NON-INTERVENTIONAL (NI) STUDY PROTOCOL

PASS information

Title	An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union
Protocol number	C5041046
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Date	07 July 2025
EU Post Authorization Study (PAS) register number	To be registered prior to the start of data collection
Active substance	Etrasimod ATC code: L04AE05
Medicinal product	Velsipity®
Product reference	EMEA/H/C/006007
Procedure number	EMA/PASS/XXXXXXXXXX (Not yet available; to be obtained after submission to health authority)
Marketing Authorization Holder(s)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
Joint PASS	No
Research question and objectives	What are the incidence rates (IRs) of the safety events of interest (macular oedema, serious liver injury, malignancy, serious opportunistic infections, neurologic events of posterior reversible encephalopathy syndrome (PRES) or convulsions, and symptomatic bradycardia [including conduction disorders]) among patients aged ≥16 years with active ulcerative colitis (UC) treated with etrasimod during routine clinical care? Study objectives are to: 1. Describe characteristics of patients with UC at the time of initiating etrasimod (Cohort 1), and of patients with UC who initiate comparator medications of interest: a) other S1P receptor modulators (Cohort 2) b) biologics (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 3)

	c) Janus-associated kinase inhibitors (JAKi, with or without concurrent use of immunomodulators/immunosuppressants; Cohort 4) 2. Estimate the IRs of safety events of interest among patients with UC who initiate etrasimod (Cohort 1) 3. Estimate the IRs of safety events of interest among patients with UC who initiate other S1P receptor modulators (Cohort 2), biologics (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 3), or JAKi (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 4) 4. Pending sufficient sample size, compare incidence of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating: a) other S1P receptor modulators (Cohort 2) b) biologics (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 3) c) JAKi (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 4) 5. Estimate IRs of eye adverse events, infections, and cardiovascular events separately among patients aged 65 years and older with UC who initiate either etrasimod (Cohort 1), other S1P receptor modulators (Cohort 2), biologics (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 3), or JAKi (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 4).
Country(ies) of study	Germany, Sweden, and the Netherlands

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2. LIST OF ABBREVIATIONS

Abbreviation	Definition
5-ASA	5-aminosalicylic acid-containing medication
ATC	Anatomical Therapeutic Chemical
BIPS	Leibniz Institute for Prevention Research and Epidemiology
BMI	body mass index
CDM	common data model
CI	confidence interval
CPE	Centre for Pharmacoepidemiology
CPR	Central pharmaceutical reference database in GePaRD
CV	Cardiovascular
DDD	daily defined dose
EBM	German Uniform Evaluation Standard – GePaRD codes for outpatient visits with procedures
EC	Ethical Committee
ED	emergency department
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
GDPR	General Data Protection Regulation
GePaRD	German Pharmacoepidemiological Research Database
GP	General Practitioner
GM	German Modification
GPP	Guidelines for Good Pharmacoepidemiology Practices
HIV	Human Immunodeficiency Virus
HMA	Head of Medicines Agency
HR	hazard ratio
IBD	inflammatory bowel disease
ICD	International Classification of Diseases
ICMJE	International Committee of Medical Journal Editors
ICPC	International Classification of Primary Care
IP	inverse probability
IPTW	inverse probability of treatment weighting
IPW	inverse probability weighting
IR	incidence rate
IRB	Institutional Review Board
ISO/IEC	International Organization for Standardization/International Electrotechnical Commission
JAKi	Janus-associated kinase inhibitors
MedDRA	Medical Dictionary for Regulatory Activities
NA	not available
NEN	*Nederlandse norm,* from the *Nederlands Normalisatie Instituut*
NI	non-interventional

Abbreviation	Definition
NPR	National Patient Register
NZa	Dutch healthcare authority (*Nederlandse Zorgautoriteit*)
PASS	post-authorization safety study
PDR	Prescribed Drug Register
PHARMO	PHARMO Institute for Drug Outcomes Research, providing the PHARMO Data Network
PML	progressive multifocal leukoencephalopathy
PPV	positive predictive value
PRAC	Pharmacovigilance Risk Assessment Committee
PRES	posterior reversible encephalopathy syndrome
PT	Preferred Term
RMP	Risk Management Plan
RWD	real-world data
S1P	Sphingosine-1-phosphate
SAP	Statistical Analysis Plan
SAS	Statistical Analytical Solutions
SMQ	Standardized MedDRA Queries
SmPC	Summary of product characteristics
SNHR	Swedish National Health Registers
SOI	serious opportunistic infection
STIZON	*Stichting Informatievoorziening voor Zorg en Onderzoek*
SWIBREG	Swedish Inflammatory Bowel Disease Registry
TNFi	Tumor-necrosis factor-α inhibitors
TTE	Target trial emulation
TTP	Trusted third party
UC	Ulcerative colitis
WHO	World Health organization

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Protocol title
An Active Surveillance, Post-Authorization Safety Study (PASS) to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union (EU)

Rationale and background
Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is a chronic condition of the colonic mucosa. A new treatment option for UC is sphingosine-1-phosphate (S1P) receptor modulators, such as Etrasimod (Velsipity®). Etrasimod is indicated for treatment of patients aged 16 years and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biological agent. Etrasimod was approved for use in the EU on 16 February 2024. This non-interventional study is a commitment to the European Medicines Agency (EMA), and is designated as a PASS to evaluate the risk of safety events of interest among patients with UC who are treated with etrasimod. Safety events of interest for this study are: macular oedema, serious liver injury, malignancy, serious opportunistic infections, neurological events of posterior reversible encephalopathy syndrome (PRES) and convulsions, and symptomatic bradycardia (including conduction disorders).

Research question and objectives
Research question: What are the incidence rates (IRs) of safety events of interest among patients aged ≥16 years with active UC treated with etrasimod during routine clinical care?

Primary objectives

1. Describe the characteristics of patients with UC at the time of initiating etrasimod (Cohort 1), and of patients with UC who initiate comparator medications of interest:
    a. other S1P receptor modulators (Cohort 2),
    b. biologics (with/without concurrent use of immunomodulators/immunosuppressants; Cohort 3),
    c. Janus-associated kinase inhibitors (JAKi; with/without concurrent use of immunomodulators/immunosuppressants; Cohort 4).
2. Estimate the IRs of safety events of interest among patients with UC who initiate etrasimod (Cohort 1)
3. Estimate the IRs of safety events of interest among patients with UC who initiate other S1P receptor modulators (Cohort 2), biologics (with/without the concurrent use of immunomodulators/immunosuppressants; Cohort 3), or JAKi (with/without concurrent use of immunomodulators/immunosuppressants; Cohort 4)
4. Pending sufficient sample size, compare incidence of safety events of interest among patients with UC initiating etrasimod (Cohort 1) to patients with UC initiating:
    a. other S1P receptor modulators (Cohort 2),
    b. biologics (with or without the concurrent use of immunomodulators/immunosuppressants; Cohort 3),
    c. JAKi (with/without concurrent use of immunomodulators/immunosuppressants; Cohort 4).

Secondary objective:

5. Estimate IRs of eye adverse events, infections, and cardiovascular (CV) events separately among patients aged 65 years and older with UC who initiate either:
    a. etrasimod (Cohort 1),
    b. other S1P receptor modulators (Cohort 2),
    c. biologics (with/without the concurrent use of immunomodulators/immunosuppressants; Cohort 3),
    d. JAKi (with/without the concurrent use of immunomodulators/immunosuppressants; Cohort 4).

Study Design

This study is a non-interventional, multi-country, active surveillance cohort study of patients with UC initiating use of etrasimod or comparator medications. The study will retrospectively assess secondary sources of data including electronic health records, healthcare claims, and registry data. This study will describe patient characteristics and estimate safety events of interest in four main Cohorts of patients with UC defined by initiation of medication. Comparative analyses will be conducted pending sufficient sample size.

Outcomes will be assessed using a 'restricted' as-treated approach, in which only the first continuous treatment episode for a Cohort-defining treatment is used, and any subsequent treatment episodes are not considered.

The study will include data from 16 February 2014 to 31 December 2032. This period comprises an indexing period of at least 8 years beginning on the 16 February 2024, the date of EU approval of etrasimod, and a maximum lookback window of 10 years prior to index date. The index date will be defined as the first date of exposure to a Cohort-defining treatment, while meeting all inclusion criteria. Patients will be followed until the first of: the first occurrence of an outcome of interest (separate analyses per outcome), the end of exposure to a Cohort-defining treatment (extended with a fixed period for malignancy outcomes), a switch to another Cohort-defining medication, initiation of use of non-Cohort-defining medication for UC (ie., deviation of a monotherapy treatment strategy for UC) (for Cohorts 1 and 2 only), surgical full removal of colon, or colon and rectum (for outcome of colorectal cancer only), a diagnosis of Crohn's disease, disenrollment, death, or the end of the study period (31 December 2032).

Population

The source population for this study will be derived from data from electronic health records, healthcare claims, and registry data capturing national-level routine clinical care from four EU data sources in three different countries.

The study population will include patients with a diagnosis of UC, with a first ever dispensing or prescription of etrasimod (Cohort 1), other S1P receptor modulators (Cohort 2), biologics (with/without the concurrent use of immunomodulators/immunosuppressants; Cohort 3), or JAKi (with/without the concurrent use of immunomodulators/immunosuppressants; Cohort 4). Patients in Cohorts 1 and 2 will be

required to adhere to a monotherapy treatment strategy for UC at index date ie., not allowing use of other non-Cohort-defining medication for UC.

To be eligible for inclusion, patients must:

- have had a diagnosis of UC,
- have a first prescription/dispensing (index date) of a Cohort-defining medication (inclusion per Cohort),
- be aged 16 years and older at the index date, and
- have a minimum of one year of data available prior to the index date.

Patients will be excluded if they had exposure to the same Cohort-defining treatment prior to the index date, had a diagnosis of Crohn's disease prior to, or on, index date, or were concurrently using non-Cohort-defining medication for UC (for Cohorts 1 and 2 only).

Variables

Exposure to Cohort-defining medication is defined as a time window, that of the first continuous treatment episode. Exposed time windows will be ascertained from hospital or outpatient pharmacy prescription/dispensing data using ATC-based codes. The number of days of supply will be estimated accounting for stockpiling and permissible gaps using a grace period. Patients will be allowed to switch to another Cohort, allowing for a maximum of four distinct first treatment episodes of Cohort-defining medication per patient; the unit of observation is the treatment episode.

Outcomes will be ascertained from outpatient and inpatient records from different settings, as available per data source. Outcomes will be defined using International Classification of Disease-10th revision (ICD-10) codes, selected based on Medical Dictionary for Regulatory Activities (MedDRA) terms, and further translated to the other coding systems, as required. When possible, validated algorithms or code lists will be used.

Patient demographics, clinical characteristics, and comedication use will be assessed using a lookback window of minimum 1 year and maximum 10 years before index date. Concomitant UC medication use and mortality will be assessed throughout follow-up.

Data sources

This study population will be derived from the following data sources: the German Pharmacoepidemiological Research Database (GePaRD) from Germany, the Swedish National Health Registers (SNHR) and Swedish Inflammatory Bowel Disease Registry (SWIBREG) from Sweden, and the PHARMO Data Network (PHARMO) from the Netherlands.

Local regulatory decisions for reimbursement will be considered when assessing etrasimod exposure per data source.

Study size
This study will report on all eligible patients and the safety events of interest occurring in the data sources' study populations during the study period. At the time of the final report comparative analyses will be conducted, pending sufficient sample size.

Data analysis
A distributed common data model (CDM) approach will be used. Code lists and identification algorithms will be created in collaboration with the participating databases/registries and medical experts, and will be detailed in the statistical analysis plan (SAP).

Descriptive statistics will be reported and IRs and their respective 95% confidence intervals will be estimated.

Subgroup analyses will focus on older adult patients (aged 65 years or over). These subgroup analyses will assess the following safety events of interest only: eye adverse events, infections, and CV events.

Results will be provided stratified by country in the interim report and final report. In the final report, data will also be pooled for meta-analysis, considering heterogeneity of country-specific results and conditional on minimum numbers of events.

Additionally, pending sufficient sample size, the incidence of outcomes between Cohort 1 and Cohort 2, Cohort 1 and Cohort 3, and Cohort 1 and Cohort 4 will be compared, and included in the final report. These comparative analyses will be guided by the use of a target trial emulation (TTE) framework. Potential confounding will be addressed using, for example, propensity score methods and inverse probability weighting.

Sensitivity analyses to the main analyses will include:

1. Changing lag-time for start of treatment episodes for malignancy outcomes, to either 0 (no lag) or 12 months.
2. Using an intention-to-treat approach for ascertaining malignancies.
3. Expanding definitions of symptomatic bradycardia by further requiring presence of symptom codes occurring on the same day as the event.
4. Repeating the main analysis restricting to patients without a history of the safety event of interest, or similar conditions.
5. Describing patients with a single prescription/dispensing per Cohort, and the proportion of these patients with a safety event of interest in the 30 days after index date.
6. Intention to treat approach for PRES.
   Allowing concurrent use of non-Cohort-defining medication for UC, per the approved SmPC, for inclusion in Cohorts 1 and 2.

Milestones

Submission of the draft study protocol to the EMA is expected 14 June 2024. Registration in the HMA-EMA Catalogue of Real-World Data Studies is expected prior to the start of data

collection. Data collection is expected to start in 15 November 2026 and end 30 June 2035. One interim report will be provided in year 5 of the study in Q1, currently expected May-2028. The final study report is expected on 31 December 2035, within 6 months of the end of data collection.

5. AMENDMENTS AND UPDATES

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
V1.0	30-OCT-2024	Substantial	PASS information Sections 4, 8, Section 9 (throughout, including changes in Tables 1, 14, 16, and 17)	Addition of Cohort 4: JAKi.	
			2	Abbreviations updated.	NA
			4	Updated objectives, outcomes for subgroup analyses, and sensitivity analyses.	To reflect body of text.
			6	Removed protocol submission milestone.	This was not a mandatory milestone per the EMA protocol template.
			9.1.1	Updated handling risk windows for sensitivity analyses.	Due to added sensitivity analyses requested by PRAC.
			9.3.2	Specification of broadening of symptomatic bradycardia (including conduction disorders) and macular oedema, and restructuring and specification of outcomes used in subgroup analyses.	Based on PRAC comments.
			9.3.2	For serious liver injury, added the 'SMQ Drug-induced liver injury (narrow scope)'.	Further refinement of concept for serious liver injury (to be fully defined in the SAP).
			9.3.2.x subsections	Edits to specify changes in how concepts of macular oedema and symptomatic bradycardia (including	Based on requests from PRAC Macular oedema concept also broadened ot include selected retinal

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				conduction disorders) will be developed.	disorders, to ensure that sufficient local codes in the data sources (using ICD) will be available to map the concept.
			9.5	Specification added in footnote of Table 16: study precision estimates for macular oedema were based on a concept slightly different from this PASS.	Concept in this PASS using secondary data differs from concept as assessed in clinical trial sources used to derive incidence rates for precision estimates.
			9.6	Updated section on data management.	Based on PRAC request to update on aspects of data access, and on Article 12.2 of the implementation regulations (EU/520/2012).
			9.7.3	Subgroup analyses outcome definitions were further specified where possible, section information restructured to be included under 9.3.2 Outcomes:	Based on PRAC request.
			9.7.5	A sensitivity analysis was added for an alternative risk window for PRES.	Based on PRAC requests.
			9.9	Added limitations: Specifications for the expected capture of biologics and JAKi in the data sources Limitations of assessment of serious liver injury limited to the inpatient setting Limitations for interpretation of the sensitivity analysis	Based on added analyses reflecting changes requested by PRAC, and new insights.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
				extending the risk window for PRES.	
			Throughout	Minor editorial changes.	Improve readability; Part of repeated quality control.
V2.0	14 March 2025	Administrative	Section 6	Added clarification to the milestone table footnote regarding data availability.	To prevent potential confusion about the data availability for the first interim report.
			9.7.5	Replaced 'nine' with 'seven' in the first sentence.	Typo needed to be corrected.
			Sections 9.1.1, 9.2.4, 9.3.1.2, 9.3.2, 9.3.2.3, 9.3.2.5, 9.3.2.6, 9.5	Updated cross-references to 9.7.5, 9.7.6.	Cross-references needed to be corrected.
V3.0	30 June 2025	Substantial	Table 14	Changed date formatting.	For consistency with rest of the study protocol.
			PASS Information, Section 3	Updated authors list.	Needed to be corrected due to personnel changes.
			Abstract, Sections 9.1.1, Footnote Figure 1, 9.2.2, 9.2.4, 9.7.2 (Table 18), 9.7.5	Clarified the treatment strategy for Cohorts 1 and 2 as monotherapy; to include patients at index date who do not use non-Cohort-defining medication for UC, and censor durig follow-up at initiation of non-Cohort-defining medication for UC.	To improve clarity of the cohort definitions. This definition improves the ability to attribute rates and potential risks of safety events to Cohort-defining medication. A sensitivity analysis allowing for certain concomitant use is also proposed in Section 9.7.5.
			Sections 8, 9.3.1	Minor updates to phrasing regarding the number of Cohorts studied in this PASS.	For consistency with the updated inclusion of 4th Cohort.

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			Section 9.3.1 (Table 1)	Added guselkumab as an example of Cohort-defining medication for Cohort 3.	To reflect expected potential use for patients with UC (Rubin et al., 2025, Lancet).
			Section 9.3.1.1	Corrected cross-reference to Figure 4, clarified 4th, bottom panel of Figure 4 indicates 2 distinct hypothetical patients.	To correct cross-referencing, and to clarify how the first continuous treatment episode will be assessed.
			Abstract, 9.1.1, Milestone Table footnote, Figure 1 footnote	Corrected the study period dates, study duration, indexing period dates.	For consistency with Section 9.4.4.
			Section 9.2.4, Figure 1 (footnote)	Revision of exclusion criterion from 'prior to index date' to 'prior to **or on** index date.'	First dispensing of Cohort-defining medication could align with a hospital discharge date where a diagnostic code of Crohn's can be recorded.
			Figure 1	Revision of the study diagram to allow for assessment prior to or on index date.	For consistency with text in Section 9.2.4 describing assessment of the history of safety events of interest or related conditions.
			Section 9.3.1	Changed reference to Cohort-defining medication to include all Cohorts, not only Cohorts 1, 2 and 3.	To include Cohort 4 consistent with other sections.
			Abstract, Sections 9.3.1.2, 9.7.5, Table 17	Revised the lag time sensitivity analysis from 3 months to 0 months (ie no lag time).	To correct a potential selection bias issue due to misalignment of treatment assignment and assessing eligibility with the time zero (start of follow-up).

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
			Table 12, Sections 9.4.2.2, 9.4.4, 9.9	Clarified that in Sweden, Cohorts will be restricted to individuals in SWIBREG. Further corrected availability of cause of death, and updated SWIBREG data description where possible.	To specify selection of Cohorts will be based on Swedish data source that has all relevant medication data covered for this PASS, and update data source information where possible.
			Section 9.7.5	Added a sensitivity analysis allowing for concurrent use of non-Cohort-defining medication for UC, per the approved SmPC, for inclusion in Cohorts 1 and 2.	To better capture real-world use and improve potential for conducting comparative analyses.
			Table 10	For co-medications (non-UC treatments/medication) and concomitant UC medications use, changed the name of the variable and clarified the lookback window to include "prior to, or on, index date."	For clarifying that co-medication will be measured separately either prior to or on index date, and during follow-up. Also, for consistency with how other variables are specified in this section.
			Table 13	Updated country-specific estimated dates for reimbursement of etrasimod.	To reflect latest available information on reimbursement.
			Abstract, Section 9.7.5, Table 17	Removed sensitivity analysis on misclassification for malignancy.	During SAP development, it became evident that, given the use of two cancer registries as data sources for the studythere was no need for alternative definitions for malignancy as the current definition was the most effective definition,

Version Identifier	Date	Amendment Type (substantial or administrative)	Protocol Section(s) Changed	Summary of Amendment(s)	Reason
					and a sensitivity analysis with alternative definitions would have limited added value
			Section 9.10	Rephrased how results from IR will be used to inform sample size estimates.	To better reflect decision making for sample size requirements based on the Interim Report.
			Section 9.7.5	Clarified windows for assessment of history of safety events of interest, or related conditions, including adding a second window for assessment of a history of symptomatic bradycardia (including conduction disorders).	For consistency with Figure 1, and to allow adequate assessment of incident acute events for symptomatic bradycardia (including conduction disorders).

6. MILESTONES

Milestone	Planned Date
Start of data collection*	15 November 2026
Registration in the HMA-EMA Catalogue of Real-world data Studies	Prior to start of data collection
Interim report	Within first quarter in year 5 of the study (expected 16 May 2028)**
End of data collection***	30 June 2035
Final study report	31 December 2035±

See Section 9.4 for details on data sources, and Section 9.4.4 on data source-specific considerations for milestones

*For secondary database studies, this is the date of starting data extraction for the purposes of the primary analysis (eg, simple counts to inform sample size calculation are not relevant) for the interim report. Start of data collection aligns with data extraction cycles for all countries (Table 12).

** The study will include data from 16 February 2014 to 31 December 2032. This period comprises an indexing period of at least 8 years beginning on the 16 February 2024, the date of EU approval of etrasimod, and a maximum lookback window of 10 years prior to index date. However, due to country-specific data lags, reimbursement timelines, and the time needed to prepare the analytic dataset and interim report, the study period included in the interim report will be from study start until 31 December 2024 for the German data source, and until 31 December 2025 for the Swedish and Dutch data sources.

***For secondary database studies, this is the date when the analytical dataset is available to perform analysis for the primary objectives. Finalized data extraction for all countries (for study periods described in Section 9.4) is expected on 30 June 2034.

±Within 6 months from the end of data collection

7. RATIONALE AND BACKGROUND

Ulcerative colitis (UC), an inflammatory bowel disease (IBD), is a chronic condition characterized by inflammation of the colonic mucosa.(1) It is thought to result from an abnormal immune response to an environmental change. UC incidence is stabilizing in the European Union (EU) but the burden of the disease remains substantial as the prevalence exceeds 0.3% in many EU countries.(2) UC typically first presents in young adulthood (ages 15-30 years) or in middle/older age (ages 50-70 years).(1)

The natural history of UC consists of flares and periods of remission. Treatment aims to induce and maintain steroid-free clinical remission. Choice of treatment depends on disease severity. Moderate to severe disease is often treated initially with systemic corticosteroids and followed by immunosuppressants, or biologics to maintain remission.(3) Some of the available therapies for patients with moderate to severe disease may lose efficacy over time or have associated serious adverse events, prompting the need for identifying new treatments. One new treatment option is sphingosine-1-phosphate (S1P) receptor modulators. The mechanism of action of S1P receptor modulators is thought to act through stopping lymphocyte mobilization to inflammatory sites. The S1P receptor modulators have demonstrated benefit among UC patients in clinical trials.(4-6)

Etrasimod (Velsipity®) is a selective S1P receptor modulator indicated for the treatment of patients 16 years of age and older with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent.(7)

Several potential or identified risks have been reported with use of etrasimod, based on animal studies and clinical trials of etrasimod, as well as safety issues associated with use of another S1P receptor modulator, ozanimod. The safety events of interest are: macular oedema, serious liver injury, malignancy, serious opportunistic infections, neurological events of posterior reversible encephalopathy syndrome (PRES) and convulsions, and symptomatic bradycardia (including conduction disorders).

This protocol describes a Post-Authorization Safety Study (PASS) to evaluate the safety events of interest of etrasimod among patients with UC in a real-world setting in the EU. This non-interventional study is designated as a PASS and is a commitment from Pfizer to the European Medicines Agency (EMA), and Pharmacovigilance Risk Assessment Committee.

The expected contribution of this PASS study is the longitudinal, systematic characterization of the safety of etrasimod in a real-world population of patients using etrasimod in the EU. This study will benefit from a larger and a more generalizable patient population than was included in the clinical trials. Additionally, the longer follow-up will enable the assessment of long latency events (eg, malignancy).

8. RESEARCH QUESTION AND OBJECTIVES

The research question is as follows: What are the incidence rates (IRs) of the safety events of interest (listed below) among patients aged ≥16 years with active UC treated with etrasimod during routine clinical care?

- Macular oedema
- Serious liver injury
- Malignancy
- Serious opportunistic infections
- Neurologic events of PRES or convulsions
- Symptomatic bradycardia (including conduction disorders)

For contextualizing safety for patients initiating etrasimod, safety events of interest will also be identified in populations of patients with UC defined by new use of other UC-indicated medications of interest, namely other S1P receptor modulators (eg, ozanimod), biologics (with or without concurrent use of immunomodulator/immunosuppressant medications), and Janus-associated kinase inhibitors (JAKi, with or without concurrent use of immunomodulator/immunosuppressant medications). The patient populations defined by their use of UC indicated medication are hereafter referred to as Cohorts. The medications defining Cohort 2, 3 and 4 are referred to as 'comparator medications of interest'. Further definitions are provided in Sections 9.2.2 (study Cohorts), 9.3.1 (exposure) and 9.3.2 (outcomes) as well as 9.7.5 (sensitivity analyses).

To address the research question, the following primary and secondary objectives are defined (Sections 8.1 and 8.2).

8.1. Primary Objectives

1. Describe characteristics of patients with UC at the time of initiating etrasimod (Cohort 1), and of patients with UC who initiate comparator medications of interest:
   a) other S1P receptor modulators (Cohort 2)
   b) biologics (with or without concurrent use of immunomodulator/immunosuppressant medications; Cohort 3)
   c) JAKi (with or without concurrent use of immunomodulator/immunosuppressant medications; Cohort 4)

2. Estimate the IRs of safety events of interest among patients with UC who initiate etrasimod (Cohort 1)

3. Estimate the IRs of safety events of interest among patients with UC who initiate other S1P receptor modulators (Cohort 2), biologics (with/without concurrent immunomodulators/immunosuppressants; Cohort 3), or JAKi (with or without concurrent use of immunomodulator/immunosuppressant medications; Cohort 4)

4. Pending sufficient sample size, compare incidence of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating:

   a) other S1P receptor modulators (Cohort 2)
   b) biologics (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 3)
   c) JAKi (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 4)

8.2. Secondary Objective

5. Estimate IRs of eye adverse events, infections, and cardiovascular (CV) events among patients aged 65 years and older with UC who initiate either:

   a. Etrasimod (Cohort 1)

   b. Other S1P receptor modulators (Cohort 2)

   c. Biologics (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 3)

   d. JAKi (with or without concurrent use of immunomodulators/immunosuppressants; Cohort 4)

9. RESEARCH METHODS

9.1. Study Design

This will be a non-interventional, multi-country, active surveillance cohort study of patients with UC initiating therapy with etrasimod or other comparator medications. The study will retrospectively assess secondary sources of data from electronic health records, healthcare claims, and registry data.

Based on the indications of use of etrasimod (8), it is expected that etrasimod will be initiated by patients with UC who previously used one or more of the comparator medications of interest as well as other immunomodulating/immunosuppressive therapies used as 2nd and 3rd line UC therapies. This PASS will describe patient characteristics and estimate IRs of safety events of interest in four main Cohorts of patients with UC: patients initiating etrasimod (Cohort 1), patients initiating other S1P receptor modulators (Cohort 2), patients initiating biologics (Cohort 3), and patients initiating JAKi (Cohort 4; see Section 9.2.2). A modified 'new user' design will be implemented that allows for including new users of etrasimod that previously used a comparator medication of interest.(9, 10) Exposure is defined by a time-at-risk window per Cohort, based on the use of a Cohort-defining medication (Section 9.3.1).

This PASS will primarily use a 'restricted' as-treated approach for analysis. Outcomes will only be identified during follow-up as long as patients are exposed per Cohort, and analyses will be restricted to only the first continuous treatment episode for that Cohort (see Section 9.3.1). Therefore, a patient can be included in each of the Cohorts only once. For the outcome of malignancy, an additional intention-to-treat analysis will be conducted as sensitivity analysis.

Comparative analyses will only be conducted pending sufficient sample size (Section 9.5). Here, a modified 'new-user' design will be used, to allow, for example, the study of etrasimod initiators that previously used one of the other comparator medications of interest. Initiation of etrasimod (Cohort 1) will be separately compared to initiating Cohort 2, Cohort 3, or Cohort 4 medications. For further details see Section 9.7.2.

Definitions of study periods, windows, and the index date are provided in Section 9.1.1.

Pooling of data on the patient level is not allowed based on governance rules of the participating data sources. A meta-analysis pooling aggregated results from all data sources will be conducted, conditional on the number of events and heterogeneity of results between data sources (see Section 9.7.4).

The proposed study design is well-suited to address the primary and secondary objectives. This study will bring together data from multiple EU data sources and will use common analytical programs across countries. This will facilitate the robust and active surveillance of etrasimod uptake and safety events across early adopters within the EU, with a relatively limited lag time.

9.1.1. Study period, time windows and index date

The following periods are defined to identify patients in the data sources and ascertain dates:

Study period: The study will include data from 16 February 2014 to 31 December 2032. The lookback window will include up to 10 years prior to start of the indexing period (ie, 10 years before 16 February 2024, or 16 February 2014). The indexing and follow-up period will be until 31 December 2032 (where follow-up extends at least 8 years after the start of the indexing).

Note that data collection for this study will continue beyond the end of the study period and will end after data source-specific lags in retrospective data extraction and data preparation for analyses are reconciled (Section 9.4). Due to data source specific lags, a slightly reduced study period is used for the German data source (Section 9.4.4);

Indexing period: The period during which new treatment episodes may be included is 16 February 2024, through 31 December 2032. The start of the indexing period begins on the date of the European Commission approval for etrasimod (11). The indexing period for Cohorts of comparator medications of interest already available in the EU will be the same, to avoid historical comparisons and issues from time trends. Note that the indexing period will vary by data source due to country-specific reimbursement decisions (see Section 9.4.4);

The index date will be defined as the first date of exposure to a Cohort-defining medication, once all inclusion criteria for a Cohort are met. Note that if a patient contributes to multiple Cohorts in the 'restricted' as-treated analysis, they will only contribute a maximum of one treatment episode per Cohort, and thus Cohort-specific index dates will be assigned (ie, patients cannot switch back to the same Cohort, see Section 9.3.1);

Follow-up period and censoring: for an individual treatment episode, the follow-up period will start at the index date and end at the first of the following:

- Occurrence of the first safety event of interest for specific analysis (eg, first occurrence of malignancy for the malignancy safety event of interest)
- Last date of exposure to Cohort-defining treatment at the active ingredient level (5th Anatomical Therapeutic Chemical [ATC] level; Section 9.3.1)
  - For malignancy outcomes, this last date of exposure is extended (Section 9.3.1.2) or the criterion is removed entirely in the intention-to-treat approach used in the sensitivity analysis, for both malignancies and PRES (Section 9.7.5)
- Switching to another Cohort-defining medication (5th ATC level)
  - For the sensitivity analysis for malignancy outcomes and PRES using an intention-to-treat approach, this criterion is removed
- Initiation of immunomodulators/immunosuppressant medication (Cohorts 1 and 2 only)

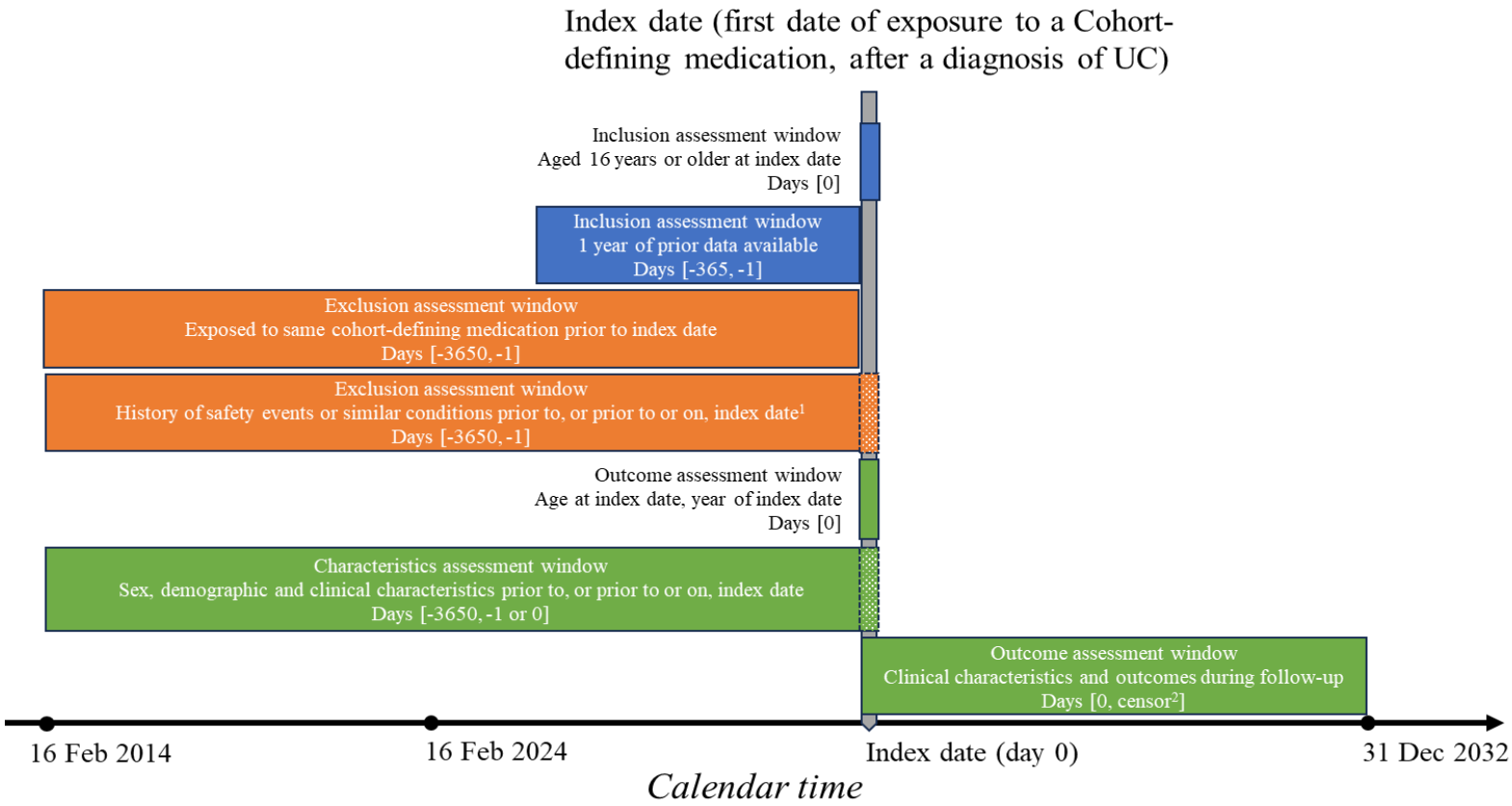
- Surgical full removal of colon, or colon and rectum (when stratifying by malignancy type and reporting colorectal cancer)
- A diagnosis of Crohn's disease
- Disenrollment, including interruption of enrolment from the data source
- End of the study period (31 December 2032)
- Death

In the 'restricted' as-treated analyses in this PASS, the follow-up period will be the time window of exposure to the Cohort-defining medication (definition of exposure in Section 9.3.1). No minimum duration will be set for the follow-up period, to allow the study of safety events of interest occurring very shortly after treatment initiation for all patients.

Lookback window: Patient characteristics at index date (Section 9.3.3 and 9.3.4) will be ascertained prior to index date with a lookback window that spans a minimum of 1 year and a maximum of 10 years. As per the inclusion criteria, patients will be required to have a minimum of 1 year of data prior to treatment initiation for that episode to be included. Up to 10 years of information will be considered whenever available to improve classification of patient characteristics such as relevant chronic comorbidities and medical history.(12-14) The maximum lookback window for patients initiating treatment in 2024 and 2032 will extend back into 2014 and 2022, respectively.
If a patient is included in more than one Cohort, characteristics will be re-ascertained by implementing a lookback of 10 years maximum at the new index date.

The study design is depicted in the diagram below (Figure 1), and the following sections provide detailed inclusion and exclusion criteria for the study population.

Figure 1. Study design diagram for etrasimod PASS



Study design diagram depicting inclusion and exclusion criteria, and windows for determining variables relative to the index date anchor.
1. For a sensitivity analysis, patients with a history of the safety of event of interest, or similar conditions, prior to, or prior to or on, index date will be excluded
2. Censoring at first of safety event of interest (outcome-specific analyses), end of exposure (except for malignancies and for sensitivity analysis in PRES, see Sections 9.3.2.3 and 9.7.5), disenrollment, incident Crohn's disease, initiation of use of immunomodulators/immunosuppressants (Cohorts 1 and 2 only), surgical full removal of colon, or colon and rectum (for colorectal cancer only), end of study period at either 31 December 2031 (Germany) or 2032 (Sweden and The Netherlands), depending on data availability (Section 9.4.4), or death.

9.2. Setting

9.2.1. Source population

The target population comprises of patients with moderate to severe UC, living in Europe, and aged 16 years and older. The source population for this study will be derived from patient-level data from electronic healthcare records, healthcare claims, and registry data derived from routine clinical care, from four EU data sources in three different countries:

- the German Pharmacoepidemiological Research Database (GePaRD) from Germany
- the Swedish National Health Registers (SNHR) and the Swedish Inflammatory Bowel Disease Registry (SWIBREG) from Sweden
- the PHARMO Data Network from the Netherlands

These data sources are described in detail in Section 9.4.

9.2.2. Study population

The eligible study population will be all patients aged 16 years and older with a diagnosis of UC in the study period. UC patients will be identified using both recorded inpatient and/or outpatient diagnoses and/or procedures based on the specific coding system and disease identification algorithms used by the individual databases per data source (Section 9.4).

This study will include four Cohorts of UC patients as follows:

Cohort 1 will consist of eligible patients initiating etrasimod

Cohort 2 will consist of eligible patients initiating other S1P receptor modulators

Cohort 3 will consist of eligible patients initiating biologics (tumor-necrosis factor-α inhibitors [TNFi], integrin receptor antagonists, interleukin inhibitors), with or without concurrent use of immunomodulating/immunosuppressive medication.

Cohort 4 will consist of eligible patients initiating JAKi, with or without concurrent use of immunomodulating/immunosuppressive medication.

A single UC patient may be included in multiple Cohorts, in the event of treatment switch.

Cohorts 1 and 2 will consider only those patients who adhere to a monotherapy treatment for UC at index date (Section 9.2.4), i.e., not allowing use of other non-Cohort-defining medication for UC at index date . Conventional therapies, such as corticosteroids or aminosalicylates, do not qualify as a relevant stand-alone comparator Cohort due to the risk of confounding by indication or disease severity. These treatments are typically used as a first-line therapy. However, their concomitant use in Cohorts 3 and 4 is permitted and will be described (see Section 9.3.4).

9.2.3. Inclusion criteria

This study includes four Cohorts of patients with UC defined by specific medication exposure. Patients must meet all of the following inclusion criteria to be eligible for inclusion in the study:

1. Have a diagnosis of UC in the lookback window, defined using an International Classification of Disease-10th revision (ICD-10) code of K51.
2. Have a first ever dispensing/prescription (index date) after UC diagnosis of one or more of the following medications (described in detail in Section 9.3.1):
    a. For Cohort 1: etrasimod
    b. For Cohort 2: other S1P receptor modulators than etrasimod
    c. For Cohort 3: biologics
    d. For Cohort 4: JAKi
3. Be aged 16 years or older at index date.
4. Have at least one year of data available prior to index date, for all linked datasets per data source, to establish the lookback window.

Confirmation of the specific algorithms to confirm presence of criteria (eg, requirement of single or multiple codes for UC to determine diagnosis) or code lists to operationalize these criteria will be provided in the SAP.

9.2.4. Exclusion criteria

Patients meeting any of the following criteria will not be included, per Cohort:

1. Are exposed to the same Cohort-defining treatment prior to the index date.
2. Have a diagnosis of Crohn's disease prior to, or on, index date, if occurring after UC diagnosis.
3. Are exposed to other non-Cohort-defining medication for UC prior to, or on, index date (for Cohorts 1 and 2 only; medication for exclusion will consider concomitant UC medication defined in Section 9.3.3, to be confirmed in the SAP)

Exclusion criteria will be assessed during a lookback window of up to 10 years prior to index date (to be specified in the SAP per exclusion criterion). Two sensitivity analyses on the exclusion criteria will be conducted:

- Patients with a history of the outcome of interest prior to, or on, the index date will be additionally excluded (this will be applied on an outcome-by-outcome basis; Section 9.7.5).
- Patients exposed to certain other non-Cohort-defining medication for UC prior to, or on index date will not be excluded (for Cohorts 1 and 2 only; Section 9.7.5)

9.3. Variables

The following subsections describe definitions of exposure, outcomes, and covariates. Detailed definitions will be included in the SAP.

9.3.1. Exposure

Currently registered and approved medications for UC will be considered for inclusion of patients in all Cohorts. The medication groups defined in Table 1 are leading, newly approved medications, or medications with label extensions may be added during the course of this PASS.

Table 1. Cohort-defining medications

Cohort	Cohort-defining medication groups (ATC codes)	Examples of Cohort -defining medications	
		Names	**ATC Codes**
Cohort 1	S1P receptor modulators, specifically only etrasimod	Etrasimod	L04AE05
Cohort 2	S1P receptor modulators, excluding etrasimod	Ozanimod	L04AA38 / L04AE02
Cohort 3	Biologics, including: - TNFi (L04AB) - Integrin receptor antagonists (L04AA) - Interleukin inhibitors (L04AC)	Infliximab Adalimumab Golimumab Vedolizumab Ustekinumab Risankizumab Mirikizumab Guselkumab	L04AB02 L04AB04 L04AB06 L04AA33 / L04AG05 L04AC05 L04AC18 L04AC24 L04AC16
Cohort 4	JAKi (L04AF)	Tofacitinib Upadacitinib Filgotinib	L04AF01 / L04AA29 L04AF03 / L04AA44 L04AF04 / L04AA45

Includes ATC codes as of 01 October 2024. For Cohorts 2, 3 and 4, a list of non-exhaustive Cohort-defining medications is provided as example. Not all Cohort-defining medications may be labelled for use in UC across all countries, nor for the entire study period. ATC-codes may be subject to change. A full listing of all concurrent and historical, altered ATC codes will be provided in the SAP. Additional medications may be included in the cohort-defining medication groups upon market entry or label extension, for use in UC. All biologic Cohort-defining medications may also include biosimilars of the same medication marketed under different brand names.
Abbreviations: ATC=Anatomical therapeutic chemical; JAKi=Janus-associated kinase inhibitors; TNFi=Tumour necrosis factor-alpha inhibitors.

The primary analysis will use a ‘restricted’ as-treated approach: exposure to Cohort-defining medication will be defined as a time window during which the patient is treated with a Cohort-defining medication. Only during this time window will the patient be considered at risk for developing the safety events of interest. Exposed time windows will be defined by constructing treatment episodes per Cohort-defining medication group. ‘Restricted’ refers to

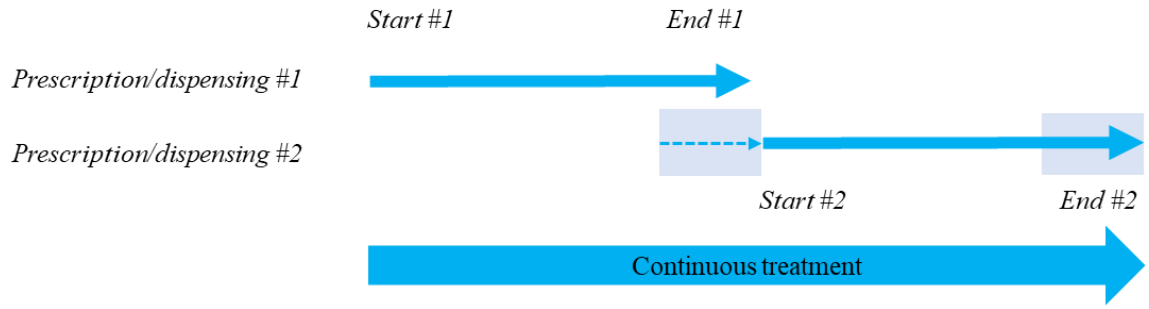
defining exposure as only the first treatment episode in the study period with Cohort-defining medication. Subsequent treatment episodes will not add person-time to exposure (eg, when a patient switches back to previously used medication). This approach has been described and used for a PASS previously.(9, 10) Exposed time windows for the medications listed in Table 1 are defined below.

9.3.1.1. Exposed time window (as-treated)

Initiation of Cohort-defining medication for UC will be defined as a first dispensing/prescription belonging to a Cohort-defining medication group in the indexing period, without any prior dispensing/prescription of the same Cohort-defining medication group during the 10-year lookback period. The index date will be the date of initiation. Only the first exposed time window to any of the Cohort-defining medications in each Cohort will be considered for the index date, independent of 5th level ATC code.

Patients may initiate multiple medications during the study period, and may transfer between Cohorts, but can contribute only one treatment episode to each of the Cohorts. When entry to a different Cohort occurs, an additional treatment Cohort-specific index date will be assigned to that patient. Characteristics will be re-ascertained with a lookback from the new medication's Cohort-specific index date.

Figure 2. Stockpiling



For two subsequent prescriptions/dispensings of the same Cohort-defining medication (5th ATC level), the new prescription/dispensing (second arrow) predates the end of the prior prescription/dispensing. The new prescription/ dispensing start date is shifted to the end of the prior dispensing, and its end date is shifted accordingly.

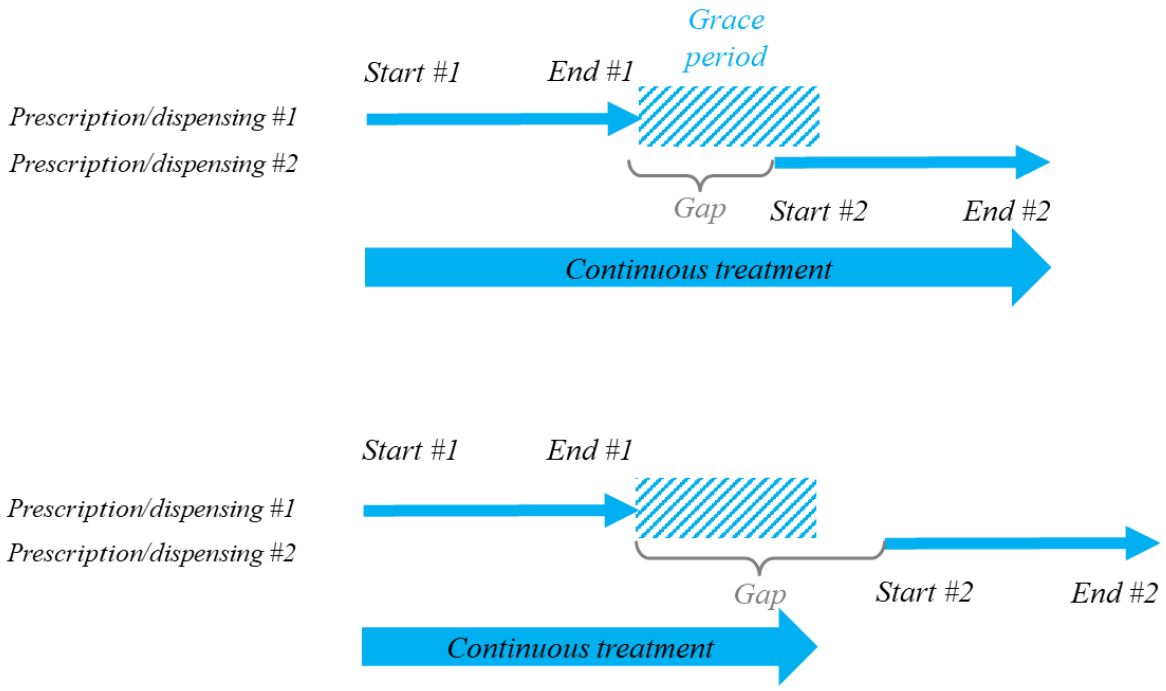
Treatment episodes will be defined at the level of the full ATC code, or 5th ATC level, allowing for stockpiling (Figure 2) and a maximum gap between all prescription/dispensing ('grace period'; Figure 3). The grace period between the end of a prior dispensing and a new dispensing allows for imperfect adherence. The estimated days' of supply of dispensed medication will be inferred using the amount dispensed and the expected frequency of administration based on available information either from recorded dosing information or the medication package level information, or estimated from the Summary of Product Characteristics (SmPC) information, including defined daily dose (DDD). For non-oral therapies, the number of days' supply per dispensing will be defined based on the length of

the cycles as specified in the product label (to be described in the SAP) and the number of injections dispensed. Permissible gaps will be 30 days for oral therapies, and otherwise will depend on the dosing cycles per medication, to be specified in the SAP.

If a given dispensing of the Cohort-defining UC treatment repeats before the presumed end of the medication's supply, then the overlapping supply will be added to the presumed end of the repeat dispensation, to form a concatenated exposure (see Figure 2). This allows for stockpiling for all self-administered medications. Note that when switching to a different Cohort-defining medication (5th ATC level), no stockpiling will be applied assuming that the prior prescribed/dispensed medication is surplus, and will not be used. Intravenous medication will be exempt from stockpiling.

A gap of more than the allowed grace period between the expected end of the medication supply based on the prior dispensing (including stockpiling) and a new dispensing will result in the end of the treatment episode. The full grace period will be included in the treatment episode for the last of any consecutive series of prescription/dispensing, per Cohort-defining medication (see Figure 3).

Figure 3. Grace period and permissible gap for continuous treatment



Top: The new prescription/dispensing of the same drug (second blue bar) represents a gap from the end of the same Cohort-defining medication's prior prescription/dispensing. The duration of the gap falls within the grace period (diagonal lined block) for the prior prescription/dispensing. The gap will be added to the duration of the exposed time window, and total duration of the exposed time window for these two prescriptions/dispensing is counted from the start of the prior dispensing to the end of the duration of the next dispensing.
Bottom: If the gap exceeds the grace period, the continuous treatment ends at the end of the grace period.

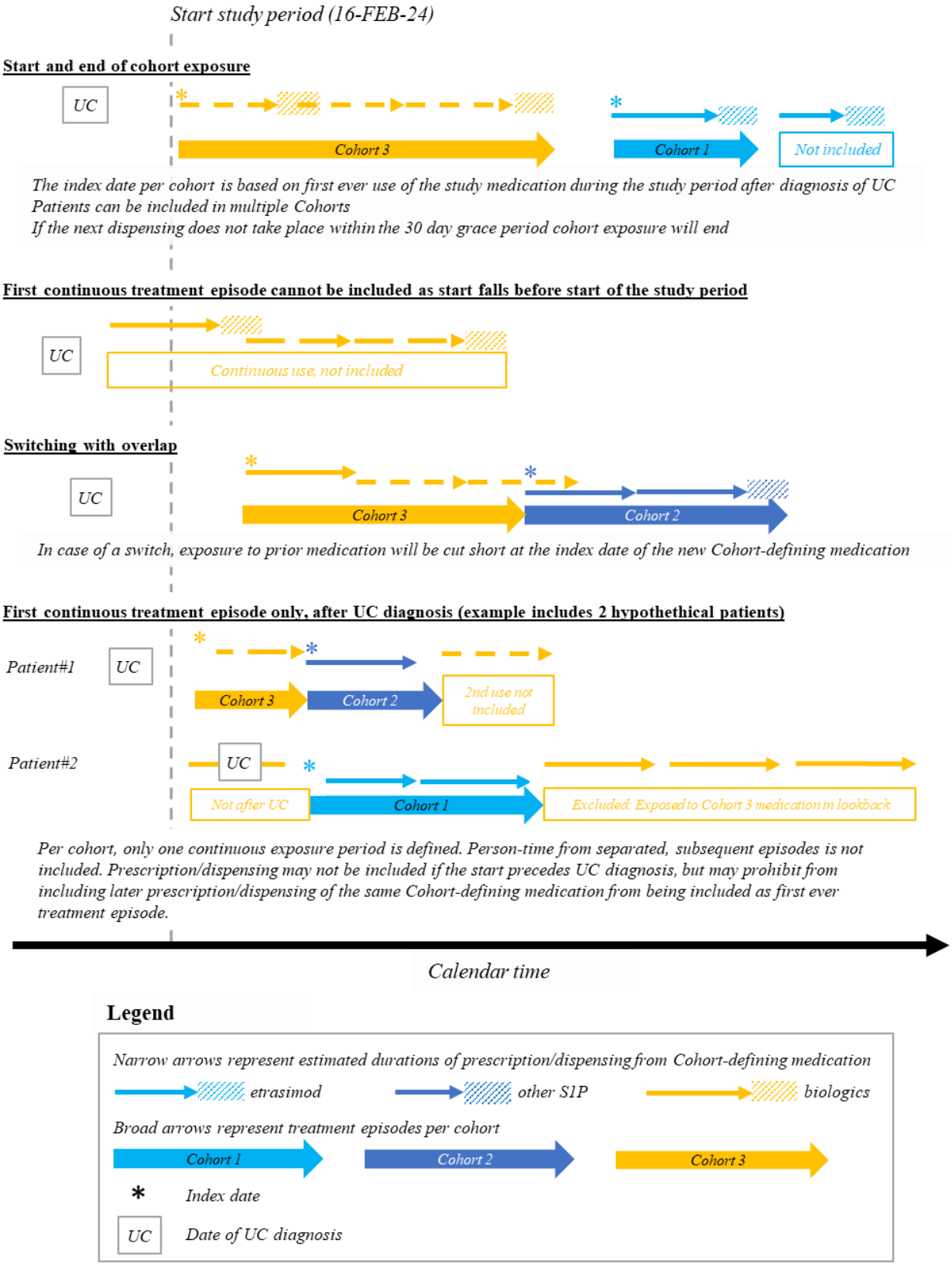
Switching between treatment episodes and exposed time window definitions per Cohort

Switching between medication can occur while staying in the same Cohort. Switching to a different medication within the same Cohort-defining medication group (eg infliximab to vedolizumab) will not be considered as switch, and these prescriptions/dispensings may be concatenated into a continuous exposed time window for the same Cohort using abovementioned rules for the grace period.

In case of switching to a different medication (5th ATC level) where the date of prescription/dispensing of the new medication starts before the end of estimated supply + grace period of the prior exposed time window (ie, overlaps), the exposed time window to the prior treatment will be censored on the date of prescription/dispensing of the new treatment (Figure 4).

Additional details on classification of the exposed time per period may be defined in the SAP.

Figure 4. Cohort exposure definitions and switching between Cohorts



9.3.1.2. Exposed time window – malignancies (as-treated)

For the assessment of malignancy outcomes, to reduce chances of establishing potential non-biologically plausible associations between a medication and a malignancy (15), the start of follow-up will be delayed with a lag-time, and the follow-up period will be extended.

A lag-time of 6 months will be applied from the index date to start of follow-up. If a malignancy occurs within the lag-time after index date, the patient will not be included when assessing malignancy as an outcome for that Cohort. For instance, a patient diagnosed with cancer 2 days after initiating etrasimod will not contribute to analysis of malignancy outcomes.

To address a potential delayed onset of a malignancy after medication exposure, an extended follow-up period for the exposed time window will be applied. Additional time will be added at the end of the estimated end of medication supply instead of the 30-day grace period. The extended follow-up period will instead continue for up to 1 year for hematologic malignancies and up to 2 years for solid tumours, with censoring otherwise being the same as in the main analyses (Section 9.1.1).

In the event of the occurrence of a malignancy during overlapping extended follow-up for the same patient in different Cohorts (switched to a different Cohort-defining medication), the malignancy is included only as outcome in the most recent Cohort, aligning with an 'as-treated' approach.

Sensitivity analyses will evaluate the impact of lag-times and the definition of the exposed time window for malignancies. The lag time after first date of prescription/dispensing until start of the exposed time window and follow-up for malignancies will be changed from 6 months to i) 0 months (ie no lag time), and ii) 12 months. Follow-up for malignancies will be prolonged under an intention-to-treat approach: once exposed, patients remain at risk even if prescription/dispensing ends (Section 9.7.4).

9.3.2. Outcomes

The safety events of interest are macular oedema, serious liver injury, malignancy, serious opportunistic infections, neurologic events of PRES or convulsions, and symptomatic bradycardia (including conduction disorders). Code sets to assess each of these outcomes will be developed for the data sources' coding systems and included in the SAP. The basis for operationalizing several of the safety events of interest is already provided here, through sets of codes developed in MedDRA, using standardized MedDRA queries (SMQ)/preferred terms (PT). Sets of MedDRA codes are presented in Table 2 and general descriptions are provided, along with specifications of the type of conditions that are targeted to be included per safety event. Further mapping of these codes to coding systems used in the data sources (Section 9.4) will be necessary, and additional code development may be required to adequately classify outcomes. Conversion of MedDRA codes to local coding systems that allow for less granularity could potentially reduce specificity for some outcomes. Codes

already specified in local coding systems (ICD-10) are preliminary and may still be adapted during SAP development.

Subgroup analyses conducted among older adult patients (ages 65+ years) only will focus on three safety events of interest (eye adverse events, infections, and CV events; Section 9.7.3). A sensitivity analysis will implement exclusions of patients with a history of the safety event of interest, or similar conditions, prior to index date (Section 9.7.5).

Table 2. Code sets (MedDRA SMQ and/or PT, ICD-10) for the safety events of interest in the main analysis

Safety event of interest	SMQ and/or PT for Main Analysis
Macular oedema	PT: Macular oedema; PT: Cystoid macular oedema; PT: Intraretinal Fluid; and PT: Subretinal Fluid Additional to these PTs, the concept of macular oedema will be broadened to include the following specific ICD-10 codes within the retinal disorders:H357 Separation of retinal layers; H358 Other specified retinal disorders; and H359 Retinal disorder, unspecified
Serious liver injury	SMQ Biliary tract disorder (Narrow scope); SMQ Cholestasis and jaundice of hepatic origin (Narrow scope); SMQ Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions (Narrow Scope); SMQ Hepatitis non-infectious (Narrow scope); SMQ Liver related investigations signs and symptoms (Narrow scope); and SMQ Drug related hepatic disorders (narrow scope)
Malignancy	*To be specified in the SAP*
Serious opportunistic infections	All PTs within the SMQ Opportunistic infection (Narrow scope).
Neurologic events of PRES or convulsions	PRES PTs: Autoimmune encephalopathy; Encephalopathy; Immune-mediated encephalopathy; Leukoencephalopathy; Posterior reversible encephalopathy syndrome; Toxic leukoencephalopathy. Convulsions PTs: Alcoholic seizure; Atonic seizures; Atypical benign partial epilepsy; Clonic convulsion; Convulsions local; Convulsive threshold lowered; Medication withdrawal convulsions; Epilepsy; Epilepsy with myoclonic-atonic seizures; Faciobrachial dystonic seizure; Frontal lobe epilepsy; Hyperglycaemic seizure; Hypocalcaemic seizure; Hypoglycaemic seizure; Hyponatraemic seizure; Idiopathic generalised epilepsy; Idiopathic partial epilepsy; Myoclonic epilepsy; Partial seizures; Partial seizures with secondary generalisation; Photosensitive seizure; Post stroke epilepsy; Post stroke seizure; Post-traumatic epilepsy; Psychogenic seizure; Seizure; Seizure anoxic; Seizure cluster; Seizure like phenomena; Status epilepticus; Tonic

Table 2. Code sets (MedDRA SMQ and/or PT, ICD-10) for the safety events of interest in the main analysis

Safety event of interest	SMQ and/or PT for Main Analysis
	clonic movements; Tonic convulsion; Postictal state; Generalised tonic-clonic seizure
Symptomatic bradycardia (including conduction disorders)	Bradycardia PTs: bradycardia; bradyarrhythmia; sinus bradycardia Conduction disorders PTs: atrioventricular block; atrioventricular block complete; atrioventricular block first degree; atrioventricular block second degree Additional to these PTs, the concept of symptomatic bradycardia (including conduction disorders) will be broadened to include rhythm disorders using the following specific ICD-10 codes: I44 Atrioventricular and left bundle-branch block I45 Other conduction disorders I49 Other cardiac arrhythmias

Code sets listed here are preliminary and will be further developed and confirmed into code lists during SAP development.

9.3.2.1. Macular oedema

Macular oedema will be identified based on specific MedDRA terms for (Cystoid) Macular oedema (Table 3). Note that the expected conversion to local coding systems may reduce granularity and therefore specificity of codes corresponding to suggested terms for macular oedema. As a result, the concept of macular oedema will be broadened to include retinal disorders (ICD 10 codes: H357 Separation of retinal layers, H358 Other specified retinal disorders, H359 Retinal disorder, unspecified).

Table 3. Macular oedema outcome variables

Variable	Definition	Timing
Date of incident macular oedema diagnosis	Defined as the calendar date of the first macular oedema occurrence during follow-up period	Collected during follow-up period
Presence of macular oedema	Binary variable (Yes/No)	For the first macular oedema event during follow-up period

9.3.2.2. Serious liver injury

Serious liver injuries will be identified by the presence of at least one specified ICD-10 or equivalent code associated with an inpatient hospitalization in the principal or primary

diagnostic position. Where available, local established algorithms based on these data may be leveraged.

Table 4. Serious liver injury outcome variables

Variable	Definition	Timing
Date of incident serious liver injury diagnosis	Defined as the calendar date of the first serious liver injury occurrence during follow-up period	Collected during follow-up period
Type of serious liver injury	Serious liver injury resulting in hospitalisation (and/or death): • Biliary tract disorder • Cholestasis and jaundice of hepatic origin • Hepatic failure, fibrosis and cirrhosis and other liver damage related conditions • Hepatitis non-infectious	Collected on the date of incident liver injury during follow-up period
Presence of serious liver injury	Binary variable (Yes/No)	For the first serious liver injury event during follow-up period

9.3.2.3. Malignancy

Malignancies will be identified based upon the presence of at least one ICD-10 diagnosis code for malignancy in cancer registries (for some countries) or associated with an inpatient hospitalization in the principal or primary diagnosis position during the follow-up window, or a dispensing of a specific outpatient treatment for cancer potentially managed in outpatient settings. Malignancies will be defined as a composite and also presented stratified by type (Table 5). Skin cancer requires inclusion of a broad group of skins cancers including non-melanoma skin cancers. Since this larger group of cancers is usually not studied, it is uncertain whether data source-specific cancer registries capture these events. Relevant variables are defined in Table 5.

For colorectal cancer, the surgical removal of the colon, or the colon and rectum, will be considered as an intercurrent event for which analyses will be censored.

In a sensitivity analysis, a more restrictive operational definition requiring the presence of an increased number of diagnosis codes for malignancy outcome(s) of interest will be applied. Several other sensitivity analyses will be conducted on how malignancies are ascertained, and are described in detail in Section 9.7.5).

Table 5 Malignancy safety event of interest variables

Variable	Definition	Timing
Date of incident malignancy diagnosis	Defined as the calendar date of the first malignancy occurrence during follow-up period	Collected during follow-up window including latent period after lag-time period. Note, analysis for colorectal cancer will additionally considering censoring at surgical removal of colon, or colon and rectum.
Type of malignancy based on primary Site	Malignancies will be defined as a composite (ie, overall) and presented stratified by type, according to the below groupings: • Haematological malignancies • Solid tumour malignancies, with specific reporting for subgroups of: – Colorectal cancer – Skin cancers, including non-melanoma skin cancers	Collected on the date of the first incident malignancy diagnosis (overall or subtype) during follow-up period Analyses on subtype will consider competing malignancy events.
Presence of malignancy	Binary variable (Yes/No)	For the first malignancy indicated during follow-up window

9.3.2.4. Serious opportunistic infections (SOIs)

Serious opportunistic infections (SOIs) will be defined by the presence of at least one ICD-10 code associated with an inpatient hospitalization or emergency department (ED) encounter. Key events include, but are not limited to, progressive multifocal leukoencephalopathy (PML), herpes viral infections, and cryptococcal infections. The analysis will consider only the first event of any SOI.

Table 6. SOI safety event variables

Variable	Definition	Timing
Date of incident SOI	Calendar date of the first SOI infection during follow-up period	Collected during follow-up period
Type of SOI	SOIs will be defined as a composite and by type (eg, PML) according to the groupings of ICD-10 codes	Collected on the date of incident SOI during the follow-up period

Table 6. SOI safety event variables

Variable	Definition	Timing
Presence of SOI	Binary variable (Yes/No)	For the first SOI indicated during follow-up period

9.3.2.5. PRES or convulsions

PRES will be identified based on the presence of a diagnostic code in any position associated with either an ED encounter or an inpatient hospitalization. Convulsion codes will include diagnoses of epilepsy, with the assumption that first occurrences of codes indicative of epilepsy are commensurate with occurrence of epileptic attacks or convulsions. Events will include diagnoses of epilepsy syndromes or diseases clearly indicative of first occurrence in childhood/adolescence, assuming the left-censored data used in this study may not pick up a paediatric history of such diseases.

A sensitivity analysis will be conducted to evaluate a longer risk window for PRES (intention to treat approach, Section 9.7.4).

Table 7. PRES or convulsions outcome variables

Variable	Definition	Timing
Date of incident PRES/convulsion	Calendar date of first PRES/convulsion during follow-up period	Collected during follow-up period
Provenance of PRES/convulsion	ED associated or hospitalisation event associated PRES/convulsion	Collected on the date of first PRES/convulsion diagnosis during follow-up period
Presence of PRES/convulsion	Binary variable (Yes/No)	Collected during follow-up period

9.3.2.6. Symptomatic bradycardia (including conduction disorders)

Symptomatic bradycardia and conduction disorders will be identified through secondary care diagnostic codes including hospitalizations and specialist care (MedDRA terms in Table 2). A broader definition of symptomatic bradycardia (including conduction disorders) will be applied consisting of ICD-10 codes that capture rhythm disorders, specifically, atrioventricular and left bundle-branch block, other conduction disorders, and other cardiac arrhythmias.

Identifying symptomatic bradycardia may be challenging in real-world data (RWD) sources since it requires simultaneous diagnostic and symptomatic codes. Not all coding systems capture symptoms well. For the primary analysis, it will be assumed that most cases of bradycardia and conduction disorders that appear in RWD are symptomatic since the patient sought healthcare for corresponding symptoms. Identification will be restricted to all events

attended in secondary care (eg, ambulatory specialist consultations, ED visits, or hospitalization). This operationalization is likely sensitive but may still include asymptomatic events. Conduction disorders will focus on those disorders commensurate with bradycardia, and not those conduction disorders primarily associated with tachy-arrhythmia syndromes.

A sensitivity analysis will be conducted to evaluate a more narrow, specific definition of symptomatic bradycardia (including conduction disorders) requiring simultaneous presence of symptoms (Section 9.7.4), for data sources that contain data on symptoms.

Table 8. Symptomatic bradycardia (including conduction disorders) safety event of interest variables

Variable	Definition	Timing
Date of incident symptomatic bradycardia	Calendar date of first bradycardia hospitalization event during follow-up period	Collected during follow-up period
Type of cardiac event (bradycardia, conduction disorder etc.)	ED associated or hospitalisation event associated bradycardia	Collected on the date of first bradycardia event during follow-up period
Presence of bradycardia event	Binary variable (Yes/No)	Collected during follow-up period

9.3.2.7. Outcomes in subgroup analyses

Subgroup analyses conducted among older adult patients (ages 65+ years) will focus on three safety events of interest (eye adverse events, infections, and CV events). The background of the subgroup analyses is described in Section 9.7.3. Definitions are provided in Table 9 and subsequent sections.

Table 9. Definitions of safety events of interest in subgroup analysis

Safety event of interest in subgroup analysis	Definition
Eye adverse events	Broad range of eye adverse events, excluding those related to trauma or hereditary conditions).
Infections	Broad range of infections, including non-serious infections that do not require hospitalization, and can be defined based on diagnostic, procedure, or medication codes.

Table 9. Definitions of safety events of interest in subgroup analysis

Safety event of interest in subgroup analysis	Definition
CV events	Broad range of acute CV events, which focus includes common arterial thrombo-embolic events and events aligned with the potential risk of bradycardia assessed in the main analysis. Events have to be attended in secondary care.

9.3.2.7.1. Eye Adverse Events

The eye adverse event definition will be defined by the following preliminary codes (to be fully developed in the SAP): conjunctivitis, keratitis, other disorders of the cornea, iridocyclitis, other cataract, other disorders of the lens, chorioretinal inflammation, other disorders of choroid, retinal vascular occlusions, other retinal disorders, glaucoma, disorders of optic nerve, not elsewhere classified, papiloedema, unspecified, other disorders of optic disc, visual disturbances, visual impairment including blindness (binocular or monocular). Traumatic or hereditary conditions will not be part of this definition.

9.3.2.7.2. Infections

This definition will include a broad range of serious and non-serious infections (Section 9.7.3). These infections will be based on predefined diagnostic or procedure codes to be specified in the SAP, and on relevant medication use as a proxy (e.g., codes for use of systemic antibiotics, ATC code J01).

9.3.2.7.3. CV Events

The CV events will be defined by the following preliminary codes (to be fully developed in the SAP): I10-I15: Hypertensive diseases, I20-I25: Ischemic heart diseases, I44:Atrioventricular and left bundle-branch block, I45: Other conduction disorders, I46: Cardiac arrest, I49: Other cardiac arrhythmias, I50: Heart failure, I60-69: Cerebrovascular diseases, I70-79: Diseases of the arteries, arterioles and capillaries, R00.1: Bradycardia, unspecified, W19: Unspecified fall , R55: Syncope and collapse
(Section 9.7.3).

9.3.3. Covariates at index date

Patient demographic and clinical characteristics will be evaluated during the lookback window prior to index date, and on index date, as appropriate. Characteristics that can be evaluated in each data source may vary based on data availability (Section 9.4). Code sets will be presented in the SAP.

Table 10. Covariates of interest

Demographic /Clinical Variable	Definition	Timing
Age	Continuous variable defined as the difference in time between date or year of birth (should exact dates be unavailable) and index date. Age will also be defined as a categorical variable with cut points to be determined based on sample size and distribution of age.	Assessed on the patient's index date for a treatment episode
Sex	Categorical variable defined as sex assigned at birth: • Female • Male • Other	Assessed on the patient's index date for a treatment episode
Socio-economic status	Categorical variable defined on the local most appropriate available indicator of socio-economic status, including (combinations of) variables (eg, educational attainment or income, either at the individual, household, or local geographical level).	Assessed over all available look-back prior to index date, with a maximum of 10 years
Year of index date	Categorical variable defined as the year the participant indexes into a study treatment Cohort. The same patient may be included in multiple Cohorts	Assessed on the patient's index date for a treatment episode
Duration of available lookback	Continuous variable	Assessed over all available look-back prior to index date, with a maximum of 10 years
Frailty	Either continuous or categorical variable based on available frailty scores/indices for healthcare database studies, to be specified in the SAP	Assessed over all available look-back prior to index date, with a

Table 10. Covariates of interest

Demographic /Clinical Variable	Definition	Timing
		maximum of 10 years
UC severity and extent	Continuous variable representing a patient's IBD severity index score, using either validated scores available in the data sources (eg, Montreal classification) or a combined score by proxy. The parameters of this variable will be specified in detail in the SAP	Assessed during the patients' lookback window prior to index date, considering the patient's first diagnosis of UC and carrying last measurement before index date forward
Smoking history/Status	Binary variable to indicate whether the individual has a history of smoking tobacco or is a current user (Yes/No)	Assessed at index date, carrying the last measurement before index date forward
Obesity	Binary variable (Yes/No)	Assessed at index date, carrying the last measurement before index date forward
History of macular oedema	Binary variable (Yes/No) for history of macular oedema	Assessed during lookback window
History of hepatic disease	Binary variable (Yes/No) for history of hepatic disease	Assessed during lookback window
History of cholelithiasis	Binary variable (Yes/No) for history of cholelithiasis	Assessed during

Table 10. Covariates of interest

Demographic /Clinical Variable	Definition	Timing
		lookback window
History of primary sclerosing cholangitis	Binary variable (Yes/No) for history of primary sclerosing cholangitis	Assessed during lookback window
History of malignancy	Binary variable (Yes/No) for history of malignancy	Assessed during lookback
History of SOI	Binary variable (Yes/No) for history of SOI	Assessed during lookback
History of human immunodeficiency virus (HIV)	Binary variable (Yes/No) for history of HIV	Assessed during lookback
History of congenital immunodeficiency	Binary variable (Yes/No) for history of congenital immunodeficiency	Assessed during lookback
History of organ transplantation	Binary variable (Yes/No) for history of organ transplantation	Assessed during lookback
History of PRES/convulsions	Binary variable (Yes/No) for history of PRES/convulsions	Assessed during lookback
History of bradycardia or cardiac conduction disorders	Binary variable (Yes/No) for history of bradycardia or cardiac conduction disorders	Assessed during lookback
History of other major comorbidities: • Chronic congestive heart failure • Congenital heart disease • Pulmonary hypertension • Chronic ischaemic heart disease • Cardiac valvular disease • Diabetes mellitus • Systemic lupus erythematosus • Chronic renal disease • Hypertension	Binary variable (Yes/No) for history of considered comorbidity	Assessed during lookback

Table 10. Covariates of interest

Demographic /Clinical Variable	Definition	Timing
• Alcohol abuse (proxy) • Thyroid disease • Respiratory disease (chronic obstructive pulmonary disease, asthma, other chronic pulmonary diseases)		
Co-medications (non-UC treatments/medications prior to, or on index date)	The following concomitant medications will be assessed using ATC codes: • Anticoagulants • Angiotensin-converting enzyme inhibitors • Beta-blockers • Calcium channel blockers • Statins • Anti-arrhythmic medications • Chemotherapy/immunotherapy for treatment of malignancy Detailed rules for defining concomitant medication exposure will be included in the SAP	Determined prior to index date with a lookback window of 1 year, or on index date
Concomitant UC medications prior to, or on, index date	The following concomitant medications will be determined using ATC codes: mesalazine, azathioprine mercaptopurine, tioguanine, corticosteroids, cyclosporin, tacrolimus Detailed rules for defining concomitant medication exposure will be included in the SAP.	Determined prior to index date with a lookback window of 1 year, or on index date. Concomitant UC medications will additionally be assessed using a shorter lookback window to define the

Table 10. Covariates of interest

Demographic /Clinical Variable	Definition	Timing
		exclusion criterion for Cohorts 1 and 2 (Section 9.2.4), to be detailed in the SAP.

9.3.4. Clinical characteristics during follow-up

The following characteristics assessed during follow-up will also be reported.

Table 11. Clinical characteristics determined during follow-up

Demographic/Clinical Variables	Definition	Timing
Duration of follow-up	Continuous variable	Throughout follow-up period, using the latest data extraction date per data source
Concomitant UC medications (during and after exposure to Cohort-defining medication)	The following concomitant medications will be determined using ATC codes: mesalazine, azathioprine mercaptopurine, tioguanine, corticosteroids, cyclosporin, tacrolimus, and the Cohort-defining medication. Categorical variables will be determined for presence of concomitant medication use, separated for those used during the exposed time window of the Cohort-defining medication, and presence after the exposed time window, per medication. Detailed rules for defining concomitant medication exposure will be included in the SAP.	Determined at index date and during the follow-up period
Duration of concomitant UC medications (during and after the exposed	Continuous variable for duration of use per concomitant UC treatments as indicated above.	Determined on index date throughout the follow-up period

Table 11. Clinical characteristics determined during follow-up

Demographic/Clinical Variables	Definition	Timing
time window to Cohort-defining medication)	Detailed rules for assessing lines of treatment will be included in the SAP.	
Mortality	Date of death	Determined during the follow-up period

9.4. Data Sources

This study uses secondary data collected during routine clinical care, including electronic health records, claims data, or registry data. These data reflect real-world circumstances and prescribing behaviors. The data sources have been selected based on a first assessment of being fit-for-purpose for the current study. Data from three EU countries are included to increase generalizability, sample size, and potential capture of the safety events of interest.

Data sources will be:

- **GePaRD**; provided by the Leibniz Institute for Prevention Research and Epidemiology – BIPS in Germany
- **SNHR** and the **SWIBREG**; provided by the Department of medicine Solna/Clinical epidemiology division at the Centre for Pharmacoepidemiology (CPE), Karolinska Institute in Sweden
- **PHARMO Data Network**,; provided by the PHARMO Institute for Drug Outcomes Research in the Netherlands

These data sources are listed under the Heads of Medicines Agency (HMA)- EMA Catalogues of Real-world data sources and studies (https://catalogues.ema.europa.eu/search; formerly European Network of Centers for Pharmacoepidemiology and Pharmacovigilance [ENCePP] resources database). All sources comply with EU guidelines on the use of medical data for medical research and have been validated for pharmacoepidemiologic research.

Key characteristics of the data sources are presented in (Table 12), and detailed descriptions of each data source are presented subsequently. Each data source is representative of its country's population in terms of age and sex, and contains data on hospital care and administration of high-budget impact medicines. Data sources contain different types of data collected primarily for different aims, including claims (GePaRD), registry data (SNHR, SWIBREG), and electronic health records (SNHR, PHARMO).

Table 12. Overview of data sources

Characteristic	**Data sources**			
	Germany	**Sweden**		**Netherlands**
	GePaRD	**SNHR**	**SWIBREG**	**PHARMO Data Network**
Data source description				
Country population size in 2023*	83.2 million	10.6 million	10.6 million	17.6 million
Estimated number of persons in data source	25 million	10.6 million since all population is covered	Approximately 63000 (as per April 2024)	Approximately 0.9M persons available in overlapping

Table 12. Overview of data sources

Characteristic	**Data sources**			
	Germany	**Sweden**		**Netherlands**
	GePaRD	**SNHR**	**SWIBREG**	**PHARMO Data Network**
				hospital, general practitioner (GP), and outpatient pharmacy data
Overall representativeness	Representative of German population with respect to age and sex distribution, the number of hospital admissions, and medication use	Representative for Swedish population. Note that this does not include primary care diagnosis or in-hospital administered medication.	Voluntary participation. Coverage is not complete	GP, outpatient pharmacy and hospital data separately representative for Dutch population
Datasets per data source to be used for this study	Outpatient General practitioners and specialist diagnoses, procedures and services. Outpatient dispensation data. Inpatient diagnoses, procedures and medication administration for subset of high-cost medications	Prescribed Drug Register, National Cancer Register, Cause of Death Register, National Patient Register	SWIBREG registry	General practitioner data Hospital data – admissions, ambulatory consultations, high-cost medicine data Outpatient pharmacy data Cancer registry

Table 12. Overview of data sources

Characteristic	**Data sources**			
	Germany	**Sweden**		**Netherlands**
	GePaRD	**SNHR**	**SWIBREG**	**PHARMO Data Network**
Type of data	Claims	Population registry	Disease registry	Electronic health records
Expected national patient volume of yearly initiators of etrasimod upon reimbursement (note, patient volumes in data source will be smaller)	Information is not available	Information is not available	Information is not available	Between 50 and 3259 (see Section 9.4.4)
Data extraction updates and lags	Update annually in Q4, with a lag of 2 years (eg, 2024 data available per Q4 2026)	Depends on the register (eg, the cancer register with the longest lag-time is updated annually, with a lag of 14 month (ie, 2024 data available per Q2 2026))	Update annually, the SWIBREG data is depended on the data from the SNHR so it will be the same lag-time.	Update annually in Q4, with a lag of 1 year (eg, 2024 data available per Q4 2025)
Disease coding systems	ICD-10 German Modification (-GM)	ICD-10	ICD-10	ICPC for GP data ICD-10 for hospital data
Exposure/medication data				
Type of medication data available	Yes, outpatient pharmacy dispensing and hospital administration for subset of high-budget	Outpatient pharmacy dispensing. Hospital medication not available. No OTC data.	Yes, including outpatient and inpatient treatments. No OTC data.	Yes, outpatient pharmacy data, GP prescriptions, hospital dispensing of high-budget impact medication since

Table 12. Overview of data sources

Characteristic	**Data sources**			
	Germany	**Sweden**		**Netherlands**
	GePaRD	**SNHR**	**SWIBREG**	**PHARMO Data Network**
	impact medicines. No OTC data.			2017, or hospital inpatient prescriptions available for only a subset. No OTC data.
Prescription or dispensing level	Dispensing	Dispensing	Use recorded by physician	Dispensing
Outpatient medication coding system	ATC-GM	ATC	ATC	ATC
Outpatient dosing regimen available	No	No	Yes	Yes
*Outcome/covariate data***				
Hospital data	Yes, admission and discharge diagnoses, operations, procedures and medication administration for subset of high-cost medications	Yes	Yes	Yes, hospital discharge diagnoses, ambulatory consultations
Emergency department visits	Not available	Yes	Yes	Not available
General practitioner data	Yes	No	No	Yes, currently only planned to be used in sensitivity analysis
Laboratory data	Yes (only order, no results)	No	No	Yes, but currently not planned to use this data. If used,

Table 12. Overview of data sources

Characteristic	Data sources			
	Germany	Sweden		Netherlands
	GePaRD	SNHR	SWIBREG	PHARMO Data Network
				additional linkage will reduce sample size
Mortality: date, cause	Yes, date of death is available, cause of death not available	Yes, date and cause of death is available	Yes, date of death is available, cause of death is not available	Yes, date of death is available, cause of death is not available

*From http://www.worldometers.info/, status per 16-JUL-2023 (retrieved 20-FEB-2024)

**May also include medication data

ATC=Anatomical Therapeutic Chemical; GePaRD=German Pharmacoepidemiological Research Database; GM=German Modification; GP=general practitioner; M=million; ICD= International Classification of Disease, ICPC=International Classification of Primary Care; Q=Quartile; SNHR=Swedish National Health Registers; SWIBREG= Swedish Inflammatory Bowel Disease Registry.

9.4.1. Germany - Pharmacoepidemiological Research Database (GePaRD)

GePaRD was established and is maintained by the Leibniz Institute for Prevention Research and Epidemiology - BIPS. GePaRD is based on medical claims data from four German statutory health insurance providers (*AOK Bremen/Bremerhaven, DAK Gesundheit, hkk Handelskrankenkasse, and Die Techniker Krankenkasse*). The database includes data on approximately 25 million insured people from all regions of Germany who have been insured with one of the participating providers since 2004 or later(16). Each data year captures information on approximately 20% of the general population.

For identification of relevant medications and for the extraction of additional information (eg, on packaging size, strength, and the DDD), the in-house central pharmaceutical reference (CPR) database is used. Preliminary analyses of age and sex distribution, the number of hospital admissions, and medication use have shown that the database is representative of the German population and that the insurance population is stable over time(17, 18). For each insured person, GePaRD contains information on demographics, all hospitalizations (including in-hospital procedures (OPS [*Operationen-und Prozedurenschlüssel codes*])), outpatient visits with procedures (EBM [German Uniform Evaluation Standard] codes), and reimbursed outpatient dispensations. All diagnoses are coded using the ICD-10-GM system.

GePaRD is updated annually and is linked via the central pharmaceutical number to information from the CPR database. GePaRD and the CPR combined contain the following:

- Sociodemographic data: year of birth, sex, statutory health insurance code, region of residence, nationality, occupational code, dates of insurance coverage (entry and exit), reasons for end of coverage (including death)

- Hospital data: diagnoses and date at admission, main diagnoses and date at discharge, a variable number of accessory diagnoses, reason for discharge (including death), diagnostic and surgical procedures (OPS codes); hospital diagnoses are coded according to ICD-10-GM (at least four digits)

- Outpatient prescription medication data: central pharmaceutical number, pharmacy identification number, date of prescription and dispensation, physician identification number and specialty, quantity prescribed. Data on underlying medical indication are not available

- Pharmaceutical information (from CPR): central pharmaceutical number, generic name, brand, manufacturer, size, strength, DDD, pharmaceutical formulation, and ATC-GM codes

- Outpatient medical treatment data: diagnostic certainty, dates of treatment, and types of treatment/diagnostic procedures with exact date (EBM codes, developed for payment of physicians for the outpatient treatment of German statutory health insurance patients). Ambulatory diagnoses are coded in ICD-10-GM (at least four digits) and are collected by calendar quarter; the exact dates of diagnoses are not available

Reasons for disenrollment from GePaRD include death, change of insurance, other reasons and missing. Disenrollment due to emigration cannot be identified. The lag time from patient encounters to the incorporation of data into the database is 2 years (ie, data from 2023 will be included in Q4 of 2025). There is no lag to access the data once approval to the project is given. Access to medical records for data abstraction or outcome validation purposes is not available in GePaRD. Access to data is allowed only for BIPS employees.

9.4.2. Sweden - SNHR and SWIBREG

The SNHR covers almost all healthcare for Swedish residents; only a small proportion of the population has supplemental private healthcare insurance. The SNHR are run by the National Board of Health and Welfare in Sweden. This study will include the following health registers: Prescribed Drug Register (PDR), National Cancer Register, the Cause of Death Register and the National Patient Register (NPR). In addition, socioeconomic and demographic variables will be added from registers held at Statistics Sweden.

All registers contain personal identification numbers, which allows deterministic linkage across registers on a patient level (19).

9.4.2.1. Swedish National Health Registers

The PDR contains information on all prescriptions filled at pharmacies in Sweden and is updated monthly (20). Data can be captured on dispensed medications using ATC codes, prescription date, dispensing date, defined daily dose, number of units per pack/pack size, strength, number of packages, healthcare professional issuing the prescription, as well as sex, age and residency of the patient. The actual dose and dosing scheme are not available from the PDR. Complete data from the register is available from 01 July 2005.

The National Cancer Register contains information on all incident primary cancer diagnoses with a high proportion of morphologically verified diagnoses (21). In addition, information about cancer diagnoses might also be obtained from the NPR.

Date and cause of death can be obtained from the Cause of Death Register (22). The statistics on causes of death comprise all deaths, covering Swedish residents, whether the person in question was a Swedish citizen or not and irrespective of whether the deaths occurred in Sweden or while they were abroad. The quality of the statistics varies, depending on the examinations made to define the underlying cause of death and due to changes in the classification system or the processing methods. Complete data from the register is available from 01 January 2000.

The NPR contains patient data, geographical data, administrative data and medical data for both inpatient and outpatient hospital care in Sweden (23). The register contains main and secondary diagnosis codes (ICD-10 codes) for each admission and outpatient hospital visit as well as procedure codes. The register contains complete inpatient data from 01 January 1987, with a coverage of approximately 99%, as well as complete outpatient data from 01 January 2001.

Most of the registers are updated annually. Extractions may take up to 12 months to receive. The cancer register has the longest lag time. Together, expected lags in data availability mean that analysis of data of 2032, for example, can be performed from Q2 2034 onwards.

9.4.2.2. SWIBREG

The SWIBREG, founded in 2005, captures detailed data on relevant parameters in IBD management that are not available through Swedish national registers such as patient-reported outcome measures, physician global assessment, disease activity (eg, Mayo endoscopy score), and hospital-administered medicines for IBD. As of MAR-2023, the SWIBREG register contains over 59,704 patients with IBD. SWIBREG's patient coverage rate was approximately 90-95% in comparison with the Swedish NPR by the end of 2022. However, the coverage varies with different regions in Sweden and also with disease severity, as the register in recent years has focused on recording patients exposed to biological treatments. SWIBREG and the Swedish national registers will be used to define exposure, outcomes, and study variables for Swedish UC patients, to conduct this PASS(25).

9.4.3. The Netherlands - PHARMO Data Network

The PHARMO Institute will use the PHARMO Data Network. The PHARMO Data Network is a population-based data source with combined anonymous electronic healthcare data from primary and secondary healthcare settings in the Netherlands (26). The multiple data sources, including data from GPs, in- and outpatient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. The data is collected, processed, linked and anonymised by the *Stichting Informatievoorziening voor Zorg en Onderzoek* (STIZON), an ISO/IEC 27001 and NEN 7510 certified foundation, compliant to the General Data Protection Regulation (GDPR). STIZON acts as a Trusted Third Party (TTP) between the data sources and users of the anonymized data, which can request proportional study-specific datasets, in accordance with the GDPR.

The longitudinal nature of the PHARMO Data Network system enables follow-up of more than 10 million persons from a well-defined population in the Netherlands for an average of twelve years. Currently, the PHARMO Data Network covers over 7 million active persons out of 17 million inhabitants of the Netherlands. Data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO Data Network include information on age and sex. Other information available is dependent on the data source. To fulfill the objectives of the PASS, the PHARMO data described below will be used.

The GP data comprise electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/medication prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Medication prescriptions are coded according to the World Health Organization (WHO) ATC Classification System (27). Diagnoses and symptoms are coded according to the International Classification of Primary Care (ICPC) (28), which can be mapped to ICD codes, but can also be entered as free text. GP data cover a catchment area representing 3.2 million residents.

The outpatient pharmacy data comprise GP- or specialist-prescribed healthcare products dispensed by outpatient pharmacies including community pharmacies as well as hospital-based outpatient pharmacies. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Medication dispensing are coded according to the WHO ATC Classification System (27). Outpatient pharmacy data cover a catchment area representing 4.2 million residents.

The hospital data comprise datasets containing data on hospital admissions, ambulatory consultations and high-cost medicines. For the PASS, all three will be used. Hospital data are collected and maintained by the Dutch Hospital Data Foundation (29) and comprise records from nearly all hospitals in the Netherlands. With permission from each hospital the data are linked for research purposes with the PHARMO Data Network via the TTP.

Hospital admissions

This dataset comprises hospital admissions for more than 24 hours and admissions for less than 24 hours for which a bed is required (ie, inpatient records). The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. Diagnoses are coded according to the WHO ICD (30) and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures (31) which links to the Dutch Healthcare Authority (NZa) declaration codes (32) and the Dutch Classification of Procedures (33). Currently, PHARMO has access to data from 1998 onwards and of over 80% of the hospitals.

Ambulatory consultations

This dataset comprises all ambulatory consultations (ie, outpatient records). The records include information on each consultation, including date, diagnoses, and procedures. Diagnoses are coded according to the WHO ICD (30) and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures (31) which links to the Dutch Healthcare Authority (NZa) declaration codes (32) and the Dutch Classification of Procedures (33). Currently, PHARMO has access to data from 2016 onwards and includes over 80% of the Dutch hospitals.

High-cost medicines

In the Netherlands, most high-cost medicines are dispensed through hospitals. The high-cost medicines dataset comprises the products that have been designated as high-cost medicine (so-called ‘add-on’ medication) by the Dutch Healthcare Authority, such as biologicals, antineoplastics, immunoglobulins. The records include information on date of dispensing, type of medication, number of units, indication of use and prescriber. Medication dispensing are coded according to the Dutch Z-index code (34). These data are available from 2017 onwards and currently PHARMO has access to data of over 80% of the Dutch hospitals.

The Cancer Registry is maintained by the Netherlands Comprehensive Cancer Organization and comprises information on newly diagnosed cancer patients in the Netherlands, including cancer diagnosis, tumor staging (according to the Tumor-Lymph node-Metastasis-classification developed and maintained by the Union for International Cancer Control), tumor site (topography) and morphology (histology) (according to the WHO International Classification of Diseases for Oncology), co-morbidity at diagnosis and treatment received directly after diagnosis. For research purposes, the data are linked with the PHARMO Data Network via the TTP. For this PASS, permission would need to be obtained from PHARMO as well as the Netherlands Comprehensive Cancer Organization to use these linked data.

9.4.4. Country- and data source-specific considerations for this PASS

Estimates for availability of etrasimod for UC per country are provided in Table 13.

Table 13. Estimated etrasimod availability per relevant country for this PASS

Country	Date etrasimod fully available on the market (ie, with reimbursement)
Germany	15-APR-2024
Sweden	1-MAR-2025*
The Netherlands	Expected 22-JUL-2025**

*Conditional reimbursement for UC when treatment with TNF inhibitors has had insufficient effect or would not have been appropriate.
**Based on published advice for reimbursement of etrasimod in the Netherlands, and expected time to final decision for reimbursement of 110 days.

The study period will be at least 8 years for three out of four data sources in this PASS, and will be slightly reduced for GePaRD (Table 14). This reduction will be implemented since GePard has a longer lag for the data to become available for analysis compared to other data sources (Table 12). The study period for GePaRD will end 1 calendar year earlier, and will reduce the lag in data availability by a full year (expected end of data collection provided in Section 6).

Table 14. Length of study period per data sources

Country	End of study period	Country- and data source-specific length of study period
Germany	31-DEC-2031	7.9 years
Sweden	31-DEC-2032	8.9 years
The Netherlands	31-DEC-2032	8.9 years

The following paragraphs provide other country- and data source-specific considerations for this PASS.

Germany

In Germany, prevalence of UC is estimated between 160 to 250 per 100,000 persons.(35) In GePaRD, UC will be assessed mainly based on main hospital discharge diagnoses, however, repeated diagnoses in the outpatient setting by specialist as well as diagnostic procedures could also be considered for the case definition.

As of now, the route of reimbursement for etrasimod for Germany is unclear, including whether use will be mostly in the outpatient or inpatient setting. Etrasimod use is expected to be captured in both the outpatient setting in GePaRD, as well as in the inpatient setting via the high-cost medications data.

Sweden

In Sweden, prevalence of UC is estimated at 510 per 100,000 persons.(28) The NPR and SWIBREG will be used to identify patients diagnosed with UC. There is overlap and

similarities in the clinical presentation of different IBD subtypes. For this reason, the same patient may be diagnosed with more than one IBD subtype during follow-up, at the beginning of the disease. To reduce misclassification, at least two UC diagnostic codes will be required in the NPR before index date.(36) Validation studies have shown that requiring two or more diagnoses of UC in the Swedish NPR had a positive predictive value (PPV) of 79%; classifications of UC in SWIBREG had a PPV of 96-100%.(37, 38)

The Cohort-defining medication in Sweden will be defined based on dispensed prescriptions from the PDR and SWIBREG. Only medication dispensed in pharmacies is recorded in the PDR, while medications administered in hospitals are not. Exposure to biologics in Sweden will not have complete coverage in the PDR in those instances when it is given in clinics intravenously and the patient has not filled a pharmacy prescription. Therefore, SWIBREG will also be used to capture exposure information.

Taken together, given the central role of SWIBREG data for assessing Cohort-defining medication for this PASS, analyses will be restricted to individuals included in SWIBREG

The Netherlands

For the Netherlands, recent estimates from 2020 suggest that the nationwide point prevalence of UC is approximately 45,000(39) to 60,000(40). Patients with UC can be identified using hospital disease codes and codes that may initially be used when at the start of a patient's care pathway (eg, generic codes for a colitis). Throughout the diagnostic work-up for a colitis, accurate coding of a diagnosis of UC by physicians or other hospital employees is incentivized by obtaining the correct reimbursement for the corresponding screening, diagnostic, and treatment activities that are initiated once a patient has been diagnosed with UC. The validity of using clinical diagnostic codes for UC from hospital data is supported by findings from a recent Dutch validation study for IBD. This study used the same hospital data as the PHARMO Data Network and found good-to-excellent predictive performance (F-scores of 0.870 and higher in cross-validation) of their model compared to pathology-confirmed diagnoses.(41) The proportion of patients with Crohn's disease misdiagnosed with UC is expected to be low.

For the Netherlands, etrasimod is expected to be captured in the hospital data's high-cost medicines dataset. Etrasimod was announced to be reimbursed through the Dutch framework for intramural medicines. The cost of etrasimod is expected to exceed 1.000 EUR per-patient-per-year,(40) which would qualify it as high-budget impact medication and therefore it is expected to be captured in the PHARMO high-cost medicines dataset.(40) A comparator S1P receptor modulator medication, ozanimod, is reimbursed in the Netherlands through the extramural framework and is dispensed in outpatient pharmacies. The final route of reimbursement and corresponding capture in PHARMO of etrasimod remains to be determined. Note, the high-cost-medicines data only capture medicine use for approved indications; off-label use may not be fully captured.

Estimated etrasimod use in the Netherlands is challenging to predict. A recent assessment suggested that upon reimbursed availability in the Netherlands, between 50-100 patients per

year will be eligible for treatment with etrasimod.(40) Another assessment of patient volume estimated 3,259 potential patients per year based on expert opinion regarding use of medications for UC with a similar indication (embedded in an advice of the Dutch National Healthcare Institute (*Zorginstituut Nederland*) on reimbursement (see below).(42)

Reimbursed availability of etrasimod in the Netherlands is expected to be delayed beyond European Commission approval. A 'lock' procedure was advised by the Dutch National Healthcare Institute for etrasimod on 24-JAN-2024.(42) This procedure aims to improve assessment of efficacy and safety, and support price negotiations of medicines with expected national or per-patient costs exceeding prespecified thresholds. Durations of lock procedures have been increasing; in 2020, the average lock procedure lasted 518 days.(20) Reimbursement is not expected until JUN-2025 (Table 13).

Considering the objectives and required data in this PASS, the primary analysis will be conducted using hospital and outpatient pharmacy data. The GP data will only be used for the sensitivity analysis on symptomatic bradycardia to facilitate ascertainment of symptom codes. Table 15 summarizes the ability of data sources to capture relevant information for this PASS.

Table 15. Expected capture of study-related information per data source

Tasks or variables	Germany	Sweden		Netherlands
	GePaRD	SNHR	SWIBREG	PHARMO Data Network
Identify use of etrasimod (Cohort 1)	☒	☒	☒	☒
Identify patients diagnosed with UC	☒	☒	☒	☒
Identify use of comparator medications of interest (Cohort 2)	☒	☒	☒	☒
Identify use of other comparator medications of interest (Cohort 3)	☒	☒	☒	☒
Identify use of other comparator medications of interest (Cohort 4)	☒	☒	☒	☒
Identify populations of special interest (ie, patients aged 65 years and older)	☒	☒	☒	☒
Ascertain safety events of interest				
Macular oedema	☒	☒[A]		☒[A]
Serious liver injury	☒	☒		☒
Malignancy	☒	☒		☒
SOI	☒	☒		☒
Neurologic events of PRES and convulsions	☒	☒		☒
Symptomatic bradycardia (including conduction disorders)	☒	☒		☒
Eye adverse events	☒	☒		☒

Table 15. Expected capture of study-related information per data source

Tasks or variables	Germany	Sweden		Netherlands
	GePaRD	**SNHR**	**SWIBREG**	**PHARMO Data Network**
Infections	☒	☒		☒
CV events	☒	☒		☒
Ascertain covariates of interest				
Sociodemographic factors (age, sex, socio-economic status)	☒	☒		☒
Mortality	☒	☒		☒
CV risk factors	☒	☒		☒
UC-specific factors	☒	☒	☒	☒
Co-medication use	☒	☒	☒	☒
Lookback period of 10 years available before expected start of reimbursement of etrasimod per country*	☒	☒		
Minimum follow-up period 5 years after index date**	☒	☒		☒

A. Based on suggested MedDRA terms to assess macular edema outcome, the data source's coding system may not allow a similar level of granularity to identify this outcome with high specificity.

*Considering different expected delayed dates of reimbursement per country. For the Netherlands, the hospital data subset for high budget impact medication is only available from 2017 onwards; reimbursement in 2026 would slightly limit the maximum lookback available that year.

**Considering dates of reimbursement, lag times for update of data sources, and different data cut-off.

9.5. Study Size

For the primary objectives, this study will describe all patients and events occurring in the data sources' study populations during the study period. There are no predefined minimum or maximum sample sizes that may preclude this study from reporting IRs and characteristics. Note, if a cell size is N<5, reporting may be suppressed to reduce chances of identifiability of individuals (Section 9.7.5).

Use of etrasimod for UC in the proposed data sources (GePaRD, SNHR/SWIBREG, and PHARMO) across the full study period cannot be determined *a priori*. Use first depends on the full reimbursement of etrasimod per country (see Section 9.4.4). Also, additional therapies becoming available for UC throughout the duration of this study additionally limit the number of patients prescribed etrasimod. Lastly, lags in data availability in the proposed data sources may reduce available number of users of etrasimod for analyses.

For descriptive analyses, estimates for expected precision for a subset of the safety events of interest are provided in Table 16 (calculation details are provided in the footnote). Background incidence rates for safety events of interest are unknown and were estimated using clinical trial data or other relevant literature (ANNEX 3. ADDITIONAL INFORMATION).

Comparative analyses (Section 9.7.2) will be conducted pending sufficient sample sizes. Calculations for sample size for comparative analyses will be provided in detail in the SAP. Feasibility for conducting comparative analyses will be informed by results from the Interim Report (eg, IRs of the events of interest and estimates for the average duration of the exposed time window for each medication of interest, to calculate sample sizes for the final report, and whether comparative analyses will be feasible).

Table 16. Estimates of expected precision based on sample sizes, per safety event of interest

Safety events of interest	Incidence rate (per 100,000 person years)	Calculated Cumulative incidence*	95% confidence intervals across sample sizes of cumulative number of patients with UC exposed to etrasimod**							
			Year 1	Year 2	Year 3	Year 4	Year 5	Year 6	Year 7	Year 8
			N=183	N=681	N=1,192	N=1,703	N=2,217	N=2,742	N=3,186	N=3,455
Macular oedema***	420	0.84%	0.20-3.50	0.38-1.85	0.46-1.54	0.50-1.40	0.54-1.31	0.56-1.26	0.58-1.22	0.59-1.20
Malignancy	650	6.29%	3.59-10.78	4.70-8.37	5.05-7.81	5.23-7.54	5.35-7.38	5.44-7.26	5.50-7.19	5.53-7.15
SOI	2,380	4.65%	2.42-8.74	3.31-6.50	3.59-6.00	3.75-5.76	3.85-5.61	3.92-5.50	3.97-5.44	4.00-5.40
PRES or convulsions	64	0.12%	0.01-2.28	0.02-0.78	0.03-0.53	0.03-0.43	0.04-0.37	0.04-0.34	0.05-0.31	0.05-0.30

The incidence rates derived from literature-based estimates described in ANNEX 3. ADDITIONAL INFORMATION were applied for a subset of four safety events of interest. Calculations assume static incidence rates over follow-up, and across patients in calendar time, for comparative purposes.

*Cumulative incidence was calculated as 1- exp(IR*t), where IR is provided as proportion and t is defined as follow-up period in years. Cumulative incidences for macular oedema, SOI, and PRES or convulsions were estimated assuming a 2-year follow-up period. For malignancy, a follow-up period of 10 years was assumed.

**Estimates derived from conservative estimates of etrasimod use and of total population of patients with UC of 40,310 across Germany, Sweden and the Netherlands together.

***Precision estimates are conservatively based on incidence rate of macular oedema per se as assessed in a pivotal clinical trial, while the concept of macular oedema investigated in this PASS will also be broadened to include retinal disorders.

9.6. Data Management

Retrospective data extraction will be done locally by each research partner. Complete centralization of analyses is not possible due to local governance. Additionally, local expertise of the database and healthcare system is essential for preparing the data for analyses and interpretation.

A distributed common data model (CDM) approach will be used to reduce analytical heterogeneity between data sources. Each database extracts study specific data locally and transforms them into CDM format, which is similar across sites and allows analysis with a centralized script. The CDM will consist of standardized files (ie, patient, exposure, outcomes), which are linkable via a unique patient identifier. Differences in findings across data sources can then be better attributed to true differences in the data rather than analytical differences.

Detailed local knowledge of the healthcare system is necessary to provide the correct definitions. Code lists and identification algorithms will be created in close collaboration with the participating databases and medical experts and will be described in the SAP. The healthcare systems, and clinical processes generating the data used in this study differ per country. This study aims to allow local data sources to determine how to best classify common concepts using local knowledge. For example, a condition such as hypertension may be included as concept in the CDM, and data sources may use different combinations of locally available data such as physical examinations, diagnostic codes, medications, or procedures to best classify that concept according to local clinical practice.

All study-related data will be archived for at least ten years after completion of the study. The data will be stored in a secure and controlled environment, with access restricted to authorized personnel only. Electronic data will be backed up regularly, and appropriate measures will be taken to protect the data from unauthorized access, loss, or corruption.

The investigators and authorized study personnel in each participating data source will have access to the data relevant to their institute. The sponsor of this PASS will have access to aggregated and anonymized data presented in the reports, and will not have access to identifiable patient data unless explicitly required by regulatory authorities, approved by relevant ethical committees, and permitted by law.

9.7. Data Analysis

Analytic programming/coding scripts will be developed centrally by PHARMO based on the CDM described in Section 9.6. The analyses described in the sections below will be executed by each research partner in the data sources they access, using the standardised analytic scripts.

Detailed methodology for all analyses of data collected in this study will be documented in the SAP, which will be dated, filed, and maintained by the study coordinator (PHARMO). The SAP may modify the plans outlined in the protocol; any major modifications of primary

endpoint definitions or their analyses will be reflected in a protocol amendment. An overview of all planned analyses is given in Table 17.

Table 17. Overview of planned analyses

Objective	Analysis
Analyses per data source	
NA	Describe selection of patients into Cohorts according to inclusion and exclusion criteria.
1	Describe characteristics at index date per Cohort
2 and 3	Estimate crude and age-sex standardized IRs per Cohort for the following safety events: - Macular oedema - Serious liver injury - Malignancy - SOI - Neurologic events of PRES or convulsions - Symptomatic bradycardia (including conduction disorders)
4a	Pending sufficient sample size, estimate adjusted hazard ratios (HR) of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating other S1P receptor modulators (Cohort 2)
4b	Pending sufficient sample size, estimate adjusted HR of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating biologics (Cohort 3)
4c	Pending sufficient sample size, estimate adjusted HR of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating JAKi (Cohort 4)
5	Estimate crude IRs and age-sex standardized IRs per Cohort among patients aged 65 years and older of: - Eye adverse events - Infections - CV events
Analyses combining data sources	
4a	Pending sufficient sample size, a meta-analysis combining estimated adjusted HR across data sources of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating other S1P receptor modulators (Cohort 2) will be performed
4b	Pending sufficient sample size, a meta-analysis combining estimated adjusted HR across data sources of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating biologics (Cohort 3) will be performed

Table 17. Overview of planned analyses

Objective	Analysis
4c	Pending sufficient sample size, a meta-analysis combining estimated adjusted HR across data sources of safety events of interest of patients with UC initiating etrasimod (Cohort 1) with patients with UC initiating JAKi (Cohort 4) will be performed
Sensitivity analyses	
1	IR of malignancy using a different lag-time (0 (no lag) and 12 months after index date) to evaluate the impact the lag-time has on incidences of malignancies
2	IR of malignancy using an intention-to-treat approach
3	IR of symptomatic bradycardia with recorded symptoms
4	Estimate crude and age-sex standardized IRs per Cohort for the following safety events of interest, restricted to patients without history of the event (or similar conditions): - Macular oedema - Serious liver injury - Malignancy - Serious opportunistic infections - Neurologic events of PRES or convulsions - Symptomatic bradycardia (including conduction disorders)
5	Describe number of patients per Cohort with only a single prescription/dispensing of Cohort-defining medication, and the proportion of these patient that had a safety event of interest in 30 days after index date
6	Intention to treat approach for PRES events, prolonging the risk window to the assessment of PRES to once exposed always at risk
7	Allowing concurrent use of non-Cohort-defining medication for UC, per the approved SmPC, for inclusion in Cohorts 1 and 2.

9.7.1. Descriptive Analyses

The study will describe patient characteristics at index date per Cohort, and estimate IRs of safety events of interest, for each of the four Cohorts.

An attrition table will show inclusion of initiators per Cohort, and the unique numbers of patients will be reported. Frequency measures of specific medications on the 5th ATC level will be described among each of the four Cohorts.

Characteristics of each of the four patient Cohorts will be ascertained at a patient's Cohort-specific index date. Characteristics will be described using lookback of a minimum of 1 year and a maximum of 10 years, except for describing co-medications for non-UC conditions which will be assessed with a maximum look-back of 1 year. Categorical variables will be

summarized by frequency counts and proportions, and means (standard deviations) or medians (1st quartile – 3rd quartile) will be presented for continuous variables.

IRs will be estimated for each outcome for each of the four Cohorts. Patients may initiate multiple therapies during the study period but can contribute only one treatment episode to each of the four Cohorts. Each patient may have a maximum of four index dates, and therefore the unit of observation will be the treatment episode, not the patient. IRs and their corresponding 95% CI will be estimated as the ratio of the number of incident outcomes that occurred during follow-up divided by the total number of at-risk person-years in the exposed time window (Section 9.3.1). Note that for malignancies a lag-time period will be added from the index date to the start of follow-up, and that follow-up is extended for a fixed period after the (estimated) medication discontinuation (Section 9.3.1.2).

Both crude IRs as well as age-sex standardized IRs will be provided across all Cohorts and outcomes; standardization will be conducted using available estimated population strata of age and sex, per time period.

Since these are RWD, they represent attended medical care, and only conditions for which a patient sought care are captured. Certain covariates, particularly lifestyle data (eg, body mass index [BMI] and smoking), are often underreported. Missingness in these variables is likely not at random. The degree of missingness will be described (see Section 9.9 on limitations regarding imputing missing data).

Pending sufficient sample size, IRs will be adjusted for sources of bias (Section 9.7.2).

9.7.2. Comparative analyses (pending sufficient sample size)

Pending sufficient sample size, comparative analyses will be conducted. This PASS will be guided by available methodological frameworks such as the framework for (TTE).(43) Use of the TTE framework improves transparency of definitions and assumptions in study design, and is recommended by ENCePP for observational causal inference studies.(44)

Table 18 describes the different study design elements for a comparative analysis in this PASS. This specifies a hypothetical target trial based on this PASS, and is not meant as a reproduction of the pivotal Phase 3, placebo-controlled RCT on which EMA-approval for etrasimod in patients with UC was based. A separate TTE will be conducted for each outcome with sufficient cases using outcome specific confounders and time windows (eg, lag time for cancer). If sample sizes do not allow performing a TTE analysis only IRs will be estimated (Section 9.7.1). Note that for sensitivity and subgroup analysis, different sample size criteria may apply.

Table 18. Generic target trial emulation (TTE) specification (43)

Protocol Component	Target Trial	Emulation
Eligibility criteria	Eligible patients will be based on the label of etrasimod Inclusion criteria (indication) • 16 years of age and older with • moderately to severely active UC • who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent Exclusion criteria (contraindications) • Hypersensitivity to the active substance or to any of the excipients listed in Section 6.1 of the SmPC. • Immunodeficient state. • Patients who in the last 6 months experienced myocardial infarction, unstable angina pectoris, stroke, transient ischemic attack, decompensated heart failure requiring hospitalization, or New York Heart Association Class III/IV heart failure. • Patients with history or presence of Mobitz type II second-degree or third-degree atrioventricular block, sick sinus syndrome, or sino-atrial block, unless patient has a functioning pacemaker. • Severe active infections, active chronic infections such as hepatitis or tuberculosis. • Active malignancies. • Severe hepatic impairment.	Inclusion criteria • First dispensing of etrasimod (Cohort 1), other S1P receptor modulators (Cohort 2), biologics (Cohort 3), or JAKi (Cohort 4) at index date • in patients 16 years of age and older with • A diagnosis of UC using ICD-10 K51 up to 10 years prior to index date • And with at least one year of available data prior to index date for confounder/covariate assessment It is assumed that the first dispensing is according to label due to inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent. Exclusion criteria • A diagnosis of Crohn's disease prior to index date, but after UC diagnosis • Exposure to other non-Cohort-defining medication for UC prior to, or on, index date (for Cohorts 1 and 2 only) It is assumed contraindications are weighed against the benefits of the medication for the individual patient. To assess safety in all exposed patients, no additional exclusion criteria will be applied.

Table 18. Generic target trial emulation (TTE) specification (43)

Protocol Component	Target Trial	Emulation
	• During pregnancy and in women of childbearing potential not using effective contraception	
Treatment strategies	(i) Use of etrasimod as monotherapy (ii) Use of S1P receptor modulators as monotherapy (iii) Use of biologics (iv) Use of JAKi	Same as for target trial
Assignment procedures	Patients are randomly assigned to a strategy at decision to change treatment (see indication) and patients and their treating physicians will be aware of the assigned treatment strategy.	Patients are classified according to the strategy that their data were compatible with. Patients are not blinded to their treatment strategy. Randomization is emulated by adjusting for confounders at index date using (eg, propensity score methods.
Follow-up period	Starts at treatment assignment and ends at the first of (i) *outcome*[1], (ii) death, or (iii) loss to follow-up; iv) for the per protocol analysis only: end of the assigned treatment strategy).	Same as for target trial
Outcome	Outcomes as defined in Section 9.3.2[1]	Same as for target trial
Causal contrasts of interest	Intention-to-treat effect and per-protocol effect comparing strategy 1 with strategy 2, strategy 1 with strategy 3, and strategy 1 with strategy 4.	Observational analogues of intention-to-treat (for malignancy outcomes only) and per-protocol effect (a 'restricted' as-treated approach)
Analysis plan	See emulation	Same as for the target trial with: • Adjustment for confounders at index date • Adjustment for loss of follow-up using (eg, inverse probability of censoring weighting).

Table 18. Generic target trial emulation (TTE) specification (43)

Protocol Component	Target Trial	Emulation
		○ To address informative censoring due to non-adherence (ie, the difference between the per-protocol and the intention-to-treat observational analogues), further adjustment for predictors of adherence and the outcome will be implemented (eg, using inverse probability of censoring weighting).

1. Macular oedema, serious liver injury, malignancy, serious opportunistic infections, neurologic events of PRES or convulsions, symptomatic bradycardia (including conduction disorders)

9.7.3. Subgroup analyses

Additional analyses for the safety endpoints of interest of eye adverse events, infections, and CV events will be conducted in patients aged ≥65 years. Etrasimod use in clinical studies for this age group has been relatively low: The European public assessment report for etrasimod reported 5.6% of patients treated with etrasimod analyzed for safety outcomes to be aged ≥65 years, and 0.3% ≥75 years.(45) Correspondingly, there is missing information on adverse events in this elderly population. Considering expected low numbers of users aged ≥65 years, key outcome definitions will be defined in a broad manner, compared to the more specific safety signals investigated in the main analysis (see definitions in Section 9.3.2.7).

9.7.4. Pooled analysis

A meta-analysis pooling aggregated results from all data sources will be conducted. Conditions for conducting a meta-analysis of country-specific results conditional on minimum numbers of events per data source.

Although the same study design is applied in each data source, and heterogeneity in analyses is reduced by applying a CDM, there may be residual heterogeneity between countries (eg, due to differences in healthcare systems, reimbursement strategies, or national UC diagnosis and treatment guidelines). If a qualitative evaluation deems pooling inappropriate for a particular analysis, then results may not be combined, or additional considerations are provided for contextualizing pooled results in a study report.

Pooling of data on patient level will not be allowed based on governance rules of the participating data sources. Effect estimates will be combined using a method considered appropriate depending on features of the estimates, including the homogeneity of the estimates across populations. Results will be reported per country and through with pooled estimates and 95% CI (tabular and forest plots), and appropriate diagnostic measures of heterogeneity are provided in case of pooling results across >2 sources.

Minimal numbers of event per data source for conducting pooled analyses, and further details for pooling will be specified in the SAP.

9.7.5. Sensitivity analyses

This study includes seven sensitivity analyses detailed in the sections below:

Malignancies

1. The lag-time will be changed to evaluate the impact the lag-time has on incidences of malignancies. As different cancer types and medications may have different plausible lag-times from exposure to detection, a sensitivity analysis will be performed where lag-time is changed to either 0 (ie no lag time) or 12 months after index date.
2. IRs of malignancies will be estimated using an intention-to-treat approach: once exposed to a Cohort-defining medication, the patient is followed up for malignancy outcomes regardless of continued prescription/dispensing for that Cohort-defining

medication after index date. Censoring events still apply, excluding exposure to another Cohort-defining treatment or to a newly approved UC medication. Malignancies occurring in overlapping follow-up periods for different Cohorts defined for the same patient will be counted as outcome for both Cohorts, instead of only the most recent Cohort as in the primary analysis using a 'restricted' as-treated approach (to be further specified in SAP).

Symptomatic bradycardia (including conduction disorders)

3. A second, narrower definition of symptomatic bradycardia (including conduction disorders) will be used, requiring presence of symptoms (eg, dizziness) occurring on the same day as the event to confirm an accurate diagnosis of the event being symptomatic (Table 19). Analyses require presence of symptom codes in the data source's coding system.

Table 19. Symptomatic bradycardia symptoms for defining sensitivity analysis outcome

Variable	Definition
Date of first symptomatic bradycardia (including conduction disorders)	In addition to symptomatic bradycardia identified within hospitalisation events, ≥1 of the following symptom sets must occur within 1 day of bradycardia (including conduction disorders) events: • Fatigue or feeling weak • Dizziness or lightheadedness • Confusion • Fainting (syncope) or near-fainting • Shortness of breath • Tires easily during exercise • Chest pain

Restriction to patients without history of outcome

4. This PASS aims to estimate incidences rates of safety events of interest in all initiators of medications of interest. The primary analysis sets no exclusion criteria with regards to having a history of the event of interest or similar conditions that could predispose to occurrence of an outcome, per outcome analysis. To estimate IRs of safety events of interest independent from any history of the same events or a pre-existing condition, a sensitivity analysis will be conducted repeating the main analyses for all safety events of interest after excluding patients with a history of that safety event of interest or similar conditions (determined per outcome). Exclusion

criteria per safety event of interest will consider label (contra-)indications, and will be aligned with the following definitions (to be detailed in the SAP):

- Macular oedema: A history of any macular oedema prior to, or on, the index date.
- Serious liver injury: A history of severe liver injury prior to, or on, the index date, including but not limited to the following aetiologies: chronic, acute, viral (including HIV), alcohol- or medication-induced, without defined cause (eg, "hepatitis unspecified"), or other hepatic conditions (eg, "other specified disorders of liver").
- Malignancies: A history of any malignancy prior to, or on, the index date.
- SOI: A history of HIV infection, congenital immunodeficiency, organ transplantation or serious opportunistic infection prior to, or on, index date.
- PRES/convulsions: Patients with a history of PRES, hypertensive crisis or epilepsy or convulsions will be excluded.
- Symptomatic bradycardia (including conduction disorders): A history of severe or chronic conduction disorders (eg, sick sinus syndrome, Mobitz type 2 or type 3 atrioventricular conduction block, presence of a pacemaker) prior to, or on, index date. Events potentially captured with this safety event of interest may be relatively common (eg, for symptomatic bradycardia, may exclude patients with vasovagal collapse, orthostatic hypotension, or for conduction disorders, will exclude patients with a bundle branch block or PR-interval prolongation of unknown clinical significance on their electrocardiogram, or patients with tachyarrhythmias and excluding patients with a history of that event may substantially reduce the study population size for this analysis).
    - As symptomatic bradycardia (including conduction disorders) may occur acutely after etrasimod exposure, two windows will be used to define a history of this group of events
        - Excluding events dated prior to <u>or on</u> index date
        - Excluding events <u>only prior to</u> index date, considering events on index date as incident events.

Describe single prescription/dispensing of Cohort-defining medication

5. Misclassification of exposure by erroneous single records of a prescription/dispensing will be explored descriptively. The number of patients per Cohort that only received a single prescription/dispensing will be described, along with the proportion who in the subsequent 30 days after initiation of that medication experienced a safety event of interest. This proportion can indirectly inform on presence of erroneous single

prescription/dispensing. Exposure will not be redefined by requiring an additional number of prescriptions/dispensings to validate exposure, since a single prescription/dispensing may be valid if that medication was discontinued due to experiencing side effects, including the safety events of interest for this PASS.

Intention to treat approach for PRES events

6. Potential occurrence of an event of PRES beyond the as-treated risk window will be explored by repeating the analyses for PRES and convulsions with changing the risk window for PRES events only to an intention to treat approach (once exposed always at risk). Further details for combining different risk windows for PRES and convulsions for this sensitivity analysis will be provided in the SAP.

Allowing concurrent use of non-Cohort-defining medication for UC for inclusion in Cohorts 1 and 2

7. This sensitivity analysis will allow assessment of the risk of safety events in patients treated with etrasimod or other S1P modulators during routine clinical care, regardless of use of concurrent non-Cohort-defining medication for UC, per the approved SmPC, i.e., will remove the restriction to a monotherapy treatment strategy. The populations for Cohorts 1 and 2 will be redefined with changing the exclusion criterion for concurrent non-Cohort-defining medication, and changing the censoring criterion for initiation of non-Cohort-defining UC medication during follow-up. Medication allowed will be consistent with those allowed in the UC ELEVATE trial (which allowed concomitant use of oral 5-ASA and corticosteroids). The estimation of IRs of the safety events of interest will be repeated in the main Cohorts, and the subgroup analysis in persons aged 65 or over at index date will be repeated. Also, comparative analyses pending sufficient sample size may be conducted for Cohorts 1 and 2 based on sample sizes assessed in the broader, unselected sensitivity Cohorts 1 and 2. Comparative analysis methods used to adjust for any effects of concurrent medication use on outcomes will be similar to those described in Section 9.7.2, including IPTW using propensity scores defined on the broader population (details provided in the SAP).

9.7.6. Reporting of small cell counts

For PHARMO (the Netherlands), local data protection rules will be followed which may limit reporting on small numbers of observations. Reporting will be supressed for strata with N<5 patients, while for strata with a total of N≥5 patients categorical characteristics or outcomes containing n<5 observations may be reported. For example, it may be reported that 3 out of 100 patients had an event during follow-up. If the group of n=100 is stratified on occurrence of the rare event, no information can be reported for the n=3 patients with the event. No reporting restrictions apply for CPE (Sweden) and BIPS (Germany)

9.8. Quality Control

Standard operating procedures at each research partner will be used to guide the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality control procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

For local programming (eg, to prepare input for the common data model), local quality standards per data source will be used. This could include for example independent senior review of programming, or double independent programming.

All key study documents, such as the SAP and study reports, will undergo quality control and senior scientific review by study teams at BIPS, CPE, and PHARMO separately.

9.9. Limitations of the Research Methods

This active surveillance study of safety events of interest primarily describes risk of specific events per Cohort. While aimed at supporting making causal statements about etrasimod initiation (compared to initiation of other medications of interest) and the risk of safety events of interest, descriptive methods are not best suited to elucidate these causal relations. Uptake of etrasimod is expected to be modest and the incidences of the safety events of interest are expected to be low. Study size within limits determined in the SAP may therefore turn out to be insufficient to perform comparative analyses to estimate the causal relation of initiating etrasimod with the safety events of interest with sufficient precision.

Confounding

For the descriptive objectives in this study, safety events of interest are assessed during certain risk windows, per Cohort. Although no common cause of exposure and outcome may hamper estimation of IRs, to allow better contextualization of IRs, this study also reports age-sex standardized IRs. To explore differences between the etrasimod and other Cohorts, patient characteristics may be compared at index date (eg, patient characteristics, disease severity, and past therapies) between Cohorts or with estimates from literature for contextualization.

Comparative analyses may be conducted pending sufficient sample size. Confounding by indication (channeling') is expected to be present in comparisons across Cohorts. Cohort populations may differ since the different medications defining the Cohorts may not be given to the same groups of patients with UC. Given that etrasimod is indicated in patients "*…who have had an inadequate response, lost response, or were intolerant to either conventional therapy, or a biological agent*"(8), a proportion of patients prescribed etrasimod or other S1P receptor modulators (Cohorts 1 and 2) will have been treated previously with biologics (Cohort 3). A smaller proportion will have been treated previously with JAKi.(46) Also, patients who initiate etrasimod will likely have a higher severity of disease than patients with UC at the time of initiating comparator medications of interest. Lastly, additional factors are involved in assigning treatments between patient and physician in daily practice that are difficult-to-measure and may create differences across Cohorts. In the case that sample size is

sufficient to conduct comparative analyses, adjustment for measured confounding factors may be addressed by the use of inverse probability weighting (IPW; eg, treatment or censoring). First, the propensity of receiving treatment is estimated (ie, propensity score). Second, weights are estimated as the inverse of the propensity score. The application of IPW to the compared Cohorts (eg, Cohort 1 and 2) in essence creates a pseudo-population in which confounders are equally distributed across each Cohort under comparison (eg, between the exposed and unexposed group). However, this approach can be vulnerable to large weights, and misspecification of propensity score models. An IPW-approach allows flexibility in estimands or inclusion of all patients.

Further details on the propensity score approach and estimation of IP weights will be outlined in the SAP. Additionally, the best strategy for reducing large weights (eg, capping or trimming) will be conditional on actual calculated weights, and as such will also be further specified in the SAP. Residual confounding due to unmeasured confounding factors is to be expected, even with the availability of a large number of potentially relevant variables from the data sources involved in this PASS.

Information and selection bias

None of the databases can confirm actual medication intake. This study therefore assumes that patients use medications as directed. Measurement error in medication use and adherence is therefore a potential source of exposure misclassification. Furthermore, the intended duration of use of each prescription/dispensing is often not recorded (days of supply). This needs to be estimated from dispensed amount and free text descriptions about dosage instructions, the interval between consecutive prescriptions/dispensing, or by label information regarding dosing frequencies for specific indications combined with the dose per unit of the dispensed medication. This can result both in over- and underestimation of the duration of the exposed time window. Misclassification of exposure by an erroneous single prescription/dispensing will be explored in a sensitivity analysis.

Outcome misclassification may be expected to some degree for the malignancy subtype of skin cancer. Skin cancer is highlighted by the SmPC for etrasimod as specific safety signal, including the non-melanoma skin cancers.(7) Non-melanoma skin cancers are not often studied and may not be well captured in data source-specific cancer registries. Although ascertainment of this outcome can be complemented using diagnostic codes or alternative identification via text mining of free text records, some under ascertainment relative to other registered cancers may occur. Additionally, inclusion of the safety signal for skin cancer in labelling may increase detection of skin cancers which could cause differential incidences between medications with different labels, even if these medications had no causal effect on skin cancer incidence. Note that labelling for etrasimod (7) but also medications in Cohort 2 (47, 48) and Cohort 3 (49) all mention risk of (non-melanoma) skin cancer; this will reduce chances of differential detection rates causing spurious differences in incidences rates between Cohorts.

This PASS implements lag-times and an extended follow-up duration for malignancy analyses to address detection biases and potential lagged effects on cancer development. The most valid durations of lag-times and of the extended follow-up for UC patients and the

Cohort-defining medications are not well known, which is addressed through sensitivity analyses. The pattern of all results from these analyses will support evaluating detection biases or potential clustering of events after initiating Cohort-defining medication.

Missing data is a frequent challenge in the use of RWD. Missing data can give rise to selection bias if that is needed for inclusion in the analysis. Eligible patients may not be visible in the data due to, for example, changes in coding conventions, or patients are visible but miss data on a key variable not recorded by a healthcare provider during an encounter.

Data extracts for German and Swedish data sources are, by design, imputing values where deemed possible on a construct-by-construct basis: the absence of claims/records (if any) are assumed to indicate the absence of a condition, or indicate a normal value. Such choices may reduce the granularity of a variable; eg, presence of obesity is measured (dichotomous variable) instead of BMI. PHARMO does not employ such imputation, and data extracts for PHARMO are expected to still have missing values for some variables. For this PASS, degree of missingness of data will be described, and not further imputed.

Some detailed clinical information is unlikely to be available across all data sources, such as score-based UC disease severity, symptom reports or codes, or patient reported outcomes. For Sweden, information on different comorbidities and clinical diagnosis is retrieved from the NPRs covering only patients treated in specialist care, since this data source does not cover diagnosis from primary care. For the Netherlands, symptom-based coding is available in GP data, and for non-registry data sources capture of UC disease severity scores from electronic health records from routine clinical care is unlikely.

In-hospital administration of medications is not recorded in PDR. For the comparator medications, biologics use may not be fully captured in PDR if it is given in clinics intravenously and the patient has not filled an outpatient pharmacy prescription. Therefore, SWIBREG will also be used in Sweden to capture exposure information to treatments.

In GePaRD, administration of biologics in hospitals is not captured except for infliximab, adalimumab, golimumab, vedolizumab, ustekinumab and risankizumab, which are listed as special and/or expensive medication and reimbursed as a procedures.

For the Netherlands specifically, this PASS will be conducted primarily using hospital and outpatient pharmacy data, which are sufficient to ascertain key variables on UC diagnosis, inclusion and exclusion criteria, exposure, outcomes, and covariates. Additional linkage of GP data will not be conducted except for the sensitivity analysis on symptomatic bradycardia (including conduction disorders; Section 9.7.5), since this is expected to substantially reduce sample sizes. This will hamper the ability to ascertain comorbidities that are primarily managed by the GP (eg, hypertension or lifestyle factors (eg, smoking status).

Assessment of serious liver injury will not consider outpatient care settings because the laboratory test results needed to define severity of liver injury are not available across data sources. Serious liver injury cases solely receiving outpatient care are expected to be very few and therefore the impact of not including outpatient data sources to define this safety event of interest is expected to be low. This is supported by European guidelines, which

recommend diagnostic work-up for (drug-induced) liver injury or liver failure to be conducted during admission.(50, 51)

Selection bias by study of only healthy users is addressed by design as this PASS primarily investigates initiators of etrasimod and comparator medications of interest.

For interpretation of the sensitivity analysis implementing an intention to treat approach for the PRES outcome, current literature suggests there may not be a (long) lag time between discontinuation of a potentially causative drug and PRES events. Generally, where cases of PRES have been observed with drugs, most cases seem to occur within weeks to months of initiation of the potentially causative drug (53,55,56). A pharmacodynamic analysis of etrasimod showed that lymphocyte levels to return to normal 7 days after discontinuation (57), which supports that a lagged impact of etrasimod specifically on safety events such as PRES, if any, may be relatively short-lived. Second, it is expected that there will be more convulsion events than PRES events in the combined outcome of PRES and convulsions; this will obscure the expected differences between results from main and sensitivity analysis. Third, combining different risk windows into one event may present analytical challenges.

Generalizability

Data sources are expected to be representative for their respective countries, supporting generalizability. For Germany, GePaRD includes data from over 25 million members of the German statutory health insurance. Analyses on age and sex distribution, the number of hospital admissions, and medication use have shown that the database is representative of the German population and that the insurance population is stable over time. (17, 18) For Sweden, the SNHR includes comprehensive data at national level including over 10 million inhabitants, ensuring generalizability to the country level (19). For individuals included in SWIBREG, the coverage among moderate to severe UC is approximately 90-95%.(24) For the Netherlands, the PHARMO Data Network hospital data and out-patient pharmacy data are both derived from national-level sources deemed representative for the population. The PHARMO GP data is nationally representative regarding demographic characteristics and primary care diagnoses.(52) Linked subsets of persons with data available from all data sources within PHARMO are assumed largely non-differential.

9.10. Other Aspects

Comparative analyses will be undertaken only if sample size permits, as informed by results from the Interim Report (Sections 6, 9.5 and 9.7.2).

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. If automated/algorithmic methods, such as natural language processing, will be used to convert unstructured data to structured data during the implementation of the protocol, no patient personal data will be accessed.

All study reports will contain aggregate data only and will not identify individual patients or physicians.

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)

Each research partner will perform all required ethics/regulatory reviews from the relevant IRBs/ECs according to local regulations.

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents (eg, informed consent forms if applicable) from the relevant IRBs/ECs. All correspondence with the IRB/EC must be retained. Copies of IRB/EC approvals must be forwarded to Pfizer.

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 the Guidelines for Good Pharmacoepidemiology Practices (GPP), the EMA ENCePP Guide on Methodological Standards in Pharmacoepidemiology, and the EMA Guidelines on Good Pharmacovigilance Practices Module VIII: Post-Authorisation Safety Studies.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study involves a combination of existing structured data and unstructured data, which will be converted to structured form during the implementation of the protocol solely by a computer using automated/algorithmic methods, such as natural language processing. In these data sources, individual patient data are not retrieved or validated, and it is not possible to link (ie, identify a potential association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (AE) (ie, identifiable patient, identifiable reporter, a suspect product, and event) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The interim report will include descriptive analyses, and report on sample size for conducting comparative analyses as detailed in the SAP. No meta-analyses are planned for the interim report, but will be conducted and presented in the final report. Patient-level data will be redacted in all study reports between the sponsor and data holders according to data privacy regulations at each site.

Results of this PASS will be registered in the HMA-EMA Catalogue of RWD studies, and may be disseminated at scientific meetings and publications.

Publications will comply with standards of the marketing authorization holder(s) and the International Committee of Medical Journal Editors (ICMJE) guidelines.

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.

13. REFERENCES

1. Ford AC, Moayyedi P, Hanauer SB. Ulcerative colitis. BMJ. 2013;346:f432.
2. Ng SC, Shi HY, Hamidi N, Underwood FE, Tang W, Benchimol EI, et al. Worldwide incidence and prevalence of inflammatory bowel disease in the 21st century: a systematic review of population-based studies. Lancet. 2017;390(10114):2769-78.
3. Feuerstein JD, Moss AC, Farraye FA. Ulcerative Colitis. Mayo Clin Proc. 2019;94(7):1357-73.
4. Sandborn WJ, Peyrin-Biroulet L, Zhang J, Chiorean M, Vermeire S, Lee SD, et al. Efficacy and Safety of Etrasimod in a Phase 2 Randomized Trial of Patients With Ulcerative Colitis. Gastroenterology. 2020;158(3):550-61.
5. Sandborn WJ, Vermeire S, Peyrin-Biroulet L, Dubinsky MC, Panes J, Yarur A, et al. Etrasimod as induction and maintenance therapy for ulcerative colitis (ELEVATE): two randomised, double-blind, placebo-controlled, phase 3 studies. Lancet. 2023;401(10383):1159-71.
6. Vermeire S, Chiorean M, Panes J, Peyrin-Biroulet L, Zhang J, Sands BE, 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(6):950-9.
7. Lee WM. Drug-induced hepatotoxicity. N Engl J Med. 2003;349(5):474-85.
8. Lachenmayr SJ, Berking S, Horns H, Strobach D, Ostermann H, Berger K. Antifungal treatment in haematological and oncological patients: Need for quality assessment in routine care. Mycoses. 2018;61(7):464-71.
9. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep. 2015;2(4):221-8.
10. Reilev M, Jensen PB, Ranch LS, Egeberg A, Furu K, Gembert K, et al. Methodology of the brodalumab assessment of hazards: a multicentre observational safety (BRAHMS) study. BMJ Open. 2023;13(2):e066057.
11. Yang YL, Xiang ZJ, Yang JH, Wang WJ, Xu ZC, Xiang RL. Adverse Effects Associated With Currently Commonly Used Antifungal Agents: A Network Meta-Analysis and Systematic Review. Front Pharmacol. 2021;12:697330.
12. Brunelli SM, Gagne JJ, Huybrechts KF, Wang SV, Patrick AR, Rothman KJ, et al. Estimation using all available covariate information versus a fixed look-back window for dichotomous covariates. Pharmacoepidemiol Drug Saf. 2013;22(5):542-50.
13. Conover MM, Sturmer T, Poole C, Glynn RJ, Simpson RJ, Jr., Pate V, et al. Classifying medical histories in US Medicare beneficiaries using fixed vs all-available look-back approaches. Pharmacoepidemiol Drug Saf. 2018;27(7):771-80.
14. Nakasian SS, Rassen JA, Franklin JM. Effects of expanding the look-back period to all available data in the assessment of covariates. Pharmacoepidemiol Drug Saf. 2017;26(8):890-9.
15. Pottegard A, Friis S, Sturmer T, Hallas J, Bahmanyar S. Considerations for Pharmacoepidemiological Studies of Drug-Cancer Associations. Basic Clin Pharmacol Toxicol. 2018;122(5):451-9.
16. Haug U, Schink T. German Pharmacoepidemiological Research Database (GePaRD). In: Sturkenboom M, Schink T, editors. Databases for Pharmacoepidemiological Research

Springer Series on Epidemiology and Public Health: Springer International Publishing; 2021. p. p. 119–24.
17. Schink T, Garbe E. Representativity of dispensations of non-steroidal anti-inflammatory drugs (NSAIDs) in the German Pharmacoepidemiological Research Database. Gesundheitswesen. 2010;Sep;72(08/09):V111.
18. Schink T, Garbe E. Assessment of the representativity of in-patient hospital diagnoses in the German Pharmacoepidemiological Research Database. Gesundheitswesen. 2010;Sep;72(8/9):P10.
19. Furu K, Wettermark B, Andersen M, Martikainen JE, Almarsdottir AB, Sorensen HT. The Nordic countries as a cohort for pharmacoepidemiological research. Basic Clin Pharmacol Toxicol. 2010;106(2):86-94.
20. Wettermark B, Hammar N, Fored CM, Leimanis A, Otterblad Olausson P, Bergman U, et al. The new Swedish Prescribed Drug Register--opportunities for pharmacoepidemiological research and experience from the first six months. Pharmacoepidemiol Drug Saf. 2007;16(7):726-35.
21. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: Possibilities and pitfalls when combining Nordic registry data. Scand J Public Health. 2017;45(17_suppl):14-9.
22. Brooke HL, Talback M, Hornblad J, Johansson LA, Ludvigsson JF, Druid H, et al. The Swedish cause of death register. Eur J Epidemiol. 2017;32(9):765-73.
23. wieLudvigsson JF, Andersson E, Ekbom A, Feychting M, Kim JL, Reuterwall C, et al. External review and validation of the Swedish national inpatient register. BMC Public Health. 2011;11:450.
24. SWIBREG. Annual 2023 Report of the Swedish Inflammatory Bowel Disease Registry (Årsrapport för verksamhetsåret 2023). 2023.
25. Ludvigsson JF, Andersson M, Bengtsson J, Eberhardson M, Fagerberg UL, Grip O, et al. Swedish Inflammatory Bowel Disease Register (SWIBREG) - a nationwide quality register. Scand J Gastroenterol. 2019;54(9):1089-101.
26. Kuiper JG, Bakker M, Penning-van Beest FJA, Herings RMC. Existing Data Sources for Clinical Epidemiology: The PHARMO Database Network. Clinical Epidemiology. 2020;12:415-22.
27. WHO Anatomical Therapeutic Chemical Classification System. http://www.whocc.no/atc_ddd_index [
28. International Classification of Primary Care https://www.nhg.org/themas/artikelen/icpc [
29. Dutch Hospital Data Foundation https://www.dhd.nl [
30. WHO International Classification of Diseases. http://www.who.int/classifications/icd/en/ [
31. Dutch Hospital Data Foundation registration system for procedures https://www.dhd.nl/producten-diensten/verrichtingenbestand/Paginas/Verrichtingenbestand.aspx [
32. Dutch Healthcare Authority declaration codes https://www.opendisdata.nl/downloads
33. Dutch Classification of Procedures https://class.whofic.nl/browser.aspx [
34. Dutch Z-index Code. https://www.farmatec.nl/prijsvorming/add-on-geneesmiddelen-sluismiddelen/actuele-publicaties.

35. Schnorbach M, Kruis W. Cost of illness of inflammatory bowel disease in Germany. Z Gastroenterol. 2021;Nov;59(11):1173-1188.
36. Everhov AH, Sachs MC, Malmborg P, Nordenvall C, Myrelid P, Khalili H, et al. Changes in inflammatory bowel disease subtype during follow-up and over time in 44,302 patients. Scand J Gastroenterol. 2019;54(1):55-63.
37. Jakobsson GL, Sternegard E, Olen O, Myrelid P, Ljung R, Strid H, et al. Validating inflammatory bowel disease (IBD) in the Swedish National Patient Register and the Swedish Quality Register for IBD (SWIBREG). Scand J Gastroenterol. 2017;52(2):216-21.
38. Mouratidou N, Malmborg P, Jaras J, Sigurdsson V, Sandstrom O, Fagerberg UL, et al. Identification of Childhood-Onset Inflammatory Bowel Disease in Swedish Healthcare Registers: A Validation Study. Clin Epidemiol. 2022;14:591-600.
39. Straatmeier, Duivestein. Inflammatory Bowel Disease. Ned Tijdschr Geneeskd. 2023;167;D7680.
40. Hall GC, Lanes S, Bollaerts K, Zhou X, Ferreira G, Gini R. Outcome misclassification: Impact, usual practice in pharmacoepidemiology database studies and an online aid to correct biased estimates of risk ratio or cumulative incidence. Pharmacoepidemiol Drug Saf. 2020;29(11):1450-5.
41. van Linschoten RCA, Huberts AS, van Leeuwen N, Hazelzet JA, van der Woude J, West RL, et al. Validity of the self-administered comorbidity questionnaire in patients with inflammatory bowel disease. Therap Adv Gastroenterol. 2023;16:17562848231202159.
42. ICD-10 Classification: Socialstyrelsen; [Available from: https://www.socialstyrelsen.se/en/.
43. Hernan MA, Robins JM. Using Big Data to Emulate a Target Trial When a Randomized Trial Is Not Available. Am J Epidemiol. 2016;183(8):758-64.
44. The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP). Guide on Methodological Standards in Pharmacoepidemiology (Revision 11). EMA/95098/2010.
45. SmPC Etrasimod
46. EPAR Velsipity.
47. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, Ekbom A. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. Eur J Epidemiol. 2009;24(11):659-67.
48. Roussel Uclaf Causality Assessment Method (RUCAM) in Drug Induced Liver Injury. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury. Bethesda (MD)2012.
49. Liu R, Wan Q, Zhao R, Xiao H, Cen Y, Xu X. Risk of non-melanoma skin cancer with biological therapy in common inflammatory diseases: a systemic review and meta-analysis. Cancer Cell Int. 2021;21(1):614.
50. Gastroenterologists DFoMSatDSo. Guideline acute liver failure 2020 [Available from: https://richtlijnendatabase.nl/richtlijn/acuut_leverfalen/startpagina_-_acuut_leverfalen.html.
51. Liver EAftSot. EASL Clinical Practical Guidelines on the management of acute (fulminant) liver failure. Journal of Hepatology. 2017;66:1047-81.
52. Overbeek JA, Swart KMA, Houben E, Penning-van Beest FJA, Herings RMC. Completeness and Representativeness of the PHARMO General Practitioner (GP) Data: A Comparison with National Statistics. Clin Epidemiol. 2023;15:1-11.

53. Abdoh Q, Rabi R, Musmar B, et al. Posterior reversible encephalopathy syndrome after infliximab infusion for fistulizing Crohn's Disease. ACG Case Reports Journal 2024;11 6:e01400.
54. Alshaikh RA, Ryan KB, Waeber C. Sphingosine 1-phosphate, a potential target in neovascular retinal disease. Br J Ophthalmol. 2022;106(9):1187-95.
55. Fugate JE, Rabinstein AA. Posterior reversible encephalopathy syndrome: clinical and radiological manifestations, pathophysiology, and outstanding questions. Lancet Neurol. 2015;14(9):914-25.
56. Glusker P, Recht L, Lane B, et al. Reversible Posterior Leukoencephalopathy Syndrome and Bevacizumab New England Journal of Medicine 2006;354 9:980-2.
57. Lee CA, Schreiber S, Bressler B, et al. Safety, pharmacokinetics, and pharmacodynamics of etrasimod: Single and multiple ascending dose studies in healthy adults. Clin Pharmacol Drug Dev. 2024;13(5):534-48.

14. LIST OF TABLES

15. LIST OF FIGURES

ANNEX 1. LIST OF STANDALONE DOCUMENTS

None

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ENCePP Checklist for Study Protocols (Revision 4)

Adopted by the ENCePP Steering Group on 15/10/2018

The European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiologic or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology, which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is "Yes", the section number of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example, in the case of an innovative study design). In this case, the answer 'N/A' (Not Applicable) can be checked and the "Comments" field included for each section should be used to explain why. The "Comments" field can also be used to elaborate on a "No" answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). The Checklist is a supporting document and does not replace the format of the protocol for PASS presented in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title: An Active Surveillance, Post-Authorization Safety Study to Characterize the Safety of Etrasimod in Patients with Ulcerative Colitis Using Real-World Data in the European Union

HMA-EMA Catalogue RWD studies register® number: Study not yet registered **Study reference number (if applicable):** C5041046 (Pfizer study ref. no.)

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	6
1.1.2 End of data collection[2]	☒	☐	☐	6

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.3 Progress report(s)	☒	☐	☐	6
1.1.4 Interim report(s)	☒	☐	☐	6
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	6
1.1.6 Final report of study results.	☒	☐	☐	6

Comments:

Section 2: Research question		**Yes**	**No**	**N/A**	**Section Number**
2.1	Does the formulation of the research question and objectives clearly explain:	☐	☐	☐	7, 8
	2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7, 8
	2.1.2 The objective(s) of the study?	☒	☐	☐	7, 8
	2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	☒	☐	☐	7, 8
	2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☒	☐	
	2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☒	☐	

Comments:

Section 3: Study design		**Yes**	**No**	**N/A**	**Section Number**
3.1	Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1
3.3	Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7
3.4	Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.2
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.2	Is the planned study population defined in terms of:	☒			
	4.2.1 Study time period	☒	☐	☐	9.1.1
	4.2.2 Age and sex	☒	☐	☐	9.2
	4.2.3 Country of origin	☒	☐	☐	9.4
	4.2.4 Disease/indication	☒	☐	☐	9.2
	4.2.5 Duration of follow-up	☒	☐	☐	9.1.1
4.3	Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	9.2.3/9.2.4

Comments:

Section 5: Exposure definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
5.1	Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.1
5.2	Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	9.3.1/9.4.4
5.3	Is exposure categorized according to time windows?	☒	☐	☐	9.1.1/9.3.1
5.4	Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	9.3.1
5.5	Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	9.3.1
5.6	Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	7, 8, 9

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7,8, 9.3.2
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.2
6.3	Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☐	☒	☐	9.3.2/9.4.4
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilization, burden of disease or treatment, compliance, disease management)	☐	☒	☐	

Comments:

Section 7: Bias		**Yes**	**No**	**N/A**	**Section Number**
7.1	Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☐	☒	☐	9.7.2/9.9
7.2	Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☐	☒	☐	9.1 / 9.7.2 /9.9
7.3	Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.1 / 9.3 / 9.7.2

Comments:

Section 8: Effect measure modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.3

Comments:

Section 9: Data sources		**Yes**	**No**	**N/A**	**Section Number**
9.1	Does the protocol describe the data source(s) used in the study for the ascertainment of:				
	9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.4
	9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.4
	9.1.3 Covariates and other characteristics?	☒	☐	☐	9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
	9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.4
	9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2 / 9.4 / 9.4.4
	9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4
9.3	Is a coding system described for:				
	9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.4
	9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.4
	9.3.3 Covariates and other characteristics?	☒	☐	☐	9.4

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.6 / 9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9, Annex 3
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.1
10.4 Are stratified analyses included?	☐	☒	☐	
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	9.7.2
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.7.5
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.7
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.5

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.8
11.3 Is there a system in place for independent review of study results?	☐	☒	☐	

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.9
12.1.2 Information bias?	☒	☐	☐	9.9
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5, Annex 3

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	10

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	5

Comments:

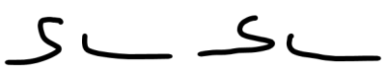
Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

None

Name of the main author of the protocol: Shahar Shmuel

Date: 7-JUL-2025

Signature: 

ANNEX 3. ADDITIONAL INFORMATION

Annex Table 1. Estimated IRs for safety events of interest used for study size calculations

Safety event of interest	Incidence rate (per 100,000 person years)	Assumptions/remarks	Source
Macular oedema	420	Based on a 1.2% (n=2) cumulative incidence of development of macular oedema in phase II trial of ozanimod for UC (Touchstone trial). Safety analysis included n=170 patients observed for an average of 2.8 years, totaling 476 person-years. The corresponding incidence rate is 2/476=420 per 100,000 person years.	Becher, Swaminath, Sultan, 2022, Ther Clin Risk Manag (doi: *10.2147/TCRM.S336139*)
Malignancy	650	Observed malignancy incidence rate in patients from a prospective registry on UC and Crohn's disease using TNFi therapy	Lichtenstein et al., 2014, Am J Gastroenterol. (doi*:* *10.1038/ajg.2013.441*)
Serious opportunistic infections	2,380	Derived from estimate among a registry of Swedish UC patients. Estimates were derived from 47,798 IBD patients followed for an average of 329,000 person-years in 47,798 patients, or 6.88 years. Follow-up was assumed similar for the subgroup of UC patients (n=27,045). For reference, the Swedish registry obtained IR was congruent with estimates derived from clinical trials investigating effect of adalimumab in UC (IR of 3,500 per 100,000 person-years reported by Colombel et al.)	Halfvarson et al., 2021, Scand J Gastroenterol. (doi: 10.1080/00365521.2021.1924259) Colombel et al., 2018, Aliment Pharmacol Ther. (doi*:* *10.1111/apt.14420*)
Neurologic events of	64	Determined by summing population-based IRs for PRES (2.7) and epilepsy (61.44) per 100,000 person-years: ~64.	PRES: Otite et al., 2023, Neurology (doi: *WNL.0000000000207604*);

Safety event of interest	Incidence rate (per 100,000 person years)	Assumptions/remarks	Source
PRES or convulsions		For PRES: 2.7; derived from US population-based study in adults. It is acknowledged that this population-based estimate is possibly conservative for estimating PRES incidence in patients with UC treated with immunosuppressive therapies. Note that estimates for PRES from clinical studies on S1P receptor modulators are available (ozanimod used in multiple sclerosis, ozanimod Risk Management Plan, version 3.0, 18 Oct 2021; EMEA/H/C/004835), reporting an IR of 37.2 per 100,000 (95% confidence interval 0.9-207.5). Yet, this estimate is not used as it is based on a single case of PRES. For epilepsy: 61.44; derived from a systematic review & meta-analysis conservatively assuming epilepsy diagnoses (including isolated convulsions/epileptic attacks in patients diagnosed with epilepsy) are a proxy for convulsions (including epileptic attacks qualifying for epilepsy diagnosis, and isolated epileptic attacks not qualifying for a diagnosis of epilepsy [disregarding misclassification and differential diagnostic considerations])	Epilepsy: Fiest et al., 2017, Neurology (doi: *10.1212/WNL.0000000000003509*)

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