NON-INTERVENTIONAL (NI) STUDY PROTOCOL

Study Information

Title	Early Experience with Etrasimod in Ulcerative Colitis Patients: an Observational Study in the United States
Protocol number	C5041059
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EU Post Authorization Study (PAS) register number	EUPAS1000000587
Active substance	L04AE05 (Etrasimod arginine)
Medicinal product	VELSIPITY ®
Research question and objectives	Research questions: What are the demographic characteristics, comorbidities, disease characteristics and treatment histories of patients with ulcerative colitis (UC) who have initiated treatment with etrasimod? What are the treatment patterns of etrasimod (adherence and persistence) among patients with UC within 12 months of treatment initiation? What is the use of corticosteroids within 12 months of etrasimod initiation? What is the change in level of fecal calprotectin from baseline through 12 months of etrasimod initiation? **Primary objective** 1. To describe the baseline demographic characteristics, comorbidities, disease and treatment characteristics of

	patients with UC who initiated treatment with etrasimod **Secondary objectives** 1. To describe the treatment patterns of etrasimod (adherence and persistence) among patients with UC within 12 months of etrasimod initiation. 2. To describe corticosteroid use among patients with UC within 12 months of etrasimod initiation. 3. To describe the change in level of fecal calprotectin in patients with UC, from baseline through 12 months of etrasimod initiation.
Country(ies) of study	United States of America
Author	Jeremie Rudant, MD, PhD RWE scientist [redacted] Pfizer [redacted] Peter Hur, PharmD, MBA Director, Value & Evidence Pfizer [redacted]

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid
AE	Adverse event
AIDS	Acquired Immunodeficiency Syndrome
anti-TNF	Anti-tumor necrosis factor
anti-TNF-α	Anti-tumor necrosis factor α
AT	Advanced Treatment
CD	Crohn's disease
CCI	Charlson Comorbidity Index
CI	Confidence interval
CPT	Current procedure terminology
CRP	C-reactive protein
EC	Ethics Committee
EMA	European Medicines Agency
EMR	Electronic Medical Record
EnCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GPP	Guidelines for Good Pharmacoepidemiology Practices
HCPCS	Healthcare Common Procedure Coding System
HIPAA	Health Insurance Portability and Accountability Act
HIV	Human Immunodeficiency Virus

Abbreviation	Definition
HMA	Heads of Medicines Agencies
HZ	Herpes Zoster
IBD	Inflammatory bowel disease
ICD	International Classification of Diseases
ICD-10	International Classification of Diseases – Tenth Revision
ICMJE	International Committee of Medical Journal Editors
IL	Interleukin
IMID	Immune-Mediated Inflammatory Diseases
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
JAKi	Janus kinase inhibitor
KM	Kaplan-meier
MMIT	Managed markets insight & technology
NDC	National Drug Center
NI	Non-Interventional
PASS	Post-authorization safety study
PDC	Proportion of days covered
RB	Rectal bleeding
RCT	Randomized controlled trial
RWD	Real-World Data
RWE	Real-World Evidence

Abbreviation	Definition
S1P	Sphingosine 1-phosphate
SAP	Statistical analysis plan
SD	Standard deviation
SF	Stool frequency
UC	Ulcerative colitis
US	United states
USA	United states of America

3. RESPONSIBLE PARTIES

Principal Investigator(s) of the Protocol

Name, degree(s)	Job Title	Affiliation	Address
Peter Hur, PharmD, MBA	Director, Value & Evidence	Pfizer [redacted]	[redacted]
Jérémie Rudant, MD, PhD	RWE Scientist [redacted]	Pfizer [redacted]	[redacted]
[redacted] PhD, MPH	[redacted]	Pfizer [redacted]	[redacted]
[redacted] MD	[redacted]	Pfizer [redacted]	[redacted]
[redacted] PhD	[redacted]	Pfizer [redacted]	[redacted]
[redacted] PhD	[redacted]	Evidera [redacted]	[redacted]

4. ABSTRACT

Title: Early experience with etrasimod in ulcerative colitis patients: an observational study in the United States

Version 1.0, 22 August 2025

Name and affiliation of the main author

Jeremie Rudant, MD, PhD
RWE scientist, [redacted]
Pfize [redacted]

Peter Hur, PharmD, MBA
Director, Value & Evidence
Pfize [redacted]

Rationale and Background

Etrasimod arginine is an orally administered, selective, synthetic sphingosine 1-phosphate (S1P) receptor 1-, 4-, 5-modulator developed to treat immune-mediated inflammatory disorders. Etrasimod was approved by the Food and Drug Administration (FDA) based on data from two phase 3 trials, ELEVATE UC 12 and ELEVATE UC 52, which examined the efficacy and safety of etrasimod among adult patients with moderately to severely active ulcerative colitis (UC). Results from both clinical trials showed that etrasimod was safe, effective, and well tolerated as an induction and maintenance therapy. In the United States (US), etrasimod is indicated to treat adults with moderately to severely active UC.

While randomized controlled trials (RCTs) provide evidence of efficacy with minimized biases and increased internal validity, the strict eligibility criteria may exclude patients seen in routine care settings, limiting generalizability. Therefore, real world data may provide useful description of drug patterns of use in real-life setting.

It is important for clinicians and payers to understand the patient population initiating etrasimod as well as treatment utilization patterns in routine clinical practice, including adherence, persistence and steroid use, to help inform their decision-making.

This non-interventional study aims to provide data describing real-world patient characteristics and treatment patterns among UC patients who initiate treatment with etrasimod.

This non-interventional study is designated as a post-authorization safety study (PASS) and is conducted voluntarily by Pfizer.

Research question and objectives

Research questions:

What are the demographic characteristics, comorbidities, disease characteristics and treatment histories of patients with ulcerative colitis (UC) who have initiated treatment with etrasimod?

What are the treatment patterns of etrasimod (adherence and persistence) among patients with UC within 12 months of treatment initiation?

What is the use of corticosteroids within 12 months of etrasimod initiation?

What is the change in level of fecal calprotectin from baseline through 12 months of etrasimod initiation?

Primary Objective

1. To describe the baseline demographic characteristics, comorbidities, disease and treatment characteristics of patients with UC who initiated treatment with etrasimod.

Secondary Objectives

1. To describe the treatment patterns of etrasimod (adherence and persistence) among patients with UC within 12 months of etrasimod initiation.

2. To describe corticosteroid use among patients with UC within 12 months of etrasimod initiation.

3. To describe the change in level of fecal calprotectin in patients with UC, from baseline through 12 months of etrasimod initiation.

Study design

This is a population-based retrospective cohort study of adults (ages ≥ 18 years of age) with UC initiating treatment with etrasimod since its marketing authorization, using claims data from a large US database.

Primary endpoint is baseline characteristics of patients. Secondary endpoints are adherence, measured by proportion of days covered method, persistence (delay until etrasimod discontinuation), the use of corticosteroids and change in level of fecal calprotectin, within 12 months of etrasimod initiation.

Population

The US UC population will be identified from the Panalgo-MMIT database, by considering all patients with an ICD-10 diagnosis code equal to K51.x (UC) between 2015 and end of the study period.

The study cohort will be defined as UC patients initiating etrasimod from its marketing authorization on October, 13, 2023 to the end of study period.

For the secondary objectives, patients with closed claims will be followed for up to 12 months after the index date or to the end of their continuous enrollment, whichever comes first.

Variables

Variables include exposure to etrasimod, baseline covariates, i.e demographic characteristics, comorbidities, disease and treatment characteristics, and outcomes, i.e. adherence to etrasimod, persistence, corticosteroid use and fecal calprotectin levels within 12 months of etrasimod initiation.

Data Source

This study will use de-identified, patient-level health data from Panalgo-MMIT database (also referred to as the NorstellaLinQ database). The database comprises open medical and pharmacy claims for more than 300 million US individuals and closed medical and pharmacy claims for 245 million individuals. The database also comprises laboratory tests results for a subset of 155 million individuals.

Study size

Preliminary feasibility (as per May 2025) count indicated a sample size of 268 UC patients with an etrasimod fill (paid or closed claim) that also met eligibility criteria. Of them, 79 had closed index etrasimod claim and had more than 6 months of continuous enrollment post-index date. The database will be refreshed each month, so that the total number of patients included in interim and final analyses will be higher than the May 2025 count.

The secondary objectives analyses will be done pending a minimal sample size of 100 patients with closed claims and ≥ 6 months continuous enrollment post-index.

Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a statistical analysis plan (SAP).

Milestones:

Milestone	Planned Date
Registration in the HMA-EMA Catalogues of RWD Studies	16 May 2025
Start of data collection	8 September 2025
End of data collection	30 June 2026
Final study report	30 October 2026

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned Date
Registration in the HMA-EMA Catalogues of RWD Studies	16 May 2025
Start of data collection	8 September 2025
End of data collection	30 June 2026
Final study report	30 October 2026

7. RATIONALE AND BACKGROUND

Ulcerative colitis (UC) is one of the two main subtypes of inflammatory bowel disease (IBD), which mainly affects the large intestine (colon). IBD is a chronic, idiopathic, autoimmune-mediated, inflammatory disorder, defined by inflammation and tissue damage of the gastrointestinal tract.[1] In the United States, the lifetime prevalence of UC among adults was reported to be 1.0%, or an estimated 1.9 million people.[2] UC has a peak incidence in the 2nd and 3rd decades of life.[3,4] It is a chronic recurrent, remittent, and progressive inflammatory condition that affect the mucosa of the gastrointestinal tract and is associated with an increased risk for colon cancer.[5]

UC is characterized by diffuse mucosal inflammation starting in the rectum and extending to proximal segments of the colon.[6] Clinical symptoms of UC include rectal bleeding (RB), high stool frequency (SF), intense bowel urgency, and abdominal pain. These often result in weight loss, fatigue, and an overall reduction in quality of life. UC causes a life-long burden, often resulting in reduced productivity in work and school, and intermittent need for hospitalizations.[7,8]

Treatment for patients with UC aims to relieve symptoms, heal the mucosa, and improve quality of life. Although the etiology of UC remains unclear, elucidating its mechanism has facilitated therapeutic development, especially in the last two decades. Among the available therapies, anti-tumor necrosis factor α (anti-TNF-α) agents are the most notable predecessors (e.g., infliximab, adalimumab, golimumab), resulting in improved health outcomes and decreased need for surgical intervention. Despite outcome improvements with the use of advanced therapies (i.e., biologics and small molecule drugs), up to 30% of patients who receive biologics may not have an adequate response to these agents and approximately 50% may experience loss of response during the first year of treatment.[9,10].

Etrasimod arginine is an orally administered, selective, synthetic sphingosine 1-phosphate (S1P) receptor 1-, 4-, 5-modulator developed to treat immune-mediated inflammatory disorders, including UC. S1P is a cell surface expressed protein that has been shown to regulate lymphocyte migration out of lymphoid tissues.[11] Synthetic small molecule S1P agonists have been observed to act as functional antagonists by inducing sustained receptor internalization, thus inhibiting lymphocyte migration out of lymphoid tissues and lowering the amount of peripheral blood lymphocytes available to be recruited to sites of inflammation.[12] Modulation of the S1P/S1P receptor axis is thought to be a potential therapeutic approach to the management of immune-mediated inflammatory disorders.[13,14]

Etrasimod was approved by the Food and Drug Administration based on data from two phase 3 trials, ELEVATE UC 12 and ELEVATE UC 52, which examined the efficacy and safety of etrasimod among adults with moderate-to-severe UC. Results from both clinical trials showed that etrasimod was safe, effective, and well tolerated as an induction and maintenance therapy.[15,16] In the US, etrasimod is indicated to treat adults with moderately to severely active ulcerative colitis.

While randomized controlled trials (RCTs) provide evidence of efficacy with minimized biases and increased internal validity, the strict eligibility criteria may exclude patients seen in routine care settings,[17,18] limiting generalizability. Therefore, real world data may provide useful description of drug patterns of use in real-life setting.

It is important for clinicians and payers to understand the patient population initiating etrasimod as well as treatment utilization patterns in routine clinical practice, including adherence, persistence and steroid use, to help inform their decision-making.

This non-interventional study aims to describe the real-world patient characteristics and treatment patterns among UC patients who initiated treatment with etrasimod. This non-interventional study is designated as a PASS and is conducted voluntarily by Pfizer.

8. RESEARCH QUESTION AND OBJECTIVES

Research questions addressed by this study are as follows:

What are the demographic characteristics, comorbidities, disease characteristics and treatment histories of patients with ulcerative colitis (UC) who have initiated treatment with etrasimod?

What are the treatment patterns of etrasimod (adherence and persistence) among patients withUC within 12 months of treatment initiation?

What is the use of corticosteroids within 12-months of etrasimod initiation?

What is the change in level of fecal calprotectin from baseline through 12 months of etrasimod initiation?

Primary Objective

The primary objective for this study is:

1. To describe the baseline demographic characteristics, comorbidities, disease and treatment characteristics of patients with UC who initiated treatment with etrasimod.

Secondary Objectives

Secondary study objectives are as follows:

1. To describe the treatment patterns of etrasimod (adherence and persistence) among patients with UC within 12 months of etrasimod initiation.

2. To describe corticosteroid use among patients with UC within 12 months of etrasimod initiation.

3. To describe the change in level of fecal calprotectin in patients with UC, from baseline through 12 months of etrasimod initiation.

9. RESEARCH METHODS

9.1. Study Design

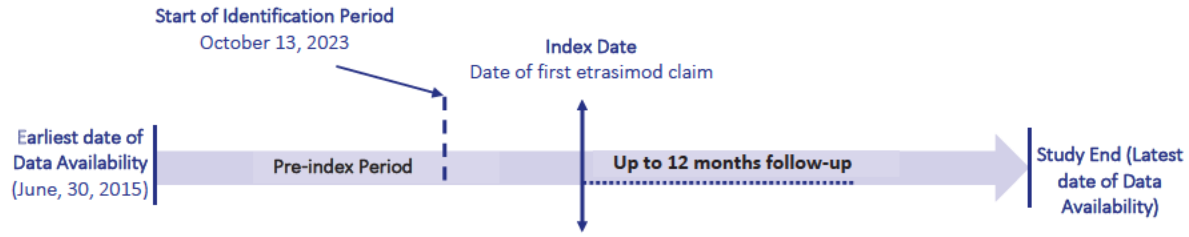
This is a population-based retrospective cohort study of adults (ages ≥ 18 years of age) with UC initiating treatment with etrasimod since its marketing authorization, using claims data from a large US database.

Primary endpoint is baseline characteristics of patients. Secondary endpoints are adherence, measured by proportion of days covered method, and persistence (delay until etrasimod

discontinuation) within 12 months of etrasimod initiation. These endpoints are commonly used in IBD real-world studies as proxies for both effectiveness and safety, to help inform clinician decision-making [19–26]. Other secondary endpoints are the use of corticosteroids and change in level of fecal calprotectin, an inflammatory marker performed in routine clinical practice to monitor disease activity, within 12 months of etrasimod initiation. Using a large US claims database to identify etrasimod patients should maximize representativeness of the study population, and limit misclassification of endpoints based on drug exposure (prior use of advanced therapy, adherence and persistence of estrasimod, steroid use) by leveraging drug dispensing data.

Study design is illustrated in Figure 1.

Figure 1. Illustration of study design for patients sourced from claims data



9.2. Setting

The population under study will be US patients diagnosed with UC and initiating etrasimod from its marketing authorization on October, 13, 2023 to the end of study period (the latest date of data availability, which will be defined in the SAP) (Figure 1).

This study will use existing data from Panalgo-MMIT database, which captures claims data from 300 million US people sufficiently representative of the US population with insurance coverage. Data from the eligible patients available in the datasource, i.e from 2015 to latest date of data availability will be used in the study, to document baseline characteristics and assess endpoints of interest.

Identification of disease populations, outcomes of interest, and drugs dispensed will be implemented using International Classification of Diseases - Tenth Revision (ICD-10) codes, current procedure terminology (CPT) and Healthcare Common Procedure Coding System (HCPCS) procedure codes, and prescribing data (e.g., National Drug Center (NDC) codes in the patients' claims structured data.

The US UC population will be identified from the Panalgo-MMIT database, by considering all patients with an ICD-10 diagnosis code equal to K51.x (UC) between 2015 to the end of study period.

The study cohort will be the cohort of UC patients initiating etrasimod (NDC Codes: 63539027428 and 0006902743) from its marketing authorization on October, 13, 2023 to the end of study period. The index date is defined as the earliest identified date of a filled pharmacy claim of etrasimod. Further, only patients with open claims data availability for more than 12 months prior to index date will be considered, to ensure to identify comorbidities, disease and treatment histories during a period of at least 12 months. Of note, the loss of patients due to this criteria is small as shown in table 3 in 9.5 study size section. Patients with Crohn's disease ICD10 codes (K50.x), a colectomy or co-prescription of immunodmodulators or advanced therapies will be further excluded to include patients treated only with etrasimod, and only for UC indication.

Regarding the follow-up period after etrasimod initiation, for the secondary objectives, patients with closed claims will be followed for up to 12 months after the index date, or to the end of their continuous enrollment, whichever comes first. Specific windows of minimal continuous enrollment will be defined in the SAP for each analysis.

9.2.1. Inclusion Criteria

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

1. Patients who have initiated etrasimod, defined by a filled pharmacy claim
2. Patients with at least ≥1 inpatient or outpatient claim with evidence of UC diagnosis in medical claims using ICD-10-CM codes: K51.x on or prior to index date
3. Patients aged ≥ 18 years at index date
4. Data availability ≥ 12 months prior to index date

9.2.2. Exclusion Criteria

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

1. Patients with medical claims with diagnosis code(s) corresponding to Crohn's disease (CD) during pre-index period or index date
2. Patients with medical claims with procedure code(s) corresponding to colectomy during pre-index period or index date
3. Any co-prescription with select immunomodulators (methotrexate, tacrolimus, cyclosporin, thiopurine) or advanced therapies for UC (biologics, anti-TNFs, interleukin 12 and 23, anti-integrin, small molecules such as Janus kinase inhibitors [JAKi], or with any other S1P receptor modulator) on index date

9.3. Variables

The variables for analysis, which include the demographic, comorbidities, disease and treatment characteristics, and outcomes, are listed below. All variables will be created based on data from the Panalgo-MMIT data source (claims or laboratory test data). Operational definitions of all variables are described in the table below, and some will be further described in SAP. Timepoints of assessment will be further described in the SAP, which will be the reference. The list of diagnosis codes used to define comorbidities is provided in Annex 3.

Table 1. List of variables

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Ulcerative Colitis	Cohort definition	Panalgo-MMIT claims data	At least ≥1 inpatient or outpatient claim with an evidence of UC diagnosis in medical claims using ICD-10-CM codes: K51.x	Pre-index period
Time in the database prior to index date (length of pre-etrasimod period)	Covariate	Panalgo-MMIT claims data	Time between first claims availability and index date	Pre-index period
Etrasimod use	Exposure	Panalgo-MMIT claims data	Filled pharmacy claim of etrasimod (NDC Codes: 63539027428, 0006902743)	Index date and follow-up
Period of etrasimod initiation	Covariate	Panalgo-MMIT claims data	Quarter of index date, since 13, October 2023, until latest date of data availability	Index date
Baseline demographics				
Age	Covariate / Baseline demographics	Panalgo-MMIT claims data	Age in years, as continuous measure and categorical variable	Index date
Gender	Covariate / Baseline demographics	Panalgo-MMIT claims data	Sex at birth reported as a categorical variable: . Male, . Female, . Unknown/missing	Index date
Race/ ethnicity	Covariate / Baseline demographics	Panalgo-MMIT claims data	Race/ ethnicity reported as one categorical variable: White, Black/African American, Hispanic,	Index date

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
			Asian, Unknown/missing	
Geographic region	Covariate / Baseline demographics	Panalgo-MMIT claims data	Geographic region, reported as a categorical variable: . Northeast . Midwest . South, . West . Unknown/missing	Index date
Insurance Type	Covariate / Baseline demographics	Panalgo-MMIT claims data	Primary payer, reported as a categorical variable: . Commercial, . Medicare, . Medicaid, . Other, . Unknown/missing	Index date or most proximal to index date
Comorbidity (code lists provided in Annex 3)				
Any malignancy, including lymphoma and leukemia, except malignant neoplasm of skin	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Cerebrovascular disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Chronic pulmonary disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Congestive heart failure	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Dementia	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no).	During pre-index period
Diabetes with chronic complications	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Diabetes without chronic complications	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Hemiplegia or paraplegia	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Metastatic solid tumor	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Mild liver disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Moderate or severe liver disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Myocardial infarction	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Peptic ulcer disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Peripheral vascular disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Renal disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Rheumatologic disease	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Acquired immunodeficiency syndrome (AIDS) / human immunodeficiency virus (HIV)	Individual Charlson comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Charlson Comorbidity Index (CCI) score	Comorbidity score	Panalgo-MMIT claims data	The CCI will be created according to Quan et al[27]. Defined as a continuous variable and categorized as 0, 1, 2, 3, 4+	During pre-index period
Extra-intestinal immune-mediated inflammatory diseases (IMID) comorbidities	Comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable(yes/no) by the presence of at least one extra-intestinal IMID comorbidity	During pre-index period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Rheumatoid arthritis	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Psoriasis	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Ankylosing spondylitis	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Psoriatic arthritis	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Pyoderma gangranosa	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Erythema Nodosum	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Episcleritis	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Primary sclerosing cholangitis	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Arthropathy/Arthralgia	Extra-intestinal IMID comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Abdominal pain	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Anemia	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Anxiety	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Coagulation defects	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Depression	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Hypertension	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Infections (all)	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Herpes Zoster infections	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Opportunistic infections	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Non-melanoma skin cancer	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Obesity	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Venous thrombosis	Other comorbidity	Panalgo-MMIT claims data	Defined as a dichotomous variable (yes/no)	During pre-index period
Baseline disease and treatment characteristics				
Disease extent	Baseline disease characteristics	Panalgo-MMIT claims data	Extent of ulcerative colitis for patient at diagnosis (derived from the closest UC diagnosis code on or prior to index date): • Ulcerative pancolitis • Left-sided colitis • Ulcerative rectosigmoiditis	Index date

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
			• Ulcerative proctitis Other: Inflammatory polyps of colon, Other ulcerative colitis, unspecified field	
Disease duration proxy	Baseline disease characteristics	Panalgo-MMIT claims data	Time between first UC code and index date	Pre-index
Prior UC-related hospitalization	Baseline disease characteristics	Panalgo-MMIT claims data	Inpatient admissions for UC or its complications	During pre-index period
Prior UC-related emergency department visit	Baseline disease characteristics	Panalgo-MMIT claims data	Emergency visit for UC or its complications	During pre-index period
Fecal calprotectin	Baseline lab test results	Panalgo-MMIT laboratory test data	Fecal calprotectin value	During pre-index period
C-reactive protein (CRP)	Baseline lab test results	Panalgo-MMIT laboratory test data	CRP value	During pre-index period
Albumin	Baseline lab test results	Panalgo-MMIT laboratory test data	Albumin value	During pre-index period
Erythrocyte sedimentation rate	Baseline lab test results	Panalgo-MMIT laboratory test data	Erythrocyte sedimentation rate value	During pre-index period
Treatment history during pre-index period	Baseline treatment characteristics /sub-group identifier	Panalgo-MMIT claims data	The number (and percent) of patients receiving ≥1 pharmacy claims for any of the treatments prior to	During pre-index period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
			etrasimod, reported as a categorical variable . 5-aminosalicylic acid (5-ASA) . Corticosteroids . Immunomodulators (methotrexate, tacrolimus, cyclosporin, thiopurine, Mycophenolate mofetil) . Biologics any, and number for each class (anti-TNFs, anti-integrin, interleukin (IL) 12/23 and IL 23 antagonists) . Small molecule any, and number for each class (JAKi, S1P receptor modulator) . Naïve/experienced status for advanced therapy (biologics or small molecules), line of etrasimod, and number of prior different classes. *Generic names corresponding to the different classes of AT are*: Anti-TNF: adalimumab, golimumab, infliximab Anti-integrin: vedolizumab IL12/23 and IL23 antagonists:	

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
			ustekinumab, guselkumab, mirikizumab, risankizumab JAKi: tofacitinib, upadacitinib S1P receptor modulator: etrasimod, ozanimod	
Co-prescription of 5-ASA	Covariate	Panalgo-MMIT claims data	Exact definition will be defined in the SAP	Index date
Corticosteroid use at etrasimod initiation	Covariate/sub-group identifier	Panalgo-MMIT claims data	This exposure will be considered to stratify the analysis for the secondary objective 2. It will be defined in the SAP.	Index date
Outcomes				
Treatment discontinuation	Outcome	Panalgo-MMIT claims data	Discontinuation of the etrasimod therapy will be defined in SAP based on gap in therapy (e.g ≥60 days and >90 days (sensitivity analyses) from the runout date (date of prescription + days' supply-1)) and date of discontinuation will be defined in SAP (e.g run out of days' supply of the last prescription filled prior to the gap in therapy, or switch to another AT, whichever comes first).	Within 12 month follow-up period

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
Adherence	Outcome	Panalgo-MMIT claims data	Adherence to etrasimod during the post-index period will be assessed using the proportion of days covered (PDC) methodology, which will be defined in the SAP (e.g the number of days covered by arrays for each prescription fill during the follow-up period post-index date; adherence will be defined at a threshold of PDC ≥0.80). PDC = Days covered/Study follow up period Different time points of assessment will be defined in SAP.	Within 12 month follow-up period
Persistence	Outcome	Panalgo-MMIT claims data	Persistence with therapy will be defined as time to etrasimod discontinuation. Persistence will be measured as the duration of continuous use of etrasimod from treatment initiation until discontinuation and will be assessed within 12 month follow-up period. Different time points of assessment will be defined in SAP.	Within 12 months follow-up period
Corticosteroid use after etrasimod initiation (outcome)	Outcome	Panalgo-MMIT	Proportion of patients with corticosteroids use after etrasimod initiation	Within 12 months

Variable(s)	Role	Data Source	Operational definition	Timepoint of Assessment
		claims data	will be assessed at different time points, which will be defined in the SAP.	follow-up period
Fecal calprotectin	Outcome	Panalgo-MMIT laboratory test data	The change in level of fecal calprotectin collected in routine clinical practice through laboratory tests in UC patients, will be described from baseline through 12 months of etasimod initiation. Detailed methodology will be provided in SAP.	Within 12 months follow-up period

9.4. Data Sources

This study will leverage existing data from Panalgo-MMIT patient-level longitudinal database from Panalgo company (part of Norstella company), also referred to as the NorstellaLinQ database.

The Panalgo-MMIT database contains de-identified, patient-level health data from individuals in the US. It includes open medical and pharmacy claims (i.e information provided to payers by data providers), for more than 300 million individuals from 2017 to June 2026, and closed medical and pharmacy claims (information coming from payers, once adjudicated) for 245 million individuals from 2015 to June 2026. The database also comprises laboratory tests results and electronic health records data for a subset of 155 million and 45 million US individuals, respectively, both linked to patients claims data through Panalgo's proprietary patient token.

De-identified, patient-level claims data are pulled from clearinghouse, payer (150+ payer), and provider data sources to follow patients as they move through the healthcare system. Closed claims, owing to their origin, present a higher accuracy and completeness in all data fields. However, this data type is occasionally subject to availability delays, due to the insurer adjudication process. On the other hand, open claims - i.e., claims awaiting insurer adjudication and not sourced directly from insurers - offer rapid data access (albeit at the expense of completeness). Closed claims have been aggregated from more than 150 private insurance providers in the US, spanning Medicaid Managed Care and Medicare Advantage plans. While closed dataset (payer complete dataset) allows researchers to conduct a robust

claims-based analysis with a large sample size and long follow-up periods, open dataset includes additional historical data. The database can be used to constitute a longitudinal history across the continuum of care, for the period a given patient is enrolled in their health plan and is eligible for medical and drug benefits. The database is fully compliant with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

This extensive reach ensures inclusion of patients from various hospital and physician networks, healthcare claim processing bodies, pharmacies, and health insurance companies.

No formal validation studies of the study endpoints measured in Panalgo-MMIT claims database have been performed. However, UC claims diagnosis codes have been shown to be very accurate to identify UC patients[28] in US claims databases. In particular, closed claims data have been widely used to describe patterns of use of UC treatments in real-life setting[19–26], and have been shown to be well suited to the measurement of persistence and adherence for chronic conditions.[29–32]

9.5. Study Size

There is no minimal or maximal sample size. All patients identified and eligible will be included. However, the secondary objectives analyses will be done pending data maturity to allow for patient accrual and a minimal sample size of 100 patients with closed claims and ≥ 6 months continuous enrollment post-index.
Table 2 shows the precision of proportions, according to sample size (normal distribution). For instance, the 95% CI for an adherence rate of 80% observed among 200 patients would be [74.5%; 85.5%].

Table 2. Precision of proportions, according to sample size

		Estimates calculated based on*		
Sample Size	**Proportion**	Lower Limit*	Upper Limit*	Half-width*
300	50.0%	44.3%	55.7%	5.7%
300	60.0%	54.5%	65.5%	5.5%
300	70.0%	64.8%	75.2%	5.2%
300	80.0%	75.5%	84.5%	4.5%
200	50.0%	43.1%	56.9%	6.9%
200	60.0%	53.2%	66.8%	6.8%
200	70.0%	63.6%	76.4%	6.4%
200	80.0%	74.5%	85.5%	5.5%
100	50.0%	40.2%	59.80%	9.8%
100	60.0%	50.4%	69.60%	9.6%
100	70.0%	61.0%	79.0%	9.0%
100	80.0%	72.2%	87.8%	7.8%
50	50.0%	36.1%	63.9%	13.9%

50	60.0%	46.4%	73.6%	13.6%
50	70.0%	57.3%	82.7%	12.7%
50	80.0%	68.9%	91.1%	11.1%

* Using the formula: w=[1.96*sqrt(p*(1-p)/n)]

A feasibility assessment based on Panalgo-MMIT (extraction on May, 2025) identified 268 UC patients with an etrasimod prescription fill (paid or closed claim) meeting eligibility criteria (Table 3), and 79 with closed claims and more than 6 months continuous enrollment post-index date. Of the 79, 55% were AT-naïve patients (n=43). The database will be refreshed each month, so that the total number of patients included in interim and final analyses will be higher than in Table 3. By considering a similar increase in the number of patients since January 2025, we would expect 130 patients with closed claims and 6 months continuous enrollment (incl. 84 AT-naïve patients), in September 2025. Considering the acceleration in the number of patients initiating etrasimod observed since July 2024, we can expect even more patients in September 2025, around 180 (117 AT-naïve) in case of 2-fold increase.

Table 3. Preliminary Feasibility Count (Panalgo-MMIT)

Cohort Selection Step	**May** 2025	**Jan.** 2025	**Nov.** 2024
All patients – open and closed claims			
1 Patients aged 18+ with at least one etrasimod fill (paid or closed claim: the first one is index date)	351	240	196
2. (1) and with at least one Ulcerative Colitis (UC) diagnosis on or prior to index date	329	211	170
3. (2) Exclude patients with 1+ claims for Crohns Disease (CD) on or prior to index date	280	180	148
4. (3) and data availability >=12 months prior to index date (patients with at least one Mx claim and at least one Rx claim ≥12 months prior to index)	**268***	172	142
Patients with closed claims			
5. (4) and Closed index claims for etrasimod	125	71	46
6. (5) and Continuous enrollment (closed claims) ≥ 6 months post-index date**	**79****	28	17

*Including 182 AT-naive patients
** Including 43 AT-naïve patients

As a comparison, on May, 28, 2025, in Marketscan, the number of patients with closed claims and 6 months continuous enrollment was much lower, equal to 14.

9.6. Data Management

[redacted]

For the current study, the US UC population will be extracted from the Panalgo-MMIT database by Panalgo data team (all patients with at least one claim ICD-10 diagnosis code equal to K51.x (UC) and/or a claim of etrasimod between 2015 and June 2026 (annex 4)). All medical and pharmacy claims data, as well as laboratory test data of specific interest, from these UC patients will be delivered to Pfizer via Secure File Transfer Protocol and stored internally at Pfizer on a secured dedicated server.

The database will be refreshed monthly by Panalgo company until June 2026, to get most recent data at the time of analyses. A new transfer of the UC patients data will be done each month by Panalgo, to Pfizer. The data will be processed by [redacted] to create analytical variables and datasets for all analyses specified in the study protocol. All study data will exist as structured data by the time of the study. [redacted] Programmers will conduct the analyses using SAS software (SAS version 9.4 (SAS Institute; Cary, NC, USA)).

Regarding ingestion of source data, Panalgo maintains strong partnerships with leading data providers across all key modalities (claims, labs, EMR). These relationships enable transparency into upstream data changes (e.g., source additions/removals, delivery delays). Upon data ingestion, automated checks ensure data integrity, including: record count validation, regression testing to flag trend breaks, daily check-ins with data partners. Any failed Quality Controls triggers immediate restatements, typically same-day or next-day, from Panalgo data partners.

Regarding client deliverable execution, Panalgo transforms source data into client-specific deliverables (e.g., lab alerts, lab datasets, patient-level EMR outputs). Deliverable specifications are defined collaboratively with clients and require client sign-off.

9.7. Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study will be documented in a (SAP), which will be dated, filed, and maintained by the sponsor. The SAP may modify the plans outlined in the protocol; any major modifications of primary endpoint definitions or their analyses would be reflected in a protocol amendment.

9.7.1. Methods

All analyses presented herein are for informative purpose and will be presented in detail in the (SAP), which will be the reference document.

Descriptive statistics will be used to summarize the demographic and clinical characteristics of patients with UC who initiated etrasimod. The specific summary statistics that best describe a variable will depend on whether that variable is continuous, categorical, or the time to some event. Continuous variables will be described using means, standard deviations

(SD), medians, and interquartile ranges. Categorical variables will be described using frequencies and percentages in each category.

Primary objective (baseline characteristics) will be analyzed among patients who have met the selection criteria described in Section 9.2 (eligible population). For the analysis of secondary objectives, analyses will be performed on patients with closed index etrasimod claim and continuous enrollment after the index date. Specific windows of minimal continuous enrollment will be defined in the SAP for each analysis.

9.7.2. Primary Objective Analysis

To describe the baseline demographic characteristics, comorbidities, disease and treatment characteristics of patients with UC who initiated treatment with etrasimod.

The baseline demographic clinical and treatment characteristics (listed in Section 9.3) of all eligible patients with UC initiating treatment with etrasimod will be presented using summary statistics as described above.

9.7.3. Secondary Objective Analyses

9.7.3.1. Secondary Objective 1 Analysis

To describe the treatment patterns of etrasimod (adherence and persistence) among patients with UC within 12-months of etrasimod initiation.

Adherence will be measured based on PDC, which will be reported as a continuous variable and dichotomized (PDC ≥0.80 vs. <0.80). Patients would need to have continuous enrollment (closed claims) for adherence. Persistence endpoints will measure the proportion of patients still taking etrasimod at certain time points (e.g., at 3, 6 and 12 months). For assessing persistence, patients who disenroll will be censored. A gap in therapy of ≥ 60 days will be used to define treatment discontinuation. The date of discontinuation will be defined by the run out of days' supply of the last prescription filled prior to the gap in therapy, or switch to another AT, whichever comes first. Kaplan-Meier (KM) time-to-event analysis will be used to estimate median (95% confidence interval [CI]) time to treatment discontinuation in the overall patient population and among advanced therapy-naïve and treatment-experienced patients (depending on sample size). The proportion of patients who discontinue with a switch to another AT will be assessed (switch before the end of gap in therapy).

9.7.3.2. Secondary Objective 2 Analysis

To describe corticosteroid use among patients with UC within 12-months of etrasimod initiation.

The frequency and percentage of patients with corticosteroid use at different time points post-index date will be assessed. The proportion of patients with corticosteroid use post-index date will be further stratified by corticosteroid use at index date. Corticosteroid use will

be described for the overall patient population and among the two cohorts (advanced therapy-naïve and treatment-experienced patients).

9.7.3.3. Secondary Objective 3

To describe the change in level of fecal calprotectin in patients with UC, from baseline through 12 months of etrasimod initiation.

The change in fecal calprotectin level will be described by the proportion of patients with normal values at different time points within 12 months of etrasimod initiation.

9.7.4. Subgroup analysis

All analyses will be stratified according to the use of advanced therapies in the pre-index period: advanced therapy naïve patients (naïve cohort), and advanced therapy-experienced cohort (experienced cohort). Any additional subgroup analyses will be described in the SAP, such as according to age group, gender,

9.7.5. Sensitivity analysis

In a sensitivity analysis, discontinuation of etrasimod therapy will be defined as a gap in therapy of ≥ 90 days. In a second one, primary objective will be described among patients with a closed first etrasimod claims and a least 12 months continuous enrollment (CE) prior to index date for both Mx and Rx closed claims.

9.7.6. Missing Data

For all variables, missing data will be quantified in terms of the number of unique patients with missing data but will not be imputed. As relevant, missing data will be assigned as "unknown" categories, and summary statistics of continuous measures will only be reported for patients without missing data or exclusive of such data.

9.8. Quality Control

Panalgo, the database owner, has standard quality control processes. They implement several layers of quality control to ensure accuracy and reliability, including both automated and manual checks tailored to the specific data sources involved. These include:

- **Column metadata** (column names/types/values/positions - ensuring that the data output matches client expectations from the file layout agreed upon).
- **Cohort Validation**: Cross-validation of inclusion/exclusion criteria against both raw and derived datasets, ensuring the analytic population matches the cohort logic as defined in the specifications.
- **Source Traceability Checks**: Verification of patient ID continuity across tokenized datasets (e.g., claims, EMR, labs), with reconciliation against the original source files to ensure no data loss during linkage.

- **Field-Level Integrity**: Automated and manual validation of key clinical variables and derived fields, including assessment of allowable ranges, temporal plausibility (e.g., diagnosis preceding treatment), and internal consistency (e.g., lab units, claim dates)
- **Volume and Distribution Reviews**: Benchmarking of patient and event volumes against historical extracts and epidemiologic expectations to identify outliers or gaps indicative of Extract, Transform, Load anomalies.
- **Table-level statistics and trends** (collecting relevant table characteristics to access easily at a later date, leverage the table statistics to ensure that changes from one deliverable to another 'make sense' and are expected).
- **Relational checks** (ensuring the client can fully make sense of our data by having all necessary dimensional fields to analyze the fact tables).
- **Version Control & Documentation**: All quality control outputs are version-controlled, with a full audit trail of checks performed, logic used, and results reviewed prior to delivery.

Analyses will be programmed according to the specifications in the protocol and SAP. Final deliverables will be reviewed and verified by a second, independent programmer who may also perform double programming, all quality checks will be documented in the programming plan.

9.9. Limitations of the Research Methods

The potential limitations of this study are as follows:

Overall, the Panalgo-MMIT database is large and covers a wide geographical area (base population of 300 million); however, limitations inherent to all claims database analyses should be noted.[33,34] Comorbidities will be identified using ICD-10-CM diagnosis codes, which may be subject to potential miscoding. The baseline period of this study is of limited duration, thus baseline comorbidities and prior treatments occurring outside of this baseline period may not be captured, which may lead to misclassification.

Typically, pharmacy fill of a drug does not necessarily indicate that the medication was taken as prescribed; similarly, medications filled over-the-counter or provided as samples by the physician will not be recorded in the database. However, regarding etrasimod, a costly drug, very few US patients (if none) are expected to get the drug without any insurance coverage. Outcomes (adherence, persistence, steroid use) will also be captured by way of pharmacy claims, ensuring comprehensive identification of etrasimod and steroid dispensings. However, some misclassification may occur as dispensing may not match totally with real intake of the patient.

The absence of granularity of clinical details and gap in patient's healthcare journey with claims data will make it difficult to capture severity of UC among patients based on patient symptoms. However, Panalgo-MMIT database includes laboratory test results data that can be used as severity proxy for patients with such data (CRP, fecal calprotectin), in addition to UC-related hospitalization or emergency room visits.

Reasons for discontinuation are not directly available in this type of data source, which will limit the interpretation of persistence. However, persistence rate is a very common outcome investigated in the field of chronic immunology and inflammatory diseases, as a proxy of both long-term effectiveness and safety of advanced therapies in the real world. [21,24,28] The utilization of open claims data may lead to incomplete information during the baseline period, as continuous enrollment in a health care plan is not available for patients with only open claims. To mitigate this, only patients with data availability for more than 12 months prior to index date are considered.

Regarding the analysis of treatment patterns and steroid use, only patients with closed claims and continuous enrolment during follow-up will be considered. Although the strength of using closed claims data lies in its comprehensive coverage, a limitation is its lack of data recency and closed claims data often have some lag time. Further there may be substantial attrition when applying continuous enrollment criteria.

These study results may not be generalizable outside of the insured population, or populations outside of the US. Further, since this study captures only early users of etrasimod post-approval, their characteristics may or may not mirror that of patients with UC who will be prescribed etrasimod at a later period.

9.10. Other Aspects

Not applicable.

10. PROTECTION OF HUMAN PARTICIPANTS

10.1. Patient Information

This study involves data that exist in deidentified/anonymized structured format and contain no patient personal information.

10.2. Patient Consent

As this study involves deidentified/anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional Review Board (IRB)/ Ethics Committee (EC)

A submission to obtain an IRB waiver will be done after final approved protocol.

10.4. Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA) European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves data that exist as structured data by the time of study start. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (i.e., identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Data may be summarized periodically for presentation at professional conferences and sessions, as appropriate. Manuscripts will be prepared with the results from this study for submission in peer reviewed journals. For all publications relating to the study, Pfizer will comply with recognized ethical standards concerning publications and authorship, including Section II – "Ethical Considerations in the Conduct and Reporting of Research" of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, established by the International Committee of Medical Journal Editors (ICMJE, 2008). The study will be appropriately disclosed on ct.gov.

In the event of any prohibition or restriction imposed (eg, clinical hold) by an applicable competent authority in any area of the world, or if the party responsible for collecting data from the participant is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

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ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Not applicable.

ANNEX 3. LIST OF CODES FOR COMORBIDITIES

All codes are ICD-10-CM diagnosis codes. For a patient to be considered as having the specified comorbidity (left column), at least one of the corresponding ICD-10 codes (right column) must be associated with the patient's claims.

Comorbidity description	ICD-10 Codes
Charlson comorbidities	
Any malignancy, including leukemia and lymphoma, except for non-melanoma skin cancer	C00.x-C26.x, C30.x-C34.x, C37.x-C41.x, C43.x, C45.x-C58.x, C60.x - C76.x, C81.x-C85.x, C88.x, C90.x-C97.x
Cerebrovascular disease	G45.x-G46.x, H34.0x, I60.x-I69.x
Chronic pulmonary disease	I27.8x-I27.9x, J40.x-J47.x, J60.x-J67.x, J68.4x, J70.1x, J70.3x
Congestive heart failure	I09.9x, I11.0x, I13.0x, I13.2x, I25.5x, I42.0x, I42.5x-I42.9x, I43.x, I50.x, P29.0x
Dementia	F00.x-F03.x, F05.1x, G30.x, G31.1x
Diabetes with chronic complications	E10.2x-E10.5x, E10.7x, E11.2x-E11.5x, E11.7x, E12.2x-E12.5x, E12.7x, E13.2x-E13.5x, E13.7x, E14.2x-E14.5x, E14.7x
Diabetes without chronic complications	E10.0x, E10.1x, E10.6x, E10.8x, E10.9x, E11.0x, E11.1x, E11.6x, E11.8x-E12.1x, E12.6x, E12.8x-E13.1x, E13.6x, E13.8x-E14.1x, E14.6x, E14.8x, E14.9x
Hemiplegia or paraplegia	G04.1x, G11.4x, G80.1x-G80.2x, G81.x-G82.x, G83.0x-G83.4x, G83.9x
Liver disease, mild	B18.x, K70.0x-K70.3x, K70.9x, K71.3x-K71.5x, K71.7x, K73.x-K74.x, K76.0x, K76.2x-K76.4x, K76.8x-K76.9x, Z94.4x
Liver disease, moderate or severe	I85.0x, I85.9x, I86.4x, I98.2x, K70.4x, K71.1x, K72.1x, K72.9x, K76.5x-K76.7x
Metastatic solid tumor	C77.x-C80.x
Myocardial infarction	I21.x, I22.x, I25.2x
Peptic ulcer disease	K25.x-K28.x
Peripheral vascular disease	I70.x-I71.x, I73.1x, I73.8x-I73.9x, I77.1x, I79.0x, I79.2x, K55.1x, K55.8x-K55.9x, Z95.8x-Z95.9x
Renal disease	I12.0x, I13.1x, N03.2x-N03.7x, N05.2x-N05.7x, N18.x-N19.x, N25.0x, Z49.0x-Z49.2x, Z94.0x, Z99.2x
Rheumatic disease	M05.x-M06.x, M31.5x, M32.x-M34.x, M35.1x, M35.3x, M36.0x
AIDS/HIV	B20.x-B22.x, B24.x
Extra intestinal immune mediated inflammatory diseases	
Rheumatoid arthritis	M05.x, M06.0x, M06.8x, M06.9x
Psoriasis	L40.x

Ankylsing spondylitis	M45.x
Psoriatic arthritis	L40.5x
Pyoderma gangranosa	L88.x
Episcleritis	H15.1x
Erythema Nodosum	L52.x
Primary sclerosing cholangitis	K83.01
Arthropathy - Arthralgia	M02.x, M26.61x, M26.62x
Other comorbidities	
Abdominal pain	R10.x
Anemia	D64.x, D50.x, D52.x
Anxiety	F41.x
Coagulation Defects	D66.x, D67.x, D68.x
Depression	F32.x, F33.x
Hypertension	I10.x, I15.x, O10.4x, O10.9x, O11.x
All infections	A00.x-A99.x, B00.x, B01.x, B03.x-B99.x, D733, G01.x-G08.x, G361, H04.01, H04.02, H04.3x, H05.0x, H10.x, H16.31, H20.03, H20.05, H21.33, H30.x, H32.x, H33.12, H44.0x, H44.1x, H59.4x, H60.x, H62.4x, H66.x, H67.x, H70.1x, H70.89, H70.9, H75.0, H94.0x, I30.1x, I33.x, I39.x, I40.x, I67.3, I76.x, I89.1x, I96.x, J00.x-J22.x, J34.0x, J36.x, J39.1x, J40.x, J47.0x, J47.1x, J65.x, J85.x, J86.9x, J95.02, J95.85, K12.2x, K35.x, K36.x, K37.x, K50.114, K51.414, K51.514, K51.814, K51.914, K57.00, K57.01, K57.12, K57.13, K57.2x, K57.32, K57.33 ,K57.4, K57.52, K57.53, K57.80, K57.81, K57.92, K57.93, K61.x, K63.0, K65.x, K68.1, K68.9, K75.0, K81.x, K83.0, K90.81, K94.02, K94.12, K94.22, K94.32, K95.01, K95.81, L01.x-L04.x, L05.0x, L08.x, L30.3x, L44.4x, M00.x, M01.x, M46.2x, M46.3x, M46.4x, M46.5x, M60.0x, M65.0x, M65.1x, M65.19, M71.0x, M72.6x, M86.x, N10.x, N13.6x, N15.1x, N28.84, N28.85, N28.86, N30.x, N34.0x, N39.0x, N41.0x, N41.1x, N41.8x, N45.1x, N45.2x, N45.4x, N48.1x, N49.3x, N53.9x, N70.x, N71.0x, N73.x, N74.x, N75.1x, N76.0x, N76.2x, N76.4x, N77.1x, N98.0x, N99.511, N99.521, N99.531, O03.38, O04.88, O07.0x, O07.38, O08.0x, O0883, O23.x, O26.8x, O29.01, O74.0x, O85.x, O86.x, O88.32, O89.01, O98.0x, O98.2x, O98.3x, P36.1x, P36.2x, P36.3x, P36.4x, P36.5x, P37.5x, P37.8x, P38.x, P39.x, P78.1x, R78.81, T80.2x, T81.4, T82.6XXA, T82.6XXD, T82.7x, T83.5x, T83.6x, T84.5x, T84.6x, T84.7x, T85.7x, T85.71, T85.72, T85.79, T86.13, T86.832, T86.842, T87.4x, T88.0x, Y82.9x
Herpes Zoster Infections	B02.x
Opportunistic infections	A01.01-A01.05, A02.1x, A02.21-A02.25, A07.2x, A15.x, A17.x, A18.x, A1.x, A31.x, A32.x, A43.x, A44.x, A48.1x, A48.2x, A60.02, A81.2x, B00.3x, B00.4x, B00.7x, B00.81, B00.82, B01.0x, B01.0x, B01.12, B01.2x, B02.0x, B02.1x, B02.7x, B25.x, B27.1x, B27.11, B27.12, B27.19, B37.0x, B37.1x, B37.5x, B37.6x, B37.7x, B37.81, B38.x, B39.x, B40.x-B46.x, B47.9x, B48.x, B55.x, B57.0x-B57.5x, B58.x, B59.x, B60.11, B60.13, B78.x, G04.8x, G04.9x, G05.x-G08.x, H20.03, H70.1x, H70.89, H70.9x, H75.0x, I67.3x, 098.0x
Non-Melanoma Skin Cancer	C44.x
Obesity	E66.x
Veinous thromboembolism	I80.1x, I80.2x, I82.0x-I82.7x, I82.7x, I82.A, I82.B, I82.C, O22.x3, O22.5x, O87.1x, O87.3x, I26.x, I27.82

ANNEX 4. PATIENT EXTRACTION DEFINITION

Defined Patient Cohort: All Patients diagnosed with UC or on etrasimod during time period of interest (latest 10 years for closed claims, and latest 8 years for open claims)			
No.	**Criteria**	**Description of Criteria**	**Code**
1	ICD 10	Ulcerative Colitis	K51*
2	NDC	[redacted] (etrasimod)	63539027428 00069027430

Document Approval Record

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