BMJ Open

Effectiveness of etrasimod on disease activity and patient-reported outcomes in ulcerative colitis—EFFECT-UC: a non-interventional, multinational, prospective cohort study protocol

Gordon W Moran,[1] Shellie J Radford,[1] Alissa Walsh,[2] Robert Battat,[3] Michael McLean,[4] Maria Kudela,[5] Elke Binder,[6] Nataliia Kulchytska,[7] Burak Sahin,[4] Ulf Helwig,[8] Peter M Irving [9]

To cite: Moran GW, Radford SJ, Walsh A, *et al*. Effectiveness of etrasimod on disease activity and patient-reported outcomes in ulcerative colitis—EFFECT-UC: a non-interventional, multinational, prospective cohort study protocol. *BMJ Open* 2025;**15**:e106141. doi:10.1136/bmjopen-2025-106141

► Prepublication history and additional supplemental material for this paper are available online. To view these files, please visit the journal online (https://doi.org/10.1136/bmjopen-2025-106141).

Received 05 June 2025
Accepted 19 November 2025

For numbered affiliations see end of article.

Correspondence to
Dr Burak Sahin;
burak.sahin@pfizer.com

ABSTRACT

Introduction Etrasimod is an oral, once-daily, selective sphingosine 1-phosphate$_{1,4,5}$ receptor modulator for the treatment of moderately to severely active ulcerative colitis (UC). While etrasimod demonstrated efficacy in randomised controlled trials, understanding its effectiveness in an observational setting is crucial.

Methods and analysis EFFECT-UC is a prospective, multinational, non-interventional study to evaluate the real-world effectiveness of etrasimod in adults with moderately to severely active UC. The study consists of a 52-week treatment period and a 28-day safety follow-up period and aims to enrol ~300 patients per cohort. Eligible patients (18–64 years) are advanced therapy naïve or experienced and are initiating etrasimod in a real-world clinical setting. Treatment will be guided independently by the clinician's judgement. Patient-reported outcomes will be collected electronically throughout the study and daily for the first 2 weeks. Exploratory data, including faecal calprotectin, endoscopy and intestinal ultrasound, will be collected at predefined visits or during standard care. Primary endpoints are symptomatic remission at week 12 and week 52. Secondary endpoints include patient-reported outcome 2 (combined rectal bleeding and stool frequency subscores) response at week 12 and week 52 and corticosteroid-free symptomatic remission at week 52.

Ethics and dissemination Ethics approval was obtained for all sites. Recruitment is underway for cohort 1, comprising patients from the UK, Germany and Canada. Interim results for this cohort are expected in 2026 and final results in 2028; these will be submitted for publication in peer-reviewed journals and presented at appropriate congresses.

Trial registration number NCT06294925.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ EFFECT-UC is a prospective, multinational, non-interventional study that will assess the real-world effectiveness of etrasimod in different subpopulations of patients with moderately to severely active ulcerative colitis.
⇒ Outcomes not previously assessed in etrasimod clinical trials will be examined, including within the first 2 weeks of treatment.
⇒ Use of a single master protocol will enable the enrolment of patients across different countries, ensuring consistency in the study population and a larger overall sample size.
⇒ The study is subject to biases inherent in real-world data collection, including selection bias and variations in standard of care practices across countries, and the reliance on routine clinical data may lead to inconsistencies in the timing and type of assessments conducted.
⇒ However, the study protocol incorporates flexibility in data collection windows and emphasises the importance of consistent electronic patient-reported outcome collection across all sites and countries to allow consistency, even if clinical practice differs.

INTRODUCTION

Ulcerative colitis (UC) is a chronic disease with a recurrent, remittent or progressive course characterised by diffuse mucosal inflammation limited to the colon, which may require life-long treatment.[1–3] It involves the rectum in approximately 95% of cases and can extend proximally to involve more or all of the large intestine.[3] The most common symptoms are rectal bleeding, urgency, diarrhoea and abdominal pain, which can cause a life-long burden and reduction of quality of life for patients.[2]

Achieving symptomatic remission and improving the endoscopic appearance of the mucosa are important goals for UC treatment.[4] The advanced-treatment landscape for adults with moderately to severely active UC is rapidly evolving to include therapies that target a range of mechanistic pathways.[5] These therapies include biologics (tumour

necrosis factor inhibitors, antiadhesion molecules and anti-interleukins) and oral small molecules such as Janus kinase inhibitors (JAKis).[5] Despite these available therapies, many patients do not respond to first-line advanced therapy or lose their response during treatment.[6] As such, there remains an unmet need for alternative treatment options.

Etrasimod is an oral, once daily, selective sphingosine 1-phosphate $(S1P)_{1,4,5}$ receptor modulator for the treatment of moderately to severely active UC. The biological effect of etrasimod leads to selective, reversible and partial sequestration of lymphocytes in lymph nodes and a decrease in peripheral lymphocyte count.[7] S1P receptor modulation is therefore an additional mechanism under investigation for the treatment of UC.

The placebo-controlled, 12-week, phase 2 OASIS clinical trial of etrasimod 2 mg once daily showed significant benefit versus placebo.[8] After completing OASIS, patients could enrol in the open-label extension and receive etrasimod for an additional 34–40 weeks.[9] Most patients with clinical response, clinical remission or endoscopic improvement at week 12 maintained that status to the end of treatment, and etrasimod demonstrated a favourable safety profile.[9] Subsequently, the efficacy and safety of etrasimod over placebo as both induction and maintenance therapy were demonstrated in adult patients with moderately to severely active UC in the phase 3 ELEVATE UC 52 and ELEVATE UC 12 trials[10] and separately in a phase 3 study conducted in Asia.[11] Etrasimod has since been approved for the management of moderately to severely active UC in several countries, including the USA (2023), Canada (2024), the European Union (2024) and the UK (2024).[12–15]

Outside of the strictly controlled conditions of a clinical trial, it is also vital to understand the effectiveness of etrasimod in a real-world setting with a more diverse patient population. Such data are not only increasingly recognised by health authorities as necessary to address evidence gaps in decision-making[16 17] but are also important for informing treatment decisions made by clinicians. Therefore, we aimed to assess the real-world effectiveness and safety of etrasimod in patients with moderately to severely active UC.

METHODS AND ANALYSIS

Study design

EFFECT-UC (NCT06294925) is an ongoing, prospective, multinational, non-interventional, real-world study to evaluate the effectiveness of etrasimod 2 mg once daily in patients with moderately to severely active UC. The study consists of a 52-week treatment period followed by a 28-day safety follow-up period (figure 1).

Per protocol V.2.0 (June 2024), patient enrolment will initially focus on recruitment from the UK, Germany and Canada; the inclusion of additional countries may be considered. Treatment decisions will be made at the discretion of the treating clinician according to the local label and guidelines. All assessments, except for electronic patient-reported outcomes (PROs), will be performed as part of standard clinical practice or standard practice guidelines for the patient population and study sites where this non-interventional study is being conducted. Data will be recorded using an electronic case report form. The study will be conducted in different healthcare settings, such as private and public outpatient clinics and hospitals.

The first patient's first visit was on 8 May 2024. As of 9 October 2025, study sites are open and actively recruiting, with 181 patients enrolled across the UK, Germany and Canada.

Patients

Eligible patients can be included in the study if their treating clinician makes a clinical decision to prescribe them etrasimod independent from the decision to enrol the patient in this study. The full study eligibility criteria are presented in box 1. Patients may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioural or administrative reasons. Written informed consent will be obtained from each patient before enrolment into the study.

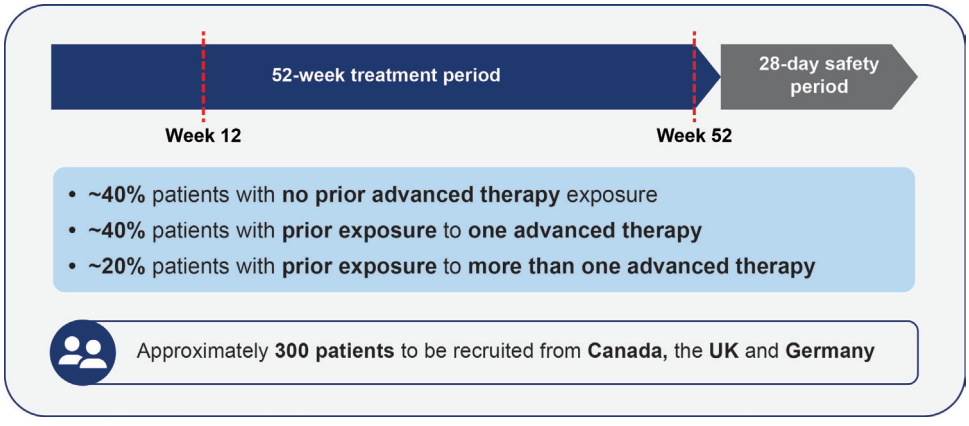

Figure 1 EFFECT-UC study design.

Box 1 Inclusion and exclusion criteria

Inclusion criteria

Patients must meet all the following inclusion criteria to be eligible for inclusion in the study:

1. Male and female patients ≥18 and ≤64 years of age at baseline.
2. Patients with a confirmed diagnosis of UC who are prescribed etrasimod for moderately to severely active UC as per the product label, independently of the decision to enrol in this study.
3. Evidence of a personally signed and dated informed consent document indicating that the patient has been informed of all pertinent aspects of the study.

Exclusion criteria

Patients meeting any of the following criteria will not be included in the study:

1. Presence of clinical findings suggestive of Crohn's disease.
2. Severe extensive colitis evidenced by:
   a. Physician judgement that the patient is likely to require hospitalisation for medical or surgical intervention of any kind for UC (eg, colectomy) within 12 weeks.
   b. Current evidence of acute severe UC, fulminant colitis or toxic megacolon.
3. Patients with a stoma or planned UC surgical intervention requiring hospitalisation.
4. Prior/concomitant therapy:
   a. Any previous exposure to etrasimod, including participation in the etrasimod clinical programme.
   b. Any comedication with one of the following conventional therapies: methotrexate or a thiopurine (azathioprine, mercaptopurine or tioguanine), or with any of the following advanced therapies for UC: biologics (a tumour necrosis factor inhibitor, integrin antagonist or cytokine antagonist); JAKis (filgotinib, tofacitinib or upadacitinib) or with any other S1P receptor modulator.
5. Not owning a digital device with internet connection and/or not willing to complete PROs on this device, or not capable of using the PRO collection tool.
6. Investigator site staff or Pfizer employees directly involved in the conduct of the study, site staff otherwise supervised by the investigator and their respective families.

JAKi, Janus kinase inhibitor; PRO, patient-reported outcome; S1P, sphingosine 1-phosphate; UC, ulcerative colitis.

The aim is to enrol patients into three subgroups according to their prior exposure to advanced therapy. Subgroup 1 (approximately 40% of the sample) will include patients with no prior exposure to advanced therapies and who have had an inadequate response, loss of response or intolerance to conventional therapy. Subgroup 2 (approximately 40% of the sample) will include patients with prior exposure to one advanced therapy, with or without prior conventional therapy. Subgroup 3 (approximately 20% of the sample) will include patients with prior exposure to more than one advanced therapy. Advanced therapies will include all licensed biologics, JAKi therapies and S1P receptor modulators.

Objectives

The primary objective of this study is to evaluate the effectiveness of etrasimod in patients with moderately to severely active UC in a real-world setting. Research objectives and endpoints are presented in table 1.

Sample size

The study plan is to enrol approximately 300 patients in cohort 1 from the UK, Germany and Canada. The inclusion of additional cohorts in other countries may be considered depending on feasibility and strategic priorities. This patient number allows for the achievement of a precision level of 5.5% when evaluating the primary study objectives. Justification for the sample size was based on achieving the desired precision when studying the proportion of patients who achieve symptomatic remission at week 12 and at week 52 (online supplemental table S1).

Assessments

Eligible patients enrolled in EFFECT-UC will be treated with etrasimod according to the local label, and data will be collected as available in clinical routine care. Patient demographics (including sex and ethnicity), medical and UC history, prior treatments and previous assessments will be collected from medical records. Patients will attend study sites according to routine care for up to seven visits, depending on the individual country. The data to be recorded during the baseline and follow-up visits are listed in table 2.

Patients will be asked to electronically complete Stool Frequency Subscore (SFS) and Rectal Bleeding Subscore (RBS) PRO assessments daily from the study baseline to 14 days after starting etrasimod (day 1) and for 7 days commencing at weeks 6, 12, 24, 36 and 52 (table 2). Patients will receive reminders to complete electronic PROs on their device each time one is available to be completed. PROs will be collected directly from the patient using an electronic PRO collection tool accessible via the patient's mobile phone or other digital device. For these datasets, the PRO collection tool will contain the source data that will be imported electronically into the study database.

Components of the modified Mayo score are commonly used to assess disease activity in UC clinical trials, including the SFS and RBS, collectively referred to as PRO2.[18–20] SFS and RBS will be calculated by averaging the daily subscores from within the 7-day period commencing at the planned visit at weeks 6, 12, 24, 36 and 52. The daily stool frequency score will be derived for each time point by comparing the current stool frequency with the patient-specific normal stool frequency reported by the patient at baseline, either during UC remission or before the initial onset of signs and symptoms of UC. The daily rectal bleeding score will be reported by the patient based on the most severe bleeding of the day.

Urgency in the past 24 hours and abdominal pain on the given day will be measured using respective numerical rating scales, scored from 0 for no urgency/pain to 10 for the worst possible urgency/pain. Fatigue will be measured based on symptoms felt during the last 7 days using the 13-point Functional Assessment of Chronic

Table 1 EFFECT-UC study objectives and endpoints

Primary objective	Primary endpoints
Real-world effectiveness of etrasimod therapy	Symptomatic remission* at week 12 Symptomatic remission* at week 52
Secondary objectives	**Secondary endpoints**
Real-world effectiveness of etrasimod on clinical response at week 12 and week 52	PRO2 response† at week 12 PRO2 response† at week 52
Real-world effectiveness of etrasimod on corticosteroid-free symptomatic remission at week 52	Corticosteroid-free symptomatic remission‡ at week 52
Exploratory objectives	**Exploratory endpoints**
Real-world effectiveness of etrasimod on corticosteroid-free symptomatic remission at SOC visits	Corticosteroid-free symptomatic remission‡ at week 24
Real-world effectiveness of etrasimod on symptomatic remission up to week 52	Symptomatic remission* at week 24 and at week 36 Complete symptomatic remission§ at week 52
Endoscopic disease activity of patients with UC at SOC visits	Endoscopic improvement¶ at week 52 Modified Mayo score at week 52
Real-world effectiveness of etrasimod on health-related electronic PROs	Change from baseline in SIBDQ scores at week 12, week 24 and week 52 Change from baseline in PRO2 score daily over the first 2 weeks and at week 12, week 24 and week 52 Change from baseline in severity of urgency collected daily over the first 2 weeks and at weeks 6, 12, 24, 36 and 52 Change from baseline in severity of abdominal pain collected daily over the first 2 weeks and at weeks 6, 12, 24, 36 and 52 Change from baseline in FACIT-F scores captured at weeks 12, 24 and 52
Real-world effectiveness of etrasimod on biomarkers collected as SOC	Biochemical remission** measured in faecal calprotectin concentration at weeks 12, 24, 36 and 52 Change from baseline in the level of hsCRP at weeks 12, 24, 36 and 52 Change from baseline in level of absolute lymphocyte count at weeks 12, 24, 36 and 52
Real-world response to etrasimod treatment based on IUS outcomes	IUS assessment†† at weeks 6, 12, 24 and 52

Baseline is defined as the day when the first questionnaire is completed (at the latest at day 1).
*Symptomatic remission is defined as an SFS=0 (or =1 with a ≥1-point decrease from baseline) and an RBS=0.
†PRO2 response is defined as a decrease of ≥20% in PRO2 score (sum of RBS and SFS) from baseline or achievement of symptomatic remission.
‡Corticosteroid-free symptomatic remission: patients in symptomatic remission who did not take any corticosteroid treatment for 12 weeks prior to the visit.
§Complete symptomatic remission is defined as an SFS=0 and an RBS=0.
¶Endoscopic improvement was defined as an ES ≤1.
**Biochemical remission is defined as a faecal calprotectin concentration ≤250 µg/g.
††According to the treating physician's assessment of bowel wall thickness, normalisation and extension; bowel wall vascularity; loss of stratification; loss of colonic haustration; structure formation and hyperechogenic reaction adjacent to the bowel wall.
ES, endoscopic subscore; FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue; hsCRP, high-sensitivity C reactive protein; IUS, intestinal ultrasound; PRO, patient-reported outcome; PRO2, patient-reported outcome 2; RBS, Rectal Bleeding Subscore; SFS, Stool Frequency Subscore; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; SOC, standard of care; UC, ulcerative colitis.

Illness Therapy—Fatigue (FACIT-F) questionnaire. Total FACIT-F scores range from 0 to 52, with higher scores representing less fatigue. Disease-specific quality of life will be measured with the Short Inflammatory Bowel Disease Questionnaire (SIBDQ), consisting of a 10-item questionnaire grouped into four dimensions: bowel function, emotional status, systemic symptoms and social function. Total SIBDQ scores range from 10 to 70, with higher scores indicating better quality of life.

Endoscopy data will be collected if endoscopic assessment is performed per standard of care (SOC), which is expected to take place at baseline and at week 52. For patients who undergo an endoscopy as SOC at any time point, stool frequency and rectal bleeding electronic

Table 2 Expected schedule of activities based on SOC

Visit identifier (recommended visit window)	Visit 1 Baseline*	Visit 2 Week 2 (±1 week)	Visit 3 Week 6 (±2 weeks)	Visit 4 Week 12 (±2 weeks)	Visit 5 Week 24 (±4 weeks)	Visit 6 Week 36 (±4 weeks)	Visit 7 Week 52 (±4 weeks)	28-day safety follow-up
Site activities								
Informed consent	X							
Inclusion/exclusion criteria	X							
Demographics	X							
Prior medication, prior vaccination, medical history including UC history	X							
Endoscopy (including flexible proctosigmoidoscopy)†	X						X	
hsCRP	X			X	X	X	X	
Complete blood count (leukocytes, haemoglobin)	X	X	X	X	X	X	X	
Baseline liver parameters†	X							
Stool sample/faecal calprotectin†	X			X	X	X	X	
IUS†	X	X	X	X	X	X	X	
Concomitant treatments and vaccinations	X	→	→	→	→	→	→	
Serious and non-serious adverse event monitoring‡	X	→	→	→	→	→	→	X
Electronic PROs								
Stool frequency	X	X	Daily for 7 days	Daily for 7 days	Daily for 7 days	Daily for 7 days	Daily for 7 days	
Rectal bleeding	X	X	Daily for 7 days	Daily for 7 days	Daily for 7 days	Daily for 7 days	Daily for 7 days	
Urgency NRS	X	X	X	X	X	X	X	
Abdominal pain NRS	X	X	X	X	X	X	X	
SIBDQ	X			X	X	X	X	
Fatigue (FACIT-F)	X			X	X	X	X	

Cells marked with an 'X' denote that data will be collected at that time point for the given activity; arrows denote that data will be collected throughout the study period.
*Baseline is defined as the day when the first questionnaire is completed (at the latest at day 1 (defined as the start of etrasimod treatment)).
†Data from these assessments will be collected if they were performed as SOC.
‡Safety data will be collected for the purpose of meeting routine pharmacovigilance reporting mandatory requirements.
FACIT-F, Functional Assessment of Chronic Illness Therapy—Fatigue; hsCRP, high-sensitivity C reactive protein; IUS, intestinal ultrasound; NRS, Numerical Rating Scale; PRO, patient-reported outcome; SIBDQ, Short Inflammatory Bowel Disease Questionnaire; SOC, standard of care; UC, ulcerative colitis.

PROs will be moved to avoid overlapping with the endoscopy time window by avoiding PRO measurements for 4 days before and 4 days after the endoscopy.

Intestinal ultrasound (IUS) data will be collected if completed according to SOC. During IUS, measurements of colonic wall thickness (in mm) will be taken from all accessible colonic segments (ascending, transverse, descending, sigmoid and rectum) as a measure of inflammation. Results from routine blood and stool tests for inflammatory markers, including high-sensitivity C reactive protein, leukocytes and faecal calprotectin, will be recorded when collected as part of SOC.

The EFFECT-UC study protocol explicitly allows patients to be treated according to physician's discretion. Discontinuation of the medication during the study will not lead to exclusion from the study. If the patient agrees to continue with the expected schedule of activities based on SOC, as outlined in table 2, data collection will continue unchanged. This approach to intercurrent events reflects real-world clinical practice and supports the non-interventional design of the study. Patients will be considered lost to follow-up if they repeatedly fail to return for doctor visits and are unable to be contacted by the study site. Patients considered

lost to follow-up by the study sites will be discontinued from the study.

Data analysis plan

Demographics and other baseline characteristics will be tabulated and summarised. Descriptive statistics for continuous variables will be reported as mean, SE, median, minimum and maximum, where appropriate. Descriptive statistics for categorical variables will be reported as the number of observations and percentage of patients in a specific study cohort, and by subgroups, where appropriate. In addition, 95% CIs will be presented when appropriate. Subgroup analyses will be performed for selected covariates, including exposure to advanced therapies at baseline and countries within the study cohort (if applicable). Safety data will be collected for the purpose of meeting routine pharmacovigilance reporting requirements and will be summarised descriptively. Interim analyses will be conducted at least once for each study cohort. Before any interim analysis is performed, details for the objectives and analysis will be documented and approved. For the primary objectives of symptomatic remission at week 12 and week 52, a point estimate and 95% CI will be presented. No formal statistical testing will be conducted, and analyses will be performed based on observed data, given the descriptive nature of the study. Should missing data occur, the data will be analysed as they are recorded in the electronic case report form; no imputation of missing data will be performed.

All data in the context of this study will be collected, stored and evaluated in accordance with the protocol, regulatory requirements and applicable guidance for electronic records. At every stage of the data management process, the data collected will be securely stored, and patient confidentiality will always be maintained in accordance with data protection laws.

Patient and public involvement

Two advisory boards were conducted with two UC patient organisations, whereby patients were asked to provide feedback on the research design, with a particular focus on the PROs the study plans to collect. The patients indicated that they would be willing to participate in this type of study, that the proposed frequency of data collection over the span of more than a year would be acceptable, and that the included PRO measures were aligned with what they felt was important to assess. During the study, patients will actively report their outcomes via validated PRO tools. On completion of the final study report, the development of lay summaries of the findings will be considered for distribution to study participants and relevant patient organisation groups.

ETHICS AND DISSEMINATION

Ethics approval

Written informed consent will be obtained from each patient before enrolment into the study. The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigour, and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices and Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research. Ethics approval for this study was obtained from the chief investigator's institution (London Bridge Research Ethics Committee; 333370; londonbridge.rec@hra.nhs.uk).

Ethics approval was also obtained from Ethikkommission der Ärztekammer Niedersachsen (Bo/09/2024), Ethikkommission der Ärztekammer Nordrhein (2024099), Ethikkommission der Landesärztekammer Hessen (2024–3695-zvBO), Ethikkommission der Ärztekammer Sachsen-Anhalt (20/24), Ethik-Kommission der Landesärztekammer Rheinland-Pfalz (2024–17585-NIS), Ethikkommission bei der Ärztekammer Schleswig-Holstein (031/24m (BO)), Ethik-Kommission bei der Landesärztekammer Baden-Württemberg (B-F-2024–050) and Advarra IRB Canada (IRB#00000971).

Dissemination

Interim analyses will be conducted at least once for each study cohort, which will allow for flexible, context-sensitive insights tailored to cohort-specific data availability. These analyses might be used to publish results of some completed study cohorts while the study is still ongoing for other study cohorts. For cohort 1 (comprising patients from the UK, Germany and Canada), interim results are expected in 2026, with final results available in 2028. The results for this cohort will be published in peer-reviewed journals and presented at appropriate congresses. A final study report containing all the study cohorts will be generated when the last study cohort has the last visit of the last patient.

DISCUSSION

The EFFECT-UC study is designed to assess the real-world effectiveness of etrasimod in patients with moderately to severely active UC. The study addresses a critical gap in the literature by complementing data from randomised controlled trials (RCTs) with real-world evidence, offering insights into the effectiveness of etrasimod across more diverse patient populations and healthcare settings. RCTs remain the gold standard for evaluating the efficacy and safety of new therapies; however, their applicability to broader patient populations can be limited due to the stringent inclusion and exclusion criteria.[21] The EFFECT-UC study will bridge this gap by evaluating the effectiveness of etrasimod in routine clinical practice. These data will help healthcare professionals make informed decisions when prescribing treatment for their patients and will inform clinical guidelines and reimbursement decisions.[22]

PROs are increasingly recognised as a crucial, patient-centric method for assessing UC therapies and understanding

patient burden.[16] An innovative aspect of this study will be the daily collection of PROs within the first 2 weeks of treatment, providing important data on the initial effectiveness of etrasimod after starting treatment. Additionally, the study will collect data for a comprehensive range of PROs to better understand treatment effects and potential domains that are important to patients. By capturing changes in quality of life, abdominal pain and bowel urgency, the EFFECT-UC study will address key concerns for patients and clinicians alike, complementing objective measures of disease activity such as stool frequency, rectal bleeding and endoscopic findings. The study will also capture measures not included in the etrasimod ELEVATE UC clinical programme, such as fatigue measured using the FACIT-F. Furthermore, the use of digital tools for electronic PRO collection will standardise data collection and minimise the risk of missing data. The use of electronic PRO data will also help with patient retention by making the process easy to complete.

An additional benefit of this study is the assessment of IUS as an exploratory endpoint, which could offer valuable insights into its real-world utilisation. IUS has been shown to be a useful tool for the diagnosis and follow-up of patients with UC.[23] Its highly sensitive detection of subtle changes in the intestinal wall during active inflammation has diagnostic value,[24] and early IUS has been shown to predict both clinical and endoscopic treatment response in UC.[25–27] The standardisation of IUS as a non-invasive, easy-to-learn and easy-to-use procedure makes it a feasible option for global implementation in inflammatory bowel disease centres.[28 29] The use of IUS does have some limitations, including that variability in operator skill can impact the accuracy and consistency of IUS measurements.[24 30] Additionally, interpretation of IUS results can be subjective if not performed using central reading, which can result in variability in clinical decision-making. Moreover, IUS is difficult to perform for patients with proctitis. Despite these limitations, the EFFECT-UC study will provide further insight into the use of IUS within a non-interventional study.

The multicentre, prospective nature of this study will ensure the collection of a robust and diverse dataset. The use of a single master protocol across countries will increase efficiency, lead to greater validity of any findings and allow the study to be replicated in additional countries as needed. The eligibility criteria are designed to reduce bias and avoid the exclusion of populations that are often excluded from RCTs. Importantly, the trial will cover a wide range of prior treatment exposures and aims to recruit predefined proportions of patients to different subgroups to ensure that meaningful comparisons can be made between groups, which could reveal differential response patterns to etrasimod treatment. This is particularly important given that patients with UC who have had multiple therapy failures often represent a challenging group to treat, for which there is a lack of RCT data. Furthermore, recruitment will occur in both private and public institutions across the world, which will reinforce the validity of the study results.

While the EFFECT-UC study has several strengths, certain limitations must be acknowledged. As an observational study, it is subject to biases inherent in real-world data collection, including selection bias and variations in SOC practices across countries. The reliance on routine clinical data may lead to inconsistencies in the timing and type of assessments conducted. For example, endoscopic evaluations may not be uniformly performed at baseline and follow-up visits. To address this, the study protocol incorporates flexibility in data collection windows and emphasises the importance of consistent electronic PRO collection across all sites and countries to allow consistency, even if clinical practice differs. Clinical trials typically derive Mayo scores by collating daily PRO assessments over several consecutive days, but this approach will not be possible for the baseline subscore within this study. However, where possible, RBS and SFS will be calculated for each visit using daily PROs completed over seven consecutive days.

The findings of the EFFECT-UC study will have significant implications for clinical practice and future research. By providing real-world evidence on the effectiveness of etrasimod, the study may inform treatment guidelines and help clinicians optimise therapy selection for patients with moderately to severely active UC, while also giving them confidence that the clinical trial findings for etrasimod translate to their real-world practice. Additionally, the data generated may support health economic evaluations, demonstrating the value of etrasimod in reducing disease burden and improving quality of life. Future studies could build on this work by exploring the long-term effectiveness and durability of response to etrasimod.

Author affiliations
[1]School of Medicine, University of Nottingham, Nottingham, UK
[2]Translational Gastroenterology Unit, Oxford University Hospital, Oxford, UK
[3]Division of Gastroenterology, Centre Hospitalier de l'Université de Montreal, Montreal, Québec, Canada
[4]Pfizer Ltd, Tadworth, UK
[5]Pfizer Inc, Cambridge, Massachusetts, USA
[6]Pfizer SLU, Alcobendas, Madrid, Spain
[7]Pfizer Pharma GmbH, Berlin, Germany
[8]Internistische Praxisgemeinschaft, Oldenburg, Germany
[9]IBD Unit, Guy's and St Thomas' Hospital, London, UK

Acknowledgements Jasper Deuring (an employee of Pfizer Inc at the time of protocol development) and John C Woolcott (Pfizer Inc) contributed to the design of the study and reviewed the protocol. Medical writing support, under the direction of the authors, was provided by Niall Tyrer, MBiolSci, CMC Connect, a division of IPG Health Medical Communications, and was funded by Pfizer, New York, USA, in accordance with Good Publication Practice (GPP 2022) guidelines (*Ann Intern Med* 2022;175:1298–304).

Contributors BS, MK, NK, PMI and UH contributed to conceptualisation or design of the study. RB contributed to data curation. RB and EB contributed to project administration. RB contributed to supervision. BS and SJR contributed to writing the original draft. GWM, SJR, AW, RB, MM, MK, EB, NK, BS, UH and PMI contributed to writing the revised draft. BS is the author guarantor.

Funding The funder did not influence the results/outcomes of the study despite author affiliations with the funder. This study was sponsored by Pfizer.

Competing interests GWM has grant income from AstraZeneca, Bristol Myers Squibb, Janssen and Pfizer Inc; received consultancy fees from AbbVie, Alimentiv Inc, Pfizer Inc and Satisfai Health and supported education events for AbbVie, Bristol Myers Squibb and Pfizer Inc. SJR has no competing interests to declare. AW received grant/research support from AbbVie, Alfasigma, Bristol Myers Squibb,

Buhlmann, Eli Lilly, Falk, Galapagos, Janssen, Pfizer Inc, Sandoz, Takeda and Tillotts. RB received speaker/consulting/moderator fees from AbbVie, Bristol Myers Squibb, Celltrion, Ferring, Janssen, Pfizer Inc and Takeda and has served on advisory boards for AbbVie, Bristol Myers Squibb, Celltrion, Janssen, Lilly, Pfizer Inc and Takeda. MM was an employee of Pfizer Ltd at the time of protocol development and is a shareholder of Pfizer Inc. MK is an employee and shareholder of Pfizer Inc. EB is an employee and shareholder of Pfizer SLU. NK is an employee of Pfizer Pharma GmbH and a shareholder of Pfizer Inc. BS is an employee and shareholder of Pfizer Ltd. UH received advisory fees from AbbVie, Amgen, Biogen, Bristol Myers Squibb, Celltrion, Janssen, MSD, Lilly, Mundipharma, Mylan Pharma, Pfizer Inc, Sandoz, Shield, Takeda and Vifor and lecture fees from AbbVie, Amgen, Biogen, Bristol Myers Squibb, Celltrion, Falk Foundation, Ferring, Janssen, MSD, Lilly, Mundipharma, Mylan Pharma, Pfizer Inc, Sandoz, Shield, Takeda and Vifor. PMI received grant support from Celltrion, Janssen, MSD and Takeda; lecture fees from AbbVie, Bristol Myers Squibb, Celgene, Celltrion, Falk Pharma, Ferring, Galapagos, Gilead, MSD, Janssen, Pfizer Inc, Sandoz, Sapphire Medical, Shire, Takeda, Tillotts and Warner Chilcott and advisory fees from AbbVie, Arena, Boehringer-Ingelheim, Bristol Myers Squibb, Celgene, Celltrion, Genentech, Gilead, Hospira, Janssen, Lilly, MSD, Pfizer Inc, Pharmacosmos, Prometheus, Roche, Samsung Bioepis, Sandoz, Takeda, Topivert, VH2, Vifor and Warner Chilcott.

Patient and public involvement Patients and/or the public were involved in the design, conduct, reporting or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See https://www.pfizer.com/science/clinical-trials/trial-data-and-results for more information.

ORCID iD

Peter M Irving https://orcid.org/0000-0003-0972-8148

REFERENCES

1 Kaser A, Zeissig S, Blumberg RS. Inflammatory bowel disease. *Annu Rev Immunol* 2010;28:573–621.
2 Magro F, Gionchetti P, Eliakim R, *et al*. Third European Evidence-based Consensus on Diagnosis and Management of Ulcerative Colitis. Part 1: Definitions, Diagnosis, Extra-intestinal Manifestations, Pregnancy, Cancer Surveillance, Surgery, and Ileo-anal Pouch Disorders. *J Crohns Colitis* 2017;11:649–70.
3 Kornbluth A, Sachar DB, Practice Parameters Committee of the American College of Gastroenterology. Ulcerative colitis practice guidelines in adults: American College Of Gastroenterology, Practice Parameters Committee. *Am J Gastroenterol* 2010;105:501–23.
4 Turner D, Ricciuto A, Lewis A, *et al*. STRIDE-II: An Update on the Selecting Therapeutic Targets in Inflammatory Bowel Disease (STRIDE) Initiative of the International Organization for the Study of IBD (IOIBD): Determining Therapeutic Goals for Treat-to-Target strategies in IBD. *Gastroenterology* 2021;160:1570–83.
5 Panaccione R, Collins EB, Melmed GY, *et al*. Efficacy and Safety of Advanced Therapies for Moderately to Severely Active Ulcerative Colitis at Induction and Maintenance: An Indirect Treatment Comparison Using Bayesian Network Meta-analysis. *Crohn's Colitis 360* 2023;5:otad009.
6 Afzali A, Lukanova R, Hennessy F, *et al*. Unmet Needs in Real-World Advanced Therapy-Naïve and -Experienced Patients with Moderately to Severely Active Ulcerative Colitis in the United States. *Adv Ther* 2023;40:4321–38.
7 Regueiro M, Siegmund B, Yarur AJ, *et al*. Etrasimod for the Treatment of Ulcerative Colitis: Analysis of Infection Events from the ELEVATE UC Clinical Programme. *J Crohns Colitis* 2024;18:1596–605.
8 Sandborn WJ, Peyrin-Biroulet L, Zhang J, *et al*. Efficacy and Safety of Etrasimod in a Phase 2 Randomized Trial of Patients With Ulcerative Colitis. *Gastroenterology* 2020;158:550–61.
9 Vermeire S, Chiorean M, Panés J, *et al*. Long-term Safety and Efficacy of Etrasimod for Ulcerative Colitis: Results from the Open-label Extension of the OASIS Study. *J Crohns Colitis* 2021;15:950–9.
10 Sandborn WJ, Vermeire S, Peyrin-Biroulet L, *et al*. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. *Lancet* 2023;401:1159–71.
11 Wu K, Zheng C, Cao Q, *et al*. DOP052 Etrasimod as induction and maintenance therapy in Asian patients with moderately to severely active Ulcerative Colitis: Results from the maintenance period of a randomised, double-blind, placebo-controlled, multi-centre Phase 3 study (ES101002). *J Crohn's Colitis* 2025;19:i184–6.
12 European Medicines Agency. VELSIPITY: summary of product characteristics, 2024. Available: https://www.ema.europa.eu/en/documents/product-information/velsipity-epar-product-information_en.pdf
13 US Food and Drug Administration. VELSIPITY (etrasimod): highlights of prescribing information, 2024. Available: https://www.accessdata.fda.gov/drugsatfda_docs/label/2024/216956s001lbl.pdf
14 Medicines & Healthcare Products Regulatory Agency. VELSIPITY summary of product characteristics, 2024. Available: https://mhraproducts4853.blob.core.windows.net/docs/f23ffb5e0a19533545161a744983a9c2321bf195
15 Health Canada. VELSIPITY product monograph [online, 2024. Available: https://pdf.hres.ca/dpd_pm/00074415.PDF
16 Hanzel J, Bossuyt P, Pittet V, *et al*. Development of a Core Outcome Set for Real-world Data in Inflammatory Bowel Disease: A European Crohn's and Colitis Organisation [ECCO] Position Paper. *J Crohns Colitis* 2023;17:311–7.
17 Canada's Drug and Health Technology Agency. Guidance for reporting real-world evidence, 2023. Available: https://www.cda-amc.ca/sites/default/files/RWE/MG0020/MG0020-RWE-Guidance-Report-Secured.pdf
18 US Food and Drug Administration. Ulcerative colitis: developing drugs for treatment, 2022. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/ulcerative-colitis-developing-drugs-treatment
19 Lewis JD, Chuai S, Nessel L, *et al*. Use of the noninvasive components of the Mayo score to assess clinical response in ulcerative colitis. *Inflamm Bowel Dis* 2008;14:1660–6.
20 Naegeli AN, Hunter T, Dong Y, *et al*. Full, Partial, and Modified Permutations of the Mayo Score: Characterizing Clinical and Patient-Reported Outcomes in Ulcerative Colitis Patients. *Crohn's & Colitis 360* 2021;3:otab007.
21 Chhibba T, Frolkis A, Stein L, *et al*. A221 GENERALIZABILITY OF RANDOMIZED CONTROLLED TRIALS TO ROUTINE CLINICAL CARE IN ULCERATIVE COLITIS. *J Can Assoc Gastroenterol* 2025;8:i92.
22 Eichler H-G, Bloechl-Daum B, Abadie E, *et al*. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. *Nat Rev Drug Discov* 2010;9:277–91.
23 Maaser C, Petersen F, Helwig U, *et al*. Intestinal ultrasound for monitoring therapeutic response in patients with ulcerative colitis: results from the TRUST&UC study. *Gut* 2020;69:1629–36.
24 Smith RL, Taylor KM, Friedman AB, *et al*. Systematic Review: Clinical Utility of Gastrointestinal Ultrasound in the Diagnosis, Assessment and Management of Patients With Ulcerative Colitis. *J Crohns Colitis* 2020;14:465–79.
25 Allocca M, Dell'Avalle C, Furfaro F, *et al*. Early Intestinal Ultrasound Predicts Long-Term Endoscopic Response to Biologics in Ulcerative Colitis. *J Crohns Colitis* 2023;17:1579–86.
26 de Voogd FA, Bots SJ, van Wassenaer EA, *et al*. Early Intestinal Ultrasound Predicts Clinical and Endoscopic Treatment Response and Demonstrates Drug-Specific Kinetics in Moderate-to-Severe Ulcerative Colitis. *Inflamm Bowel Dis* 2024;30:1992–2003.
27 Ollech JE, Eran-Banai H, Goren I, *et al*. Tofacitinib is an effective treatment for moderate to severe ulcerative colitis, and intestinal ultrasound can discriminate response from non-response: a pragmatic prospective real-world study. *Ann Med* 2024;56:2358183.

28 Ilvemark JFKF, Hansen T, Goodsall TM, *et al*. Defining Transabdominal Intestinal Ultrasound Treatment Response and Remission in Inflammatory Bowel Disease: Systematic Review and Expert Consensus Statement. *J Crohns Colitis* 2022;16:554–80.
29 Abraham BP, Reddy D, Saleh A. Integrating Intestinal Ultrasound into an Inflammatory Bowel Disease Practice: How to Get Started. *Crohn's & Colitis 360* 2023;5:otad043.
30 Bezzio C, Saibeni S, Vernero M, *et al*. The learning curve for using intestinal ultrasonography. *Dig Liver Dis* 2024;56:1511–6.