endoscopic improvement, mucosal healing and histological remission rates were maintained or improved.[20]

Table 2 summarizes the primary and secondary endpoints of the pivotal studies for ozanimod.

## Safety and tolerability of ozanimod in UC

Clinical trials of ozanimod, including the TOUCHSTONE and TRUE NORTH studies and their OLEs, have shown a favourable safety profile. Although rare cases of transient and self-limiting first-degree and second-degree atrioventricular (AV) block have been observed, their incidence was similar in both ozanimod and placebo groups.[18,20,22,23] S1P1R are expressed on endothelial cells and cardiomyocytes, where they play vital roles in maintaining vascular integrity, promoting endothelial barrier function, and modulating heart rate and vascular tone.[24] Clinical trials have shown that ozanimod's selective modulation of S1P1 and S1P5, with minimal activity on S1P2, S1P3 and S1P4, results in a favourable cardiovascular safety profile compared with non-selective S1PRMs. Transient, dose-dependent bradycardia has been observed, typically occurring at the initiation of therapy but generally resolving without clinical intervention.[19] This transient bradycardia is hypothesized to result from initial S1P1 activation on atrial myocytes, followed by receptor desensitization and downregulation, which mitigates prolonged effects on heart rate.[25] Notably, the incidence of cardiac-related AEs has been low, with no clinically significant increase in risk for thromboembolic events, cardiovascular death, myocardial infarction or stroke.[26] The implementation of a dose-escalation regimen, starting at 0.25 mg, has been shown to attenuate first-dose effects on heart rate.[22]

##### *TOUCHSTONE study and OLE*

In the phase II study, AEs were similar across groups, with 40% for both placebo and ozanimod 0.5 mg, and 39% for ozanimod 1 mg.[18] Treatment discontinuation due to AEs occurred in 6% of patients in the placebo group, 5% of those taking ozanimod 0.5 mg, and 1% of patients in the ozanimod 1 mg group, whereas serious AEs (SAEs) were reported in 9%, 2% and 4% of patients in the placebo, ozanimod 0.5 mg, and ozanimod 1 mg groups. The most common AEs were UC flare and anaemia. Adverse cardiac events occurred in 3%, 2% and 0% of patients in the placebo, ozanimod 0.5 mg, and ozanimod 1 mg group. A single patient with pre-existing bradycardia developed a transient, asymptomatic first-degree AV block in the 0.5 mg group.[18] In the OLE of the TOUCHSTONE study, over 478.7 total person-years of exposure, the most common treatment-emergent AEs (TEAEs) were UC (6.5%), hypertension (5.9%), upper respiratory tract infection (5.9%) and increased gamma-glutamyl transferase (5.3%).[20] Ozanimod-related SAEs were identified in both treatment arms. The 0.5-mg arm reported one case of death from adenocarcinoma (of unknown origin) with ascites and individual cases of pneumonia and hyperbilirubinaemia. By contrast, the 1-mg arm reported a case of haemolytic anaemia with jaundice and one spontaneous abortion. Importantly, no significant abnormalities were observed concerning heart rate or conduction. Furthermore, there were no clinically significant increases in liver enzymes nor was any serious hepatocellular injury identified. Haematological assessment noted a case of severe lymphopenia, not associated with infection or treatment discontinuation. Three patients (without grade 4 lymphopenia), on the other hand, had serious infections.[20]

##### *TRUE NORTH study and OLE*

In this phase III study, overall higher AEs were noted during the maintenance period in the ozanimod group compared with placebo; however, AEs leading to treatment discontinuation were lower in the ozanimod arm (1.3% *versus* 2.6%).[19]

There were more instances of bradycardia in the ozanimod group only during the induction period. Reassuringly, no cases of third-degree or second-degree type 2 AV block were reported.[19] Hypertensive crisis was noted in one patient in the ozanimod group during induction and one

**Table 2. Summary of ozanimod pivotal studies.**

| Trial | Phase | Trial population | Intervention | Primary endpoint | Secondary endpoint | Adverse events |
|---|---|---|---|---|---|---|
| TOUCHSTONE[18] | II | *n*=197, age 18–75, moderate–severe UC | Ozanimod 1 mg | Clinical remission at week 8: 17% (ozanimod 1 mg) *versus* 6% (placebo); *p*=0.048 | Clinical response: 57% *versus* 37%; *p*<0.05<br>Endoscopic improvement: 36% *versus* 12%; *p*<0.05 | Mild–moderate AEs similar across groups<br>Common AEs: nasopharyngitis, headache, elevated liver enzymes |
| | | | Ozanimod 0.5 mg | Clinical Remission at Week 8: 14% (ozanimod 0.5 mg) *versus* 6% (placebo); *p*=0.14 | Clinical response: 54% *versus* 37%; *p*<0.05 | |
| TRUE NORTH[19] | III | *n*=645, age 18–75, moderate–severe UC (Mayo Score 6–12) | Ozanimod 0.92 mg | Induction (week 10)<br>Clinical remission: 18.4% (ozanimod) *versus* 6.0% (placebo); *p*<0.001 | Induction<br>Endoscopic improvement: 29.1% *versus* 12.1%; *p*<0.001<br>Mucosal healing: 13.8% *versus* 4.6%; *p*<0.001 | Nasopharyngitis: 11% *versus* 7%<br>Headache: 8% *versus* 5%<br>Transient bradycardia: 5% *versus* 2% |
| | | | | Maintenance (week 52)<br>Clinical remission: 37.0% (ozanimod) *versus* 18.5% (placebo); *p*<0.001 | Maintenance<br>Durable clinical response: 60.0% *versus* 41.0%; *p*<0.001<br>Endoscopic improvement: 45.0% *versus* 26.3%; *p*<0.001 | Elevated liver enzymes: 7% *versus* 4%<br>Serious AEs: 6% *versus* 8%<br>Discontinuation due to AEs: 4% *versus* 5% |

AEs, adverse events; UC, ulcerative colitis.

each in the ozanimod and placebo groups in the maintenance phase. However, these events did not result in treatment discontinuation. Ozanimod treatment groups had higher instances of elevated liver enzymes compared with placebo, although no patient fulfilled criteria for drug-induced liver injury or severe liver injury. Treatment discontinuation was seen in 0.4% of patients in both induction and maintenance periods. During the induction period, one case of basal cell carcinoma was reported. In the maintenance period, amongst patients who received ozanimod during both induction and maintenance, one case each of basal cell carcinoma and rectal adenocarcinoma was reported. Additionally, one case each of breast and colon adenocarcinoma was noted in patients who received ozanimod during induction but placebo during the maintenance period. Macular oedema was reported in three patients, leading to treatment discontinuation.[19]

Patients on ozanimod experienced a mean reduction in absolute lymphocyte count (ALC) of approximately 54% from baseline to 10 weeks.[19] Although 1.1% of patients had an ALC <200 cells/mm$^3$, none of these patients developed serious or opportunistic infections. Serious infection rates were <2% in each group, although one death was reported in the ozanimod group. Despite all patients requiring mandatory varicella-zoster virus IgG antibody or complete varicella-zoster vaccination, 0.4% and 2.2% of those who received ozanimod in the induction and maintenance periods, respectively, developed herpes zoster infection (not requiring hospitalization). In contrast, no herpes zoster infections were reported in the placebo arm.

In the OLE of the TRUE NORTH study, there were no new safety signals during long-term follow-up (434 patient-years of exposure), with the most common TEAEs including lymphopenia, COVID-19, arthralgia, hypertension and headache. Serious TEAEs occurred in 18.3% of patients, whereas 6.1% had TEAEs leading to treatment discontinuation.[21]

There was a single instance each of bradycardia and complete AV block secondary to atherosclerotic dis-

ease (pacemaker treated), both not requiring treatment discontinuation. Notably, hypertension occurred in 16 patients (12.2%). Alanine aminotransferase (ALT) >2× elevation was noted in 13 patients.[21] Although no patients fit Hy's law criteria, there were three treatment discontinuations. More than half of patients reported infections, primarily respiratory in nature, with 6.1% experiencing serious infections. There were a few reported cases of herpes zoster 5.3% (1.7/100 patient-years), with some leading to treatment discontinuation, despite no report of disseminated herpes zoster. A sustained ALC reduction was observed through week 94 of the OLE. Ten patients experienced ALC below 0.2 × $10^9$/L but recovered spontaneously without treatment discontinuation. Three cases of cancer and one case of mild macular oedema needing treatment discontinuation were reported.[21] Table 2 summarizes the AEs from the pivotal studies of ozanimod.

## Etrasimod

Etrasimod is a once daily, oral synthetic S1PR1, S1PR4 and S1PR5 modulator, with higher selectivity for S1PR1 than for S1PR4 and S1PR5.[27,28]

### Pharmacokinetics of etrasimod

Etrasimod is a small, low-molecular-weight molecule (<1 kDa), with rapid absorption following oral administration.[29] In healthy individuals, medium time to maximum concentration is between 3.5 and 7 hours. The mean terminal half-life following a single dose is 30.7–37.4 h, and steady-state concentrations are achieved by day 7.[30]

Its metabolism involves several CYP450 enzymes (mainly CYP2C8 and CYP2C9), reducing its potential involvement in drug–drug interactions.[31] It has no major circulating metabolites. Elimination of etrasimod and its minor metabolites is primarily via hepato-biliary (faecal) excretion with negligible renal clearance.[31]

No clinically meaningful differences have been documented in etrasimod-treated patients according to sex, age and body weight, negating the need for weight-based dose adjustments.[32] Food intake and fasting conditions have no effect on etrasimod exposure.[33] Only modest variations in etrasimod exposure have been noted in patients with liver impairment, with no clinically significant safety findings, negating the need for dose adjustments in such patients. Similarly, in patients with renal impairment, dose adjustment is not required.[34]

### Therapeutic efficacy of etrasimod in UC

#### *Phase II study (OASIS)*[35]

In a phase II placebo-controlled, double-blind randomized trial, 156 patients, across 87 centres in 17 countries, with moderately to severely active UC (modified MCS 4–9, Endoscopic sub-score (ES) ≥2 and Rectal Bleeding (RB) sub-score ≥1), previously intolerant of or having failed conventional therapies, were randomized 1:1:1 to receive etrasimod 1 mg (*n*=52), etrasimod 2 mg (*n*=50) or placebo (*n*=54) for 12 weeks.[35] Approximately one-third of patients had prior anti-TNF therapy exposure. Of 156 patients, 141 (90.4%) completed 12 weeks of treatment.

The primary endpoint was improvement in modified-MCS at week 12, from baseline; achieved with statistical significance in the etrasimod 2 mg group (least squares mean (LSM) difference compared with placebo 0.99, 90% CI 0.30–1.68; $p$=0.009) but not in the etrasimod 1 mg group. Although the study was powered to draw conclusions only from the primary endpoint, amongst secondary endpoints at week 12, a significantly higher proportion of patients receiving etrasimod 2 mg achieved endoscopic improvement (ES of ≤1) *versus* those receiving placebo (41.8% *versus* 17.8; $p$=0.003). Similarly, patients treated with etrasimod 2 mg demonstrated significant improvement in the two-component-MCS (comprising RB and ES components, score range 0–6) *versus* placebo (LSM difference 0.84, 90% CI 0.36–1.32; $p$=0.02). Significant improvements in total MCS (comprising modified-MCS and Physicians Global Assessment score range 0–12) were also seen in patients receiving etrasimod 2 mg *versus* placebo (LSM difference 1.27; 90% CI 0.37–2.17; $p$=0.10). Sub-group analysis of patients previously exposed to anti-TNFα therapy revealed similar clinical improvement.[35]

Exploratory endpoints of clinical remission and histological outcomes (histological improvement defined as a Geboes score of <3.1 and histological remission as Geboes ≤2) at week 12 were also examined. Results were significantly higher at week 12 in patients receiving etrasimod 2 mg *versus* placebo (33.0% *versus* 8.1% for clinical remission (nominal $p$<0.001), 31.7% *versus* 10.2% for histological improvement (nominal $p$=0.006), 19.5% *versus* 6.1% for histological remission (nominal $p$=0.03)).[35]

#### *OLE of OASIS study*[36]

Participants completing the OASIS study, regardless of their treatment assignment or response to treatment, were eligible to enrol in the OLE, receiving open-label etrasimod 2 mg for up to 40 weeks (52 weeks total across double-blind and OLE phases).[36] The OLE study enrolled 118 patients (safety population) with 112 patients forming the intention-to-treat population for key efficacy analyses. Median duration of etrasimod exposure was 34 weeks (over and above the 12 weeks of treatment during the double-blind study); 92 (82%) patients completed the study.

At end of treatment, 64% of patients met criteria for clinical response, 33% for clinical remission and 43% had

endoscopic improvement, demonstrating a beneficial effect of etrasimod 2 mg; 22% were in steroid-free clinical remission. Amongst patients demonstrating clinical response at week 12, 85% demonstrated sustained clinical response, 60% demonstrated sustained clinical remission and 69% sustained endoscopic improvement at end of treatment. Clinical response and remission rates were numerically lower in patients previously exposed to biologic therapy.[36]

*ELEVATE phase III studies*[37]

Two phase III, randomized, double-blind, placebo-controlled trials (ELEVATE UC 12 and ELEVATE UC 52) further evaluated the efficacy and safety of etrasimod. An OLE study (up to 5 years) is also ongoing, with results expected in 2027.[37]

Eligible patients (aged 16–80 years) had moderately to severely active UC (as defined earlier) with inadequate response, loss of response or intolerance to at least one approved therapy for UC. Both trials permitted inclusion of patients with isolated proctitis (<10 cm rectal involvement) providing they met other eligibility criteria (with enrolment capped at 15%).

ELEVATE UC 12 was a 12-week induction study. Its primary endpoint was the proportion of patients achieving clinical remission at week 12. ELEVATE UC 52 used a treat-through design, with a 12-week induction phase, followed by a 40-week maintenance period (total 52 weeks). Coprimary endpoints in ELEVATE UC 52 were the proportion of patients achieving clinical remission at weeks 12 and 52. Across both trials, key secondary endpoints were endoscopic improvement (ES ≤1, excluding friability), symptomatic remission (Stool Frequency sub-score = 0 or 1 (with a ≥1 point-decrease from baseline); RB sub-score = 0) and endoscopic improvement-histological remission (ES ≤1, excluding friability and Geboes score <2.0). Additional key secondary endpoints for ELEVATE UC 52 included corticosteroid-free remission at week 52 (clinical remission at week 52 and steroid-free for ≥12 weeks by week 52) and sustained clinical remission (clinical remission at both weeks 12 and 52).

ELEVATE UC 52 and UC 12 enrolled 433 and 354 patients, respectively. Across both trials, patients were randomized (2:1) to etrasimod 2 mg or placebo.[37] Just under a third of patients in both trials had prior exposure to a biologic or a JAKi. Etrasimod achieved clinical remission by week 12 in both ELEVATE UC 52 (27 *versus* 7%; $p<0.0001$) and ELEVATE UC 12 (25 *versus* 15%; $p=0.026$) over placebo. Maintenance of efficacy was also demonstrated, with significantly higher proportions of patients in the etrasimod group achieving clinical remission *versus* placebo (32% *versus* 7%; $p=0.0001$) by week 52. Additionally, all key secondary endpoints were met for the induction phase of ELEVATE UC 52 with statistically significant differences achieved with etrasimod relative to placebo (endoscopic improvement at week 12 of 35% *versus* 14%, symptomatic remission 46% *versus* 21%, and endoscopic improvement-histological remission at week 12 of 21% *versus* 4%; $p<0.0001$). At week 52, all key endpoints were reached with statistical significance, including corticosteroid-free remission at week 52 in 32% *versus* 7% of patients and sustained clinical remission at week 52 in 18% *versus* 2% of patients ($p<0.0001$). In ELEVATE UC 12, statistically significant improvements were also observed in the etrasimod group *versus* placebo across all secondary endpoints.

## Sub-group and *post hoc* analyses

A *post hoc* analysis of the ELEVATE 12 and 52 data showed a rapid onset of treatment effect with symptom response and improvement in Stool Frequency and RB sub-scores as early as weeks 2 and 4 for ELEVATE UC 12 and 52, respectively, sustained to week 52 in ELEVATE 52. Sub-group analyses of symptomatic remission suggested a greater symptom relief benefit of etrasimod *versus* placebo in those who were biologic/JAKi naive or with prior exposure to 1 biologic/JAKi (*versus* >1).[38]

*Post hoc* analyses of the ELEVATE trials also demonstrated superiority at weeks 12 and 52 *versus* placebo for the achievement of a range of stringent composite histological endpoints, including disease clearance (defined as symptomatic remission in association with a Nancy Histological Index 0) – treatment targets that may have important implications on relapse and complication rates.[39] A more recent *post hoc* analysis has shown a similar clinical response rate for patients with moderately and severely active UC at baseline, whilst maintaining a comparable safety profile across both disease activity sub-groups.[40]

In the sub-group of patients with isolated proctitis ($n=100$) enrolled in the ELEVATE UC programme, greater proportions of patients treated with etrasimod *versus* placebo achieved clinical remission, endoscopic improvement, symptomatic remission and endoscopic improvement-histological remission at weeks 12 and 52 ($p<0.05$). Improvements in corticosteroid-free clinical remission at week 52 were also noted in etrasimod-treated patients. Improvements in RB scores were noted as early as week 2 through to week 52 in etrasimod groups. Etrasimod also demonstrated statistically significant improvements in symptoms of urgency (using the Urgency Numerical Rating Scale) at week 12 ($p<0.05$). Safety results were consistent with those of the overall trial population.[41]

**Table 3. Summary of etrasimod pivotal studies.**

| Trial | Trial population | Intervention | Primary endpoint | | Secondary endpoint | | | Adverse events | |
|---|---|---|---|---|---|---|---|---|---|
| **OASIS**[35] Phase II (*n*=156) Randomized, double blind | Age 18–80 Moderate–severely active UC (MMS 4–9 and MES ≥2 and RB ≥1) Previously intolerant of or having failed conventional therapies | **Randomization 1:1:1 (stratified by use of CS and anti-TNF agents)** | **Improvement in MMS from baseline at week 12 LSM (SE)** | **MMS magnitude of improvement from placebo, week 12 LSM (SE)** | **Endoscopic improvement week 12 (%)** | **Two-component MCS (difference from placebo) LSM (SE)** | **Total MCS (difference from placebo) LSM (SE)** | **Total AEs *n* (%)** | **SAEs leading to discontinuation *n* (%)** |
| | | Etrasimod 1 mg | 1.94 (0.31); $p<0.001$ | 0.43 (0.41)'; $p=0.146$ | 22.5; $p=0.306$ | 0.39 (0.28); $p=0.086$ | 0.60 (0.53); $p=0.128$ | 31 (59.6) | 3 (5.8) |
| | | Etrasimod 2 mg | 2.49 (0.31); $p<0.001$ | 0.99 (0.42); $p=0.009$ | 41.8; $p=0.003$ | 0.84 (0.29); $p=0.002$ | 1.27 (0.55); $p=0.010$ | 28 (56) | 4 (8) |
| | | Placebo | 1.50 (0.30); $p<0.001$ | – | 17.8 | – | – | 27 (50) | 0 |
| **ELEVATE UC 52**[37] Phase III (n=433) Randomized, double-blind | Age 16–80 Moderate–severely active UC (≥10cm rectal involvement and MMS 4–9 and MES ≥2 and RB ≥1)* Previously intolerant to or failed to respond to at least one approved UC therapy *15% enrolment cap for patients with isolated proctitis (<10cm rectal involvement) meeting other eligibility criteria | **Randomization 2:1 (stratified by previous exposure to biologics or JAKi therapy, baseline CS use and baseline disease activity)** | **Clinical remission *n* (%) week 12** | **Clinical remission *n* (%) week 52** | **Key secondary endpoint efficacy results** | | | **Total AEs *n* (%)** | **AEs leading to discontinuation *n* (%)** |

(*Continued*)

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**Table 3. Summary of etrasimod pivotal studies. (Continued)**

| Trial | Trial population | Intervention | Primary endpoint | | Secondary endpoint | Adverse events | |
|---|---|---|---|---|---|---|---|
| | | Etrasimod 2mg (*n*=289) | 74/274 (27%); *p*<0.0001 | 88/274 (32%); *p*<0.0001 | Differences achieved with etrasimod relative to placebo (*p*<0.0001 for all week 12 and 52 secondary endpoints): **Endoscopic improvement** Δ 21.2%-week 12, 26.7%-week 52 **Symptomatic remission** Δ 24.6%-week 12, 24.9%-week 52 **Endoscopic improvement–histological remission** Δ 16.9%-week 12, 18.4%- week 52 **Corticosteroid-free clinical remission (week 52)** 32 *versus* 7% Δ 25.4% **Sustained clinical remission (week 52)** 18 *versus* 2% Δ 15.8% | 206/289 (71) | 12/289 (4) |
| | | Placebo (*n*=144) | 10/135 (7%) | 9/135 (7%) | | 81/144 (56) | 7/144 (5) |
| **ELEVATE UC 12**[37] Phase III (*n*=354) Randomized, double-blind | | **Randomization 2:1 (stratified by previous exposure to biologics or JAKi therapy, baseline CS use and baseline disease activity)** | **Clinical remission *n* (%) week 12** | | **Key secondary endpoint efficacy results** | **Total AEs *n* (%)** | **AEs leading to discontinuation *n* (%)** |
| | | Etrasimod 2 mg (*n*=238) | 55/222 (25%) | | Differences achieved with etrasimod relative to placebo **Endoscopic improvement (week 12)** 31% *versus* 19%, Δ 12.1 % (*p*=0.0092) **Symptomatic remission (week 12)** 47% *versus* 29% Δ 17.5% (*p*=0.0013) **Endoscopic improvement–histological remission (week 12)** 16% *versus* 9% Δ 7.4% (*p*=0.036) **Clinical response (week 12)** 62% *versus* 41% Δ21.2% (*p*=0.0002) | 112/238 (47) | 13/238 (5) |
| | | Placebo (*n*=116) | 17/112 (15%) | | | 54/116 (47) | 1/116 (1) |

AEs, adverse events; CS, corticosteroid; JAKi, Janus kinase inhibitor; LSM, least square mean; MCS, Mayo Clinic Score; MES, Mayo Endoscopic Score; MMS, Modified Mayo Score; RB, rectal bleeding; SAE, serious adverse event; SE, standard error; TNF, tumour necrosis factor; UC, ulcerative colitis.

Table 3 summarizes the primary and secondary endpoints of the pivotal clinical trials for etrasimod.

## Safety and tolerability of etrasimod in UC

### Phase II study

The incidence of TEAEs was greater in the etrasimod compared with the placebo group; specifically, 56.0%, 59.6% and 50.0% of patients in the etrasimod 2 mg, etrasimod 1 mg and placebo groups, respectively, experienced TEAEs. Although 55.1% of patients reported ≥1 TEAE, only 7.7% were deemed to have AEs related to the study drug. Across all groups, most TEAEs (75%) were of mild-to-moderate severity, with no life-threatening TEAE or deaths reported during the study. The most frequently reported AEs were UC worsening, nasopharyngitis, upper respiratory tract infection and anaemia. Serious TEAEs occurred in 5.8% of patients receiving etrasimod 1 mg and 11.1% of patients receiving placebo, with none occurring in the etrasimod 2 mg group. TEAEs leading to treatment discontinuation occurred in seven patients (three in the etrasimod 1 mg group and four in the etrasimod 2 mg group); most commonly, this was due to worsening of UC. Three patients reported AEs of special interest; importantly, these were all asymptomatic and occurred on day 1. One patient receiving etrasimod 2 mg had a transient heart rate lowering and second-degree AV block. Two patients receiving etrasimod 2 mg experienced first-degree AV block, one of whom was found to have evidence of AV block at baseline and was assessed as not clinically significant by the investigator. All three patients were found, in retrospect, to have monitoring evidence of AV block prior to etrasimod exposure.[35]

### OLE of OASIS study

In the OLE period, in patients treated with etrasimod 2 mg, TEAEs occurred in 60% (67/112) of patients; these were of mild-to-moderate severity in 94%. Worsening UC and anaemia were the most frequently reported AEs. SAEs were reported in seven patients, and ten patients discontinued etrasimod due to a TEAE (worsening UC ($n$=8), headache ($n$=1) or atrial fibrillation ($n$=1)), with minimal effect on heart rate and AV conduction. Nevertheless, there was a single case of transient heart rate reduction to 48 beats/min in addition to three cases of first-degree AV block. These instances did not lead to withdrawal from the study. Additionally, there were two cases of herpes zoster, one in a patient administered etrasimod 2 mg and the other in a patient receiving a placebo; neither instance led to withdrawal from the study. Notably, no severe or serious infections, nor any fatalities, were recorded throughout the study period.[36]

### ELEVATE UC programme

TEAEs were reported in 71% *versus* 56% patients in the etrasimod *versus* placebo groups, respectively, in ELEVATE UC 52, and in 47% in both etrasimod and placebo groups in ELEVATE UC 12. Most AEs were considered mild or moderate. In ELEVATE UC 12, 8 patients had an SAE (6 in the etrasimod group) and 14 patients discontinued the study due to an AE (13 in the etrasimod group). In ELEVATE UC 52, 29 patients experienced an SAE (20 in the etrasimod group) and 19 patients had an AE leading to study discontinuation (12 in the etrasimod group). Overall, the rate of SAEs across both studies was low and similar across etrasimod and placebo groups. The most frequently reported AEs were anaemia, headache, worsening UC, COVID-19 infection, dizziness, fever, arthralgia and abdominal pain. Amongst etrasimod-treated patients, there were nine events of bradycardia and three events of AV block; most were mild and asymptomatic, requiring no interventional treatment. No serious events of bradycardia or AV block were reported. No increased incidence of infections (overall infections, herpes zoster or serious infections) was noted with etrasimod *versus* placebo. Macular oedema occurred in three patients across both trials, with similar incidence across treatment groups; all events resolved. No malignancy or death occurred during the study period.[37] A summary of AEs from pivotal studies for etrasimod is presented in Table 3.

## VTX 002

VTX 002 is an orally bioavailable S1PRM selectively targeting S1P1 currently in development for UC. Phase I data from healthy adults treated up to 28 days demonstrated tolerability without significant first-dose heart rate reduction or significant safety findings.[42]

Phase II data from a multi-centre, randomized, placebo-controlled study have demonstrated statistical superiority for VTX 002 over placebo at week 13 for the induction of clinical remission but also a range of secondary outcomes such as endoscopic remission and histo-endoscopic mucosal improvement. No events of bradycardia, AV block, macular oedema or death were reported. A dose-dependent decrease in mean ALC with no corresponding increase in serious infections was observed. The positive phase II findings support further phase III development of VTX 002 in the treatment of moderately to severely active UC.[43]

## Network meta-analysis and real-world evidence on efficacy and safety of ozanimod and etrasimod

There are no head-to-head trials between ozanimod and etrasimod; however, indirect evidence from a recent network meta-analysis (NMA) looking at comparative efficacy of various advanced therapies (AT) from 36 phase III randomized control trials ($n$=14,270) showed that both these S1PRMs are effective treat-

**Table 4. Key outcomes comparisons of ozanimod versus etrasimod.[44]**

| Outcome | Ozanimod (effect size/SUCRA) | Etrasimod (effect size/SUCRA) | Comparative note |
|---|---|---|---|
| Induction of clinical remission | OR 3.52/0.715 | OR 2.61/0.506 | Ozanimod ranked higher for induction |
| Maintenance of clinical remission | OR 2.58/0.406 | OR 3.25/0.583 | Etrasimod ranked higher for maintenance |
| Induction of endoscopic improvement | OR 3.74/0.807 | OR 2.52/0.619 | Ozanimod ranked higher for induction |
| Maintenance of endoscopic improvement | OR 2.56/0.436 | OR 4.22/0.759 | Etrasimod ranked higher for maintenance |
| Maintenance of histological remission | OR 3.74/0.603 | OR 3.24/0.513 | Ozanimod ranked higher on SUCRA score |

OR, odds ratio; SUCRA, surface under cumulative ranking score.

ments in moderate-to-severe UC.[44] Ozanimod showed better outcomes for the induction of clinical and endoscopic remission, whereas etrasimod ranked higher during maintenance. Table 4 highlights the key outcome comparisons between ozanimod and etrasimod.[44]

Another NMA also supported etrasimod in the maintenance phase, particularly for AT-naive patients. They noted that, in the AT-experienced cohort, etrasimod showed greater efficacy in the induction phase, albeit with limited data for the AT-experienced group.[45]

These results align with a matching-adjusted indirect comparisons study between ozanimod and etrasimod, in which etrasimod demonstrated favourable performance compared with ozanimod at the end of the maintenance period for induction phase responders, both in clinical response (RR 1.18, 95% CI 1.05–1.30) and remission (RR 1.33, 95% CI 1.12–1.55).[46]

NMA did not identify any difference in safety signals for serious infection and overall AEs when comparing etrasimod and ozanimod.[44–46]

Real-world evidence for ozanimod from a single tertiary centre (45 patients, 82% AT experienced) showed clinical response and remission of 58% and 48%, respectively, at induction, but with overall low rates of corticosteroid-free remission and notable loss of response during 1-year follow-up.[47] There were no significant differences between AT-naive and experienced groups. Five (11%) patients had a colectomy during the follow-up period. There were no new safety signals, with only two patients discontinuing treatments because of hypertensive urgency and fatigue/headache. There were no episodes of symptomatic bradycardia, infections or deaths.[47] Various ongoing observational and phase IV studies will provide more insight into ozanimod's real-world efficacy, long-term safety and its impact on patient quality of life.[23]

Similarly, a 26-week real-world observational study for etrasimod was reported from the same centre (22 patients, 23% AT experienced).[48] Although they reported a 64% clinical remission at 12 weeks, this drastically dropped to 23% at week 26. None of the AT-experienced patients achieved remission at week 26. One patient reported a transient light-headedness, but there were no new safety signals.[48]

## Special situations: use of S1PRM in UC for pregnancy and older patients

### Use of S1PRM in pregnancy

*Safety concerns and clinical data*

Preclinical studies in animals have shown that high doses of S1PRM can cause embryotoxicity and teratogenicity, raising concerns about their use during pregnancy and pre-conception.[49] Although animal studies suggested possible foetal risks, an analysis of 6057 clinical trial participants showed no increased adverse pregnancy outcomes in 78 women who used ozanimod early in pregnancy for UC, Crohn's disease or multiple sclerosis. All exposures were limited to the first trimester, with patients discontinuing the medication upon pregnancy confirmation, except for those who chose to terminate. In these 78 pregnancies, the rates of spontaneous abortion, preterm birth and congenital abnormalities were similar to those expected in the general population.[50] The incidence of spontaneous abortion was 15%, and the preterm birth rate was 10% of live births as reported in the clinical trials.

It should be remembered that pregnancy in women with active UC at the time of conception and through pregnancy can be associated with a higher risk of complications such as preterm birth, low birth weight and pre-eclampsia.[51–53] Therefore, the management of UC in pregnant women requires careful balancing of the benefits of disease control against potential risks to the foetus from medication exposure.

For women with IBD on S1PRM who are planning pregnancy, a preconception consultation is crucial to optimize disease management and minimize risks. It is recommended to avoid the use of small molecules, including S1PRM, when conception is anticipated within less than a year of treatment.[54] S1PRM discontinuation for the minimum wash-out period is recommended before attempting conception due to potential risks observed in preclinical studies.[53] Women of childbearing age should use effective contraception during treatment with S1PRMs and for at least 3 months after discontinuation.[54–57] Although limited clinical data from the ozanimod development programme did not show an increased incidence of foetal abnormalities or adverse pregnancy outcomes with early pregnancy exposure, all exposures occurred during the first trimester, and safety later in pregnancy remains unclear.[50] Transitioning to medications with better-documented safety profiles during pregnancy, such as anti-TNF agents, may be advisable. However, it should be noted that most IBD medications (except methotrexate, allopurinol, JAKi and S1PRMs) are considered safe during pregnancy and breastfeeding.[51] Ongoing research, including prospective studies and post-marketing surveillance, is essential to gather more robust data on the safety of S1PRMs in pregnant women with UC.

### Use of S1PRMs in older patients

Older patients with IBD exhibit distinct clinical characteristics and therapeutic needs, including a higher prevalence of comorbidities, potential drug–drug interactions and increased risk of adverse drug reactions.[58]

A *post hoc* analysis of the TRUE NORTH study assessed the efficacy and safety of ozanimod in patients with UC aged <60 years and ≥60 years.[19,59] Efficacy outcomes were favourable across both age groups, indicating consistent effectiveness in older patients with UC at weeks 10 and 52. Safety analysis revealed some age-related differences. During induction, TEAEs with ozanimod were lower in patients ≥60 years (36%/31% in cohort 1/2) compared with those <60 years (41%/41%). In the maintenance phase, TEAEs were more frequent in patients ≥60 years (56%) *versus* <60 years (48%), whereas serious TEAEs were less common in the older group (3% *versus* 6%). Adverse events of special interest, including infections, hepatic effects, macular oedema, malignancy and pulmonary effects, occurred at low rates in both age groups.[59] However, there was a slightly higher incidence of bradycardia and AV block, highlighting the need for careful cardiac monitoring in older patients starting on ozanimod.[19]

Similarly, in the *post hoc* analysis of the ELEVATE-UC programme, the efficacy of etrasimod was maintained regardless of patient age.[60] Although there were higher incidence rates of arthralgia, fatigue and hypertension (irrespective of treatment arm) amongst older patients (≥60 years), overall SAEs and treatment discontinuations due to TEAEs were not discernibly different across age groups.[60]

These findings suggest that S1PRMs have a favourable efficacy and safety profile in both younger (<60 years) and older (≥60 years) patients with UC. The *post hoc* nature of the analysis itself notwithstanding, the number of patients ≥60 years was small. Prospective studies specifically designed to assess S1PRMs in older populations with UC are needed to provide more robust evidence for clinical decision-making in this age group.

Older patients often require a tailored approach to therapy due to comorbidities such as hypertension, diabetes and cardiovascular diseases. Before initiating S1PRMs, a comprehensive evaluation of the patient's overall health status, concomitant medications and potential drug interactions is essential. Dose adjustments may be necessary based on renal and hepatic function, and close monitoring for adverse effects, particularly cardiovascular events, is recommended during treatment.[61]

## Positioning of S1PRMs in UC treatment paradigms

Although S1PRMs are approved for the treatment of moderately to severely active UC, current societal recommendations do not provide specific recommendations regarding therapeutic sequencing.[62–64] Given their favourable safety profile, lack of immunogenicity and oral administration, S1PRMs could be considered after loss of response to conventional treatment such as aminosalicylates or thiopurines. Etrasimod appears more effective in anti-TNF naive patients, with greater effect sizes during both induction and maintenance phases.[37] Ozanimod, on the other hand, showed similar efficacy across anti-TNF naive and experienced groups.[19] Furthermore, etrasimod is effective in isolated proctitis, whilst data are lacking for ozanimod, wherein these patients were excluded from the ozanimod pivotal clinical trials.[41] S1PRMs could also be considered after treatment failure to biologics/JAKi or those seeking a biologic alternative due to safety concerns.

Whilst no head-to-head trials are currently available to directly compare ozanimod and etrasimod, clinicians could rely on indirect evidence from NMAs as well as on the distinct pharmacological characteristics and mon-

itoring requirements of each agent to guide individualized treatment decisions.[44–46]

### Practical considerations whilst prescribing ozanimod and etrasimod

Ozanimod's gradual titration and the lack of food impact on its absorption may reduce the risk of initial dose bradycardia. Furthermore, ophthalmological evaluation is only mandatory for patients at high risk (e.g. those with a history of diabetes, uveitis or retinal disease), potentially reducing resource utilization in clinical practice.

Conversely, etrasimod's simpler dosing regimen and shorter washout period could favour its use over ozanimod in certain clinical settings. Table 1 compares key aspects of ozanimod and etrasimod that are relevant for clinical practice.

## Conclusion

S1PRMs are a novel class of therapeutic agents that present a promising option for managing UC. Existing data demonstrate that this group of drugs has a good therapeutic efficacy and safety profile. Their relatively faster onset of action, lack of immunogenicity and oral route of administration provide distinct advantages over existing therapeutic options. Both ozanimod and etrasimod have been approved for the management of moderately to severely active UC. However, caution is warranted when considering this treatment option, particularly for specific age groups such as older people and women of childbearing age who are not using contraception. Future research is essential to further elucidate the long-term safety and comparative effectiveness of these treatments. Moreover, head-to-head trials with existing therapies could provide deeper insights into their relative benefits and potential drawbacks. Studies will also be needed to assess patient response to a second S1PR modulator after losing response to the first one as well as the role of combining S1P modulators with other AT. Tailoring treatment strategies to individual patient needs will be crucial in optimizing outcomes and minimizing risks. Ultimately, integrating S1PRMs into clinical practice holds significant promise, but it must be approached carefully, considering patient-specific factors and ongoing monitoring.

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