NICE National Institute for Health and Care Excellence

Single Technology Appraisal

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Committee Papers

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NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Contents:

The following documents are made available to stakeholders:

Access the **final scope and final stakeholder list** on the NICE website.

1. **Company submission** from Pfizer:
   a. Summary of Information for Patients (SIP)
2. **Clarification questions and company responses**
3. **Patient group, professional group, and NHS organisation submission** from:
   a. Crohn's and Colitis UK
   b. UKCPA
4. **External Assessment Report** prepared by Liverpool Reviews and Implementation Group
5. **External Assessment Group response to factual accuracy check of EAR**

Any information supplied to NICE which has been marked as confidential, has been redacted. All personal information has also been redacted.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost-comparison

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Document B

Company evidence submission

September 2023

File name	Version	Contains confidential information	Date
ID5091 UC_Etrasimod Document_B	2.0	Yes	16th January 2024

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Tables

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Abbreviations

1L	First line
5-ASA	Aminosalicylates
AESI	Adverse event of special interest
BSG	British Society of Gastroenterology
CHMP	Committee for Medicinal Products for Human Use
CcT	Concomitant therapy
CrI	Credible interval
DIC	Deviance Information Criterion
DSU	Decision Support Unit
ECG	Electrocardiogram
EIHR	Endoscopic improvement-histologic remission
EMA	European Medicines Agency
ERG	Evidence Review Group
FAS	Full analysis set
GI	Gastrointestinal
HRQoL	Health-related quality of life
IBD	Inflammatory bowel disease
IBDQ	Inflammatory bowel disease questionnaire
IV	Intravenous infusion
JAKi	Janus kinase inhibitor
MHRA	Medicines and Healthcare products Regulatory Agency
MIMS	Monthly Index of Medical Specialities
MMS	Modified Mayo score
MTA	Multiple technology appraisal
NHS	The National Health Service
NICE	The National Institute for Health and Care Excellence
OLE	Open-label extension
PAS	Patient access scheme
PASLU	Patient Access Scheme Liaison Unit
PEAS	Primary efficacy analysis set
PML	Progressive multifocal leukoencephalopathy
PRES	Posterior reversible encephalopathy syndrome
PRO	Patient-reported outcome
QoL	Quality of life
RCT	Randomized controlled trial
RR	Risk ratio
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SC	Subcutaneous injection
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SOC	System organ class
SUCRA	The surface under the cumulative ranking curve
TA	Technology appraisal

TEAEs	Treatment-emergent adverse events
TNFi	Tumour necrosis factor alpha inhibitor
UC	Ulcerative colitis
WPAI-UC	Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

B.1 Decision problem, description of the technology and clinical care pathway

B.1.1 Decision problem

B.1.1.1 Population

The submission covers etrasimod's full anticipated marketing authorisation, which is for the treatment of patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules). Therefore, the phase III randomised controlled trials (RCTs), ELEVATE UC 12 and ELEVATE UC 52 which assessed etrasimod as induction and maintenance therapy for UC compared to placebo, are the main focus of the current submission.

The decision problem addressed by the submission is shown in Table 1.

B.1.1.2 Comparators

The National Institute for Health and Care Excellence (NICE) scope outlines tumour necrosis factor alpha inhibitor (TNFi; infliximab, adalimumab and golimumab), vedolizumab, ustekinumab, filgotinib, ozanimod, tofacitinib and upadacitnib as relevant comparators to etrasimod.

In the UK, there are currently 9 licensed treatments approved by NICE for moderately to severely active UC with various preparations available. All treatment options are relevant comparators, although [redacted] of the market value[1] given their wide usage in clinical practice. Subsequently, Section B.3 of the submission focuses on these 3 key comparators in order to aid a simplified assessment, with all other comparators presented in Appendix F. All three are understood to be prescribed predominately in first line (1L) of advanced therapy and therefore are the focus of this analysis. Section B.4, presents the economic case for comparators noted in the 1L advanced treatment naïve space (adalimumab, infliximab, vedolizumab, golimumab, tofacitinib, filgotinib, and upadacitinib; presented in Figure 1), with remaining comparators presented in the Appendix F and included in the model for transparency.

In the absence of head-to-head RCTs, the comparative efficacy and safety of etrasimod against advanced therapies was established through a network meta-analysis (NMA). The main clinical results focus on the biologics or janus kinase inhibitor (JAKi) naïve population, while subgroup analysis (or additional analyses given it is not a subgroup of the naïve population) is presented for biologics or JAKi experienced population.

Table 1 The decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope
Population	People with moderately to severely active ulcerative colitis when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment.	Patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules).	In line with Medicines and Healthcare products Agency (MHRA) marketing authorisation submitted indication. The main body of the submission focuses on the advanced treatment naïve population, i.e., naïve to biologics or JAKi, however for completeness and transparency advanced treatment experienced analyses are also presented (please see subgroups below).
Intervention	Etrasimod (Velsipity®)	Etrasimod (Velsipity®)	-
Comparator(s)	At least 1 of the following treatments, according to NICE guidance: • Ozanimod • JAK inhibitors (tofacitinib, filgotinib and upadacitinib) • TNF-alpha inhibitors (infliximab, adalimumab and golimumab) • Ustekinumab • Vedolizumab • Mirikizumab (subject to NICE evaluation)	• TNFi-alpha inhibitors (adalimumab, golimumab and infliximab) • Vedolizumab • JAK inhibitors (tofacitinib, filgotinib and upadacitinib)	The target population for etrasimod is patients for whom conventional therapy is inadequately effective, not tolerated or contraindicated. For this reason, conventional therapies have not been considered as comparators. In line with NICE guidance,[2] etrasimod is being assessed via the proportionate approach to technology appraisals (PATT) and compared to adalimumab, infliximab and vedolizumab to aid simplicity of the assessment given positioning, market shares, and similarities in effectiveness and costs. For completeness and transparency, remaining comparators have been provided in the Appendix F and/or in Section B.4.

			Please note, mirikizumab has not been included in the clinical analyses as at the time of analyses and writing was not approved for moderately to severely active UC. However, a placeholder for mirikizumab has been included in the model to support decision making.
Outcomes	The outcome measures to be considered include: • mortality • measures of disease activity • rates of and duration of response, relapse, and remission • rates of hospitalisation • rates of surgical intervention • endoscopic healing • endoscopic remission combined with histological improvement • corticosteroid-free remission • achieving mucosal healing • adverse effects of treatment • health-related quality of life	As per final scope: • measures of disease activity, including rates and duration of response, relapse, and remission • rates of hospitalisation • corticosteroid-free remission • endoscopic improvement-histologic remission (EIHR) • health-related quality of life • rates of surgical intervention • endoscopic improvement • endoscopic normalisation	Please note that the following assumptions regarding outcome terminology have been made: Endoscopic healing refers to the achievement of an endoscopic sub score (ES) equal to 0. This is described in the ELEVATE trials as endoscopic normalisation and in some other trials as endoscopic remission. EIHR, previously referred to as mucosal healing in the trial protocol and statistical analysis plan, is the term now recognised more in the GI community as EIHR. EIHR in the ELEVATE trials and most other trials published since 2019 refers to the composite outcome of achievement of endoscopic improvement (ES≤1, without friability) with histological remission (measured by a Geboes Index score <2.0). EIHR in trials pre-2019 refers to the achievement of an ES≤1. In the ELEVATE trials and other post-2019 trials, this is referred to as endoscopic improvement. Endoscopic remission combined with histological improvement was not an outcome captured in the ELEVATE clinical trials.

Economic analysis	This technology has been selected to be appraised as a cost comparison. The time horizon should be sufficient to reflect any differences in costs between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention and comparator technologies will be taken into account.	Drug acquisition, pre-initiation testing, and administration costs are considered from the NHS and Personal Social Services perspective – all other costs are considered equal across available treatment options. A time horizon of 5 years was selected to reflect differences in initiation costs. The model considers the cost of all available etrasimod comparators. [redacted]	
Subgroups to be considered	-	Subgroup (or additional analyses, given it is not a subgroup of the naïve population) data for etrasimod is presented among the biologic/JAKi experienced population.	Previous TAs have reported evidence by similar subgroups, therefore for transparency and completeness they have been included in this submission.

Abbreviations: ES, endoscopic score; EIHR, Endoscopic improvement-histologic remission; NA, not applicable; NHS, National Health System; NICE, The National Institute for Health and Care Excellence; TNFi, tumour necrosis factor alpha inhibitors; JAKi, janus kinase inhibitor; [redacted]; TA, Technology Appraisal.

B.1.2 Description of the technology being evaluated

The technology being evaluated is described in Table 2 below.

Table 2 Technology being appraised

UK approved name and brand name	Non-proprietary name: Etrasimod Brand name: Velsipity®
Mechanism of action	Etrasimod is a sphingosine 1-phosphate receptor modulator that binds to S1P receptors 1, 4 and 5 (S1P1,4,5) and is a balanced G-protein and beta-arrestin agonist at S1P1. Etrasimod has no activity on S1P2 or S1P3. Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood thereby lowering the number of activated lymphocytes in the tissue. The mechanism by which etrasimod exerts therapeutic effects in UC is unknown but may involve the reduction of lymphocyte migration into sites of inflammation. The etrasimod-induced reduction of lymphocytes in the peripheral circulation has differential effects on leucocyte subpopulations, with greater decreases in cells involved in the adaptive immune response known to be involved in driving UC pathology. Etrasimod has minimal impact on cells involved in innate immune response, which contribute to immunosurveillance.
Marketing authorisation/CE mark status	Regulatory submission to MHRA: The application will be submitted on [redacted]. CHMP positive opinion: anticipated [redacted] Marketing authorisation: anticipated [redacted]. UK availability: anticipated [redacted].
Indications and any restriction(s) as described in the summary of product characteristics (SmPC)	Patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules).
Method of administration and dosage	Etrasimod is formulated as a once-daily, orally administered pill (2 mg), that can be administered with or without food. The dosage does not change between induction and maintenance**.**
Additional tests or investigations	Prior to treatment initiation with etrasimod, an electrocardiogram (ECG) in all patients should be obtained to assess for pre-existing cardiac abnormalities. In patients with certain pre-existing conditions, first dose monitoring is recommended.[a] Patients with a history of diabetes mellitus, uveitis, or an underlying/co-existing retinal disease should undergo an ophthalmic evaluation prior to treatment initiation with etrasimod. A recent (i.e., within 6 months or after discontinuation of prior UC therapy) complete blood count, including lymphocyte count should be obtained.

	Recent (i.e., within last 6 months) transaminase and bilirubin levels should be available. If live attenuated vaccine immunisations are required, administer at least 4 weeks prior to initiation of etrasimod. Before initiation with etrasimod, women of childbearing potential must be counselled on the potential for a serious risk to the foetus, must have a negative pregnancy test before treatment initiation and must use effective contraception during treatment with etrasimod.
List price and average cost of a course of treatment	Acquisition costs per patient: List price: 2 mg: £843.84 per pack of 28 tablets Discounted price: 2 mg: £[redacted] per pack of 28 tablets Average annual cost of treatment per patient: List price: £11,000.00 Discounted price: £[redacted]
PAS/commercial arrangement (if applicable)	Pfizer submitted a confidential Patient Access Scheme (PAS) simple discount to NHS England on 7*th* August 2023 which was subsequently approved on 21*st* August 2023. Patient Access Scheme Liaison Unit (PASLU) acknowledged receipt of the PAS.

Abbreviations: CHMP, Committee for Medicinal Products for Human Use; ECG, electrocardiogram; EMA, European Medicines Agency; PAS, patient access scheme; PASLU, Patient Access Scheme Liaison Unit; S1P, sphingosine-1-phosphate; SmPC Summary of Product Characteristics.
[a] The number of patients with pre-existing cardiac conditions is expected to be low[3 3]; in Sweden and the US prevalence of myocardial infarction in moderate to severe UC patients ranged from 0.5% - 1.07% and prevalence of heart failure in moderate to severe UC patients ranged from 0.62%-1.6%.

B.1.3 Health condition and position of the technology in the treatment pathway

B.1.3.1 Ulcerative colitis overview

UC is the most common form of inflammatory bowel disease (IBD), and one of the most prevalent chronic autoimmune conditions globally.[4] It is a chronic bowel disorder characterized by spontaneous inflammation of the mucosa in the rectum and colon, causing damage and superficial erosions of the colonic wall, which in turn leads to discomfort and bleeding.[5]

UC presents as a relapse-remitting disease, i.e., patients experience unpredictable periods of UC symptoms with varying levels of severity, which can be followed by intermittent periods of remission. The periods of disease exacerbations with increased disease activity are known as ‘flares’ or ‘attacks’.[6] Flares are unpredictable and range from minor symptoms to life-threatening fulminant colitis (the most severe form of UC).[7] UC symptoms and severity can vary between patients and over time. Typical symptom presentations can be split into two main groups: gastrointestinal (GI), and extra-intestinal.[5, 8-11]

B.1.3.2 Epidemiology

UC can develop at any age; peak incidence is between the ages of 15 and 30 years, with a second, smaller peak between 50 and 70 years.[4, 8] A 2020 study estimated the incidence of UC in the UK to average 15.7 per 100,000 person-years.[12]

B.1.3.3 Clinical pathway to care

Management and treatment of UC aim to swiftly induce remission;[13] maintain remission once achieved,[13] EIHR,[14] improve a patients quality of life[15] and prevent any complications.[5]

Clinical guidelines for the management of UC include the NICE[12] and the British Society of Gastroenterology (BSG) consensus guidelines 2019.[13] Current guidance recommends initial pharmacotherapy with conventional anti-inflammatory and immunomodulator therapy for mild to moderate UC e.g., aminosalicylates (5-ASAs) or thiopurines with or without corticosteroids.

If a patient progresses to moderately to severely active UC a choice can be made to have biologic or an oral advanced small molecule (non-biologic) therapy.[16] The decision should be made on an individual basis, considering patient preference, likely adherence, safety data and speed of response to the drug and treatment cost (Figure 1).[15, 16]

Currently available treatment in the National Health Service (NHS) include:

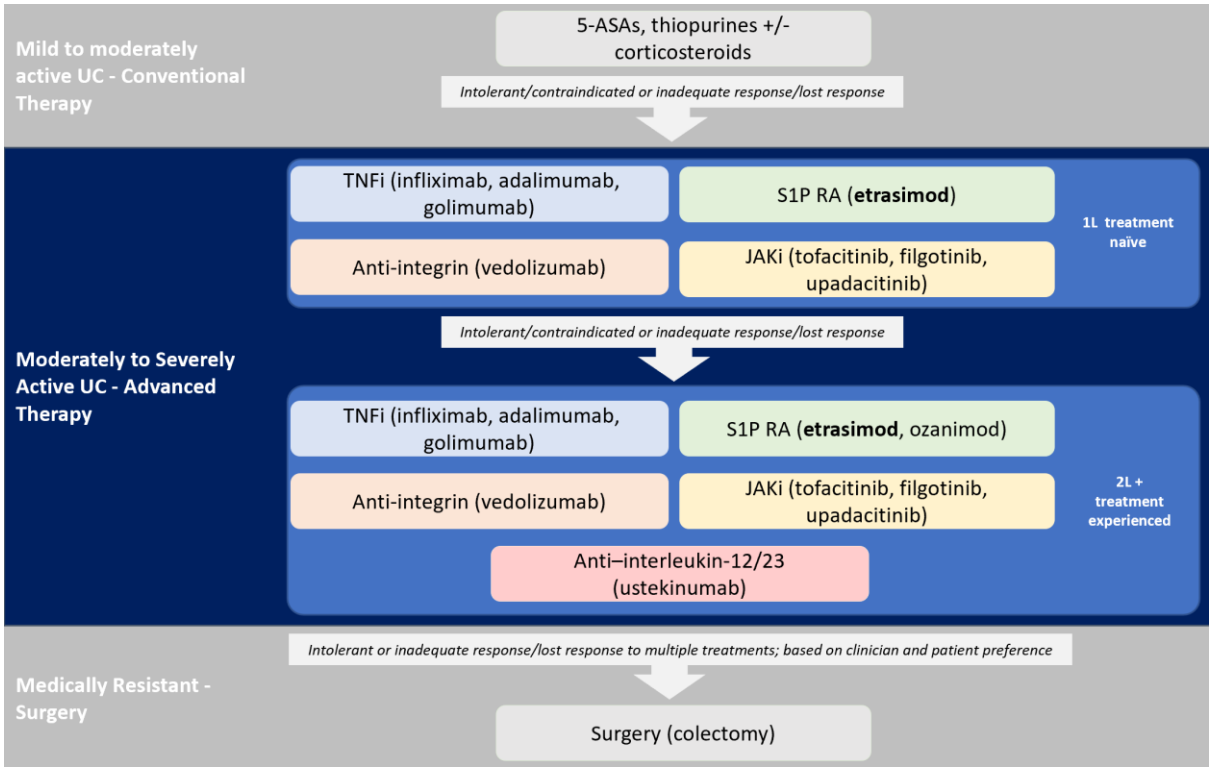
Biologics

- TNFis: adalimumab, infliximab golimumab
- Integrin inhibitor: vedolizumab
- IL 12/23 inhibitor: ustekinumab

Non-biologics

- JAKis: tofacitinib, filgotinib, upadacitinib
- Sphingosine-1-phosphate (S1P) receptor: ozanimod.

Figure 1 Clinical pathway of care for patients with UC and proposed placement for etrasimod within this pathway



Abbreviations: 1L/2L, first/second line; ASA, 5-aminosalicylate acid; JAKi, janus kinase inhibitors; S1P, sphingosine-1-phosphate; RA, receptor antagonist; TNFi, tumour necrosis factor alpha inhibitors; UC, ulcerative colitis.

B.1.3.4 Disease burden and unmet need

UC has wide-ranging effects on psychological and emotional health, education and employment, family life and social interactions, and fertility and pregnancy.[17, 18] This is exacerbated by the chronic nature of the disease, it's unpredictable course, the young age of onset and continued unmet need despite current available therapies.[17]

Physical symptoms, i.e., frequent diarrhoea and abdominal pain that have a negative impact on patients' health-related quality of life (HRQoL).[19] Due to unpredictable symptoms, people with UC may also experience:

Anxiety and depression,[20, 21] and insomnia, leading to daytime somnolence or fatigue.[21]

Extra-intestinal manifestations associated with UC that most commonly affect the joints (e.g., peripheral arthritis or ankylosing spondylitis), skin (e.g., erythema nodosum, pyoderma gangrenosum) eyes (uveitis), or the hepatobiliary tract (primary sclerosing cholangitis).[22]

Healthcare resource utilisation is substantial due to the early age of onset of UC, its chronic relapsing and remitting course, the likelihood of hospitalisation or surgery, and the association with extra-intestinal manifestations:[23]

- Indirect costs related to lost work productivity and daily activity impairment in an economically active patient group, the overall costs of UC pose a significant economic burden to society.[24]
- The average annual cost of care for treating with UC in the UK was £1,693 for a patient with UC in remission, £2,903 for a patient in relapse with mild to moderate UC, and £10,760 for a patient in relapse with severe UC in 2015.[25]

Convenience and patient satisfaction regarding the administration of therapies is important to the patient's Quality of life (QoL).[26] The most widely used advanced therapies are currently administered either as subcutaneous (SC) injection, via intravenous infusion (IV) or initiated with IV and SC thereafter. However, injectable administration has markedly lower rates of acceptance and preference among patients.[27] In consultation with both patients and clinical experts both parties indicated a preference for oral routes of administration, with 70% of patient advisors preferring oral administration.[28-31] Notably, indirect costs associated with IV drugs are often much higher than with oral formulations due to the requirements for specialist equipment and healthcare staff for administration.[32]

In addition, common and opportunistic infections (those which do not cause a disease state in healthy adults with regularly functioning immune systems) are an important safety consideration in the administration of biologic and oral small molecule therapies.[33-37] Serious bacterial infection which may require hospitalization (such as those with Mycobacterium tuberculosis) as well as herpes zoster and hepatitis B virus infection or reactivation is a persistent concern for patients with UC treated with TNFis and JAKis.[33-36] An increased risk of infection is also apparent with the use of some oral small molecule therapies in patients with UC.[3, 33] The JAKi poses a dose-related infectious risk in patients with UC, when compared to placebo.[3, 33] Further, a systematic review of clinical trials and real-world studies, investigating the association between JAKi use and herpes zoster virus infection in patients with IBD, found the risk of infection to be significantly higher for patients receiving JAKi than those receiving controls.

B.1.4 Equality considerations

Etrasimod is not likely to raise any equality or equity issues in patients with moderately to severely active UC who are eligible to receive treatment

B.2 Key drivers of the cost effectiveness of the comparator(s)

B.2.1 Clinical outcomes and measures

Our review identified two separate technology appraisals (TAs). One multiple TA (MTA) for infliximab, adalimumab and golimumab,[38] and one single TA for vedolizumab.[39] The TAs considered a cost-utility analysis, and the structure of the economic model was largely the same. The main clinical outcomes were clinical response and remission as defined by Mayo score (Table 3).

In the TA329 MTA (adalimumab and infliximab),[38] there were uncertainties surrounding the effectiveness of TNFi therapies, especially in patients with more severe disease who would start treatment at a younger age than patients in the trials. Additionally, questions arose about the optimal duration of treatment and the maintenance of efficacy outcomes of these interventions beyond limited study lengths. The committee concluded that surgery rates in actual practice might be higher than those presented and emphasised that different surgery rates should be applied for different patient cohorts. They also pointed out that the appropriate rate of surgery in the model was highly uncertain.

For TA342 (vedolizumab),[39] a significant area of uncertainty was the lack of data on strategies for withdrawing vedolizumab in people maintaining a response or remission. The committee believed the company's base case might have overestimated the surgery costs. Additionally, the Evidence Review Group's (ERG) assumptions were thought to potentially overestimate the number of surgical procedures and the duration patients spend in post-surgical complications.

Table 3 Clinical outcomes and measures appraised in published NICE guidance for the comparator(s)

TA	Outcomes	Measurement	Base-case value(s)	Impact on the ICER (£/QALY)	Committee preferred assumption	Areas of uncertainty
TA329 (infliximab, adalimumab and golimumab)	Clinical response (induction and maintenance)	Decrease from baseline in total Mayo score of ≥ 3 points and ≥ 30%, with accompanying decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1.	Response probabilities for non-biological therapy is inputted as 0.36 for induction treatment and 0.83 per 2-month cycle of maintenance therapy.	NR	NR	The effectiveness of TNFi in patients in whom these agents are likely to be used in clinical practice; that is, patients with more severe disease who would start treatment at a younger age than patients in the trials. The optimal duration of intervention treatment in responding patients. The maintenance of efficacy outcomes of interventions beyond the limited study lengths available.
	Clinical remission (induction and maintenance)	Total Mayo score of ≤ 2 points, with no individual subscore of >1.	Remission probabilities for non-biological therapy is inputted 0.09 for induction treatment, and 0.86 per 2-month cycle of maintenance therapy.	NR	NR	
	Probability of Surgery (Colectomy risk)	Probability of surgery	Every year 1.02% of patients have colectomy. A constant 6-month colectomy rate of 0.0051 was applied within the model.	NR	The Committee concluded that the actual probability of surgery is likely to be higher in clinical practice and that different probabilities should be applied for patients treated with TNFi compared to patients treated with conventional therapy. The Committee, however, acknowledged that evidence is scarce on	The Assessment Group agreed that the appropriate surgery probability to include in the model was highly uncertain.

TA	Outcomes	Measurement	Base-case value(s)	Impact on the ICER (£/QALY)	Committee preferred assumption	Areas of uncertainty
					the actual probability of surgery for both subgroups. The Committee concluded that the cost of surgery was underestimated in the model; however, they agreed that there were insufficient data to model the number and frequency of surgical procedures, and the associated costs.	
	Probability of Adverse Events of Treatment (Serious infection risk)	Hazard ratios	A hazard ratio of 1.10 for all biological therapies and a baseline risk of 0.16 for non-biological therapy.	NR	NR	NR
	Perioperative complications	Probabilities	47.3% (140/296) of patients develop transient complications, with a further 5% of patients developing chronic pouchitis. The model assumes that 19% of complications require further surgery, while the remaining 81% require medical treatment only.	High impact, analysed as the probability of chronic pouchitis.	NR	The Assessment Group listed as a main limitation in the model that the evidence on the complications of colectomy was not identified through a systematic review.

TA	Outcomes	Measurement	Base-case value(s)	Impact on the ICER (£/QALY)	Committee preferred assumption	Areas of uncertainty
	Probability of Mortality (Perioperative mortality risk)	Perioperative mortality rates	The probability of perioperative mortality was 0.03.	NR	NR	NR
TA342 (Vedolizumab)	Clinical response (induction and maintenance)	Decrease from baseline in total Mayo score of ≥ 3 points and ≥ 30%, with accompanying decrease in subscore for rectal bleeding of ≥ 1 point or absolute rectal bleeding subscore of 0 or 1.	Response rates were used to calculate transition probabilities in the cost-effectiveness model.	High impact	The Committee concluded that, although the efficacy of vedolizumab had been shown in GEMINI I, it may have underestimated the proportion of people who would have a response to induction treatment in clinical practice and that data on the outcome for those who responded after 6 weeks were not available from the trial.	The ERG commented that there are no data on withdrawal strategies of vedolizumab in people having to maintain response or remission. The ERG stated that people whose disease had not responded to treatment at the end of the induction phase may have a response during the maintenance phase. Therefore, using the proportion of people whose disease responded at the end of the maintenance phase may be an overestimation. The ERG considered that this effect was likely to be different between treatment arms. Therefore, the impact on the relative treatment effect was unclear.
	Clinical remission (induction and maintenance)	Total Mayo score of ≤ 2 points, with no individual subscore of >1	Remission rates used to calculate transition probabilities in the cost-effectiveness model.	High impact in patients in whom TNFi had failed.	NR	The ERG commented that there are no data on withdrawal strategies of vedolizumab in people having to maintain response or remission.

TA	Outcomes	Measurement	Base-case value(s)	Impact on the ICER (£/QALY)	Committee preferred assumption	Areas of uncertainty
	Probability of Surgery (Colectomy risk)	NR	NR	Moderate impact	The Committee concluded that the total costs of surgery in the company's base case were too high and those in the ERG exploratory base case were too low, due to the number of surgical procedures that were estimated.	The ERG considered that the company's assumptions would overestimate the probability of having surgical procedures and the time spent in the post-surgical complications state, which would result in increased costs and reduced health gains associated with surgery.
	Probability of Adverse Events of Treatment (Serious infection risk)	Obtained the number of patients (probability)	1.15% (serious infection risk)	NR	NR	NR
	Perioperative complications	Post surgery complications: patients who previously had a surgery and are experiencing complications from surgery such as wound infection, bowel obstruction, intra-abdominal abscess, or anastomotic leak.	NR	NR	NR	The ERG stated that the probability of repeat surgery and complications would be expected to be greater in the first 12 months after surgery, rather than remaining constant indefinitely. The ERG considered that the company's assumptions would overestimate the probability of having surgical procedures and the time spent in the post-surgical complications state, which would result in increased costs and reduced health

TA	Outcomes	Measurement	Base-case value(s)	Impact on the ICER (£/QALY)	Committee preferred assumption	Areas of uncertainty
						gains associated with surgery.
	Probability of Mortality (Perioperative mortality risk)	Mortality rate: Given recent evidence on IBD–related mortality (Button et al., 2010), deaths attributable to inflammatory bowel disease and other causes were considered in the model.	Initial annual mortality rate of 0.0015, which translates to a 6-week probability of 0.000174. Per-cycle (8-week) mortality change factor was 1.01385.	NR	NR	NR

Abbreviations: ERG, Evidence Review Group; IBD, Inflammatory bowel disease; ICER, incremental cost-effectiveness ratio; ITC, indirect treatment comparison; NR, not reported; TA, technology appraisal; TNFi, tumour necrosis factor inhibitors; QALY, quality-adjusted life year.

B.2.2 Resource use assumptions

Resource use assumptions from previous relevant NICE TAs (listed in Section B.2.1) where there was consensus across all parties include:

- Drug acquisition
- Treatment administration
    - Where treatments were IV administered, they incurred a cost. These were assumed to be the average cost of an outpatient visit.[38-40]
- Health care resource use
    - The healthcare resource use considered across all comparator appraisals were consultant visits, endoscopies (emergency or elective), inpatient visits, blood tests and colectomy (surgery) costs.
    - All comparator appraisals determined resource use from a previous economic analysis by Tsai et al. (2008).[41]

Uncertainties in the assumptions and estimates used across the NICE TAs (listed in Section B.2.1) were recorded for the following items:

- Surgery
    - In TA329 (Infliximab, adalimumab and golimumab)[38] and TA342 (vedolizumab),[39] the committee acknowledged high levels of uncertainty associated with surgery cost and frequency.
    - The committee disagreed with the manufacturer's and the ERG's surgery costs in TA329 and TA342, respectively. Both cited Buchanan (2011).[42]
- Post-surgery costs
    - In TA342 (vedolizumab),[39] the committee would have preferred stoma care to have been included in the model. Doing so would have improved the cost-effectiveness of vedolizumab.

B.3 Clinical effectiveness

B.3.1 Identification and selection of relevant studies

A systematic literature review (SLR) was conducted to identify all relevant and published clinical trial data regarding the clinical effectiveness and safety of treatments in UC. Full details of the methodology used to identify and select the clinical evidence are reported in Appendix F.

B.3.2 List of relevant clinical effectiveness evidence

The SLR of clinical evidence identified three RCTs of etrasimod in UC which were all used to support the application for marketing authorisation and are in populations relevant to the decision problem.

Etrasimod has been investigated for the treatment of moderately to severely active UC in two Phase III RCTs: ELEVATE UC 12 and ELEVATE UC 52 (NCT03996369 and NCT03945188, respectively). A summary of these two Phase III trials is shown in Table 4.

Etrasimod has also been compared with placebo in a Phase II trial: OASIS (NCT02447302),[43, 44] which is not described in detail in this submission as it focuses on safety but is included in the NMA (section B.3.9). Patients who completed OASIS were eligible to enter an open-label extension (OLE) study: OASIS OLE (NCT02536404).[40]

Patients in the ELEVATE Phase III trial programme were eligible to enter an ongoing open-label extension (OLE) study, ELEVATE UC OLE (NCT03950232). Evidence from this study and OASIS OLE were not used to inform the network meta-analysis (NMA) or the cost-comparison model because of their open-label, uncontrolled design. Further information is provided in section B.3.12.

Table 4 Clinical evidence for ELEVATE UC 12 and ELEVATE UC 52

	ELEVATE UC 12 [45]	**ELEVATE UC 52** [46]
Study title	A Phase III, Randomised, Double-Blind, Placebo-Controlled, 12-Week Study to assess the efficacy and safety of Etrasimod in subjects with moderately to severely active UC.	A Phase III, Randomised, Double-Blind, Placebo-Controlled, 52-Week Study to assess the efficacy and safety of etrasimod in patients with moderately to severely active UC.
Clinicaltrials.gov identifier	NCT03996369	NCT03945188
Study design	A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod (2 mg) versus matched placebo once daily for up to 12 weeks.	A multicentre, randomised, double-blind, placebo-controlled study to evaluate the efficacy and safety of etrasimod (2 mg) versus placebo once daily for up to 52 weeks, which included 12-Week induction and 40-Week maintenance periods.
Population	Patients aged 16 to 80 years who had a confirmed diagnosis of UC for at least 3 months. Patients had moderately to severely active disease, which was defined as a modified Mayo score of 4 to 9, with a rectal bleeding subscore of at least 1 and an endoscopic subscore of at least 2.	

Intervention(s)	Etrasimod 2 mg once daily PO
Comparator(s)	Placebo once daily PO
Trials support application for MA	Both trials support application for MA
Reported outcomes specified in the decision problem	• Measures of disease activity: modified Mayo score, full Mayo score and partial Mayo score • Rates of and duration of response and remission: modified Mayo score • Endoscopic improvement (Appendix F) • UC-related hospitalisation • UC-related surgery (Appendix F) • EIHR • Adverse effects of treatment • HRQoL: IBDQ, SF-36, SF-6D, WPAI-UC
All other reported outcomes	Corticosteroid-free clinical remission

Abbreviations: EIHR, Endoscopic improvement-histologic remission, HRQoL, health-related quality of life; IBDQ, inflammatory bowel disease questionnaire; MA, marketing authorisation; NA, not applicable; PO, per os (by mouth); SF-36, short form 36; UC, ulcerative colitis, WPAI, Work Productivity and Activity Impairment Questionnaire - Ulcerative Colitis.

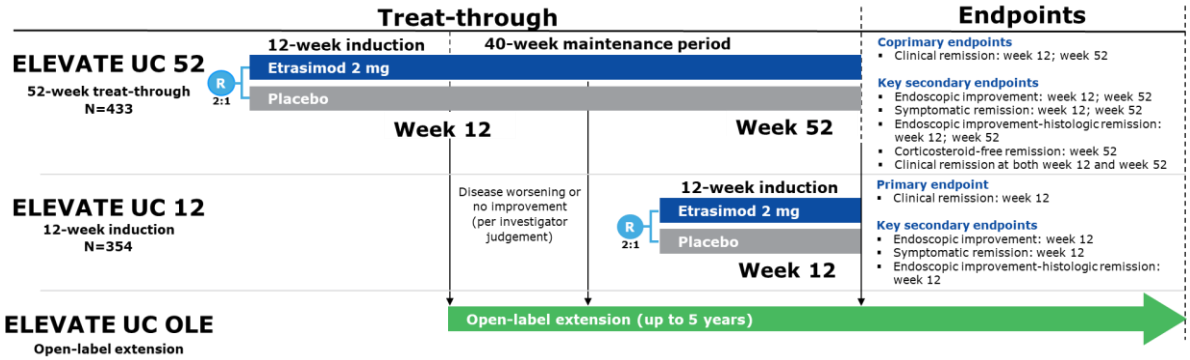
B.3.3 Summary of methodology of the relevant clinical effectiveness evidence

B.3.3.1 Methodology

B.3.3.1.1 Overall summary of ELEVATE clinical trial programme

The pivotal evidence used to support the decision problem is predominantly based on the Phase III placebo-controlled studies: ELEVATE UC 12 and ELEVATE UC 52. Figure 2 presents the clinical trial program for etrasimod, including one long-term open label extension study.[43-46] Details of the two trials are described in detail in the following sections.

Figure 2 Overview of the etrasimod clinical trial programme (Phase III to OLE studies and dose-ranging study)



Abbreviations: OLE, open-label extension; R, randomisation; UC, ulcerative colitis.

The comparative methodology of the two pivotal Phase III RCTs (ELEVATE UC 12 and ELEVATE UC 52) is summarised in Table 5. Definition of the study endpoints with a description of each endpoint measurement/disease activity index is presented in Appendix F.

Table 5 Comparative summary of trial methodology

	ELEVATE UC 12 (NCT03996369) [45]	ELEVATE UC 52 (NCT03945188) [46]
Trial design	Phase III, randomised, double-blind, placebo-controlled study	
Duration of study	12 weeks	52 weeks, inclusive of 12-week and 40-week treatment periods
Method of randomisation	Randomisation was performed centrally with the use of an interactive web response system; stratified according to previous treatment with biologic or JAKi therapies, glucocorticoid use at baseline, and baseline disease activity	
Blinding	Trials were patient-, investigator- and sponsor-blinded	
Study inclusion criteria	Disease-specific criteria: • Adults aged ≥16 to ≤80 years old • Diagnosed with UC ≥ 3 months prior to screening confirmed by endoscopy and histology • Active UC (confirmed by endoscopy with ≥ 10 cm rectal involvement) • Moderately to severely active UC (defined as MMS of 4 to 9, including an ES ≥ 2 and RB score ≥ 1) Prior treatment criteria[a,b]: • Demonstrated an inadequate response to, loss of response to, or intolerance to at least 1 of the following therapies: • Conventional therapy (oral 5-ASA, corticosteroids, thiopurines) • Biologic therapy or JAKi therapy (TNFi, anti-integrin antibodies, anti-interleukin 12/23 antibodies, JAKi)	
Study exclusion criteria	Health-related: • Severe extensive colitis • Diagnosis of CD or indeterminate colitis or the presence or history of a fistula consistent with CD • Diagnosis of microscopic colitis, ischaemic colitis, or infectious colitis • Hospitalisation for exacerbation of UC requiring IV steroids within 12 weeks of Screening (a single dose of IV steroids given was acceptable) • Positive assay or stool culture for pathogens (ova and parasite examination, bacteria) or a positive test for clostridioides difficile toxin at Screening • Had a condition or received treatment that may affect cardiovascular function • FEV1 or FVC < 70% of predicted values and FEV1/FVC ratio < 0.70 at Screening History of macular oedema or retinopathy Medication-related: • Treatment with ≥ 3 biologic agents or ≥ 2 biologics plus a JAKi approved for treatment of UC	

	ELEVATE UC 12 (NCT03996369) [45]	ELEVATE UC 52 (NCT03945188) [46]
Settings and locations where the data were collected	407 study centres across 39 countries (Argentina, Australia, Belarus, Belgium, Bulgaria, Canada, Chile, Colombia, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Germany, Hungary, India, Israel, Italy, Japan, Korea, Lebanon, Lithuania, Mexico, Moldova, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovakia, South Africa, Spain, Thailand, Turkey, Ukraine, United Kingdom, and the United States).	315 study centres across 37 countries (Australia, Austria, Belarus, Belgium, Bulgaria, Canada, Chile, Croatia, Czech Republic, Denmark, Estonia, France, Georgia, Germany, Hungary, India, Israel, Italy, South Korea, Latvia, Lithuania, Mexico, Moldova, Netherlands, Poland, Portugal, Romania, Russian Federation, Serbia, Slovakia, South Africa, Spain, Thailand, Turkey, Ukraine, United Kingdom, and the United States).
Trial drugs	2:1 ratio of etrasimod 2mg PO (n=238) and matched placebo PO (n=116)	2:1 ratio of etrasimod 2mg PO (n=289) and matched placebo PO (n=144)
Permitted concomitant medications	Oral 5-ASA, AZA, 6-MP, oral corticosteroids, or medicinal probiotics were permitted at screening and as per the inclusion criteria. During the treatment period, patients were permitted to be receiving a therapeutic dose of the following drugs: • Oral 5-ASA compounds or medicinal probiotics provided the dose was stable for ≥ 2 weeks immediately prior to randomisation. Stable doses were to be maintained during the study. • Oral corticosteroid therapy (prednisone at a dose ≤ 20 mg/day, budesonide at a dose ≤ 9 mg/day, or equivalent steroid) provided the dose was stable for ≥ 4 weeks immediately prior to the screening endoscopy. Patients were to maintain their existing stable oral corticosteroid therapy during the 12-Week treatment period and were to taper therapy during the 40-week[c] treatment period. • If oral 5-ASA or corticosteroids were recently discontinued, they were to have been stopped for ≥ 2 weeks prior to the screening endoscopy. • Immunosuppressive agents (i.e., oral AZA 6-MP) were to be discontinued ≥ 2 weeks prior to randomisation.	
Disallowed concomitant medications	Prohibited concomitant medications during the study included: • Administration of vaccines with live components (prohibited until 8 weeks after the last dose of study medication) • Moderate/strong inhibitors or inducers of CYP2C8 and CYP2C9	
Pre-planned subgroups	• Naïve to biologic or JAKi therapy at study entry (yes or no) • Baseline corticosteroid use (yes or no) • Baseline disease activity (MMS)	
Primary efficacy outcomes	Proportion of patients achieving clinical remission at Week 12	The proportion of patients achieving clinical remission at Week 12

	ELEVATE UC 12 (NCT03996369) [45]	ELEVATE UC 52 (NCT03945188) [46]
		The proportion of patients achieving clinical remission at Week 52
Secondary efficacy outcomes	Key secondary endpoints: • symptomatic remission at Week 12 • EIHR at Week 12 • endoscopic improvement at Week 12 (See Appendix F) Other secondary endpoints: • clinical response at Week 12 • endoscopic normalisation at Week 12 (see Appendix F)	Key secondary endpoints: • symptomatic remission at Week 12 • symptomatic remission at Week 52 • EIHR at Week 12 • EIHR at Week 52 • clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52 • sustained clinical remission (clinical remission at both weeks 12 and 52 • endoscopic improvement at Week 12 (see Appendix F) • endoscopic improvement at Week 52 (se Appendix F) Other secondary endpoints: • not received corticosteroids for ≥ 4 weeks and achieved clinical remission at Week 52 among patients receiving corticosteroids at baseline • clinical response at Week 12 • clinical response at Week 52 • clinical response at both Weeks 12 and 52 (see Appendix F) • clinical remission at Week 52 among patients achieving clinical response at Week 12 (See Appendix F)
Health-related quality of life measurements and healthcare resource use	Scores and change from Baseline to Week 12 were evaluated in the following: • IBDQ total score • SF-36, version 2, Physical and Mental Component and Domain Scores • SF-6D utility index	Scores and change from Baseline to Weeks 12 and 52 were evaluated in the following: • IBDQ total score • SF-36, version 2, Physical and Mental Component and Domain Scores • SF-6D utility index

	ELEVATE UC 12 (NCT03996369) [45]	ELEVATE UC 52 (NCT03945188) [46]
	• WPAI – UC • Urgency Numeric Rating Scale (see Appendix F) • Abdominal Pain Numeric Rating Scale (see Appendix F) • UC-related hospitalisations • UC-related surgeries, including colectomy	• WPAI – UC • Urgency Numeric Rating Scale (see Appendix F) • Abdominal Pain Numeric Rating Scale (see Appendix F) • UC-related hospitalisations • UC-related surgeries, including colectomy

a The medication used to qualify the patient for entry into this category must have been approved for the treatment of UC in the country of use and the patient must have received an adequate course of therapy based on local guidelines. B Inadequate response defined as: Signs and symptoms of persistently active disease despite a history of completing a dosing regimen; loss of response defined as: Recurrence of symptoms of active disease during treatment following prior clinical benefit; intolerance defined as: including, but not limited to infusion- or injection-related reaction, demyelination, congestive heart failure, infection, or any other related AE that led to a reduction in dose or discontinuation of the medication. C The 40-week maintenance treatment period applied only for patients at the ELEVATE 52 study.
Abbreviations: 5-ASA, 5-aminosalicyclic acid; AZA, azathioprine; CYP2C8/9, cytochrome P450 family 2 subfamily C member 8/9; EIHR, Endoscopic improvement-histologic remission; JAK, Janus kinase; 6-MP, mercaptopurine; PO, per os (by mouth); TNFi, tumour necrosis factor alpha inhibitor; EIM, extraintestinal manifestation; ES, endoscopic subscore; HRU, healthcare resource usage; HRQoL, health-related quality of life; IBD, inflammatory bowel disease; PRO, patient reported outcomes; RB, rectal bleeding; SF, stool frequency; SF-36, short form 36; UC, ulcerative colitis; WPAI, Work Productivity and Activity Impairment Questionnaire; CD, Crohn's disease; FEV1, forced expiratory volume; FVC, forced vital capacity; IL, interleukin; IV, intravenous; MMS, modified Mayo score; RB, rectal bleeding

B.3.3.2 Baseline characteristics

The baseline characteristics of the patients were similar across treatment groups in both ELEVATE UC 12 and ELEVATE UC 52 trials. However, in both studies, there was a higher percentage of patients with isolated proctitis in the placebo group compared with the etrasimod group.

In ELEVATE UC 12, the mean age at consent ranged from 40.3 to 40.4 years for etrasimod and placebo groups. All trial patients had moderately to severely active UC, with more than half of patients having left-sided colitis/proctosigmoiditis (59.0%). Notably, about two-thirds of patients (66.8% of etrasimod-treated patients and 66.4% of placebo-treated patients) were naïve to biologic or JAKi therapy. Approximately 20% of subjects in each treatment group had previously failed TNFi treatment for UC.

In ELEVATE UC 52, the mean age at consent was 38.9 and 41.2 years for etrasimod and placebo groups, respectively. All trial subjects had moderately to severely active UC, with more than half of subjects having left-sided colitis/proctosigmoiditis (59.5%). Almost one-fifth of patients (17.15%) had treatment failure with oral 5-ASA). Of the 21% of subjects who had previously received TNFi, the majority (over 87.9%) had experienced failure of at least one TNFi therapy. Notably, more than two-thirds of patients (70.9% of etrasimod-treated patients and 68.8% of placebo-treated patients) in ELEVATE UC 52 were naïve to biologic or JAKi therapy.

Overall, disease characteristics at baseline were representative of a population of patients with moderately to severely active UC and are relevant to the NICE decision problem. The baseline characteristics of both studies are summarised in Table 6.

Table 6 Baseline demographic and clinical characteristics of patients in ELEVATE UC 12 and ELEVATE UC 52 (full analysis set)[47]

	ELEVATE UC 12 (NCT03996369) [45]		ELEVATE UC 52 (NCT03945188) [46]	
	Placebo	**Etrasimod**	**Placebo**	**Etrasimod**
Baseline patient demographics, n (%)				
Number of patients, n	116	238	144	289
Age at consent in years, mean (SD)	40.4 (13.28)	40.3 (13.49)	38.9 (14.04)	41.2 (13.97)
Sex, Male, n (%)	73 (62.9)	135 (56.7)	88 (61.1)	152 (52.6)
BMI (kg/m2), mean (SD)	25.18 (4.405)	24.27 (4.823)	25.26 (5.367)	25.40 (5.517)
Race, n (%):				
White	88 (75.9)	176 (73.9)	129 (89.6)	256 (88.6)
Asian	25 (21.6)	47 (19.7)	9 (6.3)	22 (7.6)
Black or African American	2 (1.7)	2 (0.8)	3 (2.1)	6 (2.1)
Other combined*	1 (1.0)	13 (5.0)	5 (2.0)	3 (2.0)
Ethnicity, n (%):				
Non-Hispanic	107 (92.0)	226 (95.0)	136 (94.0)	275 (95.0)
Hispanic	9 (8.0)	10 (4.0)	7 (5.0)	12 (4.0)
Not reported	0	1 (<1.0)	1 (1.0)	1 (<1.0)
Unknown	0	1 (<1.0)	0	1 (<1.0)
Baseline clinical characteristics, n (%)				
Duration of UC (years), mean (SD)	7.7 (7.32)	7.3 (6.61)	5.9 (5.52)	7.5 (8.00)
Extent of disease (per investigator), n (%):				
Left-sided colitis / proctosigmoiditis	63 (54.3)	146 (61.3)	90 (62.5)	172 (59.5)
Pancolitis	41 (35.3)	77 (32.4)	47 (32.6)	93 (32.2)
Proctitis	12 (10.3)	15 (6.3)	6 (4.2)	22 (7.6)
Missing	0	0	1 (1.0)	2 (1.0)
Modified Mayo Score, n (%):				
mean (SD)	6.6 (1.21)	6.6 (1.23)	6.7 (1.15)	6.7 (1.20)
4–6	53 (46.0)	109 (46.0)	57 (40.0)	113 (39.0)
7–9	63 (54.0)	129 (54.0)	87 (60.0)	176 (61.0)
4	4 (3.0)	16 (7.0)	9 (6.0)	15 (5.0)

	ELEVATE UC 12 (NCT03996369) [45]		ELEVATE UC 52 (NCT03945188) [46]	
	Placebo	**Etrasimod**	**Placebo**	**Etrasimod**
5–9	112 (97.0)	222 (93.0)	135 (94.0)	274 (95.0)
BsL total Mayo score:				
n (%)	109 (94.0)	232 (97.5)	142 (98.6)	287 (99.3)
mean (SD)	8.8 (1.54)	8.7 (1.52)	9.0 (1.43)	9.0 (1.50)
Baseline ES of 3, n (%)	60 (51.7)	129 (54.2)	88 (61.1)	163 (56.4)
High-sensitivity C-reactive protein, mg/L	8.1 (15.7)	7.5 (12.6)	10.8 (18.1)	9.6 (15.5)
Faecal calprotectin, mg/kg	2640.3 (5325.0)	2459.8 (4520.9)	2053.5 (4251.5)	2333.5 (5010.0)
Prior treatment for UC, n (%):				
Prior 5-ASA, n (%)	85 (73.3)	149 (62.6)	95 (66.0)	197 (68.2)
Corticosteroids, n (%)	98 (84.5)	177 (74.4)	101 (70.1)	224 (77.5)
Thiopurines, n (%)	49 (42.2)	89 (37.4)	49 (34.0)	108 (37.4)
Exposed to biologicals or JAKi,‡ n (%)	43 (37.0)	89 (37.0)	55 (38.0)	108 (37.0)
Prior treatment with TNFi	29 (25.0)	57 (23.9)	31 (21.5)	60 (20.8)
Prior treatment anti-integrin antibodies	10 (8.6)	33 (13.9)	19 (13.2)	28 (9.7)
Prior treatment with anti-interleukin 12/23 antibodies	4 (3.4)	5 (2.1)	1 (0.7)	6 (2.1)
Prior treatment with JAKi	9 (7.8)	15 (6.3)	9 (6.3)	20 (6.9)
Concomitant UC treatment at BsL:				
Corticosteroids	38 (33.0)	78 (33.0)	46 (32.0)	96 (33.0)
5-ASA	94 (81.0)	201 (84.0)	111 (77.0)	228 (79.0)

* Comprises American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, and other.

‡ As reported by investigators during the screening period.

Abbreviations: 5-ASA, 5-aminosalicyclic acid; BMI, body mass index; BsL, baseline; ES, endoscopic subscore; IBDQ, inflammatory bowel disease questionnaire; JAKi, Janus kinase inhibitor; MMS, modified Mayo score; SD, standard deviation; TNFi, tumour necrosis factor alpha inhibitor; UC, ulcerative colitis.

B.3.4 Statistical analysis and definition of study groups in the relevant clinical effectiveness evidence

B.3.4.1 Analysis sets

All key efficacy outcomes in this submission are reported for the primary efficacy analysis set (PEAS) in the ELEVATE RCTs which includes only patients with a baseline modified Mayo score (MMS) of 5 to 9 who received at least one dose of etrasimod. The safety analysis set was defined as all randomised patients who received ≥1 dose of the study drug or placebo.

Notably, patients were analysed according to treatment received, regardless of randomisation.

B.3.4.2 Statistical information

A summary of the statistical methods used in the ELEVATE RCTs for PEAS are presented in Appendix F.

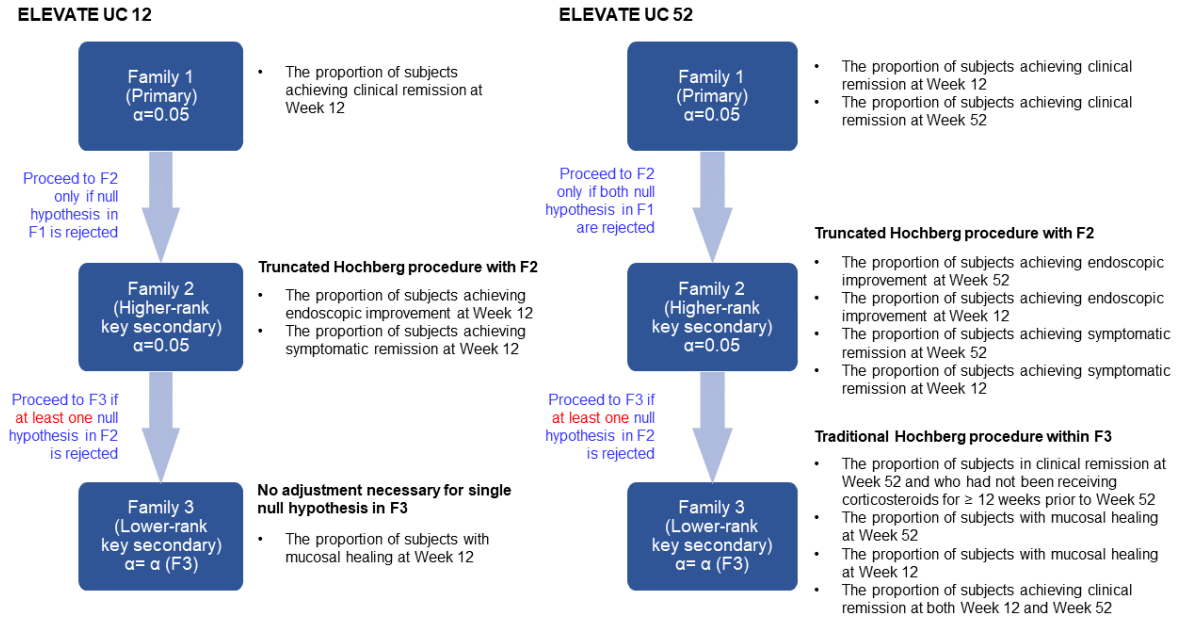
Table 7 Summary of statistical analyses in ELEVATE RCTs.

	ELEVATE UC 12 (NCT03996369)	**ELEVATE UC 52 (NCT03945188)**
Hypothesis objective	To assess the efficacy of etrasimod on clinical remission after 12 weeks of treatment, and to assess its safety for 12 weeks.	To assess the efficacy of etrasimod on clinical remission after 12 and 52 weeks of treatment, and to assess its long-term safety for up to 52 weeks.
Multiple comparisons and multiplicity	See Figure 3	See Figure 3
	For each endpoint, the comparison of etrasimod with placebo was conducted using a significance level (alpha) set at 0.025 (1-sided) or equivalently 0.05 (2-sided).	
Statistical analysis of primary endpoint	Estimates are from a CMH test, based on randomisation stratification groups: • Naïve to biologic or JAKi therapy at study entry (Yes or No) • Baseline corticosteroid use (Yes or No) • Baseline disease activity (MMS: 4 to 6 or 7 to 9) Ratio is 2:1 (etrasimod over placebo). Differences (∆) are for etrasimod minus placebo were assessed based on estimated common risk difference using the Mantel-Haenszel weights. A 2-sided Nominal p-value was used to test the hypothesis of the risk difference being 0.	
Statistical analysis of key secondary efficacy endpoints		
Data management, patient withdrawals and the advancement of patients from placebo to active treatment	In the primary analysis of the primary endpoint and main analyses of all binary responder-type endpoints, a single imputation method (NRI) was applied: • All patients with missing data, regardless of reason for missingness, were considered as non-responders. Four sensitivity analyses were implemented to explore different types of missing data approaches: • Multiple imputation under MAR • Tipping point analysis	

	• Multiple imputation with CR under MNAR • Multiple imputation under MAR/NRI hybrid imputation	
Sample size, power calculation	For the primary endpoint analysis of clinical remission, a sample size of 330 total patients (220 etrasimod, 110 placebo) was required to achieve at least 90% power to detect a difference of 12.5% between the etrasimod treatment group (18.5%) and the placebo treatment group (6.0%).	For the primary endpoint of clinical remission, a sample size of 420 patients (280 etrasimod, 140 placebo) were required to achieve 93.4% power to detect a difference of 13.5% at Week 52 between the etrasimod treatment group (23.5%) and the placebo treatment group (10.0%). With this sample size, there was 96% power to detect a difference of 12.5% in the other primary endpoint of clinical remission at Week 12, assuming a placebo rate at 6.0%. Since the two primary endpoints were expected to be at least moderately positively correlated, the actual overall power to reject both of their null hypotheses was likely >90%.

Abbreviations: CR, copy reference; FAS, full analysis set; IWRS, interactive web response system; JAK, Janus kinase; MAR, missing-at-random; MNAR, missing not at random; MMS, modified Mayo score; NRI, non-responder imputation; SAP, statistical analysis plan.

Figure 3 Gatekeeping procedure summary for ELEVATE UC 12 and ELEVATE UC 52.



Abbreviations: F1, family 1; F2, family 2; F3, family 3.

B.3.4.3 Patient flow in the relevant randomised controlled trials

Details of patient disposition in ELEVATE UC 12 and ELEVATE UC 52 are shown in Table 8.

Table 8 Summary of patient disposition in ELEVATE UC 12 and ELEVATE UC 52 (All randomised set)

	ELEVATE UC 12		ELEVATE UC 52	
	Placebo	**Etrasimod**	**Placebo**	**Etrasimod**
Total patients randomised	116	238	144	289
Patients completing treatment	105 (90.5%)	214 (89.9%)	46 (31.9%)	166 (57.4%)
Total discontinuations	11 (9.5%)	24 (10.1%)	98 (68.1%)	123 (42.6%)
Reasons for discontinuing treatment:				
Adverse event	1 (0.9%)	11 (4.6%)	5 (3.5%)	10 (3.5%)
Withdrawal by patient or parent/guardian	6 (5.2%)	5 (2.1%)	10 (6.9%)	17 (5.9%)
Physician decision	2 (1.7%)	3 (1.3%)	2 (1.4%)	3 (1.0%)
Lack of efficacy	0	3 (1.3%)	4 (2.8%)	7 (2.4%)
Lost to follow-up	1 (0.9%)	0	2 (1.4%)	1 (0.3%)
Study termination by sponsor	0	0	0	0
Disease worsening	n/a	n/a	73 (50.7%)	79 (27.3%)
Death	0	0	0	0
Protocol deviation	1 (0.9%)	1 (0.4%)	0	1 (0.3%)
Pregnancy	0	0	0	2 (0.7%)
Patient did not meet discharge criteria on Day 1 or Day 2	0	0	0	0
Other	0	1 (0.4%)	2 (1.4%)	3 (1.0%)
Patients completing the study	103 (88.8%)	213 (89.5%)	46 (31.9%)	161 (55.7%)
Patients discontinuing the study	13 (11.2%)	25 (10.5%)	98 (68.1%)	128 (44.3%)
Reasons for leaving the study:				
Adverse event	0	9 (3.8%)	5 (3.5%)	10 (3.5%)
Withdrawal by patient or parent/guardian	8 (6.9%)	6 (2.5%)	10 (6.9%)	24 (8.3%)
Physician decision	2 (1.7%)	4 (1.7%)	2 (1.4%)	2 (0.7%)
Lack of efficacy	0	4 (1.7%)	4 (2.8%)	7 (2.4%)
Lost to follow-up	1 (0.9%)	0	2 (1.4%)	1 (0.3%)
Study termination by sponsor	0	0	0	0
Disease worsening	n/a	n/a	73 (50.7%)	79 (27.3%)
Death	0	0	0	0
Protocol deviation	1 (0.9%)	1 (0.4%)	0	1 (0.3%)
Pregnancy	0	0	0	2 (0.7%)
Patient did not meet discharge criteria on Day 1 or Day 2	0	0	0	0
Other	1 (0.9%)	1 (0.4%)	2 (1.4%)	2 (0.7%)
Patients who continued to another study[a]	102 (87.9%)	208 (87.4%)	n/a	n/a
Patients who continued to the OLE study[b]	n/a	n/a	115 (79.9%)	231 (79.9%)

[a] Including patients who completed ELEVATE UC 12;[b] Including patients who either completed ELEVATE UC 52 or met the disease worsening criteria per CRF.
Note: % based on the number of patients in the analysis set.
Abbreviations: n/a, not applicable; OLE, open label extension

B.3.5 Critical appraisal of the relevant clinical effectiveness evidence

A summary of the quality assessment for the ELEVATE UC trials is presented in Table 9, with a detailed description of the quality assessment presented in Appendix F.

Table 9 Quality assessment results for ELEVATE UC trials

Study Question	ELEVATE UC 12 and 52
Was randomisation carried out appropriately?	Yes, see Table 5
Was the concealment of treatment allocation adequate?	Yes, see Table 5
Were the groups similar at the outset of the study in terms of prognostic factors?	Yes, see Table 6
Were the care providers, patients, and outcome assessors blind to treatment allocation?	Yes, see Table 5
Were there any unexpected imbalances in drop-outs between groups?	No, see Table 8[a]
Is there any evidence to suggest that the authors measured more outcomes than they reported?	No
Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?	Yes, see Table 7

[a] Although noted as unexpected in the clinical SLR report (Section 8.11, Table 48) for ELEVATE UC 52, drop out in the placebo arm was due to worsening of disease and therefore is not unexpected.

The data presented in this submission corresponds to the PEAS results for etrasimod 2 mg in the ELEVATE UC 12 and 52 trials. Data at Week 12 are presented first followed by data at Week 52.

B.3.6 Clinical effectiveness results of the relevant studies

B.3.6.1 Week 12 clinical outcomes in ELEVATE UC 12 and ELEVATE UC 52

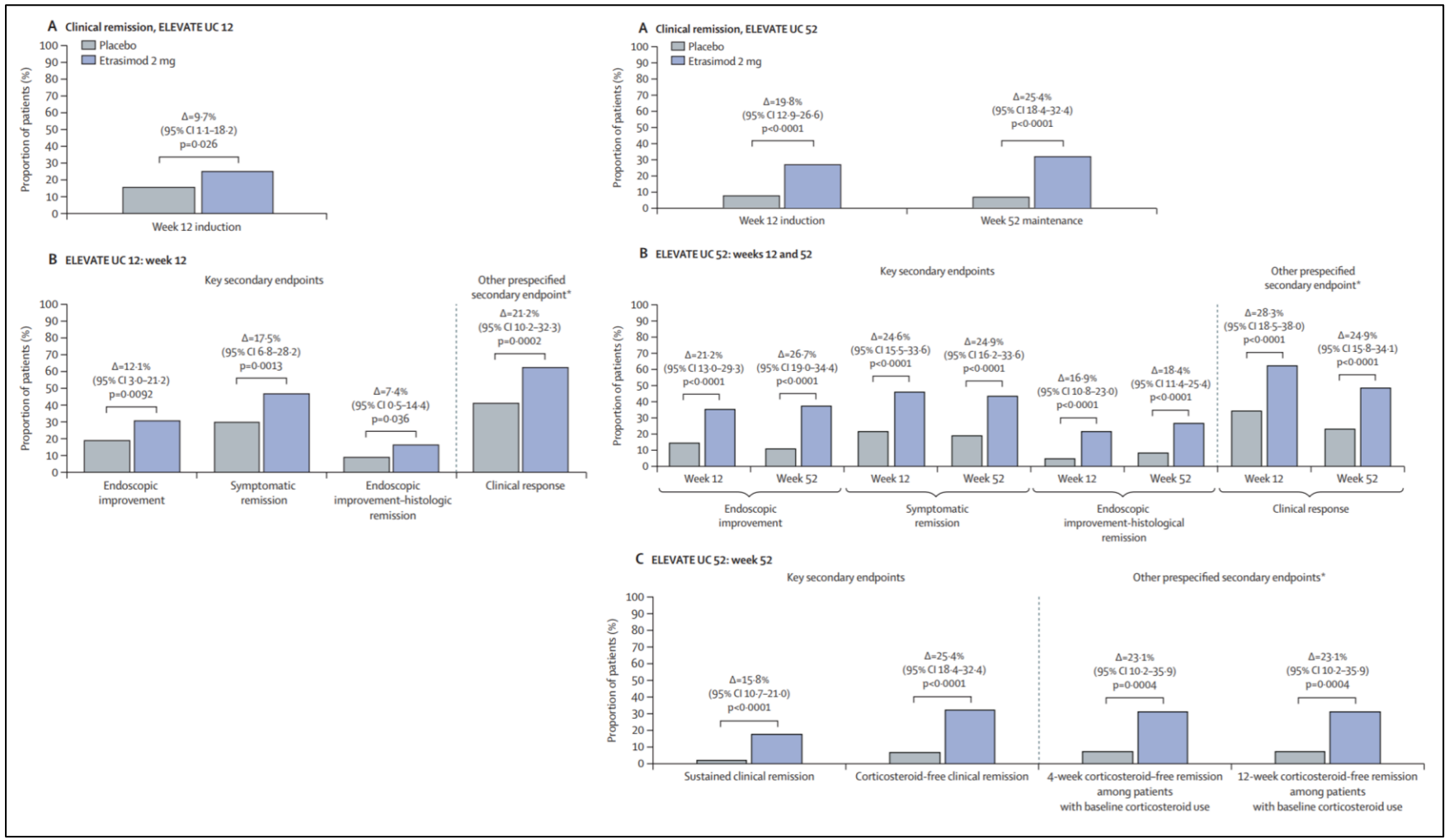
B.3.6.1.1 Primary endpoint: clinical remission at Week 12

In ELEVATE UC 12, 24.8% of patients receiving etrasimod achieved clinical remission at Week 12, compared with 15.2% in the placebo group (difference, 9.7%; $p = 0.026$) (Figure 4). In ELEVATE UC 52, the corresponding rates of clinical remission were 27.0% and 7.4% (difference, 19.8%; $p < 0.001$).

B.3.6.1.2 Key and other secondary endpoints at Week 12

Results on the key and other secondary endpoints at week 12 from both ELEVATE UC 12 and ELEVATE UC 52 studies are presented in Figure 4. Evidence from both studies show that etrasimod is significantly more effective than placebo at inducing symptomatic remission and achieving EIHR (the key secondary endpoints) as well as clinical response at week 12.

Figure 4 Primary, key secondary and additional prespecified secondary endpoints in ELEVATE UC 12 and ELEVATE UC 52



Patients with ulcerative colitis included those with a modified Mayo score of 5–9. *Significance is represented using unadjusted p values
Source: Sandborn et al. 2023[47]

B.3.6.1.3 Other clinical endpoints at Week 12

The following secondary outcomes were also assessed in ELEVATE UC 12 and ELEVATE UC 52. Detailed results are presented in Appendix F.

- Endoscopic improvement at Week 12
- Endoscopic normalisation at week 12

B.3.6.1.4 Patient-reported outcomes (PROs) at Week 12

Several PROs were assessed to support an improved HRQoL for patients in the target population treated with etrasimod compared with placebo as shown in Table 10.

Significant improvements in the etrasimod group compared with the placebo group were observed in the mean change in inflammatory bowel disease questionnaire (IBDQ) total scores from baseline at week 12 in both ELEVATE UC 12 and ELEVATE UC 52.

Details of the scores and change from Baseline to Week 12 evaluated in Urgency Numeric Rating Scale, Abdominal Pain Numeric Rating Scale in ELEVATE UC 12 and 52 are shown in Appendix F.

Table 10 PROs at week 12 in ELEVATE UC 12 and ELEVATE UC 52 (Reported Randomised Strata FAS and Actual Baseline MMS 5 to 9)

QoL Measures	ELEVATE UC 12 [45]			ELEVATE UC 52 [46]		
	LS Mean (SE)a		LS mean difference, *p*-value[a]	LS Mean (SE)a		LS mean difference, *p*-value[a]
	Etrasimod	Placebo		Etrasimod	Placebo	
IBDQ total score	47.49 (2.872)	30.16 (3.784)	17.33; *p*<0.001	42.79 (2.771)	27.35 (3.876)	15.44; *p*<0.001
IBDQ bowel system	17.62 (0.980)	11.41 (1.290)	6.21 *p*<0.001	15.77 (0.907)	9.83 (1.271)	5.94 *p*<0.001
IBDQ systemic systems	6.35 (0.481)	3.92 (0.635)	2.43 *p*<0.001	5.77 (0.443)	3.63 (0.619)	2.14 *p*=0.003
IBDQ emotional health	15.62 (1.078)	9.52 (1.420)	6.10 *p*<0.001	14.03 (1.045)	8.70 (1.460)	5.33 *p*=0.002
IBDQ social function	7.92 (0.517)	5.26 (0.680)	2.66 *p*<0.001	7.23 (0.523)	5.30 (0.730)	1.93 *p*=0.024
SF-36 Physical Component Summary	6.06 (0.501)	3.97 (0.669)	2.08; *p*=0.09	4.77 (0.497)	2.97 (0.697)	1.80; *p*=0.028
SF-36 Mental Component Summary	6.67 (0.722)	3.72 (0.964)	2.95; *p*=0.010	6.33 (0.642)	3.12 (0.901)	3.21; *p*=0.003
SF-6D utility index score	0.105 (0.009)	0.056 (0.012)	0.044; *p*=0.002	0.08 (0.008)	0.05 (0.011)	0.04; *p*=0.007
WPAI-UC work time missed due to absenteeism	-11.11 (1.880)	-8.29 (2.489)	-2.82, *p*=0.353	-15.12 (1.887)	-7.11 (2.627)	-8.01, *p*=0.012

WPAI-UC work time missed due to presenteeism	-22.37 (2.621)	-12.09 (3.468)	-10.28, *p*=0.016	-20.86 (2.540)	-11.70 (3.662)	-9.16, *p*=0.035
WPAI-UC overall work impairment	-22.81 (2.990)	-13.24 (4.061)	-9.58, *p*=0.053	-26.55 (2.748)	-12.77 (3.895)	-13.78, *p*=0.003
WPAI-UC activity impairment	-23.04 (2.078)	-12.73 (2.776)	-10.31, *p*=0.002	-20.73 (1.886)	-12.19 (2.626)	-8.54, *p*=0.006

[a]Estimates are from an MMRM model for change from baseline with a covariate for baseline score, and factors for I to biologic/JAK inhibitor therapy at study entry (Yes/No), baseline corticosteroid use (Yes/No), baseline disease activity (MMS: 4 to 6 or 7 to 9), treatment, visit, treatment by visit interaction.
Abbreviations: FAS, full analysis set; IBDQ, inflammatory bowel disease questionnaire; MMS, modified Mayo score; SF-36, 36-item short form health survey SF-6D, short-form six-dimension; WPAI-UC, work productivity and activity impairment questionnaire – ulcerative colitis.

B.3.6.1.5 Healthcare resource use at Week 12

In ELEVATE UC 12, very few patients had UC-related hospitalisations and no patients had UC-related surgery. While there were more UC-related hospitalisations in the subjects treated with etrasimod (1.4%) compared with placebo (0.0%), these small numbers do not allow for inferences.

B.3.6.2 Week 52 clinical outcomes in ELEVATE UC 52

B.3.6.2.1 Primary endpoint: clinical remission at Week 52

In ELEVATE UC 52, 32.1% of patients receiving etrasimod achieved clinical remission at Week 52, compared with 6.7% in the placebo group (difference, 25.4%; $p < 0.001$) (Figure 4).

B.3.6.2.2 Key and other secondary endpoints at week 52

Results on the key and other secondary endpoints at week 52 in ELEVATE UC 52 are presented in Figure 4. Significantly more patients treated with etrasimod achieved symptomatic remission (43.4% v 18.5%), EIHR (26.6 vs 8.1%), sustained clinical remission (17.9% vs 2.2%) and clinical response (48.2% vs 23.0%) at week 52 than patients treated with placebo. Etrasimod-treated patients were also more likely to achieve corticosteroid-free clinical remission at week 52 than placebo-treated patients.

B.3.6.2.3 Other clinical endpoints at Week 52

The following secondary outcomes were also assessed in ELEVATE UC 52. Detailed results are presented in Appendix F.

- Endoscopic improvement at Week 52
- Endoscopic normalisation at week 52
- Clinical response at both Week 12 and Week 52
- Clinical remission at week 52 among patients achieving clinical response at Week 12

B.3.6.2.4 Patient-reported outcomes (PROs) at Week 52

Several PROs were assessed to support an improved HRQoL for patients in the target population treated with etrasimod compared with placebo as shown in Table 11.

Overall, patients treated with etrasimod demonstrated significantly greater improvement in each of the four IBDQ subscores at week 52 compared with placebo (P<0.05 two-sided). There were significantly fewer patients treated with etrasimod who experienced absenteeism.

Details of the scores and change from Baseline to Week 52 evaluated in Urgency Numeric Rating Scale and the Abdominal Pain Numeric Rating Scale in ELEVATE UC 52 are shown in Appendix F.

Table 11 PROs at week 52 in ELEVATE UC 52 (Reported Randomised Strata FAS and Actual Baseline MMS 5 to 9)

QoL Measures	ELEVATE UC 52 [46]		
	Etrasimod	Placebo	LS mean difference, *p*-value (two-sided)[a]
	LS Mean (SE)[a]		
IBDQ total score	55.78 (2.960)	38.08 (4.950)	17.70; *p*=0.002
IBDQ bowel system	20.22 (0.969)	14.16 (1.651)	6.06; *p*=0.001
IBDQ systemic systems	7.29 (0.496)	5.32 (0.836)	1.97; *p*=0.039
IBDQ emotional health	19.06 (1.103)	13.18 (1.850)	5.87; *p*=0.006
IBDQ social function	6.45 (0.968)	9.71 (0.575)	3.26; *p*=0.003
SF-36 Physical Component Summary	6.64 (0.620)	5.27 (1.087)	1.37; *p*=0.267
SF-36 Mental Component Summary	9.55 (0.689)	6.71 (1.185)	2.84; *p*=0.035
SF-6D utility index score	0.12 (0.010)	0.07 (0.017)	0.05; *p*=0.008
WPAI-UC work time missed due to absenteeism	-17.37 (2.296)	-11.21 (3.863)	-6.16, *p*=0.176
WPAI-UC work time missed due to presenteeism	-27.26 (2.624)	-23.53 (4.308)	-3.73, *p*=0.456
WPAI-UC overall work impairment	-30.87 (3.497)	-22.60 (5.894)	-8.27, *p*=0.227
WPAI-UC activity impairment	-30.10 (2.098)	-26.87 (3.631)	-3.23, *p*=0.434

Abbreviations: FAS, full analysis set; IBDQ, inflammatory bowel disease questionnaire; MMS, modified Mayo score; SD, standard deviation; SF-36, 36-item short form health survey SF-6D, short-form six-dimension; WPAI-UC, work productivity and activity impairment questionnaire-ulcerative colitis.
[a]Estimates are from an MMRM model for change from baseline with a covariate for baseline score, and factors for I to biologic/JAK inhibitor therapy at study entry (Yes/No), baseline corticosteroid use (Yes/No), baseline disease activity (MMS: 4 to 6 or 7 to 9), treatment, visit, treatment by visit interaction.

B.3.6.2.5 Healthcare resource use at Week 52

In ELEVATE UC 52, very few patients had UC-related hospitalisations and no patients had UC-related surgery. The proportion of subjects with UC-related hospitalisations treated with etrasimod (2.2%) was the same as those treated with placebo (2.2%).

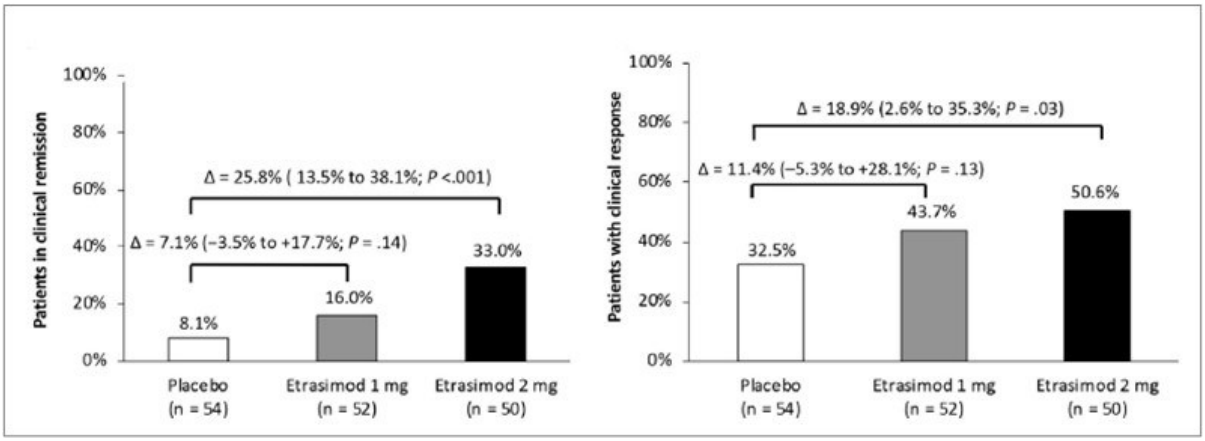
B.3.6.3 Week 12 clinical outcomes in Phase II OASIS study

Etrasimod has also been compared with placebo in OASIS, a Phase II trial (NCT02447302).[43] In the 12-week, double-blind study, adults with a confirmed diagnosis of UC, modified Mayo scores of 4 to 9 and endoscopic subscores of 2 or more and rectal bleeding subscores of 1 or more (n=156) were randomised to receive placebo or one of two doses of etrasimod (1 mg or 2 mg), administered once daily.

The clinical efficacy results in the OASIS study etrasimod 2 mg group were consistent with those in the Phase III ELEVATE trials described in section B.3.6 (Figure 5). The primary endpoint was improvement from baseline in the modified Mayo score at week 12 and exploratory outcomes included clinical remission and clinical response. More patients receiving etrasimod 2 mg than those receiving placebo achieved clinical remission (33.0% vs 8.1%). Clinical response was achieved by 50.6% of patients treated with etrasimod 2 mg and 32.5% treated with placebo.

Clinical remission and clinical response data from OASIS could not be included in the NMA as outcomes were not reported by prior biologic subgroup. OASIS study data was included in the safety NMA on the proportion of patients experiencing serious infections.

Figure 5 OASIS – summary of clinical efficacy results at week 12



Source: Sandborn *et al*. 2020[43]

B.3.7 Subgroup analysis

B.3.7.1 Subgroup analyses conducted

Primary and key secondary efficacy outcomes, including clinical remission, symptomatic remission, EIHR, clinical response, at week 12 and week 52 were analysed according to the following key pre-specified subgroups in each study:

- Naïve to biologic or JAK inhibitor therapy at study entry (yes or no)
- Baseline corticosteroid use (yes or no)
- Baseline disease activity (MMS: 4 to 6 or 7 to 9)

For ELEVATE UC 52, subgroup analyses on sustained clinical remission and steroid-free clinical remission were also conducted.

B.3.7.2 Subgroup results

Detailed results of all subgroup analyses are shown in Appendix G. Overall, subgroup analyses showed higher efficacy with etrasimod than placebo in all subgroups investigated. There was no evidence of a systematic difference in treatment effect according to prior biologic or JAKi therapy, or between baseline corticosteroid use or disease activity across the outcomes analysed at week 12 and week 52. In most analyses the difference between etrasimod and placebo was statistically significant, however, the ELEVATE trials were not powered to test the statistical significance of subgroup analyses due to the limited patient numbers in the subgroups. Therefore, *p* values from subgroup analyses of the individual trials should be treated with caution.

Subgroup analysis results according to prior biologic or JAKi therapy at baseline are summarised in Table 12.

Table 12 Summary of statistical significance of ELEVATE UC 12 and ELEVATE UC 52 outcomes according to prior biologic or JAKi therapy

Outcome assessed	ELEVATE UC 12	ELEVATE UC 52	
	Week 12		Week 52
Biologic or JAKi therapy naïve	**N=236**	**N=304**	**N=304**
Clinical remission	Sig	Sig	Sig
Symptomatic remission	Sig	Sig	Sig
EIHR	Sig	Sig	Sig
Clinical response	Sig	Sig	Sig
Sustained clinical remission	NA	NA	Sig
Steroid-free clinical remission	NA	NA	Sig
Biologic or JAKi therapy experienced	**N=118**	**N=129**	**N=129**
Clinical remission	NS	NS	Sig
Symptomatic remission	Sig	NS	NS
EIHR	NS	Sig	Sig
Clinical response	Sig	Sig	Sig
Sustained clinical remission	NA	NA	NS

Steroid-free clinical remission	NA	NA	Sig

Statistical significance = $p < 0.05$.
Abbreviations: EIHR, Endoscopic improvement-histologic remission; NA, not applicable; NS, not significant; Sig, significant difference versus placebo

B.3.8 Meta-analysis

The absence of head-to-head data prevented a standard meta-analysis of RCTs from being performed. Instead, a comprehensive NMA was conducted; this enabled comparisons with other biologic and targeted therapies included in the NICE scope and allowed for more precise estimates of treatment effects to be calculated compared with a naïve comparison of trials. The NMA is presented in section B.3.9

B.3.9 Indirect and mixed treatment comparisons

B.3.9.1 Methodology

As discussed in section B.3.1, an SLR was conducted to identify all relevant clinical evidence on the efficacy and safety of etrasimod and comparators for the treatment of moderately to severely active UC in adults. In the absence of head-to-head RCTs between all comparators specified in the NICE scope and relevant to the decision problem, an NMA was performed to assess the relative efficacy of etrasimod compared with relevant comparators in adults with moderately to severely active UC with and without prior exposure to biologic therapy.

The primary goal of treatment for UC is to induce and maintain remission: rates of clinical response and clinical remission are the most consistently reported outcomes across all studies and are the most relevant efficacy parameter in UC to allow comparative analysis, in line with previous NICE technology appraisals (see section B.2). In addition, the rate of serious infections during the induction phase of treatment have been the most commonly assessed safety endpoint across previous NICE technology appraisals.

Data for outcomes of clinical response and clinical remission were synthesised using a multinomial model with probit link. For this, it was assumed that the numbers of patients who were reported in the trial publications as being in clinical response also included those patients who were in clinical remission. That said, if both outcomes were not available a minimum of one outcome was required to be included in the analysis. The proportion of patients experiencing serious infections was also synthesised using a binomial model with logit link.

Fixed effects and random effects models were fitted and run using both an unadjusted relative effects analysis, as well as incorporating a meta-regression adjustment to account for variation in baseline risk. The preferred model was selected based on a combination of statistical and clinical considerations. From a statistical standpoint, lower Deviance Information Criterion (DIC) and residual deviance were favoured as outlined in relevant NICE Decision Support Unit (DSU) guidance. This was accompanied by an inspection of the networks of evidence available for each outcome in each subgroup. Outcomes informed

primarily by single-study connections can generate underpowered between-trial heterogeneity in the random effects models, potentially making fixed effect more suitable. The model selection rationale for each individual network is proved in section B.3.9.2. Relative effects are reported as risk ratios (RR) and associated 95% credible intervals (CrI) and absolute probabilities of response with associated 95% CrI.

Full details of the methodology for the NMA are presented in Appendix F along with the SLR that was used to identify all studies that may have been relevant for indirect comparison with etrasimod.

B.3.9.1.1 Analysis scope

For RCTs to be eligible for inclusion in the NMA of efficacy outcomes, they were required to report on clinical response and/or clinical remission at the end of an induction (6–8 weeks) or maintenance (approximately 1 year) time point. To be included in the NMA of safety endpoints, they were required to report on the incidence of serious infections at the end of induction.

EMA-licensed doses of therapies specified in the scope were included. Where the drug license allows for dose increases during the maintenance phase, both the recommended doses and higher dose were included where they had been assessed in the clinical trials. Different doses and/or dosing regimens were treated as unique comparators.

Several studies identified in the SLR did not meet the inclusion criteria for the NMA. Reasons for their exclusion, in whole or in part, are outlined in Appendix F.

B.3.9.1.2 Study selection for NMA

The studies used in the NMA are summarised in Table 13 and described in detail in Appendix F. The SLR and NMA were sufficiently broad to capture and synthesise RCT evidence for all drugs listed in the final scope; however, only the results of comparisons between etrasimod and key comparators – adalimumab, infliximab, vedolizumab – are included here. Comparisons with other drugs are presented in Appendix F.

The analyses included all relevant trials, regardless of the country in which they were undertaken. The NMAs of clinical response and clinical remission use centrally read endoscopic outcomes where reported, and locally read endoscopic outcomes were not. In line with other recent NICE technology appraisal submissions[48, 49], the base case also combined response and remission outcomes based on the full and modified Mayo scores.

In order to reduce heterogeneity and increase the comparability of the dataset, separate analyses were performed for patients with and without prior exposure to biologic therapy. The ELEVATE trials defined patients with prior exposure as having received or not received a biologic therapy or JAKi. Other studies have defined those with prior treatment exposure as exposed to TNFi (TNFi-exposed), or as exposed to biologic therapy (biologic-exposed), or as having failed TNFi (TNFi-failure) or had an inadequate response to biologic therapy (biologic-IR). The converse definition showed similar variation: patients were defined as either naïve to prior TNFi or biologic therapy (TNFi-naïve, biologic-naïve) or having not

shown an inadequate response (not TNF/biologic-IR). Most studies report data for only one subgroup contrast (e.g., naïve vs exposed), but a few studies report outcomes for multiple.

For the biologic-exposure subgroup analyses presented here, the terms TNFi-exposure, biologic exposure and biologic or JAKi exposure were assumed to be interchangeable, and it was assumed that biologic-failure can be combined with biologic exposed. The 'not biologic-IR' groups were combined with the biologic naïve group. Wherever available, subgroup data based on prior exposure was preferred as this is the most commonly reported subgroup definition. If these data were not reported, then subgroup data based on prior failure was utilised. Studies that did not report subgroup data were excluded from the subgroup analyses.

Most trials did not report safety endpoints by subpopulation (biologic-naïve or biologic-experienced) and therefore the analysis of serious infections was conducted in the overall population only. In line with prior NICE technology appraisal submissions, prior biologic exposure was considered unlikely to be an effect modifier for this safety endpoint.

Table 13 Summary of the trials used to carry out the NMA

Trial / Comparator	Placebo	Etrasimod (2 mg)	Filgotinib (100 mg)	Filgotinib (200 mg)	Ozanimod (1 mg)	Tofacitinib (10 mg)	Tofacitinib (5 mg)	Adalimumab (160/80/40 mg)	Adalimumab (80/40 mg)	Infliximab (5 mg/kg)	Golimumab (200/100 mg)	Golimumab (100 mg)	Golimumab (50 mg)	Upadacitinib (45 mg)	Upadacitinib (15 mg)	Upadacitinib (30 mg)	Ustekinumab (6 mg/kg)	Ustekinumab (Q8W)	Vedolizumab (300 mg)	Vedolizumab (IV Q4W)	Vedolizumab (IV Q8W)	Vedolizumab (SC Q2W)	Biologic-exposure subgroups: Naïve	Exposed	Not failed	Failed	Clinical response/remission	Mayo score: Total (12-pt scale)	Modified (9-pt scale)	Serious infection	Was study included in NICE TA for intervention therapy?	Has the study been included in published NICE TA?
Induction phase																																
ELEVATE 12[47]	✓	✓																					✓	✓			✓		✓	✓	NA	N
ELEVATE 52[47]	✓	✓																					✓	✓			✓		✓		NA	N
OASIS[43]	✓	✓																									✓		✓	✓	NA	N
SELECTION[50]	✓		✓	✓																			✓	✓			✓	✓		✓	Y	Y
TRUE NORTH[51]	✓				✓																		✓	✓			✓		✓	✓	Y	Y
OCTAVE Induction 1[52]	✓					✓																	✓	✓			✓	✓		✓	Y	Y
OCTAVE Induction 2[52]	✓					✓																	✓	✓			✓	✓		✓	Y	Y
ULTRA 1[53]	✓							✓	✓														✓				✓	✓		✓	Y	Y
ULTRA 2[54]	✓							✓															✓	✓			✓	✓			Y	Y
Suzuki 2014[55]	✓							✓	✓														✓				✓	✓		✓	Y	Y
HIBISCUS I[56]	✓							✓															✓				✓	✓		✓	N	Y
HIBISCUS II[56]	✓							✓															✓				✓	✓		✓	N	Y
ACT 1[35]	✓									✓													✓				✓	✓			Y	Y
ACT 2[35]	✓									✓													✓				✓	✓			Y	Y
Jiang 2015[57]	✓									✓													✓				✓	✓			N	Y

Trial / Comparator	Placebo	Etrasimod (2 mg)	Filgotinib (100 mg)	Filgotinib (200 mg)	Ozanimod (1 mg)	Tofacitinib (10 mg)	Tofacitinib (5 mg)	Adalimumab (160/80/40 mg)	Adalimumab (80/40 mg)	Infliximab (5 mg/kg)	Golimumab (200/100 mg)	Golimumab (100 mg)	Golimumab (50 mg)	Upadacitinib (45 mg)	Upadacitinib (15 mg)	Upadacitinib (30 mg)	Ustekinumab (6 mg/kg)	Ustekinumab (Q8W)	Vedolizumab (300 mg)	Vedolizumab (IV Q4W)	Vedolizumab (IV Q8W)	Vedolizumab (SC Q2W)	Biologic-exposure subgroups				Clinical response/remission	Mayo score		Serious infection	Was study included in NICE TA for intervention therapy?	Has the study been included in published NICE TA?
																							Naïve	Exposed	Not failed	Failed		Total (12-pt scale)	Modified (9-pt scale)			
Kobayashi 2016[58]	✓									✓													✓				✓	✓		✓	N	Y
NCT01551290[59]	✓									✓													✓				✓	✓			N	Y
PURSUIT-SC[60]	✓										✓												✓				✓	✓		✓	Y	Y
U-ACHIEVE Ph 2b[61]	✓													✓													✓		✓	✓	Y	Y
U-ACHIEVE Ph 3 Induction[62]	✓													✓											✓	✓	✓		✓	✓	Y	Y
U-ACCOMPLISH[62]	✓													✓											✓	✓	✓		✓	✓	Y	Y
UNIFI[63]	✓																✓								✓	✓		✓		✓	Y	Y
VARSITY[64]								✓											✓				✓	✓			✓	✓			N	Y
GEMINI 1[65]	✓																			✓			✓			✓	✓	✓		✓	Y	Y
Motoya 2019[66]	✓																				✓		✓	✓			✓	✓		✓	N	Y
Maintenance phase																																
Treat-through trial design																																
ELEVATE 52[47]	✓	✓																					✓	✓			✓		✓		NA	N
ULTRA 2[54]	✓							✓															✓	✓			✓	✓			Y	Y
Suzuki 2014[55]	✓							✓															✓				✓	✓			Y	Y
ACT 1[35]	✓									✓													✓				✓	✓			Y	Y
VARSITY[64]								✓											✓								✓	✓			N	Y
Re-randomised responder trial design																																
TRUE NORTH[51]	✓				✓																								✓		Y	Y
SELECTION[50]	✓		✓	✓																			✓	✓			✓	✓			Y	Y
OCTAVE Sustain[52]	✓					✓	✓																✓	✓			✓	✓			Y	Y
PURSUIT-M[67]	✓											✓	✓										✓				✓	✓			Y	Y
PURSUIT-J[68]	✓											✓											✓				✓	✓			N	Y
U-ACHIEVE Maintenance[62]	✓														✓	✓									✓	✓	✓		✓		Y	Y
UNIFI[63]	✓																	✓							✓	✓		✓			Y	Y
VISIBLE 1[69]	✓																				✓	✓	✓				✓	✓			N	Y
GEMINI 1[65]	✓																			✓	✓		✓			✓	✓	✓			Y	Y
Motoya 2019[66]	✓																				✓		✓	✓			✓	✓			N	Y

Abbreviations: N, no; pt, point; Y, yes.

B.3.9.1.3 Impact of trial design on assessment of maintenance phase outcomes

The fifteen included studies presenting maintenance phase outcomes are diverse in terms of their study design. Broadly speaking, there are two study design types: treat-through trials and rerandomised responder trials. Trials with a treat-through design include ELEVATE 52, ACT 1, ULTRA 2, Suzuki 2014 and VARSITY.[35, 47, 54, 55, 64] In these trials, patients are randomised at baseline and outcomes are measured at the end of an induction phase (6-8 weeks) and at the end of a maintenance phase (52–54 weeks).

Randomised responder trials, on the other hand, measured the outcomes at the end of a maintenance phase strictly among patients who achieved clinical response during either a randomised or single arm induction phase. Induction phase clinical responders are randomised to placebo or to a maintenance dose of the intervention of interest and outcomes are measured at or around 1 year. Ten included maintenance studies follow this design: TRUE NORTH, SELECTION, OCTAVE Sustain, PURSUIT-M, PURSUIT-J, U-ACHIEVE, UNIFI, VISIBLE 1, GEMINI 1 and Motoya 2019. In all studies except for OCTAVE Sustain, only patients who responded to the active intervention during the induction phase were re-randomised during maintenance. In OCTAVE Sustain, patients responding to placebo or tofacitinib in OCTAVE Induction 1 or 2 were re-randomised during the maintenance phase.[52]

Simply combining the reported maintenance phase outcomes from these alternative trial design types would be inappropriate as it would violate the similarity and homogeneity assumptions necessary for network meta-analysis. Specifically, the populations allowed to enter the maintenance phases are different and could significantly bias estimates of relative efficacy. The placebo arms also lack comparability because most of the patients who receive placebo in the maintenance phase of re-randomised responder trials received active treatment during induction.

There are two approaches available to align the outcomes such that the populations are less heterogenous between trial designs. The first is to convert the randomised responder trials to mimic the treat-through trials.[70] The alternative is to convert the outcomes of the treat-through trials to mimic the outcomes of the randomised responder trials. There are limitations to both approaches and both statistical and strategic considerations need to be considered. A limitation of the randomised responder trial design is the issue of carry-over effects. Placebo arms in randomised responder maintenance trials are not true placebo arms due to the carry over effect of active induction treatment. Most published NICE submissions in UC adjusted the treat-through trials to mimic the randomised trials. The benefit of this approach is that there are fewer assumptions required and less imputation of missing data compared to the alternative. Also, it allows for the generation of comparative effectiveness estimates both for the induction and maintenance phases, whereas using the treat-through trial design would mean results for only the induction phase and the whole trial period, which is induction plus maintenance. This would not align with analyses used to inform previous decision-making by NICE. A decision to forgo any conversion would limit the pairwise comparisons that are possible to between drugs evaluated using the same maintenance

phase design, which would limit the value of a comprehensive approach. Converting outcomes from the treat-through trials into comparable outcomes of the randomised responder trials was considered more robust, requiring less manipulation of observed data and less imputation of missing data.

For the analysis, the observed data from the ten randomised responder trials were taken “as is” from the studies. Individual patient data from ELEVATE 52 was used to isolate the maintenance phase outcomes to those among the induction phase responders. The observed data from two other treat-through trials (ACT 1 and ULTRA 2) were adjusted, based on the assumption that the number of responders at the end of induction is a proxy for the total number of patients entering maintenance. Clinical response from the treat-through trials was based on the proportion achieving sustained clinical response, as this mitigates the risk of counting maintenance phase responders who were induction phase non-responders. Unfortunately, the data necessary to make the imputation was insufficient from Suzuki 2014 and unavailable by subgroup from the VARSITY study, so these were excluded from the maintenance phase analysis. Imputed inputs to the NMA of maintenance phase outcomes are further described in Appendix F.

B.3.9.2 Results

Efficacy and safety results are presented in the following sections and are focused on comparisons of etrasimod and key comparators available in the NHS: adalimumab, infliximab and vedolizumab. These underpin the conclusion that etrasimod is likely to provide similar or greater health benefits as the comparators most widely used in the NHS. The results in Table 15 and Table 17 are reported as risk ratios with 95% CrIs for etrasimod versus relevant comparators from the models with the best fit. Please note that ‘significance’ in these results is defined by CrIs not crossing 1. In addition, results for the comparison on serious infections are presented to demonstrate etrasimod’s comparable safety profile to relevant active comparators. Further outputs of the NMAs, including treatment effects for comparisons versus placebo and rank statistics based on the surface under the cumulative ranking curve (SUCRA) are also provided in Appendix F. For completeness, comparisons between etrasimod and other drugs included in the NICE scope and captured in the SLR are presented in Appendix F.

B.3.9.2.1 Induction phase results

The network for clinical response and clinical remission during the induction period for the biologic-naïve subgroup is presented in Figure 6 and for the biologic-experienced subgroup, in Figure 7. All interventions were assessed in one or more placebo-controlled studies, with some studies evaluating multiple doses of the same drug and one study presented a head-to-head comparison of two active interventions.

Inspection of model fit statistics according to Table 14 suggested that for the biologic-naïve subgroup the fixed effect model was associated with reasonable model fits in terms of DIC and residual deviance. The random effects model, however, did not converge. Therefore, primary results for clinical response and remission during the induction period for the

biologic-naïve population were derived from the fixed effect model. For the biologic-experienced subgroup, the model fit statistics suggested that the random effects model was associated with an improved fit, given the residual deviance was lower and the DIC was substantially lower (>5 points) than the fixed effect model. Therefore, primary results for clinical response and remission during the induction period for the biologic-experienced population were derived from the random effects model.

For the outcome of serious infections, the model fit statistics suggested that the random effects model was associated with an improved fit, with a lower residual deviance and the DIC. However, due to the rarity of the event the uncertainty in the treatment effects generated by the random effects model lacked face validity. For this reason, primary results for serious infections during the induction periods were derived from the fixed effect model.

Across both subgroups and outcomes, for both the fixed and random effects models, the analyses including an adjustment to account for cross-trial variation in baseline risk failed to converge.

Table 14 Model fit statistics for induction phase analyses

Outcome	Subgroup	Model type	Number of data points	Total residual deviance	DIC
Clinical response and clinical remission	Bio-naïve	FE	90	**150.1**	**615.0**
		RE		Model did not converge	
	Bio-experienced	FE	50	81.2	307.9
		RE		**78.6**	**299.0**
Serious infection	Overall	FE	39	**41.6**	**157.2**
		RE		39.4	162.7

Abbreviations: DIC, Deviance Information Criterion; FE, fixed effects; RE, random effects; Bio-, biologics. Bold text indicates preferred model.

Figure 6 Network of evidence for induction phase clinical response and clinical remission by bio-naïve subgroup

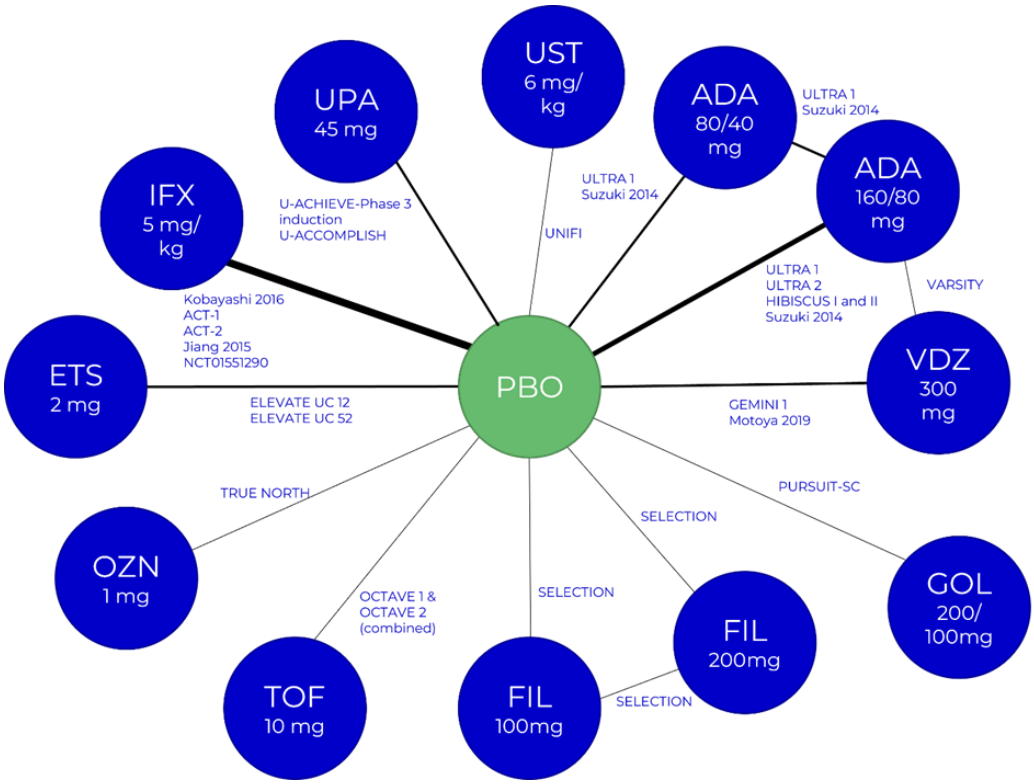


Figure 7 Network of evidence for induction phase clinical response and clinical remission by bio-experienced subgroup

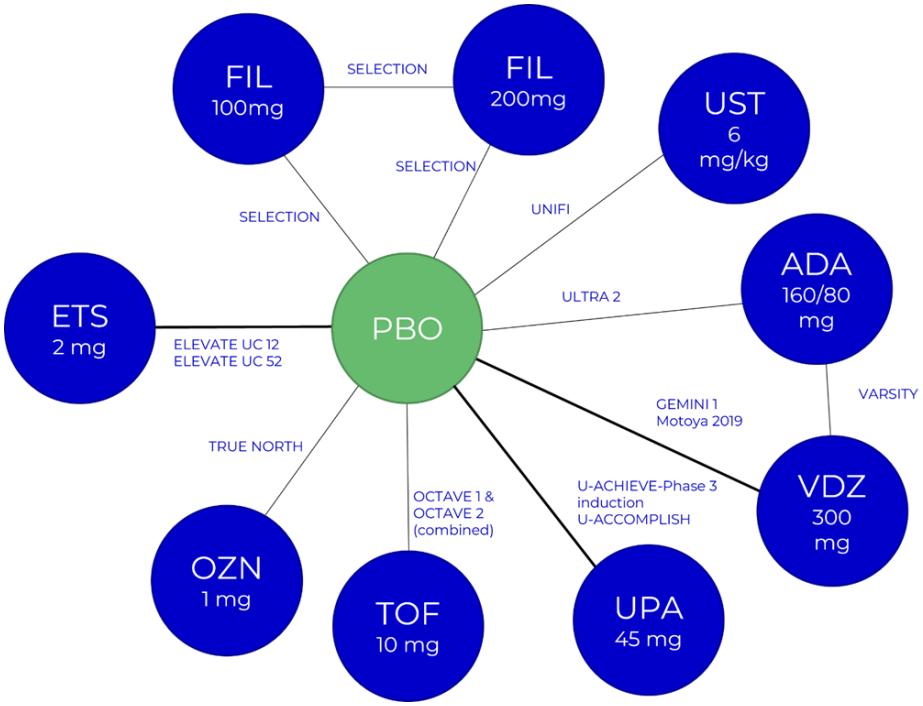
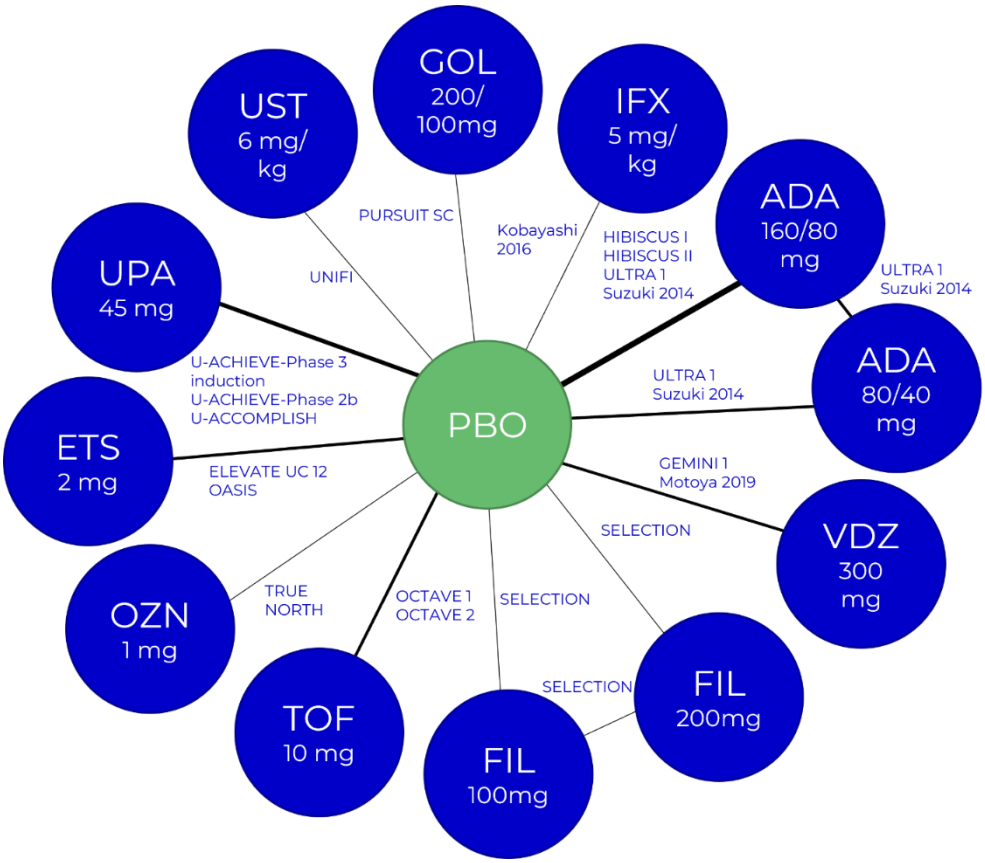


Figure 8 Network plot for the binomial analysis of serious infections during induction in the overall trial populations



In the biologic-naïve analysis, [redacted]

In the biologic-experienced analysis, [redacted] No data was available in this subgroup for infliximab; therefore, a comparison between etrasimod and infliximab among biologic-experienced patients is not possible. Serious infections were rare in the RCTs; therefore, the analysis is subject to considerable uncertainty. [redacted]

Table 15 Summary results for etrasimod and key comparators at end of induction phase

	Biologic-naïve[a]		Biologic-experienced[b]		Overall[a]
	Clinical response	Clinical remission	Clinical response	Clinical remission	Serious infections
Etrasimod vs comparator, median risk ratios (95% credible intervals)					
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

Adalimumab (160/80/40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (5 mg/kg)	[redacted]	[redacted]	-	-	[redacted]
Vedolizumab (300 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Absolute probabilities of response, median (95% credible interval)					
Etrasimod (2 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (160/80/40)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (5 mg/kg)	[redacted]	[redacted]	-	-	[redacted]
Vedolizumab (300 mg)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] Results are presented for the fixed effect model.
[b] Results are presented for the random effects model.

B.3.9.2.2 Maintenance phase results

The network for clinical response and clinical remission during the maintenance period for the biologic-naïve subgroup is presented in Figure 9 and for the biologic-experienced subgroup, in Figure 10. All interventions were assessed in one or more placebo-controlled studies, with some studies evaluating multiple doses of the same drug.

Inspection of model fit statistics according to Table 16 suggested that for both the biologic-naïve and biologic-experienced subgroups, the fixed effect model was associated with reasonable model fits in terms of DIC and residual deviance. The random effects models did not converge. Therefore, primary results for clinical response and remission during the maintenance period for both populations were derived from the fixed effect models. Across both subgroups and outcomes, for both the fixed and random effects models, the analyses including an adjustment to account for cross-trial variation in baseline risk failed to converge.

Table 16 Model fit statistics for maintenance phase analyses

Phase	Subgroup	Model type	Number of data points	Total residual deviance	DIC
Clinical response and clinical remission	Bio-naïve	FE	**63**	**158.70**	**451.9**
		RE	Model did not converge		
	Bio-experienced	FE	**49**	**77.63**	**284.2**
		RE	Model did not converge		

Abbreviations: DIC, Deviance Information Criterion; FE, fixed effects; RE, random effects; Bio-, biologics. Bold text indicates preferred model.

Figure 9 Network of evidence for maintenance phase clinical response and clinical remission by bio-naïve subgroup

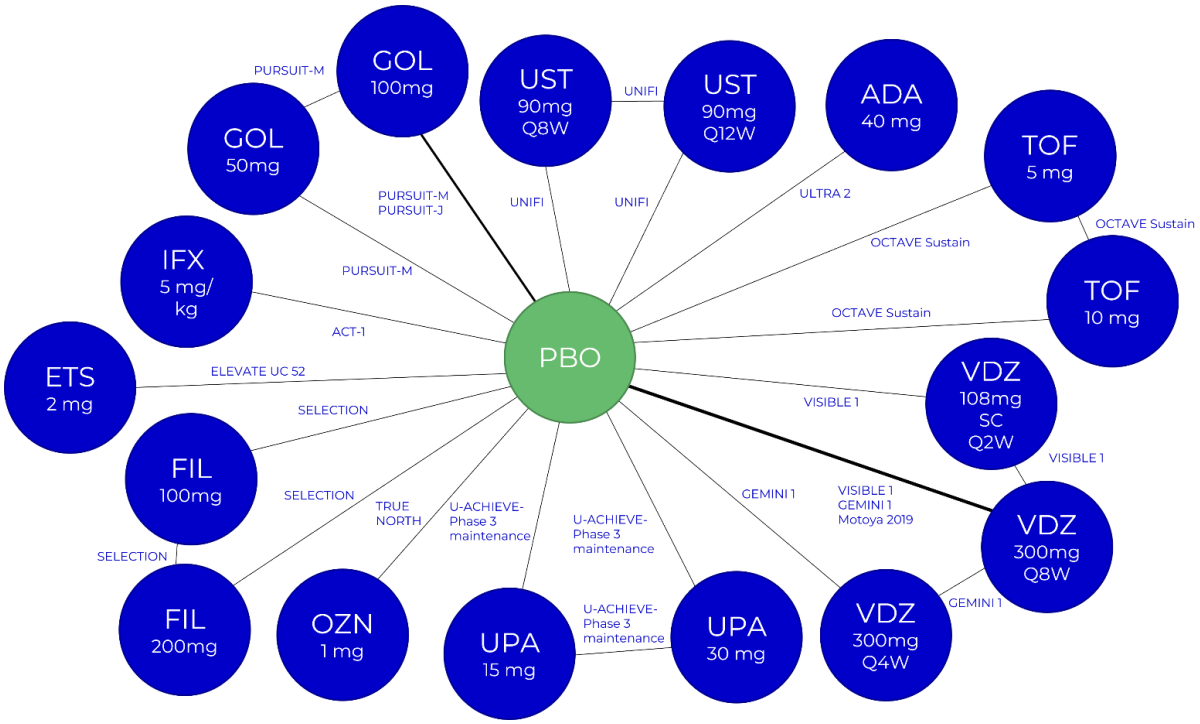
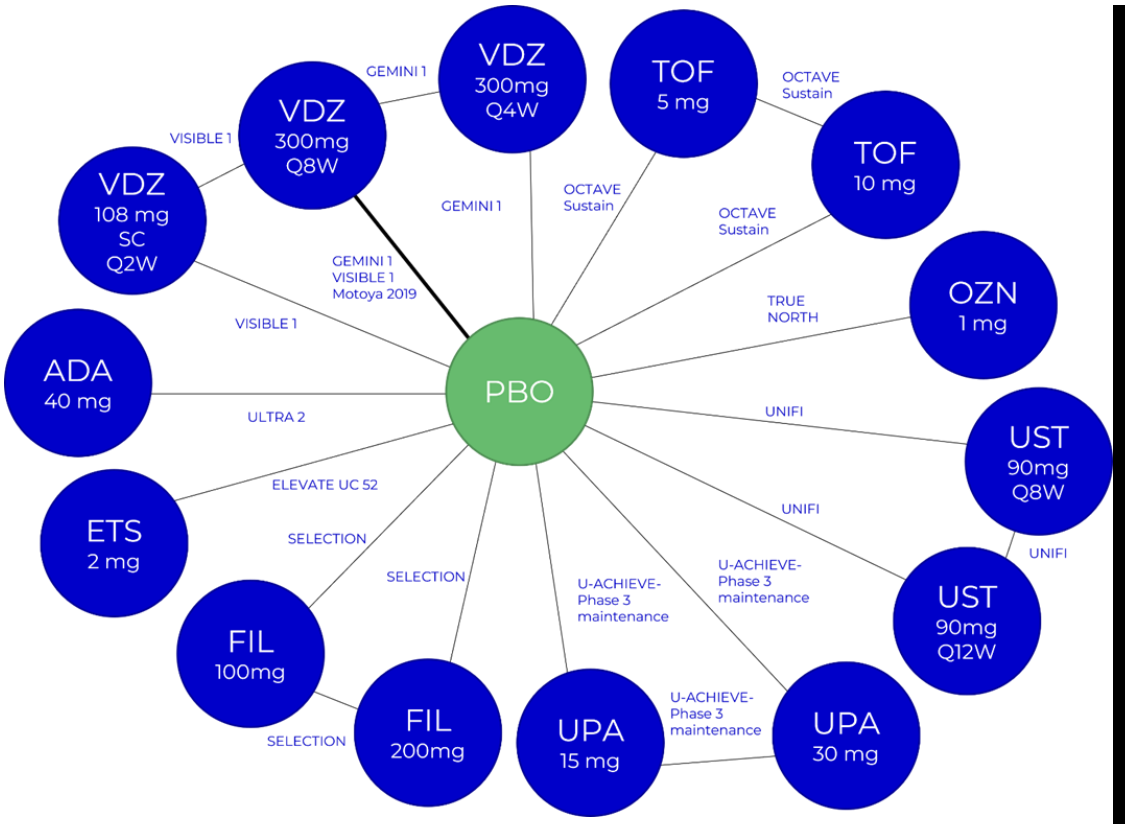


Figure 10 Network of evidence for maintenance phase clinical response and clinical remission by bio-experienced group



In the biologic-naïve analysis,

[redacted]

In the biologic-experienced analysis,

[redacted] No data was available in this subgroup for infliximab; therefore, a comparison between etrasimod and infliximab among biologic-experienced patients is not possible.

Table 17 Summary results for etrasimod and key comparators at end of maintenance phase (among induction phase responders)

	Biologic-naïve[a]		Biologic-experienced[a]	
	Clinical response	Clinical remission	Clinical response	Clinical remission
Etrasimod vs comparator, median risk ratios (95% credible intervals)				
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (40 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (5 mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]
Absolute probabilities of response, median (95% credible interval)				
Etrasimod (2 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Placebo	[redacted]	[redacted]	[redacted]	[redacted]
Adalimumab (40 mg)	[redacted]	[redacted]	[redacted]	[redacted]
Infliximab (5 mg/kg)	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]
Vedolizumab SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]

[a] Results are presented for the fixed effect model as the random effects model did not converge.
Abbreviations: IV, intravenous; SC, subcutaneous; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks.

B.3.9.3 Uncertainties in the indirect and mixed treatment comparisons

Careful consideration was given to potential sources of heterogeneity, including study design, interventions, outcome definitions and baseline characteristics (weight, disease severity, duration of disease, prior treatments, concomitant treatments). Analysis was only undertaken where it was judged that these factors were sufficiently similar across the network. Where enough data were available, distributions of these characteristics were compared across studies and treatment comparisons. This ensured that differences between the trials and comparisons were kept to a minimum.

One patient characteristic was notably different across the evidence network: prior biologic-exposure. Some studies included only biologic-naïve patients and others included patients with and without prior biologic exposure. The decision to approach the NMAs using subgroup analysis was consistent with previous technology appraisals, which have considered biologic-naïve and biologic-exposed populations separately.[40, 48, 49, 71, 72]

Steps were taken to reduce heterogeneity related to study design, including restriction of eligible studies based on induction/maintenance length and outcome definition and statistical adjustment to treat-through trials to align with the data presented in randomised responder trials. Though these adjustments improve the comparability of maintenance phase outcomes across studies, they also reduce the statistical power of treat-through trials by restricting the sample size to the subset of patients that achieved induction phase response. Further subgrouping these patients based on their prior exposure to biologic therapy, as was done for both ULTRA 2 and ELEVATE 52, reduces the sample size even further [redacted].

Previous technology appraisals have undertaken sensitivity analyses to explore the impact of excluding studies that recruited an entirely Asian population, explore the effect of centrally versus locally read endoscopic subscores, where both are available, use of 3-component Mayo scores versus 4-component Mayo scores, where both are available. All reported that the results of such analyses were consistent with the base case assumptions; therefore, these were not prioritised for inclusion in this evaluation of etrasimod.

Fixed and random effects analyses, without and with baseline risk adjustments, were explored for each of the outcomes of interest. The baseline risk adjustment models failed to converge as did several of the random effects models, please see Table 14.

B.3.9.4 Conclusion

Taken together, the results for both the naïve population and biologic-experienced subgroup in the induction and maintenance analyses suggest that, based on the available data, etrasimod is an efficacious treatment for moderately to severely active UC and is comparable to currently available therapies used in advanced UC treatment. The results also demonstrate that the incidence of serious infections during the induction phase is expected to be low for patients treated with etrasimod and comparable to placebo and its comparators.

[redacted] Due to a lack of

RCT data in the biologic-experienced population, no comparisons could be made between etrasimod and infliximab.

B.3.10 Adverse reactions

Safety results from ELEVATE UC 12 and ELEVATE UC 52 are reported in this section, with additional details provided in Appendix H.

A summary of treatment-emergent adverse events (TEAEs) experienced by patients in ELEVATE UC 12 and ELEVATE UC 52 are summarised in Table 18. TEAEs reported in ≥1% of patients in either treatment group by preferred term in ELEVATE UC 12 and ELEVATE UC 52 are summarised in Appendix H, Table 65. Full details of all TEAEs affecting > 1% of patients in any group by system organ class (SOC) in ELEVATE UC 12 and ELEVATE UC 52 are shown in Appendix H, Table 66.

B.3.10.1 ELEVATE UC 12 – safety results

The proportion of patients who reported at least one TEAE was similar in the etrasimod and placebo groups (47.1% vs. 46.6%;Table 18). Most TEAEs were mild or moderate (Grade 1 or 2) in severity. Grade 3 TEAEs were reported in 7 [2.9%] vs. 2 [1.7%] patients in the etrasimod and placebo groups, respectively. There was one Grade 4 TEAE in the etrasimod group (coronary artery disease) and none in the placebo group (Table 18). Most TEAEs were not considered related to the study treatment. All etrasimod-related TEAEs were considered mild or moderate in severity.

Headache, anaemia, and colitis ulcerative were reported with a >2% difference in proportion of patients between the etrasimod and placebo groups (Appendix H, Table 65). Notably, no TEAEs with a fatal outcome were reported during the study (Appendix H, Table 65).

B.3.10.1.1 Serious adverse events (SAEs)

The percentage of patients with at least one treatment-emergent SAE was low and balanced across treatment groups (etrasimod: 6 patients [2.5%] vs. placebo: 2 patients [1.7%]). No treatment-emergent SAEs were considered related to study treatment by the investigator.

Colitis ulcerative was the most frequently reported SAE by preferred term, reported in 3 (1.3%) patients in the etrasimod group versus none in the placebo group. All other SAEs were reported in single patients.

Grade 3 SAEs in the etrasimod group (n=4) vs. the placebo group (n=1) included colitis ulcerative (etrasimod n=3), migraine (etrasimod n=1), and abdominal pain (placebo n=1). Coronary artery disease in the etrasimod group was the only Grade 4 SAE. All SAEs were considered recovered or resolved.

Two SAEs (both colitis ulcerative) led to study treatment withdrawal and one SAE (migraine) led to study treatment interruption in the etrasimod group. One SAE (abdominal pain) led to withdrawal of study treatment in the placebo group.

B.3.10.1.2 Adverse events leading to treatment discontinuation or interruption

TEAEs leading to study treatment discontinuation (experienced by 2 or more patients) were colitis ulcerative (6 [2.5%] vs 0 patients in the etrasimod and placebo groups, respectively) and bradycardia/sinus bradycardia (3 [1.3%] vs 0 patients in the etrasimod and placebo groups, respectively). One TEAE (abdominal pain upper) leading to study treatment discontinuation in the placebo group was considered Grade 3 in severity. All other TEAEs that led to study treatment discontinuation were Grade 1 or Grade 2 in severity.

TEAEs leading to study treatment interruption occurred in 4 (1.7%) patients in the etrasimod group (one each of non-cardiac chest pain [Grade 2], COVID-19 [Grade 2], cutaneous vasculitis [Grade 1], and migraine [Grade 3]), and in 3 (2.6%) patients in the placebo group (one each of herpes zoster, anaemia and chorioretinopathy, all Grade 2).

B.3.10.1.3 Adverse events of special interest

A total of 22 TEAEs of special interest (AESIs) were identified (18 vs. 4 events in the etrasimod vs. placebo groups, respectively), which were similarly distributed between the treatment groups (etrasimod: 13 [5.5%]) patients; placebo: 4 [3.4%]) patients). No AESIs of macular oedema, pulmonary disorders, posterior reversible encephalopathy syndrome (PRES), progressive multifocal leukoencephalopathy (PML), or malignancy were reported in either treatment group in this study. AESIs in the etrasimod group were identified in the categories of cardiovascular events, liver injury, pulmonary events, and infections:

- Cardiovascular events category AESIs occurred more frequently in patients in the etrasimod vs. placebo group (8 [3.4%] vs. 2 [1.7%] patients, respectively)
- Liver injury AESIs were the second most frequently reported AESIs in the etrasimod group (3 patients [1.3%]).
- A lower proportion of patients in the etrasimod group had AESIs in the infections category compared to the placebo group: etrasimod 2 [0.8%] patients versus placebo 2 [1.7%] patients.
- AESIs related to the first dose cardiac effect (bradycardia and AV conduction delay) occurred only in etrasimod-treated patients.

B.3.10.2 ELEVATE UC 52 – safety results

The proportion of patients who reported at least one TEAE was higher in the etrasimod group than the placebo group (71.3% vs. 56.3%, exposure adjusted incidence rate [EAIR]: 2.04 vs. 1.83, respectively).

Most TEAEs were mild or moderate (Grade 1 or 2) in severity. Grade 3 TEAEs were low and balanced in both treatment groups (etrasimod: 20 [6.9%] patients; placebo: 10 [6.9%] patients). There were two Grade 4 TEAEs, one in the etrasimod group (lymphopenia) and one in the placebo group (alanine aminotransferase increased).

The most frequently reported TEAEs by preferred term were anaemia, headache, colitis ulcerative and coronavirus 2019 disease (COVID-19) (Table 18). Headache and Dizziness were reported with a > 3% higher proportion of patients in the etrasimod group than the placebo group. Overall, the percentage of patients with TEAEs of colitis ulcerative or

abdominal pain was low, and colitis ulcerative TEAEs was lower in etrasimod-treated patients versus placebo (Table 18). Notably, no TEAEs with a fatal outcome were reported during the study.

B.3.10.2.1 Serious adverse events (SAEs)

The percentage of patients with at least one treatment-emergent SAE was low and balanced across treatment groups (etrasimod: 20 patients [6.9%] vs. placebo: 9 patients [6.3%]).

UC (2.1% each group) and Anaemia (0.7% each group) were the most frequently reported SAEs by preferred term (≥ 2 patients in either treatment group); all other SAEs were reported in a single patient in either group or each treatment group. All SAEs were considered resolved, resolved with sequalae, or resolving.

Grade 3 SAEs in the etrasimod group (n=14) vs. the placebo group (n=8) included UC (n=4 and n=1, respectively) and anaemia (n=2 and n=1, respectively). There were no Grade 4 SAEs.

One SAE (UC) led to withdrawal of study treatment, and two SAEs (1 each of migraine and intracranial pressure increased) led to study drug interruption in the etrasimod group. One SAE (large intestine perforation) led to withdrawal of study treatment, and one SAE (cellulitis) led to study drug interruption in the placebo group. One patient in each treatment group had one SAE considered related to study treatment (etrasimod: anembryonic gestation; placebo: cellulitis).

B.3.10.2.2 Adverse events leading to treatment discontinuation or interruption

TEAEs leading to study treatment discontinuation were similar between treatment groups (12 [4.2%] patients vs. 7 [4.9%] patients in the etrasimod vs. placebo groups, respectively). These TEAEs (experienced by 2 or more patients) were colitis ulcerative (4 [1.4%] vs. 2 [1.4%] patients in the etrasimod and placebo groups, respectively). Two TEAEs (both UC leading to study treatment discontinuation in the etrasimod group were considered Grade 3 in severity; three TEAEs (1 each of UC, malaise, and large intestine perforation) leading to study treatment discontinuation in the placebo group were considered Grade 3 in severity and one TEAE (alanine aminotransferase increased) was considered Grade 4 in severity.

TEAEs leading to study treatment interruption occurred in 19 (6.6%) patients in the etrasimod group and 4 (2.5%) patients in the placebo group. The most frequently reported TEAEs in the etrasimod group (experienced by ≥ 2 patients) leading to study treatment interruption included 2 aspartate aminotransferase increased (Grade 1), two severe acute respiratory syndrome coronavirus-2 (SARS-CoV2) test positive (Grade 2) and three COVID-19 (two Grade 1 and one Grade 2); in the placebo the most frequently reported TEAEs leading to study treatment interruption included rash pruritic (Grade 2), COVID-19 (Grade 1), cellulitis (Grade 3), and pneumonia (Grade 2).

B.3.10.2.3 Adverse events of special interest

A total of 46 AESIs were identified (35 vs. 11 events in the etrasimod vs. placebo groups, respectively), which were similarly distributed between the treatment groups (etrasimod: 26

[9.0%]) patients; placebo: 10 [6.9%]) patients). No AESIs of PRES, PML, or malignancy were reported in either treatment group in this study. AESIs in the etrasimod group were identified in the categories of cardiovascular events, infections, liver injury, macular oedema, and pulmonary disorders:

- Cardiovascular events category AESIs, including AESIs related to the first dose cardiac effect, occurred only in patients in the etrasimod group (12 [4.2%] patients)
- Infections AESIs were less frequently reported in etrasimod-treated patients than in placebo-treated patients (8 [2.8%] vs. 7 [4.9%] patients, respectively)
- AESIs in the liver injury (4 [1.4%] vs. 2 [1.4%] patients) and pulmonary disorders (1 [0.3%] vs. 1 [0.7%] patient) categories were reported in a similar proportion of patients in the etrasimod and placebo groups, respectively
- One AESI was reported in the macular oedema category in the etrasimod group compared to none in the placebo group.

Table 18 Summary of TEAEs in ELEVATE UC 12 and ELEVATE UC 52 (Safety set)

	ELEVATE UC 12 [45]		ELEVATE UC 52 [46]	
	Placebo (N=116) n (%) [m]	Etrasimod (N=238) n (%)	Placebo (N=144) n (%)	Etrasimod (N=289) n (%)
TEAEs	54 (46.6) [107]	112 (47.1) [302]	81 (56.3) [238}	206 (71.3) [636]
Related TEAEs[a]	8 (6.9) [8]	30 (12.6) [52]	12 (8.3) [19]	46 (15.9) [79]
Serious TEAEs[b]	2 (1.7) [2]	6 (2.5) [6]	9 (6.3) [10]	20 (6.9) [22]
Related Serious TEAEs[a,b]	0	0	1 (0.7) [1]	1 (0.3) [1]
TEAEs leading to death	0	0	0	0
Liver-related[c]	0	0	0	0
TEAEs leading to study treatment discontinuation	1 (0.9) [1]	13 (5.5) [13]	7 (4.9) [7]	12 (4.2) [12]
Related[a]	0	7 (2.9) [7]	2 (1.4) [2]	7 (2.4) [7]
Liver-related[c]	0	1 (0.4) [1]	1 (0.7) [1]	1 (0.3) [1]
TEAEs leading to study treatment interruption	3 (2.6) [3]	4 (1.7) [4]	4 (2.8) [4]	19 (6.6) [25]
Related[a]	0	2 (0.8) [2]	1 (0.7) [1]	6 (2.1) [8]
TEAEs by maximum severity[d]				
Grade 1	31 (26.7) [79]	62 (26.1) [214]	40 (27.8) [163]	101 (34.9) [439]
Grade 2	21 (18.1) [26]	42 (17.6) [79]	30 (20.8) [60]	84 (29.1) [174]
Grade 3	2 (1.7) [2]	7 (2.9) [8]	10 (6.9) [14]	20 (6.9) [22]
Grade 4	0	1 (0.4) [1]	1 (0.7) [1]	1 (0.3) [1]
Grade 5	0	0	0	0
Related TEAEs by maximum severity[a,d]				
Grade 1	7 (6.0) [7]	21 (8.8) [38]	5 (3.5) [7]	30 (10.4) [59]
Grade 2	1 (0.9) [1]	9 (3.8) [14]	5 (3.5) [10]	15 (5.2) [19]
Grade 3	0	0	2 (1.4) [2]	0
Grade 4	0	0	0	1 (0.3) [1]
Grade 5	0	0	0	0
TEAEs by relationship to study treatment				
Not Related	37 (31.9) [75]	61 (25.6) [210]	57 (39.6) [195]	122 (42.2) [45.7]
Unlikely related	9 (7.8) [24]	21 (8.8) [40]	12 (8.3) [24]	38 (13.1) [100]
Probably Related	8 (6.9) [8]	24 (10.1) [44]	8 (5.6) [13]	33 (11.4) [58]
Related	0	6 (2.5) [8]	4 (2.8) [6]	13 (4.5) [21]

[a] Adverse events classified as "probably related" or "related" are counted as related. Missing relationship is counted as related. [b] Missing seriousness is counted as serious. [c] Liver-related TEAEs are defined as SOC being hepatobiliary disorders or PT being Alanine aminotransferase abnormal, Alanine aminotransferase increased, Aspartate aminotransferase abnormal, Aspartate aminotransferase increased, Hepatic enzyme abnormal, Hepatic enzyme increased, Liver function test abnormal, Liver function test increased, Transaminases abnormal, or Transaminases increased. [d] Severity is classified using CTCAE, version 5.0, i.e., Grade 1 for mild, Grade 2 for moderate, Grade 3 for severe, Grade 4 for life-threatening, Grade 5 for death related to adverse event.
TEAEs are defined as any adverse event that started or worsened in severity on or after the first dose of study treatment. Terms are coded using MedDRA v24.1.
Percentages are based on the number of patients in the analysis set; [m] is defined as number of events.
Abbreviations: TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

B.3.11 Conclusions about comparable health benefits and safety

UC is a chronic autoimmune disease characterised by mucosal inflammation, abdominal pain, and bowel urgency, with disease exacerbations that may result in daily bloody stools, frequent physician visits, risk of colectomy, extra-intestinal manifestations, and/or hospitalisation. Patients with active UC face reduced health-related quality of life (HRQoL), with poorly controlled patients facing worse outcomes such as impaired physical, emotional, and social functioning.

Etrasimod is indicated for patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules). The evidence presented in this submission demonstrates the efficacy and safety of etrasimod among patients who are naïve to biologic or JAKi therapies and patients who have previously received these treatments and supports its positioning in both patient populations, consistent with other biologic treatments for UC. Full details of treatment pathway, proposed positioning and corresponding decision problem can be found in section 0 above.

The clinical benefits of etrasimod compared with placebo have been demonstrated in two Phase III trials: ELEVATE UC 12 and ELEVATE UC 52. Across these two pivotal trials, etrasimod met the primary endpoint of clinical remission at weeks 12 and 52 (sections B.3.6.1.1 and B.3.6.2.1). In the overall populations of the etrasimod arms, a significantly greater proportion of patients achieved clinical response and clinical remission compared with placebo. Analysis of secondary efficacy outcomes demonstrated that etrasimod is associated with higher rates of symptomatic remission, EIHR, and clinical response than placebo at Week 12 of both studies (section B.3.6.1.2). This effect was maintained to Week 52 in ELEVATE UC 52 (section B.3.6.2.2).

Patients treated with etrasimod who were naive to previous treatment with biologic or JAKi therapies showed clinically meaningful improvements compared with those treated with placebo for induction and maintenance efficacy endpoints. Patients previously treated with at least one biologic or JAKi therapy showed clinically meaningful improvements compared with those treated with placebo for induction and maintenance efficacy endpoints, albeit with smaller treatment effects (section B.3.7). These results are consistent with those observed in other advanced UC therapy trials that included biological-naive and biological-experienced patients.

In the ELEVATE trials, etrasimod demonstrates rapid and sustained improvements versus placebo in disease specific HRQoL, as demonstrated by IBDQ, with improvement observed at the first assessment at week 12 and maintained to week 52. Differences between etrasimod and placebo on the generic SF-6D utility index score were also significant at week 12 in both studies and maintained to week 52 in ELEVATE UC 52 (sections B.3.6.1.4 and B.3.6.2.4).

In both ELEVATE UC 12 and ELEVATE UC 52, etrasimod showed a favourable safety profile. No increased incidence of infections (overall infections, herpes zoster, opportunistic,

or serious infections) was observed in patients treated with etrasimod compared with patients treated with placebo (section B.3.10).

In the NMA (section B.3.9.2), etrasimod was comparable to adalimumab, infliximab and vedolizumab for clinical response and clinical remission in the induction and maintenance periods. Among patients without prior exposure to biologic therapy, etrasimod was shown to be superior to adalimumab at inducing and maintaining clinical response and remission. In the NMA for serious infections, etrasimod showed comparable results to the other advanced UC therapies and placebo.

Etrasimod is formulated as a convenient, once-daily dose in an oral pill, with a dosage that does not change between induction and maintenance. Many patients report preferring oral medicines over other administration routes, including SC and IV.[27, 73-75] Oral treatments may overcome some barriers to therapy often associated with IV and SC administration, thereby improving adherence.[32, 73, 76, 77] Furthermore, oral treatment can reduce the burden on the NHS as administration can take place at home, where by for SC training is required and for IV it must be administered in hospital. As such, etrasimod provides an alternative option for patients to move conveniently from oral conventional therapies to an advanced therapy to achieve early disease control. This in turn increases the likelihood of successful outcomes for patients earlier in their treatment pathway. Another benefit of etrasimod is the simplicity of its dosing regimen. Unlike other advanced therapies for UC, etrasimod has a once daily dosing, with no dose changes needed for induction or maintenance, thus ensuring a more consistent and predictable benefit-risk ratio, regardless of the phase of therapy.

In conclusion, treatment with etrasimod was well tolerated and effective as an induction and maintenance therapy for patients with moderately to severely active UC. As an orally administered small molecule with once-daily dosing, durable efficacy, and a favourable safety profile, etrasimod is a treatment option that helps address the ongoing unmet needs of patients with moderately to severely active UC.

B.3.12 Ongoing studies

The GLADIATOR UC is an ongoing etrasimod phase II randomised, double blind, placebo-controlled, 52-week study in patients with moderately active UC (NCT04607837) expecting to provide additional evidence in the next 12 months. In addition, evidence is expected within the next year on a phase II, randomised, double-blind, placebo-controlled, 12-week dose-ranging study in Japanese patients (NCT05061446).

Other ongoing etrasimod studies, with evidence expected after the next year, include the extension study, ELEVATE UC open label extension (OLE) trial (NCT03950232) and the open label, single-arm study in adolescents with moderately to severely active UC (NCT05287126).

Another ongoing etrasimod study with unknown status includes a phase III, randomised, placebo-controlled, double-blind, multicentre study in Chinese patients (NCT04176588).

Completed studies beyond the ones presented in section B.3 include the OASIS OLE trial (NCT02536404) and the phase III double-blind, placebo-controlled, 40-week extension study in Japanese patients, ELEVATE UC 40 JAPAN (NCT04706793).

B.4 Cost-comparison analysis

B.4.1 Changes in service provision and management

Etrasimod is a once-daily oral tablet for treating moderately to severely active UC. Modes of administration of other currently available treatment options licensed for the same indication can differ. Adalimumab and golimumab are self-administered via SC, while infliximab and vedolizumab can be administered either by IV solely or initiated by IV and followed by maintenance SC.

Etrasimod is expected to be prescribed in secondary care, with all administrations taking place at home. For SC treatments, it was assumed that patients would be trained to self-administer their medication and that the manufacturer would cover the training costs. While medications administered by IV infusion would take place in a hospital setting for each dose required.

Etrasimod requires a single ECG before initiation of treatment.

B.4.2 Cost-comparison inputs and assumptions

B.4.2.1 Features of the cost-comparison analysis

The economic analysis compared the costs of etrasimod compared to existing treatments for patients with moderately to severely active UC. The base-case analysis comprised drug acquisition costs, pre-initiation ECG, Concomitant therapy (CcT) and administration costs over a 5 year period.

The analysis considered the first-year treatment costs, incorporating the initiation dose regimen of each treatment.

The base-case time horizon used in the cost comparison analysis (CCA) is 5-years, with a 2-year scenario analysis presented. A time horizon of 5-years was deemed an appropriate time horizon to demonstrate differences in the costs associated with etrasimod and comparators, given key aspects of treatment initiation are time-invariant.

The NICE user guide for submitting single technology cost-comparison assessments, stated that discounting of costs is not required for cost comparison, therefore no discounting of future costs was considered in the analysis.

B.4.2.2 Intervention and comparators' acquisition costs

All drug doses and unit cost information was obtained from the SmPCs and the Monthly Index of Medical Specialities (MIMs). [78] When more than one proprietary drug product was available, the most conservative, i.e., the least expensive, unit cost was used for the calculations in Table 24. The recommended dosing schedules are described below in Table 19, followed by the medications associated costs in Table 20.

Table 19 Dosing schedules

Drug	Route of Administration	Dosing	
		Initiation	Maintenance
Etrasimod	Oral	2 mg once daily	
Adalimumab	SC	160 mg at week 0 80 mg at week 2	40 mg every other week
Infliximab then remsima[a]	Initiation: IV Maintenance: SC	5 mg/kg at weeks 0 and 2	5 mg/kg every 2 weeks from week 6
Infliximab[a]	IV	5 mg/kg at weeks 0, 2 and 6	5 mg/kg every 2 weeks from week 8
Vedolizumab	Initiation: IV Maintenance: SC	300 mg at weeks 0, 2 and 6	300mg every 8 weeks
Vedolizumab	IV	300 mg at weeks 0 and 2	108 mg at week 6 and every other week thereafter
Golimumab	SC	200 mg at week 0, 100 mg at week 2	50 mg every 4 weeks thereafter
Tofacitinib	Oral	10 mg twice daily for 8 weeks	5 mg twice daily
Filgotinib	Oral	200mg once daily	
Upadacitinib	Oral	45 mg once daily for 8 weeks	15 mg once daily

[a] Dosing for infliximab is dependent on a patient's weight. The mean weight for men (85.1 kgs) and women (71.8 kgs) was used for the average patient in the analysis: 78.5 kgs.[75]

Table 20 Drug acquisition dosing and costs

Drug	Pack size	Strength of unit	Pack cost	Total cost - year 1	Total cost - subsequent years
Etrasimod	28	2 mg	£843.92 [redacted]	£11,000 [redacted]	£11,000 [redacted]
Adalimumab	2	40 mg	£633.60	£9,820.80	£8,236.80
Infliximab then remsima [IV then SC]	2	120mg	£755.32	£11,643.75	£9,819.16
Infliximab [IV only]	1	100 mg	£377.00	£11,830.26	£8,872.70
Vedolizumab [IV then SC]	1	300 mg	£2,050.00	£16,400.00	£12,300.00
Vedolizumab [IV only]	2	108 mg	£1,025.00	£16,400.00	£13,325.00
Golimumab	1	50 mg	£762.97	£11,826.04	£9,918.61
Tofacitinib	56	5 mg	£12.32	£10,350.45	£8,970.39
Filgotinib	30	200 mg	£28.77	£10,472.28	£10,472.28
Upadacitinib	28	15 mg	£28.77	£13,035.36	£10,472.28

Abbreviations: IV, intravenous; [redacted] SC, subcutaneous.

B.4.2.3 Intervention and comparators' healthcare resource use and associated costs

Monitoring and pre-initiation costs

In line with previous TAs,[39, 49, 71, 72] monitoring requirements were assumed similar for etrasimod and existing treatments and therefore were not included in the economic model, for example, for S1Ps an ophthalmic exam is expected for high-risk patients only (e.g., history of diabetes, uveitis, retinal disease). A single electrocardiogram (ECG) pre-initiation is required for S1Ps as specified in the SmPCs. Clinical expert opinion obtained from a UK pragmatic review in 2023, noted how the pre-initiation ECG was ranked as the least relevant consideration when considering drug choice and that most physicians didn't see it as a barrier to prescribing.[30] The ECG cost was obtained from the National Schedule of NHS costs 2021/22 and is provided in Table 21.

Table 21 Monitoring and pre-initiation testing cost

Test	Unit cost	Source
ECG	£74.91	EY51Z, Directly Accessed Diagnostic Services, Electrocardiogram, Monitoring or Stress Testing

Abbreviations: ECG, electrocardiogram.

Administration costs

The unit costs for administration were sourced from the National schedule of NHS costs 2021/22 and are presented in Table 22 below.[79]

Table 22 Administration costs

Administration method	Cost per dose or per pack	Source
IV	£133.40	Average of consultant led and non-consultant led, non-admitted face-to-face attendance, follow-up, WF01A.[79]
SC	£0.00	Assume patients self-administer and therefore there is no administration cost. Additionally, it has been assumed that the one off nurse training cost to teach patients how to self-administer the injection is covered by the manufacturer in line with previous TAs.[49, 72]
Oral tablet	£0.0	Assumed no administration costs.

Abbreviations: IV, intravenous; SC, subcutaneous injection.

Concomitant therapy

CcT costs were included in the model as per the committee preference in TA633.[72] The details of CcT are provided in Table 23. CcT usage is assumed to remain constant throughout the 5-year time horizon, as outlined in Table 23 below. The patient usage of CcT for all treatments was based off the assumptions in prior technology appraisals in UC.[39, 49, 72]

Table 23 Concomitant therapies dosing and costs

Drug	Pack Size	Strength (mg)	Pack cost	Cost per dose	Total annual Cost	Usage – S1Ps[49]	Usage – all other treatments[39, 49, 72]
Balsalazide	130	750	£30.42	£0.23	£341.64	0%	0%
Mesalazine	120	400	£15.50	£0.13	£	13%	13%
Olsalazine	60	500	£161.00	£2.68	£1,958.83	0%	0%
Sulfasalazine	112	500	£6.74	£0.06	£87.86	0%	0%
Prednisolone	28	20	£2.93	£0.10	£1.47	36%	36%
Hydrocortisone	30	20	£3.29	£0.11	£40.03	0%	0%
Azathioprine[a]	56	50	£1.46	£0.03	£9.52	0%	0% / 39%
6-mercaptopurine[a]	25	50	£34.39	£1.38	£502.09	0%	15%
Methotrexate[a]	100	2.5	4.32	£0.04	£15.77	0%	9.0%
Budesonide[a]	50	3	£37.53	£0.75	£126.10	1%	1%

[a] Patients receiving etrasimod and ozanimod are contraindicated to azathioprine, 6-mercaptopurine and methotrexate and would therefore not receive these concomitantly. Patients receiving tofacitinib are contraindicated to azathioprine and would therefore not receive it concomitantly.

B.4.2.4 Adverse reaction unit costs and resource use

In Section B.3.9, it was shown that no significant difference across the comparator treatments was found for the incidence of serious infections. Therefore, no adverse event resource use or costs were included in the analysis.

B.4.2.5 Miscellaneous unit costs and resource use

No other unit costs or resource use was considered in the analysis.

An SLR was conducted to identify cost, and resource use data relevant to the utilisation of healthcare resources and/or their associated costs in UC, summarised in Appendix K. Most commonly, direct medical costs were driven by the costs of hospitalisation, surgery, and the management of UC complications. Although not required, two SLRs were conducted by the company to identify (i) economic evaluations of advanced therapies for the treatment of moderately to severely active UC in adult patients, and (ii) HRQoL studies. The two SLRs are presented in Appendix I and Appendix J, respectively.

B.4.2.6 Clinical expert validation

None that are relevant.

B.4.2.7 Uncertainties in the inputs and assumptions

None that are relevant.

B.4.3 Base-case results

The following section's interpretation is based on the list price of etrasimod, given comparator discounts are unknown to the Company. Total costs, estimated per patient for 5-years based on a simple CCA model, range between £43,268 and £70,467; etrasimod has an estimated cost of £55,176 [redacted], see Table 24. Crucially this price point sits within the existing price range of available treatment options, and [redacted]

The significant reduction in treatment burden, and potential increased utility experienced from reduced frequency of SC/IV, have not been quantified or included within the analysis. Therefore, given the positive impact these benefits have on patients, the results of the cost-comparison can be considered an underestimation of the true value of etrasimod to the NHS. This should be taken into consideration when considering the optimum price point of etrasimod in the moderately to severely active UC.

Table 24 Base- case results

Technology	Total 5 year cost per patient	Market share
Etrasimod	£55,176 (list) [redacted]	-%
Adalimumab	£43,268	[redacted]
Infliximab	£52,488	[redacted]
Vedolizumab	£70,467	[redacted]
Golimumab	£52,001	[redacted]
Tofacitinib	£46,714	[redacted]
Filgotinib	£52,862	[redacted]
Upadacitinib	£55,425	[redacted]

Abbreviations: [redacted]

B.4.4 Sensitivity and scenario analysis

Scenario analyses were conducted and considered the following:

1. A 2-year time horizon
2. The use of infliximab (Flixabi™; IV) and Entyvio (IV) for initiation and maintenance. When only the IV route of administration was used for induction and the maintenance phase, infliximab demonstrated cost savings compared to etrasimod at list price.

Table 25 presents the results of the 2 scenarios that were considered. At list price, etrasimod was estimated to be consistently cost saving in comparison to vedolizumab and upadacitinib. When considering the 2-year time horizon, at list price etrasimod generated more costs than adalimumab, infliximab, golimumab, tofacitinib and filgotinib. When only the IV route of administration was used for induction and the maintenance phase, infliximab demonstrated cost savings compared to etrasimod at list price.

Table 25 Scenario analysis

Technology	1. 2-year time horizon	2. Flixabi™ (IV) and Entyvio (IV) for initiation and maintenance.
Etrasimod	£22,115 (list) [redacted]	£55,176 (list) [redacted]
Adalimumab	£18,258	£43,268
Infliximab	£22,730	£52,090
Vedolizumab	£30,192	£70,369
Golimumab	£21,945	£52,001
Tofacitinib	£19,514	£46,714
Filgotinib	£21,145	£52,862
Upadacitinib	£23,708	£55,425

Abbreviations: IV, intravenous; [redacted]

B.4.5 Subgroup analysis

None that are relevant. Please note, treatment naïve and treatment experienced are presented in section B.3 however, costs remain unchanged between populations.

B.4.6 Interpretation and conclusions of economic evidence

Etrasimod is a once-daily, S1P anticipated to be commercially available in the UK, with MHRA marketing authorisation [redacted]. This represents an oral, [redacted] treatment option, with proven reduced life interference and treatment burden, for patients suffering from moderately to severely active UC.

In summary, etrasimod has similar efficacy and safety to comparators, demonstrated through NMAs. Etrasimod can displace 1L advanced therapies for moderately to severely active UC as well as 2L+ therapies. It is expected to demonstrated cost-saving from treatment acquisition (including CcTs) and administration costs. Additionally, the budget impact demonstrates these savings (please see the Budget Impact Analysis (BIA) submission).

In addition, etrasimod has demonstrated improved treatment convenience and potential increase in quality of life (QoL) for patients. Demonstrating that there is additional value available to the NHSE not captured as part of this analysis, with the results depicting that etrasimod at list price has lower costs compared to two comparators routinely available on the NHS, [redacted].

The choice of product should continue to be made on an individual basis, after informed consent discussion between the treating physician and the patient, and discussions about the advantages and disadvantages of the products available.

Based on the evidence laid out in this submission, there is a very low decision risk given the [redacted] and limited uncertainty.

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INFLAMMATORY BIOMARKERS IN PATIENTS WITH MODERATELY TO SEVERELY ACTIVE ULCERATIVE COLITIS: QUASAR PHASE 2B INDUCTION RESULTS THROUGH WEEK 12. 2022;10:339.
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Appendix C: Expert nomination form

No experts were nominated by the company for this appraisal.

Appendix D: Checklist of confidential information

Appendix D is provided as a separate file. Filename:

- Appendix D – confidential information checklist & guidance note [ID5091]

Appendix E: Summary of product characteristics (SmPC) and UK public assessment report

E1.1 SmPC

The draft SmPC has been provided as a separate file. Filename:

- Etrasimod STA [ID 5091] Appendix E_SmPC

E.1.2 EPAR

An EPAR for etrasimod in moderately to severely active ulcerative colitis is not yet available.

Appendix F: Identification, selection and synthesis of clinical evidence

F. 1 Methods for reviewing clinical effectiveness

Details of the systematic literature search to identify RCT and non-RCT clinical evidence relevant to the efficacy and safety of etrasimod and other advanced therapies in patients with moderately to severely active UC are described below.

F.1.1 Identification and selection of relevant studies

A systematic literature review was conducted to identify evidence to support the clinical effectiveness and safety of etrasimod and relevant comparators used to treat moderate-to-severe ulcerative colitis. Eligible studies were limited to RCTs of etrasimod, infliximab (and biosimilars), adalimumab (and biosimilars), golimumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, ustekinumab (and biosimilars), mirikizumab, risankizumab, guselkumab and ozanimod, with the same therapies, plus thiopurines, aminosalicylates, corticosteroids or placebo as comparators. The review consisted of a set of searches ran in the relevant databases, on November 15, 2022 and updated April 12, 2023.

The list of comparators included in the systematic review was broader in scope than the decision comparator set relevant to the submission, as it was designed for use in multiple countries and to facilitate updates in the future. Where evidence included in the SLR is not relevant to the current decision problem, it has been clearly documented and then excluded from further consideration in the subsequent sections and evidence synthesis.

F.1.1.1 Search strategy

Systematic searches were conducted in established electronic databases including Medline, Embase, Cochrane Library, and supplemented by hand searching of conference proceedings and other secondary sources, including:

- Conference proceedings (2020 and later):
    - International Organization for the Study of Inflammatory Bowel Diseases (IOIBD)
    - Academy of Managed Care Pharmacy (AMCP annual and Nexus)
    - American College of Gastroenterology (ACG)
    - Advances in Inflammatory Bowel Diseases (AIBD) conference
    - European Crohn’s and Colitis Organization (ECCO)
    - Crohn's & Colitis Congress

- International Society for Pharmacoeconomics and Outcomes Research (ISPOR)
- Digestive Disease Week (DDW)
- United European Gastroenterology (UEG)

- Clinical trial registries
  - NIH trial registry (https://clinicaltrials.gov/ct2/home)
  - EU Clinical Trials Register (https://www.clinicaltrialsregister.eu/)
  - International Clinical Trials Registry Platform (https://www.who.int/clinical-trials-registry-platform/the-ictrp-search-portal)
- Bibliographies from relevant systematic reviews were also cross-checked to identify any additional studies
- Google Scholar

The PICOS approach used for the searches is shown in Table 26. The searches were conducted on November 15, 2022 and updated April 12, 2023 and covered all available records without any time limit. The searches were limited to publications in English. Terms for the database searches are presented in Table 27, Table 28 and **Table 29**.

Table 26 PICOS elements for clinical SLR

Component	Details
Population	Adult patients with moderately to severely active UC
Intervention/ Comparators	Etrasimod, infliximab (and biosimilars), adalimumab (and biosimilars), golimumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, ustekinumab (and biosimilars), mirikizumab, risankizumab, guselkumab, ozanimod
Outcomes	**Clinical efficacy:** Clinical response, clinical remission, symptomatic remission, rectal bleeding, stool frequency, mucosal healing, endoscopic improvement, and corticosteroid-free remission **Safety**: Frequencies and grades of AEs, treatment discontinuations due to adverse events, hospitalization and proportion of patients requiring surgery
Study types	Randomized controlled trials

Abbreviations: AEs: Adverse events; SLR, systematic literature review; UC, Ulcerative colitis.

F.1.1.2 Search terms

Table 27 Medline search strategy

#	Query	Description
1	exp "Colitis, Ulcerative"/	Disease
2	(proctocolitis or proctosigmoiditis or rectocolitis or rectosigmoiditis or proctitis or pancolitis or left-sided colitis or pan-ulcerative colitis).ti,ab,kw.	
3	((ulcer* or gravis) adj3 (colitis* or colorectit* or proctiti*)).ti,ab,kw.	
4	1 or 2 or 3	
5	(Etrasimod or APD334 or GTPL933 or SCHEMBL1919311).ti,ab,kw.	Etrasimod

6	exp Infliximab/	Infliximab
7	(Infliximab or infliximab abda or infliximab axxq or infliximab bdyyb or infliximab qbtx or Infliximab BS).ti,ab,kw.	
8	(Avakine or Inflix or Remicade or Remsima or inflectra or renflexis or Ixifi or Avsola or Zessly or Flammegis or Infimab or revellex or flixabi or baimaibo).ti,ab,kw.	
9	(ABP 710 or "BOW 015" or CT P13 or GP 1111 or "PF 06438179" or TA 650 or b72hh48flu or GTPL5004 or BCD-055 or "STI 002" or "NI 071" or CMAB008 or "TI 002" or sb2 or gp 2018 or bcd055 or "rtpr 015").ti,ab,kw.	
10	6 or 7 or 8 or 9	
11	exp Adalimumab/	Adalimumab
12	(Adalimumab or adalimumab adaz or adalimumab adbm or adalimumab afzb or adalimumab atto or adalimumab bwwd or adalimumab fkjp).ti,ab,kw.	
13	(Amjevita or Amgevita or Solymbic or cyltezo or humira or ABRILADA or Hadlima or Hulio or Hyrimoz or Yusimry or Imraldi or Hefiya or Halimatoz or Idacio or Yuflyma or Qletli or CinnoRA or Kromeyaor Cadalimab or Exemptia or Adfrar or Abrilada or Amsparity or Sulinno or Mabura).ti,ab,kw.	
14	("BCD 057" or BI 695501 or CHS 1420 or D2E7 or GP 2017 or LU 200134 or M 923 o MSB 11022 or ONS 3010 or SB 5 or GTPL4860 or fys6t7f842 or ABP 501 or AVT02 or FKB327 or "PF 06410293" or BCD100 or BAX 923 or "BCD 057" or BAT1406 or CT P17or CHS-1420 or UBP1211 or ZRC3197 or HLX03 or PBP1502 or PF-06410293 or M923 or IBI-303).ti,ab,kw.	
15	11 or 12 or 13 or 14	
16	(Golimumab or Simponi or Simponi Aria or CNTO 148 or HSDB 7852 or UNII 91X1KLU43E).ti,ab,kw.	Golimumab
17	(Vedolizumab or Entyvio or "LDP 02" or "MLN 0002" or "MLN 02" or UNII 9RV78Q2002 or 943609-66-3 or D08083).ti,ab,kw.	Vedolizumab
18	exp Ustekinumab/ or (Stelara or ustekinumab or cnto-1275 or fu77b4u5z0 or L04AC05 or TT 20 or UNII FU77B4U5Z0 or DB05679).ti,ab,kw.	Ustekinumab
19	(CT-P43 or FYB202 or AVT04 or ABP 654 or BAT2206 or BFI-751 or DMB-3115 or NeuLara).ti,ab,kw.	
20	18 or 19	
21	(Xeljanz or Tasocitinib or Tofacitinibum or CP 690550 or CHEMBL221959 or UNII-87LA6FU830 or HSDB 8311).ti,ab,kw.	Tofacitinib
22	(Filgotinib or Jyseleca or "GLPG 0634" or "UNII-3XVL385Q0M" or "1206101-20-3").ti,ab,kw.	Filgotinib
23	(Mirikizumab or "LY 3074828" or GTPL9846 or US9023358 or "UNII-Z7HVY03PHP").ti,ab,kw.	Mirikizumab
24	(Upadacitinib or Rinvoq or ABT 494 or 1310726-60-3 or UNII 4RA0KN46E0 or GTPL 9246).ti,ab,kw.	Upadacitinib
25	(ozanimod or Zeposia or Ozanimod hydrochloride or RPC1063 or RPC-1063 or L04AA38).ti,ab,kw.	Ozanimod
26	(risankizumab or Skyrizi or C000601773 or UNII 90ZX3Q3FR7 or ABBV-066 or L04AC18 or risankizumab-rzaa or BI 655066 or BI-655066).ti,ab,kw.	Risankizumab
27	(guselkumab or Tremfya or CNTO 1959 or CNTO-1959 or L04AC16).ti,ab,kw.	Guselkumab

28	5 or 10 or 15 or 16 or 17 or 20 or 21 or 22 or 23 or 24 or 25 or 26 or 27	Combined all drugs using OR
29	exp controlled clinical trial/	RCTs
30	exp randomized controlled trials/ or exp randomized controlled trial/	
31	(controlled clinical trial$ or randomi?ed controlled trial$).mp.	
32	exp random allocation/ or exp randomization/ or exp random assignment/ or exp random sample/ or exp random sampling/	
33	exp crossover procedure/ or exp cross over studies/ or exp crossover design/ or exp factorial design/	
34	exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/ or exp open study/	
35	or/29-34	
36	(((single$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$ or open label$)).mp.	
37	exp placebos/	
38	(crossover or cross over or (placebo$ and (random$ adj2 allocat$))).mp.	
39	or/36-38	
40	exp Clinical Trial/	
41	clinical trial.pt.	
42	exp Clinical Trials as Topic/	
43	or/40-42	
44	39 and 43	
45	35 or 44	Disease AND Drugs AND RCT
46	4 and 28 and 45	Study type not of interest
47	exp animals/ not exp humans/	
48	(comment or letter or editorial or "case reports").pt.	
49	(case stud$ or case report$).ti.	
50	(address or autobiography or biography or case reports or veterinary trials or veterinary as topic or comment or dictionary or directory or duplicate publication or editorial or festschrift or guideline or historical article or interactive tutorial or interview or lecture or legislation or letter or observational study, veterinary or patient education handout or personal narrative or practice guideline or review or editorial or erratum or letter or note or short survey or comment*).pt.	
51	or/47-50	Final results for Clinical outcomes
52	46 not 51 (limit to English language)	

Table 28 Embase search strategy

#	Query	Description
1	exp ulcerative colitis/	Disease
2	(proctocolitis or proctosigmoiditis or rectocolitis or rectosigmoiditis or proctitis or pancolitis or left-sided colitis or pan-ulcerative colitis).ti,ab,kw.	
3	((ulcer* or gravis) adj3 (colitis* or colorectit* or proctiti*)).ti,ab,kw.	

4	1 or 2 or 3	
5	exp etrasimod/	Etrasimod
6	(Etrasimod or APD334 or GTPL933 or SCHEMBL1919311).ti,ab,kw.	
7	5 or 6	
8	exp infliximab/	Infliximab
9	(Infliximab or infliximab abda or infliximab axxq or infliximab bdyyb or infliximab qbtx or Infliximab BS).ti,ab,kw.	
10	(Avakine or Inflix or Remicade or Remsima or inflectra or renflexis or Ixifi or Avsola or Zessly or Flammegis or Infimab or revellex or flixabi or baimaibo).ti,ab,kw.	
11	(ABP 710 or "BOW 015" or CT P13 or GP 1111 or "PF 06438179" or TA 650 or b72hh48flu or GTPL5004 or BCD-055 or "STI 002" or "NI 071" or CMAB008 or "TI 002" or sb2 or gp 2018 or bcd055 or "rtpr 015").ti,ab,kw.	
12	8 or 9 or 10 or 11	
13	exp adalimumab/	Adalimumab
14	(Adalimumab or adalimumab adaz or adalimumab adbm or adalimumab afzb or adalimumab atto or adalimumab bwwd or adalimumab fkjp).ti,ab,kw.	
15	(Amjevita or Amgevita or Solymbic or cyltezo or humira or Hadlima or Hulio or Hyrimoz or Yusimry or Imraldi or Hefiya or Halimatoz or Idacio or Yuflyma or Qletli or CinnoRA or Kromeyaor Cadalimab or Exemptia or Adfrar or Abrilada or Amsparity or Sulinno or Mabura).ti,ab,kw.	
16	("BCD 057" or BI 695501 or CHS 1420 or D2E7 or GP 2017 or LU 200134 or M 923 o MSB 11022 or ONS 3010 or SB 5 or GTPL4860 or fys6t7f842 or ABP 501 or AVT02 or FKB327 or "PF 06410293" or BCD100 or BAX 923 or "BCD 057" or BAT1406 or CT P17or CHS-1420 or UBP1211 or ZRC3197 or HLX03 or PBP1502 or PF-06410293 or M923 or IBI-303).ti,ab,kw.	
17	13 or 14 or 15 or 16	
18	exp golimumab/	Golimumab
19	(Golimumab or Simponi or Simponi Aria or CNTO 148 or HSDB 7852 or UNII 91X1KLU43E).ti,ab,kw.	
20	18 or 19	
21	exp vedolizumab/	Vedolizumab
22	(Vedolizumab or Entyvio or "LDP 02" or "MLN 0002" or "MLN 02" or UNII 9RV78Q2002 or 943609-66-3 or D08083).ti,ab,kw.	
23	21 or 22	
24	exp ustekinumab/	Ustekinumab
25	(Stelara or ustekinumab or cnto-1275 or fu77b4u5z0 or L04AC05 or TT 20 or UNII FU77B4U5Z0 or DB05679).ti,ab,kw.	
26	(CT-P43 or FYB202 or AVT04 or ABP 654 or BAT2206 or BFI-751 or DMB-3115 or NeuLara).ti,ab,kw.	
27	24 or 25 or 26	
28	exp tofacitinib/	Tofacitinib
29	(Xeljanz or Tasocitinib or Tofacitinibum or CP 690550 or CHEMBL221959 or UNII-87LA6FU830 or HSDB 8311).ti,ab,kw.	
30	28 or 29	
31	exp filgotinib/	Filgotinib

32	(Filgotinib or Jyseleca or "GLPG 0634" or "UNII-3XVL385Q0M" or "1206101-20-3").ti,ab,kw.	
33	31 or 32	
34	exp mirikizumab/	Mirikizumab
35	(Mirikizumab or "LY 3074828" or GTPL9846 or US9023358 or "UNII-Z7HVY03PHP").ti,ab,kw.	
36	34 or 35	
37	exp upadacitinib/	Upadacitinib
38	(Upadacitinib or Rinvoq or ABT 494 or 1310726-60-3 or UNII 4RA0KN46E0 or GTPL 9246).ti,ab,kw.	
39	37 or 38	
40	exp ozanimod/	Ozanimod
41	(Zeposia or Ozanimod hydrochloride or RPC1063 or RPC-1063 or L04AA38).ti,ab,kw.	
42	40 or 41	
43	exp risankizumab/	Risankizumab
44	(Skyrizi or C000601773 or UNII 90ZX3Q3FR7 or ABBV-066 or L04AC18 or risankizumab-rzaa or BI 655066 or BI-655066).ti,ab,kw.	
45	43 or 44	
46	exp guselkumab/	Guselkumab
47	(Tremfya or CNTO 1959 or CNTO-1959 or L04AC16).ti,ab,kw.	
48	46 or 47	
49	7 or 12 or 17 or 20 or 23 or 27 or 30 or 33 or 36 or 39 or 42 or 45 or 48	Combined all drugs using OR
50	exp controlled clinical trial/	RCTs
51	exp randomized controlled trials/ or exp randomized controlled trial/	
52	(controlled clinical trial* or randomi?ed controlled trial*).mp.	
53	exp random allocation/ or exp randomization/ or exp random assignment/ or exp random sample/ or exp random sampling/	
54	exp crossover procedure/ or exp cross over studies/ or exp crossover design/ or exp factorial design/	
55	exp double blind procedure/ or exp double blind method/ or exp double blind studies/ or exp single blind procedure/ or exp single blind method/ or exp single blind studies/ or exp open study/	
56	50 or 51 or 52 or 53 or 54 or 55	
57	(((single$ or doubl$ or trebl$ or tripl$) adj2 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$ or open label$)).mp.	
58	exp placebos/	
59	(crossover or cross over or (placebo$ and (random$ adj2 allocat$))).mp.	
60	57 or 58 or 59	
61	exp Clinical Trial/	
62	exp Clinical Trials as Topic/	
63	61 or 62	

64	60 and 63	
65	56 or 64	
66	4 and 49 and 65	Disease AND Drugs AND RCT
67	exp animals/ not exp humans/	Study type not of interest
68	(comment or letter or editorial or "case reports").pt.	
69	(case stud$ or case report$).ti.	
70	(address or autobiography or biography or case reports or veterinary trials or veterinary as topic or comment or dictionary or directory or duplicate publication or editorial or festschrift or guideline or historical article or interactive tutorial or interview or lecture or legislation or letter or observational study, veterinary or patient education handout or personal narrative or practice guideline or review or editorial or erratum or letter or note or short survey or comment*).pt.	
71	67 or 68 or 69 or 70	
72	66 not 71 (limit to English language)	Final results for Clinical outcomes

Table 29 Cochrane search strategy

#	Query	Description
1	[mh "Colitis, Ulcerative"]	Disease
2	(proctocolitis or proctosigmoiditis or rectocolitis or rectosigmoiditis or proctitis or pancolitis or left-sided colitis or pan-ulcerative colitis):ti,ab,kw (Word variations have been searched)	
3	((ulcer* or gravis) NEAR/3 (colitis* or colorectit* or proctiti*)):ti,ab,kw (Word variations have been searched)	
4	(or #1-#3)	
5	(Etrasimod or APD334 or GTPL933 or SCHEMBL1919311):ti,ab,kw (Word variations have been searched)	Etrasimod
6	[mh "Infliximab"]	Infliximab
7	(Infliximab or infliximab abda or infliximab axxq or infliximab bdyyb or infliximab qbtx or Infliximab BS):ti,ab,kw (Word variations have been searched)	
8	(Avakine or Inflix or Remicade or Remsima or inflectra or renflexis or Ixifi or Avsola or Zessly or Flammegis or Infimab or revellex or flixabi or baimaibo):ti,ab,kw (Word variations have been searched)	
9	(ABP 710 or "BOW 015" or CT P13 or GP 1111 or "PF 06438179" or TA 650 or b72hh48flu or GTPL5004 or BCD-055 or "STI 002" or "NI 071" or CMAB008 or "TI 002" or sb2 or gp 2018 or bcd055 or "rtpr 015"):ti,ab,kw (Word variations have been searched)	
10	(or #6-#9}	
11	[mh "Adalimumab"]	Adalimumab

12	(Adalimumab or adalimumab adaz or adalimumab adbm or adalimumab afzb or adalimumab atto or adalimumab bwwd or adalimumab fkjp):ti,ab,kw (Word variations have been searched)	
13	(Amjevita or Amgevita or Solymbic or cyltezo or humira or Hadlima or Hulio or Hyrimoz or Yusimry or Imraldi or Hefiya or Halimatoz or Idacio or Yuflyma or Qletli or CinnoRA or Kromeyaor Cadalimab or Exemptia or Adfrar or Abrilada or Amsparity or Sulinno or Mabura):ti,ab,kw (Word variations have been searched)	
14	("BCD 057" or BI 695501 or CHS 1420 or D2E7 or GP 2017 or LU 200134 or M 923 o MSB 11022 or ONS 3010 or SB 5 or GTPL4860 or fys6t7f842 or ABP 501 or AVT02 or FKB327 or "PF 06410293" or BCD100 or BAX 923 or "BCD 057" or BAT1406 or CT P17or CHS-1420 or UBP1211 or ZRC3197 or HLX03 or PBP1502 or PF-06410293 or M923 or IBI-303):ti,ab,kw (Word variations have been searched)	
15	(or #11-#14)	
16	(Golimumab or Simponi or Simponi Aria or CNTO 148 or HSDB 7852 or UNII 91X1KLU43E):ti,ab,kw (Word variations have been searched)	Golimumab
17	(Vedolizumab or Entyvio or "LDP 02" or "MLN 0002" or "MLN 02" or UNII 9RV78Q2002 or 943609 66 3 or D08083):ti,ab,kw (Word variations have been searched)	Vedolizumab
18	[mh "Ustekinumab"]	Ustekinumab
19	(Stelara or ustekinumab or cnto-1275 or fu77b4u5z0 or L04AC05 or TT 20 or UNII FU77B4U5Z0 or DB05679):ti,ab,kw (Word variations have been searched)	
20	(CT-P43 or FYB202 or AVT04 or ABP 654 or BAT2206 or BFI-751 or DMB-3115 or NeuLara):ti,ab,kw	
21	(or #18-#20)	
22	(tofacitinib or Xeljanz or Tasocitinib or Tofacitinibum or CP 690550 or CHEMBL221959 or UNII-87LA6FU830 or HSDB 8311):ti,ab,kw (Word variations have been searched)	Tofacitinib
23	(Filgotinib or Jyseleca or "GLPG 0634" or "UNII-3XVL385Q0M" or "1206101-20-3"):ti,ab,kw (Word variations have been searched)	Filgotinib
24	(Mirikizumab or "LY 3074828" or GTPL9846 or US9023358 or "UNII-Z7HVY03PHP"):ti,ab,kw (Word variations have been searched)	Mirikizumab
25	(Upadacitinib or Rinvoq or ABT 494 or 1310726 60 3 or UNII 4RA0KN46E0 or GTPL 9246):ti,ab,kw (Word variations have been searched)	Upadacitinib
26	(ozanimod or Zeposia or Ozanimod hydrochloride or RPC1063 or RPC 1063 or L04AA38):ti,ab,kw (Word variations have been searched)	Ozanimod
27	(risankizumab or Skyrizi or C000601773 or UNII 90ZX3Q3FR7 or ABBV 066 or L04AC18 or risankizumab rzaa or BI 655066 or BI-655066):ti,ab,kw (Word variations have been searched)	Risankizumab
28	(guselkumab or Tremfya or CNTO 1959 or CNTO 1959 or L04AC16):ti,ab,kw (Word variations have been searched)	Guselkumab
29	#5 OR #10 OR #15 OR #16 OR #17 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	Combined all drugs using OR
30	[mh "Controlled Clinical Trial"] OR [mh "Randomized Controlled Trial"]	RCTs
31	(controlled clinical trial* or randomi?ed controlled trial*) (Word variations have been searched)	
32	[mh "Random Allocation"]	

33	[mh "Cross-Over Studies"]	
34	[mh "Double Blind Method"] OR [mh "Single Blind Method"]	
35	(or #145-#34)	
36	(((single$ or doubl$ or trebl$ or tripl$) NEAR/2 (blind$ or mask$ or dummy)) or (singleblind$ or doubleblind$ or trebleblind$ or open label$))	
37	[mh "Placebos"]	
38	(crossover or cross over or (placebo$ and (random$ NEAR/2 allocat$))) (Word variations have been searched)	
39		
40	[mh "Clinical Trial"]	
41	[mh "Clinical Trials as Topic"]	
42	#40 OR #41	
43	#39 AND #42	
44	#35 or #43	
45	#4 AND #29 AND #44	Disease AND Drugs AND RCT
46	[mh "animals"] NOT [mh "humans"]	Study type not of interest
47	(comment or letter or editorial or "case reports"):pt	
48	(case stud$ or case report$):ti	
49	(address or autobiography or biography or case reports or veterinary trials or veterinary as topic or comment or dictionary or directory or duplicate publication or editorial or festschrift or guideline or historical article or interactive tutorial or interview or lecture or legislation or letter or observational study, veterinary or patient education handout or personal narrative or practice guideline or review or editorial or erratum or letter or note or short survey or comment*):pt	
50	#46 OR #47 OR #48 OR #49	
51	#45 NOT #50	Final results for Clinical outcomes

F.1.1.3 Study selection

The selection process was performed in two phases. First, the title and abstracts of the references identified from the electronic database search were screened in a double-blind manner by two independent reviewers. Any disputes between the inclusion and exclusion decisions were resolved by discussion, or where necessary, a third reviewer. The included titles and abstracts were then further assessed as full texts, to generate an overall inclusion and exclusion list.

For both phases, the researchers determined the eligibility according to prescribed inclusion and exclusion criteria shown in Table 30.

Table 30 Inclusion and exclusion criteria

Category	Inclusion criteria	Exclusion criteria
Population	Studies among adult patients with moderately to severely active UC	Non-human studies Studies with a mixed population (mild to moderate, mild to severe) were excluded if relevant data is not reported separately for the patients with moderately to severely active UC
Intervention/ comparators	Etrasimod, infliximab (and biosimilars), adalimumab (and biosimilars), golimumab, vedolizumab, tofacitinib, filgotinib, upadacitinib, ustekinumab (and biosimilars), mirikizumab, risankizumab, guselkumab, ozanimod	Any study which does not include any treatment of interest as one of the arms in the study
Outcomes	Studies reporting any clinical efficacy and safety outcomes including the following: • **Clinical efficacy:** Clinical response, clinical remission, symptomatic remission, corticosteroid-free remission, mucosal healing, endoscopic improvement, stool frequency and rectal bleeding • **Safety:** Frequencies and grades of AEs, treatment discontinuations due to adverse events, proportion of patients requiring surgery, hospitalizations	Studies not reporting any of the relevant outcomes
Study types	Randomized controlled trials	Non-randomized clinical trials Observational studies and economic studies Case studies/reports, case series, protocols, validation studies Comments, editorials, magazine, letter to editor, expert opinions, books, errata Systematic literature reviews and meta-analyses were excluded but earmarked for bibliographic check

F.1.1.4 Data extraction and critical appraisal

Data from the included records were extracted by two reviewers independently. Once extraction was completed, the data collected independently by the two reviewers were compared and collated. Any discrepancies were resolved by discussion between the two reviewers and if necessary, with the help of the intermediation of a third reviewer.

The following information was extracted from each study: (a) general information (author, title, citation, country, and study population); (b) study characteristics (study design, NCT number, sample size, study duration, primary and secondary endpoints); (c) demographic details (age,

gender, race/ethnicity, disease duration and prior advanced therapies); intervention (dosage, route of administration and duration of treatment); and (d) outcome data (efficacy and safety).

The NICE checklist was used to assess the quality of the included studies by two independent reviewers, and differences were resolved in discussion with a third reviewer.

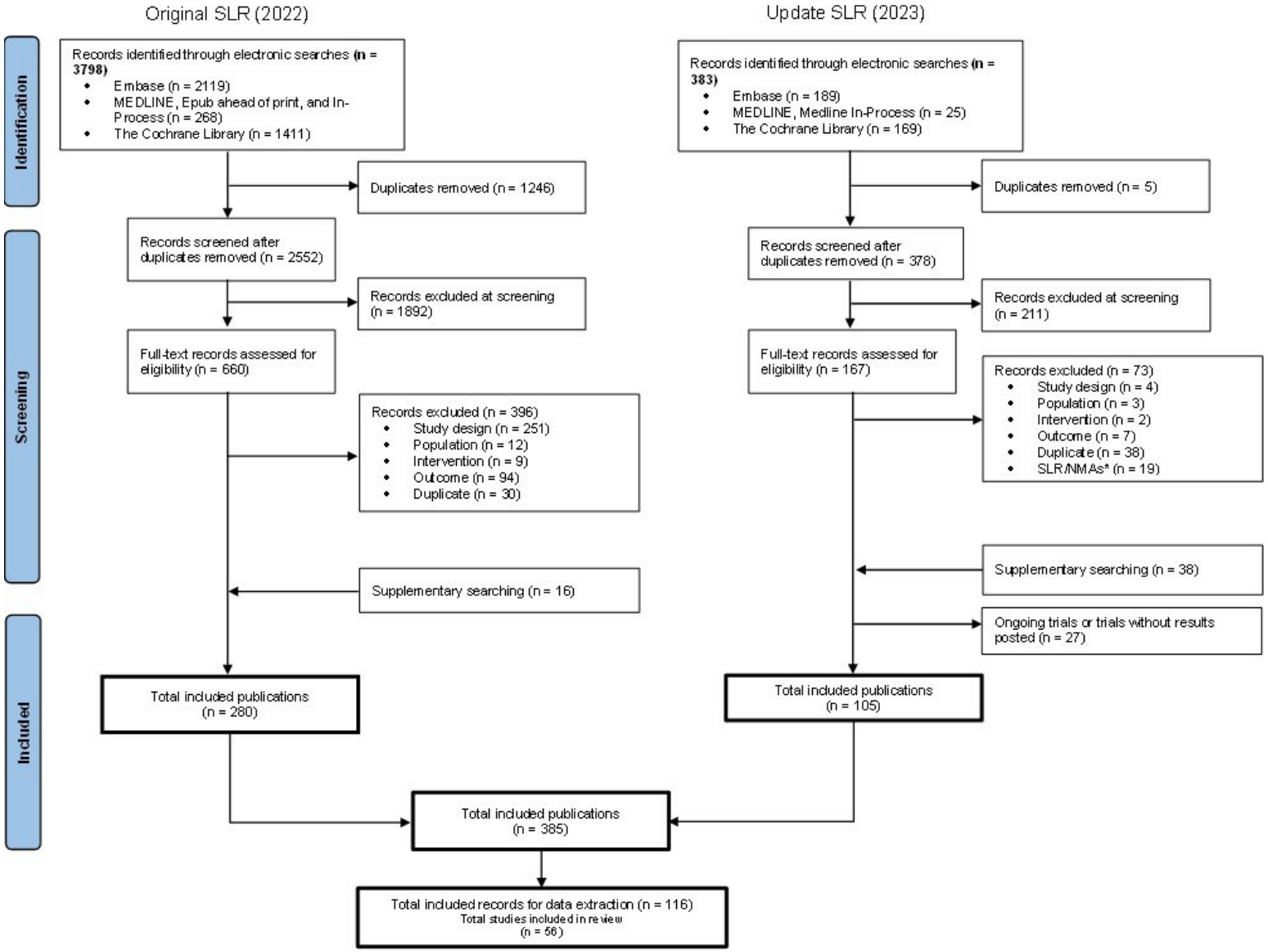
F.1.2. Results

F.1.2.1 Included and excluded studies

Across the original search on 15 November 2022 and the update on 12 April 2023, a combined total of 4,181 records were retrieved from electronic databases of which 2,930 records were screened for eligibility after removal of duplicates. Following title and abstract screening, 827 full texts were reviewed and 469 were excluded. Fifty-four records were identified through supplementary searching. The final number of included publications was 385, of which 116 were extracted, describing 56 unique studies. The PRISMA flow diagram is shown in **Figure 11**.

A total 56 RCTs were identified for 12 different active interventions. The SLR identified 19 trials for infliximab, 7 for vedolizumab, 8 for adalimumab, 6 for tofacitinib and 5 for golimumab, 3 each for etrasimod and mirikizumab, 2 each for ozanimod, upadacitinib and guselkumab, and one each for ustekinumab and filgotinib. No records reporting efficacy or safety data were identified for risankizumab. The included RCTs are shown in Table 31.

Figure 11: PRISMA flow diagram



*Publications reporting SLRs and NMAs were used for bibliographic checks, then excluded.

Table 31 List of trials included in SLR and considered for NMA

Intervention	# Records	# Studies	Trials (records)
Infliximab*[35, 57-59, 80-96]	21	19	ACT 1 (Rutgeerts 2005, Sandborn 2009) ACT 2 (Rutgeerts 2005, Sandborn 2009) Jiang 2015 Kobayashi 2016 Probert 2003 UC SUCCESS (Panaccione 2014) NCT01551290 (CSR, REMICADEUCO3001) MUNIX (NCT00984568) Sands 2001 Armuzzi 2004 Ochsenkuhn 2004 Järnerot 2005 Laharie 2012 Vande Casteele 2015 Silva 2017 GARDENIA (Danese 2020) Kobayashi 2021 Schreiber 2021 (Schreiber 2021, D'Haens 2023) LIBERTY-UC (Sands 2023, NCT04205643)
Vedolizumab*[64-66, 69, 97-105]	13	7	GEMINI 1 (Feagan 2013, Feagan 2017, Yajnik 2017) VISIBLE 1 (Sandborn 2020, Kobayashi 2021, NCT02611830) Motoya 2019 VARSITY (Sands 2019, Peyrin-Biroulet 2021, Loftus 2020) Parikh 2012 Feagan 2005 ENTERPRET (Dosing 2022)
Adalimumab*[53-56, 64, 90, 101, 106, 107]	10	8	ULTRA 1 (Reinisch 2011) ULTRA 2 (Sandborn 2012) Suzuki 2014 SERENE UC (Panés 2022, Tanida 2020) VARSITY (Sands 2019, Peyrin-Biroulet 2021, Loftus 2020) Silva 2017 HIBISCUS I (Rubin 2022) HIBISCUS II (Rubin 2022)
Tofacitinib[52, 108-121]	15	6	OCTAVE Induction 1 (Sandborn 2017, D'Haens 2016, Dubinsky 2017, Sandborn 2022, Suzuki 2019, Dubinsky 2023, Targownick 2022, Lichtenstein 2021, Loftus 2022, Sandborn 2022, Sandborn 2022) OCTAVE Induction 2 (Sandborn 2017, D'Haens 2016, Dubinsky 2017, Sandborn 2022, Dubinsky 2023, Targownick 2022, Lichtenstein 2021, Loftus 2022, Sandborn 2022, Sandborn 2022)

			OCTAVE Sustain (Sandborn 2017, Dubinsky 2017, Sandborn 2022, Suzuki 2019, Targownick 2022, Lichtenstein 2021, Loftus 2022, Sandborn 2022, Sandborn 2022) RIVETING (Vermeire 2021, NCT03281304) Sandborn 2012 ORCHID (Singh 2023)
Golimumab*[60, 67, 68, 122-124]	6	5	PURSUIT-IV (Rutgeerts 2015) PURSUIT-SC (Sandborn 2014) PURSUIT-M (Sandborn 2014) PURSUIT-J (Hibi 2017) VEGA (Sands 2022, Feagan 2023)
Etrasimod[43, 45-47, 125-130]	10	3	ELEVATE UC 12 (CSR1, Feagan 2022, Sandborn 2023, Armuzzi 2023, Vermeire 2023) ELEVATE UC 52 (CSR2, Feagan 2022, Sandborn 2023, Armuzzi 2023, Sands 2023, Vermeire 2023, NCT03945188) OASIS (Sandborn 2020, Peyrin-Biroulet 2019, Vermeire 2023)
Ozanimod[51, 131-138]	10	2	TRUE NORTH (Sandborn 2021, Sands 2021, Subrata 2020, Harris 2022, Sands 2023, CADTH) TOUCHSTONE (Sandborn 2016, Feagan 2019, Feagan 2018, Sandborn 2021)
Upadacitinib[48, 61, 62, 139-147]	11	2	U-ACHIEVE phase 2b (Sandborn 2020) U-ACHIEVE phase 3 (Danese 2022, Danese 2021, Rubin 2021, D'Haens 2019, Panaccione 2022, Dubinksy 2022, D'Haens 2023, Vermeire 2023, NICE) U-ACCOMPLISH (Danese 2022, Rubin 2021, NCT03653026, Dubinksy 2022, D'Haens 2023, Vermeire 2023, NICE)
Filgotinib[50, 148-154]	8	1	SELECTION (Feagan 2021, Vermeire 2021, Peyrin-Biroulet 2021, Loftus 2022, Danese 2023, Feagan 2021, Dotan 2023, Schreiber 2023)
Ustekinumab[63, 155-157]	4	1	UNIFI (Sands 2019, Hisamatsu 2021, Abreu 2022, NCT02407236)
Mirikizumab[158-167]	10	3	LUCENT 1 (NCT03518086, D'Haens 2022, Panaccione 2023, Navabi 2023, Sands 2022, Sands 2022, Travis 2022) LUCENT 2 (Dubinsky 2022, NCT03524092, Panaccione 2023, Navabi 2023, Sands 2022, Sands 2022, Travis 2022) I6T-MC-AMAC (Sandborn 2020)
Guselkumab*[123, 124, 168, 169]	4	2	QUASAR (Dignass 2022, Peyrin-Biroulet 2022) VEGA (Sands 2022, Feagan 2023)
Total	**116**	**56**	

Note: VARSITY, VEGA and Silva 2017 included more than one advanced treatment

F.1.2.2 Selection of evidence relevant to the scope for the network meta-analysis

The scope of the clinical SLR was broader than the scope for the evidence synthesis. As a result, we performed an initial filtering of studies from the clinical SLR based on some key

criteria (outlined below) to exclude studies from consideration for evidence synthesis. Studies from the clinical SLR were excluded if:

- the study compared treatments that were out of scope (mirikizumab, risankizumab, and guselkumab)
- if the treatment comparison in the study is not relevant for evidence synthesis (e.g., a comparison between a treatment of interest and a treatment not of interest)
- if the study did not report one of the following outcomes of interest (clinical response [induction/maintenance] or clinical remission [induction/maintenance] as measured by the Mayo score, serious infections)

In addition, only EMA-licensed doses of therapies specified in the scope were included (Table 32). Where the drug license allows for dose increases during the maintenance phase, both the recommended doses and higher dose were included where they had been assessed in the clinical trials. Different doses and/or dosing regimens were treated as unique comparators.

Table 32 Summary of EMA licensed dose range for each comparator

Treatment	EMA licensed dose range (adult population)	
	Induction	Maintenance
Filgotinib	100 mg[a] – 200 mg (q.d.)	
Tofacitinib	10 mg (b.i.d)	5 mg – 10 mg (b.i.d)
Vedolizumab	300 mg IV[b]	300 mg IV or 108 mg SC[b]
Ustekinumab	260 mg – 520 mg[b, c] (≈ 6 mg/kg)[b]	
Upadacitinib	45 mg (q.d.)	15 mg – 30 mg (q.d.)
Ozanimod	0.23 mg – 0.92 mg (q.d.)	0.92 mg (q.d.)
Adalimumab	80 mg – 160 mg[b,c]	40 mg – 80 mg[b]
Golimumab	100 mg – 200 mg[b, d]	50 mg – 100 mg[b, d]
Infliximab	5 mg/kg[b,d]	

[a] those with renal impairment; [b] not daily, given on specific weeks; [c] 80 mg is child/adolescent initial induction dose; [d] based-on body weight of patient at the time of dosing
SC, subcutaneous injection; IV, intravenous; q.d., daily; b.i.d, twice a day

After applying the additional selection criteria above, 25 studies were excluded from further consideration. Also, at least one trial arm was excluded from 13 included studies. The list of excluded studies and excluded trial arms are presented in Table 33 with reasons. Subsequent sections focus on the relevant trial arms of the 31 studies that met the inclusion criteria for the evidence synthesis.

Table 33 Studies or study arms excluded from further consideration in evidence synthesis with rationale

Study name	Reason for exclusion from NMA
Intervention out of scope or not licensed – whole study excluded	
QUASAR/ NCT04033445	Intervention (Guselkumab) out of scope
VEGA/ NCT03662542	Intervention (Guselkumab) out of scope
LUCENT-1/ NCT03518086	Intervention (Mirikizumab) out of scope
LUCENT-2/ NCT03524092	Intervention (Mirikizumab) out of scope
I6T-MC-AMAC/ NCT02589665	Intervention (Mirikizumab) out of scope
Parikh 2012/ NCT01177228	Intervention (vedolizumab weight-based dosing) inconsistent with dose stipulated in EMA daily licensed dose range and efficacy outcomes reported on partial Mayo score
Feagan 2005/ NA	Interventions (vedolizumab weight-based dosing) inconsistent with dose stipulated in EMA daily licensed dose range
PURSUIT-IV/ NCT00488774	Interventions (golimumab weight-based dosing) inconsistent with dose stipulated in EMA daily licensed dose range
Silva 2017/ NA	No baseline characteristics or intervention dosages reported and efficacy outcomes based on Mayo score were defined in a way that was inconsistent with other studies
SERENE UC/ NCT02065622	Intervention (higher induction regimen) inconsistent with dose stipulated in EMA licensed dose range therefore
Comparison not of interest – whole study excluded	
Schreiber 2021/ NCT02883452	Treatment comparison (sub-cutaneous vs intravenous biosimilar infliximab) not of interest for evidence synthesis and efficacy outcomes reported on the partial Mayo scale
Ochsenkuhn 2004/ NA	Treatment comparison (infliximab vs high-dose prednisolone) not of interest for evidence synthesis and efficacy outcomes reported on the modified Truelove and Witts activity score
Armuzzi 2004/ NA	Treatment comparison (infliximab vs methylprednisolone) not of interest for evidence synthesis and efficacy outcomes reported on the Disease Activity Index score
HAYABUSA/ NA	Treatment comparison (continuation or discontinuation of infliximab) not of interest for evidence synthesis and patient population included patients already in clinical remission
UC SUCCESS/ NCT00537316	Treatment comparison (infliximab vs azathioprine vs infliximab+azathioprine) not of interest for evidence synthesis and efficacy outcomes reported on partial Mayo scale
Laharie 2012/ NCT00542152	Treatment comparison (infliximab vs ciclosporin) not of interest for evidence synthesis and efficacy outcomes reported on the Lichtiger score among patients experiencing an acute flare
MUNIX/ NCT00984568	Treatment comparison (infliximab vs step-up strategy) not of interest for evidence synthesis
Vande Casteele 2015/ Eu2011-002061-38	Treatment comparison (infliximab guided by clinical features vs target trough concentration) not of interest for evidence synthesis and efficacy outcomes reported on Harvey-Bradshaw index and partial Mayo score

Study name	Reason for exclusion from NMA
RIVETING/ NCT03281304	Treatment comparison (maintenance vs reduction of tofacitinib dose) not of interest for evidence synthesis and patient population included patients already in clinical remission
ENTERPRET/ NCT03029143	Treatment comparison (dose-optimisation vs standard dosing vedolizumab) not of interest for evidence synthesis and patient population included patients who were non-responders with high vedolizumab clearance
GARDENIA/ NCT02136069	Treatment comparison (etrolizumab versus infliximab) not of interest for evidence synthesis
ORCHID/CTRI/2021/10/037641	Treatment comparison (tofacitinib versus corticosteroids) not of interest for evidence synthesis
Population and/or outcome not of interest – whole study excluded	
Sands 2001/ NA	Small sample (n=11); patient population included patients with severe, active UC; efficacy outcomes reported on the Truelove and Witts score at 2 weeks
Järnerot 2005/ NA	Efficacy outcomes reported on the Seo index and patient population included patients with an acute severe or moderately severe attack of UC
Probert 2003	Efficacy outcomes reported on the ulcerative colitis symptom Score (UCSS) index
Intervention out of scope or not licensed – treatment arm excluded	
OASIS/ NCT02447302	The 1 mg dose of etrasimod is not in EMA daily licensed dose range
TOUCHSTONE/ NCT01647516	The 0.5 mg dose of ozanimod is not in EMA daily licensed dose range
Sandborn 2012/ NCT00787202	The 0.5mg, 3mg and 15mg doses of tofacitinib are not in EMA daily licensed dose range
OCTAVE Induction 1/ NCT01465763	The 15mg dose of tofacitinib is not in EMA daily licensed dose range
OCTAVE Induction 2/ NCT01458951	The 15mg dose of tofacitinib is not in EMA daily licensed dose range
PURSUIT-SC/ NCT00487539	The 400 mg dose in the 400/200 mg golimumab arm is not in EMA daily licensed dose range, similarly, 50 mg is not in EMA daily licensed dose range for induction
U-ACHIEVE-Phase 2b/ NCT02819635	The 7.5 mg, 15mg and 30mg doses of upadacitinib are not in EMA daily licensed dose range for induction
UNIFI/ NCT02407236	The 130 mg dose of ustekinumab is not in EMA daily licensed dose range
HIBISCUS I/ NCT02163759	The etrolizumab arm of the trial out of scope
HIBISCUS II/ NCT02171429	The etrolizumab arm of the trial out of scope
ACT-1/ NCT00036439	The 10 mg/kg dose of infliximab is not in EMA daily licensed dose range
ACT-2/ NCT00096655	The 10 mg/kg dose of infliximab is not in EMA daily licensed dose range
Jiang 2015/ NA	The 3.5 mg/kg dose of infliximab is not in EMA daily licensed dose range

F.1.2.3 Summary of study and population characteristics

F.1.2.3.1 Study characteristics

Table 34 provides the details of the various trials. Most of the RCTs were placebo-controlled, with the exception of VARSITY, which compared adalimumab and vedolizumab.[64, 101, 102] Most trials were double-blinded. VISIBLE 1,[69] PURSUIT-J,[68] TRUE NORTH,[51] GEMINI 1[65] and Motoya 2019[66] all included either an open-label cohort or an open-label induction period. Most of the trials identified in the SLR were in phase 2 or phase 3.

The trials differed in terms of the definition used to define moderate-to-severe ulcerative colitis. Most of the earlier trials considered total Mayo score of 6-12 to define moderate-to-severe ulcerative colitis. Some of the recent trials, including those evaluating etrasimod and upadacitinib, considered the modified Mayo score criteria to define moderate-to-severe ulcerative colitis.

The 31 included trials represented 39 unique randomized sub-studies involving, induction, maintenance or both phases. Eighteen sub-studies evaluated only the induction phase of treatment. Ten trials evaluated both induction and maintenance phases of treatment. Sixteen sub-studies evaluated only the maintenance phase.

Of the trials that included an induction period, the length of these induction periods generally varied between 6 and 12 weeks. VARSITY[64] had a 14-week induction period. Duration of maintenance periods in the trials were mostly in the range of 38-52. Some studies however had shorter maintenance periods, namely ACT-2[35] and the studies reported by Jiang 2015[57] and Kobayashi 2016, which had maintenance durations of 22 weeks; NCT01551290[59], which had a maintenance duration of 18 weeks; and TOUCHSTONE[136], which had a duration of 24 weeks. The maintenance phase NMA focused on outcomes reported at or around one year; therefore, these shorter-term studies were excluded from the maintenance phase analyses and only induction phase outcomes were considered.

The trials involving a maintenance phase followed either a treat-through (TT) or a randomized responder (RR) design. The TT trial design is where patients continue receiving treatment according to the initial randomization during the induction phase, irrespective of whether a response was achieved at the end of the pre-specified induction period. In the RR trial design, only patients achieving a response during a lead-in period of induction are rerandomized for the maintenance phase. Of the 22 sub-studies involving a maintenance phase of around 1 year, six were TT while eleven followed a RR design.

Table 34 Summary of included studies

Trial name	Sub-study details	Phase	Mayo Score	Induction/ Maint	Maint design	Location	N	Arms	Study duration	Included in NMA	
										Resp/ Rem	SInf
ELEVATE UC 12 (NCT03996369) [47]	ELEVATE UC 12	Ph 3	MMS 4-9	Induction	NA	Multi-national	354	ETR 2 mg PBO	12	Y	Y
ELEVATE UC 52 (NCT03945188) [47]	ELEVATE UC 52	Ph 3	MMS 4-9	Both	TT		433	ETR 2 mg PBO	52(12;40)	Y	N[a]
OASIS (NCT02447302)[43]	OASIS	Ph 2	MMS 4-9	Induction	NA	Multi-national	156	ETR 2 mg PBO	12	N[b]	N[a]
TOUCHSTONE (NCT01647516)[136]	TOUCHSTONE	Ph 2	TMS 6-12	Both	TT	Multi-national	197	OZA 1 mg PBO	32(8;24)	N[b]	N[a]
TRUE NORTH (NCT02435992)[51]	TRUE NORTH - Ind.	Ph 3	TMS 6-12	Induction	NA	Multi-national	645	OZA 1 mg PBO	10	Y	Y
	TRUE NORTH - Maint.			Maint	RR		457	OZA 1 mg PBO	42	Y	NA
U-ACHIEVE (NCT02819635)[61] [62]	U-ACHIEVE - Ph 2	Ph 2b	MMS 5-9	Induction	NA	Multi-national	Part 1 (N=250), Part 2 (N=132)	UPA 45 mg PBO	8	N[b]	Y
	U-ACHIEVE - Ph 3 - Ind.	Ph 3	MMS 5-9	Induction	NA	Multi-national	474; 473;473	UPA 45 mg PBO	8	Y	Y
	U-ACHIEVE - Ph 3 - Maint.	Ph 3		Maint	RR	Multi-national	451	UPA 30 mg UPA 15 mg PBO	52	Y	NA
U-ACCOMPLISH (NCT03653026) [62]	U-ACCOMPLISH	Ph 3	MMS 5-9	Induction	NA	Multi-national	522; 521; 515	UPA 45 mg PBO	8	Y	Y
SELECTION (NCT02914522)[50]	SELECTION - Ind.	Ph 2b/3	TMS 6-12	Induction	NA	Multi-national	1348 A: 659; B: 689	FIL 200 mg FIL 100 mg PBO	10	Y	Y
	SELECTION - Maint.			Maint	RR		571; 558; 571	FIL 200 mg FIL 100 mg PBO	48	Y	NA
OCTAVE Ind 1 (NCT01465763)[52]	OCTAVE Ind. 1	Ph 3	TMS 6-12	Induction	NA	Multi-national	614; 598	TOF 10 mg PBO	8	Y	Y
OCTAVE Ind 2 (NCT01458951) [52]	OCTAVE Ind. 2			Induction	NA		547;541	TOF 10 mg PBO	8	Y	Y
OCTAVE Sustain (NCT01458574) [52]	OCTAVE Sustain			Maint	RR		593; 396; 395	TOF 10 mg TOF 5 mg PBO	52	Y	NA

Trial name	Sub-study details	Phase	Mayo Score	Induction/ Maint	Maint design	Location	N	Arms	Study duration	Included in NMA	
										Resp/ Rem	SInf
Sandborn 2012 (NCT00787202)[120]	Sandborn 2012	Ph 2	TMS 6-12	Induction	NA	Multi-national	195;194	TOF 10 mg PBO	8	N[b]	N[a]
UNIFI (NCT02407236)[63]	UNIFI - Ind	Ph 3	TMS 6-12	Induction	NA	Multi-national	961; 962	UST 130 mg UST 6 mg/kg PBO	8/16	Y	Y
	UNIFI - maint			Maint	RR		523	UST 90 mg Q12W UST 90 mg Q8W PBO	44	Y	NA
GEMINI 1 (NCT00783718)[65]	GEMINI 1 - Ind.	Ph 3	TMS 6-12	Induction	NA	Multi-national	374	VED 300 mg PBO	6	Y	Y
	GEMINI 1 - Maint.			Maint	RR		373	VED 300 mg Q8W VED 300 mg Q4W PBO	46	Y	NA
VISIBLE 1 (NCT02611830)[69]	VISIBLE 1	Ph 3	TMS 6-12	Maint	RR	Multi-national	216	VED 300 mg IV VED 108 mg SC PBO	46	Y	NA
VARSITY (NCT02497469)[64]	VARSITY	Ph 3b	TMS 6-12	Both	TT	Multi-national	769	VED 300 mg IV ADA 160/80/40 mg	52 (14;38)	Y	NA
Motoya 2019 (NCT02039505)[66]	Motoya 2019 - Ind	Ph 3	TMS 6-12	Induction	NA	Japan	246	VED 300 mg IV PBO	10	Y	Y
	Motoya 2019 - Maint			Maint	RR		83	VED 300 mg IV PBO	50	Y	NA
ULTRA 1 (NCT00385736)[53]	ULTRA 1	Ph 3	TMS 6-12	Induction	NA	Multi-national	576; 390	ADA 80/40 mg ADA 160/80/40 mg PBO	8	Y	Y
ULTRA 2 (NCT00408629)[54]	ULTRA 2	Ph 3	TMS 6-12	Both	TT	Multi-national	494; 517	ADA 160/80/40mg PBO	52(8;44)	Y	N[a]
Suzuki 2014 (NCT00853099)[55]	Suzuki 2014	Ph 2/3	TMS 6-12	Both	TT	Japan	274; 273	ADA160/80/40mg ADA 80/40 PBO	52(8;44)	Y	Y
HIBISCUS I (NCT02163759)[56]	HIBISCUS I	Ph 3	TMS 6-12	Induction	NA	Multi-national	358	ADA 160/80/40 mg PBO	12	Y	Y
HIBISCUS II (NCT02171429)[56]	HIBISCUS II	Ph 3		Induction	NA	Multi-national	358	ADA 160/80/40 mg PBO	12	Y	Y
PURSUIT-SC (NCT00487539)[60]	PURSUIT-SC - Ph 2	Ph 2	TMS 6-12	Induction	NA	Multi-national	291; 164	GOL 200/100 mg PBO	6	Y	Y
	PURSUIT-SC - Ph 3	Ph 3		Induction	NA		774; 761	GOL 200/100 mg PBO	6	Y	Y

Trial name	Sub-study details	Phase	Mayo Score	Induction/ Maint	Maint design	Location	N	Arms	Study duration	Included in NMA	
										Resp/ Rem	SInf
PURSUIT-M (NCT00488631)[67]	PURSUIT-M	Ph 3	TMS 6-12	Maint	RR	Multi-national	464	GOL 50 mg GOL 100 mg PBO	54	Y	NA
PURSUIT-J (NCT01863771)[68]	PURSUIT-J	Ph 3	TMS 6-12	Maint	RR	Japan	63	GOL 100 mg PBO	54	Y	NA
NCT01551290[59]	NCT01551290	Ph 3	TMS 6-12	Both	TT	China	99	INF 5 mg/kg PBO	26(8;18)	Y[c]	Y
LIBERTY-UC (NCT04205643) [95]	LIBERTY-UC	Ph 3	MMS 5-9	Maint	RR	Multi-national	438	INF SC 120 mg PBO	54	N[b]	NA
Jiang 2015[57]	Jiang 2015	NR	TMS 6-12	Both	TT	China	123	INF 5 mg/kg PBO	30(8;22)	Y[c]	N[a]
Kobayashi 2016 [58]	Japic CTI-060298	Ph 3	TMS 6-12	Both	TT	Japan	208	INF 5 mg/kg PBO	30(8;22)	Y[c]	Y
ACT-1 (NCT00036439)[35]	ACT-1	Ph 3	TMS 6-12	Both	TT	Multi-national	364	INF 5 mg/kg PBO	54(8;46)	Y	N[a]
ACT-2 (NCT00096655) [35]	ACT-2	Ph 3	TMS 6-12	Both	TT		364	INF 5 mg/kg PBO	30(8;22)	Y[c]	N[a]

[a] Safety outcomes not reported at induction phase time point.
[b] Outcomes not reported for subgroups based on prior biologic exposure
[c] Studies were included in induction phase NMA only as duration of maintenance phase was not long enough to be comparable to other maintenance studies.
Abbreviations: ITT, intention to treat; IV, intravenous; JAKi, Janus kinase inhibitor; kg, kilogram; Maint, maintenance; mg, milligram; MMS, modified Mayo score; N, no; NA, not applicable; NMA, network meta-analysis; PBO, placebo; Ph, phase; Resp, clinical response; Rem, clinical remission; RR, randomized responder trial; SC, subcutatneous; SInf, serious infections; TMS, total Mayo score; TNFi, tumor necrosis factor inhibitor; TT, Treat-through trial; UC, ulcerative colitis; UK, United Kingdom; US, Unites States; Y, yes

F.1.2.4 Quality of included evidence

A total of 31 trials were considered for quality assessment. Among these, 30 trials provided randomization details and 29 trials reported allocation concealment information. All trials had roughly comparable baseline characteristics across treatment arms. All trials were reported to double blinded, while 14 studies had treatment discontinuation patterns that were similar across treatment groups. All trials used either an intention-to-treat or full-analysis strategy to handle missing data.

Table 35 Quality assessment of included trials

Trial Name	Randomisation method adequate?	Allocation adequately concealed?	Baseline characteristics similar between treatment arms?	Participants and investigators blind to exposure & comparison?	Discontinuations dissimilar between groups?	Unreported outcomes suspected?	ITT included? If so, was this appropriate and were appropriate methods used to account for missing data?
ELEVATE UC 12[47]	Yes, Central randomization using IWRS	Yes, Central randomization using IWRS	Yes, BC were balanced between Tx arms	Yes, DB	No, Tx DC was approx. similar in both groups (ETR: 10.5%, PBO 11.2%)	No, Outcomes were reported as per the protocol	No, Full analysis set (FAS)
ELEVATE UC 52[47]	Yes, Central randomization using IWRS	Yes, Central randomization using IWRS	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Tx DC was not similar in both groups (ETR: 44.3%, PBO: 68.05%)	No, Outcomes were reported as per the protocol	No, Full analysis set (FAS)
OASIS[43]	Yes, Randomization was performed centrally with a block size of 6	Yes, Study drug were supplied as capsules with the same appearance	Yes, BC were balanced between Tx arms	Yes, DB	No, Tx DC was approx. similar in all groups (ETR 1 mg: 9.6%, ETR 2 mg: 8% , PBO: 11.11%)	No, Outcomes were reported as per the protocol	Yes, ITT population
TOUCHSTONE[136]	Yes, Randomization was performed centrally with the use of a computerized system	Yes, Investigational medicinal product and placebo capsules will be identical in physical appearance	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Tx DC was different across Tx groups (ind.: PBO 9.1%, OZA 0.5 mg 4.5%, OZA 1 mg 6%)	No, Outcomes were reported as per the protocol	Yes, ITT population
TRUE NORTH[51]	Yes, IVRS/IWRS	Yes, Patients were assigned to treatment/randomized using the IVRS/IWRS	Yes, BC were balanced between Tx arms	Yes, DB	No, Drop-out with the PBO arm having twice as many drop-outs as OZA in the ind. (11% vs 6%) and maint. (45% vs 20%) period	No, Outcomes were reported as per the protocol	Yes, ITT population
U-ACHIEVE[62]	Yes, IWRS; block randomization schedules (block size of 3)	Yes, IWRS	Yes, BC were balanced between Tx arms	Yes, DB	No, PBO had a twice higher dropout rate (12%) than UPA (4%)	No, Outcomes were reported as per the protocol	Yes, ITT population

Trial Name	Randomisation method adequate?	Allocation adequately concealed?	Baseline characteristics similar between treatment arms?	Participants and investigators blind to exposure & comparison?	Discontinuations dissimilar between groups?	Unreported outcomes suspected?	ITT included? If so, was this appropriate and were appropriate methods used to account for missing data?
U-ACCOMPLISH[62]	Yes, IWRS; block randomization schedules (block size of 3)	Yes, IWRS	Yes, BC were balanced between Tx arms	Yes, DB	Yes, PBO had a twice higher dropout rate (65%) than UPA 15mg (33%) and UPA 30mg (21%)	No, Outcomes were reported as per the protocol	Yes, ITT population
SELECTION[50]	Yes, Central randomization using IWRS	Yes, IWRS	Yes, BC were balanced between Tx arms	Yes, DB	No, Higher DC rates in the PBO (6.5%) compared to FIL 100 mg (6%) and FIL 200 mg (3%)	No, Outcomes were reported as per the protocol	Yes, ITT population
OCTAVE Induction 1[52]	Yes, Central randomization using TRS	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	No, Slightly lower proportion of patients discontinued PBO (3%) than TOF 10mg (7%)	No, Outcomes were reported as per the protocol	Yes, ITT population
OCTAVE Induction 2[52]	Yes, Central randomization using TRS	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	No, Slightly higher proportion of patients discontinued PBO (13%) than TOF 10mg (8%)	No, Outcomes were reported as per the protocol	Yes, ITT population
OCTAVE Sustain[52]	Yes, Central randomization using TRS	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Higher DC rates in PBO (73%) compared to TOF 5mg (44%) and TOF 10mg (36%)	No, Outcomes were reported as per the protocol	Yes, ITT population
Sandborn 2012[120]	Yes, Randomization was performed centrally using a CGRS (permuted blocks)	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	No, Higher DC rates in the PBO (27%), TOF 0.5mg (33%), and TOF 3mg groups (21%), compared to TOF	No, Outcomes were reported as per the protocol	Yes, ITT population

Trial Name	Randomisation method adequate?	Allocation adequately concealed?	Baseline characteristics similar between treatment arms?	Participants and investigators blind to exposure & comparison?	Discontinuations dissimilar between groups?	Unreported outcomes suspected?	ITT included? If so, was this appropriate and were appropriate methods used to account for missing data?
					10mg (6%), and TOF 15mg (8%)		
UNIFI[63]	Yes, Randomization was performed with the use of permuted blocks	Yes, permuted blocks	Yes, BC were balanced between Tx arms	Yes, DB	No, Higher drop-out was observed in PBO than the intervention (UST 6 mg/kg 4%, UST 130 mg 4% , PBO 5%)	No, Outcomes were reported as per the protocol	Yes, ITT population
GEMINI 1[65]	Yes, Randomization was performed centrally with the use of computer-generated randomization schedules	Yes, NR	Yes, BC were balanced between Tx arms	Yes, DB	No, Higher proportion of PBO discontinued Tx compared to VED in ind. phase (9% vs 2%) and maint. phase (PBO 62%, VED Q8W 37%, VED Q4W 33%)	No, Outcomes were reported as per the protocol	Yes, ITT population
VISIBLE 1[69]	Yes, IWRS	Unclear, No information	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Tx DC was not similar across the group PBO 64.2%, VED SC 29.2%, VED IV 27.7%	No, Outcomes were reported as per the protocol	No, Full analysis set (FAS)
VARSITY[64]	Yes, IVRS/IWRS	Yes, Investigational pharmacist or designee will mask the IV bags after preparation in order to maintain the study blind	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Tx DC was not similar across the group ADA: 43.7% VED: 29.8%	No, Outcomes were reported as per the protocol	No, Full analysis set (FAS)
Motoya 2019[66]	Yes, Randomization schedules were generated by sponsor-designated personnel	Yes, NR	Yes, BC were balanced between Tx arms	Yes, DB	No, Higher proportion of drop-outs in the PBO arm compared to VED in the ind. (5% vs 5%)	No, Outcomes were reported as per the protocol	Yes, ITT population

Trial Name	Randomisation method adequate?	Allocation adequately concealed?	Baseline characteristics similar between treatment arms?	Participants and investigators blind to exposure & comparison?	Discontinuations dissimilar between groups?	Unreported outcomes suspected?	ITT included? If so, was this appropriate and were appropriate methods used to account for missing data?
	(dynamic randomization was performed with the previous TNFα antagonist use)				and maint. (57% vs 27%) period		
ULTRA 1[53]	Yes, Randomization done by central randomization scheme generated by the study sponsor	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	No, Drop-out between Tx group are almost similar (PBO 7%, ADA 160/80/40 mg 7%, ADA 80/40 mg 9%)	No, Outcomes were reported as per the protocol	Yes, ITT population
ULTRA 2[54]	Yes, Randomization was performed centrally	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Unexpected imbalance in the dropout between two Tx group (PBO 48%, ADA 37%)	No, Outcomes were reported as per the protocol	Yes, ITT population
Suzuki 2014[55]	Yes, Randomized based on centrally designed randomization table	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Unexpected imbalance in the dropout between two Tx group (PBO 23%, ADA 33%)	No, Outcomes were reported as per the protocol	No, Full analysis set (FAS)
HIBISCUS I[56]	Yes, permuted block randomization using IVRS/IWRS	Yes, permuted blocks	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Unexpected imbalance in the dropout at induction and maint. phases	No, Outcomes were reported as per the protocol	Yes, ITT population
HIBISCUS I[56]	Yes, permuted block randomization using IVRS/IWRS	Yes, permuted blocks	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Unexpected imbalance in the dropout at induction and maint. phases	No, Outcomes were reported as per the protocol	Yes, ITT population
PURSUIT-SC[60]	Yes, Central randomization using IVRS	Yes, Central randomization	Yes, BC were balanced	Yes, DB	No, 2.3% of patients withdrew from each study arm	No, Outcomes were reported as per the protocol	Yes, ITT population

Trial Name	Randomisation method adequate?	Allocation adequately concealed?	Baseline characteristics similar between treatment arms?	Participants and investigators blind to exposure & comparison?	Discontinuations dissimilar between groups?	Unreported outcomes suspected?	ITT included? If so, was this appropriate and were appropriate methods used to account for missing data?
			between Tx arms				
PURSUIT-M[67]	Yes, ARP	Yes, ARP	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Slightly higher in GOL 100mg (11%) and PBO (15%) than GOL 50mg (10%)	No, Outcomes were reported as per the protocol	Yes, ITT population
PURSUIT-J[68]	Yes, A computer-generated randomization (PBR)	Yes, Computer-generated randomization	Yes, BC were balanced between Tx arms	Yes, DB	No, PBO had a twice higher dropout rate (39%) than GOL (16%)	No, Outcomes were reported as per the protocol	Yes, ITT population
NCT01551290[59]	Yes, NR	Unclear, No information	Unclear, No information	Yes, DB	Unclear, No information	Unclear, No information	Yes, ITT population
LIBERTY-UC[95]	Unclear, Randomization method was not reported	Unclear, No information	Unclear, No information	Yes, DB	Unclear, No information	Unclear, No information	Unclear, No information
Jiang 2015[57]	Yes, Central randomization	Yes, Central randomization with a dynamic treatment allocation	Yes, BC were balanced between Tx arms	Yes, DB	Yes, More than twice as many patients in the PBO group as in the other 2 groups prematurely discontinued the infusions	No, Outcomes were reported as per the protocol	Yes, ITT population
Kobayashi 2016[58]	Yes, Randomization was performed centrally with the use of CGRS	Yes, Central randomization	Yes, BC were balanced between Tx arms	Yes, DB	Unclear, No information	No, Outcomes were reported as per the protocol	No, Full analysis set (FAS)
ACT-1[35]	Yes, Central randomization	Yes, Central randomization with a dynamic treatment allocation	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Higher proportion of PBO (47%) discontinued Tx compared to INF	No, Outcomes were reported as per the protocol	Yes, ITT population

Trial Name	Randomisation method adequate?	Allocation adequately concealed?	Baseline characteristics similar between treatment arms?	Participants and investigators blind to exposure & comparison?	Discontinuations dissimilar between groups?	Unreported outcomes suspected?	ITT included? If so, was this appropriate and were appropriate methods used to account for missing data?
					(INF 5mg 32% and INF 10mg 32%)		
ACT-2[35]	Yes, Central randomization	Yes, Central randomization with a dynamic treatment allocation	Yes, BC were balanced between Tx arms	Yes, DB	Yes, Higher proportion of PBO (40%) discontinued Tx compared to INF (INF 5mg 20% and INF 10mg 20%)	No, Outcomes were reported as per the protocol	Yes, ITT population

Abbreviations: ARP: Adaptive Randomization Procedure; BC: Baseline Characteristics; CGRS: Computer Generated Randomization Schedule; DC: Discontinuation; IVRS: Interactive Voice Response System; IWRS: Interactive Web Response System; PBR: Permuted Block randomization; TRS: Tele Randomization System; Tx: Treatment

F.1.2.5 Population characteristics

The baseline characteristics of the trials included in SLR are summarized by treatment arm and by period (i.e., induction or maintenance) where reported in the respective publications. Baseline parameters assessed included age, male gender, body weight, disease duration, total Mayo score, IBDQ score, disease site, prior use of advanced therapies (biologic/JAKi/TNFi), and concomitant medications (corticosteroids).

Table 36 shows the baseline characteristics for the overall populations where reported. The reporting of baseline characteristics among biologic-naïve and biologic-experienced subgroups was particularly poor, which makes a comparison among subgroups more challenging as we cannot guarantee homogeneity. However, to conduct subgroup analyses, made the assumption that the covariates are balanced among subgroups where the baseline characteristics were only reported for overall populations.

Firstly, an assessment of within-trial baseline characteristics was conducted across the various populations. Based on the baseline characteristics assessed, the within-trial differences were minimal and generally balanced across arms.

The mean age ranged from 38 to 44 years, while males accounted for 48%-66% of the population across the trials. In some trials, the median age was reported instead of the mean. In these cases, the median ages were similar in those studies and close to that of the mean values of the other studies. Patient body weight ranged from 57 to 80 kg across studies, and the average number of years of disease duration at baseline ranged from 6 to 9 years. Left-sided colitis, pancolitis, proctosigmoiditis, and extensive colitis were the most commonly reported types of UC based on disease site.

Proportion of patients on corticosteroid (including glucocorticoids) varied across studies, ranging from 13% to over 60%. The proportion of patients with prior advanced therapies (biologic/JAKi/TNFi) also showed a wide variation across trials (range: 0%- 65%). Some studies included only patients who were TNFi-naïve.

Table 36 Baseline characteristics of patients

Study name	Trial arm	N	Age (years)		Male	Body weight (kg)		Disease duration (years)		Total Mayo score		IBDQ score		Disease site (%)				Prior adv therapy (bio/ JAKi/ TNFi) %	Con-comitant CS (%)
			Mean	SD	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	LSC	EC	PS	PC		
ELEVATE UC 12[47]	PBO	116	40.4	13.3	62.9	NR	NR	7.7	7.32	8.8	1.54	NR	NR	54.3	NR	NR	35.3	25	32.8
	ETR 2 mg	238	40.3	13.5	56.7	NR	NR	7.3	6.61	8.7	1.52	NR	NR	61.3	NR	NR	32.4	23.9	32.8
ELEVATE UC 52[47]	PBO	144	38.9	14.0	61.1	NR	NR	5.9	5.52	9	1.43	NR	NR	62.5	NR	NR	32.6	31.3	70.1
	ETR 2 mg	289	41.2	13.97	52.6	NR	NR	7.5	8	9	1.5	NR	NR	59.5	NR	NR	32.2	29.1	77.5
OASIS[43]	PBO	54	44.8	14.9	59.3	NR	NR	8.6	7.16	8.7	1.72	126	33.5	NR	NR	63	42.6	33.3	29.6
	ETR 2 mg	50	40.4	12.4	54	NR	NR	6.2	4.69	8.9	1.47	117	32.8	NR	NR	60	28	34	36
TOUCHSTONE[136]	PBO	65	41.9	12.3	54	72.6	14.9	6.1	5.5	8.6	1.5	NR	NR	63	37	NR	NR	15	37
	OZA 1 mg	67	41.8	11	72	77.4	16.3	6.7	6.8	8.5	1.6	NR	NR	61	39	NR	NR	19	40
TRUE NORTH[51]	PBO	216	41.9	13.6	66.2	NR	NR	6.8	7	8.9	1.4	NR	NR	62	38	NR	NR	30.1	NR
	OZA 1 mg	429	41.4	13.5	57.1	NR	NR	6.9	6.6	8.9	1.5	NR	NR	62.5	37.5	NR	NR	30.3	NR
U-ACHIEVE-Phase 2b-Part 1[61]	PBO	46	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	41.3	58.7	NR	NR	NR	54.3
	UPA 45 mg	56	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	46.4	53.6	NR	NR	NR	50
U-ACHIEVE induction[62]	PBO	154	44·5	23	63	70	26.5	6·0	10·0	NR	NR	122	31.0	48	52	NR	NR	51	40
	UPA 45 mg	319	43	23	62	69.3	24.6	6·6	9·6	NR	NR	122	36.5	50	50	NR	NR	53	39
U-ACCOMPLISH Induction[62]	PBO	174	42	24	61	71.5	24.3	4·9	7·4	NR	NR	123	37.7	51	49	NR	NR	51	41
	UPA 45 mg	341	40	24	63	71.2	21.4	5·6	7·5	NR	NR	123	34.5	48	52	NR	NR	50	35
U-ACHIEVE Maintenance[62]	PBO	149	40	21	57	70	21.2	6·2	8·6	NR	NR	123	33.4	53	47	NR	NR	54	40
	UPA 15 mg	148	40	22	64	71.5	25.6	6·4	10·6	NR	NR	126	35.9	45	55	NR	NR	48	37
	UPA 30 mg	154	41	7	56	68.8	29	6·0	9·7	NR	NR	121	35.0	44	56	NR	NR	47	37
SELECTION - Induction A[50]	PBO	137	41	12.9	63.5	NR	NR	6·4	7·4	8·7	1·3	NR	NR	NR	NR	NR	NR	0	24·8
	FIL 100 mg	277	42	13.3	56.7	NR	NR	6·7	7·4	8·6	1·4	NR	NR	NR	NR	NR	NR	0·7	24·2
	FIL 200 mg	245	42	13.1	50.2	NR	NR	7·2	6·9	8·6	1·3	NR	NR	NR	NR	NR	NR	0	22·0
SELECTION -Induction B[50]	PBO	142	44	14.9	60.6	NR	NR	10·2	8·2	9·3	1·4	NR	NR	NR	NR	NR	NR	97.9	35·9
	FIL 100 mg	285	43	14.3	65.3	NR	NR	9·7	7·2	9·3	1·3	NR	NR	NR	NR	NR	NR	99.3	36·1
	FIL 200 mg	262	43	14.2	56.5	NR	NR	9·8	7·6	9·2	1·4	NR	NR	NR	NR	NR	NR	98.9	35·9
SELECTION -	PBO	91	43	15.1	NR	NR	NR	7·5	7·5	NR	NR	NR	NR	NR	NR	NR	NR	35·2	30·8
	FIL 100 mg	179	42	12.6	NR	NR	NR	8·9	8·4	NR	NR	NR	NR	NR	NR	NR	NR	38·0	34·6

Study name	Trial arm	N	Age (years)		Male	Body weight (kg)		Disease duration (years)		Total Mayo score		IBDQ score		Disease site (%)				Prior adv therapy (bio/ JAKi/ TNFi) %	Con-comitant CS (%)
			Mean	SD	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	LSC	EC	PS	PC		
Maintenance[50] from Induction FIL 100 mg																			
SELECTION - Maintenance[50] from Induction FIL 200 mg	PBO	99	42	13	NR	NR	NR	8·9	7·6	NR	NR	NR	NR	NR	NR	NR	NR	43·4	31·3
	FIL 200 mg	202	43	13.8	NR	NR	NR	8·4	7·4	NR	NR	NR	NR	NR	NR	NR	NR	41·6	30·2
OCTAVE Induction 1[52]	PBO	122	41.8	15.3	63.1	72.7	16.7	NR	NR	9.1	1.4	NR	NR	30.3	54.1	15.6	NR	53.3	47.5
	TOF 10 mg	476	41.3	14.1	58.2	72.9	16.8	NR	NR	9	1.4	NR	NR	33.3	53.1	13.7	NR	53.4	45
OCTAVE Induction 2[52]	PBO	112	40.4	13.2	49.1	73.2	16.2	NR	NR	8.9	1.5	NR	NR	35.1	50.5	14.4	NR	58	49.1
	TOF 10 mg	429	41.1	13.5	60.4	74.4	16.8	NR	NR	9	1.5	NR	NR	34.8	49.3	15.7	NR	54.5	46.2
OCTAVE Sustain[52 a]	PBO	198	43.4	14	58.6	76.2	16.7	NR	NR	3.3	1.8	NR	NR	34.3	54.5	10.6	NR	46.5	50.5
	TOF 5 mg	198	41.9	13.7	52	73.4	17.8	NR	NR	3.3	1.8	NR	NR	33.7	52	14.3	NR	45.5	51
	TOF 10 mg	197	42.9	14.4	55.8	74.6	15.1	NR	NR	3.4	1.8	NR	NR	30.6	52.6	16.8	NR	51.3	44.2
Sandborn 2012[120]	PBO	48	42.5	14.7	48	74.6	15.8	8.8	5.4	8.2	1.6	NR	NR	26	43	NR	NR	31	NR
	TOF 10 mg	33	43.2	12.8	64	75.9	13.2	10.9	6.6	8	1.7	NR	NR	35	42	NR	NR	30	NR
UNIFI[63]	PBO	319	41.2	13.5	61.8	72.9	16.8	8	7.2	8.9	1.6	NR	NR	52.8	NR	NR	NR	35.1	49.2
	UST 130 mg	320	42.2	13.9	59.4	73.7	16.8	8.1	7.2	8.9	1.6	NR	NR	57.5	NR	NR	NR	33.4	54.1
	UST 6 mg/kg	322	41.7	13.7	60.6	73	19.3	8.2	7.8	8.9	1.5	NR	NR	52.5	NR	NR	NR	32.9	52.2
UNIFI - Maintenance[63]	PBO	175	42	13.9	61.1	71.7	14.6	7.5	6.8	8.7	1.52	NR	NR	50.9	NR	NR	NR	50.3	54.3
	UST 90 mg Q12W	172	40.7	13.5	55.8	73.3	18.9	8.6	8.31	8.9	1.58	NR	NR	53.5	NR	NR	NR	40.7	48.3
	UST 90 mg Q8W	176	39.5	13.3	53.4	72	19.1	8.1	6.57	8.9	1.55	NR	NR	54.3	NR	NR	NR	51.7	54
GEMINI 1[65]	PBO	149	41.2	12.5	61.7	72.4	17.6	7.1	7.2	8.6	1.7	126	34	39.6	NR	NR	NR	49	40
	VED	225	40.1	13.1	58.7	72.4	17.1	6.1	5.1	8.5	1.8	125	35	40.9	NR	NR	NR	42.2	35.1
GEMINI 1 - Maintenance[65]	PBO	126	40.3	14	55	74.7	20	7.8	7	8.4	1.8	122	34	42	13	7	37	37	38
	VED Q8W	122	41	13	57	78.2	19	6.2	5	8.4	1.8	125	34	42	11	15	32	41	39
	VED Q4W	125	38.6	14	54	71.8	17	7.6	7	8.3	1.7	124	34	36	11	11	42	42	38
VISIBLE 1[69]	PBO	56	39.4	11.7	60.7	74	20.9	7.4	7.1	NR	NR	NR	NR	42.9	7.1	12.5	37.5	35.7	42.9

Study name	Trial arm	N	Age (years)		Male	Body weight (kg)		Disease duration (years)		Total Mayo score		IBDQ score		Disease site (%)				Prior adv therapy (bio/ JAKi/ TNFi) %	Con-comitant CS (%)
			Mean	SD	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	LSC	EC	PS	PC		
	VED SC	106	38.1	13.1	61.3	71.6	17.2	8	6.2	NR	NR	NR	NR	43.4	6.6	14.2	34.9	37.7	42.5
	VED IV	54	41.6	14.1	57.4	77	16.9	8.2	5.9	NR	NR	NR	NR	38.9	13	13	35.2	44.4	38.9
Motoya 2019[66]	PBO	82	44	16	67.1	NR	NR	8.6	8	8.1	1.5	NR	NR	37.8	NR	NR	NR	50	13.4
	VED	164	42.3	14.4	60.4	NR	NR	7.2	6.2	8.3	1.5	NR	NR	38.4	NR	NR	NR	51.8	18.9
VARSITY[64]	ADA 160/80	386	40.5	13.4	56	73.4	18.4	6.4	6	8.7	1.5	NR	NR	NR	NR	NR	NR	21.0	NR
	VED	383	40.8	13.7	60.8	72.7	17	7.3	7.2	8.7	1.6	NR	NR	NR	NR	NR	NR	20.8	NR
ULTRA 1[53]	PBO	130	NR	NR	NR	78.7	17.4	NR	NR	8.7	1.56	NR	NR	NR	NR	NR	NR	0	41.5
	ADA 80/40	130	NR	NR	NR	76.8	15	NR	NR	9	1.62	NR	NR	NR	NR	NR	NR	0	37
	ADA 160/80	130	NR	NR	NR	75.5	14.2	NR	NR	8.8	1.61	NR	NR	NR	NR	NR	NR	0	37
ULTRA 2[54]	PBO	246	41.3	13.22	61.8	77.1	17.3	8.5	7.37	8.9	1.75	NR	NR	NR	NR	NR	48.8	0	57
	ADA 160/80	248	39.6	12.47	57.3	75.3	17.7	8.1	7.09	8.9	1.5	NR	NR	NR	NR	NR	48.4	0	60.5
Suzuki 2014[55]	PBO	96	41.3	13.6	72.9	60.8	14.1	7.8	6.6	8.5	1.6	148	28.9	36.5	NR	NR	61.5	0	NR
	ADA 80/40	87	44.4	15	57.5	58.7	11.1	8.3	7.7	8.5	1.4	145	28.7	36.8	NR	NR	62.1	0	NR
	ADA 160/80	90	42.5	14.6	67.8	60.1	12.3	7.8	7.1	8.6	1.4	146	31.7	30	NR	NR	70	0	NR
HIBISCUS I	PBO	72	38.4	13.3	54	NR	NR	NR	NR	8.7	1.6	NR	NR	61	14	NR	25	0	47
	ADA 160/80/40 mg	142	42	13.8	58	NR	NR	NR	NR	8.9	2.3	NR	NR	59	16	NR	25	0	47
HIBISCUS II	PBO	72	40.3	12.5	53	NR	NR	NR	NR	8.8	1.6	NR	NR	67	10	NR	24	0	46
	ADA 160/80/40 mg	143	39.7	12.6	57	NR	NR	NR	NR	8.7	1.6	NR	NR	60	9	NR	31	0	46
PURSUIT-SC[60]	PBO	331	39	13.0	52.9	NR	NR	6	6.7	8.3	1.5	NR	NR	57	43	NR	NR	0	40.5
	GOL 200/100	331	40	13.5	54.4	NR	NR	6.4	6.2	8.6	1.5	NR	NR	58.3	41.7	NR	NR	0	42.9
PURSUIT-M[67]	PBO	156	40.2	14.1	48.1	NR	NR	6.9	7.0	8.3	1.4	NR	NR	NR	NR	NR	NR	0	53.2
	GOL 50 mg	154	41.4	13.8	50	NR	NR	6.8	6.9	8.1	1.4	NR	NR	NR	NR	NR	NR	0	50
	GOL 100 mg	154	39.1	13.1	57.8	NR	NR	7.2	7.0	8.5	1.3	NR	NR	NR	NR	NR	NR	0	51.3
PURSUIT-J[68]	PBO	31	42.9	14.4	61	59.5	9.7	NR	NR	NR	NR	NR	NR	61%	39%	NR	NR	0	29
	GOL 100 mg	32	39.3	12	59	64.6	14.7	NR	NR	NR	NR	NR	NR	63%	38%	NR	NR	0	28
	PBO	49	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR

Study name	Trial arm	N	Age (years)		Male	Body weight (kg)		Disease duration (years)		Total Mayo score		IBDQ score		Disease site (%)				Prior adv therapy (bio/ JAKi/ TNFi) %	Con-comitant CS (%)
			Mean	SD	%	Mean	SD	Mean	SD	Mean	SD	Mean	SD	LSC	EC	PS	PC		
NCT01551290[59]	INF 5 mg/kg	50	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	0	NR
LIBERTY-UC[95]	PBO	e	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
	INF SC 120 mg	144	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Jiang 2015[57]	PBO	41	34.5	14.9	60.9	61.2	15.7	4.4	2.6	NR	NR	NR	NR	41.5	NR	NR	58.5	0	51.2
	INF 5 mg/kg	41	34.3	14.3	63.4	62.8	14.9	4.4	2.8	NR	NR	NR	NR	39.1	NR	NR	60.9	0	53.7
Kobayashi 2016[58]	PBO	104	37.8	12.9	64.4	60.3	11.6	7.1	6.6	8.5	1.4	NR	NR	19.2	80.8	NR	NR	0	66.3
	INF 5 mg/kg	104	40	12.7	63.5	57.6	12.7	8.1	7.2	8.6	1.4	NR	NR	20.2	79.8	NR	NR	0	65.4
ACT-1[35]	PBO	121	41.4	13.7	59.5	76.8	16.2	6.2	5.9	8.4	1.8	NR	NR	55	45	NR	NR	0	65.3
	INF 5 mg/kg	121	42.4	14.3	64.5	80	17.8	5.9	5.4	8.5	1.7	NR	NR	52.9	47.1	NR	NR	0	57.9
ACT-2[35]	PBO	123	39.3	13.5	57.7	76.1	17.4	6.5	6.7	8.5	1.5	NR	NR	58.3	41.7	NR	NR	0	48.8
	INF 5 mg/kg	121	40.5	13.1	62.8	78.4	17.8	6.7	5.3	8.3	1.5	NR	NR	59.3	40.7	NR	NR	0	49.6

[a] The patient characteristics from OCTAVE Sustain are reported for induction responders randomised at maintenance baseline

Abbreviations: BS, biosimilar; CS, corticosteroids; IBDQ, EC, extensive colitis; Inflammatory Bowel Disease Questionnaire; LSC, left-sided colitis; PBO, Placebo; PC, Pancolitis; PS, Proctosigmoiditis; SD, Standard deviation; TNFi, Tumor necrosis factor inhibitor

F.1.2.6 Intervention and comparator characteristics

Of the 31 included trials, three included etrasimod, one included filgotinib, two included ozanimod, four included tofacitinib, four included vedolizumab, six included adalimumab, three included golimumab, four included upadacitinib, one included ustekinumab and six included infliximab. These numbers include one head-to-head comparison. Only weight-based dosing was reported in infliximab trials. In the trial of ustekinumab, a combination of fixed dose and weight-based dosing was reported. Treatments were delivered orally, intravenously and via subcutaneous injection.

The licensed daily dose ranges according to the EMA summary of product characteristics for each of the comparator interventions is given in Table 32. The dose range is divided into recommended induction and maintenance doses if specified in the respective EMA summary of product characteristics for each treatment. Infliximab was given as a weight-based dose only. Ustekinumab was given as a combination of a fixed and weight-based dose. Filgotinib 100 mg was included as patients with renal impairment may be given this dose and the exclusion criteria of most studies did not specifically exclude patients with renal impairment. An initial induction dose of 80 mg of adalimumab is recommended for children and adolescents. Since we are considering patients aged 16 and over, this dose was included in the acceptable dose range.

F.1.2.7 Outcome characteristics

The analyses will be conducted on the following outcomes which are divided up into those outcomes for induction and those for the maintenance period. The relevant outcomes for the induction period are:

- Clinical response (efficacy)
- Clinical remission (efficacy)
- Serious infection (safety)

The relevant outcomes for the maintenance period are:

- Sustained clinical response, i.e., clinical response among induction phase clinical responders (efficacy)
- Clinical remission among induction phase clinical responders (efficacy)

There were two outcome definitions used to define clinical response, namely the total or full Mayo Clinic Score (fMS) and the adapted/modified MCS also called the modified Mayo score (mMS). The fMS-defined clinical response and clinical remission outcomes were standard across studies. However, among the studies that reported the mMS, there was some variation (see Table 37).

Previous clinical advice in the upadacitinib company submission to NICE stated that including trials in the NMAs reporting either full Mayo score or modified Mayo score was unlikely to be a source of bias.[48] Where a trial reported both fMS and mMS defined outcomes, given that the fMS was reported the most frequently, the fMS was used. The mMS was used for the ELEVATE trials since this was the primary outcome measure.

Table 37. Response and remission definitions across studies included in NMA

	Definition	Studies
Clinical response	A reduction in the **fMS** of ≥3 points and a decrease of ≥30% from baseline, plus a ≥1 point reduction on the RBS or an absolute RBS of ≤1	ACT 1 ACT 2 GEMINI 1 HIBISCUS I HIBISCUS II Jiang 2015 Kobayashi 2015 Motoya 2019 Sandborn 2012 OCTAVE 1 OCTAVE 2 OCTAVE Sustain PURSUIT-J PURSUIT-M PURSUIT-SC SELECTION Suzuki 2014 ULTRA 1 ULTRA 2 UNIFI VARSITY VISIBLE NCT01551290 TOUCHSTONE
	A reduction in **mMS** of ≥2 points and decrease of ≥35% from baseline, plus a ≥1 point reduction in RBS or an absolute RBS ≤1 point	TRUE NORTH
	A reduction in **mMS** of ≥2 points and decrease of ≥30% from baseline, plus a ≥1 point reduction in RBS or an absolute RBS ≤1 point	U-ACHIEVE U-ACCOMPLISH LUCENT-1 OASIS ELEVATE UC 12 ELEVATE UC 52
Clinical remission	A **fMS** of ≤2 points, with no individual subscore >1	ACT 1 ACT 2 GEMINI 1 HIBISCUS I HIBISCUS II Jiang 2015 Kobayashi 2015 Motoya 2019 OCTAVE 1 OCTAVE 2 OCTAVE Sustain Sandborn 2012 PURSUIT-J PURSUIT-M PURSUIT-SC SELECTION Suzuki 2014 ULTRA 1 ULTRA 2 UNIFI VARSITY VISIBLE NCT01551290 TOUCHSTONE
	An RBS = 0, an ES ≤ 1 and a SFS ≤ 1 with a ≥1 decrease from baseline	TRUE NORTH
	An RBS = 0, an ES ≤ 1 (without friability) and a SFS ≤ 1 and not greater than baseline	U-ACHIEVE U-ACCOMPLISH
	An RBS = 0, an ES ≤ 1 (without friability) and a SFS = 0 (or = 1 with a ≥1 decrease from baseline).	ELEVATE UC 12 ELEVATE UC 52
	An RBS ≤ 1, an ES ≤ 1 (without friability) and SFS ≤ 1 with a ≥1 decrease from baseline	OASIS

F.1.2.8 Assessment of effectiveness

F.1.2.9 Rates of response and remission

Clinical response and clinical remission were well reported across the included trials. In line with previous appraisals, it was assumed that the numbers of patients who were reported in the trial publications as being in clinical response also included patients who were in clinical remission. The induction and maintenance phase data from eligible trials were analysed using NMA methods. Definitions of clinical response and clinical remission used in the included trials are presented in Table 37.

Data relating to clinical response and clinical remission, defined using Mayo score criteria, during the induction phase of included trials are summarised in Table 38 for the overall ITT populations and biologic-naïve and biologic-experienced subgroups, where available.

Table 38 Clinical response and clinical remission – Induction

Study name	Trial arm	Time point (wk)	Overall Population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
ELEVATE UC 12[47]	PBO	12	46/112 (41%)	17/112 (15%)	Bio/ JAKi-naïve vs exp	33/77 (43%)	12/77 (16%)	15/39 (39%)	5/39 (13%)
	ETR 2 mg	12	138/222 (62.2%)	55/222 (25%)		105/159 (66%)	46/159 (29%)	46/79 (58%)	16/79 (20%)
ELEVATE UC 52[47]	PBO	12	46/135 (34.1%)	10/135 (7.4%)	Bio/ JAKi-naïve vs exp	39/99 (39%)	9/99 (9%)	13/45 (29%)	3/45 (7%)
	ETR 2 mg	12	171/274 (62.4%)	74/274 (27%)		141/205 (69%)	66/205 (32%)	41/84 (49%)	15/84 (18%)
OASIS[43]	PBO	12	NR/54 (32.5%)	NR/54 (8.1%)	Bio naïve vs exp	NR	NR	NR	NR
	ETR 2 mg	12	NR/50 (50.6%)	NR/50 (33%)		NR	NR	NR	NR
TOUCHSTONE[136]	PBO	8	24/65 (37%)	4/65 (6%)	TNFi-naïve vs exp	NR	NR	NR	NR
	OZA 1 mg	8	38/67 (57%)	11/67 (16%)		NR	NR	NR	NR
TRUE NORTH[51]	PBO	10	56/216 (26%)	13/216 (6%)	Bio naïve vs exp	38/137 (28%)	9/137 (7%)	18/79 (23%)	4/79 (5%)
	OZA 1 mg	10	205/429 (48%)	79/429 (18%)		152/287 (53%)	66/287 (23%)	53/142 (37%)	13/142 (9%)
U-ACHIEVE-Phase 2b-Part 1[61]	PBO	8	6/46 (13%)	0/46 (0%)	TNFi-naïve vs exp	NR	0/13 (0%)	NR	0/33 (0%)
	UPA 45 mg	8	28/56 (50%)	11/56 (20%)		NR	NR	NR	NR
U-ACHIEVE Phase 3[62]	PBO	8	42/154 (27%)	7/154 (5%)	Bio failure	32/76 (42·1%)	7/76 (9.2%)	10/78 (13%)	0/78 (0.4%)

Study name	Trial arm	Time point (wk)	Overall Population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
	UPA 45 mg	8	232/319 (73%)	83/319 (26%)	vs non-failure	124/151 (82%)	53/151 (35%)	108/168 (64.4%)	30/168 (18%)
U-ACCOMPLISH[62]	PBO	8	44/174 (25%)	7/174 (4%)	Bio failure vs non-failure	27/85 (32%)	5/85 (6%)	17/89 (19.3%)	2/89 (2.4%)
	UPA 45 mg	8	254/341 (74%)	114/341 (33%)		134/168 (80%)	63/168 (37.5%)	120/173 (69.4%)	51/173 (29.6%)
SELECTION[50]	PBO	10	89/279 (32%)	27/279 (10%)	Bio naïve vs exp	64/137 (47%)	21/137 (15%)	25/142 (18%)	6/142 (4%)
	FIL 100 mg	10	266/562 (47%)	80/562 (14%)		164/277 (59%)	53/277 (19%)	102/285 (36%)	27/285 (9%)
	FIL 200 mg	10	302/507 (60%)	94/507 (19%)		163/245 (67%)	64/245 (26%)	139/262 (53%)	30/262 (11%)
OCTAVE Induction 1[52]	PBO	8	40/122 (33%)	10/122 (8%)	TNFi-naïve vs exp	NR/57 (47%)	9/57 (16%)	NR/65 (19%)	1/65 (1.5%)
	TOF 10 mg	8	285/476 (60%)	88/476 (18.5%)		NR/222 (66%)	56/222 (25%)	NR/254 (54%)	32/254 (12.6%)
OCTAVE Induction 2[52]	PBO	8	32/112 (28.6%)	4/112 (3.6%)	TNFi-naïve vs exp	NR/47 (32%)	4/47 (8.5%)	NR/65 (26%)	0/65 (0%)
	TOF 10 mg	8	236/429 (55%)	72/429 (17%)		NR/195 (62%)	43/195 (22%)	NR/234 (50%)	28/234 (12%)
OCTAVE Induction 1; OCTAVE Induction 2[52]	PBO	8	NR	NR	TNFi-naïve vs exp	43/104 (41%)	13/104 (13%)	29/130 (22%)	1/125 (1%)
	TOF 10 mg	8	NR	NR		267/417 (64%)	99/418 (24%)	254/488 (52%)	60/488 (12%)

Study name	Trial arm	Time point (wk)	Overall Population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
Sandborn 2012[120]	PBO	8	20/48 (42%)	5/48 (10%)	TNFi-naïve vs exp	15/33 (46%)	NR	5/NR (33%)	NR
	TOF 10 mg	8	20/33 (61%)	16/33 (48%)		14/23 (61%)	NR	6/10 (60%)	NR
UNIFI[63]	PBO	8	99/319 (31.3%)	17/319 (5.3%)	Bio failure vs non-failure	56/158 (35.4%)	15/158 (9.5%)	44/161 (27.3%)	2/161 (1.2%)
	UST 130 mg	8	164/320 (51.3%)	50/320 (15.6%)		90/156 (57.7%)	31/156 (20%)	74/164 (45.1%)	19/164 (11.6%)
	UST 6 mg/kg	8	199/322 (62%)	50/322 (15.5%)		104/156 (66.7%)	29/156 (18.6%)	95/166 (57.2%)	21/166 (12.7%)
GEMINI 1[65]	PBO	6	38/149 (25.5%)	8/149 (5.4%)	TNFi-naïve vs exp	20/76 (26%)	5/76 (6.6%)	18/73 (25%)	3/73 (4%)
	VED	6	106/225 (47%)	38/225 (17%)		69/130 (53%)	30/130 (23%)	37/95 (39%)	8/95 (8%)
Motoya 2019[66]	PBO	10	27/82 (33%)	10/82 (12%)	TNFi-naïve vs exp	15/41 (37%)	6/41 (15%)	12/41 (29%)	4/41 (10%)
	VED	10	65/164 (40%)	30/164 (18%)		42/79 (53%)	22/79 (28%)	23/85 (27%)	8/85 (9%)
VARSITY[64]	ADA160/80/40	14	177/386 (46%)	NR/386 (21%)	TNFi-naïve vs exp	151/305 (49.5%)	72/305 (23.6%)	26/81 (32%)	10/81 (12.3%)
	VED	14	257/383 (67%)	NR/383 (26.6%)		213/304 (70%)	84/304 (27.6%)	44/79 (55.7%)	18/79 (23%)
ULTRA 1[53]	PBO	8	58/130 (44.6%)	12/130 (9%)	TNFi-naïve	58/130 (44.6%)	12/130 (9%)	-	-
	ADA 80/40	8	67/130 (51.5%)	13/130 (10%)		67/130 (51.5%)	13/130 (10%)	-	-

Study name	Trial arm	Time point (wk)	Overall Population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
	ADA 160/80/40	8	71/130 (54.6%)	24/130 (18.5%)		71/130 (54.6%)	24/130 (18.5%)	-	-
ULTRA 2[54]	PBO	8	85/246 (34.6%)	23/246 (9.3%)	TNFi-naïve vs exp	56/145 (38.6%)	16/145 (11%)	29/101 (29%)	7/101 (7%)
	ADA 160/80	8	125/248 (50.4%)	41/248 (16.5%)		89/150 (59.3%)	32/150 (21.3%)	36/98 (37%)	9/98 (9.2%)
Suzuki 2014[55]	PBO	8	34/96 (35%)	11/96 (12%)	TNFi-naïve	34/96 (35%)	11/96 (12%)	-	-
	ADA 80/40	8	37/87 (43%)	12/87 (14%)		37/87 (43%)	12/87 (14%)	-	-
	ADA 160/80/40	8	45/90 (50%)	9/90 (10%)		45/90 (50%)	9/90 (10%)	-	-
HIBISCUS I [56]	PBO	10	36/72 (50%)	6/72 (8.3%)	TNFi Naïve	36/72 (50%)	6/72 (8.3)	-	-
	ADA 160/80/40	10	NR/NR (53%)[a]	34/142 (23.9%)		NR/NR (53%)	34/142 (23.9%)	-	-
HIBISCUS II[56]	PBO	10	28/72 (39%)	8/72 (11.1%)	TNFi Naïve	28/72 (39%)	8/72 (11.1%)	-	-
	ADA 160/80/40	10	NR/NR (53%) [a]	37/143 (25.9%)		NR/NR (53%)	37/143 (25.9%)	-	-
PURSUIT-SC[60]	PBO	6	76/251 (30.3%)	16/251 (6.4%)	TNFi-naïve	76/251 (30.3%)	16/251 (6.4%)	-	-
	GOL 200/100	6	129/253 (51%)	45/253 (17.8%)		129/253 (51%)	45/253 (17.8%)	-	-
	PBO	6	13/41 (32%)	4/41 (10%)		13/41 (32%)	4/41 (10%)	-	-

Study name	Trial arm	Time point (wk)	Overall Population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
PURSUIT-SC - phase 2[60]	GOL 200/100	6	18/41 (44%)	7/41 (17%)	TNFi-naïve	18/41 (44%)	7/41 (17%)	-	-
NCT01551290[59]	PBO	8	32/50 (33%)	11/50 (10%)	TNFi-naïve	32/50 (33%)	11/50 (10%)	-	-
	INF 5 mg/kg	8	48/57 (64%)	NR/NR (22%)		48/57 (64%)	NR/NR (22%)	-	-
Jiang 2015[57]	PBO	8	6/7 (37%)	5/7 (22%)	TNFi-naïve	6/7 (37%)	5/7 (22%)	-	-
	INF 5 mg/kg	8	30/41 (78%)	21/41 (54%)		30/41 (78%)	21/41 (54%)	-	-
Kobayashi 2016[58]	PBO	8	57/104 (36%)	21/104 (11%)	TNFi-naïve	57/104 (36%)	21/104 (11%)	-	-
	INF 5 mg/kg	8	67/78 (55%)	NR/NR (20%)		67/78 (55%)	NR/NR (20%)	-	-
ACT-1[35]	PBO	8	45/121 (37.2%)	18/121 (15%)	TNFi-naïve	45/121 (37.2%)	18/121 (15%)	-	-
	INF 5 mg/kg	8	84/121 (69.4%)	47/121 (39%)		84/121 (69.4%)	47/121 (39%)	-	-
ACT-2[35]	PBO	8	36/123 (29.3%)	7/123 (6%)	TNFi-naïve	36/123 (29.3%)	7/123 (6%)	-	-
	INF 5 mg/kg	8	78/121 (64.5%)	41/121 (34%)		78/121 (64.5%)	41/121 (34%)	-	-

[a] Response data for adalimumab from HIBISCUS I and HIBISCUS II is only available based on a pooled analysis of the two trials.

Data relating to clinical response clinical remission, defined using Mayo score criteria, during the maintenance phase of included trials are summarised in Table 91. Data are presented for treat-through trials and re-randomised responder trials, separately. Data is presented for all patients as well as biologic-exposure subgroups, where available.

For the network meta-analysis, the observed data from the re-randomised responder trials were taken “as is” from the studies. The observed data from the included treat-through trials (ACT 1, ULTRA 2 and Suzuki 2014) were adjusted, based on the assumption that the number of responders at the end of induction is a proxy for the total number of patients entering maintenance. Clinical response from the treat-through trials was based on the proportion achieving *sustained* clinical response, as this mitigates the risk of counting maintenance phase responders who were induction phase non-responders. Imputed inputs to the NMA of maintenance phase outcomes are further described in section 0, and in Table 43, Table 44, Table 45 and Table 46, and final inputs are presented in Table 47.

Outcomes reported in Table 39 for ELEVATE UC 52 are consistent with the study’s treat through design. For the NMA, individual patient data from ELEVATE UC 52 was used to isolate the maintenance phase outcomes to those among the induction phase responders.

Table 39 Clinical response and clinical remission – Maintenance

Study name	Trial arm	Time point (wk)	Overall population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
Treat-through trials									
ELEVATE UC 52[47]	PBO	52	31/135 (23%)	9/135 (6.7%)	Bio/JAKi-naïve vs exp	28/99 (28%)	8/99 (8%)	7/45 (16%)	3/45 (7%)
	ETR 2 mg	52	132/274 (48.2%)	88/274 (32.1%)		111/205 (54%)	75/205 (37%)	32/84 (38%)	19/84 (23%)
TOUCHSTONE[136]	PBO	32	13/25 (20%)	4/25 (6%)	TNF-naïve vs exp	NR	NR	NR	NR
	OZA 1 mg	32	34/42 (51%)	14/42 (21%)		NR	NR	NR	NR
VARSITY[64]	ADA	52	257/386 (43%)	87/386 (22.5%)	TNFi-naïve vs exp	NR/305 (NR%)	74/305 (24%)	NR/81 (NR%)	13/81 (16%)
	VED	52	177/383 (55%)	120/383 (31.3%)		NR/304 (NR%)	104/304 (34%)	NR/79 (NR%)	16/79 (20.3%)
ULTRA 2[54]	PBO	52	45/246 (18.3%)	21/246 (8.5%)	TNFi-naïve vs exp	35/145 (24%)	18/145 (12.4%)	10/101 (10%)	3/101 (3%)
	ADA	52	75/248 (30.2%)	43/248 (17.3%)		55/150 (37%)	33/150 (22%)	20/98 (20.4%)	10/98 (10.2%)
Suzuki 2014[55]	PBO	52	17/96 (18%)	7/96 (7%)	TNF-naive	17/96 (18%)	7/96 (7%)	-	-
	ADA 40 mg	52	55/177 (31%)	41/177 (23%)		55/177 (31%)	41/177 (23%)	-	-
NCT01551290[59]	PBO	26	26/49 (53%)	5/49 (10%)	TNF-naive	26/49 (53%)	5/49 (10%)	-	-
	INF 5 mg/Kg	26	29/50 (58%)	14/50 (28%)		29/50 (58%)	14/50 (28%)	-	-
Jiang 2015[57]	PBO	30	11/41 (27%)	10/41 (24%)	TNF-naive	11/41 (27%)	10/41 (24%)	-	-
	INF 5 mg/kg	30	27/41 (66%)	21/41 (51%)		27/41 (66%)	21/41 (51%)	-	-
Kobayashi 2016[58]	PBO	30	33/104 (32%)	17/104 (16%)	TNF-naive	33/104 (32%)	17/104 (16%)	-	-
	INF	30	48/104 (46%)	22/104 (21%)		48/104 (46%)	22/104 (21%)	-	-
ACT-1[35]	PBO	54	24/121 (20%)	20/121 (16.5%)	TNFi-naïve	24/121 (20%)	20/121 (16.5%)	-	-
	INF 5 mg/Kg	54	55/121 (46%)	42/121 (34.7%)		55/121 (45.5%)	42/121 (34.7%)	-	-
ACT-2[35]	PBO	30	32/123 (26%)	13/123 (11%)	TNFi-naïve	32/123 (26%)	13/123 (11%)	-	-
	INF 5 mg/Kg	30	57/121 (47%)	31/121 (26%)		57/121 (47%)	31/121 (26%)	-	-
Randomised responder trials									

Study name	Trial arm	Time point (wk)	Overall population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
TRUE NORTH[51]	PBO	42	93/227 (41%)	42/227 (18.5%)	Bio Naïve vs exp	74/152 (49%)	36/152 (23.7%)	17/72 (23.6%)	6/72 (8.3%)
	OZA 1 mg	42	138/230 (60%)	85/230 (37%)		88/145 (60.7%)	60/145 (41.4%)	47/81 (58%)	22/81 (27.2%)
U-ACHIEVE[62]	PBO	52	25/134 (19%)	18/149 (12%)	Bio- failure vs non-failure	14/63 (22.4%)	12/68 (17.6%)	11/71 (15.6%)	6/81 (7.5%)
	UPA 15 mg	52	85/135 (63%)	63/148 (42%)		46/71 (64.8%)	34/77 (44%)	39/64 (61%)	29/71 (40.5%)
	UPA 30 mg	52	110/144 (77%)	80/154 (52%)		65/78 (83.2%)	44/81 (54%)	45/66 (68.8%)	36/73 (49%)
SELECTION[50] from Induction FIL 100 mg	PBO	48	35/89 (39%)	12/89 (14%)	Bio Naïve vs exp	28/54 (52%)	9/54 (17%)	7/35 (20%)	3/35 (9%)
	FIL 100 mg	48	87/172 (51%)	41/172 (24%)		61/105 (58%)	28/105 (27%)	26/67 (39%)	13/67 (19%)
SELECTION[50] from Induction FIL 200 mg	PBO	48	32/98 (33%)	11/98 (11%)		22/54 (41%)	9/54 (17%)	10/44 (23%)	2/44 (5%)
	FIL 200 mg	48	133/199 (67%)	74/199 (37%)		80/107 (75%)	52/107 (48.6%)	53/92 (58%)	22/92 (24%)
OCTAVE Sustain[52]	PBO	52	40/198 (20%)	22/198 (11%)	TNFi-naïve vs exp	NR/NR (25%)	NR/NR (10%)	NR/NR (15%)	NR/NR (12%)
	TOF 5 mg	52	102/198 (51.5%)	68/198 (34.3%)		NR/NR (56%)	NR/NR (41%)	NR/NR (47%)	NR/NR (27%)
	TOF 10 mg	52	122/197 (62%)	81/197 (40.6%)		NR/NR (67%)	NR/NR (46%)	NR/NR (57%)	NR/NR (37%)
UNIFI[63]	PBO	44	78/175 (44.6%)	42/175 (24%)	Bio failure vs non-failure	44/87 (50.6%)	27/87 (31%)	34/88 (38.6%)	15/88 (17%)
	UST 90 mg Q12W	44	117/172 (68%)	66/172 (38.4%)		78/102 (76.5%)	50/102 (49%)	39/70 (55.7%)	16/70 (30%)
	UST 90 mg Q8W	44	125/176 (71%)	77/176 (44%)		66/85 (77.6%)	41/85 (48.2%)	59/91 (64.8%)	36/91 (39.6%)
GEMINI 1[65]	PBO	46	30/126 (23.8%)	20/126 (15.9%)	TNFi-naïve vs exp	21/79 (27%)	15/79 (19%)	9/47 (19%)	5/47 (11%)
	VED	46	134/247 (54.3%)	107/247 (43.3%)		88/145 (60.7%)	68/145 (47%)	46/102 (45%)	39/102 (38%)
VISIBLE 1[69]	PBO	46	NR/56 (NR%)	8/56 (14%)	TNFi-naïve	NR/37 (NR%)	7/37 (19%)	NR	NR
	VED SC	46	NR/106 (NR%)	49/106 (46%)		NR/67 (NR%)	36/67 (54%)	NR	NR
	VED IV	46	NR/54 (NR%)	23/54 (43%)		NR/32 (NR%)	17/32 (53%)	NR	NR
Motoya 2019[66]	PBO	60	NR/42 (NR%)	13/42 (31%)		NR/28 (NR%)	10/28 (36%)	NR/14 (NR%)	3/14 (21%)

Study name	Trial arm	Time point (wk)	Overall population		Sub-group	Bio-naïve		Bio-experienced	
			Response	Remission		Response	Remission	Response	Remission
			n/N (%)	n/N (%)		n/N (%)	n/N (%)	n/N (%)	n/N (%)
	VED	60	NR/41 (NR%)	23/41 (56%)	TNFi-naïve vs exp	NR/24 (NR%)	13/24 (54%)	NR/17 (NR%)	10/17 (59%)
PURSUIT-M[67]	PBO	54	48/154 (31.2%)	34/154 (22%)	TNFi-naïve	48/154 (31.2%)	34/154 (22%)	-	-
	GOL 50 mg	54	71/151 (47%)	50/151 (33%)		71/151 (47%)	50/151 (33%)	-	-
	GOL 100 mg	54	76/151 (50%)	51/151 (34%)		76/151 (50%)	51/151 (34%)	-	-
PURSUIT-J[68]	PBO	54	6/31 (19%)	2/31 (7%)	TNF-naive	6/31 (19%)	2/31 (7%)	-	-
	GOL	54	18/32 (56%)	16/32 (50%)		18/32 (56%)	16/32 (50%)	-	-
LIBERTY-UC[95]	PBO	54	158/294 (53.7%)	127/294 (43.2%)	NR	NR	NR	NR	NR
	INF 120 mg SC	54	45/144 (31.3%)	30/144 (20.8%)		NR	NR	NR	NR

F.1.2.10 Safety

Safety outcomes from both induction and maintenance phases of studies were considered for comparison by means of network meta-analysis. Although several safety endpoints could have been synthesised, those that aligned with what was presented in previous technology appraisals were deemed highest priority. The meta-analysis of serious infections was considered relevant and high priority. Data were available from 18 studies comparing two treatments (Table 40). To maximise statistical power, especially in light of the rarity of analysed safety events, data from all patients were combined into a single analysis based on the assumption that the prior biologic exposure has no influence on the safety outcomes.

Though no meta-analyses were performed, data for other safety endpoints (serious AE, discontinuation due to AE) from both induction and maintenance are presented for completeness in Table 40 and Table 41.

Table 40 Safety outcomes - Induction

Study name	Trial arm	Time point (wk)	Safety pop, N	SAE, n (%)	Serious Infection, n (%)	Disc due to AEs, n (%)
ELEVATE UC 12[47]	PBO	12	116	2(1.7%)	0 (0%)	1(NR%)
	ETR 2 mg	12	238	6(2.5%)	0 (0%)	13(5.5%)
OASIS	PBO	12	54	6 (11.1%)	0 (0%)	0 (0)
	ETR 2 mg	12	50	0 (0%)	0 (0%)	4 (8%)
TOUCHSTONE[136]	PBO	8	65	4(6.2%)	NR	1(1.5%)
	OZA 1 mg	8	67	2(3%)	NR	1(1.5%)
TRUE NORTH[51]	PBO	10	216	7(3.2%)	1(0.5%)	7(3.2%)
	OZA 1 mg	10	429	17(4%)	4(0.9%)	14(3.3%)
U-ACHIEVE-Phase 2b-Part 1[61]	PBO	8	46	5(11%)	2(4%)	4(9%)
	UPA 45 mg	8	56	3(5%)	2(4%)	4(7%)
U-ACHIEVE-Phase 3 induction[62]	PBO	8	155	9(6%)	2(1%)	14(9%)
	UPA 45 mg	8	319	8(3%)	5(2%)	6(2%)
U-ACCOMPLISH [62]	PBO	8	177	8(5%)	1(1%)	9(5%)
	UPA 45 mg	8	344	11(3%)	2(1%)	6(2%)
SELECTION- Induction A & B[50]	PBO	10	279	13(4.7%)	3(1.1%)	14(5%)
	FIL 100 mg	10	562	28(5%)	6(1.1%)	20(3.6%)
	FIL 200 mg	10	507	22(4.3%)	3(0.6%)	23(4.5%)
OCTAVE Induction 1[52]	PBO	8	122	5(4.1%)	0(0%)	2(1.6%)
	TOF 10 mg	8	476	16(3.4%)	6(1.3%)	18(3.8%)
OCTAVE Induction 2[52]	PBO	8	112	9(8%)	0(0%)	8(7.1%)
	TOF 10 mg	8	429	18(4.2%)	1(0.2%)	17(4%)
Sandborn 2012[120]	PBO	12	48	4(8%)	0(0%)	4(8%)
	TOF 10 mg	12	33	2(6%)	2(6%)	1(3%)
UNIFI[63]	PBO	8	319	22(7%)	5(2%)	NR
	UST 130 mg	8	321	12(4%)	2(1%)	NR

	UST 6 mg/kg	8	320	11(3%)	1(0%)	NR
GEMINI 1[65]	PBO	6	149	10(7%)	3(2%)	NR
	VED	6	225	5(2%)	1(<1%)	NR
Motoya 2019[66]	PBO	10	82	4(4.9%)	NR(2.4%)	2(2.4%)
	VED	10	164	10(6.1%)	NR(0.6%)	8(4.9%)
ULTRA 1[53]	PBO	8	223	17(8%)	3(1%)	12(5%)
	ADA 80/40	8	130	5(4%)	2(2%)	8(6%)
	ADA 160/80/40 mg	8	223	9(4%)	0(0%)	12(5%)
Suzuki 2014[55]	PBO	8	96	7(7%)	0(0%)	4(4%)
	ADA 80/40 mg	8	87	2(2%)	0(0%)	0(0%)
	ADA 160/80/40 mg	8	90	4(4%)	3(3%)	6(7%)
HIBISCUS I[56]	PBO	12	72	2 (3%)	2 (3%)	0 (0%)
	ADA 160/80/40 mg	12	142	3 (2%)	0 (0%)	2 (1%)
HIBISCUS II[56]	PBO	12	72	5 (7%)	0 (0%)	1 (1%)
	ADA 160/80/40 mg	12	143	3 (2%)	1 (1%)	2 (1%)
PURSUIT-SC[60]	PBO	6	71	20 (6%)	6 (2%)	3 (1%)
	GOL 200/100 mg	6	331	9 (3%)	1 (0%)	1 (0%)
Kobayashi 2016[58]	PBO	14	104	13 (13%)	2 (2%)	8 (8%)
	INF 5 mg/kg	14	104	9 (9%)	1(1%)	5 (5%)

Table 41 Safety outcomes - Maintenance

Study name	Trial arm	Time point (wk)	Safety pop, N	SAEs, n (%)	Serious Infection, n (%)	Disc due to AEs, n (%)
ELEVATE UC 52[47]	PBO	52	144	9(6.3%)	5(3.5%)	7(5%)
	ETR 2 mg	52	289	20(7%)	3(1%)	12(4.2%)
SELECTION[50] from FIL 100 mg	PBO	58	91	7(7.7%)	2(2.2%)	4(4.4%)
	FIL 100 mg	58	179	8(4.5%)	3(1.7%)	10(5.6%)
SELECTION[50] from FIL 200 mg	PBO	58	99	0(0%)	0(0%)	2(2%)
	FIL 200 mg	58	202	9(4.5%)	2(1%)	7(3.5%)
TOUCHSTONE[136]	PBO	32	25	2(8%)	NR	3(12%)
	OZA 1 mg	32	42	1(2.4%)	NR	0(0%)
TRUE NORTH[51]	OZA 1 mg	52	230	12(5.2%)	2(0.9%)	3(1.3%)
	PBO	52	227	18(7.9%)	4(1.8%)	6(2.6%)
OCTAVE Sustain[52]	PBO	52	198	13(6.6%)	2(1%)	37(18.7%)
	TOF 5 mg	52	198	10(5.1%)	2(1%)	18(9.1%)
	TOF 10 mg	52	196	11(5.6%)	1(0.5%)	19(9.7%)
GEMINI 1[65]	PBO	52	126	20(16%)	4(3%)	NR(NR%)
	VED Q8W IV	52	122	10(8%)	3(2%)	NR(NR%)
	VED Q4W IV	52	125	11(9%)	2(2%)	NR(NR%)
VISIBLE 1[69]	PBO	52	56	6(10.7%)	NR	5(8.9%)
	VED SC	52	106	10(9.4%)	NR	5(4.7%)
	VED Q8W IV	52	54	7(13%)	NR	2(3.7%)
Motoya 2019[66]	PBO	60	42	3(7.1%)	NR(2.4%)	6(14.3%)

Study name	Trial arm	Time point (wk)	Safety pop, N	SAEs, n (%)	Serious Infection, n (%)	Disc due to AEs, n (%)
	VED Q8W IV	60	41	4(9.8%)	NR(2.4%)	2(4.9%)
VARSITY[64]	ADA 40 mg EOW	52	386	53(13.7%)	8(2.2%)	25(6.5%)
	VED Q8W IV	52	383	42(11%)	7(1.6%)	17(4.4%)
PURSUIT-M[67]	PBO	54	156	12(8%)	3(2%)	10(6%)
	GOL 50 mg	54	154	13(8%)	5(3%)	8(5%)
	GOL 100 mg	54	154	22(14%)	5(3%)	14(9%)
U-ACHIEVE[62]	PBO	60	149	19(13%)	6(4%)	17(11%)
	UPA 15 mg	60	148	10(7%)	5(3%)	6(4%)
	UPA 30 mg	60	154	9(6%)	4(3%)	10(6%)
UNIFI[63]	PBO	44	175	17(10%)	4(2%)	20(11%)
	UST 90 mg Q12W	44	172	13(8%)	6(4%)	9(5%)
	UST 90 mg Q8W	44	176	15(9%)	3(2%)	5(3%)
ACT-1[35]	PBO	54	121	31(26%)	5(4%)	11(9%)
	INF 5 mg/Kg	54	121	26(22%)	3(3%)	10(8%)
ACT-2[35]	PBO	30	123	24(20%)	1(1%)	12(10%)
	INF 5 mg/Kg	30	121	13(11%)	2(2%)	2(2%)
NCT01551290[59]	PBO	26	NR	NR	0(0%)	2(4%)
	INF 5 mg/Kg	26	NR	NR	0(0%)	4(8%)
Jiang 2015[57]	PBO	30	41	4(10%)	0(0%)	2(5%)
	INF 5 mg/kg	30	41	3(7%)	1(2%)	1(2%)
Kobayashi 2016[58]	PBO	30	104	19(18%)	2(2%)	8(8%)
	INF 5 mg/kg	30	104	7(7%)	1(1%)	18(17%)
ULTRA 2[54]	PBO	52	260	32(12%)	5(2%)	34(13%)
	ADA 40 mg EOW	52	257	31(12%)	4(2%)	23(9%)
NCT00853099[55]	PBO	52	96	14(14.6%)	2(2.1%)	6(6.3%)
	ADA 40 mg EOW	52	177	33(18.6%)	8(4.5%)	22(12.4%)

F.2 Network meta-analysis

F.2.1 Selection of evidence contributing to network meta-analysis

In order to reduce heterogeneity and increase the comparability of the dataset, separate analyses were performed for patients with and without prior exposure to biologic therapy. This approach and associated assumptions made are described in more detail in section B.3.9.

For the biologic-exposure subgroup analyses presented here, the terms TNFi-exposure, biologic exposure and biologic or JAKi exposure were assumed to be interchangeable, and it was assumed that biologic-failure can be combined with biologic exposed. The not biologic-failure groups were combined with the biologic naïve group. Wherever available, subgroup data based

on prior exposure was preferred as this is the most commonly reported subgroup definition. If these data were not reported, then subgroup data based on prior failure was utilised.

Several studies identified in the SLR which were considered relevant to the decision problem and inclusion in the NMA did not report subgroup data based on prior biologic exposure even though they included a mixed population. These were excluded from the efficacy analyses on clinical response and clinical remission. If, however, the study reported on the incidence of serious infections in the overall population, the study data was included in the safety NMA. Studies excluded from the efficacy analysis for this reason are described in Table 42.

Table 42 Studies or study arms excluded from further consideration in evidence synthesis with rationale

Study name	Reason for exclusion from NMA
TOUCHSTONE/ NCT01647516	Efficacy outcomes not reported for prior biologic exposure subgroups
	Serious infections not reported
LIBERTY-UC/ NCT04205643	Efficacy outcomes not reported for prior biologic exposure subgroups
	Serious infections not reported
U-ACHIEVE-Phase 2b/ NCT02819635	Prior exposure subgroup data reported for placebo arm but not UPA 45 mg.*
OASIS/ NCT02447302	Efficacy outcomes not reported for prior biologic exposure subgroups.*

*Included in serious infection NMA where outcomes included for overall trial population.

F.2.2 Inputs to network meta-analysis

F.2.2.1 Input data

The following data was used within the NMA analyses:

- Number of patients experiencing the event of interest within each arm
- Total number of patients in the population of interest within each arm

Placebo will be used as a reference treatment.

For the analysis, the observed data from the rerandomized responder trials will be taken directly, while the observed data from the treat-through trials will be adjusted, based on the assumption that the number of responders at the end of induction is a proxy for the total number of patients entering maintenance. Clinical response from the treat-through trials will be based on the proportion achieving sustained clinical response, as this mitigates the risk of counting maintenance phase responders who were induction phase non-responders.

Table 43 presents the data, as reported, in the treat-through clinical trials, including the number of randomised patients at baseline, the number of clinical responders at the end of induction, the number of sustained clinical responders and clinical remitters at the end of maintenance.

Some issues arose when attempting to synthesise the published values:

- In the ACT 1 placebo arm, the number of clinical remitters at the end of maintenance was higher than the number of sustained clinical responders. This could be a function of a stricter 3-time-point sustained clinical response definition (weeks 8, 30 and 54 instead of just weeks 8 and 54) or it could be that many patients in remission at the end-of-follow-up were not always at least clinical responders at each of the 8 and 30-week time points. Whatever the cause, these data would not fit in multinomial probit model as is.
- As per Table 44, the proportions of clinical remitters among induction phase clinical responders in the placebo arms of a number of the treat-through trials were quite a bit higher than in all of the re-randomised responder trials. This may have been a result of patients achieving clinical response after induction and going on to achieve clinical remission at the end of maintenance phase follow-up.

In order to address these issues, we looked to the placebo arms of the rerandomized responder trials in order to estimate an average proportion for the number of clinical remitters among clinical responders. Based on the percentage of clinical remitters who were also maintenance phase clinical responders from the placebo arms of rerandomized trials, an average of value was assumed to apply to all placebo arms of treat-through trials. The number of clinical remitters in the placebo arms of each treat-through trial was calculated as the number of sustained clinical responders multiplied by the appropriate average proportion, i.e., the average ratio of maintenance clinical remitters to clinical responders as per Table 45.

Finally, available data from ELEVATE UC 52 regarding the correct proportions of clinical remitters among induction phase clinical responders demonstrated that there were a small number of etrasimod 2mg patients reaching clinical remission at the end of maintenance who had not reached clinical response by the end of induction. We assumed that the number of clinical remitters in the active treatment arms of other randomized trials was likely to be similarly overestimated. Therefore, an adjustment was applied to the number of active treatment clinical remitters in the treat-through trials using the appropriate values as per Table 46.

Table 47 presents the final values used as inputs for the treat through trials in the NMA with randomised responder trials.

Table 43 Data from treat-through trials, as reported

Study	Treatment	Baseline	End of induction	End of maintenance	
		Randomised, N	Clinical response, n	Sustained clinical response, n	Clinical remission, n
Overall					
VARSITY NCT02497469	Adalimumab	386	177		87

Study	Treatment	Baseline	End of induction	End of maintenance	
		Randomised, N	Clinical response, n	Sustained clinical response, n	Clinical remission, n
	Vedolizumab	383	257		120
ULTRA 2 NCT00408629	Placebo	246	85	30	21
	Adalimumab	248	125	59	43
ELEVATE UC 52/ NCT03945188	Placebo	135	46	25	8
	Estrasimod 2mg	274	171	123	84
Biologics/JAKi naïve					
ELEVATE UC 52/ NCT03945188	Placebo	93	35	19	6
	Estrasimod 2mg	194	132	99	86
Biologics/JAKi exposed					
ELEVATE UC 52/ NCT03945188	Placebo	42	11	6	2
	Estrasimod 2mg	80	39	24	16
Prior TNFi naïve					
ACT-1 NCT00036439	Placebo	121	45	17	20
	Infliximab 5 mg/Kg	121	84	47	42
ULTRA 2 NCT00408629	Placebo	145	56	24	18
	Adalimumab	150	89	44	33
VARSITY NCT02497469	Adalimumab	305	151		74
	Vedolizumab	304	213		104
	Estrasimod 2mg	228	151	110	77
Prior TNFi use					
ULTRA 2 NCT00408629	Placebo	101	29	6	3
	Adalimumab	98	36	15	10
VARSITY NCT02497469	Adalimumab	81	26		13
	Vedolizumab	79	44		16
	Estrasimod 2mg	46	20	13	7

Table 44 Maintenance phase remission vs. Induction phase clinical responders

Re-randomised				Treat through			
Study name/NCT	Maintenance Remitters	Induction Responders	%	Study name/NCT	Maintenance Remitters	Induction Responders	%
Overall							
SELECTION/ NCT02914522	23	187	12%	ELEVATE UC 52/ NCT03945188	8	46	17%

Re-randomised				Treat through			
Study name/NCT	**Maintenance Remitters**	**Induction Responders**	**%**	**Study name/NCT**	**Maintenance Remitters**	**Induction Responders**	**%**
TRUE NORTH/ NCT02435992	42	227	19%	TOUCHSTONE NCT01647516	4	24	17%
OCTAVE Sustain/ NCT01458574	22	198	11%	ULTRA 2 NCT00408629	21	85	25%
GEMINI 1/ NCT00783718	20	126	16%				
VISIBLE 1/ NCT02611830	8	56	14%				
U-ACHIEVE-Phase 3 maintenance/ NCT02819635	18	149	12%				
UNIFI/ NCT02407236	42	175	24%				
Subtotal	**175**	**1118**	**16%**	**Subtotal**	**33**	**155**	**21%**
Prior TNFi Failure							
SELECTION/ NCT02914522	5	66	8%	ELEVATE UC 52/ NCT03945188	2	7	29%
OCTAVE Sustain/ NCT01458574	10	89	11%				
GEMINI 1/ NCT00783718	2	38	5%				
VISIBLE 1/ NCT02611830	1	19	5%				
Subtotal	**18**	**212**	**8%**	**Subtotal**	**2**	**7**	**29%**
No Prior TNFi Failure							
SELECTION/ NCT02914522	18	121	15%	ELEVATE UC 52/ NCT03945188	6	39	15%
OCTAVE Sustain/ NCT01458574	12	109	11%				
Subtotal	**30**	**230**	**13%**	**Subtotal**	**6**	**39**	**15%**
Biologics/JAKi naïve							
SELECTION/ NCT02914522	18	108	17%	ELEVATE UC 52/ NCT03945188	6	35	17%
U-ACHIEVE-Phase 3 maintenance/ NCT02819635	12	65	18%				
Subtotal	**30**	**173**	**17%**	**Subtotal**	**6**	**35**	**17%**
Biologics Naïve							
TRUE NORTH/ NCT02435992	36	152	24%	Kobayashi 2016 Japic CTI-060298	17	37	46%
UNIFI/ NCT02407236	27	84	32%				

Re-randomised				Treat through			
Study name/NCT	**Maintenance Remitters**	**Induction Responders**	**%**	**Study name/NCT**	**Maintenance Remitters**	**Induction Responders**	**%**
Subtotal	**63**	**236**	27%	**Subtotal**	**17**	**37**	46%
TNFi naïve							
TRUE NORTH/ NCT02435992	35	158	22%	ACT-1 NCT00036439	20	45	44%
GEMINI 1/ NCT00783718	15	79	19%	ACT-2 NCT00096655	13	36	36%
VISIBLE 1/ NCT02611830	7	37	19%	NA NCT01551290	5	16	31%
PURSUIT-M/ NCT00488631	34	154	22%	Jiang 2015 NA	10	15	67%
PURSUIT-J/ NCT01863771	2	31	6%	ULTRA 2 NCT00408629	18	56	32%
Subtotal	**58**	**301**	19%	**Subtotal**	**46**	**123**	37%
TNFI exposed							
TRUE NORTH/ NCT02435992	7	69	10%	ULTRA 2 NCT00408629	3	29	10%
Subtotal	**7**	**69**	10%	**Subtotal**	**3**	**29**	**10%**

Table 45 Maintenance phase outcomes for RR trials

Trial	Responders	Remitters	Remitters/Responders
Overall			
SELECTION/ NCT02914522	67	23	34%
TRUE NORTH/ NCT02435992	93	42	45%
OCTAVE Sustain/ NCT01458574	40	22	55%
GEMINI 1/ NCT00783718	30	20	67%
VISIBLE 1/ NCT02611830	16	8	50%
U-ACHIEVE-Phase 3 maintenance/ NCT02819635	25	18	72%
UNIFI/ NCT02407236	78	42	54%
Subtotal	**349**	**175**	**50%**
Biologics naïve			
SELECTION/ NCT02914522	50	18	36%
TRUE NORTH/ NCT02435992	74	36	49%
UNIFI/ NCT02407236	44	27	61%
Subtotal	**168**	**81**	**48%**
Prior TNFi naïve			
GEMINI 1/ NCT00783718	21	15	71%
PURSUIT-M/ NCT00488631	48	34	71%
PURSUIT-J/ NCT01863771	6	2	33%
Subtotal	**75**	**51**	**68%**
Prior TNFi failure			
OCTAVE Sustain/ NCT01458574	13	10	77%

Trial	Responders	Remitters	Remitters/Responders
GEMINI 1/ NCT00783718	6	2	33%
Subtotal	**19**	**12**	**63%**
No prior TNFi failure			
OCTAVE Sustain/ NCT01458574	27	12	44%
Subtotal	**27**	**12**	**44%**

Table 46 Rate of induction phase non-responders amongst maintenance phase remitters for ELEVATE UC 52

Treatment	Population	Maintenance clinical remitters that were not induction phase responders		
		n	N	%
Placebo	Overall	1	7	14%
Etrasimod 2mg	Overall	4	88	5%
Placebo	Biologics/JAKi naïve	1	7	14%
Etrasimod 2mg	Biologics/JAKi naïve	3	71	4%
Placebo	Biologics/JAKi exposed	0	2	0%
Etrasimod 2mg	Biologics/JAKi exposed	1	17	6%
Placebo	Prior TNFi failure	0	2	0%
Etrasimod 2mg	Prior TNFi failure	1	8	13%
Placebo	No prior TNFi failure	1	7	14%
Etrasimod 2mg	No prior TNFi failure	3	80	4%

Table 47 NMA inputs for treat-through trials imputed as randomised responder trials

Study	Trial arm	N	Sustained response	Remission
ELEVATE UC 52	PBO	[redacted]	[redacted]	[redacted]
	ETR 2 mg	[redacted]	[redacted]	[redacted]
ACT 1	PBO	45	17	12
	INF 5 mg/kg	84	47	40
ULTRA 2	PBO	56	24	17
	ADA 40 mg EOW	89	44	32

Unfortunately, the data necessary to make the imputation was insufficient from Suzuki 2014 and unavailable by subgroup from the VARSITY study, so these were excluded from the maintenance phase analysis.

For studies with a zero count in one arm (and a non-zero count in the other arm), a continuity correction of 0.5 will be applied if model convergence issues occur. This correction will be applied to all arms of the study.

F.2.3 Methods of network meta-analysis

The NMAs were conducted under a Bayesian framework using Markov Chain Monte Carlo (MCMC) sampling in accordance with HTA recommendations[170] using the models specified below.

All analyses were implemented in WinBUGS version 1.4.3 statistical software with non-informative priors. Results were generated using both random- and fixed effects models, and compared for goodness of fit to the data, calculated as the total residual deviance. The model with the lowest Deviance Information Criterion (DIC) is generally considered the model with the "best" fit to the data. It has been suggested that differences in DIC greater than 5 are important and can be used to rule out the model with the higher DIC, whereas differences of less than 3 indicate that there is little to choose between the models, so long as they produce similar results. Where the difference in DIC suggested indifference, the simpler fixed effect model was preferred.

An initial burn-in of at least 20,000 simulations was used, and convergence was confirmed through visual inspection the Brook-Gelman-Rubin diagnostic and history plots. This was followed by 50,000 simulations on 3 chains, thinned by a factor of 10, to estimate the sampled parameters. Convergence was assessed by visual inspection of the history, kernel density and autocorrelation plots as well as the Brooks Gelman-Rubin diagnostic plot. Summary statistics (of the joint posterior distributions) for all parameters are presented: point estimate reflecting the median value along with 95% credible intervals (95% CrI) reflecting the range of true effects with 95% probability.

To estimate absolute probabilities of experiencing each event for each treatment, we combined the treatment effects with an estimate of the placebo response, which was estimated using methods described in TSD 5.[171]

F.2.3.1 Clinical response and clinical remission

Clinical response and clinical remission were considered as ordered categorical data with three mutually exclusive categories: (1) no response; (2) clinical response; and (3) clinical remission. The data could therefore be synthesised using a multinomial model with probit link using methods described in TSD 2.[170] With this method, the ordered probit model is designed to model a discrete dependent variable that takes ordered multinomial outcomes, for example clinical response and clinical remission. The probability of an outcome was calculated by estimating a latent variable as a linear function of the independent variable (randomised treatment) plus a set of threshold/cut-off points. The higher the value of the latent variable, the more likely they are to report a stricter category of response (e.g. clinical remission).

Define r_{ikj} as the number of patients with an event in arm k of trial i belonging to different, mutually exclusive categories $j = 1, 2, \ldots, J$, where these categories represent different thresholds of the outcome on a common underlying continuous scale.[170] In the case of the outcomes of interest, clinical response, and clinical remission, one can consider clinical

response as the underlying continuous scale of which clinical remission is regarded as maximum response.

The responses for each arm k of trial i in category j will follow a multinomial distribution,

$r_{i,k,j=1,..,J} \sim$ Multinomial$(p_{i,k,j=1,..,J}, n_{ik})$

where

$$\sum_{j=1}^{J} p_{i,k,j} = 1$$

and p_{ikj} are the probabilities that a patient in arm k of trial i belongs to category j.

As p_{ikj} is a probability, and therefore restricted between 0 and 1, either a logit or probit link can be applied to map the probabilities to a continuous measure. The logit model, i.e., using the logit link function, is used to model the odds of success of an event. The probit model, i.e., using the probit link function, is used to determine the likelihood that an event will occur in one of a range of categories. Given this interpretation, the probit link function will be used for the multinomial modelling.

The probit link function is the inverse of the normal cumulative distribution function (ϕ) and thus the model of the probabilities, p_{ikj} can be written as

$$\phi^{-1}(p_{ikj}) = \mu_i + z_{ij} + \delta_{i,bk} I_{\{k \neq 1\}}$$

Where $\delta_{i,bk}$ are the trial specific treatment effects and z_{ij} as the differences on the standard normal scale between the response to category j and the response to category j-1 in all the arms of trial i. We will assume a fixed effect for differences between categories ($z_{ij} = z_j$) given the limited data informing the network comparisons.

The model was implemented as fixed effect and random effects models where possible. For the random effects model, the trial-specific treatment effects will come from a common distribution. This is described further in the next section binomial model specification.

Since there are some trials included in the analyses that feature more than two arms multi-arm adjustments were made. This involved using conditional univariate distributions for arms k > 2 to estimate the random effects for each multi-arm study so that the between-arm correlations between parameters are taken into account. This approach is in line with NICE DSU technical support document 2.[170]

The outputs of the NMA for clinical response and clinical remission include the following:

- Probability of achieving clinical response and clinical remission
- Estimates of effect (risk ratios) for each treatment compared with placebo
- Estimates of effect (difference on probit scale) for each treatment compared with placebo

- Estimates of effect (risk ratios) for etrasimod compared with each other treatment

F.2.3.2 Serious infections

The analyses for the dichotomous safety outcomes of serious infections was performed using a binomial likelihood model with logit link using methods described in TSD 2.[170]

Define r_{ik} as the number of patients with an event, out of the total number of patients in each arm, n_{ik}, for arm k of trial i. It is assumed that the data follows a binomial likelihood, i.e.

$r_{ik} \sim$ Binomial(p_{ik}, n_{ik})

where p_{ik} represents the probability of an event in arm k of trial i.

As p_{ik} is a probability, and therefore restricted between 0 and 1, a logit link will be applied to map the probabilities to a continuous measure. The probabilities will be modelled on the logit scale as

$$logit(p_{ik}) = \mu_i + \delta_{i,1k} I_{\{k \neq 1\}}$$

where

$$I_{\{k \neq 1\}} = \begin{cases} 1, if\ k \neq 1 \\ 0, if\ k = 1 \end{cases}$$

From these equations, μ_i are the trial-specific baselines, representing the log-odds an event occurring in the treatment in arm 1, and $\delta_{i,1k}$ are the trial-specific log odds ratios of an event on the treatment in arm k compared to the treatment in arm 1.

The model was implemented as fixed effect and random effects models where possible. For the random effects model, the trial-specific log-odds ratios will come from a common distribution: $\delta_{i,1k} \sim \mathcal{N}\left(d_{t_{i1},t_{ik}}, sd^2\right)$, where $d_{t_{i1},t_{ik}}$ represents the mean effect of treatment in arm k of trial i, t_{ik}, compared to treatment in arm 1 of trial i, t_{i1}, and sd^2 represents the between-trial variability in treatment effects. Therefore, the random effects model assumes that for a given pair of treatments, the outcome of interest may vary across studies and that they come from a common distribution. The fixed effect model is a special case where $sd^2 = 0$, which therefore assumes homogeneity of the underlying true treatment effects, i.e., $\delta_{i,1k} = d_{t_{i1},t_{ik}}$.

As previously described the multinomial model specification, multi-arm adjustments was made to account for between arm correlation.

The outputs of the NMA for serious infection include the following:

- Probability of experiencing serious infections
- Estimates of effect (risk ratios and log odds ratios) for each treatment compared with placebo
- Estimates of effect (risk ratios) for etrasimod compared with each other treatment

F.2.3.3 Baseline model specification

To model baseline effects the following formulation was adopted in line with NICE TSD 5.[171]

$$g(\gamma) = \theta_{ik} = \mu_i$$

$$\mu_i \sim \mathcal{N}(m, \sigma_m^2)$$

in which the study-specific baselines are drawn from a distribution of effects with a common mean and variance. Vague priors were put on the mean and on the variance, $m \sim \mathcal{N}(0, 10^4)$ and $\sigma_m \sim \mathcal{U}\text{niform}(0, 5)$.

The mean and standard deviation of the predictive distribution was used as the baseline as it is argued that the posterior mean of m and its posterior standard deviation under-represents the variation observed in the data.

The same model was used to determine the mean baseline risk among studies to inform the placebo adjustment.

All studies were used to inform the baseline risk, however, only ELEVATE trials were used to inform the baseline for the absolute outcome measures, since this reflects the most recent placebo data available.

F.2.3.4 Prior distributions

As the trial-specific baselines, μ_i, are regarded as nuisance parameters (i.e., are estimated in the model but not of interest), they will be given vague priors, where $\mu_i \sim \mathcal{N}(0, 10^4)$. Furthermore, under the consistency assumptions of NMA and that the consistency equations can be written generally as

$d_{t_{i1},t_{ik}} = d_{1,t_{ik}} - d_{1,t_{i1}}$,

The parameters d_{12} and d_{13} were given vague prior distributions: $\mathcal{N}(0, 10^4)$. These non-informative priors applied to both the fixed effect and random effects models.

In addition to this, the random effects model needs priors for the variance of parameters $\delta_{i,k}$. A vague prior was set for its standard deviation:

$$sd \sim \mathcal{U}\text{niform}(0, 5)$$

This prior may be adjusted if required to improve convergence of the models.

In addition, for the meta-regression coefficient, a vague prior will be given, $\mathcal{N}(0, 10^4)$. For the ordinal category cut-offs, a vague prior will also be used, $\mathcal{U}\text{niform}(0,2)$.

F.2.3.5 Programming language for network meta-analysis

F.2.3.6 Multinomial likelihood model with probit link – fixed effect

```
model {                                  # *** Program Starts
   for(i in 1:ns) {                      # Loop through studies
      w[i,1] <- 0                        # Adjustment for multi-arm trials is zero for control arm
      delta[i,1] <- 0                    #  Treatment effect is zero for control arm
      mu[i] ~ dnorm(0,0.0001)            # Vague priors for trial baselines

      for (k in 1:na[i]) {               # Loop through arms
         p[i,k,1] <- 1                   # Pr(Response) >0

         for (j in 1:nc[i]-1) {          # Loop through categories
            r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j])       # Binomial Likelihood
            q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]])    # Conditional probabilities
            # Linear predictor, covariate effect relative to placebo (treatment=1):
            theta[i,k,j] <- mu[i] + d[t[i,k]] - d[t[i,1]] + z[C[i,j+1]-1]
            rhat[i,k,j] <-  q[i,k,j] * n[i,k,j]                    # Predicted number events
            # Deviance contribution for each category:
            dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) +(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
            }

         dev[i,k] <- sum(dv[i,k,1:nc[i]-1])              # Deviance contribution of each arm

         for (j in 2:nc[i]) {                           # Loop through categories
            p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]         # Link function
            # Adjusting the link function for extreme values to prevent numerical errors:
            phi.adj[i,k,j] <- step(5+theta[i,k,j-1])*(step(theta[i,k,j-1]-5)+step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
            }
         }


   resdev[i] <- sum(dev[i,1:na[i]])                 # Summed residual deviance contribution for this trial
   }

   z[1] <- 0                                        # Set z_noresp=0

   for (j in 2:Cmax-1)  {                           # Set priors for z, for all categories
      z.aux[j] ~ dunif(0,2)                         # Priors
      z[j] <- z[j-1] + z.aux[j]                     # Ensures that z[j]~Uniform(z[j-1], z[j-1]+5)
   }

   totresdev <- sum(resdev[])                       # Total residual deviance

   d[1] <- 0                                        # Treatment effect is zero for reference treatment

   bcov[1] <- 0                                     # Covariate effect is zero for reference treatment

   for (k in 2:nt){                                 # Loop through treatments
      d[k] ~ dnorm(0,0.0001)                        # Vague priors for treatment effects
   }



   # Estimating treatment effects T[k] on the natural probability scale
   # Given a Mean effect, meanA, for 'standard' treatment 1, with precision, precA and covariate value z[j]
```

```
    A ~ dnorm(meanA,precA)

    for (k in 1:nt) {
        for (j in 1:Cmax-1) {  #
            T[j,k] <- 1 - phi(A + d[k] + z[j])
        }
    }

# Pairwise RRs for pairwise comparisons where placebo (treatment=1) is the reference treatment
    for(k in 1:nt) {            # Looping over treatments
        for(h in 1:nt){
            for(j in 1:2) {             # Looping over categories
                rr[j,k,h] <- T[j,k]/T[j,h]
                }
        }
    }


    # ranking on relative scale
    for (k in 1:nt) {
        rk[k] <- rank(d[],k)
        best[k] <- equals(rk[k],1)  #calculate probability that treat k is best
        for (j in 1:nt) {
            effectiveness[k,j] <- equals(rk[k],j )
            }
        }

    for (k in 1:nt) {
        for (j in 1:nt) {
            cumeffectiveness[k,j] <- sum(effectiveness[k, 1:j])
        }
    }

    # SUCRAS
    for (k in 1:nt) {
        SUCRA[k] <- sum(cumeffectiveness[k,1:(nt-1)])/(nt-1)
    }
}
```

F.2.3.7 Multinomial likelihood model with probit link – random effects

```
model {                                  # *** Program Starts
   for(i in 1:ns) {                      # Loop through studies
      w[i,1] <- 0                        # Adjustment for multi-arm trials is zero for control arm
      delta[i,1] <- 0                    #  Treatment effect is zero for control arm
      mu[i] ~ dnorm(0,0.0001)            # Vague priors for trial baselines


      for (k in 1:na[i]) {               # Loop through arms
         p[i,k,1] <- 1                   # Pr(Response) >0

         for (j in 1:nc[i]-1) {          # Loop through categories
            r[i,k,j] ~ dbin(q[i,k,j],n[i,k,j])      # Binomial Likelihood
            q[i,k,j] <- 1-(p[i,k,C[i,j+1]]/p[i,k,C[i,j]])    # Conditional probabilities
            # Linear predictor, covariate effect relative to placebo (treatment=1):
            theta[i,k,j] <- mu[i] + delta[i,k] + z[C[i,j+1]-1]
            rhat[i,k,j] <-  q[i,k,j] * n[i,k,j]                    # Predicted number events
            # Deviance contribution for each category:
            dv[i,k,j] <- 2 * (r[i,k,j]*(log(r[i,k,j])-log(rhat[i,k,j])) +(n[i,k,j]-r[i,k,j])*(log(n[i,k,j]-r[i,k,j]) - log(n[i,k,j]-rhat[i,k,j])))
            }

         dev[i,k] <- sum(dv[i,k,1:nc[i]-1])             # Deviance contribution of each arm

         for (j in 2:nc[i]) {                           # Loop through categories
            p[i,k,C[i,j]] <- 1 - phi.adj[i,k,j]         # Link function
            # Adjusting the link function for extreme values to prevent numerical errors:
            phi.adj[i,k,j] <- step(5+theta[i,k,j-1])*(step(theta[i,k,j-1]-5)+step(5-theta[i,k,j-1])*phi(theta[i,k,j-1]) )
            }
         }

      for (k in 2:na[i]) {                              # Loop through arms
         delta[i,k] ~ dnorm(md[i,k],taud[i,k])          # Trial-specific distribution
         md[i,k] <-  d[t[i,k]] - d[t[i,1]] + sw[i,k]    # Mean with multi-arm correction
         taud[i,k] <- tau *2*(k-1)/k                    # Precision with multi-arm correction
         w[i,k] <- (delta[i,k] - d[t[i,k]] + d[t[i,1]])  # Multi-arm adjustment
         sw[i,k] <- sum(w[i,1:k-1])/(k-1)               # Cumulative adjustment for multi-arm trials
      }

   resdev[i] <- sum(dev[i,1:na[i]])                     # Summed residual deviance contribution for this trial
   }

   z[1] <- 0                                            # Set znoresp=0

   for (j in 2:Cmax-1)  {                               # Set priors for z, for all categories
      z.aux[j] ~ dunif(0,2)                             # Priors
      z[j] <- z[j-1] + z.aux[j]                         # Ensures that z[j]~Uniform(z[j-1], z[j-1]+5)
   }

   totresdev <- sum(resdev[])                           # Total residual deviance

   d[1] <- 0                                            # Treatment effect is zero for reference treatment


   for (k in 2:nt){                                     # Loop through treatments
      d[k] ~ dnorm(0,0.0001)                            # Vague priors for treatment effects
   }


   sd ~ dunif(0,5)                                      # Vague prior for between-trial SD
   tau <- pow(sd,-2)                                    # Between-trial precision (=1/between-trial variance)
```

```
    # Estimating treatment effects T[k] on the natural probability scale
    # Given a Mean effect, meanA, for 'standard' treatment 1, with precision, precA and covariate value z[j]

    A ~ dnorm(meanA,precA)

    for (k in 1:nt) {
        for (j in 1:Cmax-1) {  #
            T[j,k] <- 1 - phi(A + d[k] + z[j])
        }
    }

        # Pairwise RRs for pairwise comparisons where placebo (treatment=1) is the reference treatment
    for(k in 1:nt) {            # Looping over treatments
        for(h in 1:nt){
            for(j in 1:2) {            # Looping over categories
                rr[j,k,h] <- T[j,k]/T[j,h]
                }
        }
    }


    # ranking on relative scale
    for (k in 1:nt) {
        rk[k] <- rank(d[],k)
        best[k] <- equals(rk[k],1)  #calculate probability that treat k is best
        for (j in 1:nt) {
            effectiveness[k,j] <- equals(rk[k],j )
            }
        }

    for (k in 1:nt) {
        for (j in 1:nt) {
            cumeffectiveness[k,j] <- sum(effectiveness[k, 1:j])
        }
    }

    # SUCRAS
    for (k in 1:nt) {
    SUCRA[k] <- sum(cumeffectiveness[k,1:(nt-1)])/(nt-1)
    }
}
```

F.2.4 Network meta-analysis results

F.2.4.1 Clinical response and clinical remission

Network diagrams for the induction and maintenance NMAs of clinical response and remission are included in section B.3.9 along with information regarding the model fit statistics and preferred models for each analysis.

Table 48 and Table 49 present the effects of each treatment relative to placebo on the probit scale as well as the risk ratios for clinical response and clinical remission on the natural scale for the induction and maintenance phases, respectively. Risk ratios for etrasimod compared with each other therapy are also presented along with the probabilities of achieving clinical response or clinical remission by the end of the induction phase and maintenance phase. Results from the maintenance phase should be interpreted as the outcomes achieve among induction phase responders, that is, clinical remission and sustained clinical response.

Table 48 Induction phase NMA results – comparative effects and probabilities of achieving response and remission

Comparator	Comparator vs placebo			Etrasimod vs comparator		Probability (%), median (95% CrI)		SUCRA[a]
	Treatment effect, median (95% CrI)	Risk ratio, median (95% CrI)		Risk ratio, median (95% CrI)				
	Probit scale	Clinical response	Clinical remission	Clinical response	Clinical remission	Clinical response	Clinical remission	
Bio-naïve subgroup								
PBO	[redacted]	-	-	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETR 2 mg	[redacted]	[redacted]	[redacted]	-	-	[redacted]	[redacted]	[redacted]
FIL 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OZN 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
IFX 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
GOL 200/100 mg [c]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40 mg[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 80/40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bio-experienced subgroup								
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETR 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OZN 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40 mg[b]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 45 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] based on treatment effect on probit scale. b 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6. [c] 200 mg at week 0, 100 mg at week 2.
Abbreviations: ADA, adalimumab; Bio-, biologics; CrI, credible interval; ETR, etrasimod; FIL, filgotinib; GOL, golimumab; IFX, infliximab; OZN, ozanimod; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VDZ, Vedolizumab; SUCRA, surface under cumulative ranking curve.

Table 49 Maintenance phase NMA results – comparative effects and probabilities of achieving response and remission

Comparator	Comparator vs placebo			Etrasimod vs comparator		Probability (%), median (95% CrI)		SUCRA[a]
	Treatment effect, median (95% CrI)	Risk ratio, median (95%CrI)		Risk ratio, median (95%CrI)				
	Probit scale	Clinical response	Clinical remission	Clinical response	Clinical remission	Clinical response	Clinical remission	
Bio-naïve subgroup								
PBO								
ETR 2 mg								
FIL 100 mg								
FIL 200 mg								
OZN 1 mg								
TOF 5 mg								
TOF 10 mg								
IFX 5mg/kg								
UST Q12W								
UST Q8W								
GOL 100								
UPA 15 mg								
UPA 30 mg								
VDZ Q8W								
VDZ Q4W								
ADA 40 mg								
VDZ Q2W								

Comparator	Comparator vs placebo			Etrasimod vs comparator		Probability (%), median (95% CrI)		SUCRA[a]
	Treatment effect, median (95% CrI)	Risk ratio, median (95%CrI)		Risk ratio, median (95%CrI)				
	Probit scale	Clinical response	Clinical remission	Clinical response	Clinical remission	Clinical response	Clinical remission	
GOL 50 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Bio-experienced subgroup								
PBO	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ETR 2 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 100 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
OZN 1 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 5 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST Q12W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UST Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 15 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
UPA 30 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q8W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ IV Q4W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
ADA 40 mg	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
VDZ SC Q2W	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

[a] based on treatment effect on probit scale.
Abbreviations: ADA, adalimumab; Bio-, biologics; CrI, credible interval; ETR, etrasimod; FIL, filgotinib; GOL, golimumab; IFX, infliximab; IV, intravenous; OZN, ozanimod; PBO, placebo; SC, subcutaneous; SUCRA, surface under cumulative ranking curve; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VDZ, vedolizumab;

F.2.4.2 Serious infections

Network diagrams for the induction NMAs of serious infection is included in section B.3.9 along with information regarding the model fit statistics and preferred model.

Table 50 present the effects of each treatment relative to placebo as log odds ratios as well as the risk ratio for serious infection on the natural scale for the induction. Risk ratios for etrasimod compared with each other therapy are also presented along with the probabilities of experiencing serious infection by the end of the induction phase.

Table 50 Induction phase base-case NMA results – comparative effects and probabilities of serious infections

Comparator	Comparator vs placebo		Etrasimod vs comparator	Probability (%), median (95% CrI)	SUCRA
	Treatment effect, median (95% CrI)	Risk ratio, median (95%CrI)	Risk ratio, median (95%CrI)		
PBO	[redacted]				
ETR 2 mg					
FIL 100 mg					
FIL 200 mg					
OZN 1 mg					
TOF 10 mg					
VDZ 300mg					
UPA 45 mg					
UST 6mg/kg					
ADA 160/80/40 mg [a]					
ADA 80/40 mg					
GOL 200/100 mg [b]					
IFX 5mg/kg					

[a] 160 mg at week 0, 80 mg at week 2, 40 mg at weeks 4 and 6. [b] 200 mg at week 0, 100 mg at week 2.
Abbreviations: ADA, adalimumab; Bio-, biologics; CrI, credible interval; ETR, etrasimod; FIL, filgotinib; GOL, golimumab; IFX, infliximab; OZN, ozanimod; PBO, placebo; TOF, tofacitinib; UPA, upadacitinib; UST, ustekinumab; VDZ, Vedolizumab; SUCRA, surface under cumulative ranking curve.

F.2.3 Outcome definitions for ELEVATE UC studies

Table 51 Definition of disease-specific endpoints in the ELEVATE UC studies

Endpoints	Definition of measure
Clinical remission	Per modified Mayo score, defined as stool frequency subscore = 0 (or = 1 with a ≥ 1-point decrease from Baseline), rectal bleeding subscore = 0, and endoscopic subscore ≤ 1 (excluding friability).
	Per total Mayo score, defined as a TMS of ≤ 2 points with no individual subscore of >1
Clinical response	Per modified Mayo score, defined as a ≥ 2-point and ≥ 30% decrease from Baseline in MMS, and a ≥ 1-point decrease from Baseline in rectal bleeding subscore or an absolute rectal bleeding subscore ≤ 1
	Per total Mayo score, defined as a ≥ 3-point and ≥ 30% decrease from Baseline in TMS, and a ≥1-point decrease from Baseline in rectal bleeding subscore or an absolute rectal bleeding subscore ≤ 1
Symptomatic remission	Defined as stool frequency subscore=0 [or stool frequency=1 with a ≥1-point decrease from baseline] and rectal bleeding subscore=0
Endoscopic improvement	Defined as an endoscopic subscore ≤1 (excluding friability)
Mucosal healing	Defined as an endoscopic subscore of ≤ 1 (excluding friability) and a Geboes Index score < 2.0
Corticosteroid-free remission	Defined as clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52

Abbreviations: MMS, modified Mayo score; TMS, total Mayo score.

Table 52 Description of endpoint measurement/disease activity index in the ELEVATE UC studies

Endpoints	Definition of measure
Mayo score	Comprises stool frequency subscore, rectal bleeding subscore, Physician's Global Assessment, and endoscopic appearance (endoscopic subscore) categories all assessed on a scale of 0–3 The individual categories are summed to give a total score on a scale of 0–12 with a higher score indicating increased severity of disease
Modified Mayo score	Comprises stool frequency subscore, rectal bleeding subscore, and endoscopic appearance (endoscopic subscore) categories all assessed on a scale of 0–3 The individual categories are summed to give a total score on a scale of 0–9 with a higher score indicating increased severity of disease
Stool frequency subscale	Assessed on a scale of 0–3, with a higher score indicating increased severity of disease
Rectal bleeding subscale	
Physician's Global Assessment	
Endoscopic subscore	
Geboes score	Assessed on a scale of Grade 0–5, with additional subgrades indicating various histological criteria/features of disease
IBDQ	A 32-item measure with each item scored on a 7-point Likert scale, ranging from 1 (worst health) to 7 (best health) Each item score is summed to give a total score, with higher scores reflecting better HRQoL
36-Item Short Form Health Survey (SF-36),	The SF-36 is a 36-item survey of subject health. The SF-36 measures 8 health domains: physical functioning, bodily pain, role limitations due to physical

Version 2 Physical and Mental Component and Domain Scores	problems, role limitations due to emotional problems, general health perceptions, mental health, social functioning, and vitality. The SF-36 is scored using 2 overall summaries: physical component and mental component
WPAIQ-UC	Consists of 6 questions asking about the effect of UC on the subject's ability to work and perform regular activities
Urgency Numeric Rating Scale (NRS)	The urgency NRS is a single item that measures the severity for the urgency (sudden or immediate need) to have a bowel movement in the past 24 hours using an 11-point NRS ranging from 0 (no urgency) to 10 (worst possible urgency)
Abdominal Pain NRS	The abdominal pain NRS is a single item that measures the "worst abdominal pain in the past 24 hours" using an 11-point NRS ranging from 0 (no pain) to 10 (pain as bad as can imagine)

Abbreviations: HRQoL, health-related quality of life; IBDQ, inflammatory bowel disease questionnaire; NRS, numeric rating scale; SF-36, 36-item short form health survey; WPAIQ-UC, work productivity and activity impairment questionnaire ulcerative colitis.

F.2.4 Additional endpoints from ELEVATE UC trials

F.2.4.1 Endoscopic improvement at Week 12 and Week 52

Table 53 Proportion of patients with endoscopic improvement[a] (Reported Randomised Strata FAS and Actual Baseline MMS 5 to 9)

	ELEVATE UC 12			ELEVATE UC 52		
	Placebo % (n/N)	**Etrasimod % (n/N)**	**Delta, *P*-value**	**Placebo % (n/N)**	**Etrasimod % (n/N)**	**Delta, *P*-value**
Week 12	18.8 (21/112)	30.6 (68/222)	12.1 *P*<0.0092	14.1 (19/135)	35 (96/274)	21.2 *P*<0.001
Week 52	-	-	-	10.4 (14/135)	37.2 (102/274)	26.7 *P*<0.001

a Endoscopic improvement defined as ES ≤1 (excluding friability).

F.2.4.2 Endoscopic normalisation at Week 12 and Week 52

Table 54 Proportion of patients with endoscopic normalisation[a] (Reported Randomised Strata FAS and Actual Baseline MMS 5 to 9)

	ELEVATE UC 12			ELEVATE UC 52		
	Placebo % (n/N)	**Etrasimod % (n/N)**	**Delta, *P*-value**	**Placebo % (n/N)**	**Etrasimod % (n/N)**	**Delta, *P*-value**
Week 12	8.0 (9/112)	17.1 (38/222)	9.2 *P*=0.0093	4.4 (6/135)	14.6 (40/274)	10.2 *P*=0.00027
Week 52	-	-	-	5.9 (8/135)	26.3 (72/274)	20.4 *P*<0.0001

a Endoscopic normalisation defined as ES =0

F.2.4.3 Clinical remission among patients achieving clinical response per modified Mayo score at Week 12 and Week 52

In ELEVATE UC 52, the proportion of subjects achieving clinical remission at Week 52 among subjects achieving clinical response at Week 12 per modified Mayo score was 49.1% for patients receiving etrasimod compared to 17.4% for patients receiving placebo at Week 52 (31.86% differential, P<0.001 two-sided). These results show a significantly greater proportion of patients who achieved clinical response at Week 12 achieved clinical remission at Week 52.

F.2.4.4 Sustained clinical response

In ELEVATE UC 52, the proportion of subjects achieving clinical response at both week 12 and week 52 was 44.9% for patients receiving etrasimod compared to 18.5% for patients receiving placebo (26.16% differential, P<0.001 two sided). These results demonstrate a significantly greater proportion of patients with sustained response at week 52 with etrasimod compared to placebo.

F.2.4.5 Patient-reported outcomes (PROs) at both Week 12 and Week 52

Several PROs were assessed to support an improved HRQoL for patients in the target population treated with etrasimod compared with placebo. Significant improvements in the etrasimod group compared with the placebo group were observed across several quality-of-life measures.

F.2.4.6 Urgency NRS (Using Reported Randomization Strata; Modified FAS and Actual Baseline MMS 5 to 9)

The mean change in worst sense of urgency past 24 hours from baseline at Week 12 and Week 52 were -2.9 ± 3.23 (SD) and -4.3 ± 3.00 (SD) for patients in the etrasimod 2 mg group, respectively, and -1.6 ± 2.97 (SD) and -4.0 ± 3.10 (SD) for patients in the placebo group, respectively (LS mean difference –1.27 and-0.46, respectively; P<0.001 and P=0.322 two-sided, respectively).

F.2.4.7 Abdominal Pain NRS (Using Reported Randomization Strata; Modified FAS and Actual Baseline MMS 5 to 9)

The mean change in abdominal pain past 24 hours from baseline at Week 12 and Week 52 were -2.2 ± 3.15 (SD) and -3.3 ± 2.78 (SD) for patients in the etrasimod 2 mg group, respectively, and -1.1 ± 2.37 (SD) and -1.9 ± 2.46 (SD) for patients in the placebo group, respectively (LS mean difference -0.80 in both; P=0.006 and P=0.014 two-sided, respectively).

Appendix G: Subgroup analysis

Table 55 Primary endpoint: clinical remission at Week 12 from ELEVATE UC 12 and ELEVATE UC 52

Subgroup	ELEVATE UC 12 [45]				ELEVATE UC 52 [46]			
	Placebo (N=116) n (%)		Etrasimod (N=238) n (%)		Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=77)	NO (N=39)	YES (N=159)	NO (N=79)	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	12 (15.6)	5 (12.8)	46 (28.9)	16 (20.3)	9 (9.1)	3 (6.7)	66 (32.2)	15 (17.9)
% Difference from placebo			13.4	7.43			23.1	11.19
P-value[b]			0.010	0.247			<0.001	0.057
Baseline oral corticosteroid use	YES (N=34)	NO (N=82)	YES (N=65)	NO (N=173)	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	7 (20.6)	10 (12.2)	19 (29.2)	43 (24.9)	7 (16.7)	5 (4.9)	30 (32.3)	51 (26.0)
% Difference from placebo			8.64	12.66			15.59	21.12
P-value[b]			0.330	0.006			0.036	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=53)	7 to 9 (N=63)	4 to 6 (N=109)	7 to 9 (N=129)	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	11 (20.8)	6 (9.5)	37 (33.9)	25 (19.4)	5 (8.8)	7 (8.0)	46 (40.7)	35 (19.9)
% Difference from placebo			13.2	9.86			31.94	11.84
P-value[b]			0.053	0.054			<0.001	0.004

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 56 Primary endpoint: clinical remission at Week 52 from ELEVATE UC 52

Subgroup	ELEVATE UC 52 [46]			
	Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	8 (8.1)	6 (6.7)	75 (36.6)	19 (22.6)
% Difference from placebo			28.5	15.95
P-value[b]			<0.001	0.019
Baseline oral corticosteroid use	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	4 (9.5)	7 (6.9)	29 (31.2)	65 (33.2)
% Difference from placebo			21.66	26.30
P-value[b]			<0.001	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	5 (8.8)	6 (6.9)	45 (39.8)	49 (27.8)
% Difference from placebo			31.05	20.94
P-value[b]			<0.001	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 57 Key secondary endpoint: symptomatic remission at week 12 from both ELEVATE UC 12 and ELEVATE UC 52

Subgroup	ELEVATE UC 12 [45]				ELEVATE UC 52 [46]			
	Placebo (N=116) n (%)		Etrasimod (N=238) n (%)		Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=77)	NO (N=39)	YES (N=159)	NO (N=79)	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	24 (31.2)	10 (25.6)	79 (49.7)	35 (44.3)	23 (23.2)	9 (20.0)	108 (52.7)	26 (31.0)
% Difference from placebo			18.5	18.7			29.45	10.95
P-value[b]			0.004	0.023			<0.001	0.181
Baseline oral corticosteroid use	YES (N=34)	NO (N=82)	YES (N=65)	NO (N=173)	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	14 (41.2)	20 (24.4)	29 (44.6)	85 (49.1)	13 (31.0)	19 (18.6)	42 (45.2)	92 (46.9)
% Difference from placebo			3.44	24.7			14.21	28.31
P-value[b]			0.750	<0.001			0.098	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=53)	7 to 9 (N=63)	4 to 6 (N=109)	7 to 9 (N=129)	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	19 (35.8)	15 (23.8)	60 (55.0)	54 (41.9)	16 (28.1)	16 (18.4)	59 (52.2)	75 (42.6)
% Difference from placebo			19.2	18.05			24.14	24.22
P-value[b]			0.015	0.011			0.002	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 58 Key secondary endpoint: symptomatic remission at week 52 from ELEVATE UC 52

Subgroup	ELEVATE UC 52 [46]			
	Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	20 (20.5)	8 (17.8)	103 (50.2)	24 (28.6)
% Difference from placebo			30.04	10.79
P-value[b]			<0.001	0.238
Baseline oral corticosteroid use	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	9 (21.4)	19 (18.6)	37 (39.8)	90 (45.9)
% Difference from placebo			18.36	27.29
P-value[b]			0.025	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	15 (26.3)	13 (14.9)	55 (48.7)	72 (40.9)
% Difference from placebo			22.36	25.97
P-value[b]			0.003	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 59 Key secondary endpoint: achieving mucosal healing at week 12 from both ELEVATE UC 12 and ELEVATE UC 52

Subgroup	ELEVATE UC 12 [45]				ELEVATE UC 52 [46]			
	Placebo (N=116) n (%)		Etrasimod (N=238) n (%)		Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=77)	NO (N=39)	YES (N=159)	NO (N=79)	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	8 (10.4)	2 (5.1)	31 (19.5)	10 (12.7)	9 (9.1)	0	54 (26.3)	12 (14.3)
% Difference from placebo			9.11	7.53			17.25	14.29
P-value[b]			0.039	0.123			<0.001	<0.001
Baseline oral corticosteroid use	YES (N=34)	NO (N=82)	YES (N=65)	NO (N=173)	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	5 (14.7)	5 (6.1)	10 (15.4)	31 (17.9)	5 (11.9)	4 (3.9)	20 (21.5)	46 (23.5)
% Difference from placebo			0.68	11.82			9.60	19.55
P-value[b]			0.926	0.002			0.129	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=53)	7 to 9 (N=63)	4 to 6 (N=109)	7 to 9 (N=129)	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	7 (13.2)	3 (4.8)	27 (24.8)	14 (10.9)	3 (5.3)	6 (6.9)	40 (35.4)	26 (14.8)
% Difference from placebo			11.56	6.09			30.14	7.88
P-value[b]			0.051	0.113			<0.001	0.036

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 60 Key secondary endpoint: achieving mucosal healing at week 52 from ELEVATE UC 52

Subgroup	ELEVATE UC 52 [46]			
	Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	13 (13.1)	2 (4.4)	60 (29.3)	19 (22.6)
% Difference from placebo			16.14	18.17
P-value[b]			<0.001	0.001
Baseline oral corticosteroid use	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	7 (16.7)	8 (7.8)	24 (25.8)	55 (28.1)
% Difference from placebo			9.14	20.22
P-value[b]			0.0270	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	9 (15.8)	6 (6.9)	44 (38.9)	35 (19.9)
% Difference from placebo			23.15	12.99
P-value[b]			<0.001	0.002

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 61 Other secondary endpoints: clinical response at week 12 from ELEVATE UC 12 and ELEVATE UC 52

Subgroup	ELEVATE UC 12 [45]				ELEVATE UC 52 [46]			
	Placebo (N=116) n (%)		Etrasimod (N=238) n (%)		Placebo (N=144) n (%)		Placebo (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=77)	NO (N=39)	YES (N=159)	NO (N=79)	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	33 (42.9)	15 (38.5)	105 (66.0)	46 (58.2)	39 (39.4)	13 (28.9)	141 (68.8)	41 (48.8)
% Difference from placebo			23.18	19.77			29.39	19.92
P-value[b]			<0.001	0.027			<0.001	0.035
Baseline oral corticosteroid use	YES (N=34)	NO (N=82)	YES (N=65)	NO (N=173)	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	18 (52.9)	30 (36.6)	38 (58.5)	113 (65.3)	19 (45.2)	33 (32.4)	63 (67.7)	119 (60.7)
% Difference from placebo			5.52	28.73			22.50	28.36
P-value[b]			0.609	<0.001			0.011	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=53)	7 to 9 (N=63)	4 to 6 (N=109)	7 to 9 (N=129)	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	25 (47.2)	23 (36.5)	77 (70.6)	74 (57.4)	24 (42.1)	28 (32.2)	78 (69.0)	104 (59.1)
% Difference from placebo			23.47	20.86			26.92	26.91
P-value[b]			0.003	0.005			<0.001	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 62 Other secondary endpoints: clinical response at week 52 from ELEVATE UC 52

Subgroup	ELEVATE UC 52 [46]			
	Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	28 (28.3)	7 (15.6)	111 (54.1)	32 (38.1)
% Difference from placebo			25.86	22.54
P-value[b]			<0.001	0.004
Baseline oral corticosteroid use	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	13 (31.0)	22 (21.6)	43 (46.2)	100 (51.0)
% Difference from placebo			15.28	29.45
P-value[b]			0.079	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	19 (33.3)	16 (18.4)	64 (56.6)	79 (44.9)
% Difference from placebo			23.30	26.50
P-value[b]			0.003	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 63 Other secondary endpoints: sustained Clinical Remission at Both Weeks 12 and 52 from ELEVATE UC 52

Subgroup	ELEVATE UC 52 [46]			
	Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES (N=99)	NO (N=45)	YES (N=205)	NO (N=84)
Responders[a], n (%)	2 (2.0)	2 (4.4)	45 (22.0)	9 (10.7)
% Difference from placebo			19.93	6.27
P-value[b]			<0.001	0.211
Baseline oral corticosteroid use	YES (N=42)	NO (N=102)	YES (N=93)	NO (N=196)
Responders[a], n (%)	2 (4.8)	2 (2.0)	18 (19.4)	36 (18.4)
% Difference from placebo			14.59	16.41
P-value[b]			0.007	<0.001
Baseline disease activity - Actual MMS	4 to 6 (N=57)	7 to 9 (N=87)	4 to 6 (N=113)	7 to 9 (N=176)
Responders[a], n (%)	3 (5.3)	1 (1.1)	31 (27.4)	23 (13.1)
% Difference from placebo			22.17	11.92
P-value[b]			<0.001	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Table 64 Other secondary endpoints: proportion of patients in clinical remission at Week 52 and who had not been receiving corticosteroids for ≥ 12 weeks prior to Week 52 from ELEVATE UC 52

Subgroup	ELEVATE UC 52 [46]			
	Placebo (N=144) n (%)		Etrasimod (N=289) n (%)	
Naïve to biologic or JAK inhibitor therapy at study entry	YES	NO	YES	NO
	(N=99)	(N=45)	(N=205)	(N=84)
Responders[a], n (%)	7 (7.1)	3 (6.7)	75 (36.6)	19 (22.6)
% Difference from placebo			29.51	15.95
P-value[b]			<0.001	0.019
Baseline oral corticosteroid use	YES	NO	YES	NO
	(N=42)	(N=102)	(N=93)	(N=196)
Responders[a], n (%)	3 (7.1)	7 (6.9)	29 (31.2)	65 (33.2)
% Difference from placebo			24.04	26.30
P-value[b]			<0.001	<0.001
Baseline disease activity - Actual MMS	4 to 6	7 to 9	4 to 6	7 to 9
	(N=57)	(N=87)	(N=113)	(N=176)
Responders[a], n (%)	4 (7.0)	6 (6.9)	45 (39.8)	49 (27.8)
% Difference from placebo			32.81	20.94
P-value[b]			<0.001	<0.001

[a]Responders are defined as subjects with SF subscore = 0 (or = 1 with a ≥ 1 point decrease from baseline), RB subscore = 0, and ES ≤ 1 (excluding friability).
[b]Estimates are from a CMH test within each subgroup.
Abbreviations: CMH, Cochran-Mantel-Haenszel; ES, endoscopic score; JAK, Janus kinase; MMS, modified Mayo score; RB, rectal bleeding; SF, stool frequency; UC, ulcerative colitis.

Appendix H: Adverse reactions

TEAEs reported in ≥1% of patients in either treatment group by preferred term in ELEVATE UC 12 and ELEVATE UC 52 are summarised in **Table 65**. The most frequently reported TEAEs by preferred term were anaemia, headache, colitis ulcerative and coronovirus 2019 disease (COVID-19) (**Table 65**). Headache and dizziness were reported with a > 3% higher proportion of patients in the etrasimod group than the placebo group. Overall, the percentage of patients with TEAEs of colitis ulcerative or abdominal pain was low, and colitis ulcerative TEAEs was lower in etrasimod-treated subjects versus placebo (Table 65). Notably, no TEAEs with a fatal outcome were reported during the study.

Full details of all TEAEs affecting > 1% of patients in any group by system organ class (SOC) in ELEVATE UC 12 and ELEVATE UC 52 are shown in **Table 66**.[172] The most common adverse drug reactions are lymphopenia (11%) and headache (7%).[172]

Table 65 TEAEs reported in ≥1% of patients in either treatment group by preferred term in ELEVATE UC 12 and ELEVATE UC 52 (Safety set)

Preferred Term	ELEVATE UC 12 [45]		ELEVATE UC 52 [46]	
	Placebo (N=116) n (%) [m]	Etrasimod (N=238) n (%)[m]	Placebo (N=144) n (%)[m]	Etrasimod (N=289) n (%)[m]
Anaemia	8 (6.9) [10]	14 (5.9) [14]	14 (9.7) [18]	24 (8.3) [33]
Headache	2 (1.7) [3]	11 (4.6) [21]	7 (4.9) [12]	24 (8.3) [36]
Nausea	2 (1.7) [2]	10 (4.2) [11]	2 (1.4) [2]	9 (3.1) [11]
Colitis ulcerative	1 (0.9) [1]	9 (3.8) [12]	13 (9.0) [13]	22 (7.6) [24]
Pyrexia	3 (2.6) [3]	8 (3.4) [8]	6 (4.2) [7]	14 (4.8) [15]
Abdominal distension	0	5 (2.1) [5]	3 (2.1) [4]	4 (1.4) [5]
Gamma-glutamyl transferase increased	0	5 (2.1) [6]	2 (1.4) [2]	5 (1.7) [5]
Vomiting	2 (1.7) [2]	5 (2.1) [5]	0	5 (1.7) [5]
Arthralgia	3 (2.6) [3]	4 (1.7) [4]	3 (2.1) [3]	13 (4.5) [17]
Back pain	0	4 (1.7) [4]	3 (2.1) [4]	7 (2.4) [7]
Hypophosphataemia	0	4 (1.7) [4]	-	-
Sinus bradycardia	0	4 (1.7) [4]	-	-
Urinary tract infection	0	4 (1.7) [4]	3 (2.1) [3]	6 (2.1) [8]
Abdominal pain	3 (2.6) [4]	3 (1.3) [3]	5 (3.5) [6]	11 (3.8) [14]
Alanine aminotransferase increased	0	3 (1.3) [5]	2 (1.4) [2]	8 (2.8) [12]
Blood creatinine phosphokinase increased	1 (0.9) [1]	3 (1.3) [4]	-	-
COVID-19	3 (2.6) [3]	3 (1.3) [3]	9 (6.3) [9]	20 (6.9) [20]
Diarrhoea	0	3 (1.3) [4]	1 (0.7) [1]	5 (1.7) [5]

Dizziness	0	3 (1.3) [3]	1 (0.7) [1]	15 (5.2) [17]
Fatigue	0	3 (1.3) [3]	2 (1.4) [3]	5 (1.7) [6]
Hypertension	1 (0.9) [1]	3 (1.3) [3]	1 (0.7) [1]	8 (2.8) [8]
Iron deficiency	0	3 (1.3) [3]	-	-
Iron deficiency anaemia	3 (2.6) [3]	3 (1.3) [3]	-	-
Liver disorder	0	3 (1.3) [3]	-	-
Nasopharynigits	2 (1.7) [2]	3 (1.3) [3]	4 (2.8) [4]	3 (1.0) [3]
Somnolence	1 (0.9) [1]	3 (1.3) [3]	-	-
Migraine	4 (3.4) [4]	2 (0.8) [2])	0	3 (1.0) [9]
Tachycardia	2 (1.7) [2]	2 (0.8) [2]	-	-
Abdominal pain upper	2 (1.7) [2]	1 (0.4) [1]	-	-
Toothache	2 (1.7) [2]	1 (0.4) [1]	-	-
Herpes zoster	2 (1.7) [2]	0	-	-
Asthenia	-	-	2 (1.4) [2]	7 (2.4) [7]
Haemorrhoids	-	-	0	7 (2.4) [8]
Flatulence	-	-	0	6 (2.1) [6]
Hypercholesterolaemia	-	-	0	6 (2.1) [6]
Respiratory tract infection viral	-	-	2 (1.4) [2]	6 (2.1) [6]
COVID-19 pneumonia	-	-	2 (1.4) [2]	5 (1.7) [5]
Muscle spasms	-	-	0	5 (1.7) [5]
Rash	-	-	3 (2.1) [4]	5 (1.7) [5]
Bradycardia	-	-	0	4 (1.4) [4]
Constipation	-	-	1 (0.7) [1]	4 (1.4) [4]
Cystitis	-	-	0	4 (1.4) [4]
Hyperglycaemia	-	-	1 (0.7) [1]	4 (1.4) [4]
Rhinorrhoea	-	-	0	4 (1.4) [4]
Aspartate aminotransferase increased	-	-	3 (2.1) [3]	3 (1.0) [5]
Bronchitis	-	-	0	3 (1.0) [3]
Cataract	-	-	1 (0.7) [1]	3 (1.0) [3]
Dyspepsia	-	-	2 (1.4) [2]	3 (1.0) [3]
Gastritis	-	-	0	3 (1.0) [3]
Hepatic enzyme increased	-	-	1 (0.7) [1]	3 (1.0) [3]
Neck pain	-	-	0	3 (1.0) [4]
Osteoarthritis	-	-	1 (0.7) [1]	3 (1.0) [3]
Pharyngitis	-	-	0	3 (1.0) [4]
Pruritus	-	-	1 (0.7) [2]	3 (1.0) [3]
SARS-CoV-2 test positive	-	-	1 (0.7) [1]	3 (1.0) [3]
Stomatitis	-	-	0	3 (1.0) [3]
Transaminases increased	-	-	0	3 (1.0) [4]
Upper RTI	-	-	2 (1.4) [3]	3 (1.0) [4]
Cough	-	-	2 (1.4) [2]	2 (0.7) [2]
Pain in extremity	-	-	2 (1.4) [2]	2 (0.7) [2]
Conjunctivitis	-	-	4 (2.8) [6]	1 (0.3) [1]
Depression	-	-	2 (1.4) [2]	1 (0.3) [1]
Dry skin	-	-	2 (1.4) [2]	1 (0.3) [1]

Non-cardiac chest pain	-	-	2 (1.4) [2]	1 (0.3) [1]
Oropharyngeal pain	-	-	2 (1.4) [2]	1 (0.3) [1]
Hypersensitivity	-	-	2 (1.4) [2]	0
Mouth ulceration	-	-	3 (2.1) [4]	0

* Exposure is defined as sum of either time (year) from first dose to the onset of first such event for those who experienced this adverse event, or time (year) from first dose to last participation for those who did not experience this adverse event.
Notes:
TEAEs are defined as any adverse event that started or worsened in severity on or after the first dose of study treatment.
Terms are coded using MedDRA v24.1.
Percentages are based on the number of subjects in the analysis set. Subjects are counted only once per summarisation level; [m] is defined as events.
Abbreviations: TEAE, treatment-emergent adverse event; UC, ulcerative colitis.

Table 66 TEAEs affecting > 1% of patients in any group by system organ class (SOC) in ELEVATE UC 12 and ELEVATE UC 52 [172]

System Organ Class	Very Common	Common	Uncommon
Infections and infestations		urinary tract infection[a]	
Blood and lymphatic system disorders	lymphopenia[b]		
Metabolism and nutrition disorders		hypercholesterolaemia[c]	
Nervous system disorders		headache, dizziness	
Eye disorders			macular oedema
Cardiac disorders		bradycardia[d]	atrioventricular block[e]
Vascular disorders		hypertension	
Investigations		gamma-glutamyl transferase increased, alanine aminotransferase increased	

a Urinary tract infection includes urinary tract infection and cystitis
b Lymphopenia includes lymphopenia, lymphocyte count decreased, and lymphocyte percentage decreased
c Hypercholesterolaemia includes hypercholesterolaemia and blood cholesterol increased
d Bradycardia includes bradycardia and sinus bradycardia
e Atrioventricular block includes first- or second-degree Mobitz type I

H.1.1 Description of selected adverse reactions

Bradyarrhythmia

In ELEVATE UC 52, bradycardia was reported on the day of treatment initiation in 1.0% of patients treated with etrasimod compared to none in patients who received placebo. On Day 2, bradycardia was reported in 1 patient (0.3%) treated with etrasimod compared to none in patients who received placebo. In ELEVATE UC 12, bradycardia was reported on the day of treatment initiation in 2.1% of patients treated with etrasimod compared to none in patients who received placebo. On Day 2, bradycardia was reported in 1 patient (0.4%) treated with etrasimod compared to none in patients who received placebo.

At initiation of etrasimod 2 mg, events of first- or second-degree Mobitz type I AV blocks were observed in 0.7% of etrasimod-treated patients compared to none in placebo in ELEVATE UC 52 and in 0.4% of etrasimod-treated patients compared to none in placebo in ELEVATE UC 12; however, in ELEVATE UC 52 and ELEVATE UC 12, Mobitz type II second- or third-degree AV blocks were not reported in patients treated with etrasimod.

Infections

In ELEVATE UC 52, the overall rate of infections and rate of serious infections in patients treated with etrasimod was comparable to that in patients who received placebo (24.9% vs 22.2%, and 1.0% vs 3.5%, respectively). In ELEVATE UC 12, the overall rate of infections and rate of serious infections in patients treated with etrasimod was comparable to that in patients who received placebo (11.3% vs 12.1%, and none in both groups, respectively). The most common adverse reaction for infections was urinary tract infection.

Blood lymphocyte count reduction

The proportion of patients treated with etrasimod who experienced lymphocyte counts less than 0.2 x 10^9/L was 5.6% in ELEVATE UC 52 and 0.9% in ELEVATE UC 12. These events did not lead to treatment discontinuation.

Elevated hepatic enzymes

In ELEVATE UC 52, elevations of ALT to 5-fold the ULN or greater occurred in 0.7% of patients treated with etrasimod and 0.7% of patients who received placebo, and in ELEVATE UC 12 elevations occurred in 0.8% of patients treated with etrasimod and no patients who received placebo.

In ELEVATE UC 52, elevations of ALT to 3-fold the ULN or greater occurred in 4.5% of patients treated with etrasimod and 0.7% of patients who received placebo, and in ELEVATE UC 12 elevations occurred in 2.5% of patients treated with etrasimod and no patients who received placebo.

The majority (75%) of patients with ALT greater than 3-fold the ULN continued treatment with etrasimod with values returning to less than 3-fold the ULN while on treatment.

Overall, the percentage of discontinuation because of elevations in hepatic enzymes was 0.4% in patients treated with etrasimod, and 0.4% in patients who received placebo.

Increased blood pressure

In ELEVATE UC 52 and ELEVATE UC 12, patients treated with etrasimod had an average increase of approximately 1 to 4 mm Hg in systolic blood pressure and approximately 1 to 2 mm Hg in diastolic blood pressure compared to < 1.5 mm Hg and < 1 mm Hg in patients receiving placebo, respectively. The increase was first detected after 2 weeks of treatment and remained within the specified average range in blood pressure increases throughout treatment. Hypertension was reported as an adverse reaction in 2.1% of patients treated with etrasimod and in 1.0% of patients who received placebo. The majority of the events were mild to moderate in severity.

Macular oedema

In ELEVATE UC 52, macular oedema was reported in 0.3% of patients treated with etrasimod and in no patients receiving placebo. In ELEVATE UC 12, macular oedema was reported in 0.4% of patients treated with etrasimod and in 0.9% of patients receiving placebo.

Herpes viral infections

Cases of localised herpes viral infection were seen with S1P receptor modulators, including etrasimod. In ELEVATE UC 52, herpes zoster was reported in 0.7% of patients treated with etrasimod and in none of the patients who received placebo. In ELEVATE UC 12, herpes zoster was reported in none of the patients treated with etrasimod and in 1.7% of patients who received placebo.

Appendix I: Published cost-effectiveness studies

A systematic literature review (SLR) was performed to identify economic evaluations of advanced therapies for the treatment of moderately to severely active ulcerative colitis (UC) in adults and a qualitative synthesis of the identified studies was performed. Systematic searches were performed across electronic databases including Medline, Embase, Cochrane Library, and were supplemented by hand searching of additional secondary sources. In total, 98 economic assessments were identified, comprised of 82 articles and 16 health technology assessments (HTAs) from the NICE UK, ICER (US), CADTH Canada, and PBAC Australia. Upon inclusion, quality assessment was conducted using the Drummond checklist. The majority of studies included cost utility analyses (n=85), with a smaller portion including budget-impact analyses (n=9) and cost-minimisation analyses (n=6). Therapies evaluated by the studies include infliximab (n=76), vedolizumab (n=64), adalimumab (n=63), golimumab (n=41), tofacitinib (n=29), ustekinumab (n=9), filgotinib (n=2), ozanimod (n=2), and upacitinib (n=1), as well as biosimilars of infliximab (n=12) and adalimumab (n=2). Nearly all studies (n=96) evaluated direct costs, with four including indirect costs such as productivity, absenteeism, and cost of leaving the labour market prematurely, and most studies took a payer perspective. While the full results of the SLR are not included in this report, they are available upon request.

Appendix J: Health-related quality-of-life studies

A systematic literature review was completed to identify health-related quality of life outcomes reported by patients with moderately to severely active UC. Systematic searches were conducted in electronic databases including Medline, Embase, Cochrane Library, and were supplemented by hand searching of conference proceedings and other secondary sources.

From the database searches, a total of 7,126 records were retrieved from and, following screening of these search results, 239 records were found to meet the eligibility criteria for this review. In addition, 35 records were identified from supplementary sources. Of the 274 total eligible records, the 200 records which contained the most up-to-date data from the underlying studies were used for data synthesis.

Several measures have been used to estimate HRQoL in patients with UC, including the IBDQ, SIBDQ, SF-36, EQ-5D and WPAI-UC questionnaire, and the IBDQ appears to be the most widely used tool.

Several studies explored the influence of UC on patients' QoL and concluded that the chronic nature of UC, as well as its gastrointestinal symptoms and bowel incontinence, had a negative impact on all aspects of QoL. Patients with moderate to severe UC had poorer QoL than patients in remission/with mild UC or the general population. Active treatments demonstrated a significant improvement in QoL when compared to placebo across all trials. Significant QoL improvements were seen for both the induction and maintenance periods across all trials. Surgery can improve the quality of life for UC patients, but it may not restore full health. Individuals who underwent surgery reported greater QoL than those who did not. However, the impact of surgery on QoL might vary based on factors such as the type of surgery, the patient's age and health, and any postoperative complications.

Appendix K: Cost and healthcare resource identification

Healthcare resource costs were identified through UK clinical databases. Intervention and comparator administration costs were determined through the NHS reference costs 2022/23[79], with the cost of IV administration assumed to be represented by the cost for a consultant-led, non-admitted face-to-face follow-up attendance. In line with previous TAs,[39, 49, 71, 72] monitoring requirements were assumed similar for etrasimod and existing treatments and therefore were not included in the economic model. A single electrocardiogram (ECG) pre-initiation is required for S1Ps as specified in the SmPCs.

A systematic literature review (SLR) was also conducted to identify the utilisation of healthcare resources and/or their associated costs in severely active ulcerative colitis (UC). Searches were conducted in electronic databases including Medline, Embase, Cochrane Library, and supplemented by hand searching of conference proceedings and other secondary sources. The searches identified 14,507 citations of which 514 were included in the review.

95 publications reported total direct costs including inpatient visit costs, outpatient visit costs, emergency department visit costs, pharmacy costs and diagnostics costs associated with UC. Most commonly, direct medical costs were driven by the costs of hospitalization, surgery, and the management of its complications. Given the disease's epidemiological characteristics and age distribution, black race, coexisting infections, and non-adherent treatment, indirect costs due to productivity losses contribute to the high overall total disease costs. Additionally, 18 studies reported indirect costs associated with UC, including costs incurred due to productivity losses, costs due to absenteeism/presenteeism and disability-related costs.

Healthcare resource utilisation (HCRU) was assessed for patients across all treatments. Factors affecting length of stay were race, comorbid infections, and use of surgical procedures. Surgical procedures and other treatments had a significant effect on the decrease in outpatient visits. Patients who were non-adherent to treatments and used corticosteroids frequently had more emergency room visits (25%) than treatment adherent patients who did not use steroids frequently (18%).

This review also identified publications with surgery-related outcomes. Colectomy rates vary widely among UC patients and varied from 1.3% to 44%, depending on the follow-up time and the type of population.

While surgery is viewed as a permanent cure for UC, and some studies reported a decline in healthcare costs in period post-surgery compared to the pre-surgery period, total hospitalization costs as well as follow-up costs were higher amongst patients who had undergone surgery compared to those who had not. Costs were found to vary significantly depending upon the presentation (emergent /urgent vs. elective), type of surgery and occurrence of complications.

Appendix L: Price details of treatments included in the submission

L.1.1 Price of intervention

Table 67: Details of intervention costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price per pack	Source	[redacted]
Velsipity (etrasimod)	Oral	2 mg	28	£842.92	Pfizer, on file [confidential].	[redacted]
Concomitant therapy						
Mesalazine	Oral	400 mg	120	£15.50	MIMS	Unknown
Prednisolone	Oral	20 mg	28	£2.93	MIMS	Unknown
Budesonide	Oral	3 mg	50	37.53	MIMS	Unknown

Abbreviations: [redacted]

L.1.2 Price of comparators and subsequent treatments

Table 68: Details of comparators and subsequent treatment costs, including concomitant medicines, for each formulation used in the model

Name	Form	Dose per unit	Pack size	List price per pack	Source
Amgevita (adalimumab)	Subcutaneous injection	40mg	2	£704.28	MIMS
Jyseleca (filgocitinib)	Oral	200mg	30	£863.10	MIMS
Simponi (golimumab)	Subcutaneous injection	100mg x3 induction then 50mg	1	£762.97	MIMS
Flixabi then remsima (infliximab)	Intravenous induction then subcutaneous injection	100mg x2 induction then 120mg	1 then 2	£377.00 then £755.32	MIMS
Flixabi (infliximab)	Intravenous	100mg	1	£377.00	MIMS
Omvoh (mirikizumab)	Subcutaneous injection	300mg x3 induction then 200mg	1	£2,056.56	MIMS
Zeposia (ozanimod)	Oral	2.3mg induction then 0.92mg	1 initiation pack then 28	£343.25 then £1,373.00	MIMS
Xeljanz (tofacitinib)	Oral	5mg	56	£690.03	MIMS
Rinvoq (upadacitinib)	Oral	45mg x56 induction then 15mg	28	£2087.1 then £805.56	MIMS
Stelara (ustekinumab)	Intravenous induction then subcutaneous injection	130mg	1	£2,147.00	MIMS
Entyvio (vedolizumab)	Intravenous induction then subcutaneous injection	300mg x2 induction then 108mg	1 then 2	£2,050.00 then £1,025.00	MIMS
Entyvio (vedolizumab)	Intravenous	300mg	1	£2,050.00	MIMS

Abbreviations: MIMS, Monthly Index of Medical Specialities;

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Single technology appraisal: cost comparison

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Summary of Information for Patients (SIP)

September 2023

File name	Version	Contains confidential information	Date
ID5091 UC_Etrasimod _Summary of Information for Patients (SIP)	2.0	No	13th October 2023

Summary of Information for Patients (SIP):

What is the SIP?

The Summary of Information for Patients (SIP) is written by the company who is seeking approval from NICE for their treatment to be sold to the NHS for use in England. It is a plain English summary of their submission written for patients participating in the evaluation. It is not independently checked, although members of the public involvement team at NICE will have read it to double-check for marketing and promotional content before it is sent to you.

The **Summary of Information for Patients** template has been adapted for use at NICE from the Health Technology Assessment International – Patient & Citizens Involvement Group (HTAi PCIG). Information about the development is available in an open-access IJTAHC journal article

SECTION 1: Submission summary

1a) Name of the medicine (generic and brand name):

Response:
UK approved name: Etrasimod Brand name: Velsipity®

1b) Population this treatment will be used by. Please outline the main patient population that is being appraised by NICE:

Response:
Patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules).

1c) Authorisation: Please provide marketing authorisation information, date of approval and link to the regulatory agency approval. If the marketing authorisation is pending, please state this, and reference the section of the company submission with the anticipated dates for approval.

Response:
Etrasimod is anticipated to be approved by the Medicines and Healthcare Products Regulatory Agency (MHRA), for the following indication: Patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules). Please note, at the time of writing the SIP, the Summary of Product Characteristics (SmPC) for etrasimod is not publicly available.

1d) Disclosures. Please be transparent about any existing collaborations (or broader conflicts of interest) between the pharmaceutical company and patient groups relevant to the medicine. Please outline the reason and purpose for the engagement/activity and any financial support provided:

Response:

We have had previous engagements with Crohn's & Colitis United Kingdom (CCUK) and Inflammatory bowel Disease (IBD) Relief but have not contracted or provided financial support with or to any UC related patient group to undertake any particular projects.

SECTION 2: Current landscape

2a) The condition – clinical presentation and impact

Please provide a few sentences to describe the condition that is being assessed by NICE and the number of people who are currently living with this condition in England.

Please outline in general terms how the condition affects the quality of life of patients and their families/caregivers. Please highlight any mortality/morbidity data relating to the condition if available. If the company is making a case for the impact of the treatment on carers this should be clearly stated and explained.

Response:

UC is the most common form of inflammatory bowel disease (IBD); approximately 16 out of every 100,000 people are living with UC in the UK.[1]

UC is a long-term condition where parts of the intestine, specifically the colon and rectum, become inflamed. Small ulcers can develop on the colon, which can lead to discomfort, bleeding, and the production of fluid.[2]

People living with UC may go for weeks or months with very mild or no symptoms in medical terms this is called 'remission', followed by periods where the symptoms are particularly troublesome, known as 'flare-ups' or 'relapses'.[3]

2b) Diagnosis of the condition (in relation to the medicine being evaluated)

Please briefly explain how the condition is currently diagnosed and how this impacts patients. Are there any additional diagnostic tests required with the new treatment?

Response:

To diagnose UC, a general practitioner (GP) will first ask patients about their symptoms, general health and medical history.[4] The GP will also undertake a physical examination, checking for signs such as paleness (caused by anaemia – low red blood cells count) and tenderness in a patient's stomach (caused by inflammation).[4] A poo sample can be checked for signs of infection, as gastroenteritis (infection of the stomach and bowel) can sometimes have similar symptoms to UC.[4] Blood tests may also be carried out to check for anaemia and to see if there's inflammation on any part of the body.[4] Patients may be referred to hospital for further tests if their GP suspects they have IBD. These could include an X-ray or computerised tomography (CT) scan to rule out serious complications and a detailed examination of your rectum (sigmoidoscopy) and colon (colonoscopy).[4]

Prior to starting treatment with etrasimod, an electrocardiogram (ECG) test in all patients is required to assess whether the patient has any pre-existing heart issues. In patients with certain heart conditions, observation by a doctor after the first treatment is recommended.

Patients with a history of diabetes, uveitis (inflammation inside the eye), or an underlying/co-existing retinal disease should undergo an eye examination prior to starting treatment with etrasimod.

A recent blood test is required within 6 months or after discontinuation of prior UC therapy, to measure the number of cells (found in the patient's blood), including the number of immune cells.

A blood test within 6 months investigating liver function, specifically measuring transaminase and bilirubin levels, must be available prior to starting etrasimod.

If vaccinations are required, they should be had at least 4 weeks prior to starting etrasimod. It is recommended to update immunisations in agreement with current immunisation guidelines prior to beginning etrasimod therapy.

Before starting etrasimod, women who are likely to get pregnant must discuss with their doctor about the potential for a serious risk to the baby. They must have a negative pregnancy test before staring the treatment and must use effective contraception during treatment with etrasimod.

2c) Current treatment options:

The purpose of this section is to set the scene on how the condition is currently managed:

- What is the treatment pathway for this condition and where in this pathway the medicine is likely to be used? Please use diagrams to accompany text where possible. Please give emphasis to the specific setting and condition being considered by NICE in this review. For example, by referencing current treatment guidelines. It may be relevant to show the treatments people may have before and after the treatment under consideration in this SIP.
- Please also consider:
    - if there are multiple treatment options, and data suggest that some are more commonly used than others in the setting and condition being considered in this SIP, please report these data.
    - are there any drug–drug interactions and/or contraindications that commonly cause challenges for patient populations? If so, please explain what these are.

Response:

If a patient's UC is classified as either moderate or severe by their doctor, a choice can be made to be given treatments called biologics or non-biologics (oral advanced small molecules). The decision should be made on a case by case basis, considering:

- patient preference,
- likelihood of the patient taking their treatment as often as it is required,
- side effects,
- speed of response to the drug,
- treatment cost.[5.6]

Current available treatments in the National Health Service (NHS) include:

<u>Biologics</u>

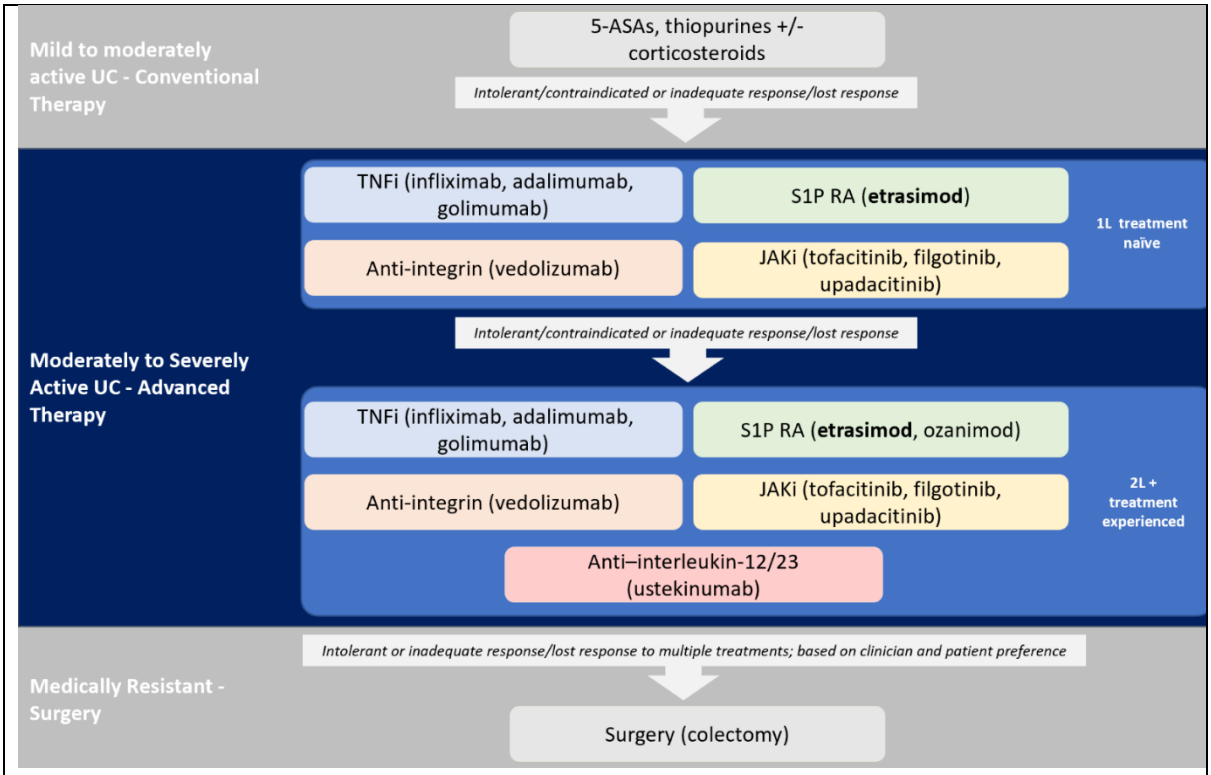
- TNFis: adalimumab, infliximab, golimumab
- Integrin inhibitor: vedolizumab
- IL 12/23 inhibitor: ustekinumab

<u>Non-biologics</u>

- JAKis: tofacitinib, filgotinib, upadacitinib
- Sphingosine-1-phosphate (S1P) receptor: ozanimod.

Etrasimod is proposed for use as a first treatment advanced therapy option (first line) once diagnosed with moderately to severely active UC or later on (second line plus) in the management of moderately to severely active UC if a previous treatment has not worked (inadequate or lost response to treatment) or if a patient becomes intolerant (unable to take the medication, usually due to side effects) or contraindicated (whereby it is too risky to take the medication, for example during pregnancy).

Figure 1 Clinical pathway of care for patients with UC and proposed placement for etrasimod within this pathway



Abbreviations: 1L/2L, first/second line; ASA, 5-aminosalicylate acid; JAKi, janus kinase inhibitors; S1P, sphingosine-1-phosphate; RA, receptor antagonist; TNFi, tumour necrosis factor alpha inhibitors; UC, ulcerative colitis.

2d) Patient-based evidence (PBE) about living with the condition

Context:

- **Patient-based evidence (PBE)** is when patients input into scientific research, specifically to provide experiences of their symptoms, needs, perceptions, quality of life issues or experiences of the medicine they are currently taking. PBE might also include carer burden and outputs from patient preference studies, when conducted in order to show what matters most to patients and carers and where their greatest needs are. Such research can inform the selection of patient-relevant endpoints in clinical trials.

In this section, please provide a summary of any PBE that has been collected or published to demonstrate what is understood about **patient needs and disease experiences**. Please include the methods used for collecting this evidence. Any such evidence included in the SIP should be formally referenced wherever possible and references included.

Response:

The burden of living with UC was shown through a Pfizer organised patient advisory board. Key emphasis was placed on the psychological aspects of care, i.e., not feeling they were receiving advanced treatment in time, and on administration of their medication with 70% preferring an oral option.

Eleven participants from across the UK with a diagnosis of IBD, which in this case was mainly UC, took part in an online patient advisory board. The advisory board discussions focused on four aspects: diagnosis journey, treatment journey, treatment preferences and impact on daily life.

The study showed an interest to receive advanced therapies sooner and a preference for oral therapies. Patients noted:

"Topical and tablet forms of treatment would be much easier to administer. Personally, I really dislike needles and I also have problem veins so it's always a bit of a nightmare if I have to have an infusion."

"The ability for the medication to be flexible around my life and work is important, the potential side effects can play a big part in choosing a medication, it can be difficult to deal with some side effects long term."

"When I went to the hospital and said suppositories aren't working, enemas aren't working, steroids aren't working, the mental side was never considered until I ended up changing hospital. So, it was a bit of a knockback every time I went, because I just felt like I wasn't being listened to a lot of the time. In terms of the actual medication side they kind of just tried to say oh, try them for longer or try them again. I mean, it never, never really worked…."

SECTION 3: The treatment

3a) How does the new treatment work?

What are the important features of this treatment?

Please outline as clearly as possible important details that you consider relevant to patients relating to the mechanism of action and how the medicine interacts with the body

Where possible, please describe how you feel the medicine is innovative or novel, and how this might be important to patients and their communities.

If there are relevant documents which have been produced to support your regulatory submission such as a summary of product characteristics or patient information leaflet, please provide a link to these.

Response:

Etrasimod is a sphingosine 1-phosphate (S1P) receptor modulator that binds to S1P receptors 1, 4 and 5 (S1P1,4,5) and is a balanced G-protein and beta-arrestin agonist at S1P1. Etrasimod partially and reversibly blocks the capacity of lymphocytes (immune cells) to escape from lymphoid organs, reducing the number of immune cells in peripheral blood thereby lowering the number of activated lymphocytes in the tissue.

Etrasimod is a pill that can be swallowed by mouth once per day, with or without food. The dose of etrasimod, 2mg once daily, does not change at any point during the duration of treatment.

Once daily etrasimod can potentially be a better treatment experience for patients when compared to other treatments which require injections or intravenous infusions, meaning less lifestyle changes are required.

Etrasimod is available in one size (2 mg pills).

3b) Combinations with other medicines

Is the medicine intended to be used in combination with any other medicines?

- Yes / No

If yes, please explain why and how the medicines work together. Please outline the mechanism of action of those other medicines so it is clear to patients why they are used together.

If yes, please also provide information on the availability of the other medicine(s) as well as the main side

effects.

If this submission is for a combination treatment, please ensure the sections on efficacy (3e), quality of life (3f) and safety/side effects (3g) focus on data that relate to the combination, rather than the individual treatments.

Response:

Etrasimod is not required to be used in combination with other medicines.

However, the use of corticosteroids alongside etrasimod is permitted.

It is possible to change, or switch, to a different treatment option if discussed and agreed with the prescribing doctor.

3c) Administration and dosing

How and where is the treatment given or taken? Please include the dose, how often the treatment should be given/taken, and how long the treatment should be given/taken for.

How will this administration method or dosing potentially affect patients and caregivers? How does this differ to existing treatments?

Response:

Etrasimod is a tablet which can be taken by mouth at home.

Not all current moderately to severely active UC treatments are taken in a similar way; some are taken via injection or intravenous infusion.

The recommended dose is 2 mg given once per day with or without food. The dose of etrasimod, does not change at any point during the duration of treatment.

Decisions to stop etrasimod treatment and/or to switch to a new treatment if required should be decided in discussion with the doctor.

Etrasimod should be stopped at least 6 days before a pregnancy is planned.

3d) Current clinical trials

Please provide a list of completed or ongoing clinical trials for the treatment. Please provide a brief top-level summary for each trial, such as title/name, location, population, patient group size, comparators, key inclusion and exclusion criteria and completion dates etc. Please provide references to further information about the trials or publications from the trials.

Response:

Etrasimod's clinical program included two phase 3, randomized, double-blind, placebo-controlled trials. The studies are briefly summarised in the table below:

Trial no. (Trial number)	Description	Key inclusion criteria	Patient numbers	Status
ELEVATE UC 12 (NCT03996369)	To assess the efficacy of etrasimod on clinical remission		330	Completed

	after 12 weeks of treatment, and to assess its safety for 12 weeks.	• Diagnosed with ulcerative colitis (UC) ≥ 3 months prior to screening • Active UC confirmed by endoscopy		December 2021
ELEVATE UC 52 (NCT03945188)	To assess the efficacy of etrasimod on clinical remission after 12 and 52 weeks of treatment, and to assess its long-term safety for up to 52 weeks.		420	Completed February 2022

3e) Efficacy

Efficacy is the measure of how well a treatment works in treating a specific condition.

In this section, please summarise all data that demonstrate how effective the treatment is compared with current treatments at treating the condition outlined in section 2a. Are any of the outcomes more important to patients than others and why? Are there any limitations to the data which may affect how to interpret the results? Please do not include academic or commercial in confidence information but where necessary reference the section of the company submission where this can be found.

Response:

Treatment with etrasimod was well tolerated and effective therapy for patients with moderately to severely active UC.

The trial data explored clinical response and remission; clinical response is the effect of a treatment on a patient's condition in terms of decreasing numbers of rectal bleeding, stool frequency and endoscopic improvement. While clinical remission is used to describe the disappearance of symptoms. The trial data showed in the overall etrasimod population a significantly greater proportion of patients achieved clinical response and clinical remission compared with placebo in both the induction period (the start of taking a medication) and the maintenance period (ongoing taking of a medication).

Additionally, etrasimod compared to placebo, at week 12 of both studies and maintained to week 52 in ELEVATE UC 52, had higher rates of:

- symptomatic remission (another measure of symptoms disappearing),
- endoscopic improvement-histologic remission (EIHR, i.e., the process of wound healing sometime referred to as mucosal healing
- clinical response (a measure of how a patient is responding to treatment)

As there were no trials directly comparing etrasimod to other treatments a study known as a network meta-analysis (NMA) was undertaken to do so. The results of the study showed etrasimod was similar to adalimumab, infliximab and vedolizumab for clinical response and clinical remission in the induction (the start of taking a medication) and maintenance (ongoing taking of a medication) periods.

3f) Quality of life impact of the medicine and patient preference information

What is the clinical evidence for a potential impact of this medicine on the quality of life of patients and their families/caregivers? What quality of life instrument was used? If the EuroQol-5D (EQ-5D) was used does it sufficiently capture quality of life for this condition? Are there other disease specific quality of life measures that should also be considered as supplementary information?

Please outline in plain language any quality of life related data such as **patient reported outcomes (PROs).**

Please include any **patient preference information (PPI)** relating to the drug profile, for instance research to understand willingness to accept the risk of side effects given the added benefit of treatment. Please include all references as required.

In both ELEVATE trials, etrasimod demonstrates rapid and sustained improvements versus placebo in disease specific health related quality of life measures, using tools such as the inflammatory bowel disease questionnaire (IBDQ) and short form- six dimensions (SF-6D).

The IBDQ captures a patients experience of IBD on functioning and well-being, bowel and systemic symptoms, emotional and social function. While, the SF-6D captures physical, role and social functioning as well as pain, mental health, and vitality.

3g) Safety of the medicine and side effects

When NICE appraises a treatment, it will pay close attention to the balance of the benefits of the treatment in relation to its potential risks and any side effects. Therefore, please outline the main side effects (as opposed to a complete list) of this treatment and include details of a benefit/risk assessment where possible. This will support patient reviewers to consider the potential overall benefits and side effects that the medicine can offer.

Based on available data, please outline the most common side effects, how frequently they happen compared with standard treatment, how they could potentially be managed and how many people had treatment adjustments or stopped treatment. Where it will add value or context for patient readers, please include references to the Summary of Product Characteristics from regulatory agencies etc.

Response:

In both ELEVATE UC 12 and ELEVATE UC 52, etrasimod showed a favourable safety profile. No increased incidence of infections (overall infections, herpes zoster, opportunistic, or serious infections) were seen in patients treated with etrasimod compared with patients treated with placebo.

3h) Summary of key benefits of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key benefits of the treatment for patients, caregivers and their communities when compared with current treatments.
- Please include benefits related to the mode of action, effectiveness, safety and mode of administration
-

Response:

Treatment with etrasimod was well tolerated and effective therapy for patients with moderately to severely active UC.

Etrasimod is formulated as a convenient, once- per day dose in an oral pill, with a dosage that does not change during treatment.

Many patients report preferring oral medicines over other administration routes, such as injections and intravenous infusions. Oral treatments may overcome some barriers to therapy often associated with injections and intravenous infusions, thereby helping to ensure patients take their medication as required.

An oral formulation has the potential to decrease the burden on patients with ease of use and not requiring trips to the hospital to receive treatment.

Furthermore, oral treatment can reduce the burden on the NHS as administration can take place at home, whereby for self-administered injection training is required and intravenous infusions must be administered in hospital which can potentially interfere with their everyday routines in terms of family time, leisure time and work life.

As such, etrasimod provides an alternative option for patients to move conveniently from oral conventional therapies to an advanced therapy to achieve early disease control. This in turn increases the likelihood of successful outcomes for patients earlier in their treatment pathway.

Another benefit of etrasimod is the simplicity of its dosing program . Unlike other advanced therapies for UC, etrasimod has a once per day dosing, with no dose changes needed for induction (start of taking a medication) or maintenance (ongoing taking of a medication).

3i) Summary of key disadvantages of treatment for patients

Issues to consider in your response:

- Please outline what you feel are the key disadvantages of the treatment for patients, caregivers and their communities when compared with current treatments. Which disadvantages are most important to patients and carers?
- Please include disadvantages related to the mode of action, effectiveness, side effects and mode of administration
- What is the impact of any disadvantages highlighted compared with current treatments

Response:

A one off ECG test is required, before a doctor can start a patient on etrasimod. This is not atypical, since another advanced treatment requires the same test.

Potentially, some patients may require the need for an eye test. It is recommended that patients with a history of diabetes mellitus, uveitis, or retinal disease undergo an eye test prior to treatment initiation with etrasimod and have follow up evaluations while receiving therapy.

Additionally, if patients report a change in their vision while taking etrasimod they should have an eye test. ECG checks for heart conditions while an ophthalmology assessment is an eye test but are relatively low in terms of burden as are considered quick, safe and painless.

3i) Value and economic considerations

Introduction for patients:

Health services want to get the most value from their budget and therefore need to decide whether a new treatment provides good value compared with other treatments. To do this they consider the costs of treating patients and how patients' health will improve, from feeling better and/or living longer, compared with the treatments already in use. The drug manufacturer provides this information, often presented using a health economic model.

In completing your input to the NICE appraisal process for the medicine, you may wish to reflect on:

- The extent to which you agree/disagree with the value arguments presented below (e.g., whether you feel these are the relevant health outcomes, addressing the unmet needs and issues faced by patients; were any improvements that would be important to you missed out, not tested or not proven?)
- If you feel the benefits or side effects of the medicine, including how and when it is given or taken, would have positive or negative financial implications for patients or their families (e.g., travel costs, time-off work)?
- How the condition, taking the new treatment compared with current treatments affects your quality of life.

Response:

Model Structure:

- A simple cost minimisation model has been included as part of the NICE evidence submission.
    - A cost minimisation model compares the cost of the new treatment incurred by the National Health Service (NHS) to the cost of the currently available treatment options to the NHS. In this case etrasimod was compared to:
        - Adalimumab
        - Golimumab
        - Infliximab
        - Vedolizumab
        - Tofacitinib
        - Upadacitnib
        - Filgotinib
    - The model also includes cost for:
        - Concomitant therapies - medications taken alongside the treatment in question.
        - Pre-initiation testing - tests required before a patient can be declared safe to start a particular treatment for example, some treatments require an ECG.
        - Administration costs – cost associated with taking the medication, for example, if it has to be done via intravenous infusion one would need to go to the hospital to have it.
- The model considers the cost of treatment for an average patient over five years.
    - Although a patient is expected to stay on treatment longer if it is effective. The costs are considered over five years to account for higher initiation costs (i.e., starting treatment costs) of some treatments. This allows the costs to stabilise over time so an accurate overall cost could be considered.

Model assumptions:

- Where multiple options for a comparator treatment (i.e., other treatments available) existed the least expensive cost was used for the calculations to ensure the most conservative approach was taken.
- Non-discounted prices known as list prices for all available treatment options were used. However, it is anticipated NICE will use confidential discounted prices in their decision making.
- Monitoring costs, for example frequent check-ups, are expected to be the same regardless of which treatment option has been selected. As such they have been excluded from the analysis.

Each treatment option has a different list price. As such the model estimates a range of treatment costs across the available options, including etrasimod. Etrasimod has shown it sits within the existing costs of the currently available preparations, despite also offering a significant reduction in treatment burden, and potential increased utility experienced from reduced frequency of injections.[7-10] This means the NHS could pay more per annum for some of the existing treatments when compared to etrasimod.

3j) Innovation

NICE considers how innovative a new treatment is when making its recommendations. If the company considers the new treatment to be innovative please explain how it represents a 'step change' in treatment and/ or effectiveness compared with current treatments. Are there any QALY benefits that have not been captured in the economic model that also need to be considered (see section 3f)
Response: Etrasimod is a once-per day, sphingosine 1-phosphate (S1P) receptor modulators, anticipated to be available in the UK, with MHRA marketing authorisation. This represents an oral treatment option, with proven reduced life interference and treatment burden, for patients suffering from moderately to severely active UC.

3k) Equalities

Are there any potential equality issues that should be taken into account when considering this condition and this treatment? Please explain if you think any groups of people with this condition are particularly disadvantaged. Equality legislation includes people of a particular age, disability, gender reassignment, marriage and civil partnership, pregnancy and maternity, race, religion or belief, sex, and sexual orientation or people with any other shared characteristics More information on how NICE deals with equalities issues can be found in the NICE equality scheme Find more general information about the Equality Act and equalities issues here
Response: Etrasimod is not likely to raise any equality or equity issues in patients with moderately to severely active UC who are eligible to receive treatment.

SECTION 4: Further information, glossary and references

4a) Further information

Feedback suggests that patients would appreciate links to other information sources and tools that can help them easily locate relevant background information and facilitate their effective contribution to the NICE assessment process. Therefore, please provide links to any relevant online information that would be useful, for example, published clinical trial data, factual web content, educational materials etc. Where possible, please provide open access materials or provide copies that patients can access.
Response: Further information on NICE and the role of patients: • Public Involvement at The National Institute for Health and Care Excellence (NICE) Public involvement | NICE and the public | NICE Communities | About | NICE • NICE's guides and templates for patient involvement in Health Technology Assessments (HTAs) Guides to developing our guidance | Help us develop guidance | Support for voluntary and community sector (VCS) organisations | Public involvement | NICE and the public | NICE Communities | About | NICE • The European Patients' Academy on Therapeutic Innovation (EUPATI) guidance on patient involvement in NICE: https://www.eupati.eu/guidance-patient-involvement/

- The European Federation of Pharmaceutical Industries and Associations (EFPIA) – Working together with patient groups: https://www.efpia.eu/media/288492/working-together-with-patient-groups-23102017.pdf
- National Health Council Value Initiative. https://nationalhealthcouncil.org/issue/value/
- The International Network of Agencies for Health Technology Assessment (INAHTA): http://www.inahta.org/
- European Observatory on Health Systems and Policies. Health technology assessment - an introduction to objectives, role of evidence, and structure in Europe: http://www.inahta.org/wp-content/themes/inahta/img/AboutHTA_Policy_brief_on_HTA_Introduction_to_Objectives_Role_of_Evidence_Structure_in_Europe.pdf

4b) Glossary of terms

Response:

Abbreviation	Definition
CCUK	Crohn's & Colitis United Kingdom
CT	Computerised tomography
ECG	Electrocardiogram
EIHR	Endoscopic Improvement-Histologic Remission
EFPIA	European Federation of Pharmaceutical Industries and Associations
EUPATI	European Patients' Academy on Therapeutic Innovation
GP	General Practitioner
IBD	Inflammatory Bowel Disease
IBDQ	The inflammatory Bowel Disease Questionnaire
INAHTA	International Network of Agencies for Health Technology Assessment
MHRA	The Medicines and Healthcare products Regulatory Agency
NICE	The National Institute for Health and Care Excellence
NHS	National Health Service
NMA	Network meta-analysis
S1P	Sphingosine 1-phosphate
SF-6D	Short Form – Six Dimensions
SIP	Summary of Information for Patients
SmPC	Summary of Product Characteristics
UC	Ulcerative colitis
UK	United Kingdom

4c) References

Please provide a list of all references in the Vancouver style, numbered and ordered strictly in accordance with their numbering in the text:

Response:

1. Lynch WD, Hsu R. Ulcerative Colitis. In: StatPearls: Treasure Island (FL) 2022.

2. Pasvol TJ, Horsfall L, Bloom S, et al. Incidence and prevalence of inflammatory bowel disease in UK primary care: a population-based cohort study. BMJ Open 2020;10:e036584.
3. National Health Service. Conditions: Ulcerative coilitis. Availiable at: https://www.nhs.uk/conditions/ulcerative-colitis/
4. National Health Service. Diagnosis: Ulcerative coilitis: Diagnosis. Availiable at: https://www.nhs.uk/conditions/ulcerative-colitis/diagnosis/
5. Lamb CA, Kennedy NA, Raine T, et al. British Society of Gastroenterology consensus guidelines on the management of inflammatory bowel disease in adults. Gut 2019;68:s1-s106.
6. National Institute for Health and Care Excellence (NICE). Ulcerative colitis: management [NG130]. Volume 2023, 2019. Available at: https://www.nice.org.uk/guidance/ng130/resources/ulcerative-colitis-management-pdf-66141712632517.
7. Shivaji UN, Nardone OM, Cannatelli R, et al. Small molecule oral targeted therapies in ulcerative colitis. Lancet Gastroenterol Hepatol 2020;5:850-861.
8. Boeri M, Myers K, Ervin C, et al. Patient and physician preferences for ulcerative colitis treatments in the United States. Clin Exp Gastroenterol 2019;12:263-278
9. Peyrot M, Rubin RR, Kruger DF, et al. Correlates of insulin injection omission. Diabetes Care 2010;33:240-5.
10. Bolge SC, Goren A, Tandon N. Reasons for discontinuation of subcutaneous biologic therapy in the treatment of rheumatoid arthritis: a patient perspective. Patient Prefer Adherence 2015;9:121-31.

NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

Cost Comparison Appraisal

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Clarification questions

September 2023

File name	Version	Contains confidential information	Date
ID5901 Etrasimod Company EAG clarification responses	**2**	**Yes**	**28.09.23**

Notes for company

Highlighting in the template

Square brackets and grey highlighting are used in this template to indicate text that should be replaced with your own text or deleted. These are set up as form fields, so to replace the prompt text in [grey highlighting] with your own text, click anywhere within the highlighted text and type. Your text will overwrite the highlighted section.

To delete grey highlighted text, click anywhere within the text and press DELETE.

Section A: Clarification on effectiveness data

A1. Priority Question. Clinical remission and clinical response NMA results are presented in the CS (Table 48 and Table 49). In addition to these results, please provide (for example, biological or pharmacological) evidence to support the claim that etrasimod is similar (during the induction and maintenance phases), for both bio-naive and bio-experienced patients, in terms of efficacy and safety to:

1. **non-biologics: ozanimod (S1P RA, non-biologic; this is the same modulator as etrasimod), tofacitinib, filgotinib and upadacitinib (JAKi)**
2. **biologics: adalimumab, golimumab, infliximab (TNFi), vedolizumab (anti-integrin) ustekinumab (anti-interleukin-12/23)**

The meta-analysis, comparator efficacy, and safety analysis focused on outcomes widely reported in clinical trials and typically used in previous technology assessments to appraise therapies with a positive recommendation for treating moderately to severely active ulcerative colitis.

This approach aligns with NICE's streamlined decision-making under the PATT program. A robust analysis of the key parameters (response and remission) showed

similarities in the main clinical outcomes. No other comparable evidence is available. However, the results for both the naïve population and biologic-experienced subgroup in the induction and maintenance analyses suggest that, based on the available data, etrasimod is an efficacious treatment for moderately to severely active UC and is comparable to currently available therapies used in advanced UC treatment.

[redacted]

The results also demonstrate that the incidence of serious infections during the induction phase is expected to be low for patients treated with etrasimod and comparable to placebo and its comparators.

Therefore, recommending etrasimod in addition to the existing care remains low risk.

*Due to a lack of RCT data in the biologic-experienced population, no comparisons could be made between etrasimod and infliximab.

A2. Priority question. In the NICE 2023 cost comparison guidance, it is stated that the company only needs to make a comparison with one of the comparators listed in the NICE scope. Which comparator does the company consider is the most appropriate? Please explain how this conclusion was reached.

Our understanding of the NICE guidelines is that more than one comparator can be included in the submission. The NICE health technology evaluations: the manual (2022) notes under section 4.2.13[1]:

'A cost-comparison analysis is for technologies that are likely to provide similar or greater health benefits at similar or lower cost than the relevant comparator(s). For technologies evaluated using cost-comparison analysis in the technology appraisal programme, relevant comparators are those recommended in published NICE guidance for the same population'

TA871 and TA876 went through the PATT process with both including more than 1 comparator in their submission.[2,3]

Currently, there are 7 licensed treatments approved by NICE for moderately to severely active UC in the 1L+ space, all of which are relevant comparators. However [redacted]. Therefore, they were deemed the most appropriate to compare against in the main body of the streamlined PATT submission while all others are presented in the appendix and model for full transparency.

A3. Priority question. Were the methods used to conduct the network meta-analysis pre-specified in a protocol or statistical analysis plan? If so, please provide this document.

Please see the NMA SAP provided alongside this response.

A4. We note the presence of closed loops in each of the evidence networks for the efficacy outcomes. Please provide the results of inconsistency assessments for each network as per NICE TSD 4 ("Inconsistency in network of evidence based on randomised controlled trials").

Please find below the information requested below:

A fixed effect unrelated mean effects (UME) model was run to assess and identify any sources of inconsistency among the analyses. In order to ensure a fair comparison between the NMA model and the UME model, each model was fit with the exact same data. Three chains were run for the UME. For each analysis the posterior median of total residual deviance and the DIC were recorded and a deviance contribution plot comparing in the NMA model with the unrelated mean effects model was produced.

Differences of more than 5 between models could be seen as meaningful differences and should be examined using the totality of evidence and available data. The differences between the posterior median of total residual deviance were all less than 5, however there were some differences with regards to the DIC. UK1 and UK4 have DIC differences of approximately 6.17 and 9.4 respectively. Examining the deviance contribution plots for these two models, we do not above any points significantly below the line of equality (>0.5 difference). For UK1, there was some moderate heterogeneity observed for the clinical response outcome for adalimumab 80/40 mg and vedolizumab 300 mg and similarly for etrasimod 2 mg for the clinical remission outcome.

There was significant heterogeneity between the two trials informing the golimumab 100 mg arm. PURSUIT J shown a significant reduction in the risk of a serious AE for golimumab 100 mg compared to placebo where the opposite was true for PURSUIT M. This resulted in a high I^2 value.

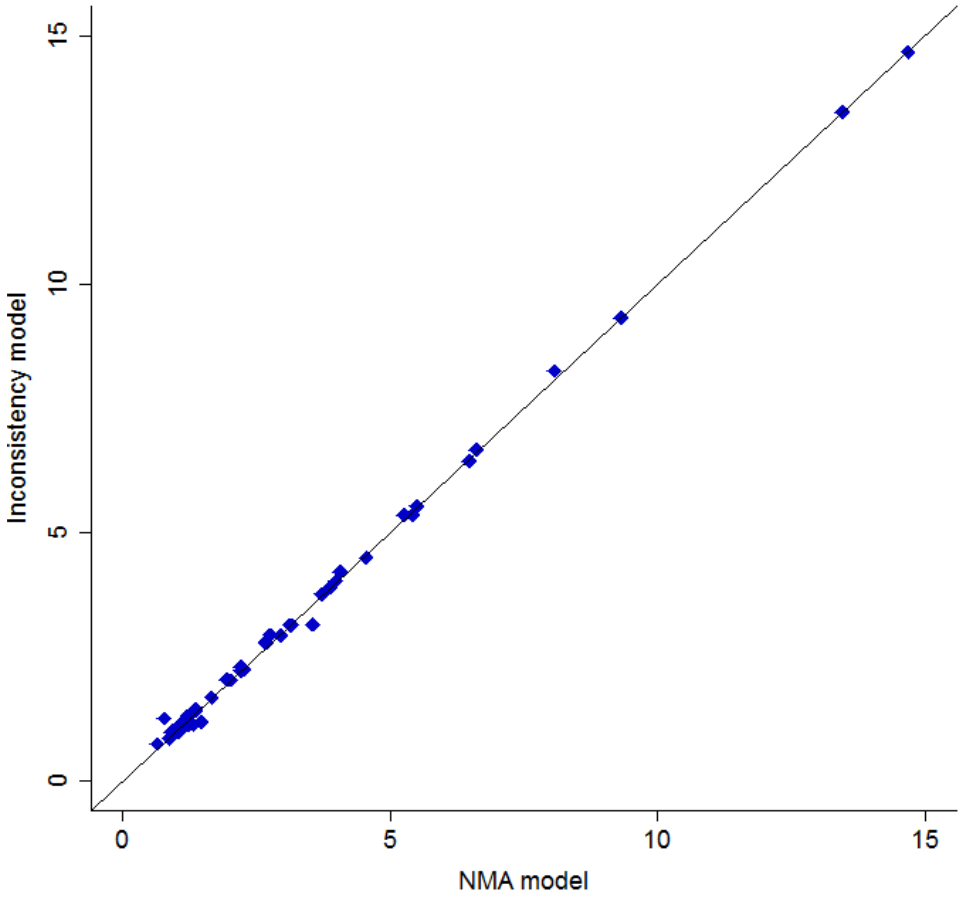
Given the assessment of the inconsistency diagnostics in conjunction with the heterogeneity assessment, we don't expect there to be any significant inconsistency among the analyses

UK1 Induction biologic naïve analysis

Model fit statistics for the main analysis (fixed effects no baseline risk adjustment) and for the unrelated mean effects model

Model	Posterior median of total residual deviance	DIC
NMA: Fixed effect	150.6	615.037
Unrelated mean effect model	151.3	608.860

Deviance contribution plot comparing the NMA model with the unrelated mean effects model

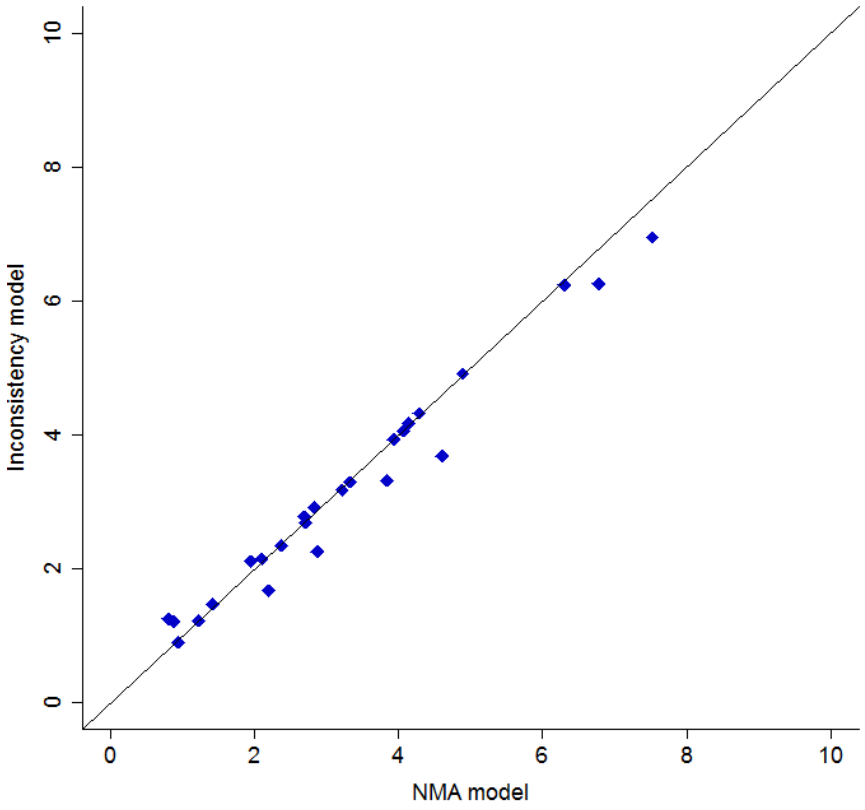


UK2 Induction biologic exposed

Model fit statistics for the main analysis (fixed effects no baseline risk adjustment) and for the unrelated mean effects model

Model	Posterior median of total residual deviance	DIC
NMA: Fixed effect	81.19	307.920
Unrelated mean effect model	78.52	305.210

Deviance contribution plot comparing the NMA model with the unrelated mean effects model

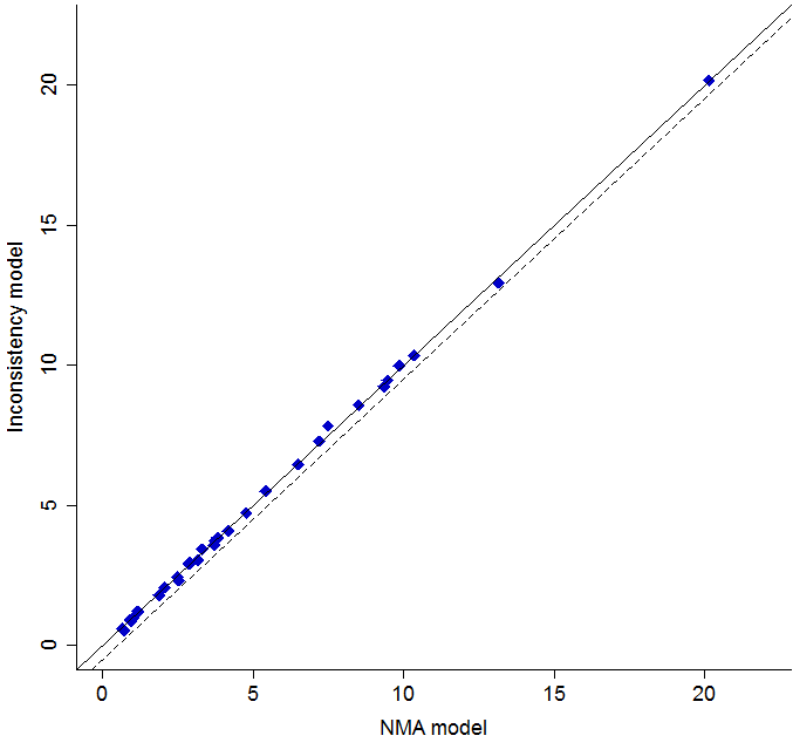


UK3 Maintenance biologic naïve

Model fit statistics for the main analysis (fixed effects no baseline risk adjustment) and for the unrelated mean effects model

Model	Posterior median of total residual deviance	DIC
NMA: Fixed effect	158.7	451.867
Unrelated mean effect model	158.3	457.659

Deviance contribution plot comparing the NMA model with the unrelated mean effects model

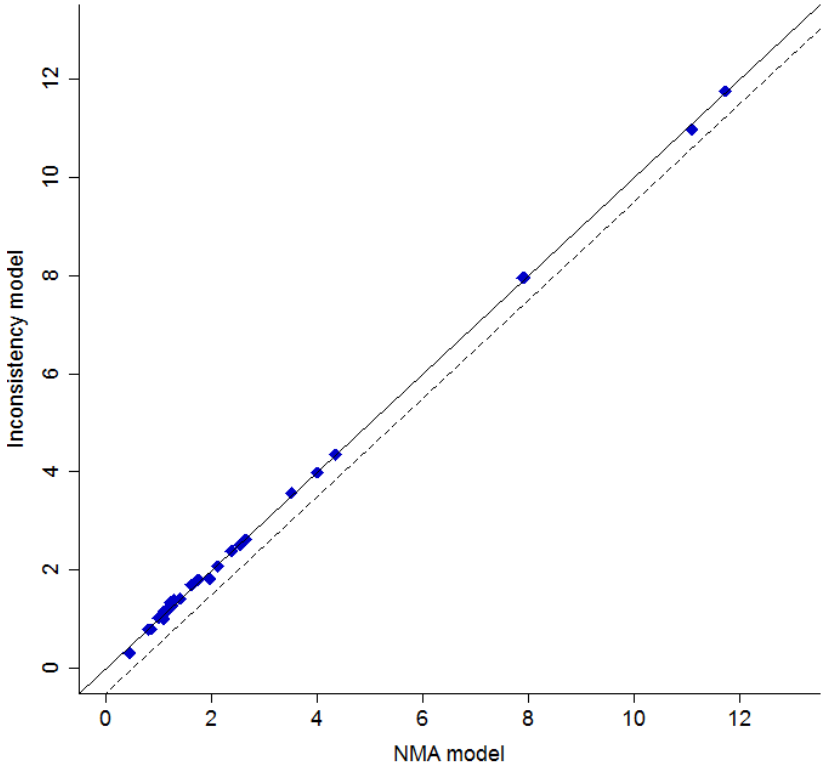


UK 4 Maintenance biologic exposed

Model fit statistics for the main analysis (fixed effects no baseline risk adjustment) and for the unrelated mean effects model

Model	Posterior median of total residual deviance	DIC
NMA: Fixed effect	77.63	284.158
Unrelated mean effect model	77.38	274.769

Deviance contribution plot comparing the NMA model with the unrelated mean effects model

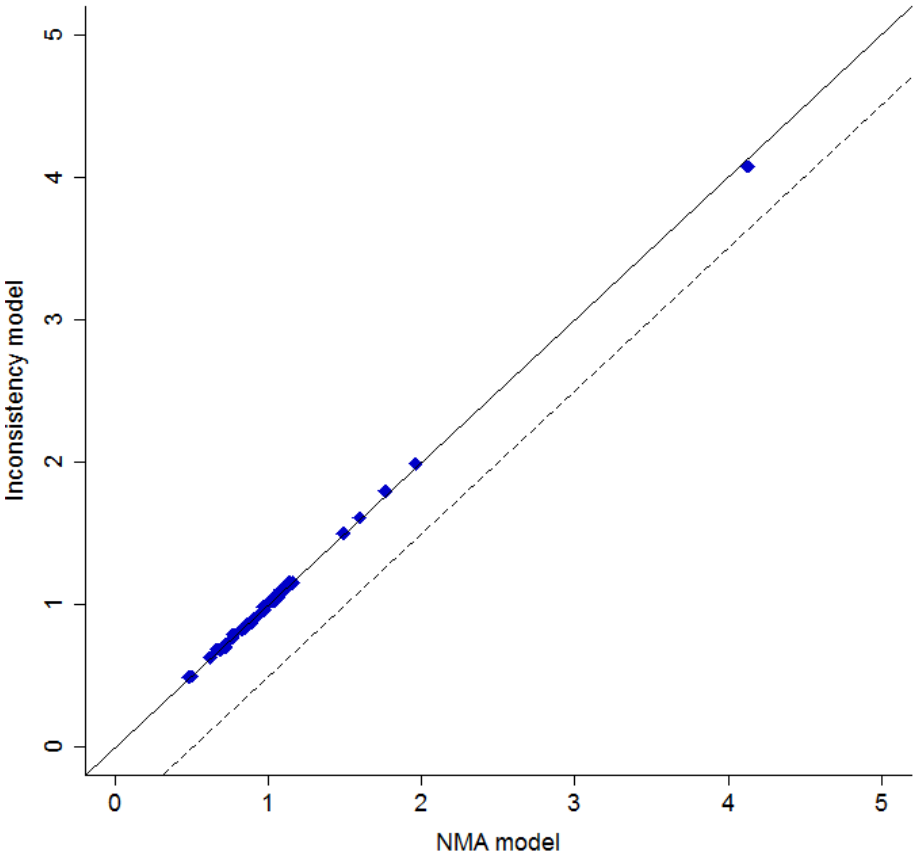


UK 5 Induction serious infections

Model fit statistics for the main analysis (fixed effects no baseline risk adjustment) and for the unrelated mean effects model

Model	Posterior median of total residual deviance	DIC
NMA: Fixed effect	41.6	157.200
Unrelated mean effect model	41.5	160.408

Deviance contribution plot comparing in the NMA model with the unrelated mean effects model



Homogeneity

Measure of heterogeneity for treatment comparisons with more than one study for the main analyses

Treatment	I^2	P value
Induction biologic naive(Clinical response)		
Etrasimod 2 mg	0.00%	0.3868
Infliximab 5mg kg	0.00%	0.5669
Adalimumab 160 80 mg	0.00%	0.4319
Upadacitinib 45 mg	0.00%	0.9787
Adalimumab 80 40 mg	41.81%	0.1899
Vedolizumab 300 mg	42.04%	0.1890
Induction biologic naive (Clinical remission)		
Etrasimod 2 mg	49.19%	0.1606
Infliximab 5mg kg	26.81%	0.2428
Adalimumab 160 80 mg	29.33%	0.2362
Upadacitinib 45 mg	0.00%	0.4764
Adalimumab 80 40 mg	0.00%	0.8467
Vedolizumab 300 mg	0.00%	0.3259
Induction biologic exposed (Clinical response)		

Treatment	I^2	P value
Etrasimod 2 mg	0.00%	0.5634
Upadacitinib 45 mg	0.00%	0.7232
Vedolizumab 300 mg	48.06%	0.1653
Induction biologic exposed (Clinical remission)		
Etrasimod 2 mg	52.41%	0.1472
Upadacitinib 45 mg	0.00%	0.8208
Vedolizumab 300 mg	0.00%	0.3915
Maintenance biologic naive (Clinical response)		
Golimumab 100 mg	50.22%	0.1564
Vedolizumab 300 mg Q8W	0.00%	0.4424
Maintenance biologic naive (Clinical remission)		
Golimumab 100 mg	79.68%	0.0265
Vedolizumab 300 mg Q8W	0.00%	0.3847
Maintenance biologic exposed (Clinical response)		
Vedolizumab 300 mg Q8W	0.00%	0.6510
Maintenance biologic exposed (Clinical remission)		
Vedolizumab 300 mg Q8W	0.00%	0.8586
Induction serious infections		
Upadacitinib 45 mg	0.00%	0.9547
Tofacitinib 10 mg	0.00%	0.5088
Adalimumab 160/80 mg	39.72%	0.1735
Adalimumab 80/40 mg	0.00%	0.9621
Etrasimod 2 mg	0.00%	0.7794
Vedolizumab 300 mg	0.00%	0.9407

P value from the chi-squared test

Section B: Clarification on cost-effectiveness data

B1. Priority question. For several ulcerative colitis treatments, including adalimumab, infliximab, golimumab and vedolizumab, NICE has recommended that treatment cessation should be considered for patients in stable clinical remission or who have had a complete response at 12 months. Please provide a cost comparison analysis that accounts for treatment stopping rules linked to a positive response.

Sensitivity analyses regarding a positive stopping rule were implemented into the model to assess its impact on costs as requested. The analyses included when a positive stopping rule was applied to all treatments ,and where it was applied to all treatments bar etrasimod.

Given the nature of the cost comparison model, i.e., NMA results demonstrate similar efficacy across comparators, we assume the same percentage of patients would stop treatment at 12 months across all treatments.

Due to the lack of long term data informing the proportion of patients that enter stable clinical remission or achieve complete response at 12 months, a user-modifiable stopping rate of 10% was assumed across all treatments (Sheet 'Cost Acquisition Model', Cells L8:L20).

The analyses, presented in Table 1, show a similar trend to the original base case results presented in Table 24 of the original submission, when a appositive stopping rule is applied to all treatments. The other analysis, whereby the positive stopping rule is not applied to etrasimod but is applied to all comparators shows [redacted]

Table 1 Positive stopping rule sensitivity analyses

Technology	Total 5 year cost per patient with a positive stopping rule of 10% per year	Total 5 year cost per patient with a positive stopping rule of 10% per year applied to all treatments except etrasimod
Etrasimod	£ 50,804 [redacted]	£55,215 (list) [redacted] (PAS)
Adalimumab	£39,970	£39,970
Infliximab	£48,217	£48,217
Vedolizumab	£65,125	£65,125
Golimumab	£48,029	£48,029
Tofacitinib	£43,123	£43,123
Filgotinib	£48,669	£48,669
Upadacitinib	£51,232	£51,232

Abbreviations: [redacted]

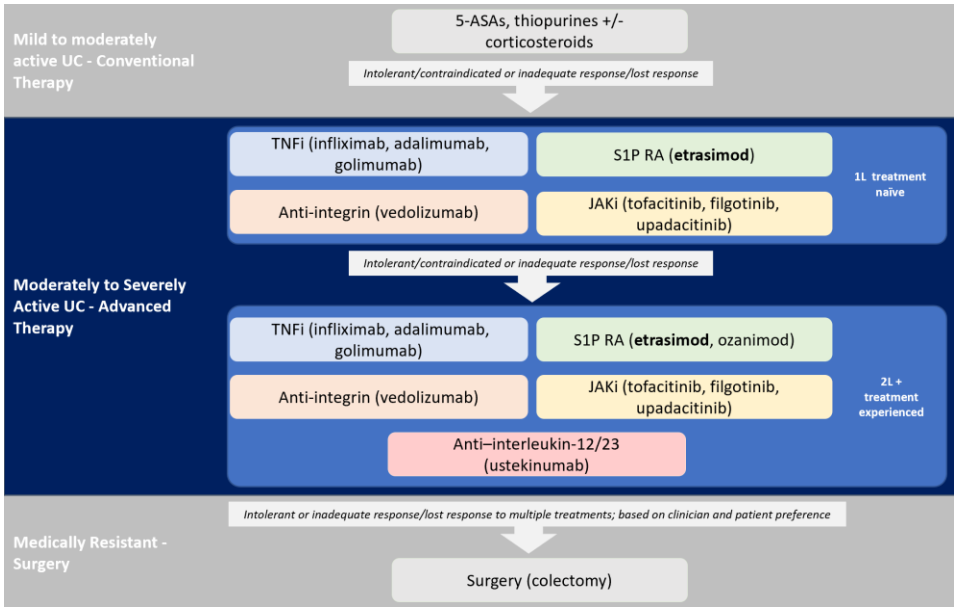
B2. Please explain why a full set of base case results was not presented in the CS (Table 24).

In the UK, there are currently 9 licensed treatments approved by NICE for moderately to severely active UC with various preparations available. All treatment options are relevant comparators, although [redacted] of the market value[1] given their wide usage in clinical practice.

- Subsequently, Section **Error! Reference source not found.** of the submission focuses on these 3 key comparators in order to aid a simplified assessment, with all other comparators presented in Appendix F. All three are understood to be prescribed predominately in first line (1L) of advanced therapy and therefore are the focus of this analysis.

- Section **Error! Reference source not found.**, presents the economic case for comparators noted in the 1L advanced treatment naïve space (adalimumab, infliximab, vedolizumab, golimumab, tofacitinib, filgotinib, and upadacitinib; presented in Figure 1), with remaining comparators included in the model for transparency.

Figure 1 Clinical pathway of care for patients with UC and proposed placement for etrasimod within this pathway



Abbreviations: 1L/2L, first/second line; ASA, 5-aminosalicylate acid; JAKi, janus kinase inhibitors; S1P, sphingosine-1-phosphate; RA, receptor antagonist; TNFi, tumour necrosis factor alpha inhibitors; UC, ulcerative colitis.

For complete transparency, please find the base case results including all treatments presented in the model below in Table 2.

Table 2 Base-case results

Technology	Total 5 year cost per patient
Etrasimod	£55,215 (list) [redacted]
Amgevita (adalimumab)	£43,308
Jyseleca (filgocitinib)	£52,901
Simponi (golimumab)	£52,040
Flixabi then remsima (infliximab) [IV then SC]	£52,527
Flixabi (infliximab)	£52,129
Omvoh (mirikizumab)	£136,673
Zeposia (ozanimod)	£89,460
Xeljanz (tofacitinib)	£46,753
Rinvoq (upadacitinib)	£55,464
Stelara (ustekinumab)	£54,348
Entyvio (vedolizumab) [IV then SC]	£70,506
Entyvio (vedolizumab) [IV then SC]	£70,408

Section C: Textual clarification and additional points

None

References:

1. National Institute for Health and Care Excellence. NICE health technology evaluations: the manual, 2022. Available at: https://www.nice.org.uk/process/pmg36/chapter/introduction-to-health-technology-evaluation

2. National Institute for Health and Care Excellence. Eptinezumab for preventing migraine, 2023. Available at: https://www.nice.org.uk/guidance/ta871

3. National Institute for Health and Care Excellence. Nivolumab with chemotherapy for neoadjuvant treatment of resectable non-small-cell lung cancer, 2023. Available at: https://www.nice.org.uk/guidance/ta876

NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Patient Organisation Submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on conditions and their treatment that is not typically available from other sources.

To help you give your views, please use this questionnaire with our guide for patient submissions.

You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type. [Please note that declarations of interests relevant to this topic are compulsory].

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- Your response should not be longer than 10 pages.

About you

1.Your name	[redacted]
2. Name of organisation	Crohn's & Colitis UK
3. Job title or position	Policy Lead
4a. Brief description of the organisation (including who funds it). How many members does it have?	Crohn's & Colitis UK is the UK's leading charity for everyone affected by Crohn's and Colitis. We're working to improve diagnosis and treatment, and to fund research into a cure; to raise awareness and to give people hope, comfort, and confidence to live freer, fuller lives. We want: • To drive world-class research that improves lives today and brings us closer to a world free from Crohn's and Colitis tomorrow • Everyone to understand Crohn's and Colitis • To support and empower everyone to manage their conditions • To drive high-quality and sustainable clinical care • Early and accurate diagnosis for all. Founded as a patients' association in 1979, we now have over 48,000 members across the UK. Our members include people living with the conditions, their families and friends, health professionals and others who support our work. We have 50 Local Networks which arrange educational meetings, generate publicity and organise fundraising. Funding is through membership subscriptions and a wide range of fundraising activities, including events, grants, legacies and corporate partnerships. Full details are available in our annual accounts Crohn's & Colitis UK's annual reports and accounts (crohnsandColitis.org.uk)

4b. Has the organisation received any funding from the company bringing the treatment to NICE for evaluation or any of the comparator treatment companies in the last 12 months? [Relevant companies are listed in the appraisal stakeholder list.] **If so, please state the name of the company, amount, and purpose of funding.**	No but we have recently applied for a grant of £20k for virtual events, our patient helpline and online/patient information.
4c. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No
5. How did you gather information about the experiences of patients and carers to include in your submission?	We gather information about the experience of patients, carers and families through: • the Crohn's & Colitis UK helpline • local networks • calls for evidence via our website and social media • one to one discussion with people with IBD, clinicians, and the wider IBD community; an • research - our own and that of external organisations.

Current treatment of the condition in the NHS

6. Do people using the technology feel that it works in the same way as the comparator(s)?	While we cannot comment on the specifics of this medication, we know that people with Ulcerative colitis are dissatisfied with the limited treatment options. Many experience lack of response (primary or secondary) and/or adverse reactions. The effects of steroids are extremely unpleasant and long-term safety profile of other treatments, including biologics, are of some concern. "*When I am unwell, I struggle with extreme tiredness and extended periods in the bathroom which makes my working life very difficult. I work in construction so spend a lot of time away from toilets. Vedolizumab, when I first started, it was my wonder drug. It was difficult spending so much time in hospital but worth it to be completely symptom free. I was in remission for nearly 4 months.* *I was then given Golimumab which was a lot more convenient, and I liked having the control of self-administering. This however never gave me remission and my CRP worsened over the period I was taking it. I am now being offered Tofacitinib but have been told this is my final option*." **Quote from a person living with Ulcerative Colitis.** "*I have suffered with UC for 13 years. It's always been moderate to severe. I have tried all drugs including all biologics. All failed after a while. The best was Infliximab, I had my first ever remission for 2 years. However, it came to an end in Aug 2017. I had 18 months of pain and blood, countless hospital admissions, yet I was still pushed to try yet another biologic, Vedolizumab then Golimumab. None of it worked. 6 weeks later I had an emergency op and my colon was removed. My recovery is slow as I was ill for quite some time before and I'm building up my stamina now."* **Quote from a person living with Ulcerative Colitis.** *"My 'moon face' from the constant use of prednisolone was depressing and because of my ill health my hair became really thin. Prednisolone also affected my mood. I was so angry and unhappy. This also kept me awake at night, so I took sleeping pills."* **Quote from a person living with Ulcerative Colitis.**
7. Are there any key differences?	This is unknown to us.

8. Will this technology be easier, the same, or more difficult to take than the comparator(s)? If so, please explain why	As an oral tablet, taken once a day at home, patients are likely to find taking Etrasimod more convenient than treatments which require hospital infusions such as Infliximab and Vedolizumab. Such treatments incur associated travels costs and require time off work for hospital appointments, which an oral therapy would avoid. This is an important consideration given that alongside efficacy and safety, convenience is a key treatment expectation for people in IBD who are experiencing active disease.[1] Oral therapy may also be a more preferable option for patients who have a phobia or a dislike to receiving or self-administering injections such as Adalimumab and Golimumab.

[1] Al Khoury, A., Balram, B., Bessissow, T. et al. Patient Perspectives and Expectations in Inflammatory Bowel Disease: A Systematic Review. *Dig Dis Sci* **67**, 1956–1974 (2022). https://doi.org/10.1007/s10620-021-07025-y

Advantages of the technology

9. What do patients or carers think are the advantages of the technology?	The range of options available for treating Ulcerative Colitis remain far from optimal for patients, a substantial number of whom experience lack of response (primary or secondary) and/or adverse reactions to biologic as well as conventional therapies. As mentioned, one of the key advantages is that Etrasimod is an oral therapy and would give patients a treatment option to be taken at home. The value of an additional treatment option, which has a different mode of action, reduced likelihood of loss of response, and a convenient delivery method would result in an associated reduction in NHS costs due to reduced infusions. Patients most likely to benefit from this drug are those for whom currently available therapies are ineffective, contraindicative or they develop an intolerance. In this group, it is likely that individuals, without further choice, will return to treatment/s which have already been established to be inadequate. This may include highly undesirable long-term steroid use or unproven unconventional therapy. It is also likely that patients in this group who exhaust all other treatment options would be forced to have a colectomy, either elective or as an emergency. *"I am well aware that these drugs have a very significant cost but without them, the last 12 years would have been very different for me. Even with them I have had to have 2 lots of surgery to remove scarred bowel but without them I think I would have had to have more extensive surgery and possibly not even be here to send this email. I am also well aware that I am on my last chance here with current available drugs having taken everything the NHS has to offer; if the vedo stops working then I have nowhere else to go with medication. New drugs and options for medication will be vital for my health going forward."* **Person with IBD, in which drug treatments have not been effective.**

Disadvantages of the technology

10. What do patients or carers think are the disadvantages of the technology?	Prescription costs faced people living with long-term and chronic conditions, including Ulcerative Colitis, in England, are shown to contribute to economic disadvantage, which can impact adherence and lead to complications and increased cancer risks and cost to the NHS. However, the disadvantage is not specific to Etrasimod, and the value of an additional treatment option may will remain beneficial as it will reduce the risk of loss of response.

Patient population

11. Are there any groups of patients who might benefit more or less from the technology than others? If so, please describe them and explain why.	Patients who have had little or no success with currently available medical treatment options, and wish to avoid or delay surgery, are likely to benefit. This would include young people wishing to complete studies and those for whom surgery would be considered unacceptable due to cultural or religious factors.

Equality

12. Are there any potential equality issues that should be taken into account when considering this condition and the technology?	For certain religious groups, the impact of active disease and the effects of surgery may interfere with religious practices and cause distress, which could be alleviated by an additional medical therapeutic option. Although not specific to Etrasimod, prescription costs may also be a factor associated with lower income.

Key messages

13. In up to 5 bullet points, please summarise the key messages of your submission.	• There is significant unmet need for people with moderate to severe Ulcerative Colitis. Current treatments remain far from optimal for patients, a substantial number of whom experience a lack of response (primary or secondary) and/or adverse reactions to medical treatments and may face the prospect of surgery with considerable anxiety. • Etrasimod offers a novel and effective treatment option and increases choice for both clinicians and patients (in the context of shared decision making). • The benefit of Etrasimod is that it is a treatment option that patients are able to take at home.

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NICE National Institute for Health and Care Excellence

Cost Comparison Appraisal

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Professional organisation submission

Thank you for agreeing to give us your organisation's views on this technology and its possible use in the NHS.

You can provide a unique perspective on the technology in the context of current clinical practice that is not typically available from the published literature.

To help you give your views, please use this questionnaire. You do not have to answer every question – they are prompts to guide you. The text boxes will expand as you type.

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- Your response should not be longer than 13 pages.

1. Your name	[redacted]
2. Name of organisation	UK Clinical Pharmacy association (UKCPA)
3. Job title or position	Gastroenterology pharmacist
4. Are you (please select Yes or No):	• An employee or representative of a healthcare professional organisation that represents clinicians? No • A specialist in the treatment of people with this condition? Yes • A specialist in the clinical evidence base for this condition or technology? Yes • Other (please specify):
5. Brief description of the organisation (including who funds it).	UKCPA is a not-for-profit organisation, which invest all surplus back into the association in order to provide better services and benefits for members, and to support initiatives which improve patient care.
6. Has the organisation received any funding from the manufacturer(s) of the technology and/or comparator products in the last 12 months? [Relevant manufacturers are listed in the appraisal stakeholder list.] If so, please state the name of manufacturer, amount, and purpose of funding.	No
7. Do you have any direct or indirect links with, or funding from, the tobacco industry?	No

8. Is the technology clinically similar to the comparator(s)? Does it have the same mechanism of action, or a completely different mechanism-of-action? Or in what way is it different to the comparator(s)?	Completely different mechanism to all comparators (excluding Ozanimod) Sphingosine 1-phosphate receptor modulator like Onzanimod but Etrasimod only target (S1P1,4,5)
9. If there are differences in effectiveness between the technology and its comparator(s) are these clinically meaningful?	Similar efficacy to Ozanimod but better safety profile. Shorter half life means faster wash out period. Easier induction dosing regimen.
10. What impact would the technology have on the current pathway of care?	Additional medical treatment option in Ulcerative Colitis but should be only be considered if conventional therapy and at least one biologic therapy failed. Patient who prefers oral therapy and not suitable for JAK inhibitor will be ideal for Estrasimod
11. In what clinical setting should the technology be used? (For example, primary or secondary care, specialist clinics.)	Secondary care
12. Will the technology be used (or is it already used) in the same way as current care in NHS clinical practice?	Yes

13. Have there been substantial changes to the treatment pathway since the comparator appraisal that might impact the relevance of the comparator's appraisal?	No
14. Overall, is the treatment likely to offer similar or improved health benefits compared with the NICE-recommended comparator?	Yes
15. Do the clinical trials on the technology reflect current UK clinical practice?	Yes
16. Is the technology likely to affect the downstream costs of managing the condition (for example, does it affect the subsequent treatments)	Electrocardiograms are recommended pre 1st dose and additional cardiac monitoring required for patients with existing cardiac conditions.

17. Are there any potential equality issues that should be taken into account when considering this treatment? Consider whether these issues are different from issues with current care and why	No

Thank you for your time.

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EAG STA REPORT

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP (LRiG)

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Confidential until published

This report was commissioned by the NIHR Evidence Synthesis Programme as project number 135815

Completed 26th October 2023

CONTAINS [redacted] DATA

UNIVERSITY OF LIVERPOOL

LIVERPOOL REVIEWS AND IMPLEMENTATION GROUP

A MEMBER OF THE RUSSELL GROUP

Title: Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

Produced by: Liverpool Reviews & Implementation Group (LR*i*G)

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Date completed: 26th October 2023

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Contributions of authors

Janette Greenhalgh	Project lead, critical appraisal of the clinical evidence and supervised the final report
Sam Bryning	Critical appraisal of the economic model
James Mahon	Critical appraisal of the economic model
Marty Chaplin	Critical appraisal of the statistical evidence
Sophie Beale	Critical appraisal of the clinical and economic evidence, editorial input
Angela Boland	Critical appraisal of the clinical and economic evidence, editorial input
Yenal Dundar	Critical appraisal of the company search strategies
Joanne McEntee	Critical appraisal of the company submission
Keith Bodger	Clinical advice and critical appraisal of the clinical evidence

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LIST OF ABBREVIATIONS

AE	Adverse event
CrI	Credible interval
DIC	Deviance Information Criterion
EAG	External Assessment Group
ECG	Electrocardiogram
EMA	European Medicines Agency
HRQoL	Health-related quality of life
IBDQ	Inflammatory bowel disease questionnaire
JAKi	Janus kinase inhibitor
MHRA	Medicines and Healthcare products Regulatory Agency
MMS	Modified Mayo score
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OLE	Open-label extension
PAS	Patient Access Scheme
PEAS	Primary efficacy analysis set
PRO	Patient-reported outcome
RCT	Randomised controlled trial
S1P	Sphingosine-1-phosphate
SAE	Serious adverse event
SLR	Systematic literature review
SmPC	Summary of Product Characteristics
SUCRA	Surface Under the Cumulative RAnking curve
TEAEs	Treatment-emergent adverse events
TNFi	Tumour necrosis factor alpha inhibitor
UME	Unrelated mean effects
WPAI-UC	Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis

1 EXECUTIVE SUMMARY

This summary provides a brief overview of the key issues identified by the External Assessment Group (EAG) as being potentially important for decision making. It also includes the EAG's cost comparison results.

Section 1.1 provides an overview of the key issues. Section 1.2 provides an overview of key model outcomes and the modelling assumptions that have the greatest effect on the results of the cost comparison analysis. Where appropriate, Sections 1.3 to 1.6 explain the key issues in more detail.

All issues identified represent the EAG's view, not the opinion of NICE.

1.1 Overview of the EAG's key issues

Table A Summary of key issues

Issue	Summary of issue	Report sections
Issue 1	Lack of direct evidence for the comparison of etrasimod versus relevant comparators	Section 2.4
Issue 2	The company's NMA results do not demonstrate conclusively that etrasimod provides similar or greater health benefits compared to any other drug in the biologic-experienced setting	Section 2.4.6
Issue 3	For patients in the biologic-experienced setting, it is not clear that a cost comparison approach is the appropriate method of economic evaluation for the comparison of etrasimod versus all other drugs	Section 3.7.8
Issue 4	Impact of subsequent treatments on cost comparison results is unknown	Section 4.6.4

There are no major differences between the company and the EAG's cost comparison analysis results. The EAG has only implemented two minor corrections in the company model and has not proposed any model revisions.

1.2 Overview of key model outcomes

NICE technology appraisals usually compare how much a new technology improves length (overall survival) and quality of life in a QALY. As the company has carried out a cost comparison analysis, the technology is not modelled to affect QALYs. The company has assumed that the results of the five network meta-analyses (NMAs) presented in the company submission demonstrate that etrasimod is at least as efficacious and as safe as the comparators in the cost comparison analysis. The EAG considers that, for biologic-naïve patients, this is a robust conclusion to draw from the results of the company's NMAs of

etrasimod versus adalimumab (induction and maintenance phases). For biologic-experienced patients, company NMA results are mixed; however, no other drug is statistically significantly better than etrasimod (induction and maintenance phases).

The company's base case analysis comprised drug acquisition and administration costs, pre-initiation electrocardiogram (for etrasimod only) and concomitant treatment costs over a 5-year period. The company/EAG cost comparison analysis results are driven by the drug acquisition costs and whether there is a confidential discount in place.

1.3 The decision problem: summary of the EAG's key issues

None

1.4 The clinical effectiveness evidence: summary of the EAG's key issues

Issue 1 Lack of direct evidence for the comparison of etrasimod versus the relevant comparators

Report section	Section 2.4
Description of issue and why the EAG has identified it as important	The company has provided clinical effectiveness evidence from two RCTs, namely the ELEVATE UC 12 and ELEVATE UC 52 trials. Trial results demonstrate the clinical effectiveness of etrasimod versus placebo. There is no direct effectiveness evidence for the comparison of etrasimod versus any of the relevant comparators listed in the final scope issued by NICE, i.e., adalimumab, infliximab, filgotinib, golimumab, ozanimod, tofacitinib, ustekinumab and vedolizumab The company has carried out NMAs to generate indirect clinical effectiveness evidence for the comparison of etrasimod versus relevant comparators[a]
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	See Issue 2 and Issue 3
What additional evidence or analyses might help to resolve this key issue?	See Issue 2 and Issue 3

[a]Due to a lack of clinical effectiveness data, infliximab and golimumab were not included in the biologic-experienced networks
NMA=network meta-analysis

Issue 2 The company's NMA results do not demonstrate conclusively that etrasimod provides similar or greater health benefits compared to any other drug in the biologic-experienced setting

Report section	Section 2.4.6
Description of issue and why the EAG has identified it as important	The company's NMA results do not demonstrate **conclusively** that etrasimod provides similar or greater health benefits compared to any other drug in the biologic-experienced setting
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown. If there is not enough evidence to demonstrate similarity, then a cost utility analysis is required
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice about whether it is appropriate to assume that, compared to other drugs, etrasimod provides similar or greater health benefits in the biologic-experienced setting

NMA=network meta-analysis

1.5 The cost effectiveness evidence: summary of the EAG's key issues

Issue 3 For patients in the biologic-experienced setting, it is not clear that a cost comparison approach is the appropriate method of economic evaluation for the comparison of etrasimod versus all other drugs

Report section	Section 2.4.6
Description of issue and why the EAG has identified it as important	Lack of clinical effectiveness evidence to demonstrate **conclusively** that etrasimod provides similar or greater health benefits compared to other drugs in the biologic-experienced setting means it is not clear that a cost comparison approach is the appropriate method of economic evaluation for the comparison of etrasimod versus all other drugs
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown. If there is not enough evidence to demonstrate similarity, then a cost utility analysis is required
What additional evidence or analyses might help to resolve this key issue?	Seek clinical advice about whether it is appropriate to assume that, compared to other drugs, etrasimod provides similar or greater health benefits in the biologic-experienced setting. If this assumption is not appropriate then a cost utility analysis is required

Issue 4 Impact of subsequent treatments on cost comparison results is unknown

Report section	Section 3.7.8
Description of issue and why the EAG has identified it as important	The company base case analysis cost comparison results are only valid for patients who stay on a single treatment for 5 years. Clinical advice to the EAG is that some patients switch treatments during this time interval. It is not possible to make a reliable assumption about second or subsequent treatment(s) for patients in either the biologic-naïve or biologic-experienced setting. As the costs of the drugs available to treat moderately to severely active UC differ, subsequent treatment costs are difficult to capture in an economic model (cost comparison analysis or cost utility analysis)
What alternative approach has the EAG suggested?	None
What is the expected effect on the cost effectiveness estimates?	Unknown
What additional evidence or analyses might help to resolve this key issue?	Seek clinical consensus on current treatment sequencing patterns

UC=ulcerative colitis

1.6 Other key issues: summary of the EAG's view

None

1.7 Summary of EAG's cost comparison analysis results

Table B Summary of company and EAG cost comparison results

Treatment	Total 5-year cost per patient	
	Company results	**EAG results**
Etrasimod	£55,215 ([redacted])	£55,215 ([redacted])
Adalimumab	£43,308	£42,991
Filgotinib	£52,901	£52,901
Golimumab	£52,040	£51,659
Infliximab (IV then SC)	£52,527	£53,754
Infliximab (IV only)	£52,129	£57,035
Ozanimod	£89,460	£89,460
Tofacitinib	£46,753	£46,753
Upadacitinib	£55,464	£55,464
Ustekinumab	£54,348	£53,070
Vedolizumab (IV then SC)	£70,506	£70,301
Vedolizumab (IV only)	£70,408	£75,314

IV=intravenous; PAS=Patient Access Scheme; SC=subcutaneous

2 INTRODUCTION AND BACKGROUND

2.1 Introduction

This appraisal focuses on the use of etrasimod (Velsipity®) to treat patients 16 years of age and older with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy (biologic-naïve patients), or advanced immunomodulators, i.e., biologic agents or small molecules (biologic-experienced patients). The company has presented evidence for biologic-naïve and biologic-experienced patients for both the induction phase and the maintenance phase of treatments (i.e., four groups).

In the final scope[1] issued by the National Institute for Health and Care Excellence (NICE), the technology (etrasimod) was selected to be appraised as a cost comparison analysis.

In this External Assessment Group (EAG) report, the term 'company submission' (CS) refers to the company's document B, which is the company's full evidence submission.

2.2 Etrasimod

Information provided in this section has been extracted from CS, Table 1 and CS, Table 2.

Etrasimod is a sphingosine 1-phosphate receptor modulator that binds to S1P receptors 1, 4 and 5 (S1P1,4,5) and is a balanced G-protein and beta-arrestin agonist at S1P1. Etrasimod partially and reversibly blocks the capacity of lymphocytes to egress from lymphoid organs, reducing the number of lymphocytes in peripheral blood thereby lowering the number of activated lymphocytes in the tissue.

Etrasimod is formulated as a once-daily, orally administered tablet (2mg) that can be taken with or without food. The dosage does not change between induction and maintenance phases of treatment.

The company anticipates that a positive Committee for Medicinal Products for Human Use (CHMP) opinion will be issued on [redacted]. The company plans to submit an application to the Medicines and Healthcare products Regulatory Agency (MHRA) for regulatory approval on [redacted]. The company anticipates that the European Medicines Agency (EMA) will issue marketing authorisation on [redacted] and that the MHRA will issue marketing authorisation on [redacted], with etrasimod becoming available in the UK on [redacted].

The anticipated MHRA marketing authorisation submitted indication is for patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules).

Etrasimod is available to the NHS at a confidential discounted Patient Access Scheme (PAS) price.

2.3 Company's overview of current service provision

Clinical guidelines for the management of UC include NICE Guidelines (NG30[2]) and British Society of Gastroenterology consensus guidelines 2019.[3] For patients who are the focus of this appraisal, i.e., patients with moderately to severely active UC, when conventional therapy or a biologic agent cannot be tolerated or the disease has responded inadequately or lost response to treatment, current guidelines recommend a biologic or an oral advanced small molecule (non-biologic) therapy.[2,3] The drugs listed in Table 1 are currently recommended by NICE as treatments for NHS patients with moderately to severely active UC.

Table 1 Comparator treatments

Drug class	Drug	Year	NICE recommendation
TNFi	Adalimumab, infliximab, golimumab TA329[4]	2015	An option for treating moderately to severely active UC in adults whose disease has responded inadequately to conventional therapy including corticosteroids and mercaptopurine or azathioprine, or who cannot tolerate, or have medical contraindications for, such therapies.
Integrin inhibitor	Vedolizumab TA342[5]	2015	An option for treating moderately to severely active UC in adults.
IL12/23 inhibitor	Ustekinumab TA633[6]	2020	An option for treating moderately to severely active UC in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment, only if: (i) a TNFi has failed or (ii) a TNFi cannot be tolerated or is not suitable.
JAKi	Tofacitinib TA547[7]	2018	An option for treating moderately to severely active UC in adults when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment.
	Filgotinib TA792[8]	2022	An option for treating moderately to severely active UC in adults when conventional or biological treatment cannot be tolerated, or the disease has responded inadequately or lost response to treatment.
	Upadacitinib TA856[9]	2023	An option for treating moderately to severely active UC in adults when conventional therapy or a biological agent cannot be tolerated, or if the condition has not responded well enough or has stopped responding to these treatments.
S1P	Ozanimod TA828[10]	2022	An option for treating moderately to severely active UC in adults when conventional or biological treatments cannot be tolerated or are not working well enough.

JAKi=Janus kinase inhibitors; S1P=sphingosine-1-phosphate; TNFi=tumour necrosis factor alpha inhibitors; UC=ulcerative colitis

The company's interpretation of the clinical care pathway for NHS patients with moderately to severely active UC and the proposed placement of etrasimod within this pathway are shown in Figure 1. Clinical advice to the EAG is that Figure 1 is a reasonable reflection of NHS clinical practice for patients with UC.

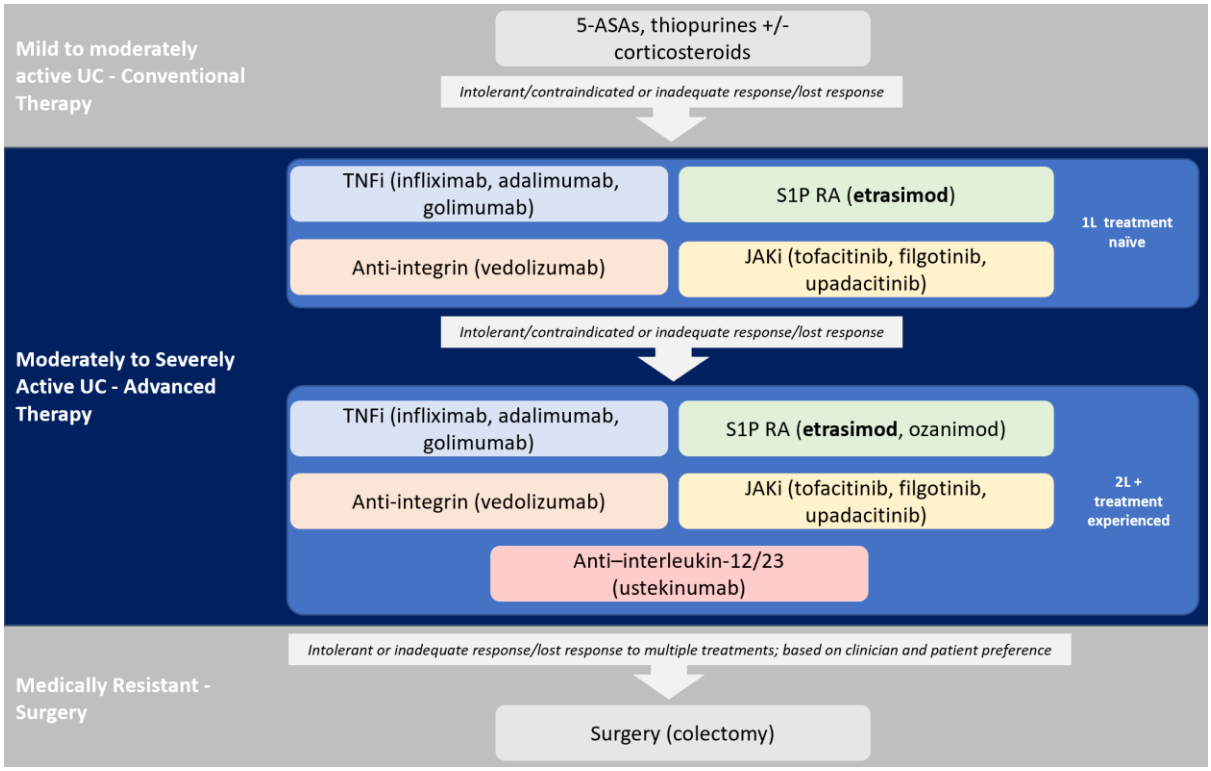

Figure 1 Company representation of the clinical pathway for patients with UC

1L/2L=first/second line; ASA=5-aminosalicylate acid; JAKi=Janus kinase inhibitors; S1P=sphingosine-1-phosphate; RA=receptor antagonist; TNFi=tumour necrosis factor alpha inhibitors; UC=ulcerative colitis
Source: CS, Figure 1

Clinical advice to the EAG is that patients with moderately to severely active UC are typically managed using a sequential treatment approach. The choice of treatment depends on several factors including patient preference, patient contraindications, safety, drug speed of onset, patient antibody responses to prior biologics, any side effects resulting from previous biologics, and cost (CS, p15). Treatment goals extend beyond the alleviation of symptoms to include outcomes such as maintaining a steroid-free remission, mucosal healing, preventing surgery and hospitalisation, and improving patient quality of life.[11]

Clinical advice to the EAG is that:

- in the first instance, most patients who are eligible for treatment with a biologic agent usually receive a TNF-alpha inhibitor (TNFi), such as adalimumab or infliximab (both are available as biosimilars)

- golimumab (a TNFi) is more expensive than adalimumab and infliximab and is therefore used infrequently in NHS clinical practice as a first-line TNFi
- vedolizumab (an integrin inhibitor) may be selected as a first-line biologic agent for patients where there is concern about using a TNFi (i.e., for patients with prior heart failure or increased risk of infections); however, clinical response with vedolizumab is slow compared with TNFi therapies
- ustekinumab (IL 12/23 inhibitor) can be used as a first-line biologic for patients who have contraindications to TNFi therapies

2.3.1 Number of patients eligible for treatment with etrasimod

The company provided estimates of the number of patients who would be eligible for treatment with etrasimod in the Budget Impact Model (BIM). Clinical advice to the EAG is that the value used by the company to estimate the proportion of patients with UC who have moderately to severely active disease (52%[10]) may be higher than the proportion of patients with moderately to severely active UC seen in NHS clinical practice.

Table 2 Company estimate of the number of patients with moderately to severely active ulcerative colitis eligible for treatment with etrasimod in Year 1 (prevalent population)

Population	Proportion	Year 1 (2023)	Source
Total population	-	61,615,234	ONS 2021[12]
Prevalence of UC in adults	0.441%	271,433	NICE TA856[9]
Proportion of UC patients who are adults	90%	244,289	Based on 75% to 80%, 21+ years
Proportion of adult UC patients who have moderately to severely active UC	52%	**127,031**	NICE TA828[10]
Proportion with moderately to severely active UC with inadequate response, loss of response or intolerant to CT	20%	**25,406**	NICE TA828[10]

CT=conventional therapy; ONS=Office for National Statistics; UC=ulcerative colitis
Source: company BIA model

The company estimates that etrasimod will have a 10% share of the market in Year 1, with this proportion rising to 18% in Year 5 (company BIM).

2.4 Critique of company's definition of decision problem

A summary of the final scope issued by NICE, the decision problem addressed by the company and EAG comments are presented in Table 3. Each parameter is discussed in more detail in the text following Table 3.

Table 3 Summary of decision problem

	Final scope issued by NICE	Decision problem addressed in the company submission	Rationale if different from the final NICE scope – EAG summary*	EAG comment
Population	People with moderately to severely active ulcerative colitis when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment.	Patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or advanced immunomodulators (biologic agents or small molecules).	The main body of the submission focuses on the advanced treatment naïve population, i.e., naïve to biologics or JAKi. For completeness, advanced treatment experienced analyses are also presented	-
Intervention	Etrasimod (Velsipity®)	Etrasimod (Velsipity®)	-	-
Comparator(s)	At least 1 of the following treatments, according to NICE guidance: • ozanimod • JAKi (tofacitinib, filgotinib and upadacitinib) • TNFi (infliximab, adalimumab and golimumab) • ustekinumab • vedolizumab • mirikizumab (subject to NICE evaluation)	• TNFi-alpha inhibitors (adalimumab, golimumab and infliximab) • vedolizumab • JAK inhibitors (tofacitinib, filgotinib and upadacitinib)	The target population for etrasimod is patients for whom conventional therapy is inadequately effective, not tolerated or contraindicated. Etrasimod is compared to adalimumab, infliximab and vedolizumab.	Clinical advice to the EAG is that the exclusion of CT and mirikizumab as comparators is reasonable. All relevant comparators have been assessed by the company via network meta-analyses; etrasimod was compared with adalimumab, golimumab, infliximab, vedolizumab, tofacitinib, filgotinib, upadacitinib, ozanimod and ustekinumab.
Outcomes	The outcome measures to be considered include: • mortality • disease activity • rates of and duration of response, relapse, and remission • rates of hospitalisation • rates of surgical intervention • endoscopic healing	As per final scope: • measures of disease activity (e.g., rates and duration of response, relapse, and remission • rates of hospitalisation • corticosteroid-free remission • EIHR • HRQoL • rates of surgical intervention • endoscopic improvement	The company has made some assumptions regarding outcome terminology (e.g., around endoscopic healing/normalisation/remission and endoscopic improvement).	Endoscopic remission combined with histological improvement was not captured in the ELEVATE clinical trials. The company NMA outcomes are relevant and NMA results can be used to inform treatment decisions.

	• Endoscopic remission combined with histological improvement • corticosteroid-free remission • achieving mucosal healing • AEs • HRQoL	• endoscopic normalisation		
Economic analysis	This technology has been selected to be appraised as a cost comparison. The time horizon should be sufficient to reflect any differences in costs between the technologies being compared. Costs will be considered from an NHS and Personal Social Services perspective. The availability of any commercial arrangements for the intervention and comparator technologies will be taken into account.	Drug acquisition, pre-initiation testing, and administration costs are considered from the NHS and Personal Social Services perspective – all other costs are considered equal across available treatment options. A time horizon of 5 years was selected to reflect differences in initiation costs. The model considers the cost of all available etrasimod comparators. [redacted]		The company has presented cost comparison analysis results over a 5-year time period. Lack of conclusive clinical effectiveness evidence to demonstrate that etrasimod provides similar or greater health benefits to other drugs in the biologic-experienced setting means that it is not clear if a cost comparison analysis approach is appropriate.
Subgroups to be considered	-	Subgroup (or additional analyses, given it is not a subgroup of the naïve population) data for etrasimod is presented among the biologic/JAKi experienced population.	Previous TAs have reported evidence by similar subgroups, therefore for transparency and completeness they have been included in this submission.	The company has provided results of subgroup analyses of trial outcomes according to prior biologic or JAKi therapy exposure (CS, Appendix G) i.e., biologic-naïve or biologic-experienced.

AEs=adverse events; CT=conventional therapy; EIHR=endoscopic improvement-histologic remission; HRQoL=health-related quality of life; JAKi=Janus kinase inhibitor; TA=technology appraisal; TNFi=tumour necrosis factor alpha inhibitor; UC=ulcerative colitis
*Full details are available in CS, Table 1

2.4.1 Source of direct clinical effectiveness data

The company has presented direct clinical effectiveness evidence for the comparison of etrasimod (2mg) versus placebo from two trials designed to assess the efficacy and safety of etrasimod in patients with moderately to severely active UC:

- ELEVATE UC 12[13] (NCT03996369) trial
- ELEVATE UC 52[13] (NCT03945188) trial

Both trials were phase III, randomised, double-blind, placebo-controlled studies. Both trials included a 12-week induction phase and ELEVATE UC 52 also included a 40-week maintenance period. Patients in the two ELEVATE UC trials were eligible to enter an open-label extension (OLE) study: ELEVATE UC OLE study (NCT03950232[14]).

2.4.2 Population

The population specified in the final scope issued by NICE is patients with moderately to severely active UC when conventional therapy or a biological agent cannot be tolerated, or the disease has responded inadequately or lost response to treatment. In line with the anticipated licensed indication, the company has presented evidence for people aged 16 years and older and has also included advanced small molecule therapies (non-biologics).

2.4.3 Intervention

The intervention is etrasimod (2mg per day). See Section 2.2 for details of the marketing authorisation.

2.4.4 Comparators

As the two key etrasimod RCTs were placebo-controlled, the company indirectly compared treatment with etrasimod versus active comparators (n=9) and presented clinical effectiveness results for four different groups:

- biologic-naïve induction phase patients
- biologic-naïve maintenance phase patients
- biologic-experienced induction phase patients
- biologic-experienced maintenance phase patients

The EAG highlights that the terms ‘biologic-naïve’ and ‘biologic-experienced’ encompass patients who are ‘JAKi-naïve’ or ‘JAKi-experienced’ respectively.

For each of the four groups, the company has presented NMA results for the comparison of etrasimod versus adalimumab, infliximab and vedolizumab in the main body of the CS; the NMA results for the comparison of etrasimod versus filgotinib, golimumab, ozanimod, tofacitinib, upadacitinib and ustekinumab are presented in an appendix (CS, Appendix F).

2.4.5 Outcomes

The outcomes included in the company's direct and indirect analyses were relevant to this appraisal.

2.4.6 Economic analysis

In line with the final scope issued by NICE, the company has carried out a cost comparison analysis; drug costs were assessed over 5 years.

Appropriateness of a cost comparison analysis

The EAG considers that, for biologic-naïve patients, the company has conclusively shown that treatment with etrasimod is likely to provide similar or greater health benefits at similar or lower costs compared to adalimumab; NMA results showed that etrasimod was statistically significantly superior to adalimumab. However, as the company NMA results did not show that etrasimod was statistically significantly superior to infliximab or vedolizumab, there is no conclusive evidence of similarity versus these treatments (or versus any other treatments in the network).

The EAG considers that, for biologic-experienced patients, the company has not conclusively shown that treatment with etrasimod is likely to provide similar or greater health benefits at similar or lower cost when compared to adalimumab, infliximab or vedolizumab as there were no statistically significant differences versus any of the comparator treatments.

By carrying out a cost comparison analysis (etrasimod versus nine comparator drugs), the company has implicitly assumed that etrasimod is likely to provide similar or greater health benefits compared to these nine comparator treatments. However, versus most comparator drugs, there is no statistically significant NMA evidence that etrasimod provides similar or greater health benefits.

2.4.7 Subgroups

The final scope issued by NICE does not stipulate any subgroup analyses. However, the company has provided results of subgroup analyses of trial outcomes according to prior biologic or JAKi therapy exposure (CS, Appendix G) i.e., biologic-naïve or biologic-experienced. The company cautions that the ELEVATE UC trials were not powered to detect statistically significant treatment effects within subgroups defined by prior biologic exposure status.

2.4.8 Other considerations

The company has generated cost comparison analysis results using the Patient Access Scheme (PAS) price for etrasimod and list prices for all other drugs. However, all comparators, are available to the NHS at confidential discounted prices (adalimumab, infliximab and ustekinumab have Commercial Medicines Unit [CMU] prices; filgotinib, golimumab, ozanimod, tofacitinib, upadacitinib and vedolizumab have PAS prices).

Cost comparison analysis results (etrasimod versus all comparators) using all confidential prices are available in a confidential appendix.

3 CLINICAL EFFECTIVENESS

3.1 Critique of the methods of review(s)

Full details of the methods used by the company to identify and select clinically relevant evidence to demonstrate the effectiveness of etrasimod are presented in the CS (CS, Appendix F). An assessment of the extent to which the systematic literature review (SLR) was conducted in accordance with the LR*i*G in-house systematic review checklist is presented in Table 4. The EAG conducted its own searches and did not identify any additional trials that provided information on the clinical effectiveness of etrasimod. The EAG considers that the company's review was conducted to a good standard.

Table 4 EAG appraisal of the company's systematic review methods

Review process	EAG response	Note
Was the review question clearly defined in terms of population, interventions, comparators, outcomes, and study designs?	Yes	CS, Appendix F.1.1, Table 26
Were appropriate sources searched?	Yes	CS, Appendix F.1.1.1
Was the timespan of the searches appropriate?	Yes	CS, Appendix F.1.1
Were appropriate search terms used?	Yes	CS, Appendix F.1.1.2, Table 27
Were the eligibility criteria appropriate to the decision problem?	Yes	CS, Appendix F.1.1.3, Table 30
Was study selection applied by two or more reviewers independently?	Yes	CS, Appendix F.1.1.3
Was data extracted by two or more reviewers independently?	Yes	CS, Appendix F.1.1.4
Were appropriate criteria used to assess the risk of bias and/or quality of the primary studies?	Yes	CS. Table 9 CS, Appendix F.1.1.4 and Appendix F.1.2.4, Table 35
Was the quality assessment conducted by two or more reviewers independently?	Yes	CS, Appendix F.1.1.4
Were attempts to synthesise evidence appropriate?	Yes	NMAs were conducted to allow a comparison of etrasimod with appropriate comparators. The EAG summary and critique of the company's approach are presented in Section 3.7

NMA=network meta-analysis
Source: LR*i*G in-house checklist

3.2 EAG summary and critique of clinical effectiveness evidence

3.2.1 Trials included in the company systematic review

Two phase III randomised controlled trials (RCTs) that provide clinical effectiveness evidence for etrasimod versus placebo were identified by the company: the ELEVATE UC 12 (NCT03996369) trial and the ELEVATE UC 52 (NCT03945188) trial.

The company also identified a phase II RCT, the OASIS trial (NCT02447302).[15] The OASIS trial compares treatment with two different doses of etrasimod (1mg or 2mg) versus placebo over a period of 12 weeks. OASIS trial results are included in the company's safety NMA (CS, p25).

Patients in the ELEVATE UC 12 and the ELEVATE UC 52 trials were eligible to take part in an open-label extension study, ELEVATE UC OLE (NCT03950232[14]). Patients in the OASIS study were eligible to take part in the OASIS OLE study (NCT02536404[16]). Results from the OLE studies[14,16] were (appropriately) not used to inform the NMAs or the cost comparison analyses; the OLE studies were open-label studies with no control arm.

To compare the clinical effectiveness of treatment with etrasimod versus the comparator treatments listed in the final scope issued by NICE, the company conducted NMAs. The NMAs were conducted for patients with moderately to severely active UC who had not received previous treatment with biologic or JAKi therapies (biologic-naïve) or had received previous treatment with biologic or JAKi therapies (biologic-experienced). The EAG critique and discussion of the company's NMAs is presented in Section 3.7 of this EAG report. Details of the comparator trials included in the company NMAs are available in the CS (CS, Appendix F, Section F.1.2).

3.2.2 Etrasimod trials

Trial characteristics

A summary of the design and methodologies of the ELEVATE UC 12 and UC 52 trials is presented in the CS (CS, Figure 2 and Table 5). Both trials recruited patients with moderately to severely active UC (defined as modified Mayo score [MMS] of 4 to 9, including an endoscopic subscore ≥2 and a rectal bleeding score ≥1). Patients were randomised (in a 2:1 ratio) to either treatment with etrasimod (2mg) or to placebo. Randomisation was stratified according to previous treatment (biologic or JAKi), baseline use of glucocorticoids and baseline disease activity. The primary endpoint in the trials was the proportion of patients achieving clinical remission defined as a composite of stool frequency subscore=0 (or stool frequency subscore=1 with a ≥1-point decrease from baseline), rectal bleeding subscore=0,

and endoscopic subscore of ≤1 by independent, centrally read assessment (without friability). Patients who did not take part in the ELEVATE OLE study were followed up for 4 weeks.

The ELEVATE UC 12 trial treatment period was 12 weeks and the primary outcome was the proportion of patients achieving clinical remission at 12 weeks. Patients were recruited to the trial from 407 treatment centres across 39 countries. Overall, 238 patients were randomised to receive etrasimod and 116 to receive placebo. Three patients were treated in the UK.

The ELEVATE UC 52 trial treatment period was 52 weeks and the co-primary outcomes were the proportion of patients achieving clinical remission at 12 weeks and at 52 weeks. At the 12-week assessment, patients whose disease activity had shown no improvement, or had worsened compared with baseline, could discontinue treatment and enrol in the ELEVATE UC OLE study (subject to specific criteria being met). Patients whose disease activity had shown no improvement or had worsened during the 40-Week Treatment Period, or who completed all study procedures at Week 52, had the option to enter OLE Study. Patients were recruited to the ELEVATE UC 52 trial from 315 treatment centres across 37 countries. Overall, 289 patients were randomised to receive etrasimod and 144 to receive placebo. One patient was treated in a UK centre.

Clinical advice to the EAG is that the inclusion and exclusion criteria for the ELEVATE UC 12 and the ELEVATE UC 52 trials are reasonable and the results are as generalisable to NHS patients as results from previous trials of UC treatments.

Patient baseline characteristics

The baseline characteristics of patients recruited to the ELEVATE UC 12 and the ELEVATE UC 52 trials are presented in the CS (CS, Table 6). Clinical advice to the EAG is that the patients in the trials are comparable to patients recruited to similar trials in this disease area and are representative of patients treated in the NHS. Clinical advice to the EAG is that the ELEVATE trials do not include patients who are hospitalised with acute severe active UC.

3.2.3 Quality assessment of the etrasimod trials

The company conducted a quality assessment of the ELEVATE UC 12 and ELEVATE UC 52 trials using the minimum criteria recommended by NICE[17] (CS, Table 9). The EAG agrees with the company's assessments and considers both trials are of good methodological quality.

3.2.4 Statistical approaches used to analyse data

In addition to the information provided in the CS, information relevant to the statistical approaches taken by the company to analyse trial data has been extracted from the CSRs,[18,19] the trial statistical analysis plans (TSAP[20]) and the trial protocols.[21,22] The EAG considers that

the approaches adopted by the company were appropriate. See Appendix 6.1 for details.

3.3 Efficacy results from the etrasimod trials

The key efficacy outcome results reported in the CS from the ELEVATE trials are derived from the primary efficacy analysis set (PEAS) and are reported here. The company defines the PEAS population (CS, p35) as patients with an MMS of 5 to 9 who received ≥1 dose of the study drug or placebo. The trial inclusion criteria allowed for the recruitment of patients with an MMS of 4. However, to meet regulatory body requirements,[13] the company has limited the analysis population to patients with an MMS of 5 to 9. In the ELEVATE UC trials, 44 patients had an MMS of 4. The EAG is satisfied that the PEAS population was clearly defined and pre-specified in the TSAP for each of the ELEVATE UC trials.

The EAG has not presented results for the biologic-naïve or biologic experienced patients as trials were not powered to test the statistical significance of subgroup analyses due to the limited numbers in the subgroups (CS, p44). For all subgroup analyses investigated etrasimod showed higher efficacy than placebo. Detailed results are available in CS, Appendix G.

Summary of patient disposition

Table 5 shows that few patients in the ELEVATE UC 12 trial discontinued treatment (etrasimod=10.1%, placebo=9.5%). In the ELEVATE UC 52 trial, the rate of discontinuation was lower in the etrasimod arm than in the placebo arm (42.6% versus 68.1%). The main reason for discontinuing treatment in both trials was worsening of disease. The full list of reasons for treatment discontinuation is presented in the CS (CS, Table 8).

Table 5 Summary of patient disposition in the ELEVATE trials

	ELEVATE UC 12		ELEVATE UC 52	
	Etrasimod	Placebo	Etrasimod	Placebo
Number of patients randomised	238	116	289	144
Patients completing treatment	214 (89.9%)	105 (90.5%)	166 (57.4%)	46 (31.9%)
Total discontinuations	24 (10.1%)	11 (9.5%)	123 (42.6%)	98 (68.1%)

Source: adapted from CS, Table 8

Key efficacy results from the ELEVATE UC 12 and ELEVATE UC 52 trials (Week 12)

The primary outcome of the ELEVATE UC 12 trial was the proportion of patients who achieved clinical remission at Week 12. One of the two co-primary outcomes of the ELEVATE UC 52 trial was the proportion of patients who achieved clinical remission at Week 12. The results for the primary endpoint at Week 12 and for four key secondary endpoints (endoscopic improvement, symptomatic remission, endoscopic improvement-histologic remission and clinical response) for the PEAS population are presented in the CS (CS, Figure 4).

A summary of the outcomes is presented in Table 6. In both ELEVATE trials, statistically significantly more patients treated with etrasimod achieved clinical remission at Week 12 compared with placebo (difference versus placebo in the ELEVATE UC 12 trial was 9.7%; difference versus placebo in the ELEVATE UC 52 trial was 19.8%).

For all four key secondary outcomes, treatment with etrasimod was more effective than placebo (Table 6). Results for the outcomes of clinical remission, endoscopic improvement, endoscopic improvement-clinical remission were all statistically significant. The outcome of clinical response was not included in the company's multiple testing procedure.

Table 6 Primary outcome and key secondary results at Week 12 (ELEVATE UC 12 and ELEVATE UC 52 trials)

	ELEVATE UC 12		ELEVATE UC 52	
	Week 12		Week 12	
Outcome	**Etrasimod**	**Placebo**	**Etrasimod**	**Placebo**
	N=238	**N=116**	**N=274**	**N=135**
Clinical remission	24.8%	15.2%	27.0%	7.4%
Clinical remission Difference vs placebo	9.7% (95% CI=1.1 to 18.2) p=0.026		19.8% (95% CI=12.9 to 26.6) p<0.0001	
Endoscopic improvement Difference vs placebo	12.1% (95% CI=3.0 to 21.2) p=0.0092		21.2% (95% CI=13.0 to 29.3) p<0.0001	
Symptomatic remission Difference vs placebo	17.5% (95% CI=6.8 to 28.2) p=0.0013		24.6% (95% CI=15.5 to 33.6) p<0.0001	
Endoscopic improvement-histological remission Difference vs placebo	7.4% (95% CI=0.5 to 14.4) p=0.036		16.9% (95% CI=10.8 to 23.0) p<0.0001	
Clinical response Difference vs placebo	21.2% (95% CI=10.2 to 32.3) Nominal p=0.0002[a]		28.3% (95% CI=18.5 to 38.0) Nominal p<0.0001[a]	

CI=confidence interval; vs=versus
[a]Hypothesis testing for clinical response was not adjusted for in the company's multiple testing procedure, so the p-value is nominal only
Source: Adapted from CS, Figure 4

Hospitalisations during the ELEVATE UC 12 trial

More patients treated with etrasimod (compared with placebo) were admitted to hospital due to UC (1.4% versus 0%). The company highlights (CS, p41) that the small numbers of hospitalised patients do not allow statistically meaningful conclusions to be drawn. None of the patients in the trial had disease-related surgery (CS, p41).

Key efficacy results from the ELEVATE UC 52 trial at Week 52

The results for the primary endpoint at Week 52 and for other key secondary outcomes for the PEAS population are presented in the CS (CS, Figure 4). A summary of the outcomes is

presented in Table 7. Statistically significantly more patients treated with etrasimod achieved clinical remission at Week 52 compared with placebo (difference versus placebo was 25.4%). For all key secondary outcomes, treatment with etrasimod was more effective than placebo (Table 7).

Table 7 Primary and key secondary results at Week 52 from the ELEVATE UC 52 trial

Clinical	**Etrasimod**	**Placebo**
	N=274	**N=135**
Clinical remission	32.1%	18.5%
Clinical remission Difference vs placebo	25.4% (95% CI=18.4 to 32.4) p<0.001	
Endoscopic improvement Difference vs placebo	26.7% (95% CI=19.0 to 34.4) p<0.0001	
Symptomatic remission Difference vs placebo	24.9% (95% CI=16.2 to 33.6) p<0.0001	
Endoscopic improvement-histological remission Difference vs placebo	18.4% (95% CI=11.4 to 25.4) p<0.0001	
Clinical response Difference vs placebo	24.9% (95% CI=15.8 to 34.1) Nominal p<0.0001[a]	
Sustained clinical remission Difference vs placebo	15.8% (95% CI=10.7 to 21.0) p<0.0001	
Corticosteroid-free clinical remission Difference vs placebo	25.4% (95% CI=18.4 to 32.4) p<0.0001	
4-week corticosteroid-free remission among patients with baseline corticosteroid use Difference vs placebo	23.1% (95% CI=10.2 to 35.9) Nominal p=0.0004[a]	
12-week corticosteroid-free remission among patients with baseline corticosteroid use Difference vs placebo	23.1% (95% CI=10.2 to 35.9) Nominal p=0.0004[a]	

CI=confidence interval; vs=versus
[a]Hypothesis testing for this outcome was not accounted for in the company's multiple testing procedure, so the p-value is nominal only
Source:Adapted from CS, Figure 4

Results for other secondary outcomes from the ELEVATE UC 52 trial are reported in the CS (CS, Appendix F) and all show a clinical benefit for etrasimod compared with placebo.

Hospitalisations during the ELEVATE UC 52 trial

[redacted] (CS, p43).

3.4 Health-related quality of life in the ELEVATE UC 12 and ELEVATE UC 52 trial

The HRQoL measures used in the etrasimod trials were the Inflammatory Bowel Disease Questionnaire (IBD-Q), the Short Form 36 questionnaire (SF-36), the Short Form 6D (SF-6D) and the Work Productivity and Activity Impairment Questionnaire – Ulcerative Colitis (WPAI-UC). The results of the patient reported outcomes (PROs) from the ELEVATE UC 12 trial and the ELEVATE UC 52 trial at Week 12 are presented in the CS (Table 10). Results of the PROs from the ELEVATE UC 52 trial at Week 52 are presented in the CS (Table 11).

At Week 12, in the ELEVATE UC 12 trial, patients treated with etrasimod reported greater improvements in HRQoL than patients in the placebo arm across most measures. The exceptions were the SF-36 physical component summary and the WPAI-UC work time missed due to absenteeism. In the ELEVATE UC 52 trial, patients treated with etrasimod reported greater improvements in HRQoL compared to patients in the placebo arm across all measures.

At Week 52, patients in the ELEVATE UC 52 trial treated with etrasimod reported greater improvements in HRQoL than patients in the placebo arm for all IBDQ components, for the SF-36 mental component summary and the SF-6D utility index. There were no statistically significant differences between the treatment arms for the SF-36 physical component summary or for any of the WPAI-UC components.

Results from the OASIS trial

As noted in Section 3.2.1, the company identified the OASIS trial;[15] a phase II study of etrasimod versus placebo. In the OASIS trial,[15] 50 patients were randomised to receive etrasimod (2mg) and 54 patients were randomised to the placebo arm. The company reports (CS, p43) that the results of the OASIS trial[15] were consistent with the results reported in the ELEVATE trials, i.e., more patients treated with etrasimod achieved clinical remission (33.0% versus 8.1%) and clinical response (50.6% versus 32.5%). OASIS trial[15] clinical remission and clinical response data were not included in the company NMAs as data stratified by prior biologic use were not available; however, OASIS trial[15] safety data were included in the safety NMA (proportion of patients with serious infections).

3.5 Subgroup analyses from the ELEVATE UC 12 and UC 52 trials

The final scope issued by NICE does not stipulate any subgroup analyses. However, the company has provided results of subgroup analyses of trial outcomes according to prior biologic or JAKi therapy (CS, Table 12). For the biologic-naïve population, treatment with etrasimod was statistically significantly more effective compared with placebo for all outcomes and all timepoints. For the biologic-experienced population, Week 12 and Week 52 were mixed. The company has used a p-value of <0.05 as a marker of statistical significance and highlights (CS, p44) that p-values should be treated with caution as the ELEVATE trials were not powered to detect statistically significant treatment effects within subgroups defined by prior biologic exposure status.

Additional subgroup analyses (CS, Appendix G) of trial outcomes were conducted for the biologic-naïve and biologic experienced groups based on baseline corticosteroid use (yes/no) and baseline disease activity (MMS 4 to 6 or MMS 7 to 9).

3.6 Adverse events

The AEs experienced by patients in the ELEVATE trials are summarised in the CS (CS, Table 18). Specific AEs are reported in the CS, Appendix H (Table 65 and Table 66).

In the ELEVATE UC 12 trial, the company highlights (CS, p58):

- the proportion of patients who reported at least one TEAE was similar in the etrasimod and placebo arms (47.1% versus 46.6%). Most TEAEs were not considered related to the study treatment
- most TEAEs were mild or moderate (Grade 1 or 2) in severity. Grade 3 TEAEs were reported in 7 (2.9%) versus 2 (1.7%) patients in the etrasimod and placebo arms, respectively.
- there was one Grade 4 TEAE in the etrasimod arm (coronary artery disease) and none in the placebo arm
- headache, anaemia, and colitis ulcerative were reported with a >2% difference in the proportion of patients between the etrasimod and placebo arms
- no TEAEs with a fatal outcome were reported during the study.

In the ELEVATE UC 52 trial, the company highlights (CS, p60):

- the proportion of patients who reported at least one TEAE was higher in the etrasimod arm than the placebo arm (71.3% versus 56.3%, exposure adjusted incidence rate: 2.04 versus 1.83, respectively)
- most TEAEs were mild or moderate (Grade 1 or 2) in severity. Grade 3 TEAEs were low and balanced in both treatment arms (etrasimod: 20 [6.9%] patients; placebo: 10 [6.9%] patients)
- there were two Grade 4 TEAEs, one in the etrasimod arm (lymphopenia) and one in the placebo arm (alanine aminotransferase increased)

- the most frequently reported TEAEs were anaemia, headache, colitis ulcerative and coronavirus. Headache and dizziness were reported by >3% more patients in the etrasimod arm than in the placebo arm. Overall, the percentage of patients with TEAEs of colitis ulcerative or abdominal pain was low, and colitis ulcerative TEAEs were lower in etrasimod-treated patients than in patients treated with placebo
- no TEAEs with a fatal outcome were reported during the study.

As noted by the company (CS, Table 2), the SmPC[23] for etrasimod stipulates that all patients should be assessed (using an electrocardiogram) for pre-existing cardiac abnormalities prior to starting treatment and that patients with pre-existing cardiac conditions should be monitored after their first dose.

Beyond the potential impact on patients with pre-existing cardiac conditions, clinical advice to the EAG is that there were no specific or unusual safety concerns or signals in the data presented by the company. Longer-term studies and post-marketing surveillance data would be needed to establish true safety.

3.7 Critique of the indirect evidence

In the absence of head-to-head evidence comparing the clinical effectiveness of etrasimod with the relevant comparators, the company conducted NMAs. The company conducted NMAs for the following outcomes:

- clinical response
- clinical remission
- serious infections

The company performed separate NMAs to assess clinical response and clinical remission for two populations i.e., biologic-naïve, biologic-experienced populations; the NMA for serious infections only includes overall patient population data (Table 8).

Table 8 Main network meta-analyses carried out by the company*

Population	Induction phase data (Duration: 6-14 weeks)	Maintenance phase data (Duration: 42-54 weeks)
Biologic-naive	Clinical remission Clinical response	Clinical remission Clinical response
Biologic-experienced	Clinical remission Clinical response	Clinical remission Clinical response
Overall population	Serious infections	-

Source: CS, p45

A narrative summary of data for the safety endpoints of SAE and discontinuation due to AE across the studies included in the NMAs is presented in the CS (CS, Appendix F.1.2.10, Table 40 and Table 41).

3.7.1 Selection of trials for inclusion in the network meta-analyses

As discussed in Section 3.2.1, the company carried out a global SLR to identify relevant RCTs reporting the efficacy and safety of etrasimod and other relevant comparators for patients with moderately to severely active UC. However, the scope of the company's SLR was broader than the scope required for the NMAs and so the company applied additional selection criteria to identify trials for inclusion in the NMAs. Trials from the SLR were excluded if:

- the trial compared treatments that were out of scope (mirikizumab, risankizumab, and guselkumab)
- the treatment comparison in the trial is not relevant for evidence synthesis (e.g., a comparison between a treatment of interest and a treatment not of interest)
- the trial did not report one of the outcomes of interest (clinical response [induction/maintenance] or clinical remission [induction/maintenance] as measured by the Mayo score, serious infections).

Furthermore, the company only included trials in the NMAs that assessed the efficacy of EMA-licensed doses of therapies specified in the scope. For therapies with a licence that allows for dose increases during the maintenance phase, the company included trials that assessed either the recommended dose or the higher dose. Different doses and/or dosing regimens were treated as unique comparators.

The company states (CS, p46) that, "For RCTs to be eligible for inclusion in the NMA of efficacy outcomes, they were required to report on clinical response and/or clinical remission at the end of an induction (6 to 8 weeks) or maintenance (approximately 1 year) time point". However, the EAG highlights that no trials were excluded based on the induction or maintenance phases not matching these time-points. Indeed, several trials were included that reported induction periods longer than 8 weeks, and several trials were included that reported maintenance phases of less than 1 year (CS, Appendix F, Table 34). For the safety endpoint NMA, trials were required to report on the incidence of serious infections at the end of the induction phase.

Several trials identified in the company's SLR did not meet the inclusion criteria for the NMAs. The company provided reasons for the exclusion of these trials in the CS (CS, Appendix F). The EAG considers that the exclusion of these trials was reasonable.

3.7.2 Trials included in the company NMAs

After application of inclusion/exclusion criteria, 31 original trials (116 records) were eligible for inclusion in the company NMAs; a summary of the key characteristics of these 31 trials was included in the CS (CS, Appendix F, Table 34).

A full reference list of the 31 identified trials is presented in the CS (CS, Appendix F, Table 34). Three of the identified trials were not included in any of the company NMAs, the TOUCHSTONE trial,[24] the Sandborn 2012 trial[25] and the LIBERTY-UC trial.[26] These trials do not provide data for subgroups based on prior biologic exposure (CS, p105), or report safety data at the end of an induction period. The remaining 28 trials provide efficacy and safety data for the following treatments:

- adalimumab (6 trials)[27-31]
- etrasimod (3 trials)[13,15]
- filgotinib (1 trial)[32]
- golimumab (3 trials)[33-35]
- infliximab (5 trials)[36-39]
- ozanimod (1 trial)[40]
- tofacitinib (3 trials)[41]
- upadacitinib (2 trials)[42,43]
- ustekinumab (1 trial)[44]
- vedolizumab (4 trials)[31,45-47]

The information presented in Table 9 shows the numbers of RCTs included in the company NMAs, as described in the main body of the CS. The company SLR identified more biologic-naïve population RCT data than biologic-experienced population RCT data, and more induction phase RCT data than maintenance phase RCT data.

Table 9 Number of trials included in the company network meta-analyses

Population	Induction phase data (duration: 6 to 14 weeks)		Maintenance phase data (duration: 42 to 54 weeks)	
Biologic-naive	Clinical remission/clinical response (n=23)	Adalimumab (n=6)[27-31] Etrasimod (n=2)[13,15] Filgotinib (n=1)[32] Golimumab (n=1)[34] Infliximab (n=5)[36-39] Ozanimod (1)[40] Tofacitinib (n=2)[41] Upadacitinib (n=2)[42,43] Ustekinumab (n=1)[44] Vedolizumab (n=3)[31,45-47]	Clinical remission/clinical response (n=13)	Adalimumab (n=1)[29] Etrasimod (n=1)[13] Filgotinib (n=1)[32] Golimumab (n=2)[33,35] Infliximab (n=1)[39] Ozanimod (n=1)[40] Tofacitinib (n=1)[41] Upadacitinib (n=1)[42,43] Ustekinumab (n=1)[44] Vedolizumab (n=3)[45-47]
Biologic-experienced	Clinical remission/clinical response (n=13)	Adalimumab (n=2)[29,31] Etrasimod (n=2) [13,15] Filgotinib (n=1)[32] Ozanimod (n=1)[40] Tofacitinib (n=2)[41] Upadacitinib (n=2)[42,43] Ustekinumab (n=1)[44] Vedolizumab (n=3)[45-47]	Clinical remission/clinical response (n=10)	Adalimumab (n=1)[29] Etrasimod (n=1)[13] Filgotinib (n=1)[32] Ozanimod (n=1)[40] Tofacitinib (n=1)[41] Upadacitinib (n=1)[42,43] Ustekinumab (n=1)[44] Vedolizumab (n=3)[45-47]
Overall	Serious infections (n=17)	Adalimumab (n=4)[27,28,30] Etrasimod (n=2)[13,15] Filgotinib (n=1)[32] Golimumab (n=1)[34] Infliximab (n=1)[37] Ozanimod (n=1)[40] Tofacitinib (n=2)[41] Upadacitinib (n=2)[42,43] Ustekinumab (n=1)[44] Vedolizumab (n=2)[46,48]	-	-

Source: adapted from CS, Table 13, Figure 6, Figure 7 and Figure 8

Trial characteristics: all included trials

Key characteristics of the designs of the trials eligible for inclusion in the NMAs are provided in the CS (CS, Table 13 and Appendix F, Table 34). Key patient baseline characteristics are also provided in the CS (CS, Table 36).

The company notes (CS, p102) that most of the RCTs were placebo controlled, except the VARSITY[31] trial (adalimumab versus vedolizumab). It is also noted in the CS that most trials were double blinded, although the VISIBLE 1,[47] PURSUIT-J,[33] TRUE NORTH,[40] GEMINI 1[45] and Motoya 2019[46] trials included an open-label cohort or an open-label induction period.

Characteristics of trials included in the induction phase NMAs

The induction phase trials ranged in duration from 6 weeks[35] to 14 weeks.[31] Eleven[27,29,30,34,36-39] trials enrolled biologic-naïve patients only, while the remaining trials enrolled a mixed patient cohort of biologic-naïve and biologic-experienced patients. A comparison of the baseline patient and disease characteristics across each of the arms of the trials included in the induction phase NMAs showed that patients were of a comparable age (mean age ranged from 34.3[36] to 44.5 years[43,49]); however, disease duration (mean 4.4[36] to 10.4[32] years), the proportion of patients with extensive colitis or pan-colitis (9%[28] to 80.8%[37]), and the levels of use of concurrent corticosteroid use varied (13.4%[46] to 77.5%[13]).

Characteristics of trials included in the maintenance phase NMAs

The maintenance trials ranged in duration from 42 weeks[40] to 54 weeks.[29,33,34,39] Four[29,33,34,39] of the trials enrolled biologic-naïve patients only. Three[13,29,39] of the trials used a treat-through study design, with the remaining 10[32,33,35,40-47] trials re-randomising patients who entered the maintenance phase. Two other treat-through trials (Suzuki 2014[30] and VARSITY[31]) were eligible for inclusion in the maintenance phase NMAs, however, due to the limitations of the trial data (Section 3.7.4), the company was unable to include data from the Suzuki 2014[30] and VARSITY[31] trials in the maintenance NMAs.

A comparison of the baseline patient and disease characteristics across each of the arms of the trials included in the maintenance phase NMAs, showed that the mean ages of patients were comparable (mean age ranged from 38.1[47] to 44 years[46]); however, there was variation between trials in disease duration (mean 5.9[13,42] to 8.9 years[32]), the proportion of patients with extensive colitis or pan-colitis (6.6%[47] to 58.7%[40]), and levels of concurrent corticosteroid use varied (13.4%[46] to 77.5%[13]).

3.7.3 Quality assessment of the trials included in the NMAs

The company quality assessed the trials included in the NMAs using the minimum criteria recommended by NICE.[17] The company quality assessments and EAG comments are

presented in Appendix 6.2. The EAG notes that, in trials where mixed populations were enrolled, patient characteristics were often only reported for the overall population; the EAG therefore considers the assessment of baseline patient comparability is challenging. Overall, the EAG considers that the quality of the trials included in the NMAs was acceptable.

3.7.4 Methodological approach to network meta-analyses

A summary of the EAG checks of the company's methodological approach to conducting the NMAs is provided in Appendix 6.3. Overall, the EAG considers that the company's methodological approach was appropriate. Key features of the NMA methodology are outlined in this section.

Subgroup analysis by prior biologic exposure

The company performed separate NMAs for biologic-naïve and biologic-experienced patients. Prior biologic exposure was described using different terminology across the included trials. The company assumed the terms 'TNFi-exposure', 'biologic exposure' and 'biologic or JAKi exposure' were interchangeable. If subgroup data based on prior biologic exposure were unavailable, the company used subgroup data based on prior biologic failure. Data for patients who experienced biologic-failure were included in the NMAs for patients with prior exposure to biologic therapy, and data for patients who did not experience biologic-failure were included in the NMAs for patients without prior exposure to biologic therapy. The EAG considers that the different definitions of biologic-exposure status could introduce heterogeneity into the networks of evidence. Trials that did not report subgroup data were excluded from the subgroup analyses.

The NMA for serious infections was conducted using overall trial population data as most included trials did not report this outcome by prior biologic exposure status.

Treat-through trials versus randomised responder trials

Of the 31 trials that were eligible for inclusion in the NMA, 15 assessed outcomes at the end of a maintenance phase. These trials were either treat-through trials[13,29-31,39] or randomised responder trials.[32,33,35,40-47] In the treat-through trials, patients were randomised at baseline and outcomes were measured at the end of an induction phase and at the end of a maintenance phase. In the randomised responder trials patients who achieved clinical response during an induction phase (randomised or single-arm) were then randomised to either placebo or to the maintenance dose of the intervention. Outcomes were then measured for these induction-phase responders at the end of the maintenance phase.

The company highlights, and the EAG agrees, that simply combining the reported maintenance phase outcomes from these different types of trial would be inappropriate as it would violate the similarity and homogeneity assumptions necessary for network meta-analysis. Specifically, the patient populations allowed to enter the maintenance phases are incomparable; patients in the randomised responder trials had to have had a response during the induction phase, whereas patients in the treat-through trials may not have had a response during the induction phase. Furthermore, some patients receiving placebo in the maintenance phase of the randomised responder trials would have received active treatment during the induction phase, whereas patients receiving placebo in the maintenance phase of the treat-through trials would have also received placebo during the induction phase.

To account for the differences between the two trial designs, the company converted the outcomes of the treat-through trials to mimic the outcomes of the randomised responder trials. For the ELEVATE 52 trial, the company was able to isolate maintenance phase outcome data for the subset of patients who had responded to treatment during the induction phase as the company had access to individual patient data (IPD) for this trial. For two other treat-through trials (ACT 1[39] and ULTRA 2[29]), the company assumed that the number of responders at the end of induction in each treatment arm could be used as a proxy for the total number of patients who entered the maintenance phase for each treatment arm (if the study had used the randomised responder design). For the induction phase responders, the company established how many of these patients also responded during the maintenance phase by using the number of patients who achieved sustained clinical response. The company would not have been able to use the number of patients who achieved response during the maintenance phase as this would have included some patients who did not respond during the induction phase. For two trials (Suzuki 2014[30] and VARSITY[31]), data were insufficient to apply the adjustments and so these trials were excluded from the maintenance phase analysis.

The EAG considers that the company's approach to accounting for differences between the two trial types was appropriate. However, the EAG highlights that the company's method of adjustment does not account for the fact that the placebo arms of trials included in the company maintenance NMAs are often fundamentally different; some of the placebo arm patients had received and responded to placebo induction (effectively 'skipping' the induction phase), whereas other placebo arm patients had received and responded to active treatment induction. The EAG is unaware of a solution that would account for these differences in placebo arm patients during the maintenance phase.

3.7.5 Results of the network meta-analyses: clinical response and clinical remission

The networks of evidence for the analyses of clinical response and clinical remission are provided in Figure 6, Figure 7, Figure 9 and Figure 10 of the CS. A summary of the results from the company's NMAs for clinical response and clinical remission are provided in Table 10. The EAG has not presented results for each comparator versus placebo, or the probabilities of achieving response and remission for each treatment, or surface under cumulative ranking curve (SUCRA) values; these results are available in the CS (CS, Appendix F, Table 48 and Table 49). The EAG has only presented results for comparator doses that are used in NHS clinical practice (and the company economic model).

Table 10 Summary of the company's NMA results: clinical response and clinical remission

Comparator	Induction phase Etrasimod vs comparator Risk ratio, median (95% CrI)		Maintenance phase Etrasimod vs comparator Risk ratio, median (95% CrI)	
	Clinical response	Clinical remission	Clinical response	Clinical remission
Biologic-naïve subgroup; fixed-effects model[a]				
PBO	[redacted]	[redacted]	[redacted]	[redacted]
OZN 1mg	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10mg induction, 5mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200mg	[redacted]	[redacted]	[redacted]	[redacted]
UPA 45mg induction, 15mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40mg [b] induction, 40mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
GOL 200/100mg [c] induction, 50mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
IFX 5mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg induction, 300mg Q8W maintenance	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg induction, 108mg Q2W maintenance	[redacted]	[redacted]	[redacted]	[redacted]
UST 90mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]
UST 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]
Biologic-experienced subgroup; random-effects model for induction phase,[d] fixed-effects model for maintenance phase[a]				
PBO	[redacted]	[redacted]	[redacted]	[redacted]
OZN 1mg	[redacted]	[redacted]	[redacted]	[redacted]
TOF 10mg induction, 5mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
FIL 200mg	[redacted]	[redacted]	[redacted]	[redacted]

Comparator	Induction phase Etrasimod vs comparator Risk ratio, median (95% CrI)		Maintenance phase Etrasimod vs comparator Risk ratio, median (95% CrI)	
	Clinical response	Clinical remission	Clinical response	Clinical remission
UPA 45mg induction, 15mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
ADA 160/80/40mg [b] induction, 40mg maintenance	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg induction, 300mg Q8W maintenance	[redacted]	[redacted]	[redacted]	[redacted]
VDZ 300mg induction, 108mg Q2W maintenance	[redacted]	[redacted]	[redacted]	[redacted]
UST 90mg Q12W	[redacted]	[redacted]	[redacted]	[redacted]
UST 6mg/kg	[redacted]	[redacted]	[redacted]	[redacted]

Green shading indicates that the point estimate of the risk ratio favours etrasimod; red shading indicates that the point estimate of the risk ratio favours the comparator; no shading indicates that the point estimate is 1. Statistically significant results are in bold (95% CrIs do not cross 1)
[a]Fixed-effects model was associated with reasonable model fits in terms of DIC and residual deviance; the random-effects model did not converge
[b]160mg at Week 0, 80mg at Week 2, 40mg at Weeks 4 and 6
[c]200mg at Week 0, 100mg at Week 2
[d]Model fit statistics suggested that the random-effects model was associated with an improved fit, given the residual deviance was lower and the DIC was substantially lower (>5 points) than the fixed-effects model
ADA=adalimumab; Bio=biologics; CrI=credible interval; DIC=deviance information criterion; ETR=etrasimod; FIL=filgotinib; GOL=golimumab; IFX=infliximab; IV=intravenous; OZN=ozanimod; PBO=placebo; SC=subcutaneous; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab
Source: CS Appendix F, Table 48 and Table 49

The EAG has grouped comparators as follows: S1P (ozanimod); JAKi (filgotinib, tofacitinib, upadacitinib); TNFi (adalimumab, golimumab, infliximab); other biologic agents (vedolizumab, ustekinumab).

Etrasimod versus S1P

[redacted]

Etrasimod versus JAKi

[redacted]

Etrasimod versus TNFi

[redacted]

Etrasimod versus other biologic agents

[redacted]

[redacted]

Results of inconsistency assessments

The company provided results of inconsistency assessments for the NMAs of clinical response and clinical remission in their response to clarification question A4.

Comparing the fixed-effects unrelated mean effects (UME) model and the fixed-effects NMA model for each analysis, differences in the residual deviance values were all less than 5. However, there were some differences in the deviance information criterion (DIC) values. For the analysis of efficacy outcomes in the biologic-naïve population during the induction phase, the difference in DIC values between the fixed-effects UME model and the NMA model was 6.17. For the analysis of efficacy outcomes in the biologic-experienced population during the maintenance phase, the difference in DIC values between the fixed-effects UME model and the NMA model was 9.4. For each of these analyses, the company examined deviance contribution points, noting no points fell significantly below the line of equality.

To supplement the assessment of inconsistency, the company also measured heterogeneity for each pairwise comparison to which more than one study contributed. In the biologic-naïve population during the induction phase, the company noted moderate heterogeneity for several pairwise treatment comparisons. In the biologic-experienced population during the maintenance phase, no heterogeneity was detected.

Considering the assessment of the inconsistency in conjunction with the assessment of heterogeneity for pairwise comparisons, the company concluded that they did not “expect there to be any significant inconsistency among the analyses”.

3.7.6 Results of the network meta-analyses: serious infections

The networks of evidence for the analyses of serious infections are provided in Figure 8 of the CS. A summary of the results from the company’s NMA for serious infections is provided in Table 11. The EAG has not presented results for each comparator versus placebo, or the probabilities of experiencing a serious infection for each treatment, or SUCRA values. These results are available in the CS (CS, Appendix F, Table 50). The EAG has only presented results for comparator doses that are used in NHS clinical practice (and in the company economic model).

Table 11 Summary of the company’s NMA results: serious infections (fixed-effects model)

Comparator	Etrasimod vs comparator
	Risk ratio, median (95%CrI)
PBO	[redacted]
ETR 2mg	[redacted]
OZN 1mg	[redacted]
TOF 10mg	[redacted]
FIL 200mg	[redacted]
UPA 45mg	[redacted]
ADA 160/80/40mg [a]	[redacted]
GOL 200/100mg [b]	[redacted]
IFX 5mg/kg	[redacted]
VDZ 300mg	[redacted]
UST 6mg/kg	[redacted]

Green shading indicates that the point estimate of the risk ratio favours etrasimod; red shading indicates that the point estimate of the risk ratio favours the comparator; no shading indicates that the point estimate is 1
Model fit statistics suggested that the random-effects model was associated with an improved fit. However, due to the rarity of the event the uncertainty in the treatment effects generated by the random-effects model lacked face validity. For this reason, primary results for serious infections during the induction periods were derived from the fixed-effects model
[a]160mg at Week 0, 80mg at Week 2, 40mg at Weeks 4 and 6
[b]200mg at Week 0, 100mg at Week 2
ADA=adalimumab; Bio-=biologics; CrI=credible interval; ETR=etrasimod; FIL=filgotinib; GOL=golimumab; IFX=infliximab; OZN=ozanimod; PBO=placebo; TOF=tofacitinib; UPA=upadacitinib; UST=ustekinumab; VDZ=vedolizumab; SUCRA=surface under cumulative ranking curve

Results from the company's NMA for serious infections were mixed; several relative efficacy estimates favoured comparator treatments over etrasimod, and several favoured etrasimod over comparator treatments. All credible intervals were very wide, with no statistically significant differences observed.

Results of inconsistency assessments

The company provided results of inconsistency assessments for the NMAs of serious infections in their response to clarification question A4. Comparing the fixed-effects unrelated UME model and the NMA model, differences in the residual deviance and DIC values were less than 5. The company concluded that they do not "expect there to be any significant inconsistency among the analyses".

3.7.7 EAG comment on NMA methods

Generally, the EAG considers that the NMAs were well-conducted. However, the EAG considers that the company's assessment of inconsistency was limited in the following ways:

- It is not clear how the assessment of heterogeneity for pairwise comparisons (clarification question A4) was conducted as only the name of one treatment was provided for each comparison. Most pairwise treatment comparisons in the networks of evidence were comparisons with placebo but, in the biologic-naïve induction phase network, there was one comparison of two different doses of adalimumab (two studies contributed data).
- The company compared the fixed-effects UME model and the fixed-effects NMA model for each analysis. The EAG considers that, for the biologic-experienced population during the induction phase, it would have been more appropriate to compare the random-effects UME model with the random-effects NMA model as the results presented in the CS for this network of evidence were from the random-effects model.
- The company did not compare estimated treatment effects from the UME model with estimated treatment effects from the NMA model.

The EAG agrees with the company that the results of the inconsistency assessments suggested no strong evidence of inconsistency. However, it is not clear how the results of the inconsistency assessments would be impacted if the previously discussed limitations were addressed. Furthermore, the EAG highlights guidance from NICE DSU TSD4,[50] which states that "while tests for inconsistency must be carried out, they are inherently underpowered, and will often fail to detect it. Investigators must therefore also ask whether, if inconsistency is not detected, conclusions from combining direct and indirect evidence can be relied upon".

The EAG notes the following sources of heterogeneity which should be considered when interpreting the company's NMA results:

- patients in the placebo arms had received and responded to different induction treatments (including various active treatments and placebo) with potentially different

persistent effects after treatment has ended (relevant to analyses of maintenance phases)

- different definitions of biologic-exposure status (see Section 3.7.4)
- variation between trials in terms of patient characteristics, including disease duration, the proportion of patients with extensive colitis or pan-colitis, and levels of concurrent corticosteroid use (see Section 3.7.2)

3.7.8 EAG comment on NMA results

In the main body of the CS (CS, p51), the company considers that, for both biologic-naïve and biologic-experienced patients, NMA results underpin the claim that etrasimod is likely to provide similar or greater health benefits compared to treatment with adalimumab, infliximab and vedolizumab, the three most widely used NHS comparator treatments. The company presents NMA results for etrasimod versus the remaining comparators in CS, Appendix F; however, these results are not discussed in the text and claims of treatment similarity have not been explicitly made by the company. For completeness (and because the full set of treatments is included in the cost comparison analysis), the EAG has commented on the full set of NMA results.

Biologic-naïve patients: efficacy

[redacted]

Biologic-experienced patients: efficacy

[redacted]

All patients: safety (serious infections)

[redacted]

4 EAG CRITIQUE OF COMPANY COST COMPARISON EVIDENCE

4.1 Introduction

In the final scope issued by NICE, it is stated that etrasimod has been selected to be appraised as a cost comparison analysis. The company considered that NMA efficacy and safety results demonstrated that treatment with etrasimod was likely to provide similar or greater health benefits than the three comparator treatments most commonly used in the NHS (i.e., adalimumab, infliximab and vedolizumab) and carried out a cost comparison analysis.

4.2 Company cost comparison model

The company model was developed in MS Excel. As part of the company clarification response, the company provided a model that included additional scenario analysis. These results that were generated using the assumption that 10% of patients (all treatments) would have a complete response at 12 months and discontinue treatment (Section 4.5.2).

4.2.1 Population

The company performed separate efficacy NMAs (etrasimod versus comparators) to consider clinical response and clinical remission for four populations:

- biologic-naïve: induction
- biologic-naïve: maintenance
- biologic-experienced: induction
- biologic-experienced: maintenance

The company also performed a safety NMA (etrasimod versus comparators) to consider serious infections using overall population data (i.e., biologic-naïve and biologic-experienced patients).

For the purposes of the cost comparison analysis, the company has assumed that treatment costs for biologic-experienced patients are the same as those for biologic naïve patients.

4.2.2 Intervention and comparators

Cost comparison results have been provided for the comparison of etrasimod versus adalimumab, filgotinib, golimumab, infliximab, ozanimod, tofacitinib, upadacitinib, ustekinumab and vedolizumab. The company included the comparison of etrasimod versus mirikizumab in the company model (but not in the CS); mirikizumab is currently under NICE evaluation and is therefore not relevant to this appraisal.

4.2.3 Perspective, time horizon and discounting

The company's base case analysis comprised drug acquisition and administration costs, pre-initiation ECG (for etrasimod and ozanimod) and concomitant treatment costs over a 5-year period. The company did not discount costs.

4.3 Treatment costs

The analysis considered the cost of (i) induction (part of first year costs only) and (ii) maintenance treatment over a 5 year period.

4.3.1 Drug costs

The dosing schedules used in the company model are presented in Table 12. Drug acquisition costs and administration costs are presented in Table 13 and Table 14, respectively. Where different drug prices are available, the company has used the lowest price to estimate drug costs.

Table 12 Drug costs: dosing schedules used in the company model

Drug	Route of Administration	Dosing	
		Initiation	Maintenance
Company model			
Etrasimod	Oral	2mg once daily	
Adalimumab	SC	160mg at Week 0 80mg at Week 2	40mg every other week
Infliximab then Remsima*	Initiation: IV Maintenance: SC	5mg/kg at Weeks 0 and 2	120mg every 2 weeks from Week 6
Infliximab*	IV	5mg/kg at Weeks 0, 2 and 6	5mg/kg every 8 weeks
Vedolizumab	IV	300mg at Weeks 0, 2 and 6	300mg every 8 weeks
Vedolizumab	Initiation: IV Maintenance: SC	300mg at Weeks 0 and 2	108mg at Week 6 and every other week thereafter
Golimumab	SC	200mg at Week 0, 100mg at Week 2	50mg every 4 weeks thereafter
Tofacitinib	Oral	10mg twice daily for 8 weeks	5mg twice daily
Filgotinib	Oral	200mg once daily	
Upadacitinib	Oral	45mg once daily for 8 weeks	15mg once daily
Company clarification model			
Ozanimod	Oral	Dose escalation from day 1 to day 7 (0.23mg once daily for days 1 to 4 then 0.46mg once daily for days 5 to 7)	0.92mg once daily
Ustekinumab	IV and SC	Assume patient weight 56-85kgs; 390mg (IV) then 90mg after 8 weeks (SC)	90mg every 12 weeks (SC)

*Average weight of 78.5kgs was used to calculate required dose
IV=intravenous; SC=subcutaneous injection
Source: company model

Table 13 Drug acquisition costs

Drug	Total cost	
	Year 1	Subsequent years
Company model		
Etrasimod (oral)	£11,000 [redacted]	£11,000 [redacted]
Adalimumab (SC)	£9,820.80	£8,236.80
Infliximab then Remsima (IV then SC)	£11,643.75	£9,819.16
Infliximab (IV only)	£11,830.26	£8,872.70
Vedolizumab (IV then SC)	£16,400.00	£12,300.00
Vedolizumab (IV only)	£16,400.00	£13,325.00
Golimumab (SC)	£11,826.04	£9,918.61
Tofacitinib (oral)	£10,350.45	£8,970.39
Filgotinib (oral)	£10,472.28	£10,472.28
Upadacitinib (oral)	£13,035.36	£10,472.28
Company clarification model		
Ozanimod (oral)	[redacted]	[redacted]
Ustekinumab (IV and SC)	[redacted]	[redacted]

Source: CS, Table 20 and company clarification model

Table 14 Drug administration costs

Administration method	Cost	Reference
IV	£133.40	Average of consultant led and non-consultant led, non-admitted face-to-face attendance, follow-up, WF01A[51]
SC	£0.00	Assume patients self-administer and therefore there is no administration cost. Additionally, it has been assumed that the one off nurse training cost to teach patients how to self-administer the injection is covered by the manufacturer in line with previous TAs (TA856[9] and TA547[7])
Oral	£0.00	Assumed no administration cost

IV=intravenous; SC=subcutaneous
Source: CS, Table 22

The concomitant medications included in the model are shown in

Table 15. Concomitant medication usage is assumed to stay constant over the model time horizon.

Table 15 Concomitant medications

Drug	Total annual cost	Utilisation	
		S1Ps[10]	All other treatments[5,6]
Balsalazide	£341.64	0%	0%
Mesalazine	£201.66	13%	13%
Olsalazine	£1,958.83	0%	0%
Sulfasalazine	£87.86	0%	0%
Prednisolone	£1.47	36%	36%
Hydrocortisone	£40.03	0%	0%
Azathioprine*	£9.52	0%	0% or 39%
6-mercaptopurine*	£502.09	0%	15%
Methotrexate*	£15.77	0%	9.0%
Budesonide	£126.10	1%	1%

S1P=sphingosine-1-phosphate
*Patients receiving etrasimod and ozanimod are contraindicated to azathioprine, 6-mercaptopurine and methotrexate and would therefore not receive these concomitantly. Patients receiving tofacitinib are contraindicated to azathioprine and would therefore not receive it concomitantly
Source: CS, Table 23

4.3.2 Monitoring and pre-initiation costs

A single ECG is required prior to treatment with an S1P (etrasimod and ozanimod). The company has assumed that the cost of an ECG is £74.91 (EY51Z,[51] Directly Accessed Diagnostic Services, Electrocardiogram, Monitoring or Stress Testing).

Monitoring costs were assumed similar for etrasimod and existing treatments and were not included in the model.

4.4 Adverse events

Company safety (serious infection) NMA results (etrasimod versus existing treatments) demonstrated that there were no statistically significant differences between treatments (CS, p70). Therefore, the company did not include AE-related costs in the analysis.

4.5 Company cost comparison results

4.5.1 Base case results

The company base case results are presented in Table 16.

Table 16 Company cost comparison base case results

Treatment	Total 5-year cost per patient	Current market share
Etrasimod	£55,215 ([redacted]	-
Adalimumab	£43,308	[redacted]
Infliximab (IV then SC)	£52,527	[redacted]
Infliximab (IV only)	£52,129	
Vedolizumab (IV then SC)	£70,506	[redacted]
Vedolizumab (IV only)	£70,408	
Golimumab	£52,040	[redacted]
Tofacitinib	£46,753	[redacted]
Filgotinib	£52,901	[redacted]
Upadacitinib	£55,464	[redacted]
Ozanimod	£89,460	[redacted]
Ustekinumab	£54,348	[redacted]

Source: company model and company clarification response, Table 2; CS, Table 24

4.5.2 Company cost comparison scenario results

The company carried out three scenario analyses; results are provided in Table 17.

Table 17 Company cost comparison scenario analysis results

Technology	2-year time horizon	5-year time horizon Infliximab (IV only) and vedolizumab (IV only) for initiation and maintenance	Positive stopping rule of 10% at 12 months applied to all treatments
Etrasimod	£22,131 (list) [redacted]	£55,215 (list) [redacted]	£50,804 (list) [redacted]
Adalimumab	£18,273	£43,308	£39,970
Infliximab (IV then SC)	£22,746	-	£48,556
Infliximab (IV only)	£22,786	£52,129	£48,217
Vedolizumab (IV only)	£30,783	£70,408	£65,125
Vedolizumab (IV then SC)	£30,208	-	£65,133
Golimumab	£21,960	£52,040	£48,029
Tofacitinib	£19,529	£46,753	£43,123
Filgotinib	£21,160	£52,901	£48,669
Upadacitinib	£23,723	£55,464	£51,232
Ozanimod	£35,829	£89,460	£82,309
Ustekinumab	£26,113	£54,348	£50,583

IV=intravenous; PAS=Patient Access Scheme
Source: company model

4.6 EAG critique of company cost comparison analysis

4.6.1 Company approach to cost comparison analysis

In the final scope issued by NICE, it is stated that etrasimod has been selected to be appraised as a cost comparison. To establish that the clinical efficacy and safety of etrasimod is similar to comparator treatments, the company carried out several NMAs. The company has focussed its discussion and presentation of the NMA results on the comparison of etrasimod versus adalimumab, infliximab and vedolizumab. For completeness (and because all treatments were included in the company cost comparison analysis), the EAG has commented on the full set of company NMA results.

Company **biologic-naïve** NMA results showed that:

- in the induction and maintenance phases, etrasimod is only statistically significantly superior to adalimumab (clinical response and clinical remission)
- in the induction phase, etrasimod is statistically significantly inferior to upadacitinib (clinical response and clinical remission)
- for all other comparisons, the difference between treatments is not statistically significant (clinical response and clinical remission).

Company **biologic-experienced** NMA results showed that:

- induction and maintenance phases, etrasimod is not statistically significantly superior to any of the drugs in the network (clinical response and clinical remission)
- for the comparison of etrasimod versus infliximab or golimumab, there was no relevant evidence available to include in the NMA

In the absence of non-inferiority or equivalence testing, the EAG considers that only statistically significant NMA results favouring etrasimod can provide conclusive evidence that etrasimod is likely to provide similar or greater health benefits versus comparator treatments.

The EAG considers that the results from previous NMAs[4-10] conducted as part of similar NICE appraisals are mixed and it is often difficult to determine whether the new intervention is likely to provide greater health benefits than comparator treatments. Previous NICE appraisals[4-10] of comparator drugs have all included cost utility analyses, except for mirikizumab which used a cost comparison approach.

4.6.2 Minor errors

The EAG identified and corrected the following minor errors in the company cost comparison model):

- the number of infliximab, adalimumab, golimumab, ustekinumab and vedolizumab maintenance doses in the first year were slightly overestimated

- the unit cost for simple delivery of chemotherapy (NHS Reference Cost SB12Z: £286.17) should have been applied for the IV administration cost

The EAG has identified the following three issues that may require further consideration: drug acquisition costs, duration of treatment and time horizon.

4.6.3 Drug acquisition costs

The EAG notes that some dosing regimens described in the CS were incorrect; however, the correct regimens were applied in the company cost comparison model.

The company analyses have been conducted using list prices for all other drugs; confidential discounted prices (PAS and CMU) are available for comparator drugs. Cost comparison results generated using all discounted prices are available in a confidential appendix.

4.6.4 Duration of treatment

Subsequent treatments

Clinical advice to the EAG is that for patients who do not relapse and have no tolerability issues, it may be reasonable to assume treatment on the same drug continues for 5 years; however, for patients who relapse, this assumption may not be appropriate as these patients will receive one or more subsequent treatments.

Subsequent treatment costs are not included in the company cost comparison analysis; implicitly, therefore, the company has assumed that first-line treatment does not influence choice of subsequent treatments. Clinical advice to the EAG is that choice of subsequent treatment will be influenced by prior treatment. Further, company NMA results suggest that the efficacy, and therefore (implicitly) treatment duration, of UC treatments may differ according to setting (biologic-naïve/biologic-experienced). For example, if a biologic-experienced patient had previously failed on a TNFi, a non-TNFi is likely to be considered; results from the company NMA and a published NMA[52] suggest JAKis could be one of the most effective treatment options in this setting.

Clinical advice to the EAG is that a significant proportion of patients fail first-line treatment and subsequent lines of treatment; therefore, it may be important to consider subsequent treatment costs.[52] The EAG acknowledges that the high number of available subsequent treatment options and lack of sequential efficacy data are likely to present challenges for modelling and therefore subsequent treatment costs remain an area of uncertainty.

Treatment discontinuation due to benefit

In line with NICE recommendations,[4,5] patients who have a complete response at 12 months may pause or withdraw from treatment. In response to clarification question B4, the company has attempted to address the uncertainty associated with the impact on cost effectiveness results of some patients discontinuing treatment due to benefit by presenting results from a scenario analysis in which 10% of patients stopped treatment at 12 months; information about the source of this proportion were not provided.

There is a lack of long-term data informing the proportions of patients who relapse or pause treatment (and when this happens); therefore, the extent to which patients pause and receive subsequent treatments is unknown. Clinical advice to the EAG is that NHS patients in complete remission with no tolerability issues rarely discontinue treatment at 12 months and are likely to continue longer-term treatment, especially if disease history is well established. The EAG therefore considers that if all treatments have equal efficacy and safety, assuming equivalent time on treatment is reasonable.

Time horizon

The annual costs of each treatment are the same from Year 2 onwards, the EAG considers that it may be more appropriate to use results from a 2-year, rather than a 5-year, time horizon to inform decision making (company scenario analysis [CS, Table 25]).

4.7 EAG cost comparison results

After implementing the minor corrections described in Section 4.6.2, the EAG's updated cost comparison results are presented in Table 18. The EAG corrections had a minimal impact on the company cost comparison results. Details of the EAG's minor corrections to the company model are presented in Appendix 6.4.

Table 18 EAG cost comparison base case results (etrasimod PAS price, list price all other drugs)

Treatment	Total 5-year cost per patient	Total 2-year cost per patient	5-year difference (etrasimod vs comparator)	2-year difference (etrasimod vs comparator)
Etrasimod	[redacted]	[redacted]		
Adalimumab	£42,991	£17,957	[redacted]	[redacted]
Filgotinib	£52,901	£21,160	[redacted]	[redacted]
Golimumab	£51,659	£21,579	[redacted]	[redacted]
Infliximab (IV then SC)	£53,754	£23,972	[redacted]	[redacted]
Infliximab (IV only)	£57,035	£24,933	[redacted]	[redacted]
Ozanimod	£89,460	£35,829	[redacted]	[redacted]
Tofacitinib	£46,753	£19,529	[redacted]	[redacted]
Upadacitinib	£55,464	£23,723	[redacted]	[redacted]
Ustekinumab	£53,070	£24,835	[redacted]	[redacted]
Vedolizumab (IV then SC)	£70,301	£30,002	[redacted]	[redacted]
Vedolizumab (IV only)	£75,314	£32,930	[redacted]	[redacted]

IV=intravenous; SC=subcutaneous

4.8 Conclusions

Clinical advice to the EAG is that etrasimod, as an oral drug, is a valuable addition to the currently available basket of treatments for patients with moderately to severely active UC. In addition, clinical advice to the EAG is that current NICE recommended treatments for moderately to severely active UC are generally considered to have similar efficacy and safety and that choice of treatment depends on several factors, including patient preferences and cost.

In the final scope issued by NICE, it is stated that etrasimod has been selected to be appraised as a cost comparison. The company (via the NMAs) has shown that etrasimod is statistically significantly superior to adalimumab (biologic-naïve patients, induction and maintenance phases, clinical remission/clinical response) and statistically significantly inferior to upadacitinib (biologic-naïve patients, induction, clinical remission/clinical response). For all other comparisons, company NMA results did not show that etrasimod was statistically significantly superior/inferior to any of the other drugs listed in the final scope.

If the NICE AC considers that etrasimod and comparator drugs are similar and any differences in patient outcomes can be ignored, then the EAG considers that the company cost comparison analysis may produce a robust estimate of the likely cost savings for patients treated with etrasimod, provided the following assumptions are considered reasonable:

- subsequent treatment costs are likely to be similar irrespective of the first-line treatment received
- treatment costs for biologic-experienced patients are assumed to be the same as those for biologic-naïve patients

Due to an absence of treatment sequencing data, the EAG considers that a cost utility analysis may not reduce the uncertainty around comparative effectiveness, treatment duration and subsequent treatments.

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6 APPENDICES

6.1 Appendix 1: EAG summary and critique of the company's methodological approach in the ELEVATE trials

Table 19 EAG assessment of statistical approaches used in the ELEVATE UC 12 and ELEVATE UC 52 trials

Item	EAG assessment	Statistical approach with EAG comments
Were all analysis populations clearly defined and pre-specified?	Yes	All key efficacy outcomes are reported for the primary efficacy analysis set (PEAS) in the ELEVATE UC trials. The PEAS population includes only patients with a baseline modified Mayo score (MMS) of 5 to 9 who received at least one dose of study drug or placebo. The safety analysis set was defined as all randomised patients who received ≥1 dose of the study drug or placebo (CS, p35) The EAG notes that the inclusion criteria of the ELEVATE UC trials allowed for the recruitment of patients with a MMS of 4. The EAG is satisfied that the PEAS populations was clearly defined and pre-specified in the TSAP for each of the ELEVATE UC trials (TSAP Table 1).
Was an appropriate sample size calculation pre-specified?	Yes	A trial sample size calculation was pre-specified in the TSAP for ELEVATE UC 12 (p19). For the primary endpoint analysis of clinical remission at Week 12, the company estimated that a sample size of 330 patients (220 etrasimod, 110 placebo) was required to achieve at least 90% power to detect a difference of 12.5% between the etrasimod treatment group (18.5%) and the placebo treatment group (6.0%). A trial sample size calculation was pre-specified in the TSAP for ELEVATE UC 52 (p23). For the primary endpoint analysis of clinical remission, the company estimated that a sample size of 420 patients (280 etrasimod, 140 placebo) was required to achieve 93.4% power to detect a difference of 13.5% at Week 52 between the etrasimod treatment group (23.5%) and the placebo treatment group (10.0%). With this sample size, there was 96% power to detect a difference of 12.5% in the other primary endpoint of clinical remission at Week 12, assuming a placebo rate at 6.0%. Since the two primary endpoints were expected to be at least moderately positively correlated, the actual overall power to reject both of their null hypotheses was likely >90%. The EAG is satisfied that the sample size calculations were appropriate.
Were all changes in the conduct of the trial or planned analysis made prior to analysis?	Yes	Changes in the conduct of the trial are listed in the CSR for each of the ELEVATE UC trials (Table 2).

Item	EAG assessment	Statistical approach with EAG comments
Were all primary and secondary efficacy outcomes pre-defined and analysed appropriately?	Yes	The primary and secondary efficacy endpoints are listed in the CSR for the primary data analysis of the ELEVATE UC trials (CSR, Table 1). Definitions and analysis approaches for these endpoints were pre-specified in the TSAPs for each of the ELEVATE UC trials (Section 16). The ELEVATE UC trials used a gatekeeping procedure to account for multiple testing of hypotheses. The procedure was pre-specified in the TSAPs (Figure 2). See text in Section 3.2.4 of this EAG report for further discussion of the analysis approach for the primary and secondary efficacy endpoints
Was the analysis approach for PROs appropriate and pre-specified?	Yes	All PROs in the ELEVATE UC trials were listed as supportive efficacy outcomes (TSAP, Section 17). The EAG considers that the analysis approach for the PROs was prespecified and appropriate.
Was the analysis approach for AEs appropriate and pre-specified?	Yes	Safety data presented in the CS for the ELEVATE UC trials included a summary of TEAEs, SAEs, AEs leading to treatment discontinuation, or interruption and AEs of special interest (CS, Section B.3.10). Safety analyses were descriptive only and were pre-specified in the TSAP for each of the ELEVATE UC trials (Section 17).
Was a suitable approach employed for handling missing data?	Yes	The company's approach to handling missing data is outlined in the TSAP for each of the ELEVATE UC trials (Section 16.1.2). The EAG is satisfied that the approach described was appropriate.
Were all subgroup and sensitivity analyses pre-specified?	Yes	Primary and key secondary efficacy outcomes, including clinical remission, symptomatic remission, endoscopic improvement-histologic remission, clinical response, at week 12 and week 52 were analysed according to the key pre-specified subgroups in each of the ELEVATE UC studies: •Naïve to biologic or JAK inhibitor therapy at study entry (yes or no) •Baseline corticosteroid use (yes or no) •Baseline disease activity (MMS: 4 to 6 or 7 to 9) For ELEVATE UC 52, subgroup analyses on sustained clinical remission and steroid-free clinical remission were also conducted. The EAG is satisfied that the subgroup analyses presented in the CS were prespecified in the TSAP for each of the ELEVATE UC trials (Section 8.5)

AE=adverse event; CSR=clinical study report; JAK=Janus kinase; MMS=modified Mayo score; PEAS=primary efficacy analysis set; PROs=patient-reported outcomes; SAE=serious adverse event; TEAE=treatment-emergent adverse event; TSAP=trial statistical analysis plan
Source: CS, CSR, TSAP

6.2 Appendix 2: Company and EAG quality assessment of trials included in the company NMAs

Table 20 Company and EAG quality assessment of trials included in the company NMAs

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
ELEVATE UC 12[13]	Yes, central randomisation using IWRS	Yes, central randomisation using IWRS	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, treatment discontinuation was approximately similar in both groups (ETR: 10.5%, PBO 11.2%)	No, outcomes were reported as per the protocol	No, full analysis set (FAS)
EAG comment			Yes (except for prior treatment with 5-ASA)				The company analysed the results from the primary efficacy analysis set. This was appropriate
ELEVATE UC 52[13]	Yes, central randomisation using IWRS	Yes, central randomisation using IWRS	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, treatment discontinuation was not similar in both groups (ETR: 44.3%, PBO: 68.05%)	No, outcomes were reported as per the protocol	No, full analysis set (FAS)
EAG comment			Yes (except for duration of UC, which is longer in the ETR than PBO arm {7.5 years vs 5.9 years)				The company analysed the results from the primary efficacy analysis set. This was appropriate
OASIS[15]	Yes, randomisation was performed	Yes, study drug were supplied as capsules with the	Yes, baseline characteristics were balanced between	Yes, double blind	No, treatment discontinuation was approximately	No, outcomes were reported as per the	Yes, ITT population

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
	centrally with a block size of 6	same appearance	treatment arms		similar in all groups (ETR 1mg: 9.6%, ETR 2mg: 8%, PBO: 11.11%)	protocol	
EAG comment		Yes (randomisation codes were generated by a statistician not directly involved with the study)	Yes (except duration of UC which is longer in the PBO arm than the ETR arm [8.6 years vs 6.2 years])				
TRUE NORTH[40]	Yes, IVRS/IWRS	Yes, patients were assigned to treatment/randomised using the IVRS/IWRS	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, drop-out with the PBO arm having twice as many drop-outs as OZA in the induction (11% vs 6%) and maintenance (45% vs 20%) period	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment						Yes (pre-specified "other efficacy endpoints" including change in Mayo score from baseline to Week 10 were not reported)	
U-ACHIEVE[43,49]	Yes, IWRS; block randomisation schedules (block size of 3)	Yes, IWRS	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, PBO had a twice higher dropout rate (12%) than UPA (4%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG						Yes (pre-specified	

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
comment						additional outcomes including PROs were not reported)	
U-ACCOMPLISH[49]	Yes, IWRS; block randomisation schedules (block size of 3)	Yes, IWRS	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, PBO had a twice higher dropout rate (65%) than UPA 15mg (33%) and UPA 30mg (21%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment						Yes (pre-specified additional outcomes including PROs were not reported)	
SELECTION[32]	Yes, central randomisation using IWRS	Yes, IWRS	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, higher discontinuation rates in the PBO (6.5%) compared to FIL 100mg (6%) and FIL 200mg (3%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment					Yes (discontinuation rates appear low in all treatment arms)		Partly (the trial definition for FAS was consistent with an ITT population for the induction phase but not the maintenance phase)
OCTAVE Induction 1[41]	Yes, central randomisation using TRS	Yes, central randomisation	Yes, baseline characteristics were balanced between	Yes, double blind	No, slightly lower proportion of patients	No, outcomes were reported as per the protocol	Yes, ITT population

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
			treatment arms		discontinued PBO (3%) than TOF 10mg (7%)		
EAG comment							
OCTAVE Induction 2[41]	Yes, central randomisation using TRS	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, slightly higher proportion of patients discontinued PBO (13%) than TOF 10mg (8%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment			Yes (except for a higher percentage of males in the TOF arm compared with PBO [60.4% vs 49.1%])				
OCTAVE Sustain[41]	Yes, central randomisation using TRS	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, higher discontinuation rates in PBO (73%) compared to TOF 5mg (44%) and TOF 10mg (36%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment			Yes (except for never smoker status which was greater in the TOF 5mg arm than in the PBO arm [71.7% vs 57.1%])	Unclear (no mention of who was blinded to treatment)			
UNIFI[44]	Yes,	Yes, permuted	Yes, baseline	Yes, double blind	No, higher drop-out	No, outcomes were	Yes, ITT population

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
	randomisation was performed with the use of permuted blocks	blocks	characteristics were balanced between treatment arms		was observed in PBO than the intervention (UST 6mg/kg 4%, UST 130mg 4%, PBO 5%)	reported as per the protocol	
EAG comment				Unclear (no mention of who was blinded to treatment)			
GEMINI 1[45]	Yes, randomisation was performed centrally with the use of computer-generated randomisation schedules	Yes, NR	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, higher proportion of PBO discontinued treatment compared to VED in ind. phase (9% vs 2%) and maintenance phase (PBO 62%, VED Q8W 37%, VED Q4W 33%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment							
VISIBLE 1[47]	Yes, IWRS	Unclear, No information	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, treatment discontinuation was not similar across the group PBO 64.2%, VED SC 29.2%, VED IV 27.7%	No, outcomes were reported as per the protocol	No, full analysis set (FAS)
EAG comment		Yes (IWRS)					Yes (the trial definition for FAS

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
							was consistent with an ITT population)
VARSITY[31]	Yes, IVRS/IWRS	Yes, investigational pharmacist or designee will mask the IV bags after preparation in order to maintain the study blind	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, treatment discontinuation was not similar across the group ADA: 43.7% VED: 29.8%	No, outcomes were reported as per the protocol	No, full analysis set (FAS)
EAG comment		Yes (IWRS)					Yes (the trial definition for FAS was consistent with an ITT population)
Motoya 2019[46]	Yes, randomisation schedules were generated by sponsor-designated personnel (dynamic randomisation was performed with the previous TNFα antagonist use)	Yes, NR	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, higher proportion of drop-outs in the PBO arm compared to VED in the induction (5% vs 5%) and maintenance (57% vs 27%) period	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment					Partly (a higher proportion of patients in the placebo arm discontinued treatment during the		

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
					maintenance period than in the vedolizumab arm)		
ULTRA 1[27]	Yes, randomisation done by central randomisation scheme generated by the study sponsor	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, drop-out between treatment group are almost similar (PBO 7%, ADA 160/80/40mg 7%, ADA 80/40mg 9%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment							
ULTRA 2[29]	Yes, randomisation was performed centrally	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, unexpected imbalance in the dropout between two treatment group (PBO 48%, ADA 37%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment					No, discontinuations appear similar between groups		
Suzuki 2014[30]	Yes, randomised based on centrally designed randomisation table	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, unexpected imbalance in the dropout between two treatment group (PBO 23%, ADA 33%)	No, outcomes were reported as per the protocol	No, full analysis set (FAS)
EAG comment		Unclear (the EAG has no information on how	Yes (except sex)	Unclear (no mention of who was blinded to		Unclear (unable to access protocol)	Yes (the trial definition for FAS was consistent with

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
		randomisation table was accessed)		treatment)			an ITT population)
HIBISCUS I[28]	Yes, permuted block randomisation using IVRS/IWRS	Yes, permuted blocks	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, unexpected imbalance in the dropout at induction and maintenance phases	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment					Partly (treatment discontinuation rate was high [>75%] in all treatment arms but was highest in the placebo arm)		Yes (modified ITT population) defined as all randomly assigned patients who received at least one dose of study drug
HIBISCUS I[28]	Yes, permuted block randomisation using IVRS/IWRS	Yes, permuted blocks	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, unexpected imbalance in the dropout at induction and maintenance phases	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment					Partly (treatment discontinuation rate was high [>75%] in all treatment arms but was highest in the placebo arm)		Yes (modified ITT population)
PURSUIT-SC[34]	Yes, central randomisation using IVRS	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, 2.3% of patients withdrew from each study arm	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment				Unclear (no mention of who was			

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
				blinded to treatment)			
PURSUIT-M[35]	Yes, ARP	Yes, ARP	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, slightly higher in GOL 100mg (11%) and PBO (15%) than GOL 50mg (10%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment				Unclear (no mention of who was blinded to treatment)	No (discontinuation rates were similar between treatment arms)		
PURSUIT-J[33]	Yes, a computer-generated randomisation (PBR)	Yes, computer-generated randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	No, PBO had a twice higher dropout rate (39%) than GOL (16%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment				Unclear (no mention of who was blinded to treatment)			
NCT01551290[38]	Yes, NR	Unclear, no information	Unclear, no information	Yes, double blind	Unclear, no information	Unclear, no information	Yes, ITT population
EAG comment	Unclear (randomisation method not given)	Unclear (randomisation method not given)		Unclear (no mention of who was blinded to treatment)			Partly (ITT but no mention of methods for missing data handling)
Jiang 2015[36]	Yes, central randomisation	Yes, central randomisation with a dynamic treatment allocation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, more than twice as many patients in the PBO group as in the other 2 groups	No, outcomes were reported as per the protocol	Yes, ITT population

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
					prematurely discontinued the infusions		
EAG comment				Unclear (no mention of who was blinded to treatment)			Partly (ITT but no mention of methods for missing data handling)
Kobayashi 2016[37]	Yes, randomisation was performed centrally with the use of CGRS	Yes, central randomisation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Unclear, no information	No, outcomes were reported as per the protocol	No, full analysis set (FAS)
EAG comment				Unclear (no mention of who was blinded to treatment)			Partly (FAS but no definition provided and no mention of methods for missing data handling)
ACT-1[39]	Yes, central randomisation	Yes, central randomisation with a dynamic treatment allocation	Yes, baseline characteristics were balanced between treatment arms	Yes, double blind	Yes, higher proportion of PBO (47%) discontinued treatment compared to INF (INF 5mg 32% and INF 10mg 32%)	No, outcomes were reported as per the protocol	Yes, ITT population
EAG comment				Unclear (no mention of who was blinded to treatment)			Partly (ITT but no mention of methods for missing data handling)
ACT-2[39]	Yes, central randomisation	Yes, central randomisation with a dynamic	Yes, baseline characteristics were balanced between	Yes, double blind	Yes, higher proportion of PBO (40%) discontinued	No, outcomes were reported as per the protocol	Yes, ITT population

Study[a]	Was the randomisation method adequate?	Was allocation adequately concealed?	Were baseline characteristics similar between treatment arms?	Were participants and investigators blind to exposure & comparison?	Were discontinuations dissimilar between groups?	Were any outcomes measured but not reported?	Did the analysis include an ITT analysis? If so, was this appropriate and were appropriate methods used to account for missing data?
		treatment allocation	treatment arms		treatment compared to INF (INF 5mg 20% and INF 10mg 20%)		
EAG comment				Unclear (no mention of who was blinded to treatment)			Partly (ITT but no mention of methods for handling missing data)

[a] An EAG comment is provided where either the EAG assessment differs from the company assessment or where extra information was required
ADA=adalimumab; AE=adverse event; ARP=adaptive randomisation procedure; CGRS=computer generated randomisation schedule; discontinuation=discontinuation; ETR=etrasimod; FIL=filgotinib; GOL=golimumab; INF=infliximab; ITT=intention to treat; IVRS=interactive voice response system; IWRS=interactive web response system; OZA=ozanimod; PBO=placebo; PBR=permuted block randomisation; PRO=patient reported outcome; TOF=tofacitinib; TRS=tele randomisation system; UPA=upadacitinib; UST=ustekinumab; VED=vedolizumab
Source: CS, Appendix F, Table 35 with EAG comment

6.3 Appendix 3: EAG summary and critique of the company's methodological approach for NMAs

Table 21 EAG summary and critique of the company's methodological approach for NMAs

Item	EAG assessment	EAG comment
Were appropriate outcomes synthesised in NMAs?	Yes	The company conducted NMAs for the following outcomes: • clinical response • clinical remission • serious infections For the NMAs of clinical response and clinical remission, the company preferentially extracted data for centrally read endoscopic outcomes; if these were not available, the company extracted data for locally read endoscopic outcomes. Clinical response and clinical remission could be defined using either the full or modified Mayo score. Clinical advice to the EAG is that including trials in the NMAs reporting either full or adapted Mayo Score is not of concern.
Was an appropriate model used to conduct the NMAs?	Yes	The NMAs were conducted under a Bayesian framework using MCMC sampling. All analyses were implemented in WinBUGS version 1.4.3 statistical software with non-informative priors. An initial burn-in of at least 20,000 simulations was used, and convergence was confirmed through visual inspection of the Brook-Gelman-Rubin diagnostic and history plots. This was followed by 50,000 simulations on 3 chains, thinned by a factor of 10, to estimate the sampled parameters. Convergence was assessed by visual inspection of the history, kernel density and autocorrelation plots as well as the Brooks Gelman-Rubin diagnostic plot. For clinical response and clinical remission, the company synthesised data using a multinomial model with probit link. It was assumed that the numbers of patients who were reported in the trial publications as being in clinical response also included those patients who were in clinical remission. Trials could be included in the analysis if they provided data for only one of these outcomes (i.e., clinical response, or clinical remission). The EAG notes that the company provided treatment effects on the probit scale, which are difficult to interpret. Using a logit link would have overcome this problem. However, the EAG notes that the use of the probit link was pre-specified in the NMA SAP (p17). Furthermore, in addition to the treatment effects expressed on the probit scale, the company also provides risk ratios, and SUCRA values, which are comparatively easy to interpret. For the proportion of patients experiencing serious infections, the company synthesised data using a binomial model with logit link.
Were the methods of selection between fixed-effects and random-effects models appropriate?	Yes	The company selected whether to use fixed-effects or random-effects based on a combination of statistical and clinical considerations. The company considered whether each network of evidence consisted primarily of single-trial connections, as in this scenario, fixed-effects models may be more suitable than random-effects models, due to a lack of information available to estimate between trial heterogeneity. The company also examined DIC and residual deviance values. The EAG considers that the company's methods to select between fixed-effects and random-effects models were appropriate.
Were any additional analyses pre-specified and conducted appropriately?	Yes	Fixed-effects and random-effects models were fitted and run using both an unadjusted relative effects analysis, as well as incorporating a meta-regression adjustment to account for variation in baseline risk. Both analyses were pre-specified in the NMA SAP (p18). However, the analyses including an adjustment to account for cross-trial variation in

		baseline risk failed to converge, and results from these analyses are not presented in the CS.
Were appropriate methods used to assess inconsistency?	Partial	A UME model was run to assess and identify any sources of inconsistency among the analyses. Three chains were run for the UME model. For each analysis, the posterior median of total residual deviance and the DIC were recorded and a deviance contribution plot comparing the NMA model with the UME model was produced. The company considered differences of more than 5 (in either the DIC or residual deviance values) between models to be potentially meaningful differences that should be investigated further by examining the deviance contribution plot. The EAG considers that a comparison of the estimated treatment effects from the UME model with the estimated treatment effects from the NMA model would have been a useful addition to the assessment of inconsistency.

DIC=deviance information criterion; MCMC=Markov Chain Monte Carlo; NMA=network meta-analysis; SAP=statistical analysis plan; UME=unrelated mean effects; SUCRA=surface under cumulative ranking curve

6.4 Appendix 4: EAG revisions to the company model

This appendix contains details of the changes that the EAG made to the company model.

Table 22 EAG revisions to the cost comparison model

EAG revisions	Implementation instructions
Corrections to first year maintenance doses	**Insert sheet "EAG Revisions"** Set value in cell C3 = "C1" Set value in cell D3 = 1 In Sheet 'Cost_Drug' Set value in cell O14 =(WeeksInYear-IF('EAG Revisions'!D3=1,4,2))/2 Set value in cell O21 =WeeksInYear-IF('EAG Revisions'!D3=1,6,2) Set value in cell P21 =N21*IF('EAG Revisions'!D3=1,ROUNDUP(O21/4,0),O21/4) Set value in cell R21 =IF('EAG Revisions'!D3=1,N21,O21)*WeeksInYear/4 Set value in cell O40 =(WeeksInYear-IF('EAG Revisions'!D$3=1,20,8))/12 Set value in cell S39 =J39*3+J40+J40*IF('EAG Revisions'!D3=1,ROUNDUP(O40,0),O40) Set value in cell S43 =2*K41*L41+SUM(IF('EAG Revisions'!D3=1,0,M43),P43)*L43
Correction to IV administration cost	In Sheet 'EAG Revisions' Set value in cell C4 = "C2" Set value in cell D4 = 1 In Sheet 'Cost_Drug' Set value in cell E51 =IF('EAG Revisions'!D4=1,286.71,"") Set value in cell H55 =F55*IF('EAG Revisions'!D3,D51, F51) Copy formula in cell H55 Paste to range H55:I60

Single Technology Appraisal

Etrasimod for treating moderately to severely active ulcerative colitis [ID5091]

EAG report – factual accuracy check and confidential information check

"Data owners may be asked to check that confidential information is correctly marked in documents created by others in the evaluation before release." (Section 5.4.9, NICE health technology evaluations: the manual).

You are asked to check the EAG report to ensure there are no factual inaccuracies or errors in the marking of confidential information contained within it. The document should act as a method of detailing any inaccuracies found and how they should be corrected.

If you do identify any factual inaccuracies or errors in the marking of confidential information, you must inform NICE by **5pm on Tuesday 7 November 2023** using the below comments table.

All factual errors will be highlighted in a report and presented to the appraisal committee and will subsequently be published on the NICE website with the committee papers.

Please underline all confidential information, and information that is submitted as [redacted] should be highlighted in turquoise and all information submitted as '[redacted]' in pink.

Issue 1 Minor typo - Section 2.3.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 of the EAG report, the title of sub-section 2.3.1 should be corrected as it currently states, “Number of patients eligible for treatment with upadacitinib”.	The title of this sub-section should change to “Number of patients eligible for treatment with etrasimod”.	The name of the wrong active substance, which is not under review in this current appraisal, has been given.	Thank you for the comment. We have amended the report as suggested

Issue 2 Minor typo - Table 2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 14 of the EAG report, Table 2 under column Year 1(2023), the number recorded for the “proportion of adult UC patients who have moderately to severely active UC” is 127,030, which is a minor typo.	In Table 2 under column Year 1(2023), the number recorded for the “proportion of adult UC patients who have moderately to severely active UC” should be 127,031.	In the submitted BIM the company’s proposed figure (127,031) has been provided based on the NICE TA828.	Thank you for the comment. We have amended the report as suggested

Issue 3 Conclusions - Section 2.3.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
On page 14, in the critique of the company's overview of the current service provision (section 2.3.1), the EAG suggested that the proportion of patients with moderate to severe disease was overestimated concerning the patients in NHS clinical practice. The EAG did not provide an alternative estimate.	The conclusion should be deleted without a clear value for the model or direction for the analysis.	The submission estimate was taken from the "NICE assumptions of current practice" in the material developed with the publication of the guidance and referring to the resource impact, published in October 2022.	This is not a factual inaccuracy. The statement in the EAG report is based on clinical advice to the EAG. No change is required

Issue 4 Minor typo - Table 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 15, Table 3 under EAG comment on the outcomes, the EAG states that "EIHR was not captured in the ELEVATE clinical trials."	The EAG comment should be revisited to indicate that "Endoscopic remission combined with histological improvement was not captured in the ELEVATE clinical trials".	The company has submitted evidence for endoscopic improvement with histological remission (EIHR) as outlined in the submission document.	Thank you for the comment. We have updated the report as suggested

		The submission states that "endoscopic remission combined with histological improvement was not an outcome captured in the ELEVATE clinical trials."	

Issue 5 Minor typo - Table 3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 16, Table 3 under the column “Final scope issued by NICE” and in the row outlining the outcomes, EHIR has been included in the list of outcomes. However, this outcome was not included in the NICE’s final scope.	Replace EHIR with “endoscopic remission combined with histological improvement”.	The final scope issued by NICE stated "endoscopic remission combined with histological improvement", therefore, the EIHR should be removed.	Thank you for the comment. We have updated the report as suggested

Issue 6 Amendment - Section 2.1.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 19, Section 2.1.1: The EAG states that *"the company has provided results of subgroup analyses of trial outcomes according to prior biologic or JAKi therapy exposure (CS, Appendix G) i.e., biologic-naïve or biologic-experienced."* However, in the submission additional subgroups have been included: • Baseline corticosteroid use (yes or no) • Baseline disease activity (MMS: 4 to 6 or 7 to 9) For ELEVATE UC 52, subgroup analyses were conducted on: • sustained clinical remission	To add to the text, that additional subgroup analysis of the trial outcomes was conducted on the following pre-specified groups: • Naïve to biologic or JAK inhibitor therapy at study entry (yes or no) • Baseline corticosteroid use (yes or no) • Baseline disease activity (MMS: 4 to 6 or 7 to 9) For ELEVATE UC 52, subgroup analyses on sustained clinical remission and steroid-free clinical remission were also conducted	In the submission, in section B.3.7.1, it is outlined that: "Primary and key secondary efficacy outcomes, including clinical remission, symptomatic remission, EIHR, clinical response, at week 12 and week 52 were analysed according to the following key pre-specified subgroups in each study: • Naïve to biologic or JAK inhibitor therapy at study entry (yes or no) • Baseline corticosteroid use (yes or no) • Baseline disease activity (MMS: 4 to 6 or 7 to 9) For ELEVATE UC 52, subgroup analyses on	Thank you for the comment. We have updated the report: However, the company has provided results of subgroup analyses of trial outcomes according to prior biologic or JAKi therapy (CS, Table 12). EAG report text now reads (Section 3.5, p27): "Additional subgroup analyses (CS, Appendix G) of trial outcomes were conducted for the biologic-naïve and biologic experienced groups based on baseline corticosteroid use (yes/no) and baseline disease activity

• steroid-free clinical remission		sustained clinical remission and steroid-free clinical remission were also conducted."	(MMS 4 to 6 or MMS 7 to 9)." We have also corrected the Section numbering to be 2.4.7

Issue 7 Minor typo - Section 3.2.2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22, the EAG report states "The ELEVATE UC 12 trial treatment period was 12 weeks and the primary outcome was the proportion of patients achieving clinical remission at 12 weeks. Patients were recruited to the trial from 409 treatment centres across 39 countries." According to the company's submission which is based on the trials CSR, patients were recruited to the trial from 407 treatment centres".	To change the number "409 treatment centres" to "407 treatment centres".	According to the submission (Table 5) which is based on the trials CSR, patients were recruited to the trial from 407 treatment centres".	Thank you for the comment. We have amended the report as suggested

Issue 8 Clarification - section 3.2.2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 22, the EAG report states that “At the 12-week assessment, patients whose disease activity had shown no improvement, or had worsened compared with baseline, could discontinue treatment and enrol in the ELEVATE UC OLE study.”	It should be added that “patients whose disease activity had shown no improvement or had worsened during the 40-Week Treatment Period, or who completed all study procedures at Week 52, had the option to enter OLE Study”	The CSR of ELEVATE UC 52 study states that: “Subjects who experienced disease worsening following the completion of the Week 12 Visit, or who experienced disease worsening during the 40-Week Treatment Period, or who completed all study procedures at Week 52, had the option to enter OLE Study APD334-303 provided they met eligibility criteria."	Thank you for the comment. We have updated the report as suggested

Issue 9 Addition - Section 3.3

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23, under section 3.3, it is stated that “In the ELEVATE UC trials, 44 patients had an MMS of 4”. However, according to the submission and the CSRs	To add: “44 patients had an MMS of 4 to 6”.	According to the submission and the CSRs, in the ELEVATE UC trials, 44 patients had an MMS of 4 to 6.	The number ‘44’ is given in Table 6 of the CS (add together the numbers of patients with a MMS of 4 across all columns.

that should be MMS of 4 to 6.			These data also appear in the ELEVATE trial publication. No change required

Issue 10 Minor Typo - Table 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 23, Table 6: the number of patients in the etrasimod and placebo groups for both trials are not in line with those provided in the submission. Please note that the submission is predominately based on the published ELEVATE studies in the Lancet rather than the CSR.	Under ELEVATE UC 12: Etrasimod, N=238 Placebo, N=116 Under ELEVATE UC 52: Etrasimod, N=274 Placebo, N=135	In the submission and in Table 6, the proposed numbers are being outlined.	Thank you for the comment. We have amended the report as suggested

Issue 11 Minor typo - Table 6

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 24, Table 6: Under the ELEVATE UC 52 columns, the equal sign (=) has been used rather than the less sign (<).	To change the equal sign (=) the less sign (<) under the ELEVATE UC 52 columns for the rows of: • Endoscopic improvement Difference vs placebo • Symptomatic remission Difference vs placebo • Endoscopic improvement-histological remission Difference vs placebo • Clinical response Difference vs placebo	In Figure 4 of the submission, the less sign is used to showcase statistical significance when p<0.0001.	Thank you for the comment. We have amended the report as suggested

Issue 12 Minor typo - Table 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25, Table 7 under Etrasimod column, clinical remission is recorded as 43.4% instead of 32.1%.	To change the clinical remission for etrasimod to 32.1%	Under section B.3.6.2.1 of the submission, it is stated that "In ELEVATE UC 52, 32.1% of patients receiving etrasimod achieved clinical remission at Week 52, compared with 6.7% in the	Thank you for the comment. We have amended the report as suggested

		placebo group (difference, 25.4%; p < 0.001).” Similarly, this is shown in Figure 4.	

Issue 13 Minor typo - Table 7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 25, Table 7: the equal sign (=) has been used rather than the less sign (<) when p=0.0001	To change the equal sign (=) the less sign (<) under the rows of:	In Figure 4 of submission the less sign is used to showcase statistical significance when p<0.0001.	Thank you for the comment. We have amended the report as suggested

	• Endoscopic improvement Difference vs placebo • Symptomatic remission Difference vs placebo • Endoscopic improvement-histological remission Difference vs placebo • Clinical response Difference vs placebo • Sustained clinical remission Difference vs placebo • Corticosteroid-free clinical remission Difference vs placebo		

Issue 14 Minor typo - Section 3.7.2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, under "Characteristics of trials included in the induction phase NMAs", the EAG	To remove duplication of the sentence "enrolled biologic-naïve patients only".	Duplication of a sentence "enrolled biologic-naïve patients only".	Thank you for the comment. We have updated the report as suggested

report states that" Eleven[27,29,30,34,36-39] trials enrolled biologic-naïve patients only enrolled biologic-naïve patients only,.."			

Issue 15 Minor typo – Section 3.7.2

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 32, under "Characteristics of trials included in the induction phase NMAs", the EAG report states that "however, disease duration (mean 4.4[36] to 10.2[32] years),…"	To change the text to say "mean 4.4[36] to 10.9 [32] years"	According to table 36 of submission based on the Sandborn 2012 reference the mean years were 4.4 to 10.9.	Thank you for the comment. We have amended the report as suggested

Issue 16 Clarification - Section 3.7.7

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 42, in the first bullet point "patients in the placebo arms had received and responded to different induction treatments	In the first bullet point "patients in the placebo arms had received and responded to different induction treatments (including various active treatments and placebo) with	The text should clarify the context of the analysis.	Thank you for the comment. We have added the suggested text to the bullet point:

(including various active treatments and placebo) with potentially different persistent effects after treatment has ended" should be noted that this is relevant only for the maintenance phase analyses.	potentially different persistent effects after treatment has ended" should be noted that this is relevant only for the maintenance phase analyses.		patients in the placebo arms had received and responded to different induction treatments (including various active treatments and placebo) with potentially different persistent effects after treatment has ended (relevant to analyses of maintenance phases)

Issue 17 Clarification - Section 4.6.1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49, the last sentence of sub-section 4.6.1: "Previous NICE appraisals[4-10] of comparator drugs have all included cost utility rather than cost comparison analyses." Please note that guidance on mirikizumab was just	The sentence should be revised to reflect the latest mirikizumab assessment which follows the cost-comparison approach.	The guidance on mirikizumab was recently published and used a cost-comparison approach.	Thanks for this information. The EAG submission deadline was the 26th October 2023 and we missed the publication of the mirikizumab guidance (25th October 2023). Text

published and used a cost-comparison approach.			has been amended as follows: "Previous NICE appraisals[4-10] of comparator drugs have all included cost utility rather than cost comparison analyses, except for mirikizumab which used a cost comparison approach."

Issue 18 Minor error - cost comparison model

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 49 In the critique of the cost comparison model, the EAG identified several minor errors in the *"the number of infliximab, adalimumab, golimumab, ustekinumab and vedolizumab maintenance*	A correction is necessary in the number of doses, and consequently, the total cost for the first year for infliximab, golimumab and ustekinumab.	The EAG corrections for infliximab, golimumab and ustekinumab underestimated the number of dosages applied in the first year.	Thank you for highlighting this error. The results in Table 18 of the EAR and model revision instructions in Table 22 have been updated.

doses in the first year were slightly overestimated" The EAG corrections for infliximab, golimumab and ustekinumab underestimated the number of dosages applied in the first year. For infliximab, the EAG estimated 3 + 4 doses in a year. The dosing regimen for infliximab is "*5 mg/kg IV at weeks 0, 2, and 6, and Q8W thereafter",* during the maintenance phase in the first year, patients would receive infliximab at week 14, 22, 30, 38 and 46; amounting to 3 + 5 administrations. For golimumab, the EAG estimated 2 + 11 doses (rounded down from 11.5). The dosing regimen for golimumab is "*200 mg at week 0, 100 mg at week 2, and 50 mg Q4W thereafter",* during the maintenance phase in the first year,			

patients would receive golimumab at week 6, 10, 14, 18, 22, 26, 30, 34, 38, 42, 46 and 50; amounting to 2 + 12 administrations. For ustekinumab, the EAG estimated 2 + 2 doses (rounded down from 2.67). The dosing regimen for ustekinumab is "*390 mg, then (by subcutaneous injection) 90 mg after 8 weeks, then (by subcutaneous injection) 90 mg every 12 weeks",* during the maintenance phase in the first year, patients would receive ustekinumab at week 20, 32 and 44; amounting to 2 + 3 administrations.			

Issue 19 Typo in Appendix 1

Description of problem	Description of proposed amendment	Justification for amendment	EAG response
Page 58: Appendix 1, under "statistical approach with EAG comments and under row "Was an appropriate sample size calculation pre-specified?", it is stated that "A trial sample size calculation was pre-specified in the TSAP for ELEVATE UC 52 (p23). For the primary endpoint analysis of clinical remission, the company estimated that a sample size of 420 patients (220 etrasimod, 140 placebo)". However, according to the ELEVATE UC 52 SAP, "a sample size of 420 patients (280 etrasimod, 140 placebo).	To revise the sentence, to indicate (280 etrasimod, 140 placebo).	According to the ELEVATE UC 52 SAP, "a sample size of 420 patients (280 etrasimod, 140 placebo).	Thank you for the comment. We have amended the report as suggested

Issue 20 Issue 21 Confidential marking

Location of incorrect marking	Description of incorrect marking	Amended marking	EAG response
Pages 37-39, the text should be redacted as results on the direction, magnitude and significance of effects from the NMAs were either not presented or were redacted in the submission.	The text should be redacted as results on the direction, magnitude and significance of effects from the NMAs were either not presented or were redacted in the submission.	**Etrasimod versus S1P** [redacted] **Etrasimod versus JAKi** [redacted]	Thank you for pointing this out. We have amended the report accordingly. In addition, related EAG report text (serious infections) has also been marked confidential

		– [redacted] – [redacted] – **Etrasimod versus TNFi** [redacted] **Etrasimod versus other biologic agents** [redacted]	

		[redacted]	
Page 42, the full text under "Biologic-naïve patients: efficacy" and "Biologic-experienced patients: efficacy" should be redacted as information on the direction, magnitude and significance of effects has either not been included in the	The text should be redacted as results on the direction, magnitude and significance of effects from the NMAs were either not presented or were redacted in the submission.	• **Biologic-naïve patients: efficacy** [redacted] • **Biologic-experienced patients: efficacy** [redacted]	•

submission or has been redacted.		[redacted]	