A prospective observational long-term safety surveillance study in the Big MS Data (BMSD) Group network

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2. List of abbreviations

AE	Adverse Event
BMSD	Big MS Data group
CI	Confidence Interval
CIS	Clinically Isolated Syndrome
CNS	Central Nervous System
DMT	Disease Modifying Therapy
EDSS	Expanded Disability Status Scale
EMA	European Medicine Agency
EUROCAT	European surveillance of congenital anomalies
FDA	Food and Drug Administration
HR	Hazard Ratio
ICD	International Classification of Diseases
IRR	Incidence Rate Ratio
JCV	John Cunningham Virus
LMP	Last Menstrual Period
MAH	Marketing Authorisation Holder
MedDRA	Medical Dictionary for Regulatory Activities
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
PASS	Post Authorisation Safety Study
PDDS	Patient Determined Disease Steps
PY	Person-Years
RWD	Real World Data
SAE	Serious Adverse Event
SOP	Standard Operating Procedure

3. Responsible parties

Marketing Authorisation Holders (MAHs):

- Biogen
- Celgene
- Merck KGaA
- Novartis
- Roche
- Sanofi

Due to the dynamics inherent to marketing authorisations and post-approval commitments, MAHs involved in this collaboration may change over time.

Big MS Data (BMSD) Group:

- Swedish MS Registry (Jan Hillert, Director at Karolinska Institute)
- Danish MS Registry (Melinda Magyari, Director of The Danish Multiple Sclerosis Registry)
- Italian Registry (Maria Trojano, Chair of the Italian Multiple Sclerosis Registry)
- French (OFSEP) Registry (Sandra Vukusic, President of the EDMUS Foundation)
- MSBase International MS Registry (Helmut Butzkueven, Managing Director)

4. Abstract

Not included in this core protocol.

5. Amendments and updates

None.

6. Milestones

Cumulative safety reports will be prepared on a yearly basis at the minimum. Additional reports (e.g. comparative assessments) may be defined as part of each product-specific final post-authorisation safety study (PASS) protocol according to specific agreed secondary data analysis plans.

7. Rationale

Multiple Sclerosis (MS) is a chronic, inflammatory, and demyelinating disease of the central nervous system (CNS) that affects approximately 2.3 million people worldwide.[1] There is currently no cure for MS; however, there are several disease modifying therapies (DMTs) available for its treatment. While the safety and efficacy of DMTs are assessed in clinical trials, these are of relatively short duration and always confined to highly selected patient groups. They specifically exclude women who are pregnant/plan to be pregnant, children, adolescents, older people, and people with significant co-morbidities. Although the number of therapeutic options has increased rapidly in the recent years, real-world data (RWD) on their long-term safety is still scarce. The evaluation of RWD is vital as it offers long-term data collection and is patient rather than product-focused during the lifetime of MS, and thus includes the capacity to capture sequences of treatments throughout patients' disease course.

Registries can capture information from multiple practice settings, including non-trial centres and private practices, and from nations and regions with different DMT exposure characteristics and DMT sequencing due to patient and care team preferences, influence of key opinion leaders in particular jurisdictions and differing DMT approval and reimbursement rules.

The EMA Initiative for Patient Registries recognises the potential value of using existing MS patient registries to conduct post-authorization studies of safety and effectiveness of MS treatments.[2] Although MS patient registries have been extensively used to conduct studies assessing the effectiveness of DMTs, they are currently not focussed on safety. However, all five participating registries recognise the increasing importance of harmonised and consistent safety collection for the benefit of patients. This is particularly important in the modern era where long-acting, highly potent medications will be used and sequenced.

All stakeholders acknowledge that registry-based safety collection will be classified as secondary use of data. Registries will not be subject to any legal requirements for individual case-based adverse event (AE) reporting. This responsibility rests exclusively with the treating physicians according to applicable laws and rules in their jurisdictions.

Information specific to each DMT, including exploration of safety profile or risk management measures that led to the initiation or imposition of a PASS, and a critical

review of available published and unpublished data will be outlined separately, in each respective product-specific final PASS protocol with the intention for this to be applied in secondary analyses of data collected according to this general protocol.

8. Research question and objectives

This study aims to assess and characterise the risk of certain safety events in patients with MS (exposed and unexposed to approved DMTs for the treatment of MS), by collecting serious adverse events (SAEs) information in specific disease registries.

Primary objective is to:

- Estimate the incidence/event rates of SAEs (including non-melanoma skin cancers) in patients with MS exposed to approved DMTs (overall and by individual DMTs)

Secondary objectives are to:

- Compare the incidence/event rates of specific SAEs between different DMTs and/or in untreated (i.e. control) MS populations [*subject to customization in each product-specific PASS*]
- Estimate the frequency of adverse pregnancy outcomes in women with MS exposed to DMTs during pregnancy or before last menstrual period (LMP) *[for those registries collecting pregnancy data]*

9. Research methods

9.1. Study design

This PASS is a non-interventional cohort study based on secondary use of data. The study will estimate rates of SAEs (including non-melanoma skin cancer) as a primary objective in patients with MS. Additionally, comparative assessments between different DMTs or with unexposed groups and estimation of adverse pregnancy outcomes will be conducted as secondary objectives. Study period will be defined in each product-specific protocol.

9.2. Setting

This study will include patients with MS who are either untreated or have initiated treatment with DMTs in routine clinical practice. Countries with registries affiliated with the BMSD Group will be considered for inclusion; this is expected to cover a broad range of countries.

9.2.1. Inclusion criteria

This study will include patients who:

- Have a diagnosis of clinically isolated syndrome (CIS) or MS
- Provide informed consent (unless the data source and project are exempt according to applicable regulatory requirements)

Additional inclusion/exclusion criteria may be defined as part of each product-specific PASS.

9.3. Variables

This section is divided into "**primary variables**" comprised of the data elements that are key to conduct a successful PASS, and "**secondary variables**" that includes data elements considered important but not mandatory for the conduct of a PASS. Ideally, definitions should be harmonised across different registries and a data dictionary with exact variable definitions should be available for each registry. The large majority of all primary variables will be available from all registries. However, a small number of variables may be incompletely collected in some registries (see Appendix for detail).

9.3.1. Primary variables

Patient specific information

- Date of birth
- Date of death, if applicable
- Primary and underlying causes of death, if applicable
- Sex
- Country of residence

Disease specific information

- Date of MS onset (first clinical manifestation)
- MS type:
    - CIS
    - Relapsing remitting
    - Secondary progressive
    - Primary progressive
- Expanded Disability Status Scale (EDSS) score (including date of assessment) or a proxy measure (e.g. patient determined disease steps [PDDS]) if EDSS not available
- Relapses (including date of onset), including glucocorticoid treatment (yes/no)
- JCV antibody status (Pos/Neg with Index) (including date of sample)

MS Treatment information: DMT, with start date and end date *(current treatment and treatment history, including all known immunosuppressants for the treatment for MS)*

- ☐ No: No DMT
- ☐ Yes: DMT initiated or ongoing
  OR equivalent, e.g.: Change of treatment Y/N

If yes, the following information on the DMT should be recorded:

- Drug name
- Start date
- Stop date (e.g. date of last administration) (for medications ceased)
- Major reason for discontinuation/switch (if available) (for medications ceased)

Serious Adverse Events (including non-melanoma skin cancer)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose results in death, is life-threatening requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a

congenital anomaly/birth defect [DIR 2001/20/EC Art 2(o)].[3] A SAE does not necessarily have to have a causal relationship with the treatment.

For a given period, the absence or occurrence of a SAE must be specified with a yes/no box in four categories:

Yes/No for each of

- ☐ Malignancy
- ☐ Non-melanoma skin cancer
- ☐ Infection
- ☐ Other

If yes, verbatim, date of onset and outcome should be recorded. Information on the SAEs should be classified using MedDRA terms whenever possible.

9.3.2.Secondary variables if collected in registries

Patient specific information

- Employment status
- Smoking status (never, former, current)
- Weight, height, ethnicity

Disease specific information

- Date of MS diagnosis
- MS diagnostic criteria used
- MRI information (including date of assessment)
- Lab test results (i.e., lymphocyte counts, liver enzymes), including date of test. *Classification can be provided as normal and value if abnormal.*
- Current co-morbid disease (when available) (e.g. none, cardiovascular, respiratory, gastrointestinal, psychiatric, metabolic, malignancies, musculo-skeletal, other auto-immune conditions, other). Co-morbidities should be classified using MedDRA terms or other standard coding system (e.g. ICD)
- Past major disease (e.g. malignancies)

Treatment information

- **MS Symptomatic therapy**
  - Drug name
  - Start date
  - Stop date and reason of discontinuation (for medications ceased)
  - Dose, schedule

- **Any Other therapies**
  - Drug Name
  - Indication
  - Start and stop dates
  - Dose, route, schedule

Adverse pregnancy outcomes

- Date of last menstrual period or other estimated date of pregnancy start
- Ectopic pregnancy (including date of occurrence)

- Spontaneous abortion (pregnancy loss at < 20 weeks) (including date of occurrence)
- Elective termination (including date of occurrence)
  - With foetal defects (classified using EUROCAT) [5].
  - No foetal defects or unknown
- Stillbirth (≥20 completed weeks) (including date of occurrence)
  - With foetal defects (classified using EUROCAT)
  - Without foetal defects or unknown
- Preterm delivery (live birth at < 37 completed weeks) (including date of occurrence)
  - With congenital anomaly (*classified using EUROCAT)*
  - No congenital anomaly or unknown
- Full term birth and outcome (including date of occurrence)
  - With congenital anomaly (*classified using EUROCAT)*
  - No congenital anomaly or unknown

9.4. Data sources

European healthcare registries have been previously used to assess the long-term safety in post-marketing commitments requested by the United States Food and Drug Administration (FDA) and EMA. Furthermore, EMA began a patient registry initiative in 2015 to facilitate the use of registry data to inform regulatory decisions [2].

As such, this study focuses on secondary use of data from MS registries affiliated with the BMSD Group network.

9.5. Study size

All relevant patients with CIS or MS in the BMSD group network will be considered for the purpose of this study.

9.6. Data management

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

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

9.7. Data analysis

9.7.1. Analysis schedule

Data will be analysed by each registry individually annually or bi-annually as defined in registry and company-specific protocols and contracts. Variables (e.g. age, sex, MS

type, etc.) will be summarized as descriptive statistics using the appropriate summary measures for continuous or categorical data. The incidence of a given safety event is defined as the number of patients who presented with the given AE during the follow-up/observation period. The total number of safety events and respective rates per 1000 person-years (PY) with 95% CIs will be provided. Two types of rates may be presented (overall, untreated patients, and by individual DMTs):

- **Event rates:** rates per 1000 PY, including all events reported within the qualifying exposure window (i.e. multiple events allowed)
- **Incidence rates:** rates per 1000 PY, using first events only (i.e. censoring at the time of first event)

Consistent exposure duration definitions for each DMT will be defined and applied Event/Incidence rates will be stratified according to sex and age groups.

Comparison of risk between DMTs (or with untreated patients) will be carried out following the frequency and methods outlined in each product-specific PASS protocols. Unadjusted and adjusted hazard ratios (HRs) or incidence rate ratios (IRR) through Poisson regression model will be presented. Differences between the groups in potential confounders will be minimized through standard regression-based covariate adjustments and/or through propensity score methods. Potential confounders include, but will not be limited to, age, sex, disease duration, EDSS, comorbidities, prior drug exposure, and concomitant drugs.

Analyses (including assessment of pregnancy outcomes) will be specified in separate product-specific statistical analyses plans.

9.7.2. Patient level datasets

The patient-level datasets from participating registries will be merged under existing BMSD procedures and governance rules and combined results across all DMTs and untreated patients will be provided for the below (see Appendix for limitations) by:

- Event rates: rates per 1000PY, including all events reported within the qualifying exposure window (i.e. multiple events allowed)
- Incidence rates: rates per 1000PY, using first events only (i.e. censoring at the time of first event)

Consistent exposure duration definitions for each DMT will be defined and applied

9.7.3. Further analyses

Further analyses, e.g. risk modelling, can be conducted as required on the merged or individual datasets but details on data analysis are out of scope for this protocol, as the methodology will depend on the circumstances (e.g. EMA requests to companies)

9.7.4. Product-specific data

Specific details of the product-specific data analysis will be outlined in each respective product-specific PASS final protocol.

9.8. Quality control

Each registry will use its own standard operating procedures, internal policies and process guidance. This study will be conducted as part of routine clinical practice. The Standard Operating Procedures (SOPs) may include rules for data storage, methods to maintain and archive project and study documents, quality-control procedures for programming, standards for writing analysis plans, review of analysis programs and study documents by senior staff as well as internal audits if applicable. Registries will seek relevant certification either individually or as a group (e.g. EMA certification).

9.9. Limitations of the research methods

This study will have the main limitations typical of secondary use of data studies (e.g. sample size dependent of medication uptake in clinical practice, channelling bias, residual confounding, etc.). Further details of potential limitations will be outlined in each product-specific PASS final protocol.

9.10. Other aspects

None.

10. Protection of human subjects

This is a non-interventional study using secondary data and does not pose any risks for patients. All data used in the study will be de-identified with no breach of confidentiality with regard to personal identifiers or health information. Each registry will apply for an independent ethics committee review, if required according to local regulations. Data protection and privacy regulations will be observed in collecting, forwarding, processing, and storing data from study participants.

11. Management and reporting of adverse events/adverse reactions

For non-interventional studies that are solely based on secondary use of data, reporting of adverse events/adverse drug reactions is not required. Reports of adverse events/adverse drug reactions should only be summarized in the study report, where applicable.[4]

12. Plans for disseminating and communicating study results

Regardless of the outcome of study, all MAHs are dedicated to openly providing information on the results to healthcare professionals and to the public. Safety reports will be prepared over the data collection period and submitted by each respective MAH to EMA through scheduled regulatory safety reporting.

13. References

[1] Multiple Sclerosis International Federation (MSIF), "Atlas of MS 2013: Mapping Multiple Sclerosis Around the World," 2013.

[2] European Medicines Agency, "Report in Multiple Sclerosis Registries - Workshop 7 July 2017," 2017.

[3] European Medicines Agency and Heads of Medicines Agencies, "Guideline on good pharmacovigilance practices (GVP) - Annex I - Definitions (Rev 4)," 2017.

[4] European Medicines Agency and Heads of Medicines Agencies, "Guideline on good pharmacovigilance practices (GVP) - Module VI – Collection, management and submission of reports of suspected adverse reactions to medicinal products (Rev 2)," 2017.

[5] EUROCAT SYNDROME GUIDE: Definition and Coding of Syndromes (Revised 2017)

Appendix: Known limitations of primary variable collection and procedures

Variable not collected/incomplete:	**In registry:**
JCV status and index	OFSEP registry
Date and course of death	Will be incomplete because the MS centre may not be notified. Available as complete data through data linkage from Sweden and Denmark.
Big MS data merge	The Italian registry may agree to merge safety data annually or biannually under existing BMSD procedures and governance rules, but only aggregated results of this analysis may be provided to pharma companies.