IM047-1037

Bristol Myers Squibb™

PASS INFORMATION

Title	Long-term real-world safety of ozanimod – A post-authorisation safety study (PASS) in patients diagnosed with ulcerative colitis
Protocol Version Identifier	Version 4.0
Date of Last Version of Protocol	29-Aug-2023
EU PAS Register Number	Study not yet registered
Active Substance	Ozanimod (ATC code: L04AA38)
Medicinal Product	Zeposia®
Product Reference	EU/1/20/1442/001-003
Procedure Number	EMEA/H/C/004835
Marketing Authorisation Holder(s)	Bristol-Myers Squibb Pharma EEIG
Joint PASS	No
Research Question and Objectives	**Research Question:** What is the risk of developing adverse events of interest (malignancy, serious opportunistic infections [SOIs], major adverse cardiovascular events [MACE], venous thromboembolism [VTE], severe liver injury, macular oedema, posterior reversible encephalopathy syndrome [PRES] or progressive multifocal leukoencephalopathy [PML]) in a real-world European population of adults with moderately to severely active UC treated with ozanimod versus advanced therapies, including tumour necrosis factor-alpha inhibitors, anti-integrins, Janus kinase inhibitors, or interleukin antagonists? **Primary Objective:** • To evaluate the risk of the following outcomes in ozanimod-exposed patients versus those treated with advanced therapy: – Malignancies – Serious opportunistic infections (SOIs), – Major adverse cardiovascular events (MACE) – Venous thromboembolism, including pulmonary embolism (VTE) – Severe liver injury.

	Secondary Objectives: • To evaluate the risk of the outcomes of interest by subgroups (age, disease history, previous outcome history) in ozanimod-exposed patients versus those treated with advanced therapy. • To describe, in ozanimod-exposed patients and those treated with advanced therapy, the frequency, baseline and clinical characteristics of patients experiencing: – Macular oedema – Posterior reversible encephalopathy syndrome (PRES) – Progressive multifocal leukoencephalopathy (PML). • To evaluate the risk of macular oedema, PRES and PML (if sufficient sample size, according to descriptive analysis) in ozanimod-exposed patients versus those treated with advanced therapy. • To evaluate the risk of cancer, by subtype, in ozanimod-exposed patients versus those treated with advanced therapy: – Solid tumours excluding non-melanoma skin cancer (NMSC) – NMSC – Colorectal cancer – Advanced colonic neoplasia, ie, composite endpoint including colorectal cancer and high-grade dysplasia, and – Lymphoma. • To evaluate the risk of MACEs, by component, in ozanimod-exposed patients versus those treated with advanced therapy: – Acute nonfatal myocardial infarction – Acute nonfatal stroke – Cardiovascular (CV) mortality.
Countries of Study	Denmark, France, Germany, Netherlands, Norway, and the United Kingdom
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MARKETING AUTHORISATION HOLDER

Marketing Authorisation Holder	Bristol-Myers Squibb Pharma EEIG Plaza 254 Blanchardstown Corporate Park 2 Dublin 15, D15 T867 Ireland
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This protocol has been reviewed and approved by the marketing authorization holder's Qualified Person for Pharmacovigilance. The electronic signature is available on file.

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Replace all previous version(s) of the protocol with this revised protocol and please provide a copy of this revised protocol to all study personnel under your supervision and archive the previous versions.

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2 LIST OF ABBREVIATIONS

Abbreviation	Definition
ACE	Angiotensin-Converting Enzyme
AMI	Acute Myocardial Infarction
ATC	Anatomical Therapeutic Chemical (Classification System)
ATE	Average Treatment Effect
BIPS	Leibniz Institute for Prevention Research and Epidemiology – BIPS
BMS	Bristol-Myers Squibb
BPE	Bordeaux Pharmacoepi, Université de Bordeaux (France)
CESREES	Comité Éthique et Scientifique pour les Recherches, les Études et les Évaluations dans le domaine de la Santé (France)
CHD	Coronary Heart Disease
CI	Confidence Interval
CIF	Cumulative Incidence Function
CNAM	Caisse Nationale de l'Assurance Maladie (France)
CNIL	French Data Protection Commission [Commission Nationale de l'Informatique et des Libertés]
CPR	Central Pharmaceutical Reference
CPRD	Clinical Practice Research Datalink (UK)
CRO	Contract Research Organization
CV	Cardiovascular
DAP	Data Access Partner
DDD	Defined Daily Dose
DMT	Disease Modifying Treatment
DNBHD	Danish National Board of Health Data
DVT	Deep Vein Thrombosis
EBM	German Uniform Evaluation Standard
ED	Emergency Department
eDRIS	electronic Data Research and Innovation Service
EMA	European Medicines Agency
EMIS	Egton Medical Information Systems
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorization Studies
GDPR	General Data Protection Regulation

Abbreviation	Definition
GEP	Good Epidemiological Practice
GePaRD	German Pharmacoepidemiologic Research Database
GP	General Practitioner
GPP	Good Pharmacoepidemiology Practices
GPS	Good Practice of Secondary Data Analysis
GVP	Guideline on Good Pharmacovigilance practices
HAS	Haute Autorité de Santé
HES	Hospital Episode Statistics
HGD	High-Grade Dysplasia
HIV	Human Immunodeficiency Virus
HR	Hazard Ratio
HRR	Hazard Ratio's Ratio
IBD	Inflammatory Bowel Disease
ICD-10	International Classification of Disease-10th revision
ICD-10-GM	International Classification of Disease-10th revision-German Modification
ICMJE	International Committee of Medical Journal Editors
IM	Immunomodulator
IPTW	Inverse Probability of Treatment Weighting
IR	Incidence Rate
IS	Immunosuppressant
ISPE	International Society for Pharmacoepidemiology
IV	Intravenous
JAKi	Janus Kinase Inhibitor
LTD	Long-term Disease
MACE	Major Adverse Cardiovascular Events
MAH	Marketing Authorization Holder
MHRA	Medicines and Healthcare products Regulatory Agency (UK)
MI	Myocardial Infarction
MS	Multiple sclerosis
NC	North Carolina
NHS	National Health Service
NIPH	Norwegian Institute of Public Health
NMSC	Non-Melanoma Skin Cancer

Abbreviation	Definition
NRS	National Records Scotland
NSAID	Non-Steroidal Anti-Inflammatory Drug
NSS	National Services Scotland
OPS	Operationen-und Prozedurenschlüssel codes
PASS	Post-Authorization Safety Study
PE	Pulmonary Embolism
PICOS	Population, Intervention, Comparators, Outcomes, and Study design
PML	Progressive Multifocal Leukoencephalopathy
PRES	Posterior Reversible Encephalopathy Syndrome
PS	Propensity Score
PY	Person-Year
PZN	Central pharmaceutical number
QC	Quality-Control
RRMS	Relapsing-Remitting Multiple Sclerosis
RTI-HS	RTI Health Solutions, a Division of RTI International, a not-for-profit Research Organization
S1P	Selective Sphingosine 1-Phosphate
SAP	Statistical Analysis Plan
SDU	University of Southern Denmark
SHI	Statutory Health Insurance
SmPC	Summary of Product Characteristics
SNDS	French Claims Healthcare Database [Système National de Données de Santé]
SNOMED CT	Systemized Nomenclature of Medicine–Clinical Terms
SOI	Serious Opportunistic Infections
SOP	Standardized Operational Procedure
TNFi	Tumour Necrosis Factor-alpha inhibitor
TTP	Trusted Third Party
UDD	Usual Daily Dose
UC	Ulcerative Colitis
UK	United Kingdom
US	United States
VTE	Venous Thromboembolism

3 RESPONSIBLE PARTIES

Please see APPENDIX 1 for list of responsible parties.

4 ABSTRACT

4.1 Title

Long-term real-world safety of ozanimod – A post-authorisation safety study (PASS) in patients diagnosed with ulcerative colitis (IM0471037, Version 4.0, 22-Dec-2023).

4.2 Rationale and Background

Ozanimod (Zeposia®), an oral selective sphingosine 1-phosphate (S1P) receptor modulator was approved in the European Union on 18-Nov-2021 for the treatment of adult patients with moderately to severely active ulcerative colitis (UC) who have had an inadequate response, lost response, or were intolerant to either conventional therapy (ie, aminosalicylates, corticosteroids for systemic use, corticosteroids acting locally, conventional immunomodulators) or a biologic agent. Bristol-Myers Squibb (BMS), the ozanimod marketing authorization holder, collaborated with the SIGMA consortium to draft the core protocol of a post-authorisation safety study agreed upon with the European Medicines Agency, which will be implemented in multiple data sources in Europe.

4.3 Research Question and Objectives

Research question: What is the risk of developing adverse events of interest (malignancy, serious opportunistic infections, major adverse cardiovascular events, venous thromboembolism, severe liver injury, macular oedema, posterior reversible encephalopathy syndrome or progressive multifocal leukoencephalopathy [PML]) in a real-world European population of adults with moderately to severely active UC treated with ozanimod versus advanced therapies—including tumour necrosis factor-alpha inhibitors (TNFi), anti-integrins, Janus kinase inhibitors (JAKis), or interleukin antagonists?

Objectives

Primary objective:

- To evaluate the risk of the following outcomes in ozanimod-exposed patients versus those treated with advanced therapy:
  - Malignancies
  - Serious opportunistic infections (SOIs),
  - Major adverse cardiovascular events (MACE)
  - Venous thromboembolism, including pulmonary embolism (VTE)
  - Severe liver injury.

Secondary objectives:

- To evaluate the risk of the outcomes of interest by subgroups (age, disease history, previous outcome history) in ozanimod-exposed patients versus those treated with advanced therapy.
- To describe, in ozanimod-exposed patients and those treated with advanced therapy, the frequency, baseline and clinical characteristics of patients experiencing:
  - Macular oedema

  - Posterior reversible encephalopathy syndrome (PRES)
  - Progressive multifocal leukoencephalopathy (PML).
- To evaluate the risk of macular oedema, PRES and PML (if sufficient sample size, according to descriptive analysis) in ozanimod-exposed patients versus those treated with advanced therapy.
- To evaluate the risk of cancer, by subtype, in ozanimod-exposed patients versus those treated with advanced therapy:
  - Solid tumours excluding non-melanoma skin cancer (NMSC)
  - NMSC
  - Colorectal cancer
  - Advanced colonic neoplasia, ie, composite endpoint including colorectal cancer and high-grade dysplasia, and
  - Lymphoma.
- To evaluate the risk of MACEs, by component, in ozanimod-exposed patients versus those treated with advanced therapy:
  - Acute nonfatal myocardial infarction
  - Acute nonfatal stroke
  - Cardiovascular (CV) mortality.

4.4 Study Design

This will be a non-interventional cohort study of patients with UC initiating therapy with ozanimod or advanced therapies, between 01-Jan-2023, and 31-Dec-2031. The study period will end on 31-Dec-2032.

Propensity score (PS)-based inverse probability of treatment weighting (IPTW) will be used to account for potential confounding when comparing outcomes between the ozanimod and advanced therapy cohorts. All patients qualifying under inclusion and exclusion criteria will receive a propensity score.

For each outcome, hazard ratios (HRs) and corresponding 95% confidence intervals (CI) will be calculated before and after IPTW, to compare the risk of each outcome between the 2 cohorts. Secondary analyses will include assessment of risk by age (≥ 55 versus < 55 years), by previous outcome occurrence before start of exposure (previous history versus non-previous history) and risk of individual outcomes (malignancy subtypes and components of MACE).

Investigators will conduct separate analyses for each participating data source using their respective data. These locally generated results will be pooled using meta-analytical methods and final results will be generated.

4.5 Population

The study will include European patients aged 18 years or older who have a diagnosis of UC and are new users of ozanimod (ozanimod-exposed cohort) or a UC advanced therapy (advanced therapy-exposed cohort) during the indexing period. The index date (cohort entry date) is the date

of the first prescription/dispensing of a qualifying drug. Patients may initiate more than 1 therapeutic regimen during the study period but can contribute only 1 treatment episode to each of the 2 cohorts.

Treatment episodes that meet any of the following criteria will be excluded:

- Patient has less than 365 days of historical data in the data source prior to the treatment index date
- Patient has a history of total colectomy or proctocolectomy prior to the treatment index date
- Patient has a history of multiple sclerosis (MS) within 1 year prior to index date
- Patient is exposed to the same drug ingredient or to an S1P treatment prior to the treatment index date
- Patient initiates 2 different cohort-defining treatments on the treatment index date

4.6 Variables

Outcomes of interest will be ascertained from outpatient and inpatient records available from each data source. Definitions will be based on International Classification of Disease-10th revision (ICD-10) codes and translated to other codification systems as required. Where relevant, validated algorithms and code sets will be preferred. Not all outcomes may be available in all data sources. Details will be provided in the statistical analysis plan (SAP).

UC treatment will be defined by the active ingredient. Duration of treatment exposure will be derived in order of preference from administration, prescription or dispensing data. When using dispensing data, drug strength, box size, and product label will be used to define a usual daily dose, from which exposure length will be derived.

For non-oral therapies, time at risk will be defined based on the length of cycles as specified on the product label (eg, every 8 weeks for vedolizumab after the third infusion).

Exposure is defined as time at risk for a specific outcome.

- For non-cancer outcomes, risk is assumed to start on the index date and continue until 30 days after the presumed end of drug supply (grace period);
- For malignancy outcomes, a lag-time period of 6 months will be applied from the index date and an at-risk period will be added at the presumed end of drug exposure: 1 year for hematologic malignancies and 2 years for solid tumours. In other words, cancers detected in the first 6 months after the start of exposure will not be attributed to the drug and outcomes for 1 or 2 years after the end of drug exposure will be attributed to the drug.

Patient demographic and clinical characteristics, including prior UC management and conventional treatments received, will be collected from available data during the baseline (historical) period up to and including the index date.

Concomitant use of conventional treatment, as well as colectomy, high-grade dysplasia and other covariates of interest reported in the data source during the follow-up period will also be described.

4.7 Data Sources

The following data sources were selected for this PASS and will be included when ozanimod is made available in their corresponding national market:

- The German Pharmacoepidemiological Research Database (GePaRD), Germany: access provided by the Leibniz Institute for Prevention Research and Epidemiology- BIPS (BIPS)
- The Danish Registries, Denmark: access provided by the University of Southern Denmark (SDU)
- The PHARMO Data Network, Netherlands: access provided by the PHARMO Institute
- The Norwegian Registries, Norway: access provided by the Norwegian Institute of Public Health (NIPH)
- The Clinical Practice Research Datalink (CPRD), United Kingdom: access provided by RTI-Health Solutions
- The Scottish Prescribing Information System, UK-Scotland: access provided by the University of Dundee
- *The Système National des Données de Santé* (SNDS), France: access provided by the Bordeaux PharmacoEpi platform (BPE) from Bordeaux University

4.8 Study Size

BMS expects the market share of ozanimod to increase by 1% to 4% per year over the next few years. The prevalence of UC is estimated at 0.2% to 0.6% in the participating countries. Background rates for severe liver injuries, malignancies, serious infections, VTEs, and MACE have been respectively estimated to be 0.94, 6.4, 34.7, 13.6, and 24 per 1,000 patient-years in populations of patients using TNFi for UC or Crohn's disease.

As an example, by 2032, $\geq$ 682 ozanimod-exposed and $\geq$ 12,850 advanced therapy-exposed patients would be needed to detect a crude HR $\geq$ 1.6 with an 80% statistical power for an outcome with a background incidence rate $\geq$ 13.6 per 1,000 person-years (ie, VTE). This estimate assumes the ozanimod group represents 5% of patients, with an expected average follow-up of 4 years.

4.9 Study Analysis

Data management will be conducted by each data source independently. Analyses will be executed independently by each data source provider. The unit of observation will be the treatment episode.

Clinical and demographic variables will be reported by treatment cohorts before and after the application of IPTW. An overall attrition table for the study will be generated for each cohort. Crude incidence rates (IRs) and 95% CIs will be calculated for each outcome by treatment cohort, before and after IPTW.

A single propensity score model will be created for all outcomes. Propensity scores (PS) will be estimated using a logistic regression model, including potential confounders as independent variables. The pairwise distributions of PS for patients initiating ozanimod versus advanced therapy will be examined side by side to evaluate the degree of overlap. Potential methods to address lack of overlap will be addressed in the SAP.

Inverse probability of treatment weighting will be estimated based on information known as of the index date for each treatment episode. Stabilized weights will be calculated for each individual as *the proportion of ozanimod-exposed episodes/PS* for the ozanimod-exposed group and *the proportion of ozanimod-unexposed episodes/ (1 - PS)* for the advanced therapy-exposed group. Extreme weights may be trimmed (and will be outlined in the SAP).

The covariate balance between the cohorts (before and after IPTW) will be evaluated using standardized differences for continuous covariates and standardized differences of proportion for each (non-missing) category for categorical covariates. Standardized differences greater than 0.10 between the cohorts will indicate imbalance and will be adjusted for in the comparative analyses.

Hazard ratios and associated 95% CIs will be estimated using the Cox proportional hazards model. Robust variance estimators will be used to address lack of independence induced by weighting. In case of a small number of outcomes, a Firth's correction will be applied. Specifically for the assessment of colorectal cancer outcome, the occurrence of proctocolectomy will be considered as a competing event and a Fine-Gray sub-distribution hazard model will be used. Time-to-event data will also be summarized by Kaplan-Meier methodology. (1-Kaplan-Meier) curves and time-to-event probabilities at key time points will be presented to approximate cumulative incidence rates.

For secondary analyses (by age-subgroups, by previous outcome onset subgroups and for components of malignancy and MACE), incidence rates, time-to-event and HRs will be computed before and after IPTW with their corresponding 95% CI.

Sensitivity analyses will be conducted for the final report, only for the outcomes in the primary objective, assessing a different length of the at-risk period after end of last prescription fill (from 30 to 90 days) and different lengths of the at-risk period for cancer outcomes (2 years for haematologic malignancies, 5 years for solid tumours). We will also assess the impact of exclusive attribution of malignancy in overlapping time-at-risk-periods, a more restrictive malignancy definitions (≥ 2 occurrences of diagnosis codes to qualify). Lastly, analyses will be conducted to assess the impact of: 1) excluding patients with concomitant conventional therapy at index date and censoring treatment episodes when conventional treatment is later added, 2) considering only oral therapies in the advanced therapy cohort, and 3) considering only the first continuous episode of advanced therapy or ozanimod (whichever comes first).

Aggregated results including summary estimates resulting from the main analysis of the primary objective of each data source will be pooled for meta-analysis. The heterogeneity between results will be checked, and a forest plot will be produced showing the data source–specific and pooled estimates.

4.10 Milestones

Milestone	Planned Date
Registration in the EU PAS Register	Within 1 month of protocol approval
Anticipated Start of Data Accrual	Q1 2023
Planned Study Period	2023-2032
Study Progress Reports	Q4 2024-2032
Interim Report 1	Q3 2026
Interim Report 2	Q3 2029
Anticipated End of Data Collection	Q4 2032
Final Report of Study Results	Q4-2033

5 AMENDMENTS AND UPDATES

None.

6 MILESTONES

Milestone	Planned Date
Registration in the EU PAS Register	Within 1 month of protocol approval
Anticipated Start of Data Accrual	Q1 2023
Planned Study Period	2023-2032
Annual Study Progress Reports	Q4 2024-2032
Interim Report 1	Q3 2026
Interim Report 2	Q3 2029
Anticipated End of Data Collection	Q4 2032
Final Report of Study Results	Q4 2033

Abbreviations: EU, European Union; PAS, post-authorisation study.

Table 6-1: Schedule of Reports

Schedule of Reports	Expected Data Availability Period for Each Report, by Data Source						
	GePaRD, (Germany)	**Danish Registries, (Denmark)**	**PHARMO, (Netherlands)**	**Norwegian Registries, (Norway)**	**CPRD, (UK)**	**Scottish Prescribing Information System, (Scotland)**	**SNDS, (France)**
Interim Report 1 Q3 2026	*Jan-2004 to Dec-2023*	*Jan-1995 to Dec-25*	*Jan-2004 to Dec-2024*	*Jan-2004 to Dec-2024*	*Jan-1998 to Dec-2024*	*Jan-2009 to Dec-2025*	*Jan-2012 to Dec-2024*
Interim Report 2 Q3 2029	*Jan-2004 to Dec-2026*	*Jan-1995 to Dec-2028*	*Jan-2004 to Dec-2027*	*Jan-2004 to Dec-2027*	*Jan-1998 to Dec-2027*	*Jan-2009 to Dec-2028*	*Jan-2012 to Dec-2027*
Final Report Q4 2033	*Jan-2004 to Dec-2031*	*Jan-1995 to Mar-2033*	*Jan-2004 to Dec-2031*	*Jan-2004 to Dec-2031*	*Jan-1998 to Dec-2031*	*Jan-2009 to Dec-2032*	*Jan-2012 to Dec-2031*

Abbreviations: CPRD, Clinical Practice Research Datalink; GePaRD, German Pharmacoepidemiological Research Database; PHARMO, Network of Healthcare Databases in the Netherlands; SNDS, French Administrative Healthcare Database; UK, United Kingdom

7 RATIONALE AND BACKGROUND

Ulcerative Colitis

Ulcerative colitis (UC) is a chronic, idiopathic inflammatory disease that affects the colon, starting in the rectum and extending to proximal segments of the colon, resulting in disability.[1,2] Some studies suggest a bimodal incidence of UC with peaks between ages 15 to 30 years and between ages 50 to 70 years.[2,3,4,5] UC usually presents with bloody diarrhoea.[1]

The clinical course of UC is unpredictable; there is no cure and it is a lifelong disorder that has a significant impact on a patient's mental and physical well-being.[1,2] Disease severity is typically classified as mild, moderate, severe, or in remission.[2] Most patients with UC have a mild to moderate course, generally most active at diagnosis and then with varying periods of remission and/or mild activity. Approximately 15% of patients may experience an aggressive course, and 20% of these patients may require hospitalization for severe disease activity.[6,7] The aetiology of UC is unknown but there are genetic and environmental factors that are associated with the disease.[8] Several factors may exacerbate UC including non-steroidal anti-inflammatory drug (NSAID) use, antibiotic use, and smoking cessation.[1,2] Appendectomy appears to confer a protective effect against developing UC, especially when done for acute appendicitis before age of 20 years.[1,2]

Diagnosis of UC is based on clinical findings from biopsy, endoscopy, histology, and the absence of alternative diagnoses. Treatment options for patients are based on UC severity and the extent of the disease.[1,2] In first line, UC is often managed with aminosalicylates and corticosteroids. Patients with moderate to severe UC are dependent on (or refractory to) corticosteroids, have severe endoscopic disease activity (presence of ulcers), or are at high risk of colectomy.[9] In these cases, other drug classes may be required: immunomodulators (azathioprine), tumour necrosis factor-alpha inhibitors (TNFi), anti-integrin agents (vedolizumab), Janus kinase inhibitor (JAKi) (tofacitinib), and interleukin 12/23 antagonist (ustekinumab).[10,11]

Burden in Europe

At the European level, the burden of UC is substantial with an estimation of more than 2 million cases.[12,13] Annual incidence estimation showed large variations, ranging from 8.8 to 23.1 per 100,000 person-years (10^5PY) in North America, and 0.6 to 24.3 /10^5PY in Europe with the highest incidence rates reported in Scandinavia and lower rates observed in southern and eastern Europe.[8] A Danish nationwide registry study found an annual UC incidence of 18.6 /10^5PY in 2013, with a steady increase over the last 30 years (the rate had been estimated at 10.7 /10^5PY in 1980).[14] In Norway, UC annual incidence estimates have been relatively stable, from 24.7 to 28.4 /10^5PY between 2010 and 2017, using a nationwide registry and prescription database.[15] In France, 109,889 patients with UC were identified in the nationwide claims and hospitalization database over a 5-year period (2009 and 2013) with an incidence rate of 11 /10^5PY.[16]

Ozanimod Efficacy and Safety Profile

Ozanimod (Zeposia®), an oral selective sphingosine 1-phosphate (S1P) receptor modulator was approved in the European Union (EU) on 20-May-2020, for the treatment of adults with

relapsing-remitting multiple sclerosis (RRMS) with active disease, and on 18-Nov-2021 for the treatment of adult patients with moderately to severely active UC who have had an inadequate response, lost response or were intolerant to either conventional therapy (ie, aminosalicylates, corticosteroids for systemic use, corticosteroids acting locally, conventional immunomodulators) or a biologic agent.[17]

The efficacy of ozanimod as an induction and maintenance therapy for UC was demonstrated in a phase 3, multicentre, randomized, double-blind, placebo-controlled trial.[18] The primary endpoint, clinical remission, was significantly higher in the ozanimod group during the 10-week induction period (18.4% vs 6.0%, $p < 0.001$) and maintenance period through week 52 (37.0% vs 18.5%, $p < 0.001$). Secondary endpoints were also statistically significant during both induction and maintenance: clinical response (47.8% vs 25.9%, $p < 0.001$ and 60.0% vs 41.0%, $p < 0.001$, respectively), endoscopic improvement (27.3% vs 11.6%, $p < 0.001$ and 45.7% vs 26.4%, $p < 0.001$, respectively), and mucosal healing (12.6% vs 3.7%, $p < 0.001$, and 29.6 vs 14.1%, $p < 0.001$, respectively).

The overall incidence of adverse events and serious adverse events was 40.1% and 4.0% in the ozanimod group vs 38.0% and 3.2% in the placebo group during the induction period, and 49.1% and 5.2% vs 36.6% and 7.9% during the maintenance period. More specifically, there were more cases in the ozanimod group of alanine aminotransferase increased, γ-glutamyl transferase increased, infection, bradycardia, hypertension, hypertensive crisis, macular oedema.

However, after any randomized placebo control trial with a relatively small group of patients and only a one-year follow-up for the maintenance period, questions remain about the benefit-risk of ozanimod in real-world settings compared to other alternative therapies. To address this point at the time of the European Medicines Agency (EMA) marketing authorization, a post-authorization safety study (PASS) was agreed upon with EMA to monitor the long-term safety profile of ozanimod in adult patients with moderately to severely active UC to address the following safety concerns: malignancies, serious opportunistic infections (SOIs), major adverse cardiovascular events (MACEs), venous thromboembolisms (VTEs), severe liver injury, macular oedema, and posterior reversible encephalopathy syndrome (PRES) or progressive multifocal leukoencephalopathy (PML).[19]

Bristol Myers Squibb (BMS), the ozanimod marketing authorization holder (MAH), solicited the SIGMA consortium to draft the core protocol of this PASS, which will be implemented in data sources of multiple European countries (Denmark, France, Germany, Netherlands, Norway) and the United Kingdom (UK).

8 RESEARCH QUESTION AND OBJECTIVES

8.1 Research Question

What is the risk of developing adverse events of interest (malignancy, serious opportunistic infections, major adverse cardiovascular events, venous thromboembolism, severe liver injury, macular oedema, posterior reversible encephalopathy syndrome) in a real-world European population of adults with moderately to severely active UC treated with ozanimod versus advanced

therapies, including tumour necrosis factor-alpha inhibitors (TNFis), anti-integrins, Janus kinase inhibitors (JAKis), or interleukin antagonists?

8.2 Research Objectives

8.2.1 Primary Objective

To evaluate the risk of the following outcomes in ozanimod-exposed patients versus those treated with advanced therapy:

- Malignancies
- Serious opportunistic infections (SOIs)
- Major adverse cardiovascular events (MACE)
- Venous thromboembolism, including pulmonary embolism (VTE)
- Severe liver injury.

8.2.2 Secondary Objectives

- To evaluate the risk of the outcomes of interest by subgroups (age, disease history and previous outcome history) in ozanimod-exposed patients versus those treated with advanced therapy.
- To describe, in ozanimod-exposed patients and those treated with advanced therapy, the frequency, baseline and clinical characteristics of patients experiencing:
  - Macular oedema
  - Posterior reversible encephalopathy syndrome (PRES)
  - Progressive multifocal leukoencephalopathy (PML).
- To evaluate the risk of macular oedema, PRES and PML (if sufficient sample size, according to descriptive analysis) in ozanimod-exposed patients versus those treated with advanced therapy.
- To evaluate the risk of cancer, by subtype, in ozanimod-exposed patients versus those treated with advanced therapy:
  - Solid tumours excluding non-melanoma skin cancer (NMSC)
  - NMSC
  - Colorectal cancer
  - Advanced colonic neoplasia, ie, composite endpoint including colorectal cancer and high-grade dysplasia, and
  - Lymphoma.
- To evaluate the risk of MACEs, by component, in ozanimod-exposed patients versus those treated with advanced therapy:
  - Acute nonfatal myocardial infarction
  - Acute nonfatal stroke
  - Cardiovascular (CV) mortality.

8.2.3 Exploratory Objectives

Not applicable.

9 RESEARCH METHODS

9.1 Study Design

This will be a non-interventional cohort study of patients with UC initiating therapy with ozanimod or advanced therapies, between 01-Jan-2023, and 31-Dec-2031. The study period will end on 31-Dec-2032.

This "new user" design ensures the capture of events more likely to be observed shortly after the initiation of a new treatment, bypasses depletion-of-susceptible bias, allows appropriate confounding adjustment by capturing pre-exposure variables, and reduces the potential for immortal time bias.

In order to reduce the susceptibility to confounding by indication or disease severity, ozanimod should be compared to alternative therapies sharing the same place in UC management (2nd, 3rd or nth line) such as advanced therapies (eg, TNFis, anti-integrins, JAKis, or interleukin antagonists). Conventional therapies are often used alone as first-line treatments and do not qualify for a relevant stand-alone comparative cohort. However, their concomitant use in the cohort of interest will be described.

The follow-up period during which outcomes will be assessed will end on 31-Dec-2032. If available in a data source, a 7-year baseline period will be used. A minimum 365-day baseline period will be required for each included patient.

The cohort entry date (or index date) is defined as the date of the first prescription or dispensing of a drug of interest without prior dispensing of the same drug ingredient (5th ATC level) or biosimilar during the baseline period.

Patients may initiate more than 1 therapeutic regimen during the study period but can contribute only 1 treatment episode to each of the 2 cohorts (ozanimod or advanced therapy; see Section 9.2.2). If and when entry to a second cohort occurs, an additional treatment cohort-specific index date will be assigned to that patient, as well as a corresponding baseline period prior to the new treatment cohort-specific index date. For all outcomes except cancer, the at-risk period for a qualifying drug will end the day before the index date for the second qualifying drug.

To account for potential confounding when comparing outcomes between ozanimod and advanced therapy, propensity score (PS) methods will be used—namely inverse probability of treatment weighting (IPTW).[20,21] The PS is the probability that patient would receive ozanimod versus an advanced therapy for UC, with demographic and baseline covariates used as potential predictors of treatment assignment (see Section 9.7.3.1). Under some assumptions, the PS can act as a balancing score that mimics the randomization implemented in clinical trials.[20] Based on this approach, a comparative risk analysis will be conducted to address the primary objective, generating a measure of association with therapy received for each outcome of interest. Stratification of this analysis on age, disease history, previous outcome onset (previous history versus non-previous history), and analysis by outcome subcategories/components will address the secondary objectives.

Data management will be conducted by each data source independently. Analyses will be executed independently by each data source provider. The unit of observation will be the treatment episode.

9.2 Setting

This study will be include routinely collected health data captured in European countries and in the UK.

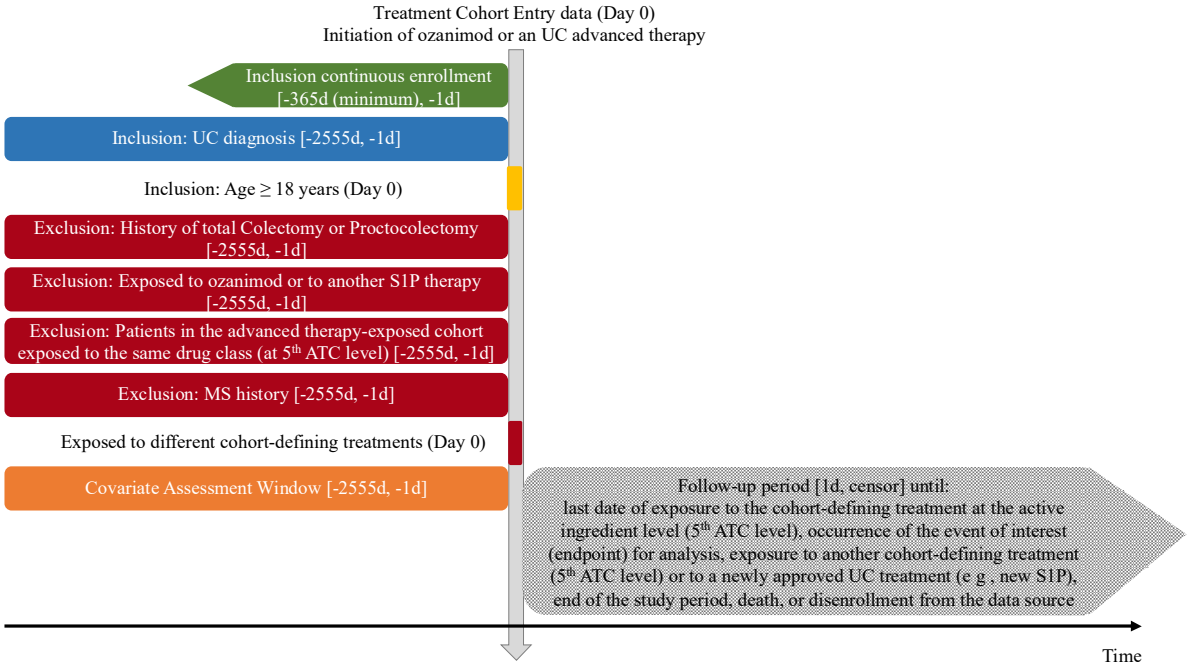
- Denmark: Danish population registries
- Germany: German Pharmacoepidemiologic Research Database (GePaRD)
- Netherlands: PHARMO Data Network
- Norway: Norwegian population registries
- England: Clinical Practice Research Datalink (CPRD)
- Scotland: Scottish Prescribing Information System
- France: *Système National des données de Santé* (SNDS), if applicable

9.2.1 Time-based Definitions

The following definitions will be used to identify patients and time periods eligible for inclusion in the study (Figure 9.2.1-1):

- Study period: The time during which patient data may be included is 01-Jan-2016 through 31-Dec-2032. This includes the maximum possible baseline period through the maximum possible follow-up.
- Indexing period: The time during which new treatment episodes may be included is from 01-Jan-2023 through 31-Dec-2031. The indexing period ends 1 year before final data collection to ensure sufficient follow-up for the last patients accrued.
- Baseline period: The time prior to the initiation of a new treatment episode during which data are available. Each patient must have at least 1 year of data to be included but can have as much as 7 years.
- Index date: The date of first prescription/dispensing of a qualifying treatment. Note that if a patient contributes to both cohorts, 2 different cohort-specific index dates will be assigned.
- Follow-up period: The time during which a patient can be followed, from initiation of a treatment episode until the first of the following:
  - End of the study
  - Death
  - Disenrollment from the data source
- At-risk period (time-at-risk): The time over which an outcome is attributed to a cohort-defining exposure within the follow-up period. They are outcome specific (see Section 9.3.2).

Figure 9.2.1-1: Study Design Diagram



Abbreviations: d, day; MS, Multiple sclerosis; S1P, Selective sphingosine 1-phosphate receptor modulator; UC, Ulcerative colitis

9.2.2 Study Population

The study will include patients at least 18 years or older who have a diagnosis of UC and are new users ("initiators") of a cohort-defining treatment (Table 9.2.2.1-1) during the indexing period. The 2 cohorts for the analysis are:

- Ozanimod: patients initiating ozanimod as UC therapy for the first time, without any prior dispensing of ozanimod or other S1P therapy during the baseline period;
- Advanced therapy: patients initiating a UC-indicated TNFi, or vedolizumab or ustekinumab or tofacitinib, under these conditions: no prior dispensing of a drug with the same active ingredient (5th ATC level); not having received S1P therapy (including ozanimod) during the baseline period.

In each cohort, time-at-risk period will be defined based on exposure to cohort-defining treatment (see Section 9.3.2). Patients from the advanced therapy-exposed cohort who have been censored for initiating ozanimod can enter the ozanimod-exposed cohort, provided they meet the inclusion criteria a new treatment episode (see Section 9.2.2.1).

As a sensitivity analysis, an as-treated design with the same inclusion/exclusion criteria, considering only the first continuous episode of advanced therapy or ozanimod (whichever comes first) will be conducted (see Section 9.7.5).

If new biologics or other UC medications are approved after study initiation, they will not be added to the study. However, patient exposure would be censored at the time of initiation of this new treatment.

9.2.2.1 Inclusion Criteria

A treatment episode will be included if (Figure 9.2.1-1):

- Patient initiated ozanimod or a UC advanced therapy listed in Table 9.2.2.1-1, without prior dispensing of the same drug ingredient (5th ATC level) during the baseline period.
- Patient has a recorded diagnosis of UC prior to or at the index date
- Patient is at least 18 years of age at the index date
- Patient has a minimum of 365 days of historical data in the data source prior to the index date

Table 9.2.2.1-1: Cohort-defining Treatments

Initiation of Cohort-defining UC Treatment	Drug	ATC Codes
Ozanimod-exposed Cohort	Ozanimod*	L04AA38
Advanced Therapy-exposed Cohort	Tofacitinib*	L04AA29
	Vedolizumab	L04AA33
	Upadacitinib*	L04AA44
	Filgotinib*	L04AA45
	Golimumab	L04AB06
	Ustekinumab	L04AC05

*Oral therapies.

Abbreviations: ATC, anatomical therapeutic chemical; UC, ulcerative colitis.

Note: ATC codes as of 01-Jan-2023.

9.2.2.2 Exclusion Criteria

Treatment episodes that meet any of the following criteria will be excluded:

- Patient has less than 365 days of historical data in the data source prior to the index date
- Patient had a history of total colectomy or proctocolectomy prior to the index date
- Patient had a history of multiple sclerosis (MS) within 1 year prior to the index date defined as ≥ 3 encounters among MS-related hospitalizations, outpatient visits, or prescription release for a specific MS disease-modifying treatment (DMT) (list specified in APPENDIX 2) in any combination.[22]
- Patient is exposed to the same drug ingredient (5th ATC level) or to an S1P treatment prior to the index date
- Patient begins 2 different cohort-defining treatments on the index date (see Table 9.2.2.1-1); for instance, if a patient initiates ozanimod and tofacitinib, the patient will not be included in the ozanimod-exposed cohort, nor in the advanced therapy cohort.

9.3 Variables

At the proposal stage, members or partners of the SIGMA consortium were offered the possibility to participate in the study. Several research partners with protocol-based access to data sources indicated the willingness and ability to participate. BMS pre-selected partners based on data availability and ozanimod expected sales. The research partners involved in the study and the data sources associated are detailed in Section 9.4. Table 9.3-1 below shows the specific data available in each.

Table 9.3-1: Data Available in the Participating European Data Sources

Data Source (Country)	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
Age	X	X	X	X	X	X	X
Sex	X	X	X	X	X	X	X
Level of Education	X			X			
Geographical Location	X[a]	X	X	X		X	X
Smoking History Status	X[b]		X		X		
Outpatient Data							
Exposure Data	X	X	X	X	X	X	X
Outcomes	X		X	X	X		
Laboratory Test, Including Results	X[c]	X	X[d]	X[e]	X[d]	X[f]	X[c]
Inpatient Data							
Exposure Data	Some	X	X	X		X	X[g]
Outcomes	X	X	X	X	X	X	X[h]
Laboratory Test, Including Results	X[c]	X		X[e]		X[f]	X[c]
Malignancy Data	X	X	X	X	X	X	X
Emergency Data		X		X	X		X

[a] On district level.
[b] Smoking history not assessable, only heavy smoker yes/no based on ICD-10-GM proxies.
[c] Laboratory test procedures are captured, not the results.
[d] Only include the laboratory results found within the GP data (not the specialist requested clinical laboratory data).
[e] Only positive tests for notifiable diseases.
[f] Only available regionally.
[g] Only innovative or expensive drugs and medical devices invoiced in addition to the hospitalisation.
[h] Including codes of event of interest.

Abbreviations: CPRD, Clinical Practice Research Datalink; GePaRD, German Pharmacoepidemiological Research Database; GP, General Practitioner; ICD-10-GM, International Classification of Disease-10th revision-German Modification; SNDS, Système National des Données de Santé; UK, United Kingdom.

9.3.1 Outcomes/Endpoint Variables

Outcome variables will be ascertained from outpatient and inpatient records available from each data source, others from some country-specific registries. Definitions of UC diagnosis, outcomes, and comorbidities will be based on the International Classification of Disease-10th revision (ICD-10) codes as specified in the subsequent sections. The receipt of ozanimod or advanced therapy will be the primary indicator of sufficient UC severity.

Because data sources may have other codification systems, a correspondence list between other codes and ICD-10 is presented in Table 9.3.1-1 for UC. This correspondence list will be consolidated in the statistical analysis plan (SAP), if necessary, with the support of experts from each data source to ensure information granularity and quality are maintained.

Table 9.3.1-1: Codes to Identify UC In The Participating European Data Sources

Data Source (Country)	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
Vocabulary	ICD-10-GM	ICD-10	ICD-10	ICD-10	SNOMED CT	ICD-10	ICD-10
UC Codes	K51	K51	K51	K51	128600008	K51	K51
					14311001		
					196987008		
					201727001		
					201807008		
					235714007		
					24829000		
					275549008		
					295046003		
					404908004		
					410484008		
					414156000		
					442159003		
					444546002		
					444548001		
					445243001		
					52231000		
					52506002		

Table 9.3.1-1: Codes to Identify UC In The Participating European Data Sources

Data Source (Country)	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
					64766004		
					697969008		
					78324009		
					78712000		

Abbreviations: CPRD, Clinical Practice Research Datalink; GePaRD, German Pharmacoepidemiological Research Database; ICD-10(-GM), International Classification of Disease-10th revision (-German modification); PHARMO, Network of Healthcare Databases in the Netherlands; SNDS, French Administrative Healthcare Database; SNOMED-CT, Systemized Nomenclature of Medicine – Clinical Terms. ; UK, United Kingdom.

Some data sources may use fewer digits in ICD-10 coding, or a coding system allowing a less specific identification of outcomes. In these cases, identification algorithms may be required. Where relevant, previously validated algorithms and code sets will be used. If needed, ad-hoc algorithms and code sets will be created in close collaboration with participating research partners and medical experts, and then validated where possible.

Specific exclusion criteria for some outcomes may differ across data sources and not all outcomes may be available in all data sources. These issues will be assessed and then detailed in the SAP. The SAP will also provide final medical code sets and case-identifying algorithms per data source.

9.3.1.1 Malignancies

Depending on the data source, malignancies will be identified by meeting any of these criteria:

- The presence of at least 1 ICD-10 diagnosis code for malignancy in cancer registries (for some countries)
- Codes associated with an inpatient hospitalization in the principal or primary diagnosis position during the follow-up period.
- Dispensing of a specific treatment for cancer that is potentially managed in outpatient settings (eg, prostate cancer) (APPENDIX 2)

Relevant variables are defined in Table 9.3.1.1-1.

Note that the occurrence of proctocolectomy will be considered as a competing event for the assessment of colorectal cancer.

The incidence rate of malignancy (by treatment cohort), as well as the hazard ratio of malignancies between treatment groups, will be reported.

As a sensitivity analysis, a more restrictive operational definition will be used in non-registry data, requiring the presence of at least 2 diagnosis codes for malignancy outcome(s) of interest (see Section 9.7.5).

The typically long period of cancer development (induction) and latency after the exposure to any carcinogenic or anti-neoplastic drug implies a specific definition of the follow-up time (see Section 9.3.2.2), which will be tested in sensitivity analyses (see Section 9.7.5).[23]

Table 9.3.1.1-1: Malignancy Outcome Variables

Variable	Definition	Timing
Date of Incident Malignancy Diagnosis	Defined as the calendar date of the first malignancy occurrence during follow-up.	Collected during follow-up period
Type of Malignancy	Malignancies will be defined as a composite and by type, according to the below groupings: • Solid malignancies excluding NMSC, • NMSC, • Colorectal cancer, • Advanced colonic neoplasia, ie, composite endpoint including colorectal cancer and high-grade dysplasia, • Lymphoma. Type of malignancy will be determined by ICD-10 codes presented in APPENDIX 2.	Collected on the date of incident malignancy diagnosis during follow-up
Primary Site of Malignancy	The primary site of malignancy will be identified by the ICD-10 diagnosis code associated with the claim. Sites of malignancy can include but are not limited to: • Lip, oral cavity and pharynx, • Digestive organs • Respiratory and intrathoracic organs • Bone and articular cartilage • Neoplasms of skin • Neoplasms of mesothelial and soft tissue • Breast • Genital organs by sex • Urinary tract • Eye, brain, and other parts of central nervous system • Thyroid and endocrine glands • Ill-defined, other secondary and unspecified sites • Neuroendocrine tumours (primary and secondary) • Lymphoid, hematopoietic, and related tissue • In situ neoplasms, and • Neoplasms of uncertain behaviour, polycythaemia vera and myelodysplastic syndromes	Collected during follow-up period

Table 9.3.1.1-1: Malignancy Outcome Variables

Variable	Definition	Timing
	Primary site of malignancy will be determined by ICD-10 codes presented in APPENDIX 2.	

9.3.1.2 Serious Opportunistic Infections, Including Progressive Multifocal Leukoencephalopathy

Serious opportunistic infections will be defined by the presence of at least 1 ICD-10 code from APPENDIX 2 associated with an inpatient hospitalization or emergency department (ED) encounter.

PML will be defined by the presence of at least 1 ICD-10 code (A81.2) listed as principal or primary diagnosis for an inpatient hospitalization, or the presence of UC as the principal or primary discharge diagnosis with PML diagnosis in secondary position. This outcome ascertainment algorithm was adapted from the MS literature given the absence of published studies on PML identification among patients with UC.[24]

SOIs will be reported in accordance with the primary and secondary objectives through the variables presented in Table 9.3.1.2-1.

As it is expected to be rare, the incidence rate of serious opportunistic infections (by treatment cohort) as well as their hazard ratio between groups, will be reported if sample size allows.

Table 9.3.1.2-1: Serious Opportunistic Infections (Including PML) Outcome Variables

Variable	Definition	Timing
Date of Incident SOI	Calendar date of the first SOI infection during follow-up.	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 specified in APPENDIX 2.	Collected during follow-up period

Abbreviations: ICD-10, International Classification of Desease-10th revision; PML, Progressive multifocal leukoencephalopathy; SOI, serious opportunistic infections.

9.3.1.3 Major Adverse Cardiac Events

The clinical and operational definitions for MACE can be found in Table 9.3.1.3-1. Because cardiovascular outcomes have similar mechanisms and risk factors, a composite MACE outcome will be examined in addition to the individual outcomes.

In the composite outcome, MACE will be defined as the first event of incident acute myocardial infarction (AMI), stroke, or CV death during the follow-up period. The incidence rate of MACE (by treatment cohort), as well as the hazard ratio of MACE between treatment groups, will be reported.

The ICD-10 codes for MACE are presented in Table 9.3.1.3-1.[25,26,27]

Table 9.3.1.3-1: Major Adverse Cardiovascular Events Definition

Composite Outcome	Individual Components		Clinical Description	Operational Definitions
MACE	AMI diagnosed in hospital (inclusive of fatal and non-fatal events)		AMI will be defined clinically as evidence of myocardial necrosis in a clinical setting consistent with myocardial ischemia, including ST-elevation myocardial infarction (MI) and non–ST-elevation MI. Any AMI noted with death certificates will be categorized as CHD death.	≥ 1 ICD-10 code for AMI (I21.xx) in the principal or primary diagnosis position on at least 1 facility claim for inpatient hospitalization only.
	Stroke diagnosed in hospital (inclusive of fatal and non-fatal events)		An acute stroke is defined as the rapid onset of a persistent neurological deficit attributed to an obstruction or rupture of the arterial system. Patients with stroke can die before reaching the hospital; a complete assessment of acute stroke events requires the identification of community stroke deaths. Both haemorrhagic and ischemic strokes will be included in the case definition.	≥ 1 ICD-10 code for stroke (I60.xx, I61.xx, I62.xx, I63.xx, or I64.xx) in the principal or primary diagnosis position on at least 1 facility claim for hospitalization only.
	CV mortality	Coronary heart disease (CHD) mortality	Fatal episode of AMI or CHD death.	The following ICD-10 codes in the primary cause of death position will define CV mortality: I20.0, I20.9, I21.xx, I60.xx, I61.xx, I62.xx, I63.xx, or I64.xx.
		Cerebrovascular disease mortality	Fatal episode of stroke or cerebrovascular disease death.	

Abbreviations: AMI, acute myocardial infarction; CHD, coronary heart disease; CV, cardiovascular; GePaRD, German Pharmacoepidemiologic Research Database; ICD-10, International Classification of Disease-10th Revision; MACE, major adverse cardiovascular event; MI, myocardial infarction; SNDS, Système National des Données de Santé.

9.3.1.4 Venous Thromboembolism

Venous thromboembolism will be identified via the presence of ≥ 1 ICD-10 code (Table 9.3.1.4-1) in the principal or primary diagnosis position in any care setting during follow-up. Imaging procedure codes combined with administrated treatments may also be considered to define these outcomes.[28] Venous thromboembolism is clinically defined as pulmonary embolism (PE) or deep vein thrombosis (DVT). Variables defining VTE occurrence and subtype are displayed in Table 9.3.1.4-2.

The incidence rate of VTE (by treatment cohort), as well as the hazard ratio of VTE between treatment groups, will be reported.

Table 9.3.1.4-1: Venous Thromboembolism Event Operational Definitions

VTE Subtype	ICD-10 Codes
PE	I26.0x; I26.9
DVT	I80.1x; I80.2x; I80.3x; I80.8x; I80.9x; I81.xx; I82.xx

Abbreviations: DVT, deep vein thrombosis; ICD-10, International Classification of Disease-10th Revision; PE, pulmonary embolism; VTE, venous thromboembolism.

Table 9.3.1.4-2: Venous Thromboembolism Event Outcome Variables

Variable	Definition	Timing
Date of Incident VTE	Calendar date of the first VTE event during follow-up.	Collected during follow-up period
Subtype of VTE	PE or DVT, according to the categorization in Table 9.3.1.4-1.	Collected during follow-up period

Abbreviations: DVT, deep vein thrombosis; ICD-10, International Classification of Disease-10th Revision; PE, pulmonary embolism; VTE, venous thromboembolism.

9.3.1.5 Severe Liver Injury

Severe liver injuries will be defined by the presence of at least 1 ICD-10 code from Table 9.3.1.5-1 associated with an inpatient hospitalization in the principal or primary diagnostic position. The occurrence of severe liver injury will be assessed during the follow-up period. The incidence rate of severe liver injury (by treatment cohort), as well as the hazard ratio of severe liver injury between treatment groups, will be reported.

Table 9.3.1.5-1: ICD-10 Codes to Identify Suspected Severe Liver Injury From Hospital Diagnoses

ICD-10 Code	Description
K71.1	Toxic liver disease with hepatic necrosis
K71.2	Toxic liver disease with acute hepatitis
K71.6	Toxic liver disease with hepatitis, not elsewhere classified
K71.9	Toxic liver disease, unspecified
K72.0	Acute and subacute hepatic failure
K72.9	Hepatic failure, unspecified
K75.4	Autoimmune hepatitis
K76.8	Other specified diseases of liver
K76.9	Liver disease, unspecified
R17	Unspecified jaundice, excludes neonatal
Z94.4	Liver transplant

Abbreviations: ICD-10, International Classification of Disease-10th Revision.

9.3.1.6 Macular Oedema

Macular oedema will be identified based on the presence of at least 1 ICD-10 diagnosis code for macular oedema (H35.8) associated with a procedure code for optical coherence tomography in any setting. The occurrence of macular oedema will be assessed during the follow-up period. As it is expected to be rare, the incidence rate of macular oedema (by treatment cohort) as well as the hazard ratio of macular oedema between groups, will be reported if sample size allows.

9.3.1.7 Posterior Reversible Encephalopathy Syndrome

PRES will be identified based on the presence of at least 1 ICD-10 diagnosis code (I67.8) in any diagnostic position associated with either an ED encounter or an inpatient hospitalization. The occurrence of PRES will be assessed during the follow-up period. As it is expected to be rare, the incidence rate of PRES as well as the hazard ratio of PRES between groups, will be reported if sample size allows.

9.3.2 Exposure

9.3.2.1 Time-at-risk, General Case

Initiation is defined as dispensing of 1 of the cohort-defining UC treatments without prior dispensing of the same drug ingredient (5th ATC level) or S1P treatment including ozanimod during the baseline period (see Section 9.2.2).

The type of data captured regarding the exposure to drugs (prescription, dispensing, or administration) and the local codification system used to record exposure (eg, ATC/ local drug identifiers) are presented in Table 9.3.2.1-1.

Table 9.3.2.1-1: Exposure Types and Vocabularies Recorded In The Participating European Data Sources

Data Source (Country)	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
Vocabulary	**ATC** for outpatient dispensing, **OPS** for drugs administered in hospital which can be matched to ATC	**ATC** for drugs **NPU** for lab values Procedure codes for biologic dispensing In-patient drug register	**ATC**	**ATC and and Vnr (Nordic Product Number)**	**dm+d**	**BNF**	**ATC** **CIP** for non-hospital outpatient, dispesning **UCD** for inpatient or hospital outpatient, dispensing[b]
Data Types							
Administration	X[c]			X[d]			
Prescription	X		X		X	X	

Table 9.3.2.1-1: Exposure Types and Vocabularies Recorded In The Participating European Data Sources

Data Source (Country)	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
Dispensing	X	X	X	X			X

[a] The Scottish data for this study will partly be taken from a new resource of which there is little experience: the information in this table relating to Scottish Prescribing Information System data is an anticipation of how the data will be used and is subject to change.

[b] Though a code UCD is present, all drugs may not be captured in inpatient records. Only drug invoiced in addition of the hospital stays are recorded in hospital settings.

[c] Only for those drugs administered in hospital that are reimbursed as procedures

[d] Drugs administered in hospital

Abbreviations: ATC, Anatomical Therapeutic Chemical; BNF, British National Formulary; CIP, *Code d'Identification de Présentation*; dm+d, Dictionary of Medicines and Devices; CPRD, Clinical Practice Research Datalink; GePaRD, German Pharmacoepidemiological Research Database; ICD-10 (-GM), International Classification of Disease-10th revision (-German modification); NPU, Nomenclature, Properties and Units; OPS, *Operationen- und Prozedurenschlüssel* (ie, German procedure classification for the encoding of operations, procedures and general medical measures); PHARMO, Network of Healthcare Databases in the Netherlands; SNDS, French Administrative Healthcare Database; SNOMED-CT, Systemized Nomenclature of Medicine – Clinical Terms; UCD, *Unité Commune de dispensation*; UK, United Kingdom.

Exposure time at risk starts on the day of treatment cohort entry (index date) and continues until 30 days after the presumed end of drug supply (grace period) or initiation of another therapy, except for malignancy outcomes (see Section 9.3.2.2).

Duration of treatment exposure will be inferred in order of preference, from administration data whenever available, then from prescription data, and dispensing data. In case of dealing with dispensing data, box size and treatment strength will be retrieved from records and used to derive exposure length using Usual Daily Doses (UDD). These UDDs rely on summaries of product characteristics and were refined based on the doses that are most likely received by patients per day based on the size and strength of the boxes which were dispensed (see APPENDIX 3). Unlike Defined Daily Doses (DDDs), this approach allows for dosage variations to be considered. For instance, Tofacitinib posology range from 2*5mg, (10mg) per day to 2*10mg (20mg) per day. It is likely that a person receiving a box of 56 5mg tablets would be treated at a dosage of 2*5mg per day for 28 days, and that a person receiving a box of 56 10mg tablets would be treated at a dosage of 2*10mg per day for 28 days too. The UDDs for these 2 boxes would therefore be 10mg and 20mg respectively. Note that Tofacitinib DDD is 10mg. Applying DDD in this context would have led to overestimate the exposure of the patient taking 20mg per day to a 56-day coverage.

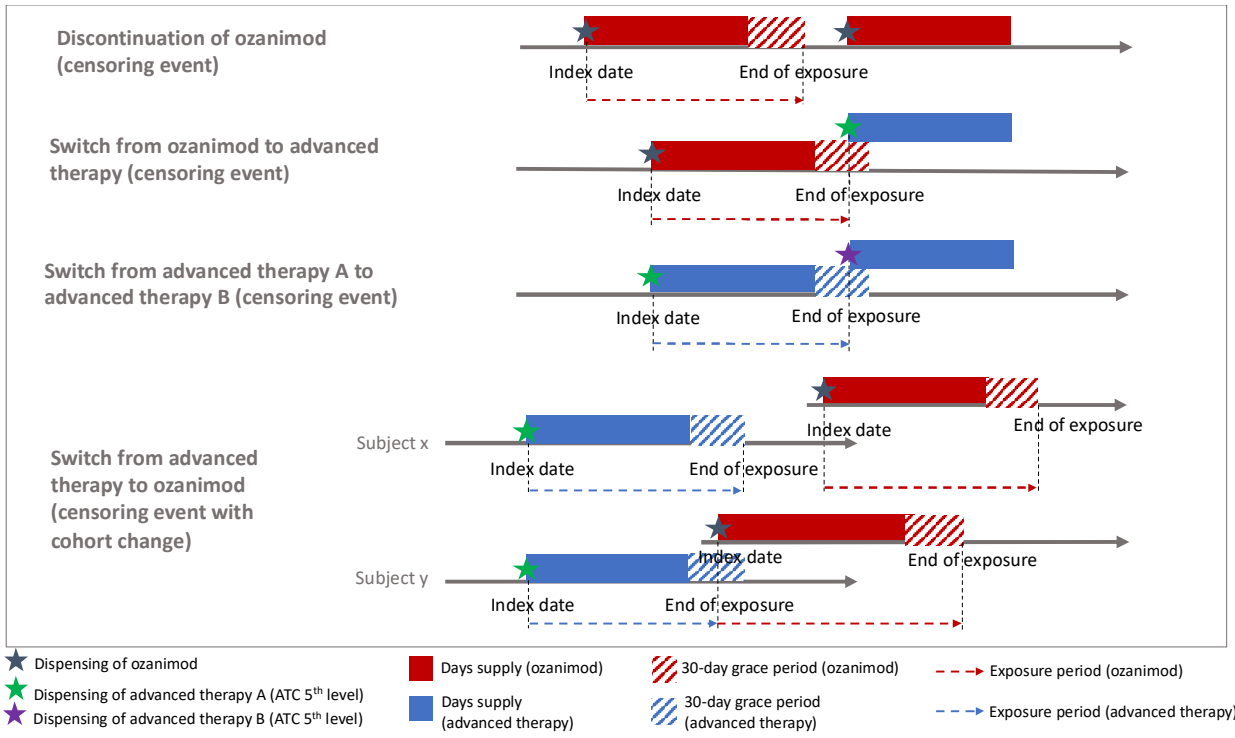
A continuous episode will be defined as the person-time with a continual drug supply, allowing for gaps of no more than 30 days.

Only use in the first continuous treatment episode will be considered per cohort.

If a re-dispensing (refill) of the index medication occurs before the presumed end of the drug's supply, the overlapping supply will be added to the end of a concatenated exposure period. This accounts for situations of imperfect adherence and allows for the possibility of a drug effect that may extend beyond the total number of days supplied.

In case of switching to another cohort-defining treatment or a newly approved UC treatment before the end of drug exposure (ie, drug supply + grace period), the exposure will be censored on the date of dispensing of this new treatment (Figure 9.3.2.1-1).

Figure 9.3.2.1-1: Exposure Periods Diagram



9.3.2.2 Time-at-risk, Malignancy Outcomes

For assessment of malignancy outcomes, a lag-time period of 6 months will be considered from the index date to avoid a non-biologically plausible association between a drug and a malignancy.[23] If a malignancy occurs within the lag-time period, it will not be counted in the numerator and not be considered as an outcome for that cohort. (For example, a cancer diagnosed 2 days after the ozanimod initiation will not be counted in the numerator of the ozanimod-exposed cohort.)

To address a potential delayed onset of a malignancy, a latent period will be added at the end of the presumed exposed period. This latent period will be set to:

- 1 year for hematologic malignancies (extended to 2 years in a sensitivity analysis, see Section 9.7.5)
- 2 years for solid tumours (extended to 5 years in a sensitivity analysis, see Section 9.7.5)

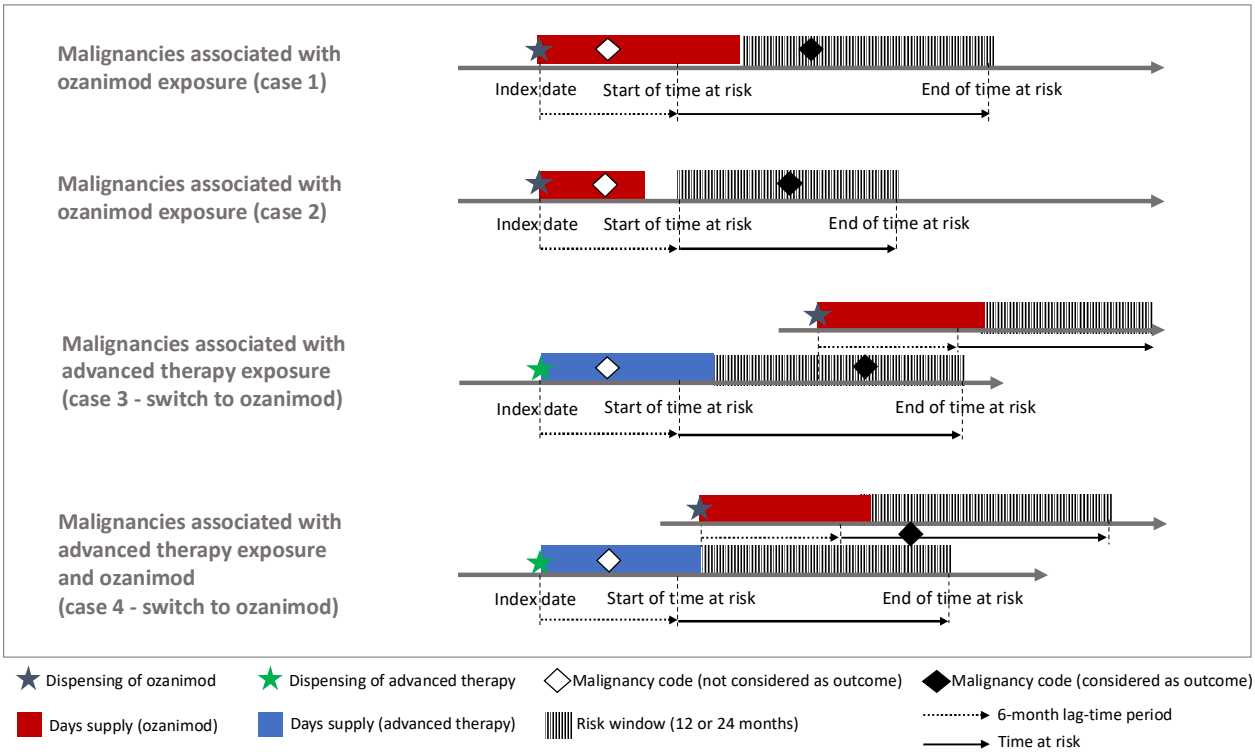
- For a treatment cohort, if a malignancy occurs after the end of the lag-time period and before the end of the latent period, it will be considered as an outcome potentially related to that treatment (Figure 9.3.2.2-1).

Censoring events defined in Section 9.3.4 will apply, except for exposure to another cohort-defining treatment or to a newly approved UC treatment. Since follow-up time for malignancy will not stop with exposure to another drug, overlapping risk periods may occur.

In the event of a malignancy during overlapping time-at-risk periods (Figure 9.3.2.2-1, Case 4), the outcome will be counted in the numerators of both treatment-exposed cohorts. A sensitivity analysis where malignancy occurring in overlapping time-at-risk periods will be exclusively attributed to 1) ozanimod, and to 2) the alternative treatment will also be conducted (see Section 9.7.5).

Such cases will also be described in detail in order to aid in the interpretation of results.

Figure 9.3.2.2-1: Time-at-risk for Malignancy Outcomes



9.3.2.3 Exposure to Conventional Therapies

Dispensing of conventional therapy for UC (Table 9.3.2.3-1) during exposure periods will be considered as concomitant exposure. It will not be considered as a switch nor censor the exposure period. These exposure patterns occur in the real-world setting and should be accounted for.

There will be many patterns of use for conventional treatments during exposure to the study drugs of interest during this study. Also, based on drug labels, it is expected that the advanced therapy group will have more concomitant use of conventional therapies than the ozanimod group.

As a consequence, conventional therapies will not be considered as competing treatments in the primary analyses. To better assess the potential impact of conventional treatment on the outcomes of interest, a sensitivity analysis will exclude patients with concomitant conventional therapy at the index date and censor the at-risk period at conventional therapy dispensing (see Section 9.7.5).

Conventional treatment utilization during follow-up will be described and quantitatively summarized for each treatment cohort in the primary analyses.

Table 9.3.2.3-1: Conventional Therapy for Ulcerative Colitis

Conventional Therapy	Drug	ATC Codes
Aminosalicylates	Mesalazine	A07EC02
	Olsalazine	A07EC03
	Sulfasalazine	A07EC01
Corticosteroids for Systemic Use	Betamethasone	H02AB01
	Dexamethasone	H02AB02
	Methylprednisolone	H02AB04
	Prednisolone	H02AB06
	Prednisone	H02AB07
Corticosteroids Acting Locally	Betamethasone	A07EA04
Conventional Immunomodulators	Cyclosporine	L04AD01
	Tacrolimus	L04AD02
	Azathioprine	L04AX01
	Methotrexate	L04AX03
	Mercaptopurine	L01BB02

Note: ATC codes as of 01-Jan-2023.
Abbreviations: ATC, anatomical therapeutic chemical.

To ensure a good classification of exposure, note that ATC codes for the identification of cohort-defining treatments and conventional treatments will be aligned in each data source to drug national identifier codes, when available.

9.3.3 Variables

9.3.3.1 Demographic and Clinical Characteristics

Patient demographic and clinical characteristics will be evaluated during the baseline period through the index date. Characteristics that can be evaluated in each data source may vary based on data availability (Table 9.3.3.1-1).

Frequency measures of stipulated medicinal products will be reported descriptively and used in propensity score models.

Table 9.3.3.1-1: Covariates of Interest

Demographic/Clinical Variables	Definition	Timing
Age	Continuous variable defined as the difference in time between date of birth and cohort entry 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
Sex	Categorical variable defined as sex at birth: • Female • Male	Assessed on the patient's index date
Level of Education	Categorical variable defined as the highest level of education attained by the patient.	Assessed on the patient's index date
Geographic Location	Categorical variable defined as the geographical setting in which the patient resides (eg, region of France).	Assessed on the patient's index date
Smoking History/Status	Binary variable: history of smoking (or current smoker) and non-smoking (never smoked). ICD-10 codes to evaluate smoking status are F17, Z71.6, and Z72.0[29] or by country-specific algorithm.	Assessed during the patient's baseline period [-2555, -1]
Year of Cohort Entry	Categorical variable defined as the year the participant indexes into a study treatment cohort. A patient can have 2 index dates if he was first on advanced therapy then on ozanimod cohort.	Assessed on the patient's index date
Level of UC Severity	Continuous variable representing a patient's Inflammatory bowel disease (IBD) severity index score. The scores are based on Charlson Comorbidity scores, age, anaemia, weight loss, intravenous (IV) corticosteroid use, prior gastrointestinal-related ED visit and hospitalization, number of previous UC treatments, and time from diagnosis to first UC therapy.[30] During SAP development, this indicator of severity may also be categorized (eg, > 8 indicative of intermediate-severe UC disease).	Assessed during the patient's baseline period [-2555, -1]
History of Prior Colonoscopy	Binary variable (Yes/No) defined by using procedure codes indicating occurrence of a colonoscopy.	Assessed during the patient's baseline period [-2555, -1]
Date of Most Recent Colonoscopy	Relative date of the patient's colonoscopy during the baseline period. If the patient has had multiple colonoscopies, the 1 that occurs closest to the index date will be captured.	Assessed during the patient's baseline period [-2555, -1]
Presence of High-grade Dysplasia	Binary variable (Yes/No).	Assessed during the patient's baseline period [-2555, -1]

Table 9.3.3.1-1: Covariates of Interest

Demographic/Clinical Variables	Definition	Timing
Obesity	Binary variable (Yes/No).	Assessed during the patient's baseline period [-2555, -1]
History of Cholelithiasis	Binary variable (Yes/No) for history of cholelithiasis. Assessed using ICD-10 code K80.XX.	Assessed during the patient's baseline period [-2555, -1]
History of Hepatic Disease or Impairment	Binary variable (Yes/No) for history of hepatic disease. Assessed using ICD-10 code K71.XX, K72.0, K72.9, K76.8, K76.9.	Assessed during the patient's baseline period [-2555, -1]
Primary Sclerosing Cholangitis	Binary variable (Yes/No) for the assessment of history of primary sclerosing cholangitis. Assessed using ICD-10 codes K83.0 and K83.01.	Assessed during the patient's baseline period [-2555, -1]
History of Neoplasia	Binary variable (Yes/No) for the history of malignant neoplasia. Assessed according to the ICD-10 codes specified in APPENDIX 2.	Assessed during the patient's baseline period [-2555, -1]
Varicella Zoster Virus Vaccination Status	Binary variable (Yes/No) to indicate immunization status. Assessed with the Z23 ICD-10 code or ATC code J07BK01 or country-specific codes.	Assessed during the patient's baseline period [-2555, -1]
History of Other Major Comorbidities: • Diabetes • Chronic Congestive Heart Failure • Congenital Heart Disease • Pulmonary Hypertension • Chronic Ischaemic Heart Disease • Sickle Cell Disease • Cardiac Valvular Disease • Systemic Lupus Erythematosus • Human Immunodeficiency Virus • Chronic Renal Disease • Hypertension • Alcohol Abuse (Proxy) • Asthma • Thyroid Disease • Respiratory Disease (Excluding Asthma) • Anxiety/Depression • Others	Binary variable (Yes/No) indicating presence of considered comorbidity. Assessed using specific ICD-10 codes, ATC codes or relevant procedure codes.	Assessed during the patient's baseline period [-2555, -1]

9.3.3.2 Measures of Drug Exposure Before and at Index Date

The below exposure variables will be assessed (Table 9.3.3.2-1), reported descriptively, and used to define exposures at or prior to index date.

Table 9.3.3.2-1: Exposure Variables of Interest

Exposure Variable	Definition	Timing
Exposure Group	Exposure to cohort-defining therapy indicated by at least 1 prescription/dispensation of a cohort-defining therapy (Table 9.2.2.1-1).	The dispensing of treatment to be assessed starting 01-Jan-2023, or upon the date of the ozanimod market launch in the country of interest.
Medicinal Products	Detailed medicinal product of the comparator cohorts (ATC codes, Table 9.2.2.1-1).	The dispensing of treatment to be assessed starting 01-Jan-2023, or upon the date of the ozanimod market launch in the country of interest.
Dose	Dose of the treatment.	Continually assessed during the follow-up period.
Low dose regimen	Binary variable (Yes/No) based on the cumulative dispensed dose of each treatment over the corresponding exposed period	Continually assessed during the follow-up period.
Days Supplied	Days supplied of a study treatment indicated by the dispensing or derived.	Continually assessed during the follow-up period.
Initiation Date or Index Date	Calendar date representing the first date of dispensing of a study treatment for a given participant.	Assessed during the indexing period for an eligible participant.
Switch Date	Calendar date representing the date of dispensing of another cohort defining treatment (5th ATC level) or to a newly approved UC treatment for a given participant.	Continually assessed during the follow-up period.
Switch reason	If available, indication of dispensing of another cohort defining treatment (5th ATC level) or to a newly approved UC treatment for a given participant.	Continually assessed during the follow-up period.
End of Exposure Date	Calendar date representing the period covered by the days supplied plus the grace period, when followed by a period without dispensing, or date of switch, for a given participant.	
Concomitant UC Medications	Binary variables (Yes/No) indicating active prescription or dispensing on the index date for each of the UC medications specified in Table 9.3.2.3-1.	Assessed on the index date.
Prior Conventional UC Therapy	Binary variable (Yes/No) indicating history of conventional therapy (see Table 9.3.2.3-1 which will be assessed through prescription or dispensing data.	Assessed during the patient's baseline period [-2555, -1].

Table 9.3.3.2-1: Exposure Variables of Interest

Exposure Variable	Definition	Timing
Prior Advanced UC Therapy	Binary variable (Yes/No) indicating history of advanced therapy (see Table 9.2.2.1-1) which will be assessed through prescription or dispensing data.	Assessed during the patient's baseline period [-2555, -1].
Number of Prior Advanced UC Therapy Prescriptions	Continuous variable representing the total number of prescriptions or dispensations of advanced UC therapies.	Assessed during the patient's baseline period [-2555, -1].

Note that additional categorical variables defining exposure to the different conventional and advanced UC therapies will be created and may be used to build the propensity score model (see Section 9.7.3.1.1).

9.3.4 Clinical Characteristics During Follow-up

The following characteristics (Table 9.3.4-1) will be assessed during follow-up (see Section 9.3.4) and reported descriptively.

Table 9.3.4-1: Clinical Characteristics Collected During Follow-up

Clinical Variables	Definition	Timing
Subsequent UC Treatments (post-discontinuation of ozanimod or other treatments)	Categorical variable capturing the subsequent UC treatment name used by a patient after index treatment discontinuation. Detailed rules for assessing lines of treatment will be included in the SAP.	Collected during the follow-up period
Subsequent Colectomy (post-discontinuation of ozanimod or other treatments)	Binary variable representing whether a patient had a subsequent colectomy and date of subsequent colectomy after discontinuation of index treatment.	Collected during the follow-up period
Subsequent High-grade Dysplasia (HGD)	Binary variable representing whether a patient had an HGD and date of HGD.	Collected during the follow-up period
Concomitant Medications (during exposure to ozanimod or other treatments)	The following concomitant medications will be assessed using ATC codes: • Anticoagulants, • Angiotensin-converting enzyme (ACE) inhibitors, • Beta-blockers, • Calcium channel blockers, • Statins, and • Chemotherapy/immunotherapy for treatment of malignancy. • UC conventional treatment Detailed rules for defining concomitant medication exposure will be included in the SAP.	Collected at index date and during the follow-up period

9.4 Data Sources

The planned data sources for the study are established general population healthcare claims or electronic medical records databases, or national health registries in European countries in which ozanimod is launched or anticipated to be launched, and in countries where reimbursement status has been granted or is anticipated to be granted by the time of data collection (see Section 9.3.4). The specific data sources found suitable for inclusion include are outlined below.

- German Pharmacoepidemiological Research Database (GePaRD), Germany: access provided by the Leibniz Institute for Prevention Research and Epidemiology- BIPS (BIPS),
- Danish Registries, Denmark: access provided by the University of Southern Denmark (SDU),
- PHARMO Data Network, Netherlands: access provided by the PHARMO Institute,
- Norwegian Registries, Norway: access provided by the Norwegian Institute of Public Health (NIPH),
- Clinical Practice Research Datalink (CPRD), United Kingdom (UK): access provided by RTI-Health Solutions,
- Scottish Prescribing Information System, UK-Scotland: access provided by the University of Dundee,
- *Système National des Données de Santé* (SNDS), France: access provided by the Bordeaux PharmacoEpi platform (BPE) from Bordeaux University.

Given the long timescale of this study, the number of countries in which ozanimod is marketed will evolve. Countries in which the drug is not yet approved for UC, such as France, could be brought into the study at a later date. The descriptions below were provided by the data holders.

9.4.1 GePaRD (Germany)

GePaRD was established and is maintained by the Leibniz Institute for Prevention Research and Epidemiology – BIPS (BIPS). GePaRD is based on medical claims data from 4 German statutory health insurance (SHI) 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 1 of the participating providers since 2004 or later.[31] Per data year, there is information on approximately 20% of the general population.

For the identification of relevant drugs 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 drug use have shown that the database is representative of the German population and that the insurance population is stable over time.[32,33] For each insured person, GePaRD contains demographic information; information about all hospitalizations, including in-hospital procedures (OPS [*Operationen-und Prozedurenschlüssel* codes]); information about outpatient visits with procedures (EBM [German Uniform Evaluation Standard] codes); and reimbursed outpatient dispensations. All diagnoses are coded according to ICD-10-German modification (GM).

GePaRD is updated every year and is linked via the central pharmaceutical number (PZN) to information from the CPR database. The contents of GePaRD and the CPR are as follows:

- Sociodemographic data: year of birth, sex, SHI 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 (German modification) (at least 4 digits);
- Outpatient prescription drug data: PZN, pharmacy identification number, date of prescription and dispensation, physician identification number and speciality, quantity prescribed. Data on underlying medical indications are not available;
- Pharmaceutical information (from CPR): PZN, generic name, brand, manufacturer, size, strength, DDD, pharmaceutical formulation, and ATC GM code;
- Outpatient medical treatment data: diagnostic certainty, dates of treatment, and types of treatment/diagnostic procedures with exact dates (EBM codes, developed for payment of physicians for the outpatient treatment of German SHI patients). Ambulatory diagnoses are coded in ICD-10-GM (at least 4 digits) and are collected by calendar quarter; the exact dates of diagnoses are not available.

9.4.2 Danish Registries (Denmark)

The project will leverage the nationwide Danish registries hosted by the Danish National Board of Health Data (DNBHD). All prescriptions redeemed in primary care pharmacies by Danish residents since 1995 have been recorded and are available for research,[34] in addition to diagnoses from all hospital admissions since 1977 and all outpatient hospital contacts and emergency room visits since 1994.[35] In addition, a large variety of other data sources, such as secondary care lab tests, the cancer registry, data on migration, dates of death, and data on death certificates are available as well. For a given project, the data required to address the research question are made available in a pseudonymised format that the researcher can analyse through a remote desktop at the DNBHD server.[36] The data never leave the hosting server at DNBHD, but the researcher can mail the output from his/her analyses to his/her own computer, provided that no data that can potentially be referred to a given individual are sent.[36] In addition, several layers of real-time password protection are implemented. Thereby, the setup provides flexible access to individual-level high-quality healthcare data, while at the same time effectively assuring data confidentiality.

9.4.3 PHARMO Data Network (Netherlands)

The PHARMO Data Network is a population-based data source with combined anonymous electronic healthcare data from different primary and secondary healthcare settings in the Netherlands.[37] The different data sources, including data from general practitioners, inpatient 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 anonymized by STIZON, an ISO/IEC 27001 and NEN 7510 certified

foundation, compliant with 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 to follow-up more than 10 million persons of 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. The data collection period, catchment area and overlap between data sources differ. All electronic patient records in the PHARMO Data Network include information on age, sex, socioeconomic status and mortality. Other information available is dependent on the data source.

9.4.4 Norwegian Registries (Norway)

Norway has several healthcare registers and administrative databases that cover the entire population of Norway.[38] Registers can be linked together by the unique personal identity number issued to all citizens at birth or immigration and individual persons can be followed over time and between registers. Reporting to these registers is mandatory. All prescribed drugs dispensed from pharmacies to patients in ambulatory care have been collected in the nationwide Norwegian Prescription Database since 2004. The National Patient register has since 2008 collected information from all inpatient and outpatient hospital contacts as well as contacts with outpatient specialists.[39,40] Several other data sources can be linked using personal identifiers, such as the Norwegian Register for Primary Health Care, the Cancer Register, the Causes of Death Register, as well as socioeconomic data from Statistics Norway and dates of death or migration from the National Population Register. For a given project, the data required to address the research question is made available with project-specific identity numbers to protect the integrity of patients/participants.[41]

9.4.5 CPRD (United Kingdom)

The Clinical Practice Research Datalink (CPRD) collates the computerised medical records of a network of general practitioners (GPs) in the UK who act as the gatekeepers of health care and maintain patients' lifelong electronic health records. CPRD Aurum contains routinely-collected data from practices using Egton Medical Information Systems (EMIS) Web® electronic patient record system software. The data are sourced from over 1,500 primary care practices and include 46.7 million patients (including transferred out and deceased patients), of whom 15.7 million are currently registered and active.[42] General practitioners act as the first point of contact for any non-emergency health-related issue, which may then be managed within primary care and/or referred to secondary care, as necessary. Secondary care teams also provide information to GPs about their patients, including key diagnoses. The data in CPRD are updated monthly and include demographics, all GP/health care professional consultations, diagnoses and symptoms, results from laboratory tests, information about treatments (including prescriptions), data on referrals to other care providers, hospital discharge summaries, hospital clinic summaries, preventive treatment and immunisations, and death (date and cause).[43] Detailed information on prescriptions written by GPs, including prescribed dose and duration, is routinely recorded in the database and

coded using the Dictionary of Medicines and Devices. Read 2, Systemized nomenclature of medicine-clinical terms (SNOMED CT), and local EMIS codes are used for diagnoses.

Linkage of CPRD primary care data with other patient-level data sets is available for English practices that have consented to participate in the linkage scheme. In more than 80% of CPRD panel practices, the GPs have agreed to permit CPRD to link at the patient level other healthcare data sets (eg, hospitalisation records and national mortality data). This includes linkage to the Hospital Episode Statistics (HES) database contains details of all admissions to the National Health Service (NHS) hospitals in England (accident and emergency, admitted subject care, and outpatient). Additional CPRD-linked data sets include death registration data from the Office for National Statistics, which includes information on the official date and causes of death (using ICD codes). These data are linkable via the patient's National Health Service number, sex, date of birth, and postal code. Updated, valid, linked CPRD data are available through the CPRD Division of the UK Medicines and Healthcare products Regulatory Agency (MHRA).

The validity of the CPRD as a reliable data source for drug safety studies in numerous therapeutic areas is well established.[44,45,46,47] The CPRD is listed under the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) resources database, and access will be provided by RTI-Health Solutions (HS).

9.4.6 Scottish Prescribing Information System (United Kingdom-Scotland)

The Scottish record linkage system contains electronic coded information on all outpatient prescriptions and all nonpsychiatric hospitalizations in Scotland. The following information, among others, is included in the hospitalization data: birth date, age, sex, main condition, reason for admission, other conditions present, investigative procedures and treatments, and admission and discharge dates.[48] Outpatient diagnoses are not available, except by accessing individual GP medical records on an ad hoc basis. Case validation for hospitalizations can be obtained by accessing the original case records. The fact and date of death and underlying cause of death can be identified by linkage to the national death register. Prescriptions issued by the GP and dispensed by pharmacies are contained in the prescription database. They are entered into the system by the GP, pulled down by the pharmacist from the cloud computing system, and then dispensed; if the prescription is handwritten or the practice is not yet set up to utilize the cloud computing system, then the pharmacist enters it into the prescription database. All prescriptions are centrally scanned. In Scotland, all community prescribing is done by GPs; this may be done on the advice of a specialist.[49] Each record contains the strength, number dispensed, and patient instructions.

9.4.7 SNDS (France)

The *Système National des Données de Santé* (SNDS) is the French nationwide healthcare claims database. It currently covers the overall French population (about 67 million persons) from birth (or immigration) to death (or emigration), even if a subject changes occupation or retires.[50,51] Using a unique pseudonymised identifier, the SNDS merges all reimbursed outpatient claims from all French health care insurance schemes, hospital-discharge summaries from French public and private hospitals, and the national death register. SNDS data contains information on general characteristics (eg, gender, year of birth, area of residence); registration for Long-term Disease

(LTD) with ICD-10 code, qualifying for full insurance coverage; outpatient encounter details (eg, medical and paramedical visits, medical and imaging procedures, laboratory tests, drugs dispensed [including ozanimod] medical devices); inpatient details (eg, hospital discharge ICD-10 diagnostic codes, procedures and laboratory tests performed, innovative or expensive drugs and medical devices invoiced in addition to the hospitalisation, length of the hospital stay), including outcomes of interest. For each expenditure, dates, associated costs, and prescriber and caregiver information are provided.

SNDS data can be accessed in different versions, corresponding to the different levels of data quality check ("consolidation") and different lag times:

- Complete and consolidated SNDS data for Year N are available in Q4 Year N+1 (ie, consolidated data from the Year 2022 will be available at the end of 2023). This is the version ensuring the highest level of data accuracy and completeness.
- Unconsolidated SNDS data for a month N are available with a 4-month lag, with the first data of the year made available in May (ie, unconsolidated data from Q1 2022 will be available in Q3 2022). This version relies on data that have not passed through all the validation steps executed by the *Caisse Nationale d'Assurance Maladie* (CNAM), hospital diagnoses may be missing or inexact. This version should not be used to work on outcome assessment.

Access to these data sources is strictly regulated by French law and needs approval from the Committee in Health data research (*Comité Ethique et Scientifique pour les Recherches, les Etudes et les Evaluations dans le domaine de la Santé* – CESREES), and from the French data protection commission (*Commission Nationale de l'Informatique et des Libertés* – CNIL). Four to 6 months are required to obtain CESREES and CNIL approvals. An agreement between the CNAM and the SNDS research partner then needs to be signed to access data extraction. BPE will oversee requesting access to SNDS data.

9.5 Study Size

The size of the exposed population will depend on the use of ozanimod for UC during the study period. BMS expects the market share of ozanimod to increase by 1% to 4% per year over the next few years. The exact exposure to ozanimod is a result of this study. Nevertheless, the database sample size estimates are presented in Table 9.5-1.

Table 9.5-1: Database Sample Size Estimates

Database (Country)	Number of Individuals in Each Database: # Total	# with UC (years considered)	# with UC ≥ 18 Years	# With UC ≥ 18 Years Treated With UC Advanced Therapy[a] (if available)	Ozanimod Status in UC Indication
GePaRD, (Germany)	17 million per data year; 25 million in total across all data years	69,281 (2020)[b]			Reimbursement for UC indication since Nov-2021
Danish Registries, (Denmark)	5.8 million	31,005 (2017)	> 90% (2013)	*Approximatively 2000*[c]	Reimbursement for UC indication since Sep-2022 recommended as alternative to biological (Medicinrådet)
PHARMO, (Netherlands)	4.2 million	14,000 (2016-2021)	13,840		Reimbursement for UC indication since Jun-2022. UC indication (adult patients with moderately to severely active UC who have had an inadequate response, lost response, or were intolerant to either conventional therapy or a biologic agent)
Norwegian Registries, (Norway)	5.5 million	26,548 (2017)[15]			Reimbursement for UC indication since 26-Sep-2022
CPRD, (UK)	13.3 million	52,801 (2018)[52]	52,273		Treatment of moderately to severely active UC in adults, when conventional or biological treatments cannot be tolerated or are not working well enough[d] Reimbursement for UC indication since Jan-2023
Scottish Prescribing Information System, (Scotland)	5.48 million	23,673 (2018)[53]	23,496[53]		UC indication since Oct-2022 with restriction
SNDS, (France)	67 million	110,000 (2008-2013)[16] 84,090 (2019) 55% women, 99% ≥ 18 years[e]	83,000		No UC indication on 01-Jun-2023

[a] Infliximab, Adalimumab, Golimumab, Vedolizumab, Ustekinumab, Tofacitinib

[b] Considering 20% of coverage of GePaRD

[c] https://medicinraadet.dk/media/0odjhdea/medicinr%C3%A5dets-behandlingsvejledning-vedr-l%C3%A6gemidler-til-colitis-ulcerosa-vers-1-1_adlegacy.pdf (in Danish)

[d] NICE Ozanimod for treating moderately to severely active ulcerative colitis. Technology appraisal guidance [TA828] published: 05-Oct-2022. https://www nice.org.uk/guidance/ta828

[e] http://www.observatoire-crohn-rch.fr/les-mici-en-france/ (in French)

Abbreviations: CPRD, Clinical Practice Research Datalink; GePaRD, German Pharmacoepidemiological Research Database; PHARMO, Network of Healthcare Databases in the Netherlands; SNDS, French Administrative Healthcare Database; UC, Ulcerative Colitis; UK, United Kingdom.

The prevalence of UC is estimated to be 0.2% to 0.6% in the countries involved in the study. For instance, in a recent assessment of tofacitinib by the *Haute Autorité de Santé* (HAS), UC appears to affect 1 to 2 out of 1,000 patients in France, including less than 10,000 patients with moderate or severe UC for whom steroid and immunosuppressant therapy have failed.[54] Around 15% of patients with UC would benefit from ozanimod or advanced treatments.

Background rates for severe liver injuries,[55] malignancies, infections, VTEs, and MACE have been respectively estimated to be around 0.94, 6.4, 34.7, 13.6, and 24 per 1,000 patient-years in populations of patients using TNFi for UC or Crohn's disease.[56,57,58,59] The other outcomes (PRES, macular oedema, PML) are expected to be rare with low incidence rates.

The sample sizes presented in Table 9.5-2 are based on the estimates provided by the research partners and coordinated by SIGMA. It shows the minimum number of patients in the ozanimod and advanced therapy groups needed for given ranges of incidence rates (IRs) and hazard ratios (HRs), with alpha=5%, an 80% statistical power, and an expected average follow-up of 4 years. The estimates are stratified by the percentage of patients receiving ozanimod over time (a projection at this point).

As an example, if we use the background incidence rate of VTE to ≥ 13.6 per 1,000 person-years and estimate that ozanimod has a 5% share of the market during the study period, we would be able to detect a crude HR ≥ 1.6 for the outcome of VTE with 682 ozanimod-exposed and 12,850 advanced therapy-exposed patients.

These assumptions will be further elaborated and tested in the SAP.

Table 9.5-2: Detectable Crude Hazard Ratio and Minimum Number of Subjects Exposed in Ozanimod and Advanced Therapy Groups, According to Incidence Rates of Several Events, and the Proportion of Patients in the Ozanimod Group, with Alpha = 5%, and Power = 80%

Background Incidence Rate (/1,000 PYs)	% Oza	HR											
		1.4		1.6		1.8		2		2.5		3	
		Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy
0.01 (other rare outcomes)	5%	1789488	34000000	910534	17300000	575795	10940000	410530	7800000	229032	4300000	155529	2920000
	10%	1855556	16700000	931112	8380000	584445	5260000	413334	3720000	225556	2030000	151112	1360000
	15%	1923530	10900000	961765	5450000	598236	3390000	418236	2370000	225883	1280000	147134	833754
0.1 (other rare outcomes)	5%	178959	3400000	91059	1730000	57373	1090000	40953	777909	22891	434731	15562	295480
	10%	185556	1670000	93131	838171	58445	525997	41264	371368	22587	203275	15058	135514
	15%	192353	1090000	95896	543406	59673	338142	41792	236816	22452	127223	14718	83397
0.94 (severe liver injury)	5%	19066	362216	9677	183825	6128	116394	4365	82897	2440	46322	1659	31483
	10%	19739	177644	9926	89326	6230	56062	4399	39583	2409	21673	1606	14446
	15%	20506	116196	10222	57920	6361	36041	4456	25246	2395	13567	1571	8897
6.5 (malignancy)	5%	2790	52623	1416	26699	897	16906	639	12038	358	6736	244	4585
	10%	2888	25991	1453	13070	913	8209	645	5797	354	3178	237	2125
	15%	3002	17006	1497	8478	933	5282	654	3701	352	1990	232	1310
13.6 (VTE)	5%	1352	25491	682	12850	433	8151	308	5793	173	3246	118	2208
	10%	1400	12592	701	6301	440	3952	311	2791	171	1531	115	1027
	15%	1455	8240	722	4086	450	2545	316	1786	171	964	113	635

Table 9.5-2: Detectable Crude Hazard Ratio and Minimum Number of Subjects Exposed in Ozanimod and Advanced Therapy Groups, According to Incidence Rates of Several Events, and the Proportion of Patients in the Ozanimod Group, with Alpha = 5%, and Power = 80%

Background Incidence Rate (/1,000 PYs)	% Oza	HR											
		1.4		1.6		1.8		2		2.5		3	
		Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy	Oza	Adv Therapy
24.0 (MACE)	5%	783	14745	398	7477	253	4746	180	3371	101	1884	69	1281
	10%	812	7300	409	3673	257	2305	182	1630	101	901	68	604
	15%	844	4778	422	2386	264	1491	185	1043	101	567	67	375
34.7 (serious infection)	5%	554	10434	282	5302	179	3359	128	2397	72	1340	49	906
	10%	574	5158	290	2602	182	1630	129	1153	72	640	48	424
	15%	597	3378	299	1689	187	1055	132	743	72	403	48	267

Abbreviations: Adv therapy, Advanced therapy (comparator); Oza, Ozanimod; PY, person-year.

Note: This table shows the number of Ozanimod and Advanced therapy users needed to obtain an alpha risk of 0.05 with 80% power for different scenarios of incidence of events, HR and % of patients in the Ozanimod group, with average follow-up period is 4 years, true risk is 1.0 and 0% dropout *(software: NQuery v9.2.1.0 (Statistical Solutions Ltd – Sheet STT5 / Two sample test of survival curves using Cox regression).*[60,61]

9.6 Data Management

Files from different data sources will be kept behind separate firewalls. Each research partner will analyse data from its own data source. Individual-level data will not be merged across data sources.

Routine procedures will include checking electronic files, maintaining security and data confidentiality, following the analysis plan, and performing quality control checks of all scripts. The study is conducted by multiple research partners, and each research partner will maintain any patient-identifying information securely on-site according to internal/local standard operating procedures (SOPs) or guidance documents. Security processes will be in place to ensure the safety of all systems and data. Every effort will be made to ensure that data are kept secure so that they cannot be accessed by anyone except selected study staff.

Appropriate data storage and archiving procedures will be followed, with a periodic backup of files. Standard procedures will be in place at each research centre to restore files in the event of hardware or software failure.

Each research partner will follow its own established procedures and generate results according to the analysis plan and specifications. All aggregated data sets of results, and no individual patient identifiers, will be provided to the Principal Investigator Centre, which will compile the aggregated data and prepare the tables of results and develop the reports in collaboration with research partners.

For requests to access to data for audit purposes, only aggregated data from all research centres will be available at the coordinating centre. The audit trail will consist of a detailed description of the methods to extract and process the electronic health records or claims data, as applicable. Access to raw data at each database research centre will require the data requestor to obtain a licence or apply for approval from a research committee and to fulfil the conditions required under the governance rules of each database research centre.

9.6.1 GePaRD (Germany)

At BIPS, only validated software is used for statistical analyses. Data management and analyses are conducted using SAS 9.4 or later versions (SAS Institute Inc.; Cary, North Carolina [NC], United States [US]). According to BIPS SOPs, all study data sets are created using double-independent programming, and statistical analyses are validated by a second statistician. All outputs are reviewed by at least 1 epidemiologist and a senior epidemiologist.

9.6.2 Danish Registries (Denmark)

Among the principles of programming is that no information is ever entered manually into tables but instead filled tables are generated directly by programming. Thereby, transfer errors are avoided. Programming is structured such that the entire package can be run from 1 single command. Thereby, all analytic steps from raw data verification to final table output are accounted for in the scripts.

9.6.3 PHARMO (Netherlands)

The PHARMO Data Network combines data from different primary and secondary healthcare settings (pharmacy, hospital, GP etc).[37] These data sources are probabilistically linked through validated algorithms that do not invade the privacy of the patients. Before linkage of the different data sources, patients for whom crucial information needed for linkage is missing (date of birth, sex, GP) are removed.

Healthcare databases are used as administration tools in patient care and have limitations regarding their use in scientific research. For example, the completeness of data may differ per healthcare centre. Therefore, with each update of the data, the completeness of registration per healthcare centre is evaluated (overall and within specific care areas, number of records, internal consistency and comparison of calendar years).

For each study, specific study checks on the linked data are performed. These partially depend on which specific data is required for the study and their importance to the selection of patients or outcomes. For each data source it is determined per patient from which time point onwards the patient is registered in the specific data source and from which time point the patient is lost to follow-up (due to for example death or moving out of the PHARMO catchment area). Patients are regarded as eligible to be included in a study if they are registered and can be followed in all required data sources.

Study data are manipulated and analysed using the utility SAS Enterprise Guide, an environment for SAS enabling the storage of syntaxes or codes belonging to a single study in 1 project file, subdivided into project flows for different aspects of a study.

9.6.4 Norwegian Registries (Norway)

Data management and analyses are conducted using Stata Version 17 or R Version 4 or later versions. All data management and statistical analysis steps will be executed on the secure servers. The programming of scripts is performed by an experienced programmer with code revision by a second programmer. Statistical analysis is supervised by an experienced epidemiologist or statistician. Tables and figures are populated directly by programming without manual transfer of information. All steps from data verification and transformation to final analytical program are accounted for in scripts. Analytical programs should be possible to run as 1 package that can be run as a single command. Scripts and a copy of the linked database used for each analysis (interim and final analyses) are locked and stored for later validation if needed.

9.6.5 CPRD (United Kingdom)

RTI-HS will be the responsible centre for the analysis of CPRD data. Data management will be conducted in accordance with RTI-HS standard operating procedures. Routine procedures include checking electronic files, maintaining security and data confidentiality, following the statistical epidemiological analysis plan, and performing quality control (QC) checks of all programmes. All programming written by 1 study analyst will be independently reviewed by a different analyst. All analyses will be conducted using SAS Version 9.4 or later versions (SAS Institute Inc., Cary, NC, US).

9.6.6 Scottish Prescribing Information System (United Kingdom-Scotland)

Anonymised patient-level data are made available through the National Services Scotland (NSS) National Safe Haven coordinated by the electronic Data Research and Innovation Service (eDRIS). This Safe Haven provides a secure working environment with restricted ability to move or copy files or other material in to or out of the working area. Data available for linkage include routinely collated NHS Scotland data, and birth, death and other data from National Records Scotland (NRS). Bespoke linkages are also possible with correct approvals. Data can be accessed remotely by approved researchers only from the University of Dundee. eDRIS, a service provided by Public Health Scotland, act as a single point of contact, and assist researchers in study design, approvals and data access in the secure environment. Analysis within the Safe Haven is possible using statistical analysis software such as SAS. Approval is required from NHS Scotland Public Benefit and Privacy Panel, an independent panel which scrutinises research projects/proposals wishing to access to NHS-controlled data.

9.6.7 SNDS (France)

The BPE has implemented a quality management system for all its activities and is certified ISO 9001:v2015 for its activities in pharmacoepidemiologic research. The SNDS database extraction criteria will be described in a data extraction plan approved prior to initiating extraction. After data extraction, the CNAM will provide the requested SNDS raw data to the BPE research platform. All data management and statistical analysis steps will be executed on the BPE-secured server according to internal/local SOPs and ENCePP guidance. Data management reports are automatically edited, and programme logs are saved on the BPE server. All documents are reviewed and validated by several data managers/statisticians. In case of a data problem (eg, missing data, files), BPE informs the CNAM, which sends restored files within a short period of time. In case of inconsistency identified in the data set, programmes are adapted and processes are re-launched until the problem is solved. The database will be locked for statistical analysis. Data management and statistical analysis will be performed using SAS 9.4 or later versions (SAS Institute Inc.; Cary, NC, US). Independent double programming and/or programme code review will be performed by a second statistician for main criteria and analyses, and the results compared for validation. All statistical logs are kept and can be provided. In the case of interim analyses, the database for the interim analysis is locked and kept for later validation, if needed. The statistical analysis report is included in the final study report.

9.7 Data Analysis

9.7.1 General Considerations

Statistical analysis will be performed using R (The R Foundation for Statistical Computing Platform, latest current version) or SAS® (SAS Institute, most recent version, NC, US) software. The analyses described below will be executed independently by each data access provider in the data sources they access. Data will be presented observing the specific rules for small cell counts of data sources. The proceeding aggregated results will then be pooled for final meta-analysis and reporting.

The final approach to statistical analysis will be presented in a separate SAP, to be developed prior to data collection. All planned analyses (main, secondary, and sensitivity) are summarized in APPENDIX 5.

9.7.2 Descriptive Analysis

Patients may initiate more than 1 therapeutic regimen during the study period but can contribute only 1 treatment episode to each of the cohorts (ozanimod or advanced therapy). The unit of observation will be the treatment episode, not the patient. Treatment episodes meeting the inclusion and exclusion criteria (Section 9.2.2) will contribute information to the analysis for the relevant treatment group (Table 9.2.2.1-1). Advanced therapy cohort will be described overall and by advanced therapy.

9.7.2.1 Baseline Characteristics

The clinical and demographic variables defined in Section 9.3.3.1 will be reported by treatment cohort (Table 9.3.3.1-1) using descriptive statistics both before and after weighting by inverse probability of treatment (IPTW) (Section 9.7.3.1.2). Categorical variables will be summarized by frequencies and proportions of each modality. For continuous variables, missing values, means, standard deviations, median, interquartile range, percentile 25 and percentile 75 will be estimated.

Missing data will not be imputed unless otherwise specified. For each clinical or demographic variable that will be reported, missing data will be quantified. If there is at least 1 patient with a missing value for a given characteristic, a missing category will be added and the number of unique patients with missing values will be reported. Metrics reported for continuous variables will be calculated if there is at least 1 non-missing value in a treatment cohort.

An attrition chart will be provided, depicting the number of subjects included in each analysis by treatment cohort. Some of the analyses may be limited due to a small number of exposed episodes, events and/or data privacy-driven cell count restrictions at each research partner's place.

9.7.2.2 Crude Incidence Rate

Crude incidence rates will be calculated for each outcome by treatment cohort before and after IPTW. Crude incidence rates and their corresponding 95% confidence intervals (CIs) will be calculated as the ratio between the number of incident outcomes that occurred during the considered at-risk period and the total number of at-risk person-days in this period.

For malignancies, a lag-time period will be defined from the index date regarding the possible association between the treatment and the risk of malignancy, as well as a latent period after the presumed exposed period (see Section 9.3.2.2).

9.7.3 Primary Analysis: Comparative Risk Analysis

An attrition table will show how treatment episodes are included in each of the 2 treatment cohorts. The number of unique patients across the treatment cohorts will also be reported.

9.7.3.1 Propensity Score Methodology

9.7.3.1.1 Propensity Score

For the comparative analyses, each qualifying treatment episode (unit of observation) will be assigned a propensity score (PS) at the index date. PS is a measure of the probability that a patient will receive ozanimod *versus* an advanced therapy, according to baseline demographic and clinical covariates considered as potential confounders. PS will be used for the IPTW to reduce potential confounding.[62]

Propensity scores will be estimated using a logistic regression model. The model will include covariates that could act as potential confounders (independent variables), with ozanimod use versus advanced therapy use as the dependent variable.

The timeframe for measurement of covariates is described in Section 9.3.3.2, and only variables known (or highly suspected) to be confounders will be included in the propensity score model. A single propensity score model will be used for all outcomes in the comparison of ozanimod-exposed episodes to advanced therapy episodes. Variables for the propensity score modelling will include prespecified variables from Sections 9.3.1, 9.3.3.1 and 9.3.3.2, in particular:

- Sex
- Age
- UC severity (as defined in Table 9.3.3.1-1)
- Year of UC diagnosis
- History of malignancies (excluding non-melanoma skin cancer), history of diagnoses of VTE (see Section 9.3.1)
- History of SOI, history of diagnoses of MACE, history of severe liver injury, history of macular oedema, history of PRES (see Section 9.3.1)
- History of hepatic disease or impairment
- Other major comorbidities (see Section 9.3.3)
- UC drugs used in the 7 years prior to the index date with potential impact on main outcomes (see Table 9.2.2.1-1)
- Variables known to be associated with the outcomes and known prognostic variables judged clinically pertinent (to be discussed with clinician experts).

For the propensity score model, the pairwise distributions of PS for patients initiating ozanimod and advanced therapy will be examined side by side to evaluate the degree of overlap. This evaluation may be done graphically. Limited overlap in the propensity score distributions can result in decreased precision of study estimates. If a limited overlap between propensity score distributions is observed (eg, less than 50% of the data in the region of overlap), then the PS model may be regenerated after removing/adding variables. This process will be detailed further in the SAP.

9.7.3.1.2 Inverse Probability of Treatment Weighting (IPTW)

IPTW estimates the average treatment effect (ATE). The ATE reflects the effect of the treatment in the scenario that every patient within the population received the exposure of interest (ozanimod). In essence, this shifts the entire population from comparator-exposed to ozanimod-exposed.[21] IPTW will be considered and estimated at the index date for each treatment episode.[62,63] Stabilized weights will be calculated for each individual as the *proportion of ozanimod-exposed episodes/PS* for the ozanimod-exposed group and the *proportion of ozanimod unexposed episodes /(1 - PS)* for the advanced therapy-exposed group. The application of these weights to the study population creates a pseudo-population in which confounders are equally distributed across exposed and unexposed groups.

IPTW has several advantages. First, unlike matching, weighting keeps most observations in the analysis and hence, can offer increased precision when estimating treatment effects. Second, unlike regression adjustment by the propensity score, weighting lends itself to transparent reporting of the balance achieved between treatment and reference populations. As an additional measure, extreme weights may also be addressed through truncation (ie, trimming). Weights are typically truncated at the 1st and 99th percentiles,[64] although other lower thresholds (2.5th and 97.5th percentiles) can be used to reduce variance.

9.7.3.1.3 Standardized Differences

Prior to outcome analyses, the covariate balance between the cohorts (before and after IPTW) will be evaluated using standardized differences for continuous covariates and standardized differences of proportion for each (non-missing) category for categorical covariates. Standardized differences greater than 0.10 between the cohorts will indicate imbalance and will be adjusted for. Further detail on covariate balance methodology will be provided in the SAP.

9.7.3.2 Measure of Association

Hazard ratios (HRs) and corresponding 95% CIs will be calculated before and after IPTW, comparing the risk of outcomes between the ozanimod-exposed episode cohort and the advanced therapy-exposed episode cohort, for the following primary outcomes:

- Malignancies, overall
- SOIs, overall
- MACE, overall
- VTE, overall
- Severe liver injury

HRs and associated 95% CIs will be estimated using the Cox proportional hazards model. Imbalanced covariates after weighting will be incorporated for adjustment in the models. Robust variance estimators will be used to address any lack of independence induced by weighting and the inclusion of patients in multiple cohorts (at different times).[65]

Model diagnostics will be performed evaluating the proportional hazards assumptions, nonlinearity, and presence of outliers. In case of a small number of outcomes, a Firth's correction

will be applied. Specifically for the assessment of colorectal cancer outcome, the occurrence of proctocolectomy will be considered as a competing event and a Fine-Gray sub-distribution hazard model will be used.

Time-to-event data will also be summarized by Kaplan-Meier methodology. Kaplan-Meier curves and time-to-event probabilities at key time points will be presented to approximate cumulative incidence rates. In presence of competing risks, cumulative incidence functions (CIF) curves will be estimated. Additional modelling methodology will be specified in the SAP.

9.7.4 Secondary Analyses: Stratification and Subcategories Analyses

The following analyses mainly intended to address the secondary objectives.

9.7.4.1 Age-subgroup Analyses

Age-subgroup analyses will be conducted on cohorts before and after IPTW, to report all outcomes associated with the primary objective. Incidence rates, time-to-event, HRs and 95% CIs will be presented according to the following subgroups:

- Patients aged 55 years and older
- Patients aged less than 55 years

Comparison of the HRs between the 2 age subgroups will be processed by using HR's Ratio (HRR) and associated 95% CIs.

9.7.4.2 Year of Cohort Entry-subgroup Analyses

Treatment pattern over the first years of commercialisation of a medicinal product may differ from the others. To account for this, year of cohort entry-subgroup analyses will be conducted on cohorts before and after IPTW, to report all outcomes associated with the primary objective. Incidence rates, time-to-event, HRs and 95% CIs will be presented according to the following subgroups:

- Patients with a cohort entry in the first 2 years of commercialisation of ozanimod
- Patients with a cohort entry after 2 years of commercialisation of ozanimod

Comparison of the HRs between these 2 subgroups will be processed by using HRR and associated 95% CIs.

9.7.4.3 Previous Outcome History-subgroup Analyses

Previous outcome onset-subgroup analyses will be conducted on cohorts before and after IPTW, to report all outcomes associated with the primary objective. Incidence rates, time-to-event, HRs and 95% CIs will be presented according to the following subgroups:

- Patients with previous history of the outcome of interest
- Patients without previous history of the outcome of interest

Comparison of the HRs between these 2 subgroups will be processed by using HRR and associated 95% CIs.

9.7.4.4 Rare Outcomes Analyses

As they are expected to be rare, the following outcomes will be described in terms of frequency, baseline and clinical characteristics, in ozanimod-exposed patients and those treated with advanced therapy:

- macular oedema
- posterior reversible encephalopathy syndrome (PRES)
- progressive multifocal leukoencephalopathy (PML).

If sufficient sample size allows, the risk of these outcomes will be compared between the ozanimod-exposed group and the advanced therapy-exposed group, using same methods as for the primary analyses. Otherwise, models adapted for rare outcomes will be used such as Poisson regression model, that will estimate incidence rate ratios and their corresponding 95% CIs, before and after IPTW.

9.7.4.5 Subgroup Analysis by Presence or Absence of Prior Advanced Ulcerative Colitis Treatment

Stratified analyses based on the presence or absence of prior advanced UC treatment exposure (see Table 9.2.2.1-1) will be conducted on cohorts before and after IPTW, to report all outcomes associated with the primary objective. Incidence rates, time-to-event, HRs and 95% CIs will be presented according to the following subgroups:

- Patients with no previous exposure to any cohort-defining treatment before the index date
- Patients with previous exposure to a cohort-defining treatment before the index date

For example, patients exposed to ozanimod with prior advanced therapy exposure will be compared to patients initiating advanced therapy with prior exposure to another advanced therapy.

9.7.4.6 Risk of Outcomes by Subtype

Crude incidence rates, time-to-event and HRs (with corresponding 95% CIs) will be estimated before and after IPTW, among the 2 treatment cohorts, for the following outcome subtypes:

- Malignancies
  - Solid malignancies excluding non-melanoma skin cancer (NMSC)
  - NMSC
  - Colorectal cancer
  - Advanced colonic neoplasia, ie, composite endpoint including colorectal cancer and high-grade dysplasia, and
  - Lymphoma
- MACE
  - Acute nonfatal myocardial infarction
  - Acute nonfatal stroke
  - CV mortality

Specifically for colorectal cancer outcome, the occurrence of a proctocolectomy during follow-up will be considered as a competing event and will censor the considered at-risk period.

9.7.5 Sensitivity Analyses

The following sensitivity analyses are planned for the final report and will be further detailed in the SAP:

- In the main analysis, for all outcomes except malignancies, exposure is defined as time at risk and is assumed to start on the day of treatment cohort entry (index date) and continue until 30 days after the presumed end of drug supply (grace period). A sensitivity analysis will extend the at-risk period to 90 days after the end of supply.
- In the main analysis, for malignancies, exposure is defined as time at risk and is assumed to start on the first day following the 6-month lag-time period and continue until the end of the at-risk period for hematologic and solid malignancies outcomes after the presumed end of drug supply: 1 or 2 years, respectively. A sensitivity analysis will extend this latent period to 2 years for haematologic malignancies and 5 years for solid tumours.
- In the main analysis, for malignancies, the occurrence of an outcome during overlapping time-at-risk periods is counted in the numerators of both treatment-exposed cohorts. A sensitivity analysis will exclusively attribute malignancy that occurs in overlapping time-at-risk periods to 1) ozanimod, and 2) the alternative treatment.
- In the main analysis, the occurrence of malignancy may be ascertained based on a single ICD-10 diagnosis code. As a sensitivity analysis, a more restrictive operational definition will be used in non-registry data requiring the presence of at least 2 diagnosis codes for malignancy outcome(s) of interest will be applied.
- In the main analysis, conventional therapy for UC during exposure periods will be considered as concomitant exposure. It will not be considered as a switch nor censor the exposure period. A sensitivity analysis will exclude patients with concomitant conventional therapy at the index date and censor the at-risk period at conventional therapy dispensing.
- In the main analysis, ozanimod is compared to advanced therapies that include oral and non-oral medications (see Table 9.2.2.1-1). A sensitivity analysis will also present results to assess the risk of outcomes of interest between ozanimod and oral advanced therapies only, recalculating PS.
- In the main analysis, ozanimod-exposed patients will not be able to move into the advanced therapy cohort (because they have already been under S1P). However, the opposite - moving from the advanced therapy cohort to the ozanimod cohort - is not excluded (see Section 9.3.2.1). As a sensitivity analysis, an as-treated design with the same inclusion/exclusion criteria, considering only the first continuous episode of advanced therapy or ozanimod (whichever comes first) will be conducted. Patients will be followed until discontinuation, switch to the other treatment of interest, death or end of follow-up and so, only contributed to a single treatment group.

9.7.6 Meta-analysis

Qualitative and quantitative approaches to determining whether meta-analysis is appropriate and specific evaluation criteria will be provided in the SAP. In brief, the results will be synthesized if

the individual studies are similar in terms of population, intervention, comparators, outcomes, and study design (PICOS).[66]

Planned analyses in each primary data source will be conducted according to this common protocol to facilitate future comparison and potential integration of results. While the studies in each data source are designed to be similar, external factors could impact the appropriateness of combining results from the different data sources (eg, if national treatment guidelines change resulting in different study populations across the different data sources).

If meta-analytic techniques are deemed appropriate based on the PICOS criteria, meta-analytic techniques will be used to combine the results obtained from the primary analysis performed in the cohort study in the different data sources.[67] No individual-level data will be pooled across data sources, and an appropriate method to combine effect estimates across data sources will be applied, depending on features of the estimates, including the homogeneity of the estimates across populations.

Data source-specific estimates (incidence rates and HRs with 95% CIs) will be analysed, and a summary of the data (tabular and forest plots) along with pooled estimates and 95% CIs will be provided, as well as diagnostic measures of heterogeneity (if there are more than 2 data sources).[68] Results from both random effects and fixed effects meta-analysis will be reported. For the interim reports, no meta-analysis will be performed. Additional details of the planned meta-analyses will be outlined in the SAP.

9.7.7 Reporting of Small Cell Counts

Local data protection rules may impose small cell count restrictions on participating data sources. These measures are summarised in Table 9.7.7-1.

Table 9.7.7-1: Small Cell Count Rules for Reporting

	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
Numbers to be Masked	No	1-4	No	1-4	1-4	1-4	1-10
Text to be Used in Redactions	No	< 5	N.A.	< 5	< 5	< 5	≤ 10
Possible to Share with Ozanimod PASS Research Centres	Yes	No	Yes	Maybe	Yes	No	No
Possible to Share with Regulatory Authorities.	Yes	No	Yes	Maybe	Yes	No	No

Table 9.7.7-1: Small Cell Count Rules for Reporting

	GePaRD (Germany)	Danish Registries (Denmark)	PHARMO (Netherlands)	Norwegian Registries (Norway)	CPRD (UK)	Scottish Prescribing Information System (Scotland)	SNDS (France)
Note: report is provided to authorities by MAH (BMS)							
Comments	No small cell rules	Not possible to export any original data or any small cells.	If stratification of study sample such as age group (so N of an entire row or column) is < 5 then data will be reported as < 5.	Sharing must be negotiated with ethics committee and register holders	Cells that may lead to calculation of a cell count of 1 to 4, must be suppressed before publication.		

Abbreviations: CPRD, Clinical Practice Research Datalink; GePaRD, German Pharmacoepidemiological Research Database; SNDS, Système National des Données de Santé; UK, United Kingdom.

9.7.8 Missing Data

The databases included in this PASS were chosen for the completeness of the data related to the exposures and outcomes of interest and missing data are expected to be minimal. In these medico-administrative databases and registries, data are collected prospectively and systematically following patient healthcare encounters, ensuring the quasi-exhaustiveness and the quality of the information of interest. Moreover, the inclusion criteria requiring at least 365 days of history period ensures that the included patient will have enough data to compute propensity score and perform the comparative analyses. In the presence of records for a given medical condition, it is assumed the medical condition is present, and in the absence of such records, it is assumed that the medical condition is absent. Otherwise, where relevant, the percentage of missing data will be reported.

9.8 Quality Control

Rigorous quality control will be applied to all deliverables. Data transformation will be conducted by each subcontracted research partner in its associated database, with processes as described in the following corresponding Sections. Standard operating procedures or internal process guidance at each research centre will be used to guide the conduct of the study. These procedures include rules for secure and confidential data storage, backup, and recovery; methods to maintain and archive project documents; quality control procedures for programming; standards for writing analysis plans; and requirements for scientific review by senior staff.

9.8.1 Leibniz Institute for Prevention Research and Epidemiology (BIPS)

At BIPS, all analyses are conducted according to the Guidelines for Good Pharmacoepidemiology Practices (GPP), Good Practice of Secondary Data Analysis (GPS),[69] Guidelines and Recommendations for Ensuring Good Epidemiological Practice (GEP),[70] as well as the ENCePP Guide on Methodological Standards in Pharmacoepidemiology.[71] All procedures from data delivery to data entry in GePaRD, as well as the conduct of PASS projects based on data from GePaRD, are governed by SOPs. To ensure content quality, each project is supervised by a senior epidemiologist and, if necessary, a senior statistician. All project staff members receive comprehensive orientation training and are regularly trained.

9.8.2 University of Southern Denmark (SDU)

The integrity and quality of raw data are assured at the DNBHD. In addition, an initial quality control is performed, ensuring that all requested data is available and that, for example, not a portion of prescription or hospital data is missing. The analytic programming is conducted by 1 of 4 experienced programmers with extensive training in epidemiological methodology.

Among the principles for programming is that no information is ever entered manually into tables but instead filled tables are generated directly by programming. Thereby, transfer errors are avoided. Programming is structured such that the entire package can be run from 1 single command. Thereby, all analytic steps from raw data verification to final table output are accounted for in the scripts.

Programming and statistical analysis are supervised by an experienced senior epidemiologist, and all analytic code is reviewed by a second programmer. All errors and all changes to the analysis or SAP are logged.

9.8.3 PHARMO

PHARMO adheres to high standards throughout the research process based on robust methodologies, transparency and scientific independence. PHARMO conducts studies in accordance with the ENCePP Guide on Methodological Standards in Pharmacoepidemiology and the ENCePP Code of Conduct. PHARMO is ISO 9001:2015 certified. Standard operating procedures, work instructions and checklists are used to guide the conduct of a study. These procedures and documents include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, rules and procedures for execution and quality control of SAS programming, standards for writing protocols and reports, and requirements for senior scientific review of key study documents.

9.8.4 Norwegian Institute of Public Health (NIPH)

The size of the population in the extracted raw data and the number of exposed and outcomes will be checked against the expected numbers from aggregate statistics published by the various register holders. The programming of scripts is performed by an experienced programmer with code revision by a second programmer. Statistical analysis is supervised by an experienced epidemiologist or statistician. Tables and figures are populated directly by programming without manual transfer of information. All steps from data verification and transformation to final

analytical program are accounted for in scripts. Analytical programs should be possible to run as 1 package that can be run as a single command. Scripts and a copy of the linked database used for each analysis (interim and final analyses) are locked and stored for later validation if needed.

9.8.5 RTI-Health Solution

Standard operating procedures or internal process guidance at RTI-HS 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, QC procedures for programming, standards for writing analysis plans, and requirements for senior scientific review.

For RTI-HS, an independent Office of Quality Assurance will perform audits and assessments that involve various aspects of the project, including but not limited to education and training documentation, data entry and data transfer procedures and documentation, and institutional review board documentation. Such audits will be conducted by the Office of Quality Assurance according to established criteria in SOPs and other applicable procedures. Appropriate data storage and archiving procedures will be followed, with periodic backups of files. Standard procedures will be in place to restore files in the event of a hardware or software failure.

9.8.6 University of Dundee

Investigators at the University of Dundee will perform study activities following internal standard operating procedures (SOPs), with bespoke SOPs being developed when needed. 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. Procedures will be consistent with the International Society for Pharmacoepidemiology (ISPE) Guidelines for Good Pharmacoepidemiology Practices and the ENCePP Code of Conduct. All programming written by 1 study analyst will be independently reviewed by a different analyst, with oversight by a senior statistician. All project deliverables will be reviewed internally by a secondary reviewer and a senior reviewer, and documented according to internal SOPs. The quality of the underlying data will remain the responsibility of eDRIS and NSS.

9.8.7 Bordeaux PharmacoEpi, Université de Bordeaux

As the scientific lead centre, all key study documents will undergo a quality control review, senior scientific review, and editorial review. Senior reviewers with expertise in the appropriate subject matter area will provide advice on the design of research study approaches, the conduct and management of the study, and will review results, reports, and other key study documents.

As the Research Partner (if applicable) for French data from the SNDS database, the BPE has implemented a quality management system for all its activities and is certified ISO 9001:v2015 for its activities in pharmaco-epidemiology research. CNAM data extraction will be validated using the expected population size estimated using the SNDS. All statistical logs are kept and can be provided. In the case of interim analyses, the database for the interim analysis is locked and kept for ulterior validation if needed.

9.9 Limitations of the Research Methods

This study is subject to limitations related to the study design and the use of secondary healthcare data:

- Confounding
  - All observational studies are potentially subject to confounding because treatment assignment is not randomized. In this study, propensity score weighting will be implemented to facilitate the control of confounders.[21] The propensity score is a statistical technique that attempts to estimate the probability to be treated by a drug versus another by accounting for the covariates that predict receiving the treatment. Weighting (IPTW) adjusts potentially unbalanced risk factors between the groups being compared, which addresses the confounding potentially induced by this absence of randomization, as long as the risk factors have been correctly identified and captured.
  - Channelling bias may be present due to the observational nature of the study design. Drugs with similar therapeutic indications may be prescribed to groups of patients with prognostic differences, thus limiting treatment-to-treatment comparisons. For instance, patients initiating treatment with a newly marketed drug might have more severe or "resistant" disease than patients initiated on more routine or established treatment regimens. Moreover, dissimilar indications (eg, treatment of adult patients with moderately to severely active UC who have had an inadequate response *versus* first-line treatment of adult patients with moderately to severely active UC) may lead to the prescription of drugs to patients with different baseline risks (confounding by indication). To maximize the chance to comprehensively address confounding, the comparisons between ozanimod and comparators will be conducted between groups with similar treatment line ranks. This will be achieved by including treatment lines preceding the index date for a given exposure period to the propensity score.
- Misclassification: The identification of study variables from automated health databases for research is vulnerable to misclassification. This misclassification risk is particularly high for outcomes for which the ICD-10 code is not specific (eg, macular oedema, PRES). Hence, outcome definition codes and algorithms will be carefully reviewed with each data partner. Whenever available, validated algorithms will be used to increase the reliability of variable definitions, and *ad-hoc* case validation of outcomes will be conducted when required. Despite the coding accuracy, it may be impossible to retrieve actual UC patients who have been coded as having unspecified inflammatory bowel disease, as well as distinguishing macular oedema and PRES from other specified retinal disorders and other specified cerebrovascular diseases respectively.
- Measurement error: Exposure information captured by the claims databases used here is of high quality. When a drug is recorded as dispensed, the patient likely received it. However, it is impossible to assume that the patient will be fully observant. This study assumes that patients use medications as directed but this cannot be confirmed. Measurement error in medication use and adherence is therefore a potential source of exposure misclassification. Such assumptions are typical of observational studies and do provide an assessment of what happens in real-world settings.

- Generalizability to Europe:
  - For GePaRD (Germany), included patients are representative of the German population with statutory health insurance (German Gesetzliche Krankenversicherung) in terms of age, sex and dispensations of medication. The SNDS (France) provides exhaustive coverage of the French population and all patients meeting the inclusion and exclusion criteria will be included. Current patients in CPRD Aurum cover approximately 23% of the UK population; included patients are representative of the English population in terms of age, sex, geographical spread and deprivation. The Scottish Prescribing Information System (SPIS) covers the entire Scottish population. The PHARMO Data Network includes data from over 7 million of the 17 million inhabitants of the Netherlands and is nationally representative with regard to demographic characteristics and primary care diagnoses.[37,72] The Norwegian registers cover the entire Norwegian population. The Danish Registries cover the entire Danish population.
  - Changes in clinical guidelines and newly approved UC medicines may appear throughout the study period, potentially impacting UC management before the initiation of our drugs of interest or after. Variables related to previous UC management, especially exposure to UC drugs, will be included in the PS. As a consequence, the comparative analyses will be adjusted for these potential changes. In the event that a patient is exposed to a newly marketed UC drug after the index date, this exposure will censor the follow-up. This will ensure that the potential effects of this new drug are not wrongly attributed to our drugs of interest.
  - As of 01-Jun-2023, ozanimod was not granted reimbursement for UC in France, therefore, SNDS database will not contribute to the results until this status changes. The absence of France during the first years of the study will not impact other national analyses, though the overall precision of the final meta-analyses will be reduced. The long-term nature of the study will enable incremental recruitment of newly exposed patients in countries already involved or new ones, allowing adequate precision to be achieved for the final report.
- Lost to Follow-up: A small number of patients may be lost to follow-up in these secondary databases. For GePaRD (Germany), patients may be lost-to-follow-up due to an end of insurance coverage, switching of statutory health insurance company, emigration or death. For France, Norway, Scotland, and Denmark data sources, patients may be lost to follow-up due to emigration or death. In CPRD and PHARMO, patients may be lost to follow-up due to transfer out to other practices not contributing to the database, emigration, or death.

9.10 Other Aspects

None.

10 PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the EMA Guidelines on Good Pharmacovigilance Practices (GVP) Module VIII: Post-Authorisation Safety Studies,[73] the Medicines and Healthcare products Regulatory Agency Guidance on the use of real-world data in clinical studies to support regulatory decisions,[42] the GPP issued by the International Society for Pharmacoepidemiology (ISPE),[74] the ENCePP Guide on Methodological

Standards in Pharmacoepidemiology,[75] the Declaration of Helsinki and its amendments, and any applicable national guidelines, laws and regulations.

This study will be registered in the European Union electronic Register of Post-Authorization Studies (EU PAS Register)[76] before data collection starts, and the research team, as well as the study sponsor, should adhere to the general principle of transparency and independence of the ENCePP Code of Conduct.[77]

10.1 Ethics Committee Review and Informed Consent

Each Research Partner should perform all required ethics/regulatory reviews according to local regulations. This study is a non-interventional study using secondary data collection and for which subject informed consent is not required.

10.2 Responsibilities Within the Study

The study shall be conducted as described in this approved protocol. All revisions to the protocol must be discussed with and prepared by BMS.

10.3 Confidentiality of Study Data

All patient-level data collected in the study will be de-identified with no breach of confidentiality concerning personal identifiers or health information. Data protection and privacy regulations (General Data Protection Regulation, GDPR) will be respected for this study. Only aggregate results will be shared with the project coordinating centre and Sponsor.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study is based on the secondary use of data without any spontaneous reporting. Study outcomes will be reported in aggregate in the final study report, and no individual or expedited reporting is required, according to the EMA GVPs,[73,78] as well as the ENCePP *Guide on Methodological Standards in Pharmacoepidemiology*.[77]

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

Annual progress reports will include updates on available data sources and counts of patients in the exposed and comparator treatments in each data source. Interim reports will include descriptive analyses of each cohort (including mean patient follow-up time) and adjusted comparative analyses for all primary outcomes by data source, if feasible. No meta-analyses are planned for the interim reports. Study reports will exclusively rely on aggregated results. No patient-level data will be shared. Results from this PASS will be disseminated at scientific meetings and in published literature. Scientific Publications (such as abstracts, congress podium presentations and posters, and manuscripts) of the study results will be a collaborative effort between the study Sponsor and the external authors. No public presentation or publication of any interim results may be made by any principal investigator, sub-investigator, or any other member of the study staff without the prior written consent of the Sponsor.

Authorship of publications at BMS is aligned with the criteria of the International Committee of Medical Journal Editors (ICMJE, www.icmje.org). Authorship selection is based upon significant

contributions to the study (ie, ICMJE Criterion #1). Authors must meet all 4 ICMJE criteria for authorship:

1) Substantial intellectual contribution to the conception or design of the work; or the acquisition of data (eg, evaluable subjects with quality data or data generation), analysis, or interpretation of data for the work (eg, problem-solving, advice, evaluation, insights, and conclusion); AND
2) Drafting the work or revising it critically for important intellectual content; AND
3) Final approval of the version to be published; AND
4) Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Those who make the most significant contributions, as defined above, will be considered for authorship of the publication.

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APPENDIX 1 RESPONSIBLE PARTIES

Centre	Role	Address	Name, Title
Bristol-Myers Squibb (BMS)	Sponsor		• [redacted] Senior Director, Epidemiology Strategy, TA Head, Immunoscience
Bordeaux PharmacoEpi (BPE)	Project Coordinating Centre Principal Investigator Centre Research Partner (data provider, depending on the marketing) France	Université Bordeaux Bâtiment Le Tondu Case 41 146, rue Léo Saignat 33076 Bordeaux cedex France	• Nicolas Thurin, Scientific Officer, Principal investigator • Laure Carcaillon-Bentata, Scientific Officer • Patrick Blin, Senior Scientific Consultant • Cecile Droz-Perroteau, Director • Caroline Dureau-Pournin, Project Manager • Estelle Guiard, Assistant Project Manager • Régis Lassalle, Biostatistics & Data management Chief • Jérémy Jové, Senior Statistician
Leibniz Institute for Prevention Research and Epidemiology - BIPS (BIPS)	Research Partner (data provider) Germany	Achterstraße 30 28359 Bremen Germany	• Prof. Dr. Ulrike Haug, Head of department of clinical epidemiology • Jonas Reinold, Epidemiologist, project manager
University of Southern Denmark (SDU)	Research Partner (data provider) Denmark	JB Winsløwsvej 19 5000 Odense Denmark	• Jesper Hallas, Senior Consultant in Clinical Pharmacology, Professor of Clinical Pharmacology • Metter Reilev
The PHARMO Institute (PHARMO)	Research Partner (data provider) Netherlands	Van Deventerlaan 30 /40 3528 AE Utrecht Netherlands	• Josine Kuiper, Senior Business Development Manage • Ben van Nieuwenhuizen
Norwegian Institute of Public Health (NIPH)	Research Partner (data provider) Norway	PO Box 222 Skøyen N-0213 Oslo	• Øystein Karlstad, Senior Researcher • Kari Furu, Senior Researcher • Ingvild Odsbu, Senior Researcher • Erle Refsum, Researcher
RTI Health Solutions	Research Partner (data provider) United Kingdom	Av. Diagonal 605, 9-1 08028, Barcelona Spain	• Elena Rivero, Senior Director, Epidemiology

Centre	Role	Address	Name, Title
University of Dundee	Research Partner (data provider) Scotland	Nethergate Dundee DD1 4HN United Kingdom	• Thomas MacDonald • Rob Flynn, Superintendent Pharmacist • Isla Mackenzie, Clinical Professor • Rebecca Barr, Senior Research Manager

APPENDIX 2 MEDICATIONS AND DIAGNOSES CODE LISTS

Code List for Specific DMT Drugs (for MS exclusion criteria)

ATC Code	Description
IM Treatments (injectables)	
L03AB07	Interferon beta-1a
L03AB08	Interferon beta-1b
L03AX13	Glatiramer acetate
L03AB13	Pegylated interferon beta-1a
L04AC01	Daclizumab
IS Treatments	
Oral	
L04AA31	Teriflunomide
L04AA27	Fingolimod
L04AX07	Dimethyl fumarate
Injectables	
L04AA34	Alemtuzumab
L04AA23	Natalizumab

Abbreviations: ATC, Anatomical Therapeutic Chemical; DMT, Disease Modifying Treatment; IM, immunomodulator; IS, immunosuppressant

Code Lists for Malignancies

ICD-10 Code	Description
C00-C14	Malignant neoplasms of lip, oral cavity and pharynx
C15	Malignant neoplasm of oesophagus
C16	Malignant neoplasm of stomach
C17	Malignant neoplasm of small intestine
C18	Malignant neoplasm of colon
C19	Malignant neoplasm of rectosigmoid junction
C20	Malignant neoplasm of rectum
C21	Malignant neoplasm of anus and anal canal
C22	Malignant neoplasm of liver and intrahepatic bile ducts
C23	Malignant neoplasm of gallbladder
C24	Malignant neoplasm of other and unspecified parts of biliary tract

Code Lists for Malignancies

C25	Malignant neoplasm of pancreas
C26	Malignant neoplasm of other and ill-defined digestive organs
C30-C39	Malignant neoplasms of respiratory and intrathoracic organs
C40-C41	Malignant neoplasms of bone and articular cartilage
C43-C44	Melanoma and other malignant neoplasms of skin
C45-C49	Malignant neoplasms of mesothelial and soft tissue
C50-C50	Malignant neoplasms of breast
C51-C58	Malignant neoplasms of female genital organs
C60-C63	Malignant neoplasms of male genital organs
C64-C68	Malignant neoplasms of urinary tract
C69-C72	Malignant neoplasms of eye, brain and other parts of central nervous system
C73-C75	Malignant neoplasms of thyroid and other endocrine glands
C76-C80	Malignant neoplasms of ill-defined, other secondary and unspecified sites
C7A-C7A	Malignant neuroendocrine tumours
C7B-C7B	Secondary neuroendocrine tumours
C81-C96	Malignant neoplasms of lymphoid, hematopoietic and related tissue
D00-D09	In situ neoplasms
D37-D48	Neoplasms of uncertain behaviour, polycythaemia vera and myelodysplastic syndromes

ATC Code	**Description**
L01CD04	cabazitaxel
L02BX03	abiraterone acetate
L02BX02	degarelix
L02BB01	flutamide
L02BB02	nilutamide
L02BB03	bicalutamide
L02BB04	enzalutamide
L02AE01	buserelin
L02AE02	leuprorelin
L02AE03	goserelin
L02AE04	triptorelin
L02AE05	histrelin
L01XX11	estramustine
L02AA01	diethylstilbestrol

Code Lists for Malignancies

L02AA04	fosfestrol
V10BX01	strontium (89 sr) chloride
V10XX	various therapeutic radiopharmaceuticals
G03HA01	cyproterone acetate

Abbreviations: ATC, Anatomical Therapeutic Chemical; ICD-10, International Classification of Disease-10th Revision.

Code Lists for Serious Opportunistic Infections

ICD-10 Code	Description
A15	Respiratory tuberculosis, bacteriologically and histologically confirmed
A150	Tuberculosis of lung, confirmed by sputum microscopy with or without culture
A151	Tuberculosis of lung, confirmed by culture only
A152	Tuberculosis of lung, confirmed histologically
A153	Tuberculosis of lung, confirmed by unspecified means
A154	Tuberculosis of intrathoracic lymph nodes, confirmed bacteriologically and histologically
A155	Tuberculosis of larynx, trachea and bronchus, confirmed bacteriologically and histologically
A156	Tuberculous pleurisy, confirmed bacteriologically and histologically
A157	Primary respiratory tuberculosis, confirmed bacteriologically and histologically
A158	Other respiratory tuberculosis, confirmed bacteriologically and histologically
A159	Respiratory tuberculosis unspecified, confirmed bacteriologically and histologically
A16	Respiratory tuberculosis, not confirmed bacteriologically or histologically
A160	Tuberculosis of lung, bacteriologically and histologically negative
A161	Tuberculosis of lung, bacteriological and histological examination not done
A162	Tuberculosis of lung, without mention of bacteriological or histological confirmation
A163	Tuberculosis of intrathoracic lymph nodes, without mention of bacteriological or histological confirmation
A164	Tuberculosis of larynx, trachea and bronchus, without mention of bacteriological or histological confirmation
A165	Tuberculous pleurisy, without mention of bacteriological or histological confirmation
A167	Primary respiratory tuberculosis without mention of bacteriological or histological confirmation
A168	Other respiratory tuberculosis, without mention of bacteriological or histological confirmation
A169	Respiratory tuberculosis unspecified, without mention of bacteriological or histological confirmation
A17	†Tuberculosis of nervous system
A178	†Other tuberculosis of nervous system
A18	Tuberculosis of other organs

Code Lists for Serious Opportunistic Infections

ICD-10 Code	Description
A180	†Tuberculosis of bones and joints
A181	†Tuberculosis of genitourinary system
A182	Tuberculous peripheral lymphadenopathy
A183	Tuberculosis of intestines, peritoneum and mesenteric glands
A184	Tuberculosis of skin and subcutaneous tissue
A185	Tuberculosis of eye
A186	Tuberculosis of ear
A188	Tuberculosis of other specified organs
A19	Miliary tuberculosis
A190	Acute miliary tuberculosis of a single specified site
A191	Acute miliary tuberculosis of multiple sites
A192	Acute miliary tuberculosis, unspecified
A198	Other miliary tuberculosis
A199	Miliary tuberculosis, unspecified
A319	Mycobacterial infection, unspecified
A43	Nocardiosis
A430	Pulmonary nocardiosis
A431	Cutaneous nocardiosis
A438	Other forms of nocardiosis
A439	Nocardiosis, unspecified
A812	Progressive multifocal leukoencephalopathy
B00	Herpesviral [herpes simplex] infections
B000	Eczema herpeticum
B001	Herpesviral vesicular dermatitis
B002	Herpesviral gingivostomatitis and pharyngotonsillitis
B003	Herpesviral meningitis
B004	Herpesviral encephalitis
B005	Herpesviral ocular disease
B007	Disseminated herpesviral disease
B008	Other forms of herpesviral infection
B009	Herpesviral infection, unspecified
B25	Cytomegaloviral disease
B372	B37.2 Candidiasis of skin and nail
B377	B37.7 Candidal septicaemia

Code Lists for Serious Opportunistic Infections

ICD-10 Code	Description
B451	B45.1 Cerebral cryptococcosis
B457	B45.7 Disseminated cryptococcosis
B580	B58.0 Toxoplasma oculopathy
B59	B59 Pneumocystosis
H000	H00.0 Hordeolum and other deep inflammation of eyelid
H601	H60.1 Cellulitis of external ear
J13	J13 Pneumonia due to Streptococcus pneumoniae
J14	J14 Pneumonia due to Haemophilus influenzae
J15	J15 Bacterial pneumonia, not elsewhere classified
J150	J15.0 Pneumonia due to Klebsiella pneumoniae
J151	J15.1 Pneumonia due to Pseudomonas
J153	J15.3 Pneumonia due to streptococcus, group B
J154	J15.4 Pneumonia due to other streptococci
J157	J15.7 Pneumonia due to Mycoplasma pneumoniae
J159	J15.9 Bacterial pneumonia, unspecified
J16	J16 Pneumonia due to other infectious organisms, not elsewhere classified
J160	J16.0 Chlamydial pneumonia
J168	J16.8 Pneumonia due to other specified infectious organisms
J17	J17 Pneumonia in diseases classified elsewhere
J170	J17.0 Pneumonia in bacterial diseases classified elsewhere
J173	J17.3 Pneumonia in parasitic diseases
K122	K12.2 Cellulitis and abscess of mouth
L030	L03.0 Cellulitis of finger and toe
L030	L03.0 Cellulitis of finger and toe
L031	L03.1 Cellulitis of other parts of limb
L032	L03.2 Cellulitis of face
L033	L03.3 Cellulitis of trunk
L038	L03.8 Cellulitis of other sites
L039	L03.9 Cellulitis, unspecified

APPENDIX 3 DERIVATION OF EXPOSURE LENGTH USING USUAL DAILY DOSES

Treatment Cohort	Generic Name	ATC Code	Dosing and Assigned Days' Supply	Strength	Form	Usual Daily Dose	Presentation	Exposure Time (days)
Ozanimod	Ozanimod[a]	L04AA38	0.23 mg once daily (days 1 to 4)	0.23 mg	capsule	0.23 mg per day	4	4
			0.46 mg once daily (days 5 to 7)	0.46 mg	tablet	0.46 mg per day	3	3
			0.92 mg daily, or once every 2 days for mild or moderate hepatic impairment	0.92 mg	tablet	0.92 mg per day	28	28
Advanced Therapy	Ustekinumab[b]	L04AC05	Initiation: Weight ≤ 55 kg: initial dose 260 mg once. Weight > 55kg to ≤ 85 kg: initial dose 390 mg once. Weight > 85 kg: initial dose 520 mg once.	130 mg	vial	Maintenance dose starting 8 weeks after treatment initiation	1	56
				45 mg [c]	syringe		1	42
			Maintenance:	45 mg [c]	vial		1	42
			Week 8: 90 mg	90 mg	pen	1.07 mg per day	1	84
			Week 8 onwards: 90 mg every 12 weeks (or every 8 weeks)	90 mg	syringe	1.07 mg per day	1	84
	Golimumab[d]	L04AB06	Weight < 80 kg: Week 0: 200 mg Week 2: 100 mg Week 2 onwards: 50 mg every 4 weeks	50 mg	pen	1.78 mg per day	1	28
				50 mg	syringe	1.78 mg per day	1	28
				100 mg	pen	3.57 mg per day	1	28
				100 mg	syringe	3.57 mg per day	1	28
			Weight > 80 kg: Week 0: 200 mg Week 2: 100 mg Week 2 onwards: 100 mg every 4 weeks					

Treatment Cohort	Generic Name	ATC Code	Dosing and Assigned Days' Supply	Strength	Form	Usual Daily Dose	Presentation	Exposure Time (days)
	Filgotinib[e]	L04AA45	200 mg once per day except for people aged 65 and more, reduced dose 100 mg once per day	100 mg	tablet	100 mg per day	30	30
				200 mg	tablet	200 mg per day	30	30
	Upadacitinib[f]	L04AA44	Initiation: 45 mg every day over 8 weeks (could be extended to 16 weeks)	45 mg	tablet	45 mg per day	28	28
				15 mg	tablet	15 mg per day	28	28
			Maintenance: from 15 to 30 mg per day	30 mg	tablet	30 mg per day	28	28
	Vedolizumab[g]	L04AA33	Week 0, 2, 6: 300 mg Week 6 onwards: 300 mg every 8 weeks Possibility to switch to subcutaneous injections after at least 2 infusions: 108 mg every 2 weeks	300 mg	vial	5.36 mg per day	1	56
				108 mg	pen	7.7 mg per day	1	14
				108 mg	syringe	7.7 mg per day	1	14
				108 mg	vial	7.7 mg per day	1	14
				108 mg	vial	7.7 mg per day	1	14
	Tofacitinib[h]	L04AA29	From 10 to 20 mg per day	5 mg	tablet	10 mg per day	56	28
				10 mg	tablet	20 mg per day	56	28
	Adalimumab[i] (or biosimilar)	L04AB04	Induction: Week 0: 2×80 mg on day 1 or 1×80 mg on day 1 and 1×80 mg on day 2. Week 2: 80 mg Week 2 onwards: 40 mg every 2 weeks (or 80 mg every 2 weeks)	80 mg	pen	8.57 mg per day	3	28
				80 mg	pen	5.71 mg per day	1	7
				80 mg	syringe	5.71 mg per day	1	7
				40 mg	syringe	2.85 mg per day	1	14
				40 mg	syringe	2.85 mg per day	2	28
				40 mg	syringe	2.85 mg per day	4	56
				40 mg	syringe	2.85 mg per day	6	84
				40 mg	pen	2.85 mg per day	1	14
				40 mg	pen	2.85 mg per day	2	28
				40 mg	pen	2.85 mg per day	4	56
				40 mg	pen	2.85 mg per day	6	84

Treatment Cohort	Generic Name	ATC Code	Dosing and Assigned Days' Supply	Strength	Form	Usual Daily Dose	Presentation	Exposure Time (days)
	Infliximab[j]	L04AB02	Week 0, 2, 6: 5 mg/kg. Week 6 onwards: 5 mg/kg every 8 weeks	100 mg	vial			56
			120 mg every 2 weeks	120 mg	pen	8.57 mg per day	1	14
				120 mg	pen		2	28
				120 mg	syringe		1	14
				120 mg	syringe		2	28

[a] ZEPOSIA 0.23, 0.46, 0.95 mg hard capsules. EPAR. October 2021. Available from URL : https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf

[b] STELARA 130 mg concentrate for solution for infusion. EPAR. December 2022. Available from URL: https://www.ema.europa.eu/en/documents/product-information/stelara-epar-product-information_en.pdf

[c] Usually not recommended for UC management

[d] SIMPONI 45 mg/0.45 mL solution for injection in pre-filled pen. EPAR. November 2023. Available from URL: https://www.ema.europa.eu/en/documents/product-information/simponi-epar-product-information_en.pdf

[e] JYSELECA 100, 200 mg film-coated tablets. EPAR. May 2023. Available from URL: https://www.ema.europa.eu/en/documents/product-information/jyseleca-epar-product-information_en.pdf

[f] RINVOQ 15, 30, 45 mg prolonged-release tablets. EPAR. August 2023. Available from URL: https://www.ema.europa.eu/en/documents/product-information/rinvoq-epar-product-information_en.pdf

[g] ENTYVIO 300 mg powder for concentrate for solution for infusion. EPAR. September 2023. Available from URL: https://www.ema.europa.eu/en/documents/product-information/entyvio-epar-product-information_en.pdf

[h] XELJANZ 5, 10 mg film-coated tablets. EPAR. October 2023. Available from URL: https://www.ema.europa.eu/en/documents/product-information/xeljanz-epar-product-information_en.pdf

[i] Humira 20 mg solution for injection in pre-filled syringe. EPAR. October 2022. Available from URL: https://www.ema.europa.eu/en/documents/product-information/humira-epar-product-information_en.pdf

[j] Remicade 100 mg powder for concentrate for solution for infusion. EPAR. September 2022. Available from URL: https://www.ema.europa.eu/en/documents/product-information/remicade-epar-product-information_en.pdf

APPENDIX 4 ENCEPP CHECKLIST

Study title: Long-term real-world safety of ozanimod – A postauthorisation safety study (PASS) in patients diagnosed with ulcerative colitis

EU PAS Register® number:
Study reference number (if applicable):

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
	1.1.3 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 and 8
	2.1.1 Why the study is conducted? (eg, to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7 and 8
	2.1.2 The objective(s) of the study?	☒	☐	☐	8
	2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7 and 9.2.2

[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 2: Research Question		**Yes**	**No**	**N/A**	**Section Number**
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? (eg, 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, 9.2 and 9.4
3.3	Does the protocol specify measures of occurrence? (eg, rate, risk, prevalence)	☒	☐	☐	8 and 9.7
3.4	Does the protocol specify measure(s) of association? (eg, risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7
3.5	Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (eg, 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?	☒	☐	☐	9.1, 9.2 and 9.4
4.2	Is the planned study population defined in terms of:				
4.2.1	Study time period	☒	☐	☐	9.1, 9.2.1
4.2.2	Age and sex	☒	☐	☐	9.2.2

Section 4: Source and Study Populations	**Yes**	**No**	**N/A**	**Section Number**
4.2.3 Country of origin	☒	☐	☐	9.2
4.2.4 Disease/indication	☒	☐	☐	9.2.2
4.2.5 Duration of follow-up	☒	☐	☐	9.2.1
4.3 Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	9.2.2

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? (eg, operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.2
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	9.3.2
5.3 Is exposure categorised according to time windows?	☒	☐	☐	9.3.2
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	9.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.3.2
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.2.2 and 9.3.2

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?	☒	☐	☐	9.3.1
6.2	Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3.1
6.3	Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	9.3.1
6.4	Does the protocol describe specific outcomes relevant for Health Technology Assessment? (eg, HRQoL, QALYs, DALYS, health care services utilisation, 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? (eg, confounding by indication)	☒	☐	☐	9.7.3.1, 9.9
7.2	Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	9.9
7.3	Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.3.1, 9.9

Comments:

Section 8: Effect Measure Modification		**Yes**	**No**	**N/A**	**Section Number**
8.1	Does the protocol address effect modifiers? (eg, collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7

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? (eg, pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3 and 9.4
9.1.2	Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3 and 9.4
9.1.3	Covariates and other characteristics?	☒	☐	☐	9.3 and 9.4
9.2	Does the protocol describe the information available from the data source(s) on:				
9.2.1	Exposure? (eg, date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3 and 9.4
9.2.2	Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3 and 9.4
9.2.3	Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3 and 9.4
9.3	Is a coding system described for:				
9.3.1	Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.2 and 9.4
9.3.2	Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	9.3.1 and 9.4
9.3.3	Covariates and other characteristics?	☒	☐	☐	9.3.3 and 9.4
9.4	Is a linkage method between data sources described? (eg, 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?	☒	☐	☐	9.7
10.2	Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3	Are descriptive analyses included?	☒	☐	☐	9.7.2
10.4	Are stratified analyses included?	☒	☐	☐	9.7.4
10.5	Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7
10.6	Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	9.9
10.7	Does the plan describe methods for handling missing data?	☒	☐	☐	9.7.8
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? (eg, software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6 and 9.8
11.2	Are methods of quality assurance described?	☒	☐	☐	9.6 and 9.8
11.3	Is there a system in place for independent review of study results?	☒	☐	☐	9.8

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? (eg, anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.9
12.2 Does the protocol discuss study feasibility? (eg, study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.5 and 9.7.8 and 9.9

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?	☒	☐	☐	9.4 and 10
13.2 Has any outcome of an ethical review procedure been addressed?	☒	☐	☐	9.4 and 10
13.3 Have data protection requirements been described?	☒	☐	☐	9.4 and 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 (eg, to regulatory authorities)?	☒	☐	☐	12
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	12

Comments:

Name of the Main Author of the Protocol: Nicolas Thurin

Date: 06/07/2023

Signature: _____

APPENDIX 5 ANALYSES PLANNED

List of Analyses Planned

	Primary Definitions (outcome and exposure)	Extended At-risk Period	Extended Latent Period (malignancies)	Alternative Malignancy Definitions	Outcome Occurring During Overlapping Time-at-risk Periods	Excluding and Censoring at Concomitant Conventional Treatment Exposure	Comparator Groups Based on Route of Administration	As-treated Design (first continuous episode of treatment)
Main Analysis								
Overall Cohort								
• Baseline Characteristics	✓						✓	
• Outcomes IR (crude)	✓	✓	✓	✓	✓	✓	✓	✓
• Comparative Risk Analysis (IPTW, Cox model)	✓	✓	✓	✓	✓	✓	✓	✓
Secondary Analyses								
Subgroup Analyses for Elderly Patients								
• Baseline Characteristics	✓							
• Outcomes IR (crude)	✓							
• Comparative Risk Analysis (IPTW, Cox model)	✓							
Subgroup Analyses by Year of Cohort Entry								
• Baseline Characteristics	✓							
• Outcomes IR (crude)	✓							
• Comparative Risk Analysis (IPTW, Cox model)	✓							

	Primary Definitions (outcome and exposure)	Extended At-risk Period	Extended Latent Period (malignancies)	Alternative Malignancy Definitions	Outcome Occurring During Overlapping Time-at-risk Periods	Excluding and Censoring at Concomitant Conventional Treatment Exposure	Comparator Groups Based on Route of Administration	As-treated Design (first continuous episode of treatment)
Subgroup Analyses by Previous Outcome History								
• Baseline Characteristics	✓							
• Outcomes IR (crude)	✓							
• Comparative Risk Analysis (IPTW, Cox model)	✓							
Subgroup Analyses by Presence or Absence of Prior UC Advanced Treatment								
• Baseline Characteristics	✓							
• Outcomes IR (crude)	✓							
• Comparative Risk Analysis (IPTW, Cox model)	✓							
Risk of Outcomes by Subtype								
• Outcomes IR (crude)	✓							
• Comparative Risk Analysis (IPTW, Cox model)	✓							
Meta-analysis								
• Comparative Risk Analysis (Cox model)	✓							

Abbreviations: IPTW, inverse probability of treatment weighting; IR, incidence rate.