PASS information

Title	A Long-Term Observational Study of the Safety of Ublituximab Patients with Relapsing Multiple Sclerosis in a Real-World Setting (ENLIGHTEN)
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Procedure number	Not applicable
Marketing authorisation holder(s)	Neuraxpharm Pharmaceuticals, S.L. Avda Barcelona, 69 08027 - Sant Joan Despí Spain
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Research question and objectives	The overall objective of the study is to characterize the long-term safety of ublituximab in adult patients diagnosed with relapsing multiple sclerosis (RMS) in a post-approval real-world setting. The primary objective of the study is to estimate the incidence rate of long-term safety events of interest, including total malignancies (including non-melanoma skin cancer [NMSC]), malignancies (excluding NMSC) (delayed-onset) and serious infections (acute-onset), in patients treated with ublituximab for RMS, as compared to RMS patients treated with other approved disease-modifying therapies (DMTs). The secondary objectives of this study are: • To estimate the incidence rate of NMSC in patients treated with ublituximab for RMS as compared to RMS patients treated with other approved DMTs. • To assess the overall safety of ublituximab in patients with RMS as compared to patients with RMS exposed to other approved DMTs
Country(-ies) of study	Primarily Germany with European (EU) countries participating in MSBase or United States (US) as needed
Author	Andreas Schmitt, MD (Neuraxpharm Pharmaceuticals, S.L.)

	Apurva Parikh, MD (TG Therapeutics, Inc.)

Approval page

The undersigned have reviewed the format and content of this protocol and have approved Protocol TG1101-RMS402 for issuance.

Protocol Title:	A Long-Term Observational Study of the Safety of Ublituximab Patients with Relapsing Multiple Sclerosis in a Real-World Setting (ENLIGHTEN)
Protocol Number:	TG1101-RMS402
Study Drug:	Ublituximab
Date:	21 August 2024

SPONSOR CONTACTS, Neuraxpharm Pharmaceuticals, S.L. (NxP)

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1. Table of contents

2. List of abbreviations

AE	Adverse event
BMI	Body mass index
CHMP	Committee for Medicinal Products Human Use
CI	Confidence interval
CNS	Central nervous system
DMT	Disease modifying therapy
DMSG	German Multiple Sclerosis Society
EC	European Commission
EDC	Electronic Data Capture
EDSS	Expanded Disability Status Scale
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU PAS Register	European Union electronic Register of Post-Authorisation Studies
GCP	Good Clinical Practice
GMSR	German Multiple Sclerosis Registry
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard ratio
ICH	International Conference on Harmonization
IR	Incidence Rate
ITT	Intention-to-Treat
MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mechanism of action
MRI	Magnetic resonance imaging
MS	Multiple sclerosis
MSFC	Multiple Sclerosis Functional Composite
NMSC	Non-melanoma skin cancer
NxP	Neuraxpharm
PML	Progressive multifocal leukoencephalopathy

PS	Propensity score
PT	Preferred term
PV	Pharmacovigilance
RCT	Randomized clinical trials
RMS	Relapsing multiple sclerosis
RWD	Real world data
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardised MedDRA query
SOC	System organ class
US	United States

3. Responsible parties

3.1. Principal Investigators

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4. Abstract

Rationale and background

Ublituximab (BRIUMVI) is a type I chimeric IgG1 monoclonal antibody that selectively binds the CD20 antigen on pre-B cells, mature and memory B-lymphocytes (Briumvi - Committee for Medicinal Products for Human Use (CHMP). Assessment report 2023, Briumvi - Committee for Medicinal Products for Human Use (CHMP) - positive opinion 2023). The European Commission (EC) granted a marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Briumvi - ublituximab", a medicinal product for human use on May 31, 2023. A safety concern associated with the class of anti-CD20 disease modifying therapies (DMTs) is their immunosuppressive properties and their potential to increase the risk of serious infections and malignancies, especially with prolonged use (Oksbjerg, et al. 2021, Melamed and Lee 2020). MS subjects treated with anti-CD20 monoclonal antibodies may require continuous lifetime treatment and, presently, the safety risks associated with the long-term use of ublituximab are not well-established. While pivotal studies have established efficacy and identified the safety concerns of ublituximab in a controlled setting with a selected patient population, more data is essential to further characterize the safety of ublituximab over a long-term treatment duration. This study will evaluate the long-term safety of ublituximab treatment by assessing the incidence rate of malignancies (delayed-onset) and serious infections (acute-onset) in the real-world setting over a longer duration of exposure time to ublituximab and confirm the overall long-term safety profile of ublituximab in a post-approval real-world setting.

Research question and objectives

The overall objective of the study is to characterize the long-term safety of ublituximab in adults diagnosed with relapsing multiple sclerosis (RMS) in a post-approval real-world setting.

The primary objective of this study is to estimate the incidence rate of long-term safety events of interest, including total malignancies (including non-melanoma skin cancer [NMSC]), malignancies (excluding NMSC) (delayed-onset) and serious infections (acute-onset), in patients treated with ublituximab for RMS, as compared to RMS patients treated with other approved DMTs.

The secondary objectives of this study are:

- To estimate the incidence rate of NMSC in patients treated with ublituximab for RMS as compared to RMS patients treated with other approved DMTs.
- To assess the overall safety of ublituximab in patients with RMS as compared to patients with RMS exposed to other approved DMTs.

Study design

This will be a multi-country, multi-centre, long-term, observational, prospective cohort study of adult RMS patients (≥18 years) treated with ublituximab or a comparator medication approved for the treatment of RMS, dependent on the timing of approval in other countries. The enrolment period is estimated to occur in the first 3 years of the 10-year study and will continue throughout the study period until planned number of patients has been enrolled. For acute-onset events of serious infections, enrolment will occur throughout the first 8.5 years of the study, allowing for at least 1.5 years of follow-up.

Study population

Study population will be primarily drawn from the German Multiple Sclerosis Society (DMSG) MS Registry (GMSR) and will consist of adult RMS patients (≥18 years) treated for MS in routine care. Supplementary data sources such as the international MSBase Neuro-Immunology Registry or a United States (US)-based registry may be added. Of note, the inclusion of MSBase in the study will be pursuant to the regulatory approval, market availability and product usage of ublituximab in countries and sites participating in MSBase data collection. Study subjects will be divided into 3 study cohorts, i.e., patients treated with ublituximab, patients treated with other anti-CD20 treatments, and patients treated with other standard RMS treatments acting through a different mechanism that are approved in the countries participating in the study at the time of patient enrolment.

Variables

Study exposure will be defined as receiving RMS treatment with ublituximab, receiving treatment with other anti-CD20 antibodies, or receiving other standard medications (DMTs) acting through a different mechanism that are approved for RMS treatment in participating countries.

The safety outcomes investigated in the study will include total malignancies (including NMSC), malignancies (excluding NMSC), NMSC, and serious infections (overall and by sub-categories), as well as overall safety in the context of long-term ublituximab treatment. All safety events of interest for the study will be collected and classified using the Medical Dictionary for Regulatory Activities (MedDRA) dictionary. Other variables collected as part of the GMSR registry (and possibly other registries such as MSBase or a United States [US]-based registry) will include patient demographics, history of comorbidities, disease activity, past and present DMT use, and other factors that may be associated with the prescribed RMS treatment and safety outcomes examined in the study.

Primary data source

Data for this study will be collected through the GMSR, which captures real-world data (RWD) on the treatments and outcomes in the German MS population. In 2001, the German Multiple Sclerosis Society, facing lack of data, founded the GMSR as a long-term data repository for MS healthcare research. Through the establishment of a network of over 190 participating neurological centres of different healthcare sectors across Germany, GMSR provides observational real-world data on long-term disease progression, sociodemographic factors, treatment, and the healthcare status of people with MS. Physicians and other medical staff carry out patient enrolment and data collection for the registry during routine examinations. After the provision of written informed consent by adult patients with MS, previous medical data can be collected, and prospective data collection starts and is carried out until the patient's death or withdrawal of informed consent. Members of the medical staff enter data into a web-based electronic data capture (EDC) system. This system allows a single patient's data to be reported by multiple centres.

In 2005, the GMSR started regular operations and has been continuously improved since then. Since 2016, it is mandatory to document via the standardised web-based platform and device-independent EDC-system secuTrial®. The web-based EDC-system is compliant with established tools and concepts of the Technology and Methods Platform for Networked Medical Research e.V.

(TMF, http://www.tmf-ev.de/EnglishSite/Home.aspx) and is certified for conducting clinical trials (GCP, GAMP5, FDA 21 CFR Part 11). Data entry happens directly through interfaces of the EDC system. Data collection, storage and analysis are conducted according to current European and national legislation for data protection. The GMSR is registered at the German registry of clinical trials with registration number DRKS00011257, and at the European Network of Centres for pharmacoepidemiology and Pharmacovigilance with reference number ENCEPP/DSPP/21378.

The current minimal dataset contains information on disease onsets, diagnoses, MS disease courses, disabilities, disease activity, MS therapy and socioeconomic statuses. Physicians schedule frequency of visits according to patients' needs for medical care and routine follow-ups, which the registry recommends being carried out at least on an annual basis. Relapses, adverse events, and pregnancies are documented as separate events.

To constantly ensure high data quality, the GMSR established a wide range of quality control measures. The web-based EDC system ensures that centres have the latest versions of questionnaires. Each questionnaire is checked for consistency of dates, of value ranges and for plausibility. Branching logic (asking only relevant questions based on previous answers) ensures that data is only entered for applicable fields. Furthermore, cross-reference-checks compare data between different questions and forms. Longitudinal checks aim at preventing implausible data changes over time. Additionally, the registry uses R-syntax for automated quality control to find discrepancies and implausibilities. Participating centres receive those findings through a query management system within the EDC-system. All data changes are recorded in audit trails. The database only accepts records with the completed minimal dataset. The GMSR currently follows over 42,000 MS patients residing in Germany, specifically for safety-related outcomes over 5,100 patients with MS are monitored (as of 31st August 2023) in more than 40 participating specialized centres. As Germany is planned to be the first European country in which ublituximab will be launched, the GMSR will enable early and fast data accrual in the ublituximab population in the EU and serve as the primary data source. The GMSR uses the MedDRA dictionary for safety outcomes classification and additionally ICD-10GM for comorbidities.

Additional data sources

Based on the ongoing recruitment rates and pursuant to the regulatory approval and sequential market availability of ublituximab in countries and sites participating, additional data sources such as MSBase or a US-based registry may be added to this study based on ublituximab usage in other countries.

Study size

Assuming that it will take approximately 3 years to achieve full enrolment for delayed-onset outcomes, the study's primary objective will achieve 80% power to detect a hazard ratio (HR) of 2.0 for malignancy in the ublituximab cohort relative to the comparator cohort of other anti-CD20 antibodies with the sample sizes of 886 ublituximab-treated patients and 886 comparator patients (assumed incidence rate 0.47 per 100 patient-years (Hauser, Kappos, et al. 2021)). These initial estimated sample sizes also allow for detection of an HR for serious infections of 1.97 between treatment groups with 80% power assuming an incidence rate of 2.04 per 100 patient-years; however, the study will continue to enrol patients throughout the first 8.5 years of the study, allowing for at least 1.5 years of follow-up for acute-onset events of serious infections in line with the average time on therapy in other registries.

Data analysis

For all analyses, ublituximab will be the treatment of interest. Comparisons will be made with the other anti-CD20 antibody cohort and the cohort receiving approved RMS DMTs acting through a different mechanism. Baseline demographics and clinical characteristics will be examined by cohort, as well as the crude rate, per 100 patient-years, for total malignancies (including NMSC), malignancies (excluding NMSC), NMSC, nd serious infections. Descriptive summary statistics of baseline demographic and clinical characteristics will be provided by treatment cohort for each study outcome. Balance in the baseline covariates between the two cohorts will be examined by standardised differences. Propensity score trimming of the study population for common support, will be used to account for differences between exposure cohorts at baseline. Cox proportional hazards regression will be used to estimate the risk of safety outcomes in ublituximab versus the comparators by estimating the hazard ratio (HR) and associated two-sided 95% confidence interval (95% CI) in the propensity score trimmed populations. Any covariates chosen a priori or not balanced in the trimmed population will be considered for inclusion in the Cox model. If available, data from additional sources will be analysed in parallel performing comparative analyses if appropriately powered. Sensitivity analyses will include completing the Cox model analysis with propensity-score matched populations and applying an Intention-to-Treat (ITT) exposure definition for the delayed-onset cohort. Additionally, sensitivity analyses that examine the effects of unmeasured confounding and the effect of pooling the cohorts from multiple registry sources are planned.

5. Amendments and updates

None

6. Milestones

Milestones	Planned Dates
Date of study registration in the HMA-EMA Catalogues	Anticipated within one month after protocol approval
Start of data collection	Following registration in the HMA-EMA Catalogues anticipated Q3 2024
Annual/Periodic progress report submission in PBRER*	06 Mar 2025 06 Mar 2026 06 Mar 2027 06 Mar 2028 06 Mar 2030 06 Mar 2031 06 Mar 2032
Interim study report submission in PBRER (cumulative up to data cut-off)*	06 Mar 2029
End of data collection	1 January 2034
Final study report submission*	1 June 2034

*Data cut-off: 27 Dec of the report year
PBRER: Periodic Benefit Risk Evaluation Report

7. Rationale and background

Multiple sclerosis (MS) is a chronic and debilitating disease requiring long-term disease modifying therapy (DMT) to reduce the risk of relapse and prevent disability progression and Central Nervous System (CNS) lesion burden. Continuous MS treatment is associated with improved outcomes, and conversely, interruptions in therapy have been associated with return of disease activity and disability accumulation.

Ublituximab (BRIUMVI) is a type I chimeric IgG1 monoclonal antibody that selectively binds to the trans-membrane CD20 antigen found on pre-B cells, mature and memory B-lymphocytes (Briumvi - Committee for Medicinal Products for Human Use (CHMP). Assessment report 2023, Briumvi - Committee for Medicinal Products for Human Use (CHMP) - positive opinion 2023, Lee 2023). The European Commission (EC) granted a marketing authorisation under Regulation (EC) No 726/2004 of the European Parliament and of the Council for "Briumvi - ublituximab", a medicinal product for human use on May 31, 2023. DMTs, including anti-CD20 monoclonal antibodies approved for relapsing forms of multiple sclerosis (RMS), help to reduce relapses by modifying the immune system and lowering the risk of inflammation. One safety concern associated with DMT mechanism of action is their immunosuppressive properties and their potential to increase the risk of serious infections and malignancies, especially with prolonged

use (Oksbjerg, et al. 2021, Melamed and Lee 2020). Pooled data from ocrelizumab trials (OPERA I, II, and ORATORIO) implied an imbalance in malignancies in the ocrelizumab treatment group versus pooled IFN β-1a and placebo group (Hauser, Kappos, et al. 2021). The rate of malignancies in ocrelizumab-treated patients, however, remained within the range reported in MS epidemiological studies (Hauser, Bar-Or and Comi, et al. 2017). In pooled Phase III data of ocrelizumab in RMS, the proportion of adverse events (AEs) and serious AEs (SAEs) were comparable to the comparator group of IFN β-1a. Fewer serious infections were reported for ocrelizumab-treated patients than in a group of IFN β-1a-treated patients (1.3% vs. 2.9%, respectively). In pooled Phase III data comparing ofatumumab and teriflunomide, the percentage of patients who reported a serious infection was 2.5% with ofatumumab and 1.8% with teriflunomide. Additionally, five neoplasm cases occurred in the ofatumumab group (0.5%) and four (0.4%) in the teriflunomide group (Hauser, Bar-Or and Cohen, et al. 2020).

Malignancies and serious infections were specifically examined in the ublituximab clinical development program which included 5 Phase II/Phase III studies. In the pivotal trials TG1101-RMS301 and TG1101-RMS302, there was a low incidence of malignancies reported in subjects receiving ublituximab, despite the potential class risk of malignancies. Additionally, serious infections were infrequently reported in ublituximab-treated subjects. There were 3 infection-related deaths that occurred in the pivotal trials, all in subjects receiving treated with ublituximab; the infections leading to death were post-measles encephalitis, pneumonia, and post-operative salpingitis following an ectopic pregnancy. Of note, serious infections are also a known class effect for anti-CD20 monoclonal antibodies. The long-term safety of ublituximab in subjects diagnosed with RMS is currently being investigated in study TG1101-RMS303 open label extension.

MS subjects treated with anti-CD20 monoclonal antibodies require continuous treatment and, presently, the safety risks associated with the long-term use of ublituximab are not well-established. While the pivotal studies established efficacy and identified potential safety risks of ublituximab in a controlled setting with a selected patient population, more data is essential to further characterize the safety of ublituximab over long-term treatment duration. This study will evaluate the long-term safety of ublituximab treatment by assessing the incidence rate of malignancies and serious infections in the real-world setting over a longer duration of exposure time to ublituximab and confirm the overall safety profile of ublituximab.

8. Research question and objectives

The overall objective of the study is to characterize the long-term safety of ublituximab in adults diagnosed with RMS in a post-approval real-world setting.

8.1. Primary objective

The primary objective of this study is to compare the incidence rate of long-term safety events of interest, including total malignancies (including non-melanoma skin cancer [NMSC]) (delayed-onset), malignancies (excluding NMSC) (delayed-onset), and serious infections (acute-onset), in patients with RMS treated with ublituximab relative to other approved DMTs.

8.2. Secondary objectives

The secondary objectives of this study are:

- To estimate the incidence rate of NMSC (delayed-onset) in patients treated with ublituximab for RMS as compared to RMS patients treated with other approved DMTs.
- To assess the overall safety of ublituximab in patients with RMS as compared to patients with RMS exposed to other approved DMTs, based on available data, where consistently collected from each data source.

9. Research methods

9.1. Study design

This will be a multi-registry, multi-centre, long-term, observational study of adult RMS patients (≥18 years) treated with ublituximab or comparator RMS standard of care medication that may comprise multiple countries and registries, dependent on the timing of approval in other countries. The study will use existing data which will not be collected primarily for this research but do reflect care in usual clinical practice. The enrolment period is estimated to occur in the first 3 years of the 10-year study and will continue throughout the study period until planned number of patients has been enrolled. For acute-onset events of serious infections, enrolment will occur throughout the first 8.5 years of the study, allowing for at least 1.5 years of follow-up in line with the average time on therapy in other registries. This follow-up period is anticipated to be a conservative estimate for MS patients' longer-term use of therapies. Longer average time exposure to drug will result in more observed events and higher power, while shorter average time exposure to drug will result in few observed events and lower power.

Data from the German Multiple Sclerosis Society (DMSG) MS Registry will be used to follow up on study cohorts that will be analysed to meet the study objectives. The international MSBase Neuro-Immunology Registry or a US-based registry with favourable access may be added as an additional source of study population.

The safety events of interest will be categorized into 2 groups: *delayed-onset events* including total malignancies (including NMSC), malignancies (excluding NMSC), NMSC, and *acute-onset events* including serious infections (overall and categorized by different types), as described in detail in Section 9.3.2. The exposure definitions used for the primary and secondary analyses are outlined in Section 9.3.1. The definitions determine the exposure time a patient will contribute to each cohort for both the delayed-onset and acute-onset outcomes, including assessment of the overall safety of ublituximab.

9.2. Setting

The primary data source for this study is the German MS Society (DMSG) MS-Registry (GMSR) (Ohle, et al. 2021), The GMSR is a network of MS centres across different healthcare sectors in Germany. Sites participating in the GMSR are selected from the centres accredited by the German MS Society as 'MS Centre', 'Specialized MS Centre', or 'MS Rehabilitation Centre', and include university clinics, acute care clinics, rehabilitation clinics, MS outpatient clinics and resident neurologists complying with the accreditation criteria. In the participating centres, physicians and other medical staff carry out MS patient enrolment and data collection for the registry during routine clinical visits. Enrolment in the GMSR is voluntary. The GMSR currently follows over 42,000 MS patients who reside in Germany.

Germany represents a significant portion of the EU MS population and is the first country outside of the United States with commercial availability of ublituximab. Additionally, currently all EU-

licensed MS medications are available and reimbursed by the German statutory health insurances. Therefore, the earliest and fastest patient enrolment in this study is expected to take place in the GMSR.

Data from additional sources, such as MSBase or a US registry, may be included as representation of the target population. MSBase is an international collaborative group of researchers dedicated to evaluating outcomes data in MS. Enrolment in the MSBase Registry is voluntary. The MSBase Registry allows for access to approximately 90,000 MS patients across a range of countries, including countries in the EU. Of note, the inclusion of MSBase in the study will be pursuant to the regulatory approval and market availability of ublituximab in countries and sites participating in MSBase data collection.

9.2.1. Population

The primary population for this study will be drawn from the patients enrolled in the GMSR. Other registry sources may be included based on market availability and patient enrolment. The study population will consist of adult RMS patients (≥18 years) divided into 3 study cohorts for delayed-onset outcomes and 3 study cohorts for acute-onset outcomes, i.e., patients treated with ublituximab, patients treated with other anti-CD20 treatments, and patients treated with other standard RMS treatments acting through a different mechanism that are approved in the countries participating in the study at the time of patient enrolment (see Section 9.2.2.). Detailed eligibility criteria for study enrolment are provided below.

9.2.1.1. Inclusion criteria

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

1. Patient diagnosed with relapsing forms of multiple sclerosis (RMS), to include clinically isolated syndrome, relapsing-remitting disease, and active secondary progressive disease, based on MS diagnostic criteria fulfilling McDonald criteria.
2. Patient is at least 18 years of age or older at time of treatment start.
3. Patients (both treatment-naive and patients treated with DMTs other than ublituximab) who initiate use of ublituximab or a comparator medication for RMS at registry enrolment or during the course of registry follow-up (post-enrolment).
    - Exposures of comparator medication for RMS will be limited to those at or after the initiation date of first ublituximab patient.

9.2.1.2. Exclusion criteria

1. Patient is unable or unwilling to provide informed consent to participate in the registry.
2. Patient is participating in a double-blind clinical trial for the treatment of MS.
3. Patient is receiving an off-label therapy (such as rituximab) for the treatment of MS.
4. Patient is receiving an MS therapy for an indication outside of relapsing forms of MS.

9.2.2. Study cohorts

For the evaluation of delayed-onset outcomes of total malignancies (including NMSC), malignancies (excluding NMSC), NMSC, and PML, three drug exposure cohorts will be created following a *hierarchical exposure classification* as described in Section 9.3.1.2.

For the acute-onset outcome of serious infections, three drug exposure groups will be created applying an *as-treated approach* as described in Section 9.3.1.2.

The study cohorts will be defined differently for delayed-onset and acute-onset outcomes but each outcome type will consist of three cohorts:

- ublituximab cohort consisting of new users at or after enrolment
- other DMT comparator cohort, consisting of patients newly initiating other DMTs acting through a different mechanism that are approved for RMS treatment in participating countries and captured in the participating sites (including new therapies as they become approved) at or after enrolment; and
- other anti-CD20 comparator cohort consisting of patients newly initiating other anti-CD20 antibody treatments approved for RMS treatment in participating countries and captured in the participating sites (including new therapies as they become approved) at or after enrolment.

The above three cohorts will include new users of the specific medications (while other medications on beforehand would be allowed).

The following is a list of the eligible MS DMTs in GMSR for the comparator cohorts:

Cohort	**MS DMT**
Other anti-CD20 comparator cohort	Ocrelizumab
	Ofatumumab
Other DMT comparator cohort	Alemtuzumab
	Cladribine
	Dimethyl fumarate
	Diroximel fumarate
	Glatiramer acetate
	Interferon beta
	Ozanimod
	Fingolimod
	Ponesimod
	Natalizumab
	Peginterferon β-1a
	Teriflunomide
	Mitoxantrone

9.2.3. Follow-up

Study enrolment is estimated to occur in the first 3 years of the 10-year study and will continue throughout the study period until planned number of patients has been enrolled. For acute-onset events of serious infections, enrolment will occur throughout the first 8.5 years of the study, allowing for at least 1.5 years of follow-up in line with the average time on therapy in other registries. Each subject will be followed from study index date to the earliest of the following

events for delayed-onset outcomes: initiation of other DMT acting through a different mechanism (other anti-CD20 cohort only) or initiation of ublituximab (other DMT or other anti-CD20) comparator cohorts), end of the study period, withdrawal from the registry, occurrence of study outcome, or death. For acute-onset outcomes each subject will be followed from study index date to the earliest of the following events: switch to other cohort medication, end of the study period, withdrawal from the registry, occurrence of study outcome, or death. For details on delayed-onset and acute-onset outcomes and their follow-up parameters for statistical analyses see Sections 9.7.3 and 9.7.4.

9.3. Variables

Study variables will be collected during routine patient care visits and will include demographic, clinical, and safety information.

The following variables but not limited to will be collected at the enrolment visit and follow-up visits, as available:

- Demographics including age, sex, height, weight, education, employment status, partnership status, geographic area of residence
- Anamnesis including
    - MS diagnostic criteria (McDonald Revision 2017)
    - Date of first MS symptoms
    - Date of first MS diagnosis
    - Number of previous MS relapses
- Medical history and concurrent/comorbid medical conditions
- Physical examination information
- MS disease activity status and symptoms
    - EDSS total score
    - MRI parameters
    - Relapse status including date and treatment
    - MS Functional Composite (MSFC)
- Current MS treatment
- Information on recent treatment switch
    - Main reason for recent treatment switch (lack of effectiveness of previous DMT, safety considerations, tolerability consideration, patient wish, physician's decision, etc.)
    - Additional reasons supporting treatment switch decision
- Information on concomitant drugs
    - Medication name and class
    - Start date
    - End date

9.3.1. Exposure

Drug exposure windows will be defined separately for the evaluation of delayed-onset outcomes (i.e., malignancy, NMSC, PML) and acute-onset outcomes (i.e., serious infections). The assignment to exposure groups will be hierarchical for delayed-onset outcomes and an as-treated approach will be used for acute-onset outcomes.

9.3.1.1. Exposure definition for delayed-onset outcomes

Incident subjects (those prescribed or initiating medication for RMS at or after registry enrolment) will be included in exposure cohorts for delayed-onset outcomes.

For delayed-onset outcomes (total malignancies [including NMSC], malignancies [excluding NMSC], NMSC, and PML), time will be categorized into 1 of the 3 delayed-onset study cohorts, i.e., ublituximab cohort, other DMT cohort, or the other anti-CD20 comparator cohort. The exposure cohort assignment for malignancy is based on a hierarchical definition (see **Figure 1** for a visual representation). Exposure will first be classified according to treatment at the index date. Subjects are assigned to the ublituximab cohort at initiation of ublituximab and remain in this cohort regardless of discontinuation or subsequent exposure to a comparator drug in the other DMT or other anti-CD20 cohort. If a subject receives ublituximab after exposure to a comparator drug (other DMT or other anti-CD20) during the study period, the subject will be assigned to the respective comparator cohort first and will be censored at the time the subject qualifies for entry into the ublituximab cohort. A second index date marking the start of a ublituximab exposure episode will be assigned and all subsequent person-time will be classified as exposure to ublituximab. If a subject received other DMT after exposure to other anti-CD20 treatment, the subject will be assigned to the other anti-CD20 comparator cohort initially and will be censored at the time the subject qualifies for entry into the other DMT comparator cohort. An index date marking the start of the other DMT comparator exposure episode will be assigned and all subsequent person-time will be classified as exposure to other DMT if exposure to ublituximab does not occur. If discontinuation of the other anti-CD20 comparator occurs with no switch to ublituximab or the other DMT comparator cohort, the remaining time in the study will be attributed to the other anti-CD20 comparator cohort. This definition encompasses the broadest definition of ublituximab exposure (once exposed, always at risk) while ensuring the comparator cohort is free from any prior or subsequent ublituximab exposure. This is equivalent to a dichotomized categorization of person-time as being "ever exposed" to ublituximab versus "not yet exposed" to ublituximab and will be descriptively summarized in the baseline tables.

<u>Ublituximab cohort</u>

For subjects initiating ublituximab, the exposure will begin (index date) at registry enrolment. For subjects with subsequent treatment initiation, their index date will be from date of initiation and their exposure episode will continue until end of the study period, withdrawal from the registry, occurrence of event, or death, whichever comes first.

<u>Other DMT comparator cohort</u>

For subjects initiating a DMT treatment acting through a different mechanism without previous exposure to ublituximab or other anti-CD20 comparators in the study, the exposure episode will begin at registry enrolment (index date) and continue until the initiation of ublituximab, end of study period, withdrawal from the registry, occurrence of event, or death, whichever comes first.

<u>Other anti-CD20 comparator cohort</u>

For subjects initiating an anti-CD20 medication other than ublituximab without previous exposure to ublituximab in the study, the exposure episode will begin at registry enrolment (index date). For subjects with subsequent anti-CD20 treatment other than ublituximab initiation, their index date will be from the date of initiation and continue until the initiation of ublituximab or other DMT treatment, end of study period, withdrawal from the registry, occurrence of event, or death, whichever comes first.

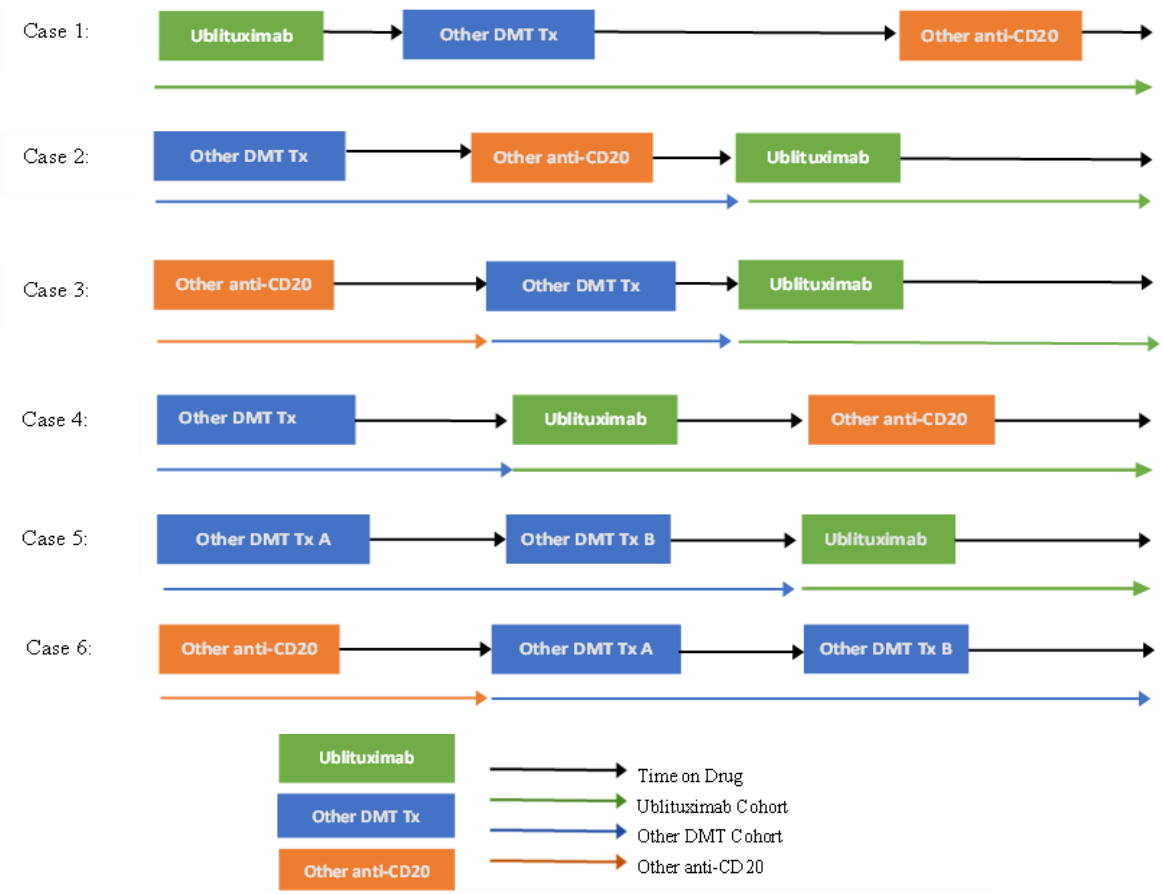

Figure 1. Example of exposure classification for delayed-onset outcomes using the hierarchical definition

Case 1 illustrates an existing registry patient contributing one exposure episode to the ublituximab cohort.

Case 2 illustrates an existing registry patient contributing two exposure episodes, one to the other DMT cohort and one to the ublituximab cohort.

Case 3 illustrates an existing registry patient contributing three exposure episodes, one to the other anti-CD20 cohort, one to the other DMT cohort, and one to the ublituximab cohort. The sequence shown in case 3 is the only way a patient could have 3 exposure episodes under the hierarchical exposure definition.

Case 4 illustrates an existing registry patient contributing two exposure episodes, one to the other DMT cohort and one to the ublituximab cohort. Based on the hierarchical exposure definition, time in the ublituximab cohort continues despite the initiation of another anti-CD20 treatment).

Case 5 illustrates an existing registry patient contributing two exposure episodes, one to the other DMT cohort and one to the ublituximab cohort. Switching medications within the other DMT cohort does not trigger a new index date for the exposure cohort.

Case 6 illustrates an existing registry patient contributing two exposure episodes, one to the other anti-CD20 cohort and one to the other DMT cohort.

9.3.1.2. Exposure definition for acute-onset outcomes

Only incident subjects (i.e., subjects initiating or restarting medication for RMS at or after registry enrolment) will be able to contribute an exposure episode to at least one treatment cohort for serious infections.

For serious infections, time associated with each exposure episode will be categorized into 1 of the 3 acute-onset study cohorts, i.e., ublituximab cohort, other DMT cohort, or the other anti-CD20 comparator cohort, using an as-treated approach where person-time accrued is based on the treatment received (see Figure 2 for a visual representation). At each treatment switch, subjects will contribute to a new exposure episode; therefore, subjects may contribute multiple exposure episodes to the ublituximab, other DMT and other anti-CD20 comparator cohorts corresponding to their usage.

The risk window for acute-onset outcomes will depend on the DMT and will be based on the half-life as well as the mechanism of action, including lymphocyte count recovery, as described in the Summary of Product Characteristics and the literature. Sensitivity analyses will vary the risk window to assess the robustness of findings, including but not limited to 1) 364 days for ublituximab and a proportionate increase for other DMTs up until the date of switch to another DMT. The half-life and risk window for each DMT are listed in **Table 1**.

Table 1 MS DMT Risk Windows

Cohort	**MS DMT**	**Half-life**	**Primary Risk Window (days)**	**Larger Risk Window (days) for Sensitivity Analysis**
Ublituximab	Ublituximab[1]	22 days	182	364
Other anti-CD20 comparator cohort	Ocrelizumab[2]	26 days	182	364
	Ofatumumab[3]	16 days	182	364
Other DMT comparator Cohort	Interferon β-1b[4]	5 hours	91	182
	Interferon β-1a[5]	50-60 hours	91	182
	Glatiramer acetate[6]	<24 hours	91	182
	Natalizumab[7]	27 days	91	182
	Fingolimod[8]	6-9 days	91	182
	Teriflunomide[9]	19 days	121	242
	Alemtuzumab[10]	4-5 days	364	1820
	Dimethyl fumarate[11]	1 hour	91	182
	Cladribine[12]	1 day	364	1456
	Mitoxantrone[13]	75 hours	91	182
	Peginterferon β-1a[14]	78 hours	91	182

	Diroximel fumarate[15]	1 hour	91	182
	Ozanimod[16]	21 hours; active metabolite 11 days	91	182
	Ponesimod[17]	33 hrs	91	182

1. Briumvi® (ublituximab-xiiy) Summary of Product Characteristics
2. Ocrevus® (ocrelizumab) Summary of Product Characteristics
3. KESIMPTA® (ofatumumab) Summary of Product Characteristics
4. EXTAVIA® (interferon beta-1b) Summary of Product Characteristics
5. Rebif® (interferon beta-1a) Summary of Product Characteristics
6. Copaxone® (glatiramer acetate) Summary of Product Characteristics
7. Tysabri® (natalizumab) Summary of Product Characteristics
8. GILENYA® (fingolimod) Summary of Product Characteristics
9. AUBAGIO® (teriflunomide) Summary of Product Characteristics
10. LEMTRADA® (alemtuzumab) Summary of Product Characteristics
11. Tecfidera® (dimethyl fumarate) Summary of Product Characteristics
12. MAVENCLAD® (cladribine) Summary of Product Characteristics
13. NOVANTRONE® (mitoxantrone) Summary of Product Characteristics
14. JAYEMNI (azathioprine) Summary of Product Characteristics
15. VUMERITY® (diroximel fumarate) Summary of Product Characteristics
16. ZEPOSIA® (ozanimod) Summary of Product Characteristics
17. PONVORY® (ponesimod) Summary of Product Characteristics

Exposure episodes for each cohort are defined below.

Ublituximab cohort

Exposure episodes for subjects starting ublituximab will begin at the date of treatment start and will continue until the earliest of ublituximab medication discontinuation plus 24 weeks, a start of a comparator drug (other DMT or other anti-CD20), end of study period, withdrawal from the registry, occurrence of event, or death.

Other DMT comparator cohort

Exposure episodes for subjects starting a DMT treatment acting through a difference mechanism will begin at the date of treatment start and will continue until date of medication discontinuation plus the applicable risk window outlined in Table 1, start of ublituximab or another comparator medication, end of study period, withdrawal from the registry, occurrence of event, or death, whichever comes first.

Other anti-CD20 comparator cohort

Exposure episodes for subjects starting a anti-CD20 drug other than ublituximab will begin at the date of treatment start and will continue until date of medication discontinuation plus 24 weeks, start of ublituximab or another comparator medication, end of study period, withdrawal from the registry, occurrence of event, or death, whichever comes first.

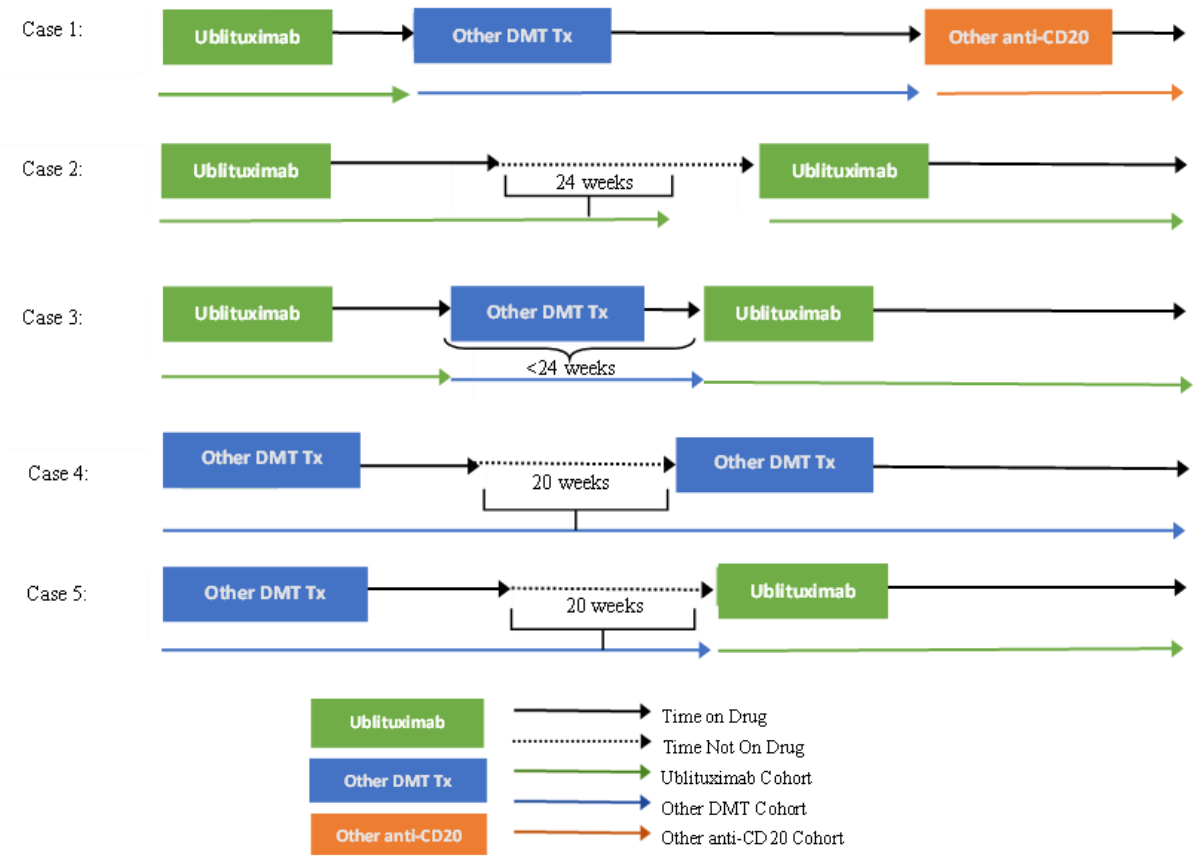

Figure 2. Example of exposure classification for acute-onset outcomes

Case 1 illustrates a patient contributing three exposure episodes, one to the ublituximab cohort, one to the other DMT cohort, and one to the other anti-CD20 cohort.

Case 2 illustrates a patient contributing two exposure episodes to the ublituximab cohort. The second exposure episode is considered a medication restart, with a new index date assigned at the restart of the ublituximab medication, because the restart occurred more than 24 weeks after discontinuation.

Case 3 illustrates a patient contributing three exposure episodes, two to the ublituximab cohort and one to the other DMT cohort. While ublituximab is restarted within 24 weeks of discontinuation, since another DMT drug is initiated between discontinuation and restart, a new index date is assigned and a second ublituximab exposure episode is created.

Case 4 illustrates a patient contributing one exposure episode to the other DMT cohort. While the patient discontinues and restarts the other DMT treatment, the restart occurs within 24 weeks of discontinuation and does not result in a separate exposure episode and a new index date is not created at medication restart.

Case 5 illustrates a patient contributing two exposure episodes, one to the other DMT cohort and one to the ublituximab cohort. The 24-week risk continuation window after discontinuing the other DMT treatment ends at the initiation of ublituximab. Time from ublituximab initiation to 24 weeks post ublituximab discontinuation contributes to the ublituximab cohort.

9.3.2. Outcomes

9.3.2.1. Primary outcomes

9.3.2.1.1. Total malignancies (including NMSC)

Total malignancy includes skin cancers, solid cancers, and hematologic cancers. Cases of malignancy will be identified using the Medical Dictionary for Regulatory Activities (MedDRA) Standardised MedDRA query (SMQ) "Malignancy". Total malignancy events including NMSC (defined in Section 9.3.2.2.1. will be assessed in the primary analysis.

9.3.2.1.2. Malignancies (excluding NMSC)

Malignancy excluding NMSC includes solid cancers and hematologic cancers. Cases of malignancy will be identified using the MedDRA SMQ "Malignancy". All malignancy events excluding NMSC (defined in Section 9.3.2.2.1. will be assessed in the primary analysis.

9.3.2.1.3. Serious infections

Serious infections include infections requiring or prolonging hospitalisation; life-threatening infections; infections leading to death; infections causing disability; infections causing permanent damage or congenital abnormality; or medically significant infections (e.g., infections requiring parenteral or intravenous antibiotics). Cases of serious infection will be identified using the MedDRA System Organ Class (SOC) "Infections and Infestations". All serious infection events will be assessed in the primary analysis. Serious infection sub-categories including but may not be limited to PML (treated as a delayed onset outcome) and hepatitis B reactivation will also be assessed.

9.3.2.2. Secondary outcomes

9.3.2.2.1. NMSC

The most common types of non-melanoma skin cancer include basal cell carcinoma and squamous cell carcinoma. Cases of NMSC will be identified using the MedDRA Preferred Terms (PTs) for NMSC (see bulleted list of PTs below). All NMSC events will be assessed in the secondary analysis.

- Adenosquamous cell carcinoma
- Basal cell carcinoma
- Basal cell carcinoma metastatic
- Basosquamous carcinoma
- Basosquamous carcinoma of skin
- Dermatofibrosarcoma protuberans
- Dermatofibrosarcoma protuberans metastatic
- Eccrine carcinoma
- Keratinising squamous cell carcinoma of nasopharynx
- Lip squamous cell carcinoma
- Metastatic squamous cell carcinoma
- Neuroendocrine carcinoma of the skin
- Sarcoma of skin
- Sebaceous carcinoma

- Skin angiosarcoma
- Skin squamous cell carcinoma metastatic
- Skin squamous cell carcinoma recurrent
- Squamous cell carcinoma
- Squamous cell carcinoma of skin

9.3.2.2.2. Overall safety

Overall safety includes the following adverse event information collected in the registry:

- All serious adverse events;
- Post-marketing surveillance and enhanced pharmacovigilance events (immune-mediated colitis, serious/opportunistic infections (including hepatitis B, progressive multifocal leukoencephalopathy, and central nervous system infections), hepatotoxicity/hepatic disorders independent of hepatitis B, pancreatitis, thrombocytopenia, and pregnancy complications).

9.3.3. Other covariates

The following covariates will be collected as available for each patient to aid in confounding adjustment, including but not limited to:

- Patient demographics (including age, sex, country, height, weight, education)
- MS history and severity (e.g., disease duration, number of relapses, disease course, EDSS score, MRI results, MSFC)
- DMT treatment history including prior B-cell depleting MS therapies (drug name, start/end dates, dose, reason for discontinuation) [grouping/classing of DMTs will be in accordance with the German MS guideline in GMSR].
- Other medical history including prior infections and comorbidities such as cardiovascular disease, diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD), human immunodeficiency virus (HIV), hematologic malignancy (leukemia, lymphoma, multiple myeloma), transplant history, chronic lung disease, liver disorder, ischemic heart disease, congestive heart disease, periodontal disease
- Previous immunosuppressive medication use
- Pregnancy status (mode of delivery, outcome, complications)
- Concomitant drugs(start/end dates, dose, indication)
- Active NMSC

9.4. Data sources

This study will use real-world data (RWD) collected in the context of routine clinical care from existing international MS registries. The use of registries, utilizing patients enrolled in routine practice setting, in both academic and community-based clinics, is expected to include patients who are representative of the general MS population, thus providing adequate generalisability of the safety study findings.

To recruit a sufficient number of patients and obtain meaningful safety estimates, the GMSR registry has been identified for use in this study. The international MSBase Neuro-Immunology

Registry or a US-based MS registry may be added as an additional source of study population. These registries were established to study the MS population and to document the long-term safety risks of MS therapies in a real-world setting, thus providing an adequate data source for the proposed safety study. Of note, the inclusion of MSBase in the study will be pursuant to the regulatory approval and market availability of ublituximab in countries and sites participating in MSBase data collection.

9.4.1. Data Source: German MS registry

The GMSR currently follows over 42,000 MS patients, who reside in Germany. Specifically for safety-related outcomes, a sub-cohort of centres, which collect additional pharmacovigilance data, was initiated and there is an ongoing inclusion of additional participating sites (over 5,100 patients as of 31 August 2023). As Germany will serve as the first European country in which ublituximab will be launched, the GMSR will enable early data accrual in the ublituximab population in the EU. In regard to the comparator treatments, the GMSR population in Germany currently (20 February 2024) has access to all EU-licensed MS-DMT and the German statutory health insurance covers in-label treatment of pwMS as per prescription of the treating physician. The GMSR uses the MedDRA dictionary for safety outcomes classification and additionally ICD-10GM for comorbidities.

9.4.1.1 Enrolment visits in the GMSR

See Section 9.3 for the variables that will be collected at the enrolment visit in GMSR.

9.4.1.2 Follow-up visits in the GMSR

The following variables will be collected at follow-up visits in GMSR:

- Changes in demographics (graduation, training, employment, domestic support, change of residence, etc.)
- MS disease activity status
    - EDSS total score
    - MRI parameters
    - Relapse status including date, treatment
    - MSFC
- Reason for visit
    - Planned or unplanned
    - Therapy delivery, adverse event, disease progression, change of disease course/severity, other (e.g., pregnancy)
- Changes, interruptions, and permanent discontinuation of treatment (if applicable)
    - Number and duration of temporary treatment interruptions
    - Reasons for temporary treatment interruptions
    - Date of permanent discontinuation of treatment
    - Reasons for permanent discontinuation of treatment
    - Name, dose, frequency, route of administration, start date of planned DMT (for switch patients only)
- Concomitant symptomatic medications
- Adverse events and serious adverse events

9.4.2. Data Source: MSBase registry

The MSBase Registry currently enrols approximately 90,000 MS patients across a range of countries, including countries in the EU, to ensure generalisability and an established data source for real-world MS research, and specifically for long-term safety outcomes of MS treatment.

9.5. Study size

Sample size and detectable difference calculations were performed using the assumed incidence rate for the comparator cohort to adequately detect at most a 2.0-fold increase in the risk of total malignancies (including NMSC) and malignancies (excluding NMSC) among the ublituximab-treated cohort relative to patients in the comparator cohort. The following assumptions were made for the calculations for the delayed-onset cohort sample size calculations:

- Two-sided Type I error rate of 0.05
- 80% Power
- Background incidence rate of malignancy, excluding NMSC: 0.47 per 100 patient-years (Hauser, Kappos, et al. 2021, Hauser, Kappos, et al. 2022)
- Uniform accrual and 10% annual attrition rate per cohort
- 1:1 accrual (ublituximab : comparators)

The study will achieve 80% power to detect a hazard ratio (HR) of 2.0 for malignancy excluding NMSC in the ublituximab cohort relative to the other DMT comparator cohort with an estimated sample size of 886 for each cohort. All HRs will be reported with two-sided 95% CIs using Cox model estimates. The analysis of malignancy will occur at the end of the 7-year follow-up period which will be approximately 10 years after the start of the study and will include only those patients accrued during the study enrolment period.

Preliminary estimates of projected sample size for delayed- and acute-onset safety events were based on the feasibility of enrolment.

Because the acute-onset exposure definition is based on time on drug, power calculations for serious infections consider average duration exposed to drug, assumed to 1.5 years. The estimated sample sizes determined to power delayed-onset outcomes (886 per cohort) will allow for detection of a HR of 1.97 in acute-onset safety outcomes between treatment groups with 80% power assuming a serious infection background incidence rate of 2.04 per 100 patient-years (Hauser, Kappos, et al. 2021, Hauser, Kappos, et al. 2022) with an average of at least 1.5 years of patient follow-up during the study for serious infections. However, accrual of patients will continue to occur throughout the first 8.5 years of the study, which will increase the sample size for the acute-onset cohorts, lowering the detectable HR.

Sample size and power calculations were performed using the PASS software (PASS Power Analysis and Sample Size Software 2020).

9.6. Data management of the primary data source

The web-based EDC-system used for data collection in GMSR is compliant with established tools and concepts of the Technology and Methods Platform for Networked Medical Research e.V. (TMF, http://www.tmf-ev.de/) and is certified for conducting clinical trials (GCP, GAMP5, FDA 21 CFR Part 11).

To constantly ensure high data quality, the GMSR established a wide range of quality control measures. The web-based data entry system ensures that centres have the latest versions of questionnaires. Each questionnaire is checked for consistency of dates, of value ranges and for plausibility. Branching logic (asking only relevant questions based on previous answers) ensures that data is only entered for applicable fields. Furthermore, cross-reference-checks compare data between different questions and forms. Longitudinal checks aim at preventing implausible data changes over time. Additionally, the registry uses R-Syntax for automated quality control to find discrepancies and implausibilities. Participating centres receive findings through query management system within the EDC-System. All data changes are recorded in audit trails. The database only accepts records with the completed minimal dataset. Participating centres are provided with training materials and tutorials.(Ohle, et al. 2021).

9.7. Data analysis

Exposure cohorts will be created as described in Section 9.3.1. using registry data. Analyses will be conducted separately for each outcome by the GMSR or the respective registry or its subcontractor and will include descriptive analyses, comparative analyses (where appropriate), and any relevant sensitivity analyses. Descriptive statistics will include percentages, means with standard deviations, and event incidence rates. Baseline tables will include the number of patients contributing multiple exposure episodes, including those patients who begin in the comparator cohort(s) before contributing to the ublituximab cohort and those patients who only contribute exposure episodes to the comparator cohort(s).

Propensity scores will be calculated for each exposure episode and used to create a common support population and address imbalances in the patient population that may confound the association between treatment and study outcomes. Inferential statistics include hazard ratios from frailty Cox proportional hazard models and a two-sided type I error rate of 0.05 will be used. Including the frailty term in the Cox model accounts for the possibility of multiple exposure episodes per patient per cohort when the PS model is applied to the exposure-level dataset. The proportional hazards assumption will be evaluated prior to fitting the Cox model. Details of the statistical approach are provided in the following sections. For all analyses, ublituximab will be the treatment of interest and the comparator cohort (either other DMT or other anti-CD20 treatments) will be the reference group. Comparisons with patients receiving other anti-CD20s is intended to provide information about the potential risk of secondary outcomes associated with ublituximab that may not be found with a comparison to other DMT medications. The GMSR will conduct its analyses in R Stat (R Core Team 2021).

9.7.1. Analysis population

The analysis population for all outcomes includes all patients with outcome information who have given informed consent, are enrolled in the GMSR, MSBase, or other potential registry sources, and whose follow-up time is included in the drug exposure groups defined in Sections 9.3.1.1. and 9.3.1.2. The analysis of delayed-onset outcomes will include registry follow-up time for medications initiated at or after enrolment. The analysis of acute-onset outcomes will include registry follow-up time for medications initiated at or after enrolment. The primary analysis population includes patients enrolled in the GMSR. If attainable, other registry data sources will be analysed in tandem, performing comparative analyses only if appropriately powered.

Additional sensitivity analyses will be explored to examine the impact of analysis decisions and assumptions. A sensitivity analysis limiting the analysis population to treatment-naïve patients in the study will be investigated. Other sensitivity analyses will include applying an Intention-to-

Treat exposure analysis approach to delayed-onset outcomes, PS matching or other possible sub-groups that will be described in detail in the Statistical Analysis Plan (SAP).

9.7.2. Propensity score models

A propensity score is an estimate of the probability that a patient receives a particular treatment, conditional on measured characteristics at the time a treatment decision is made (Rosenbaum and Rubin 1983). For this study, a patient's propensity score will reflect the predicted probability of exposure given his or her characteristics at the index date. Propensity scores will be estimated for each exposure episode using logistic regression models predicting the probability of ublituximab exposure compared to the comparator exposure group (other DMT users and other anti-CD20 users), separately for the delayed- and acute-onset cohorts. A new propensity score will be calculated for each exposure episode (i.e., each time there is a switch in treatment). For delayed-onset outcomes, these models will be constructed separately for each primary and secondary outcome. The PS model will be fit on the exposure-level data for all analyses of delayed- and acute-onset outcomes. The models will include a priori variables that are known risk factors for the safety outcomes of interest and associated with systemic treatments for RMS. Covariates considered for inclusion in the PS models are provided in **Table *2*Error! Reference source not found.**. The inclusion of interaction and nonlinear terms will be guided by clinical judgement.

Trimming for common support is relatively straightforward with 2 cohorts but becomes increasingly complex as the number of groups increases. Multiple cohorts and the limited registry sample available for this study mean that matching may results in a high number of unmatched patients and stratifications may result in strata with few or no patients. Therefore, this study will examine pairwise comparison of exposure cohorts: the ublituximab cohort versus the other DMT comparator cohort, and the ublituximab cohort versus the other anti-CD20 comparator cohort. A trimmed population will be identified based on the common support. That is, the trimmed population will exclude (trim) any exposures in one cohort with a propensity score larger than largest propensity score in the other cohort or smaller than the smallest propensity score in the other cohort. This process is repeated for each cohort to retain only exposures with propensity scores in an overlapping range for each outcome of interest.

Table 2 Baseline Covariates for Consideration in Each Outcome-Specific Analysis

Outcome	**Baseline Covariates for Consideration in the Propensity Score Model**
Total malignancies (including NMSC)	Age, sex, body mass index (BMI), education, MS disease duration, history of relapse, active NMSC, previous exposure to other DMTs, previous exposure to B-cell depleting therapies, comorbidities such as cardiovascular disease, diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD)
Malignancy (excluding NMSC)	Age, sex, body mass index (BMI), education, MS disease duration, history of relapse, previous exposure to other DMTs, previous exposure to B-cell depleting therapies, comorbidities such as cardiovascular disease, diabetes mellitus, asthma, chronic obstructive pulmonary disease (COPD)
NMSC only	Age, sex, body mass index (BMI), education, MS disease duration, history of relapse, active NMSC, previous

	exposure to other DMTs, previous exposure to B-cell depleting therapies
Serious infection (including sub-categories of PML and HBV reactivation)	Age, sex, BMI, education, MS disease duration, history of relapse, diabetes mellitus, human immunodeficiency virus (HIV), hematologic malignancy (leukemia, lymphoma, multiple myeloma), transplant history, chronic lung disease, liver disorder, ischemic heart disease, congestive heart disease, periodontal disease, previous immunosuppressive medication use, previous exposure to other DMTs, previous exposure to B-cell depleting therapies, immunosuppressive co-medications
Overall safety[1]	Age, sex, body mass index (BMI), education, MS disease duration, history of relapse, previous exposure to other DMTs, previous exposure to B-cell depleting therapies
[1] Descriptive, based on available data, where consistently available across data sources; to be further described in the Statistical Analysis Plan for this study.	

Propensity score (PS) trimming for common support will be used to control for confounding in addition to adjustments in the primary analyses as described in the section below. The ability of the PS model to balance the distribution of baseline confounders and reduce bias will be evaluated before initiating any safety outcomes analyses.

The appropriateness of the PS modelling is, in part, judged by whether balance on pretreatment characteristics is achieved between the treatment and reference groups (D'Agostino and D'Agostino 2007, Rubin 2007, Spreeuwenberg, et al. 2010). Standardised differences will be used to assess balance between the cohorts across all measured baseline covariates before and after propensity score trimming. As a rule, an absolute value of the standardised differences greater than 0.10 indicate an imbalance that may require further investigation (Austin 2011). Higher-level terms or interactions may be considered when a variable is unbalanced across the ublituximab and comparator cohorts, or when informed by clinical judgement. Any covariates not balanced after applying propensity score trimming will be considered for inclusion in the Cox model.

9.7.3. Primary analysis

The primary analyses will employ propensity score trimming for common support to address confounding by indication (channelling bias). Propensity score models will be fit separately on the exposure level data in the delayed-onset exposure cohorts and the acute-onset exposure cohorts comparing ublituximab versus other DMT comparator cohort and ublituximab versus other anti-CD20 comparator cohort separately. Each propensity score trimmed population will be summarized across cohorts. For the primary outcomes of total malignancies (including NMSC) and malignancies excluding NMSC, incidence rates (IRs) will be estimated in the ublituximab delayed-onset exposure cohort, the other DMT comparator delayed-onset exposure cohort, and the other anti-CD20 comparator delayed-onset exposure cohort in both the full and propensity-score trimmed populations. Frailty models addressing potential multiple exposures per patient will be fit to estimate adjusted HRs and 95% CIs to compare the risk of an event in the ublituximab delayed-onset exposure cohort to that in each comparator delayed-onset exposure cohort in the propensity score trimmed populations.

Cox proportional hazards regression models including a frailty (random effects) term to address potential multiple exposures per patient per cohort will be used to estimate the risk in the

ublituximab cohort versus the comparator cohort (other DMT and other anti-CD20) by estimating the hazard ratios (HRs) and 95% confidence intervals (CIs) in the PS trimmed populations for each of the delayed- and acute-onset outcomes of interest. Each model will be estimated on the exposure-level data for the corresponding exposure cohort (delayed- or acute-onset), including a random effects variable and additional baseline variables that may remain unbalanced in the trimmed population (Table 2).

Adjusting covariates will include a random effects variable, a priori variables selected due to their known relationship to malignancy risk, and characteristics that may remain unbalanced after propensity score trimming. All analyses of malignancy will include patients who accrued to the study as described in Section 9.2.3.

For the primary acute-onset outcome of serious infection, IRs will be estimated in the ublituximab acute-onset exposure cohort and each comparator acute-onset exposure cohort in both the full and propensity-score trimmed populations. Separate frailty models addressing potential multiple exposures per patient per cohort will be fit to estimate adjusted HRs and associated 95% CIs to compare the risk of an event in the ublituximab acute-onset exposure cohort to that in the other DMT comparator acute-onset exposure cohort and the other anti-CD20 comparator acute-onset exposure cohort in the propensity score trimmed population. Adjusting covariates will include a random effects variable, a priori variables selected due to their known relationship to risk of the outcome and characteristics that may remain unbalanced after PS trimming. All analyses of serious infection will include patients who accrue during the first 8.5 years of the study period (spanning the delayed-onset 3-year accrual period and its associated 7-year follow-up period, allowing for at least 1.5 years of follow-up for each patient in the acute-onset cohorts) provided the start or switch to eligible treatment occurs at least 1.5 years prior to data extraction for the final report.

9.7.4. Secondary analyses

For the secondary outcome of NMSC, the analyses will proceed in the same way as for the delayed-onset primary outcomes of total malignancies including NMSC and malignancies excluding NMSC.

Cox proportional hazards regression models including a frailty (random effects) term addressing potential multiple exposures per patient will be used to estimate the HRs and 95% CIs of newly diagnosed NMSC among patients in the ublituximab cohort versus the other DMT or other anti-CD20 comparator cohorts. The model will contain exposure cohort, a random effects variable and additional variables that may remain unbalanced after PS trimming is applied (Table 2).

Descriptive statistics will be used to assess the secondary outcome of overall safety while applying the cohort exposure definitions outlined in Section 9.3.1.2. All serious adverse events and post-marketing surveillance and enhanced pharmacovigilance events collected as overall safety events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). For each study cohort the number of treatment-emergent AEs and crude incidence rates will be tabulated by preferred term and system organ class.

9.7.5. Sensitivity Analysis

Several sensitivity analyses will be performed to examine the impact of analysis decisions and assumptions on study conclusions.

9.7.5.1. Propensity Score Matched Analysis

Propensity score matching will be completed as a sensitivity analysis to the primary approach of PS trimming, the latter of which limits the population to the common support. Matched exposure episodes will be limited to those in the PS trimmed common support population. It is expected that PS matching may achieve better balance on potential confounders but will also likely have reduced sample size due to exclusion of unmatched exposures. PS models will be fit for the delayed- and acute-onset outcomes as described in the primary analyses above. A 1:1 PS matched population will be identified using a greedy matching algorithm, used to match the logit of the estimated PSs using an optimal caliper (equal to 0.2 times the standard deviation of the logit of propensity scores) to limit the maximum distance between the matched pairs. Matched pairs will be analysed with statistical tests for paired data.

9.7.5.2. Patient Treatment History

Treatment-naïve patients are expected to be a small proportion of the population. As a sensitivity analysis to the primary analysis, descriptive statistics, incidence rates and comparative (Cox proportional hazard model comparing time-to-first event between cohorts in a propensity score trimmed population) analyses will be performed for each outcome of interest in treatment-naïve patients. However, these analyses will be considered exploratory given the small number of treatment-naïve patients expected in the registry.

Comparative analyses will only be performed if adequately powered.

9.7.5.3. Pooling of data sources and assessment of heterogeneity (if applicable)

Sensitivity analyses will be conducted to assess the robustness of the primary analysis powered by the German registry if additional registry sources are attainable. Stratified descriptive analyses of baseline characteristics and outcomes for all cohorts from each data registry source will be provided. Primary and secondary outcomes will be assessed in a meta-analysis study design.

Incidence rate ratios with exact confidence intervals, pooled and by registry, will be calculated for each cohort. A random-effects meta-analysis using restricted maximum likelihood estimation (Viechtbauer 2005) will be applied as each registry may reflect a different patient population. Variation in outcomes, that is the heterogeneity between registries, will be assessed using Cochran's Q test and I^2 statistic. A significant Q-value will be considered to suggest statistically significant heterogeneity. Heterogeneity will be considered low, moderate or high when the I^2 values are below 25%, between 25% and 75%, or above 75%, respectively. In addition, use of the random-effect model will allow statistical inference to be made to a population of registry sources beyond those included in the meta-analysis (Berkeljon and Baldwin 2009).

9.7.5.4. Intention-to-Treat (ITT) Approach for Delayed Onset Cohorts

An intention-to-treat (ITT) approach to exposure classification will be conducted among the delayed onset cohorts for the primary analysis. This will provide a sensitivity analysis to the primary approach of the hierarchical exposure classification. The main analysis on the delayed onset outcomes will be repeated with the new exposure classification, ITT.

With this approach, patients will be assigned to the exposure cohort for which they first initiate a study-qualifying therapy at or after registry enrollment. The exposure episode will continue even

if they discontinue or switch therapies until the earliest of the following: first delayed onset event, registry withdrawal, death, or end of the study.

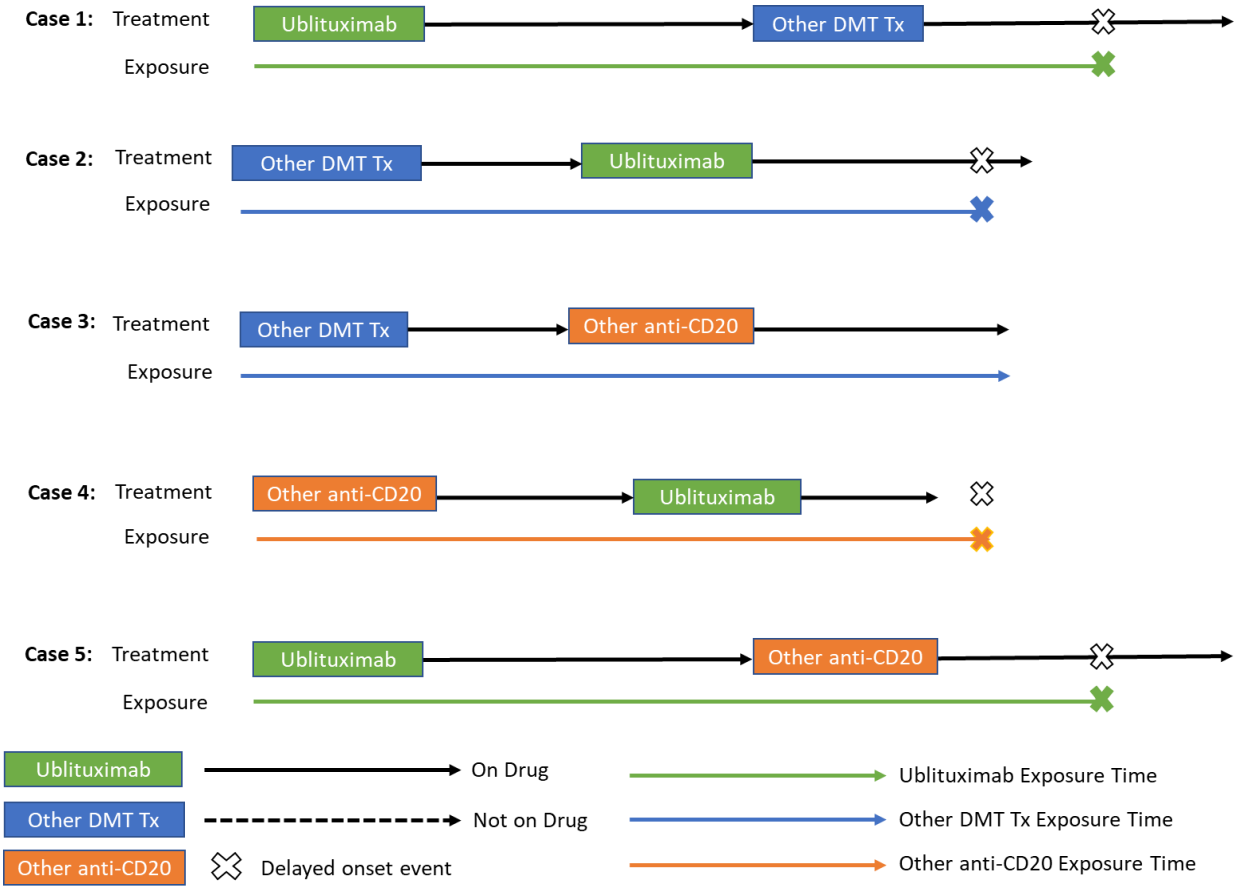

Figure 3. Example of ITT exposure classification for delayed-onset outcomes

The proposed sensitivity analysis will ensure the primary approach of hierarchical exposure classification does not unduly bias the conclusions by providing context justification for the approach and ensuring robustness of final conclusions for the delayed onset outcomes.

9.8. Quality control

Data storage, management and analyses will adhere to GMSRs' and other registries', as applicable, standard operating procedures. These procedures encompass secure data storage, backup, and recovery measures to ensure the integrity and protection of the data. Additionally, methods will be employed to maintain and archive project documents, ensuring proper documentation and traceability. Quality control procedures for programming will be implemented to ensure accuracy and reliability in the analysis process. These practices will ensure that data is handled and analysed in accordance with established standards and protocols. Quality control for data entry is performed by a multilayered approach including but not limited to: a) range checks, b) cross-reference checks, c) branching logic. Furthermore, regular offline data quality controls are applied and feedback to the centres is provided via the query management tool of the EDC system (Ohle, et al. 2021) .

9.9. Limitations of the research methods

This study is subject to several limitations commonly associated with real-world registry data. In real-world observational studies, drug exposure is determined through provider and patient decision-making in routine clinical care and not through random allocation as in randomized clinical trials (RCTs). Systematic bias due to channelling of patients into a particular drug exposure due to prior medical history and disease severity can be mitigated through accurate measurement and data collection of these factors prior to follow-up. However, the possibility of residual confounding by indication cannot be entirely ruled out. In order to minimize the potential for this form of bias, factors associated with both treatment choice and study outcomes, as well as risk factors for the outcomes (e.g. previous exposure to other DMTs and B-cell depleting therapies, history of relapse and MRI activity as well as the most recent EDSS), will be mandatory fields collected at study enrolment. To further address this form of confounding, the primary analyses of safety outcomes will employ a propensity score trimming method (details described in Section 9.7.2. above). In addition, certain confounders which are known to be associated with an elevated risk of malignancy, such as family history, genetic predisposition, or occupational exposure to known carcinogens may not be collected for study participants. Since there is no compelling reason for patients with these pre-existing conditions to be differentially distributed between the study cohorts, the comparative safety estimates are not expected to be strongly affected by this lack of information.

Since GMSR collects information during routine clinical visits, there may be limited active follow-up (which may result in an underestimation of the AE rates). Also, due to the observational nature of the study, some necessary clinical information needed to fully assess and characterize the safety events of interest may be unavailable. Nonetheless, the GMSR has long-standing practices for the collection of safety events in the MS population and has been used for regulatory needs (Ohle, et al. 2021).

As mentioned above, to assure a robust and generalisable sample enrolment, this study is prepared to add MSBase or a US-based registry with favourable access. Of note, in the event of supplementing the study with MSBase or other registry data, the quality of the data collected across the registries included in the study may vary. To address this limitation, if additional data sources are used this study plans to implement a sensitivity analysis as described in Section 9.7.5.

10. Protection of human subjects

This study will be non-interventional, retrospective and will not affect the treatment of the patients. No study-related activities will be carried out prior to receiving subjects' informed consent to participate in the registry. To guarantee patient privacy, only de-identified medical data is stored in the GMSR's database and used for analysis. Local and global data protection and privacy regulations will be observed in collecting, managing, processing, and storing subject data. NxP, the sponsor of this study, will be responsible for ensuring that the study will be conducted in accordance with applicable global and local, legal and regulatory requirements, as well as the Guidelines for Good Clinical Practice (International Conference on Harmonization [GCP ICH] 1996) and the Health Insurance Portability and Accountability Act of 1996 (HIPAA), where applicable.

11. Management and reporting of adverse events

All malignancies, serious infections, and overall safety based on available data collection from each participating data source as outlined in Section 9.3.2 for patients who received ublituximab or other approved DMTs for RMS will be analysed using registry data.

As this is a non-interventional PASS using a secondary data source, the reporting of adverse events in the form of Individual Case Safety Reports is not required.

Periodic reporting is performed in accordance with the safety assessment requirements of the respective ICH Guideline per MS drug every six months and is sent directly to the MAH who contribute to the joint financing of the registry. Centres participating in the additional documentation receive annual summary reports on the serious adverse events notified to the registry.

12. Plans for disseminating and communicating study results

The study will be registered on the HMA-EMA Catalogues of real-world data sources and studies (RWD Catalogues) (https://catalogues.ema.europa.eu/), within 30 calendar days after the study protocol is finalised and approved by the EMA. The full study protocol will be disclosed to the RWD Catalogues within a target of 30 calendar days following the end of data collection. The study findings will be disclosed within 30 business days after the study report is finalised and shared with the regulatory agency. The GMSR will publish a basic synopsis/outline of the study on its website for transparency towards patients.

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