POST-AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

PASS INFORMATION

TITLE	A real-world observational study of treatment patterns and outcomes for patients with neuromyelitis optica spectrum disorders (NMOSD) treated with inebilizumab (UPLIZNA) in Europe
PROTOCOL VERSION IDENTIFIER	2.0
DATE OF LAST VERSION OF PROTOCOL	28 February 2023
EU PAS REGISTER NUMBER	Study not yet registered
ACTIVE SUBSTANCE	Inebilizumab (ATC code L04AA47 / L04AG10 [alteration in the ATC index from 2024])
MEDICINAL PRODUCT(S)	UPLIZNA
PRODUCT REFERENCE	N/A
PROCEDURE NUMBER	EMEA/H/C5818
MARKETING AUTHORIZATION HOLDER(S) (MAH)	Horizon Therapeutics Ireland DAC
JOINT PASS	No
RESEARCH QUESTION AND OBJECTIVES	The overall research questions for this study are: 1) What are the demographic, clinical, and treatment characteristics of a population of patients who initiate inebilizumab in real-world practice? 2) What are inebilizumab treatment patterns in the first 12 months following treatment initiation? 3) What is the incidence of adverse events of special interest (AESI) in the first 12 months following treatment initiation? Specific objectives are: • To describe demographic, clinical and treatment characteristics of patients at the time of first inebilizumab treatment • To describe inebilizumab treatment patterns in the first 12 months following treatment initiation in terms of dosing, duration of treatment, frequency of drug discontinuation, switching, and use of add-on therapies • To quantify the incidence of AESI, including serious infections, opportunistic infections, hepatitis B reactivations, serious infusion related reactions, and malignancies. Analyses will be performed in the overall study population and in sub-groups of special interest: patients concomitantly

	receiving other immunosuppressive agents and patients aged >65 years at index date.
COUNTRY(-IES) OF STUDY	France, Germany; Italy; the Netherlands; Spain.
AUTHOR	IQVIA [redacted]

MARKETING AUTHORIZATION HOLDER(S)

MARKETING AUTHORIZATION HOLDER(S)	Horizon Therapeutics Ireland DAC 70 St. Stephen's Green, Dublin 2, D02E2X4
MAH CONTACT PERSON	[redacted]

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LIST OF ABBREVIATIONS

Abbreviation	Definition
AESI	adverse event of special interest
AQP4	aquaporin-4 antibodies
ATC	Anatomic Therapeutic Chemical
CCI	Charlson Comorbidity Index
CI	confidence intervals
CRO	contract research organization
ERB	Ethics Review Boards
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
GM	German modification
GP	general practitioner
GPP	good pharmacoepidemiology practice
GVP	good pharmacovigilance practice
ICH	International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use
ICD	International Classification of Diseases
IEC	independent ethics committee
IRB	institutional review board
ISPE	International Society for Pharmacoepidemiology
IV	intravenous
KM	Kaplan-Meier
NMO	neuromyelitis optica
NMOSD	neuromyelitis optica spectrum disorder
MAH	marketing authorization holder
MOG	myelin-oligodendrocyte glycoprotein
MRI	magnetic resonance imaging
MS	multiple sclerosis
NOMADMUS	*Neuro-Optico-Myélite Aiguë de Devic et des syndromes neurologiques apparentés*
OFSEP	*Observatoire Français de la Sclérose en Plaques* (french multiple sclerosis registry)
OPS	operation and procedure classification system
PALGA	*Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief* (dutch nationwide pathology databank)
PAS	post-authorization study
PASS	post-authorization safety study
PHARMO	Dutch Institute for Drug Outcomes Research
PML	progressive multifocal leukoencephalopathy
PMSI	*Programme de Médicalisation des Systèmes d'Information* (Hospital discharge summaries database system)
PSUR	periodic safety update report
QPPV	qualified person for pharmacovigilance
RIMS	*Registro Italiano Sclerosi Multipla e Patologie Correlate* (Italian Multiple Sclerosis and Related Disorders Registry)
SAP	statistical analysis plan
SHI	Statutory Health Insurance
SIDIAP	*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària´* (The Information System for Research in Primary Care)
SNDS	*Système National des Données de Santé* (french national health data system)

SNIIRAM	*Système national d'information interrégimes de l'Assurance malady* (french National health insurance information system)
STROBE	STrengthening the Reporting of OBservational studies in Epidemiology
TTP	trusted third party
WHO	World Health Organization

RESPONSIBLE PARTIES

Name, degree(s)	Job Title	Affiliation	Address
[redacted]	[redacted]	[redacted]	[redacted]
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Study Coordination

Horizon Therapeutics has contracted IQVIA, contract research organization (CRO), a European Network of Centres of Pharmacoepidemiology and Pharmacovigilance (ENCePP). The CRO designed and will conduct the study with review and input from the MAH.

INVESTIGATOR SIGNATURE PAGE

Study Title: A real-world observational study of treatment patterns and outcomes for patients with neuromyelitis optica spectrum disorders (NMOSD) treated with inebilizumab (UPLIZNA) in Europe; Protocol version 2.0 dated 28 February 2023

I have read and understand the protocol and agree that it contains the ethical, legal and scientific information necessary to participate in this study. My signature confirms the agreement of both parties that the study will be conducted in accordance with the protocol and all applicable laws and regulations including, but not limited to Good Pharmacoepidemiology Practices (GPP), Good Pharmacovigilance Practices (GVP), the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ethical principles that have their origins in the Declaration of Helsinki and applicable privacy laws.

I will provide copies of this protocol as needed to all physicians, nurses, and other professional personnel responsible to me who will participate in the study. I will discuss the protocol with them to assure myself that they are sufficiently informed regarding the conduct of the study. I am aware that this protocol will need to be approved by an appropriate Ethics Committee prior to any patients being enrolled and that I am responsible for verifying whether that requirement is met. I agree to adhere to the attached protocol and if requested to provide copies of medical information for the purpose of verification of submitted information, I will comply.

Since the information in this protocol is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

Investigator:

[redacted]

Print Name

_____ _____

Signature Date

IQVIA

Print Name of Institution or Practice and Location

RETURN ORIGINAL TO HORIZON THERAPEUTICS

RETAIN A COPY

CLIENT SIGNATURE PAGE

Reviewed and Approved by:

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1 ABSTRACT

Full Study Title: A real-world observational study of treatment patterns and outcomes for patients with neuromyelitis optica spectrum disorders (NMOSD) treated with inebilizumab (UPLIZNA) in Europe

Protocol version 2.0 dated 28 February 2023

Main author: Olga Rocha, IQVIA

Rationale and background: New monoclonal antibody therapies have recently been approved for the treatment of NMOSD. Treatment with inebilizumab has demonstrated a significant impact on the frequency of relapses; however, knowledge gaps remain regarding real-world treatment patterns and outcomes for patients with NMOSD. To address this, we seek to characterize real-world inebilizumab use in Europe.

Research question and objectives: This study aims to characterize patients who initiate inebilizumab, describe treatment patterns and incidence of adverse events of special interest (AESI) in the first 12 months following treatment initiation.

Specific objectives are:

1. To describe patients at the time of first inebilizumab treatment in terms of demographics, comorbidities, NMOSD-related clinical characteristics, previous immunosuppressive therapies, and inebilizumab initiation characteristics (setting of healthcare and specialty of prescribers and treatment indication).
2. To describe inebilizumab treatment patterns in the first 12 months of starting treatment in terms of duration of treatment, dosing, frequency of drug discontinuation, switching, and use of add-on therapies.
3. To quantify the incidence of AESI including serious infections, opportunistic infections (including progressive multifocal leukoencephalopathy [PML]), hepatitis B reactivations, serious infusion related reactions, and malignancies.

Study design: This will be a non-interventional multi-center cohort study of patients initiating inebilizumab conducted with secondary data sources in France, Germany, Italy, the Netherlands, and Spain. The study will be based on a cohort-event monitoring design to capture both drug utilization and selected safety outcomes in patients initiating inebilizumab.

The overall study period will be from the date of inebilizumab market availability (the earliest Q3 2022) until December 2027 the latest. Index date will be defined as the date of inebilizumab initiation (first administration/prescription/dispensation depending on data available in selected data source). Patients will be followed for 12 months after the index date or censored if end of the study period or loss of follow-up (death, disenrollment/de-registering) whichever occurs first.

Population: The study population will be identified in national healthcare administrative databases, claim databases and disease-specific registries and will include adult (18 years old or more at the index date) female and male patients diagnosed with NMOSD and initiating inebilizumab during the study period.

Variables: Exposure to inebilizumab will be defined by the existence of records of administration/prescription/dispensation with the Anatomic Therapeutic Chemical (ATC) code L04AA47/ L04AG10 from 2024 onwards). Baseline characterization will consider demographics, comorbidities, NMOSD-related clinical characteristics (disease duration, NMOSD core symptoms and NMOSD-associated conditions, presence of autoantibodies against aquaporin-4 and myelin-oligodendrocyte glycoprotein, history of relapses), previous immunosuppressive therapies, and inebilizumab initiation characteristics (setting of healthcare and specialty of prescribers, and treatment indication).

Inebilizumab treatment patterns during a 12-month follow-up will be characterized in terms of duration, dosing, frequency of drug discontinuation, switching, and use of add-on therapies considering the dates of inebilizumab administration/prescription/dispensation and the respective estimated end dates of the drug exposure period.

AESI grouped in 5 categories (serious infections, opportunistic infections, hepatitis B reactivations, serious infusion related reactions, and malignancies) will be identified using the International Classification of Diseases, 9th or 10th revision codes. Serious infection, opportunistic infections, hepatitis B reactivations and serious infusion related reactions will be captured if leading to inpatient hospitalization or outpatient visit during the follow-up.

Data Sources: This study involves secondary use of data from data sources across 5 European countries:

- France: French National Health Data System (*Système National des Données de Santé* [SNDS]*)* and Multiple Sclerosis Registry (*Observatoire Français de la Sclérose en Plaques* [OFSEP])
- Germany: German Government Health Insurance (*Gesetzliche Krankenversicherung* [GKV])
- Italy: Italian Multiple Sclerosis and Related Disorders Registry (*Registro Italiano Sclerosi Multipla e Patologie Correlate* [RISM])
- The Netherlands: PHARMO Database Network
- Spain: Information System for Research in Primary Care (*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària* [SIDIAP])

Study size: In this study there is no a priori hypothesis testing and no prespecified sample size requirement. The final study size will be determined by the length of the study period and uptake of inebilizumab in the countries and population covered in the data sources. It is estimated that a pooled cohort of 400 NMOSD patients across data sources would enable a patient characteristic or AESI with an assumed incidence of 1% to be estimated with a precision of +/- 1% for 95% confidence interval (CI).

Data analysis:

Analyses will be performed for the overall study population and in sub-groups of special interest: patients concomitantly receiving other immunosuppressive agents and patients aged >65 years at index date.

To characterize new inebilizumab users, all patients of the study cohort will be described. Treatment patterns will be analysed only in patients with 12 months of complete follow-up and will be described as the number and proportion of patients who continue and discontinue treatment, respectively, who switch therapy and are exposed to add-on therapies. The median time to switching and the median time to use of add-on drugs will be described.

Estimation of the incidence will be conducted separately for each AESI category and will include cumulative incidence, incidence rate, and time to AESI onset. The cumulative incidence (with 95% CI) will be calculated as the total number of reports of an AESI during follow-up divided by the total number of patients initiating inebilizumab. The cumulative incidence estimates may also be calculated for shorter periods of time e.g., in monthly intervals after index date.

The incidence rate (with 95% CI) will be calculated as the total number of first reports of an AESI divided by the total risk time of the patients. Additionally, the Kaplan-Meier method will be applied to estimate the median time from inebilizumab initiation to AESI onset if the number of events allows.

Milestones

Anticipated start of data collection (date of the first data extraction): April 2024

Anticipated end of data collection (date of the last data extraction): April 2028

Date(s) of study progress reports: Progress updates provided with each PSUR

Registration in the EU PAS register: September 2023

Final report of study results (to be submitted as a standalone procedure): December 2028

2 AMENDMENTS AND UPDATES

None (original protocol).

3 MILESTONES

The planned dates for key study milestones are:

Milestone	**Planned date**
PRAC endorsement of protocol	June 2023
Registration in the EU PAS register	September 2023
Start of data collection (date of the first data extraction)	April 2024
End of data collection (date of the last data extraction)	April 2028
Study progress reports	Progress updates provided with each PSUR
Final report of study results (to be submitted as standalone procedure)	December 2028

4 RATIONALE AND BACKGROUND

4.1 Background

Neuromyelitis optica spectrum disorder (NMOSD; also known as Devic's syndrome and previously known as neuromyelitis optica [NMO]) is a rare, chronic, autoimmune, inflammatory disorder of the central nervous system, characterized by attacks of optic neuritis and longitudinally extensive transverse myelitis and, less frequently, affecting the brain and brainstem (1). Commonly reported symptoms include ocular pain, unilateral or bilateral loss of visual acuity that can lead to blindness, loss of sensation, weakness (including paraplegia), bladder and bowel dysfunction, paroxysmal tonic spasms of the trunk and limbs, and Lhermitte's phenomenon (1). Up to 90% of patients with NMOSD have recurring episodes of optic neuritis and/or myelitis rather than following a monophasic course (2). Attacks can be severe and result in blindness, paralysis, and even death due to neurogenic respiratory failure (3). An important paraclinical feature of NMOSD seen in 80% patients and used to help differentiate the condition from multiple sclerosis (MS) is the presence of serum autoantibodies against aquaporin-4 (AQP4) (i.e., AQP4-immunoglobulin [Ig]G or NMO-IgG) (4).

Worldwide, incidence rates of adult NMOSD are reportedly between 0.04-0.73/100,000 person-years (5), while the prevalence of NMOSD in adults is approximately 0.5–4/100,000 and may be up to 10/100,000 in certain racial groups (6). NMOSD can occur at any age, and disproportionately affects females (70%-90%), with a mean age of onset of approximately 40 years (6).

Treatment of NMOSD comprises 2 main goals: recovery from acute attacks and prevention of future attacks (relapse) as well as prevention of sequelae.

Recently, inebilizumab, an anti-CD19 B-cell depleting antibody, was approved for the treatment of NMOSD in AQP4-IgG seropositive patients in the US, Japan, and South Korea, and in November 2021 the Committee for Medicinal Products for Human Use of the European Medicines Agency (EMA) also recommended approval for the same patient population. The current recommended initial dose is 300 mg intravenous (IV) infusion followed 2 weeks later by a second 300 mg IV infusion. The recommended maintenance dose is a single 300 mg IV infusion every 6 months thereafter, starting 6 months from the first infusion (7).

So far, no real-world observational studies of treatment patterns, outcomes, and safety for patients treated with inebilizumab have been conducted for NMOSD patients. This document summarizes the design of a real-world study to characterize new users of inebilizumab in Europe which can help capture dosing, duration of treatment, discontinuation, switching as well as add-on medications (8).

4.2 Rationale

New monoclonal antibody therapies have recently been approved for the treatment of NMOSD. Treatment with inebilizumab has demonstrated a significant reduction in the frequency of relapses (8); however, knowledge gaps remain regarding real-world treatment patterns and outcomes for patients with NMOSD. To address this, we seek to characterize real-world inebilizumab use in Europe. This non-interventional study, designated as a Post-Authorization Safety Study (PASS) to meet global regulatory post-marketing requirements, intends to provide important information regarding patterns of drug utilization and the safety profile of inebilizumab in a real-world population.

5 RESEARCH QUESTION AND OBJECTIVES

The overall research questions for this study are:

1. What are the demographic, clinical, and treatment characteristics of a population of patients who initiate inebilizumab in real-world practice?
2. What are inebilizumab patterns in the first 12 months following treatment initiation?
3. What is the incidence of adverse events of special interest (AESI) in the first 12 months following treatment initiation?

Specific objectives are:

1. To describe patients at time of first inebilizumab treatment – in the overall study population and in sub-groups of special interest (patients concomitantly receiving other immunosuppressive agents and patients aged >65 years at index date) – in terms of:
   - demographics
   - comorbidities
   - NMOSD-related clinical characteristics
   - previous immunosuppressive therapies
   - inebilizumab initiation characteristics (setting of healthcare and specialty of prescribers and treatment indication)
2. To describe inebilizumab treatment patterns in the overall study population and sub-groups of special interest in the first 12 months after starting treatment - in terms of:
   - duration of treatment
   - dosing
   - frequency of drug discontinuation
   - switching
   - use of add-on therapies
3. To quantify the incidence of AESI in the overall study population and sub-groups of special interest, including:
   - serious infections
   - opportunistic infections (including progressive multifocal leukoencephalopathy [PML])
   - hepatitis B reactivations
   - serious infusion related reactions
   - malignancies

6 RESEARCH METHODS

6.1 Study Design

This will be a non-interventional multi-center cohort study of patients initiating inebilizumab conducted with secondary data sources in France, Germany, Italy, the Netherlands, and Spain. The study will be based on a cohort-event monitoring design to capture both drug utilization and selected safety outcomes in patients initiating inebilizumab. The proposed study design allows for an efficient initial descriptive evaluation of AESI.

The **study period** in individual countries will start on different dates, depending on the launching time of the drug (the earliest in the second quarter of 2022) (Table 1). The end of the study period will be also country-specific (the latest in December 2027) and will depend on the dates of data availability in individual data sources (different lag times and data release dates).

Table 1 Study periods, by country

	France	Germany	Italy	Netherlands	Spain
	SNDS/ NOMADMUS	GKV	RISM	PHARMO	SIDIAP
Launch date (quarter, year)	Q2, 2022	Q3, 2022	Q2 2023	Q3, 2023	Q2, 2023
Start of study period	May 2022	Aug 2022	May 2023	Aug 2023	May 2023
End of study period	Dec 2026	Dec 2026	Dec 2027	Dec 2026	Sep 2027
Study period duration (months)	57	54	56	41	53

Q2, 2nd quartile; Q3, 3rd quartile

The study population will be constituted by a cohort of adult female and male patients diagnosed with NMOSD with entry trigger by inebilizumab initiation.

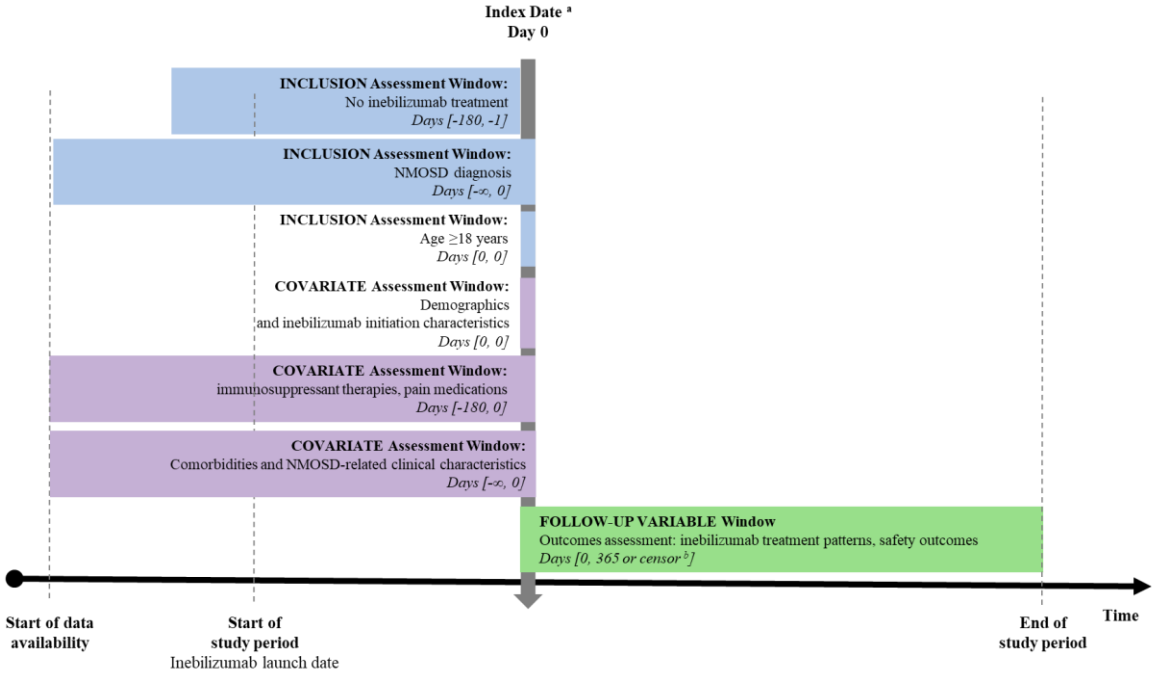
The **index date** (Day 0) will be defined as the date of first treatment (date of administration/prescription/dispensation, depending on data available in selected data sources) (Figure 1). Patients initiating the treatment will be identified throughout the study period. After the index date, enrolled patients will be followed for 12 months or censored at end of study period or loss of follow-up (death, disenrollment/de-registering) whichever occurs first.

A **baseline period**, including any time from when data are available up to the index date, will be used to establish comorbidities and NMOSD-related clinical characteristics, whereas a short period of 6 months prior to or at index date will be used to determine previous immunosuppressive therapies.

At index date, patients will be described in terms of demographics, comorbidities, NMOSD-related clinical characteristics (disease duration, NMOSD core symptoms, differential diagnoses, NMOSD-associated conditions, history of relapses), previous immunosuppressive therapies, and inebilizumab initiation characteristics (setting of healthcare and specialty of prescribers and treatment indication).

As of the index date, data on inebilizumab treatment will be used to assess the 12-month treatment patterns, considering duration of treatment, dosing, frequency of the drug discontinuation, switching, and use of add-on therapies. AESI will be captured during the first 12 months following the index date. Cumulative incidence and incidence rates of AESI will be quantified for the overall follow-up period. Additionally, the estimates will be calculated for shorter periods of exposure (e.g., monthly) allowing the assessment of periods of higher or lower frequency of each outcome.

Figure 1 Study Design



Abbreviations: NMOSD, neuromyelitis optica spectrum disorder

[a]First inebilizumab administration/prescription/dispensation, depending on the available data.
[b]Censoring criteria will be the earliest of loss to follow-up (death, disenrollment/de-registering) or end of study period.

Data will be analyzed for the overall cohort of patients initiating inebilizumab and for sub-groups of special interest: patients concomitantly receiving other immunosuppressive agents and patients over 65 years of age at index date.

6.2 Setting

Because NMOSD is a rare disease and inebilizumab is a novel therapy, it is crucial to identify data sources with sufficiently large and representative patient populations to evaluate patterns of use and the safety profile of the drug in real-world practice (section 6.5). Data sources in 5 European countries: France, Germany, Italy, the Netherlands and Spain were selected for use in this study. The study population will be identified in national healthcare administrative databases, claim databases, and disease-specific registries. Please refer to section 6.4 for further details on the selected data sources.

Throughout the study period data will be extracted annually and the number of patients exposed to inebilizumab will be monitored to update and inform the study size. While patients will be followed up prospectively during the study period, data will be acquired

retrospectively at each data extraction time point according to the protocol and the statistical analysis plan (SAP).

Due to the nature of the study (a drug for a rare disease used in real-world clinical practice), limited inclusion and exclusion criteria will be applied; nevertheless, to minimize bias associated with existing users (including prevalence bias, survivor bias and follow-up bias), only first-time users during the study period will be analyzed.

6.2.1 Inclusion Criteria

An eligible population will consist of all inebilizumab users identified during study period in the selected databases. Within this population, patients who meet all the following criteria will be included for this study:

- First time administration/prescription/dispensation of inebilizumab, i.e., no inebilizumab treatment in the 6 months prior to index date
- Diagnosis of NMOSD before or at the index day
- At least 18 years old at index date

6.2.2 Exclusion Criteria

No exclusion criteria will be applied.

6.3 Variables

NMOSD[1], NMOSD-associated conditions, comorbidities, and safety outcomes will be defined using the International Classification of Diseases (ICD), 9th or 10th revision codes or local modifications thereof. Medications will be defined using the Anatomic Therapeutic Chemical (ATC) codes or operation and procedure classification system (OPS) codes recorded in each data source (9,10).

6.3.1 New Inebilizumab Users

This is an observational study of real-world clinical practices and this protocol does not recommend the use of any specific treatments.

New inebilizumab users will be defined as patients with a first inebilizumab treatment (identified through first administration/prescription/dispensation, depending on how the information on the drug is collected in the data sources) during the study period with no previous inebilizumab treatment in 6 months prior to the index date.

Inebilizumab treatment (first and each subsequent administration/ prescription/ dispensation) will be identified by the ATC code (L04AA47 / L04AG10 from 2024). Information accompanying every drug administration/prescription/dispensation, including date and time, dose, indication, setting of healthcare and specialty of prescriber will be retrieved, if available.

6.3.2 Characterization Variables

Characteristics of new inebilizumab users at index date will include demographics, comorbidities, NMOSD-related clinical characteristics (disease duration, NMOSD core

[1]The use of Orphanet coding system for rare diseases (https://www.orpha.net/) will be explored in the SAP as appropriate

syndromes, differential diagnoses, NMOSD-associated conditions, history of relapses), previous immunosuppressive therapies, and inebilizumab initiation characteristics (setting of healthcare and specialty of prescribers and treatment indication). Please note that the list of characterization variables may be refined based on the databases availability and specificity. Detailed operational definitions and lists of local codes will be provided in the SAP.

Demographic characteristics include sex, age at the index date and race/ethnicity, depending on availability.

Comorbidities will be assessed by the presence of an ICD-9/ICD-10 codes during the baseline period in the data sources (Table 6 in Annex 3). The codes for the following specific conditions are provided (Table 6 in Annex 3):

- Coronary heart disease
- Heart failure
- Cerebrovascular disease
- Lung disease
- Renal disease
- Rheumatic disease
- Diabetes
- Hypertension
- Malignancy
- Osteoporosis
- Anxiety
- Depression
- Skin ulcers/cellulitis
- Renal transplantation
- Infections

Charlson comorbidity index (CCI) (11) will be retrieved as an overall measure of the burden of concomitant diseases. A CCI code list will be provided in the SAP.

Prescriber of inebilizumab will be described in terms of the type of facility he/she works at (hospital or other) and specialty (e.g., Neurology, Neuroradiology, Ophthalmology, Rheumatology, Psychiatry, or other), if available.

NMOSD has a wide range of clinical and imaging manifestations, which overlap with those of MS and myelin-oligodendrocyte glycoprotein (MOG) antibody-associated disease. In a retrospective study of patients with NMOSD, 42.5% with available data were initially misdiagnosed with MS (12). NMOSD patients can be hidden within the large MS population, although after AQP4-IgG testing has become available, it is now easier to differentiate NMOSD from MS. In this study, all patients diagnosed with NMOSD at baseline or index date, regardless of other preceding or subsequent documented diagnoses, will be included if they initiate inebilizumab. The drug is expected to be prescribed only for those with NMOSD as the indication. However, the study population will be screened for differential diagnoses (Table 2). Treatment indication, if not directly available in the data sources, will be defined according to an algorithm that will distinguish between diagnoses such as NMO and/or other NMO core manifestations and differential diagnoses within a specified time-window around the index date. The algorithms will be described in detail in SAP.

Other NMOSD-related symptoms such as paroxysmal symptoms, loss of sensation, nausea/vomiting, bladder/bowel dysfunction will be described if available in the data sources.

Table 2 Diagnoses accepted to define NMOSD and differential diagnoses

Condition Description	Diagnosis ICD-9-CM Codes*	Diagnosis ICD-10-CM Codes*
Diagnosis codes recorded for NMO and/or other NMO core manifestations		
Neuromyelitis Optica	341.0	G36.0
Optic neuritis	377.3, 377.39	H46.1x, H46.8, H46.9
Retrobulbar neuritis	377.32,	H46.1, H46.10, H46.11, H46.12, H46.13
Acute (transverse) myelitis	341.2, 341.21, 341.22	G37.3
Differential Diagnoses		
Neuro-Behçet's disease	136.1	M35.2
Multiple sclerosis	340	G35
Parainfectious disorders	045.x, 047.9, 062, 063, 064, 066.41, 071, 138, 323.0, 323.1, 323.2, 323.4, 323.6, 357.0	A80.x, A81.x, A82.x, A83.x, A84.x, A85.x, A86.x, A87.x, A88.x, A89.x, B00.4, B02.0, B05.0, B10.0, B25.8, B26.2, B91, B94.1, G04.01, G14, G61.0

Abbreviations: ICD-9/ICD-10, 9th/10th Revision of International Classification of Diseases; NMO, neuromyelitis optica; NMOSD, neuromyelitis optica spectrum disorder; CM, Clinical Modification
*ICD-X-CM codes will be translated into local ICD-X codes and provided in SAP

NMOSD disease burden and clinical characteristics up to the index date will include the presence of each of the diagnoses part of the NMOSD core symptom, disease duration, AQP4 and MOG seropositivity, NMOSD-associated conditions, history of relapses, and previous acute and maintenance therapies.

Disease duration will be estimated as the difference between the index date and the first NMOSD diagnosis date.

Where available, laboratory results most recent to the index date will be used to classify patients according to the presence of autoantibodies against AQP4 and MOG. Patients will be classified as positive, negative or unknown serology. As it is recommended to repeat AQP4-antibody testing if the result is non-conclusive or negative, the presence of at least one positive result will be sufficient to classify the patient as positive. Thus, data on serology during follow-up will be also analysed to present the most updated serology status of the patients.

Information on spinal cord and brain Magnetic Resonance Imaging (MRI) scans performed in the previous year will be extracted whenever available in the data sources. Patients will be defined as having had performed spinal MRI only, brain MRI only, spinal and brain MRI or no MRI scan in the previous year.

NMOSD as an autoimmune disease has been reported to coincide with other disorders including systemic autoimmune diseases, organ-specific autoimmune diseases, and other diseases with possible immunologic pathogenesis (13). The association of clinical or even subclinical autoimmunity is a supportive feature for the diagnosis of the disease (14).

NMOSD-associated conditions listed below will be identified by the respective ICD-9/ICD-10 codes (**Error! Reference source not found.** in Annex 3):

- Hypothyroidism
- Pernicious anemia
- Ulcerative colitis
- Myasthenia gravis
- Idiopathic thrombocytopenic purpura
- Hemiplegia/paraplegia
- Bladder dysfunction
- Neuropathic pain
- Antiphospholipid syndrome
- Sarcoidosis
- Scleroderma
- Sjogren's syndrome
- Systemic lupus erythematosus
- Dorsalgia
- Disorders of lipoprotein metabolism and other lipidemias
- Other acute disseminated demyelination
- Disorders of refraction and accommodation
- Visual disturbances
- Disturbances of skin sensation
- Somatoform disorders
- Other dorsopathies, not elsewhere classified

History of relapses will be ascertained depending on available data in the data sources (e.g., using documented relapse episodes as defined by individual disease-specific registries or considering the previous use of acute treatments such as intravenous corticosteroids, intravenous immunoglobulin or plasmapheresis therapy, or hospital admission with selected principal diagnoses) and will be defined in detail in SAP. Patients will be characterized according to the number of relapses in the previous 1 and 2 years (none, one, two or more).

Baseline use of **acute treatments** will include intravenous corticosteroids, intravenous immunoglobulin or plasmapheresis therapy in a 6-month period prior to the index date (Table 7 NMOSD-Associated Conditions

NMOSD-associated Conditions	**Diagnosis ICD-9-CM Codes***	**Diagnosis ICD-10-CM Codes***
Hypothyroidism	244.x	E89.0, E03.2, E03.8, E03.9
Pernicious anemia	281.0, 281.1	D51.x
Ulcerative colitis	556.x [excl. 556.2 and 556.3]	K51.xx [excl. K51.2x and K51.3x]
Myasthenia gravis	358.0x	G70.0x
Idiopathic thrombocytopenic purpura	446.6	M31.1
Hemiplegia/paraplegia	334.1, 342.x, 343.x, 344.0x-344.6x, 344.9	G11.4, G81.xx, G80.x, G83.0, G83.1x, G83.2x, G83.3x, G83.4, G83.9, G82.xx

NMOSD-associated Conditions	Diagnosis ICD-9-CM Codes*	Diagnosis ICD-10-CM Codes*
Bladder dysfunction	788.30, 788.31, 788.33, 788.34, 788.36, 788.37, 788.39-788.43, 596.xx	N30.xx, N31.x, N32.xx, N33
Neuropathic pain	353.x, 354.x, 355.x, 356.x, 357.x, 250.6, 729.2, 782	E08.40-E08.42, E09.40, E09.42, E10.40-E10.42, E11.40-E11.42, E13.40-E13.42, G50.0, G50.1, G54.x, G55.x, G56.x, G57.x, G58.x, G60.x, G61.x, G62.x, G63, G64, G65.x, G90.5x, M05.5x, M79.2, M54.1, R20
Antiphospholipid syndrome	289.81	D68.61
Sarcoidosis	135	D86.xx
Scleroderma	357.4, 359.6, 517.2, 701.0, 710.1	M34.xx, L90.0, L94.0, L94.1, L94.3
Sjogren's syndrome	710.2	M35.0x
Systemic lupus erythematosus	710	M32.xx
Dorsalgia	724.5	M54
Disorders of lipoprotein metabolism and other lipidemias	272.0, 272.1, 272.2, 272.3, 272.4, 272.5, 272.9	E78
Other acute disseminated demyelination	341.9	G36.9
Disorders of refraction and accommodation	367	H52
Visual disturbances	368	H53
Disturbances of skin sensation	782	R20
Somatoform disorders	300.81	F45
Other dorsopathies, not elsewhere classified	723.2, 723.3, 723.8, 723.9	M53

Abbreviations: ICD-9/ICD-10, 9th/10th Revision of International Classification of Diseases; CM, Clinical Modification; NMOSD, Neuromyelitis optica spectrum disorder
*ICD-X-CM codes will be translated into local ICD-X codes and provided in SAP

Table 8 in Annex 3). To characterize **maintenance therapy** in the same period, the use of recommended drugs such as oral corticosteroids, immunosuppressants, B-Cell targeting therapies, tocilizumab, eculizumab, satralizumab (Table 9 in Annex 3) and other immunosuppressive treatments (Table 10 in Annex 3) will be retrieved.

The use of pain medications in the 6 months prior to the index date will be determined taking into account drugs specified in Table 11 in Annex 3.

6.3.3 Treatment patterns

During follow-up, treatment patterns will be characterized in terms of dose, treatment duration, frequency of drug discontinuation, switching and use of add-on therapies. All patients included in the study will be deemed exposed (at least one inebilizumab treatment), but only those with complete 12-month follow-up will be considered in the evaluation of the treatment patterns as described below.

According to the product specifications, the 12-month follow-up will cover 3 potential inebilizumab administrations: initial intravenous (IV) infusion followed by a second

infusion 2 weeks later and a subsequent infusion 6 months after the first treatment (Figure 2A). The first and third infusion will be considered in defining inebilizumab treatment patterns.

Treatment duration will be the sum of days under inebilizumab exposure during the follow-up. Number of days under exposure will be calculated for the first and the third infusion as the difference between end date of inebilizumab exposure period and the administration/prescription/dispensation date (Figure 2B).

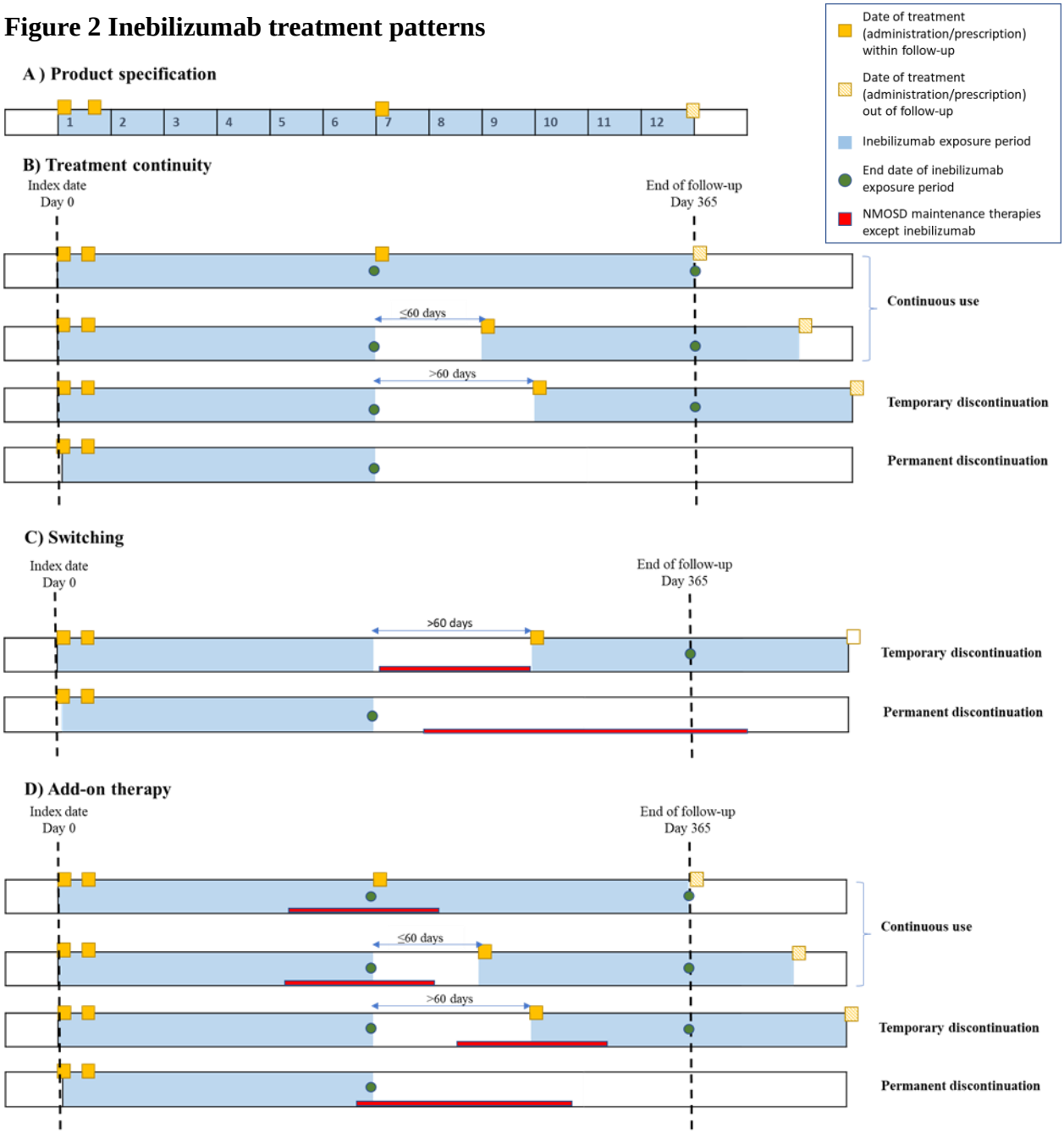
Inebilizumab complete **exposure period** will be assumed to last 180 days after drug administration/prescription/dispensation**.** The **end date of the exposure** period will be defined as the end of each inebilizumab exposure period within follow-up or the end date of follow-up if comes first (Figure 2B).

A patient will be considered to be in inebilizumab **continuous use** if no gap longer than 60 days occurs between the end date of the first inebilizumab exposure period and the beginning of the third (2B). **Temporary discontinuation** (intermittent users) will be defined in patients with gaps between inebilizumab exposure periods longer than 60 days but with a subsequent inebilizumab administration/prescription/dispensation during the follow-up. A patient will be defined as having **permanently discontinued** inebilizumab if no subsequent inebilizumab treatment is registered during the follow-up after the end date of the first inebilizumab exposure period.

Switchers will be a subgroup of patients who discontinue inebilizumab (temporarily or permanently) during the follow-up and have other NMOSD maintenance drug administered/ prescribed (Table 9) after the end date of inebilizumab exposure period (2C). The alternative NMOSD drugs will be described.

The use of **add-on therapies** will be identified by administration/prescription/dispensation of other NMOSD maintenance or other immunosuppressive drug(s) (Table 9 and Table 10) during any of inebilizumab exposure period (2D). Corticosteroid pre-medication before inebilizumab infusion (used to reduce potential infusion reactions) will not be considered as an add-on therapy.

Figure 2 Inebilizumab treatment patterns



6.3.4 Safety outcomes

The AESI evaluated in this study include the following categories:

- serious infections
- opportunistic infections including PML
- hepatitis B reactivations
- serious infusion related reactions
- malignancies

Diagnosis codes to identify safety outcomes of interest are listed in Table 12 in Annex 3. Real-world study operational definitions for serious infection, opportunistic infections and hepatitis B reactivations will be defined as local ICD-9/ICD-10 diagnoses codes in

inpatient hospitalizations during the follow-up. Real-world study operational definitions for serious infusion related reactions will be defined as local ICD-9/ICD-10 diagnoses coded in inpatient hospitalizations, outpatient visits or as documented adverse events depending on available data. Safety outcomes will be retrieved during the follow-up with their date of occurrence.

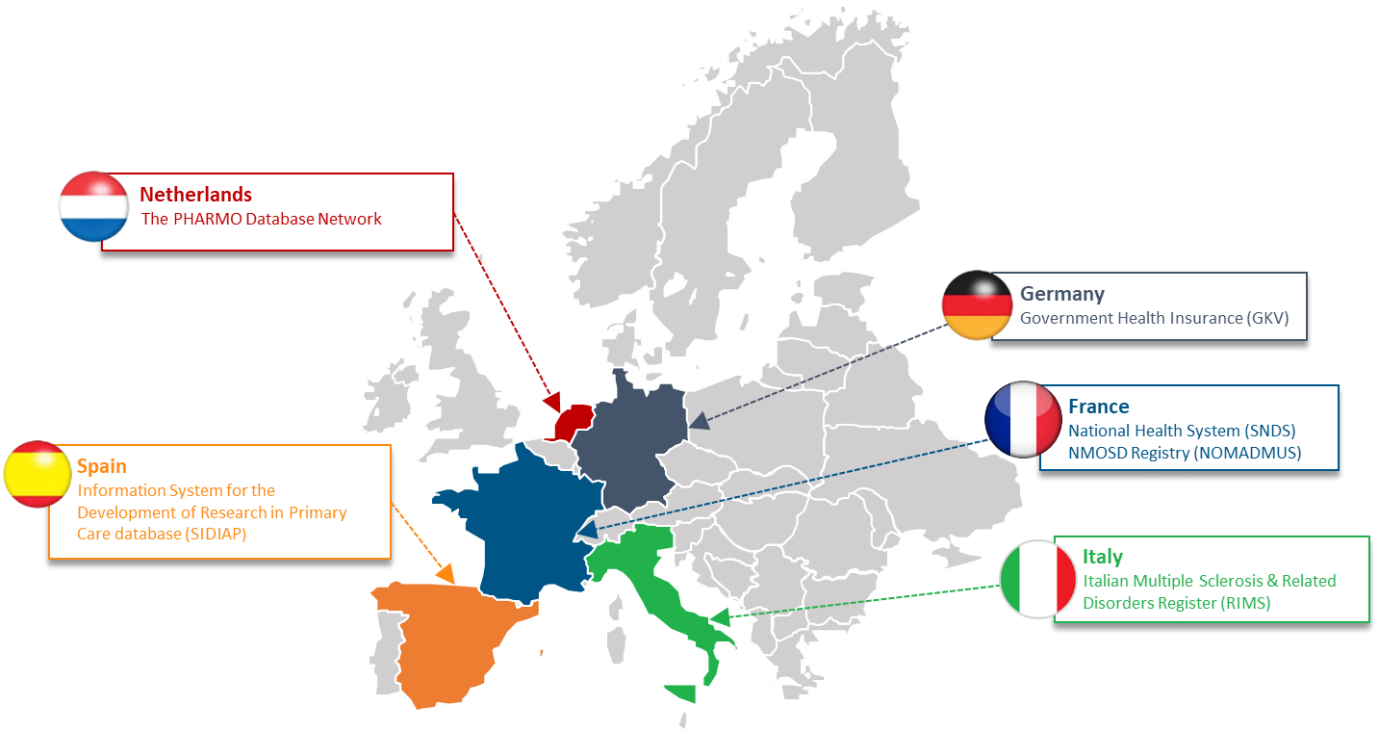
6.4 Data Sources

The inclusion of a country/data source in the study was based on the evaluation of the following aspects:

- time of inebilizumab launch (focus on the initial countries to launch inebilizumab)
- availability of data required to meet the study objectives (i.e., exposure to inebilizumab and other disease modifying drugs, safety outcomes)
- data bases in which the number of exposed patients was relatively high
- data availability in the defined study period, after taking into account the lag time (time from data capture to data available in the system)

The evaluation of the last 3 aspects was carried out through a detailed qualitative feasibility assessment in 17 different data sources in 9 countries. Ultimately, 6 data sources from 5 European countries were included in the study (Figure 3 Data Sources Included.

Figure 3 Data Sources Included



6.4.1 France

The French National Health Data System (Système National des Données de Santé [SNDS])

SNDS is the largest and most comprehensive healthcare dataset available in Europe with a 10-year longitudinal follow-up for more than 65 million individuals (including 50 million adults), and is highly representative of the French residents, covering 99% of the total population (15). Individuals enter the data source once born within or immigrating to the specific geographical area, and exit the data source either at date of death, emigration, or ending their insurance.

SNDS contains anonymized administrative and healthcare claims data from the French national health care insurance system databases including main health care claims database, ie., French National health insurance information system (*Système national d'information interrégimes de l'Assurance maladie* [SNIIRAM]), hospital discharge summaries (*Programme de Médicalisation des Systèmes d'Information* [PMSI]), and national death registry (Centre d'épidémiologie sur les causes médicales de Décès) (16).

SNDS contains information on beneficiaries age, sex, region of residence, death date, complementary universal health coverage status, and all out-patient healthcare drugs including all reimbursed prescription drugs identified by their ATC code, the date of delivery, quantity, and brand name. Medical procedures performed on an out-patient basis or in a healthcare institution are identified by the common classification of medical procedures (*classification commune des actes médicaux*), laboratory procedures are identified by the clinical pathology test nomenclature (*nomenclature des actes de biologie médicale*), and paramedical or medical visits are identified by the general nomenclature of professional procedures (*nomenclature générale des actes professionnel*).

The French National Health Insurance Information System, SNIIRAM

SNIIRAM was created in 2003 and contains healthcare information generated through the reimbursement scheme of the French national health insurance. The French National Health Insurance Fund for Salaried Workers (*la Caisse nationale de l'assurance maladie des travailleurs salaries* [CNAMTS]) (the general scheme) covers approximately 87% of the population including employees in the industry, business, and service sectors; public service employees; and students. A range of additional insurance schemes, such as those dedicated for self-employed and agricultural workers and others, cover the remaining population.

SNIIRAM includes data on sociodemographic, diagnoses of chronic conditions, health care encounters such as physician or paramedical visits, medicines, medical devices, and lab tests (without results); outpatient medical expenses including dispensed medication, medical visits and procedures, date and duration of hospitalizations, inpatient diagnoses and procedures (15). However, some health care consumptions cannot be seen, such as consumptions not claimed for reimbursement, not reimbursable health services, and self-medication. Moreover, the only in-hospital prescriptions included are those of expensive drugs that are excluded of the hospital diagnosis-related groups (e.g., targeted cancer therapies and monoclonal antibodies) (16).

French Hospital Décharge Sommaires, PMSI

SNIIRAM claims database can be linked with the PMSI via unique individual identifiers. Data from PMSI includes medical summaries of all hospitalizations from all private or public hospitals across different types of care centers: acute care (short duration stays) at hospital, home hospitalizations stays, follow-up and rehabilitation care stays.

PMSI provides the date of stay, medical procedures performed during hospital stay, costly innovative drugs (*medicaments* "*listed en sus*") or implantable devices received during the hospital stay, the primary diagnosis (main reason for admission), related diagnoses (specific to the disease context of the primary diagnosis), and diagnoses related to other comorbidities, all encoded according to the ICD-10. Information on occupational diseases and sick leaves is also available.

French MS Registry

French MS Registry (Observatoire Français de la Sclérose en Plaques [OFSEP]) was established in 2003; it is a national register actively covering data from 36 centers corresponding to 42 databases, of which 2 contain exclusively NMOSD patients. The data is collected from participating centers using the European Database for Multiple Sclerosis software. OFSEP covers approximately 50% of the total MS population in France and holds data for approximately 55,000 patients in total. Of these, 23,000 patients have records after June 2013, when a minimal data threshold was established. OFSEP contains information such as personal and sociodemographic information, clinical, paraclinical (e.g., MRI), and therapeutic data (disease-modifying treatments). Access to the data is made directly via an application to the database: the National Coordination Center and the Scientific Board of the database evaluate the applications and the Steering Committee makes the final decision (17).

French NMOSD Registry

Nested within the OFSEP is a French NMOSD registry recruiting patients with NMOSD presentations in France (*Neuro-Optico-Myélite Aiguë de Devic et des syndromes neurologiques apparentés* [NOMADMUS]). The cohort was initiated in 2010 and gathers clinical, biological and imaging data (18). The patients are regularly tested for anti-AQP4 and anti-MOG, and all cases are reviewed by an expert committee (19).

6.4.2 Germany

German Government Health Insurance (*Gesetzliche Krankenversicherung* [GKV]) claims from approximately 8-10 different statutory health insurance providers (SHIs) are collected by Team Gesundheit. This is an established research institute which has been working for more than 1000 health insurance companies, companies and ministries since 1997. With branches in Essen, Hamburg, Bielefeld, Berlin, Frankfurt and Munich they are active in German health management nationwide. Since an SHI is a requirement for individuals with a permanent place of residence in Germany, even for short-term stays, the general population coverage in the SHI is considered nationwide. The SHIs also allow insurance coverage for children and spouses within a family insurance policy. The population size available through Team Gesundheit is approximately 5 million individuals which represents an estimated 6.9% of the SHI-insured population in Germany. Available data history through collaboration with Team Gesundheit reaches back to January 2008. Since 2012 all individuals in Germany have lifelong specific ID and SHI numbers which would not change throughout lifetime.

The database contains information from primary care, in- and out-patient hospital care as well as sick leaves. Relevant measures are available in the German database allowing demographic characteristics, treatments, healthcare utilization and clinical outcomes to be assessed, for example:

- registration data including age, gender;
- out-patient care data including ICD-10 diagnoses (not granular and per quarter), physician specialty
- inpatient care claim including ICD-10 diagnoses (up to 3 principal and 30 secondary diagnoses per stay), billed diagnosis-related group (German classification), up to 30 OPS-Codes per stay, duration of hospitalizations, and medical department; drug prescription data including ATC codes of prescribed medications

Diagnosis information is available and captured in the ICD-10 coding system with German modification (GM). Data on surgical and medical procedures is recorded using operation and procedure classification system (OPS) codes which is the GM of the international classification of procedures in medicine (ICPM). Due to the nature of the claims data, information on data that is not subject to reimbursement is not visible in the database, e.g., information on symptoms captured by ICD-10 coding would have little or no coverage as they are usually not subject to reimbursement. Similarly, information on a conducted diagnostic test is only available if being subject to reimbursement. Test results are not available from the claims data. The estimated lag time from the time data is recorded until it is available for research is currently 16 months meaning that data until the end of 2022 would be available in March/April 2024. SHI data in Germany is updated yearly.

6.4.3 Spain

The Information System for Research in Primary Care (*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària* [SIDIAP]), IDIAP Jordi Gol (Spain) is a primary care records database that covers approximately 7 million people, equivalent to an 80% of the population of Catalonia, North-East Spain. SIDIAP is collected from EHR records of patients receiving primary care delivered through Primary Care Teams (PCT), consisting of general practitioners, nurses and non-clinical staff. The Catalan Health Institute manages 286 out of 370 such PCT with a coverage of 5.6 million patients, out of 7.8 million people in the Catalan population (74%). The database started to collect data in 2006. The mean follow-up is 10 years. The observation period for a patient can be the start of the database (2006), or when a person is assigned to a Catalan Health Institute primary care center. Date of exit can be when a person is transferred-out to a primary care center that does not pertain to the Catalan Health Institute, or date of death, or date of end of follow-up in the database. Drug information is available from prescriptions and from dispensing records in pharmacies. Studies using SIDIAP data require previous approval by both a Scientific and an Ethics Committee (20). For a subset of patients included in the SIDIAP database, linkage to hospital data is available as obtained from the Catalan Institute of Health hospitals (21) and will be further explored in the feasibility assessment. Healthcare is universal and taxpayer funded in the region, and primary care physicians are gatekeepers for all care and responsible for repeat prescriptions. SIDIAP-Hospitalization Linked Data has contributed to studies involving patients with MS (21).

6.4.4 Italy

The Italian Multiple Sclerosis & Related Disorders Register (*Registro Italiano Sclerosi Multipla e Patologie Correlate* [RISM])) was officially established in 2015. As of February 2023, the register was actively covering 133 MS centers, corresponding to a total of 80,353 patients, of which 273 are diagnosed with NMOSD. Since July 2022, the

register comprises a module for the collection of information on NMOSD, and has projects dedicated to NMOSD patients (22). Nonetheless, data on NMOSD patients were collected previous to 2022, without a specific module implemented. The data are collected from participating centers through a web-based system developed for the study, available at the IMS&RD website. Data are collected from accrual to exit of database, which may occur at date of death, when patient moves to a center outside of the covered network or withdraws their consent to participate. The data are centrally monitored to ensure quality of data, completeness, accuracy, and consistence (23). Requests to access the data are evaluated by the Scientific Committee, composed by clinicians, methodologists, representatives of MS centers, and of the Italian Neurological Society (23).

To ensure the collection of sufficient data for the clinical characterization of the single patient mandatory variables collected by the register include patient identification, demographics, vital status, disease onset date, diagnosis date, relapses, treatments and severe adverse events. This minimum dataset may be completed with an extension to optional information on family history, comorbidities, laboratory tests and MRI. Furthermore, the register has data on patient's unique personal identifier, to avoid inclusion of the same patient by more than 1 center. Diagnosis information is available and captured with ICD-9-CM coding system.

6.4.5 The Netherlands

Established in 1998, the Dutch Institute for Drug Outcomes Research (PHARMO) Database Network is a population-based network of electronic healthcare databases and combines anonymous data from different primary and secondary healthcare settings in the Netherlands. These different data sources, including data from general practices, in- and out-patient pharmacies, clinical laboratories, hospitals, the cancer registry, pathology registry and perinatal registry, are linked on a patient level through validated algorithms. To ensure the privacy of the data in the PHARMO Database Network, the collection, processing, linkage and anonymization of the data is performed by STIZON. STIZON is an independent, ISO/IEC 27001 certified foundation, which acts as a Trusted Third Party (TTP) between the data sources and the PHARMO Institute. Detailed information on the methodology and the validation of the used record linkage method can be found elsewhere (24).

The longitudinal nature of the PHARMO Database 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 Database Network covers over 7 million active persons out of 17 million inhabitants of the Netherlands. Data collection period, catchment area and overlap between linked data sources differs. Therefore, the final cohort size for any study will depend on the data sources included. As data sources are linked on an annual basis, the average lag time of the data is one year. All electronic patient records in the PHARMO Database Network include information on age, sex, socioeconomic status and mortality. Other information available is dependent on the data source.

General Practitioner Database

The General Practitioner Database comprises data from electronic patient records registered by GPs. The records include information on diagnoses and symptoms, laboratory test results, referrals to specialists and healthcare product/drug prescriptions. The prescription records include information on type of product, prescription date, strength, dosage regimen, quantity and route of administration. Drug prescriptions are

coded according to the WHO (World Health Organization) Anatomical Therapeutic Chemical (ATC) Classification System. Diagnoses and symptoms are coded according to the International Classification of Primary Care (25), which can be mapped to ICD codes, but can also be entered as free text. The General Practitioner data cover a catchment area representing 3.2 million residents (approximately 0% of the Dutch population).

Out-patient Pharmacy Database

The Out-patient Pharmacy Database comprises GP or specialist prescribed healthcare products dispensed by the out-patient pharmacy. Some high budget impact medications cannot be dispensed by community pharmacies and are dispensed by hospital-based out-patient pharmacies. For a subset of patients, information is available on medication dispensed by these hospital-based out-patient pharmacies. The dispensing records include information on type of product, date, strength, dosage regimen, quantity, route of administration, prescriber specialty and costs. Drug dispensing are coded according to the WHO ATC Classification System. Out-patient pharmacy data cover a catchment area representing 4.2 million residents (approximately 25% of the Dutch population).

Inpatient Pharmacy Database

The Inpatient Pharmacy Database comprises drug dispensing from the hospital pharmacy, given during a hospitalization (or for which a bed is required, i.e., most IV drugs). The dispensing records include information on type of drug, start and end date of use, strength, dosage regimen and route of administration. Drug dispensing are coded according to the WHO ATC Classification System. Inpatient pharmacy data cover a catchment area representing 2 million residents (approximately 10% of the Dutch population).

Clinical Laboratory Database

The Clinical Laboratory Database comprises results of tests performed on clinical specimens. These laboratory tests are requested by GPs or medical specialists in order to get information concerning diagnosis, treatment, and prevention of disease. The electronic records include information on date and time of testing, test result, unit of measurement and type of clinical specimen. Laboratory tests are coded according to the Dutch Coding System (*Werkgroep Coordinatie Informatie Automatisering* [WCIA]) (26). Clinical laboratory data cover a catchment area representing 1.2 million residents (approximately 5% of the Dutch population).

Hospital Database

The Hospital Database comprises datasets containing information on hospital admissions, ambulatory consultations, and high budget impact medication. The Hospital Database is collected and maintained by the Dutch Hospital Data Foundation and comprises records from nearly all hospitals in the Netherlands. With permission from each hospital the data are linked for research purposes with the PHARMO Database Network via the TTP. For more information, please see www.dhd.nl. Permission on a project basis is needed to obtain these data.

Hospital Admissions

This dataset comprises hospital admissions lasting more than 24 hours and admissions for less than 24 hours for which a bed is required (i.e., inpatient records). The records include information on hospital admission and discharge dates, discharge diagnoses and procedures. Diagnoses are coded according to the WHO ICD and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures (27)

which links to the Dutch Healthcare Authority (*Nederlandse Zorgautoriteit*, NZa) declaration codes (28) and the Dutch Classification of Procedures (29). Currently, PHARMO has access to data from 1998 onwards and of over 80% of the hospitals.

Ambulatory Consultations

This dataset comprises all ambulatory consultations (i.e., out-patient records). The records include information on each contact, including date, diagnoses and procedures. Diagnoses are coded according to the WHO ICD and procedures are coded according to the Dutch Hospital Data Foundation registration system for procedures which link to the Dutch Healthcare Authority declaration codes and the Dutch Classification of Procedures. Currently, PHARMO has access to data from 2016 onwards and of over 50% of the hospitals.

High Budget Impact Medication

In the Netherlands high budget impact medication is dispensed through hospitals. The dataset comprises all dispensed high budget impact medication. This data is available for all patients identified in the ambulatory consultation dataset. The records include information on date of dispensing, type of medication, number of units, indication of use and prescriber. Drug dispensing are coded according to the Dutch Z-index code (30). Currently, PHARMO has access to data from 2017 onwards and of over 50% of the hospitals.

It is expected that inebilizumab will be indicated as 'high-cost medicine' by the Dutch Healthcare Authority and can only be dispensed through hospitals. If this new therapy will not be indicated as 'high-cost medicine' it may be found in the In-patient Pharmacy Database which comprises drug dispensing from the hospital pharmacy given during a hospitalization (or for which a bed is required, ie, most IV drugs). This data is available for a subset of the patients identified in the ambulatory consultation dataset.

Pathology Registry

The nationwide network and registry of histopathology and cytopathology in the Netherlands is maintained by the *Pathologisch-Anatomisch Landelijk Geautomatiseerd Archief* (PALGA) foundation and comprises excerpts of histological, cytological and autopsy examinations. For research purposes the data can be linked with the PHARMO Database Network via the TTP. Electronic records include a summary of the pathology report and the so-called PALGA diagnosis which is structured along 5 classification axes: topography, morphology, function, procedure and diseases. For more information, please see www.palga.nl

Permission on a project basis is needed from PHARMO as well as the PALGA foundation to obtain these data.

6.5 Study Size

This is a descriptive study that will identify and characterize the patients who are treated with inebilizumab. There is no *a priori* hypothesis testing and no prespecified requirement of sample sizes. The final study size will be determined by the length of study period and uptake of inebilizumab in the countries and population covered in the data sources. In order to comply with pharmacovigilance reporting commitments, multiple data extractions are planned for EU countries. Slow uptake may impact on the ability to meet the study objectives; in this instance the feasibility of study completion within the proposed time frame and need for further data extractions, should be open to re-evaluation.

For this observational study, the interpretation of results focuses on the precision of estimands (proportions). Table 3 presents the sample sizes across a range of expected incidences (of patient characteristics or AESI) and levels of precision. The sample sizes are derived assuming a normal approximation for the 95% confidence intervals (CI). Thus, in this study a pooled cohort of 400 patients across data sources would enable a patient characteristic (or AESI) with an assumed incidence of 1% to be estimated with a precision of +/- 1%, and for a patient characteristic (or AESI) with an assumed incidence of 4% to be estimated with a precision of +/- 2%.

Table 3 Sample Sizes of Patients Required to Estimate the Expected (True) Cumulative Incidence of a Patient Characteristic or AESI With 95% Confidence Intervals of Different Precisions (0.2% to 5%)

Estimated Incidence (%)	Precision 0.20%	Precision 0.50%	Precision 1%	Precision 2%	Precision 3%
0.30	2 872	-	-	-	-
0.40	3 826	-	-	-	-
0.50	4 778	764	-	-	-
0.70	6 675	1 068	-	-	-
0.80	7 621	1 219	-	-	-
1.00	9 508	1 521	380	-	-
2.00	18 823	3 012	753	188	-
3.00	27 947	4 471	1 118	279	124
4.00	36 878	5 900	1 475	369	164
5.00	45 617	7 299	1 825	456	203

AESI, adverse events of special interest

Feasibility – Patient estimates

Data sources and study countries were selected following a high-level feasibility assessment. It addressed the appropriateness of data sources for completion of this study regarding the ability to identify the target population and the presence of some variables of interest (such as results for AQP4 testing).

Inebilizumab is recommended to patients with NMOSD and the expected number of patients identified with the disease may vary considerably due to the imprecision of the prevalence estimates. Considering countries' population, data sources coverage, and expected NMOSD prevalence, the number of patients is likely to vary between 576 and 4,870 if 2006 NMO diagnosis criteria (31) were used for diagnosis; it may be higher depending on the criteria adopted in each setting. Around 80% of NMOSD are likely to be AQP4+ and thus eligible for inebilizumab, resulting in the identification of 461 to 3,896 patients (up to 8,855) (Table 4).

Table 4 Expected number of patients with a NMOSD diagnosis in each country (new and prevalent cases)

Country of Interest	Population ≥18 years	2006 NMO diagnosis criteria		2015 NMOSD diagnosis criteria
		Annual number of new cases (range)[a]	Number of patients with the disease (range)[b]	Number of patients with the disease (range)[c]
Germany[d]	5 000 000	(3-20)	(26-220)	(35-500)
Spain (Catalonia)[d]	5 600 000	(3-22)	(29-246)[g]	(39-560)[g]
Netherlands[d]	7 000 000	(4-28)	(36-308)[h]	(49-700)[h]
France[e]	53 179 816	(27-213)	(277-2 340)	(372-5 318)
Italy[f]	39 908 080	(20-160)	(208-1 756)	(279-3 991)
All countries	**110 687 896**	**(57-443)**	**(576-4 870)**	**(774-11 069)**
AQP4+ patients[i]	**88 550 317**	**(46-354)**	**(461-3 896)**	**(619-8 855)**

Abbreviations: AQP4, aquaporin-4 antibodies; NMOSD, neuromyelitis optica spectrum disorder
[a]Based on an estimated incidence rate between 0.05 and 0.40 per 100.000 people (32)
[b]Based on an estimated prevalence between 0.52 to 4.4 per 100.000 people (32)
[c]Based on an estimated prevalence between 0.7 to 10 per 100.000 people (33)
[d]Data sources do not cover 100% population: Netherlands (PHARMO) is 7 million; Catalonia (*Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària* [SIDIAP]) is 5.6 million and Germany (Gesetzliche Krankenversicherung [GKV]) is 5 million.
[e]Coverage is around 100%, population on 1st January 2021 (34)
[f]Coverage is around 80%, population on 1st January 2021 (34)
[g]Expect between 50 to 150 patients, based on feasibility counts provided from the data source but considerable proportion based on ICD-10 code H46; no data available on AQP4-Ig results
[h]Expect 50 patients in 2020, based on feasibility counts provided from the data source
[i]Assuming 80% of NMOSD patients AQP4+ (4)

6.6 Data Management

6.6.1 Database Management

The processes for database management differ by country. Generally, the data is stored at the database level and analyzed in accordance with local policy. SAS, STATA or R language will be utilized for access to the raw data, to manage the analytic datasets and to conduct data analysis. If the study is conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures. This study will follow the relevant chapters of the ENCePP and the International Conference on Harmonisation (ICH) guidelines for data management (27, 28)

6.7 Data Analyses

6.7.1 General Considerations

A generic description of the analysis methods proposed for this study is presented in section 6.7.2 followed by a description of the analysis proposed for each specific objective of the study.

A global SAP will be developed to describe in full details the variable definitions for exposures, outcomes, covariates, and sub-groups of interest. All analytic methods will be detailed, and a full set of table shells will be included. The SAP will be developed after the final protocol approval.

Descriptive analysis will consist of the summary statistics for continuous and categorical variables. For continuous variables, the number of observations, number of missing values, mean, standard deviation, median, lower (1st) and upper (3rd) quartiles, as well as 5th and 95th percentiles will be presented. For categorical variables, the numbers and percentages of observations for each of the categories and numbers and percentages of missing values will be reported. Confidence intervals of 95% may be presented, if data allow. Only available data will be summarized.

All descriptive analyses will be undertaken by country/data source, and for specified outcomes, a meta-analysis may be performed if a sufficient number of events per data source is observed.

The respective data sources' small number masking rules will define the lower limit for the number of units that can be reported in the result tables. The small number masking rules vary by data sources, and for example, PHARMO has a limit of 5. The small number masking rules of the data sources will be considered when presenting the study results for the analysis and numbers lower than the limit will be masked in the result tables. Further details on the masking rules and their impact on the result tables will be provided in the SAP.

6.7.2 Planned Analyses

An eligible population will include all inebilizumab users identified during the study period in the selected data sources. From the eligible population, the population for analysis will be created by applying the study inclusion criteria, as defined in section 6.2.1. The number and proportion of patients not included in the study for specific reasons will be presented in a STrengthening the Reporting of OBservational studies in Epidemiology (STROBE) (37) diagram.

All analyses will be conducted for the overall study population and in sub-groups of special interest: patients concomitantly receiving other immunosuppressive agents (Table 9 and Table 10 in Annex 3), and patients aged >65 years at the index date, if the sample size permits. Further details for the sample size required to conduct each of the analysis will be provided in the SAP.

6.7.2.1 Objective 1: New inebilizumab users' characterization

For objective 1, all new inebilizumab users (as defined in section 6.3.1) included in the study, regardless of the follow-up time will be described in terms of demographics, comorbidities, NMOSD-related clinical characteristics, previous immunosuppressive therapies, and inebilizumab initiation characteristics (including information on prescriber and treatment indication). Characterization will consist of summary statistics for continuous and categorical variables, as described in section 6.7.1.

6.7.2.2 Objective 2: Treatment patterns of inebilizumab

The number and proportion of patients in the overall study population receiving the drug, and by dose stratification, (below or above the recommended dose in the product characteristics [300 mg/IV infusion]) will be reported at each of the first, second, and third infusion. Additionally, the number and proportion of patients who change dose between the individual infusions as well as the time (in days) between the first and each subsequent treatment (regardless of dose) will be reported.

Inebilizumab treatment patterns, as described below, will be assessed in the period of 12 months from index date and only patients with a complete 12-month follow-up, regardless of inebilizumab discontinuation, will be considered.

The number and proportion of patients who experience the following treatment pattern related events will be reported separately for each of the events: continuous and discontinuous treatment, switching, use of add-on therapies, according to what is defined in section 6.3.3. For all the events, the denominator consists of all patients exposed to inebilizumab and followed for the full 12-month period.

The median time to switching and the median time to use of add-on drugs will be described in the subgroups of switchers and patients using add-on therapies (as defined in section 6.3.3), respectively. For the subgroup of switchers (as defined in section 6.3.3), the time to switch will be calculated as the time from the index date until the first recorded start date of another NMOSD maintenance drug. For the subgroup of patients using add-on therapies (as defined in section 6.3.3), the time to add-on drug use will be calculated as the time from the index date until the first recorded start date of an add-on drug.

6.7.2.3 Objective 3: Incidence of AESI

The AESI evaluated in this study include the following categories: serious infections, opportunistic infections, hepatitis B reactivations, infusion related reactions, and malignancies. Analysis of AESI will include estimation of the cumulative incidence (i.e., risk), incidence rate, and time to AESI onset (Table 5). All analysis for AESI events (i.e., cumulative incidence, incidence rate and time-to-onset) will be performed using an intention-to-treat approach i.e., patients will be considered exposed regardless of subsequent discontinuation.

The cumulative incidence (with 95% CI) will be calculated separately for each AESI category considering the overall study population. For all AESI categories, except infusion related reactions, the cumulative incidence (with 95% CI) will be calculated as the total number of incident reports of AESI during the follow-up divided by the total number of patients. An algorithm to identify incident reports of AESI will be developed and described in the SAP. For infusion related reactions, the cumulative incidence (with 95% CI) will be calculated as the total number of all reports of infusion related reactions on the day of infusion (if date of inebilizumab administration is available) or during the first 3 days following prescription/dispensation (if date of inebilizumab administration is not available), divided by the total number of patients in the overall study cohort. Additional details of this calculation will be provided in the SAP.

The cumulative incidence estimates for each AESI category, except infusion related reactions, may also be calculated for shorter periods e.g., in monthly intervals after index date. In this case, the cumulative incidence in the first month after index date would consider patients with AESI reports in the first month in the numerator and patients with complete 12-month follow-up in the denominator. The cumulative incidence in the second month would consider patients with reports recorded only in the second month in the numerator and patients with complete 12-month follow-up included in the denominator. Due to the limited sample size, the time intervals may need to be clustered into e.g., 3-month intervals with the numerator and denominator adjusted accordingly.If sample size permits, the difference (with 95% CI) in cumulative incidence between 2 time periods of observation may be calculated.

The incidence rate and time to onset of AESI will be estimated in the overall study population. The incidence rates will be estimated separately for each AESI category, except infusion related reactions, as the total number of first reports of an AESI divided by the time at risk of the patients. The patients' time at risk will be counted from the initiation of inebilizumab treatment until occurrence of AESI, end of the 12-month follow-up or censoring. Incidence rate will be expressed as the number of first reports of an AESI per 1,000 patient-months.

Kaplan-Meier estimates of the median time from index date to AESI onset will be provided separately for each AESI category, except infusion related reactions, if number of events allows. If there is no AESI during the follow-up, the patient will be censored at the end of follow-up. Descriptive statistics on the time-to-event will be provided in further detail in the SAP.

Table 5 Overview of estimates of incidence and time to event defined for objective 3.

AESI category	Estimate	Time at risk	Event	Population
Infusion related reactions	Cumulative incidence	Day of infusion if date of inebilizumab administration available or 3 days following prescription/dispensation	All recorded reactions	Overall population
Serious Infections / Opportunistic infections	Cumulative incidence	12 months	All recorded infections during the follow-up	Overall population
	Cumulative incidence	Short periods	First infection during follow-up	Patients with complete 12-month follow-up
	Incidence rate	From index date to AESI, end of follow-up or censored*	First infection	Overall population
	Time to event	From index date to AESI end of follow-up or censor*	First infection	Overall population
Hepatitis B reactivations	Cumulative incidence	12 months	All recorded reactivations during the follow-up	Overall population
	Cumulative incidence	Short periods	First reactivation	Patients with complete 12-month follow-up
	Incidence rate	From index date to AESI end of follow-up or censor*	First reactivation	Overall population
	Time to event	From index date to AESI, end of follow-up or censor*	First reactivation	Overall population

AESI category	Estimate	Time at risk	Event	Population
Malignancies	Cumulative incidence	12 months	All recorded malignancies during the follow-up	Overall population
	Cumulative incidence	Short periods	First malignancy	Patients with complete 12-month follow-up
	Incidence rate	From index date to AESI end of follow-up or censor*	First malignancy	Overall population
	Time to event	From index date to AESI, end of follow-up or censor*	First malignancy	Overall population

* Censoring criteria will be the earliest of permanent treatment discontinuation, loss to follow-up (death, disenrollment/de-registering) or end of study period.

6.8 Quality Control

The study will use existing databases, which are being used widely for research. The study will be executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional PASS, including but not limited to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology (36), the ENCePP Checklist for Study Protocols, and the Guidelines for GPPs (38) of the International Society for Pharmacoepidemiology (ISPE) as well as the specific IQVIA Standard Operating Procedures on retrospective analysis. The study will be recorded in the European Union electronic register of post-authorization studies (EU PAS register) maintained by the European Medicines Agency.

For the IQVIA EU data sources, quality control is conducted at several levels depending on the database. At the database level, the quality unit of the production department of IQVIA verifies continuously the quality of its sources in terms of representativeness and consistency of collected data. All study programs, log files, and output files will be stored on the secure server. If the study is being conducted by a third party, the datasets and analytic programs will be stored according to the vendor's procedures.

6.9 Limitations of Research Methods

Automated healthcare databases are appropriate for real-world studies due to the recording of prescriptions and clinical data from routine clinical practice, independently of any study purposes.

The use of secondary data allows the identification of all drug users which limits selection bias, since all patients fulfilling the inclusion criteria are included in the study. Inebilizumab is available in secondary care settings (hospitals and specialized centers) which narrows down the area of searching for eligible patients. This is particularly relevant to answer the research objectives due to the fact NMOSD is a rare condition and inebilizumab is expected to be used by a small number of individuals. Furthermore, the

inclusion of several countries contributes to the representativeness of European inebilizumab users.

However, some limitations should be addressed:

- Inebilizumab is a novel drug, so one can expect changes over time in clinical practice regarding the use of the drug. The uptake of inebilizumab in the population covered by the data sources may be slow at the beginning of the study period and is likely to increase closer to the end. This pattern may result in a small sample of patients with complete follow-up, i.e., eligible to answer objectives 2 and 3. Thus, treatment patterns and safety outcomes may lack precision. Additionally, long-term treatment patterns and safety outcomes will not be assessed in this study.
- Despite the anticipated high reliability and validity of the data sources proposed for the study, there may be a potential of under- or misreporting of diagnostic information. In addition to variation in ICD-10 coding practices across countries, NMOSD is a rare and complex condition, with wide extent of the diagnostic work-up and diverse diseases can mimic NMOSD (39), making a late diagnosis or potential misclassification more probable. NMOSD-associated conditions may also be prone to misclassification, particularly the less severe ones, which may underestimate their frequency.
- Data collected for administrative purposes may be incomplete for medical information not directly related to reimbursement. This can affect the measurement of variables to characterize inebilizumab users and safety outcomes, underestimating its frequency. When available, the use of disease registries may minimize this limitation.
- Data sources relying on drug prescription/dispensation - and not administration - may result in exposure misclassification and bias in the treatment patterns characterization and time-to-event analyses. Additionally, reasons for treatment discontinuation, switching or augmentation are not possible to capture not allowing the documentation of changes in treatment.
- Some variables, such as drug dose, laboratory results of biomarkers and exams such as MRI may not be available in all data sources which will limit comparability and the ability of a more detailed characterization of inebilizumab users in those countries.
- Other variables, such as treatment indication, if not available in the data sources, will be based on pre-defined algorithms.
- The evaluation of drug safety using secondary databases does not allow for a causal assessment between inebilizumab exposure and the experienced outcome. NMOSD has been shown to be highly associated with other diseases including cancer (40). Additionally, an increased risk of malignancies or serious infections in NMOSD may be induced by the exposure to other immunosuppressive therapies (41,42). Please note, most malignancies have long latency periods in the absence of immunosuppression (43), and although immunosuppressive therapies possibly shorten the period (44), current study follow-up time may be too short (up to 1 year is the maximum) to identify some malignancies. Therefore, safety outcomes should be considered as signals of a possible safety concern of inebilizumab exposure.
- This study will capture safety outcomes that were serious enough to come to medical attention, which may underestimate the frequency of mild events. Additionally, misclassification is a possibility as it relies on the diagnosis codes. Identified serious infections, serious infusion related reactions or malignancies

represent a subgroup of all serious adverse events but for which the validity is expected to be higher.

- For some data sources, reporting of small numbers (e.g., <5) requires compliance with the local policies regarding data anonymization and the risk of patients' identification in observational research. For example, if a real value is 2, it may need to be presented as ≤4 in the results table. This may be a potential limitation for analyses that require stratification, such as the number of malignancies in a specific age groups. Furthermore, minimum and maximum values cannot be reported.

6.10 Other Aspects

6.10.1 Changes to the Protocol

Changes to the protocol will be documented in written protocol amendments. Major (i.e., substantial, significant) amendments will be approved by the relevant regulatory authorities and may require submission or notification to the relevant data source institutional review board (IRB)/independent ethics committee (IEC) or regulatory authorities where required by pertinent regulations. In such cases, the amendment will be implemented only after approval or favorable opinion has been obtained.

6.10.2 Study Management

This study will be performed by IQVIA, with guidance, input, review, and approval of Horizon Therapeutics, including development of materials, data management, analysis and reporting.

7 PROTECTION OF HUMAN SUBJECTS

To ensure the quality and integrity of research, this study will be conducted under the guidelines for GVPs (45) and GPPs (38) issued by the ISPE and any applicable national guidelines.

7.1 Independent Ethics Committee/Institutional Review Board

The study protocol will be submitted to the responsible IRB / IEC for its review / approval whenever required by local law. Regulatory authorities will be notified, and approval sought as required by local laws and regulations. Progress reports will be submitted to Ethics Review Boards (ERB) and regulatory authorities as required by local laws and regulations.

When the approval has been granted, the formal procedure of applying for access to and retrieval of patient level health information can be performed to each governing health authority in the respective countries. A prerequisite for approval from an ERB is that the research project is thoroughly described in a study protocol with a clear scientific objective and purpose.

This study is non-interventional, and analysis is based on secondary data use. No identifying data are collected or stored by IQVIA in any of the planned approaches.

IQVIA will adhere to all local and regional laws on data protection and privacy.

8 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This study will adhere to the ISPE GPP guidelines (38). This is a non-interventional study design which is based on secondary data use. Expedited reporting of adverse events and Adverse Drug Reactions at the individual case level is not required.

9 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

9.1 Progress Report

The progress reports will be produced annually for inclusion in the scheduled PSUR for the product. Progress reports will contain descriptive analysis of the cohorts within each country, including number of patients treated with the study drug where possible (data applications permitting), in order to monitor the feasibility of the study. Multiple extractions are planned. The number of extraction and dates may vary by country due to differences in data governance and product launch date. Examination of aggregate cohort characteristics, drug utilization, and AESI will be presented in final report.

9.2 Annual/Interim Analyses and Reporting

Not Applicable.

9.3 Final Analyses and Reporting

A final study report will be generated after all data collection is complete, including up to 57 months of study period (Table 1). The final study report will be submitted as a standalone procedure to the competent authorities 12 months after the availability of final analytical data set. The final report will encompass all planned analyses, including a description of the complete study population, as described above and in the SAP.

In accordance with the 2010 EU pharmacovigilance legislation (Articles 10 or 10a of Regulation (EC) No 726/2004; Articles 21a or 22a of Directive 2001/83/EC) (46,47), information about this PASS will be entered into the publicly available EU PAS register (http://www.encepp.eu/encepp/studiesDatabase.jsp). The study protocol will be entered into the register before the start of data collection. Updates to the study protocol in case of substantial amendments, progress reports where applicable, and the final study report will also be entered in the register.

9.4 Publications

Study findings will be published in a peer reviewed journal.

Any publication of the results from this study must be consistent with the Horizon Therapeutics publication policy and guided by the Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication of the International Committee of Medical Journal Editors, updated April 2010 (48). The rights of the investigator and of the Horizon Therapeutics with regard to publication of the results of this study are described in the investigator contract.

All reporting will be consistent with the STROBE Initiative checklist for cohort studies (37).

In order to allow competent authorities to review in advance the results and interpretations to be published, the MAH should communicate to the Agency and the competent authorities of the Member States in which the product is authorized the final manuscript of the article within 2 weeks after first acceptance for publication.

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ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

	Document reference number	**Date**	**Title**
1	<Number>	<DD Month YYYY>	<Text>
2	<Number>	<DD Month YYYY>	<Text>
…	<Number>	<DD Month YYYY>	<Text>

ANNEX 2. ENCEPP CHECKLIST FOR STUDY PROTOCOLS.

ENCePP Checklist for Study Protocols (Revision 4)

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

Study title: A real-world observational study of treatment patterns and outcomes for patients with Neuromyelitis optica spectrum disorders (NMOSD) treated with inebilizumab (UPLIZNA) in Europe
EU PAS Register® number: Study not yet registered **Study reference number (if applicable): N/A**

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[2]	☒	☐	☐	
1.1.2 End of data collection[3]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	3.0
1.1.4 Interim report(s)	☐	☐	☒	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results	☒	☐	☐	

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	5
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)	☒	☐	☐	4.2
2.1.2 The objective(s) of the study?	☒	☐	☐	5
2.1.3 The target population? (ie, population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	5
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☒	☐	☐	6.5

[2] 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.

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

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)	☒	☐	☐	6.1
3.2	Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	6.1
3.3	Does the protocol specify measures of occurrence? (eg,, rate, risk, prevalence)	☒	☐	☐	6.7.2
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))	☐	☐	☒	
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)	☐	☐	☒	

Comments:

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	6.1
4.2	Is the planned study population defined in terms of:				6.1
	4.2.1 Study time period	☒	☐	☐	6.1
	4.2.2 Age and sex	☒	☐	☐	6.4
	4.2.3 Country of origin	☒	☐	☐	6.1
	4.2.4 Disease/indication	☒	☐	☐	6.3
	4.2.5 Duration of follow-up	☒	☐	☐	6.1
4.3	Does the protocol define how the study population will be sampled from the source population? (eg, event or inclusion/exclusion criteria)	☒	☐	☐	6.2

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)	☒	☐	☐	6.3.1 6.3.3

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (eg, precision, accuracy, use of validation sub-study)	☒	☐	☐	6.3.1 6.9
5.3 Is exposure categorised according to time windows?	☒	☐	☐	6.3.2
5.4 Is intensity of exposure addressed? (eg, dose, duration)	☒	☐	☐	6.3.2
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☐	☒	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

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?	☐	☐	☒	
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	6.3 Annex 3
6.3 Does the protocol address the validity of outcome measurement? (eg, precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	6.9
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:

Please note the study is descriptive by nature, however we considered the safety events as the outcome.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (eg, confounding by indication)	☐	☐	☒	
7.2 Does the protocol address selection bias? (eg, healthy user/adherer bias)	☒	☐	☐	6.2 6.9
7.3 Does the protocol address information bias? (eg, misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	6.9

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)	☒	☐	☐	6.1

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)	☒	☐	☐	6.3.1 6.3.3
9.1.2 Outcomes? (eg, clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	6.3.4
9.1.3 Covariates and other characteristics?	☒	☐	☐	6.3.2
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)	☒	☐	☐	8.4.1 8.4.2 8.4.3
9.2.2 Outcomes? (eg, date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	8.4.1 8.4.2 8.4.3
9.2.3 Covariates and other characteristics? (eg, age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	8.4.1 8.4.2 8.4.3
9.3 Is a coding system described for:				
9.3.1 Exposure? (eg, WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	8.3.1
9.3.2 Outcomes? (eg, International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities)	☒	☐	☐	Annex 3
9.3.3 Covariates and other characteristics?	☒	☐	☐	6.3.2 Annex 3
9.4 Is a linkage method between data sources described? (eg, based on a unique identifier or other)	☒	☐	☐	6.4.1 6.4.2

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	6.7.2
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	6.5
10.3 Are descriptive analyses included?	☒	☐	☐	6.7.2
10.4 Are stratified analyses included?	☒	☐	☐	6.7.2
10.5 Does the plan describe methods for analytic control of confounding?	☐	☐	☒	
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☐	☐	☒	
10.8 Are relevant sensitivity analyses described?	☐	☐	☒	

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g., software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	6.8
11.2 Are methods of quality assurance described?	☒	☐	☐	6.8
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	9.4

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				6.9
12.1.1 Selection bias?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☐	☒	
12.2 Does the protocol discuss study feasibility? (e.g.,. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	6.4

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?	☒	☐	☐	7.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	7.1

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?	☒	☐	☐	2.0

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)?	☒	☐	☐	9
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	9.4

Comments:

Name of the main author of the protocol: [redacted]

Date: 28 February 2023

Signature: _____

ANNEX 3. ADDITIONAL INFORMATION

Table 6 List of Comorbidities

Comorbidities	Diagnosis ICD-9-CM Codes*	Diagnosis ICD-10-CM Codes*
Coronary heart disease	410.xx, 411.xx, 412, 413.x, 414.xx	I21.xx, I24.x, I25.2, I20.x, I25.xxx
Heart failure	398.91, 402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 428.xx	I09.81, I11.0, I13.0, I13.2, I50.xx
Cerebrovascular disease	430, 431, 432.x, 433.xx, 434.xx, 435.x, 436, 437.0, 437.1, 437.8, 437.9, 438.xx, 997.02	I60.9, I61.9, I62.xx, I63.xx, I65.xx, I66.xx, G45 [excl. G45.4], I67.84, I67.2, I67.81, I67.82, I67.89, I67.9, I69.8, I69.9x, I97.81, I97.82
Lung disease	493.00-493.02, 493.10-493.12, 493.20-493.22, 493.81, 493.82, 493.90-493.92, 491.0, 491.1, 491.20-491.22, 491.8, 491.9, 492.0, 492.8, 496, 490, 494.0, 494.1, 495.0-495.9, 500, 501, 502, 503, 504, 505, 506.4	J45.2x-J45.5x, J45.9xx, J41.x, J42, J43.x, J44.x, J60, J61, J62.x, J63.x, J64, J65, J66.x, J67.x, J68.4
Renal disease	403.01, 403.11, 403.91, 404.02, 404.03, 404.12, 404.13, 404.92, 404.93, 582.x, 583.0-583.7, 585.x, 586, 588.xx, V42.0, V45.1x, V56.x	I12.0, I13.11, I13.2, N03.x, N05.9, N05.2, N05.5, N17.1, N18.x, N19, N25.xx, Z94.0, Z99.2, Z91.15, Z49.xx
Rheumatic disease	446.5, 710.0-710.4, 714.0-714.2, 714.81, 725	M31.5, M31.6, M32.xx, M34.xx, M35.0x, M33.xx, M05.xxx, M35.3
Diabetes	249.xx, 250.xx, 357.2, 362.0x, 366.41, 648.0, E932.3, V58.67	E08.xx, E09.xx, E10.x, E11.xx, E13.xx, O24 [excl. O24.4], Z79.4
Hypertension	401.x, 402.xx, 403.xx, 404.xx, 405.xx	I10, I11.x, I12.x, I13.xx, I15.x, I16.x
Malignancy	140.x-171.x, 174.x-195.x, 200.x-207.x, 209.0x - 209.3x, 173.00, 173.09, 173.10, 173.19, 173.20, 173.29, 173.30, 173.39, 173.40, 173.49, 173.50, 173.59, 173.60, 173.69, 173.70, 173.79, 173.80, 173.89, 173.90, 173.99, 796.76, 795.06, 795.16	C00.x-C43.x, C4A.x, C45.x-C96.x, C44.00, C44.09, C44.10x, C44.19x, C44.20x, C44.29x, C44.30x, C44.39x, C44.40, C44.49, C44.50x, C44.59x, C44.60x, C44.69x, C44.70x, C44.79x, C44.80x, C44.89, C44.90, C44.99, R85.614, R87.614, R87.624
Osteoporosis	733.0x, 733.1x	M80.xxxx, M81.x
Anxiety	300.2x, 300.0x, 300.3	F40.xxx, F41.x, F42.x
Depression	296.21, 296.22, 296.23, 296.26, 296.31, 296.32, 296.33, 296.36	F32.x, F33.xx
Skin ulcers/cellulitis	681.00, 681.10, 681.9, 682.x, 707.xx	L03.01x, L03.03x, L03.11x, L03.21x, L03.31x, L03.81x, L03.90, L89.x, L97.x

Comorbidities	Diagnosis ICD-9-CM Codes*	Diagnosis ICD-10-CM Codes*
Renal transplantation	55.69, V42.0	Z94.0
Infections	Available upon request	Available upon request

Abbreviations: ICD-9/ICD-10, 9th/10th Revision of International Classification of Diseases; CM, Clinical Modification
*ICD-X-CM codes will be translated into local ICD-X codes and provided in SAP

Table 7 NMOSD-Associated Conditions

NMOSD-associated Conditions	Diagnosis ICD-9-CM Codes*	Diagnosis ICD-10-CM Codes*
Hypothyroidism	244.x	E89.0, E03.2, E03.8, E03.9
Pernicious anemia	281.0, 281.1	D51.x
Ulcerative colitis	556.x [excl. 556.2 and 556.3]	K51.xx [excl. K51.2x and K51.3x]
Myasthenia gravis	358.0x	G70.0x
Idiopathic thrombocytopenic purpura	446.6	M31.1
Hemiplegia/paraplegia	334.1, 342.x, 343.x, 344.0x-344.6x, 344.9	G11.4, G81.xx, G80.x, G83.0, G83.1x, G83.2x, G83.3x, G83.4, G83.9, G82.xx
Bladder dysfunction	788.30, 788.31, 788.33, 788.34, 788.36, 788.37, 788.39-788.43, 596.xx	N30.xx, N31.x, N32.xx, N33
Neuropathic pain	353.x, 354.x, 355.x, 356.x, 357.x, 250.6, 729.2, 782	E08.40-E08.42, E09.40, E09.42, E10.40-E10.42, E11.40-E11.42, E13.40-E13.42, G50.0, G50.1, G54.x, G55.x, G56.x, G57.x, G58.x, G60.x, G61.x, G62.x, G63, G64, G65.x, G90.5x, M05.5x, M79.2, M54.1, R20
Antiphospholipid syndrome	289.81	D68.61
Sarcoidosis	135	D86.xx
Scleroderma	357.4, 359.6, 517.2, 701.0, 710.1	M34.xx, L90.0, L94.0, L94.1, L94.3
Sjogren's syndrome	710.2	M35.0x
Systemic lupus erythematosus	710	M32.xx
Dorsalgia	724.5	M54
Disorders of lipoprotein metabolism and other lipidemias	272.0, 272.1, 272.2, 272.3, 272.4, 272.5, 272.9	E78
Other acute disseminated demyelination	341.9	G36.9
Disorders of refraction and accommodation	367	H52
Visual disturbances	368	H53
Disturbances of skin sensation	782	R20
Somatoform disorders	300.81	F45
Other dorsopathies, not elsewhere classified	723.2, 723.3, 723.8, 723.9	M53

NMOSD-associated Conditions	Diagnosis ICD-9-CM Codes*	Diagnosis ICD-10-CM Codes*

Abbreviations: ICD-9/ICD-10, 9th/10th Revision of International Classification of Diseases; CM, Clinical Modification; NMOSD, Neuromyelitis optica spectrum disorder
*ICD-X-CM codes will be translated into local ICD-X codes and provided in SAP

Table 8 Acute Treatments

Name of Agent	Description	Coding
Intravenous Corticosteroids*	H02 - Corticosteroids for systemic use	ATC
Intravenous Immunoglobulin (IVIG)*	J06B - Immunoglobulins	ATC
	8-810.w Human immunoglobulin, polyvalent	OPS
Plasma Exchange (PLEX)	6A550Z3 - Pheresis of Plasma, Single 6A551Z3 - Pheresis of Plasma, Multiple	ICD-10-PCS ICD-10-PCS
	8-820 Therapeutic plasmapheresis	OPS

Abbreviations: ATC, Anatomical therapeutic chemical; ICD-10: 10th Revision of International Classification of Diseases; OPS, operation and procedure classification system, PCS, Procedure Coding System
* Only intravenous administrations

Table 9 NMOSD Maintenance Therapies

Name of Agent	Description	Coding
1. **Oral Steroids**	H02 - Corticosteroids for systemic use	ATC
2. **Immunosuppressive therapies**		
a. Azathioprine	L04AX01	ATC
b. Mitoxantrone	L01DB07	ATC
c. Mycophenolate Mofetil	L04AA06	ATC
d. Methotrexate	L01BA01; L04AX03	ATC
e. Cyclophosphamide	L01AA01	ATC
3. **B-Cell Targeting Therapy (anti-CD20)**		
a. Ocrelizumab	L04AA36 /L04AG08 from 2024	ATC
	6-00a.e Atezolizumab, parenteral	OPS
b. Ofatumumab	L04AA52/ L04AG12 from 2024	ATC
	6-006.4 Ofatumumab, parenteral	OPS
c. Rituximab	L01FA01	ATC
	6-001.h Rituximab, intravenously 6-001.j Rituximab, subcutaneous	OPS
4. **Tocilizumab**	L04AC07	ATC
	6-005.m Tocilizumab, intravenously 6-005.n 8 Tocilizumab, subcutaneous	OPS
5. **Eculizumab**	L04AA25/L04AJ01 from 2024	ATC
	6-003.h Eculizumab, parenteral	OPS
6. **Satralizumab**	L04AC19	ATC

Abbreviations: ATC, Anatomical therapeutic chemical; NMOSD, Neuromyelitis optica spectrum disorder; OPS, operation and procedure classification system

Table 10 Other Immunosuppressive Drugs of Interest

Name of Agent	Description	Coding
1. Interferon beta-1a and 1b	L03AB07; L03AB08	ATC
2. Dimethyl-fumarate	L04AX07; L04AX09	ATC
3. Alemtuzumab	L04AA34/L04AG06 from 2024	ATC
	6-001.0 Alemtuzumab, parenteral	OPS
4. Fingolimod	L04AA27/L04AE01 from 2024	ATC
5. Natalizumab	L04AA23/L04AG03 from 2024	ATC
	6-003.f Natalizumab, parenteral	OPS
6. Glatiramer acetate	L03AX13	ATC
7. Peginterferon beta-1a	L03AB13	ATC
8. Teriflunomide	L04AA31/L04AK02 from 2024	ATC
9. Bortezomib	L01XG01	ATC
	6-001.9 Bortezomib, parenteral	OPS
10. Cladribine	L01BB04; L04AA40	ATC
	6-00a.4 Cladribine, oral	OPS
11. Daclizumab	L04AC0	ATC
	6-009.9 Daclizumab, parenteral	OPS
12. Ozanimod	L04AA38/L04AE02 from 2024	ATC
13. Siponimod	L04AA42/L04AE03 from 2024	ATC
14. Tacrolimus	L04AD02	ATC

Abbreviations: ATC, Anatomical therapeutic chemical; OPS: operation and procedure classification system

Table 11 Pain Medication

Name of Agent	Description	Coding
1. Anti-inflammatory and antirheumatic drugs	M01	ATC
2. Topical products for joint and muscular pain	M02	ATC
3. Muscle relaxants	M03	ATC
4. Anesthetic drugs	N01	ATC
5. Analgesics	N02	ATC
6. Antiepileptic drugs	N03A	ATC
7. Psycholeptics	N05	ATC
8. Psychoanaleptics	N06	ATC
9. Opium alkaloids and derivatives	R05DA	ATC

Abbreviations: ATC, Anatomical therapeutic chemical

Table 12 Safety Outcomes

Classification	Conditions	Diagnosis ICD-9 -CM Codes*	Diagnosis ICD-10-CM Codes*
Hepatitis B Reactivation#	Hepatitis B Reactivation	070.20, 070.21, 070.30, 070.31, 070.32, 070.33, 070.49, 070.59	B16.0, B16.1, B16.9, B17.8, B18.0, B18.1, B19.10, B19.11
Opportunistic Infections#	Pneumocystis jirovecii	136.3	B59
	Cytomeglovirus disease	078.5	B25
	Post-transplant lymphoproliferative disorder	238.77	D47.Z1
	Bartonellosis (disseminated disease only)	088.0	A44
	Blastomycosis	116.0	B40
	Toxoplasmosis	130	B58
	Coccidioidomycosis	114	B38
	Histoplasmosis	115	B39
	Aspergillosis (invasive disease only)	117.3 with 484.6	B44.0
	Candidiasis (invasive disease or pharyngeal)	112.0	B37.0
	Cryptococcosis	117.5	B45.0, B45.7, B45.9
	Other invasive fungi	117.7, 117.6, 117.8	B46.5, B46.4, B46.9, B46.8, B48.2, B48.8
	Legionellosis	482.84	A48.2, A48.1
	Listeria monocytogenes	027.0 with 995.91	A32.7
	Tuberculosis	010-018	A15-A19
	Nocardiosis	039.0, 039.1, 039.8, 039.9	A43
	Non-tuberculous mycobacterium disease	031.2	A31
	Herpes Simplex	054	B00
	Salmonellosis	003	A02
	Strongyloides (hyperinfection syndrome)	279.8	D82.4
	Progressive multifocal leukoencephalopathy	046.3	A81.2

Classification	Conditions	Diagnosis ICD-9 -CM Codes*	Diagnosis ICD-10-CM Codes*
Serious Infections#	Meningitis/encephalitis	036.0, 047.x, 049.x, 072.1, 091.81, 094.2, 098.82, 100.81, 320.x, 036.1, 054.3, 056.01, 058.21, 058.29, 062.x, 063.x, 064.x, 066.41, 072.2, 094.81, 130.0, 323.x	A39, A87, B26.1, A51.41, A52.13, A54.81, A27.81, G00, A39.81, B00.4, B06.01, B10.01, B10.09, A83, A84, A85, A92.31, B262.2, A52.14 , B58.2, G04, G05, B01.1
	Bacteremia/Sepsis (without pneumonia code)	038.x, 790.7, 995.91, 995.92	R78.81, A41, A40, R65.2
	Cellulitis/Soft-Tissue Infections	035, 040.0, 569.61, 681.x, 682.x, 728.86, 785.4	A46, A48.0, K94.02, K94.12, L03, K12.2, N72.6, I96
	Endocarditis	036.42, 074.22, 093.2x, 098.84, 421.x, 422.92	A39.51, B33.21, A52.03, A54.83, I33, I40.0
	Pyelonephritis	590.x	N11, N10, N16
	Pneumonia	003.22, 480.x, 481, 482.x, 483.x, 484.x, 485.x, 486.x, 487.0	J12, J13, J14, J15, J16, J17, J18, P23
	Creutzfeldt Jacob Disease	046.1,	A81.0, F02.80
	Tachycardia	785.0	R00.0
	Bradycardia	427.89	R00.1
	Nausea and vomiting	787.01	R11
	Dyspepsia	536.8	R10.1
	Diarrhea	787.91 787.7 787.99	R19.4 R19.5
	Pyrexia	780.60	R50 R50.2 R50.8 R50.9
	Chills	780.64	R68.8
	Fatigue	780.79	R68.8
	Chest discomfort	786.5 786.50 786.59	R07 R07.3 R07.4
	Pain	Pain, not elsewhere classified Acute pain	R52 R52.0 R52.9
	Back pain	724.5	M54.9
	Myalgia	729.1	M79.1

Classification	Conditions	Diagnosis ICD-9 -CM Codes*	Diagnosis ICD-10-CM Codes*
	Headache	784.0	R51
	Dysgeusia	781.1	R43.2
	Dizziness	780.4	R42
	Dyspnea	786.05	R06.0
	Oropharyngeal pain	784.1	R06.0
	Cough	786.2	R05
	Rash	782.1	R21
	Urticaria/ Erythema	708 708.9 782.9	R23 R23.8 L50 L50.9
	Pruritus	782.1 698	R21
	Rash pruritic	782.1	R21
	Flashing	782.62	R23.2
Infusion related reactions	Generalized skin eruption due to drugs and medicaments	693.0	L27.0
	Localized skin eruption due to drugs and medicaments	-	L27.1
	Complications following infusion, transfusion and therapeutic injections	999.34 999.39	T80
	Other complications following infusion, transfusion and therapeutic injection	999.88 999.89	T80.8
	Unspecified complication following infusion, transfusion and therapeutic injection	999.80	T80.9
	Anaphylactic shock due to adverse effect of correct drug or medicament properly administered	999.4	T88.6
	Unspecified adverse effect of drug or medicament	995.20 995.29	T88.7
	Anaphylactic shock, unspecified	995.0	T78.2
	Angioneurotic oedema	995.1	T78.3

Classification	Conditions	Diagnosis ICD-9 -CM Codes*	Diagnosis ICD-10-CM Codes*
	Allergy, unspecified	995.3	T78.4
	Shock, not elsewhere classified		R57
	Other shock	785.59	R57.8
	Shock, unspecified	785.50	R57.9
Malignancies		140-209	C00-C96

Abbreviations: ICD-9/ICD-10: 9th/10th Revision of International Classification of Diseases, CM, Clinical Modification.
*ICD-X-CM codes will be translated into local ICD-X codes and provided in SAP
#captured if leading to infection-related in-patient hospitalization during the follow-up