NON-INTERVENTIONAL POST AUTHORIZATION SAFETY STUDY (PASS) PROTOCOL

A NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY TO INVESTIGATE THE RISK OF MORTALITY IN MULTIPLE SCLEROSIS PATIENTS TREATED WITH ALEMTUZUMAB (LEMTRADA®) RELATIVE TO COMPARABLE MULTIPLE SCLEROSIS PATIENTS USING OTHER DISEASE MODIFYING THERAPIES: A COHORT STUDY

Version 1.5, 24th June 2022

COMPOUND: Alemtuzumab

PRIME STUDY NUMBER: CSA0002

The Study is conducted by [redacted] hereinafter referred also as the Study Management.

NAMES AND ADDRESSES

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PASS Information

Title	**A non-interventional post-authorisation safety study to investigate the risk of mortality in multiple sclerosis patients treated with alemtuzumab (LEMTRADA®) relative to comparable multiple sclerosis patients using other disease modifying therapies: a cohort study**
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Medicinal product	LEMTRADA
Product reference	EU/1/13/869/001
Procedure Number	EMEA/H/C/003718
Marketing authorization holder(s)	Sanofi Belgium
Joint PASS	No
Research question and objectives	**Question:** What is the risk of mortality in multiple sclerosis patients treated with LEMTRADA as compared to multiple sclerosis patients treated with other highly efficacious disease modifying therapies? **Primary objective:** To ascertain whether multiple sclerosis patients treated with LEMTRADA have a higher risk of all-cause mortality than comparable multiple sclerosis patients treated with other highly efficacious disease modifying therapies.
Country(-ies) of study	Sweden, Denmark, United Kingdom, Czech Republic, Belgium, Germany
Author	[redacted]

Marketing authorization holder(s)

Marketing authorization holder(s)	Sanofi Belgium
MAH/MAH REPRESENTATIVE contact person	[redacted]

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2. LIST OF ABBREVIATIONS

aHR:	Adjusted hazard ratio
AIM-IMA:	L'Agence Intermutualiste - Het InterMutualistisch Agentschap (Belgian Social Security database)
ATT:	Average treatment effect among treated
BMSD:	Big MS Data
CIOMS	Council of International Organization of Medical Sciences
DAG:	Directed Acyclic Graph
DMT:	Disease modifying therapy
ECCS:	External Comparison Cohort Study
EDSS:	Expanded Disability Status Scale
EMA:	European Medicines Agency
FU:	Follow-up
Hd-PS:	High dimensional propensity score
HE-DMT:	Highly efficacious DMT
HR:	Hazard ratio
[redacted]	[redacted]
ITT:	Intent-to-treat
LEM:	LEMTRADA
LFTU:	Lost-to-follow-up
MAH	Marketing authorization holder
MS:	Multiple sclerosis
OP:	Operating protocol
PASS:	Post-authorization safety study
P-DMT:	Platform DMT
PPMS:	Primary progressive multiple sclerosis
PRAC:	Pharmacovigilance Risk Assessment Committee
PS:	Propensity score
PY:	Person-Years
RR:	Relative Risk
RRMS:	Relapsing remitting multiple sclerosis
SAP	Statistical analysis plan
SMR:	Standardised mortality ratio
SPMS:	Secondary progressive multiple sclerosis
95% CI:	95% confidence interval

3. RESPONSIBLE PARTIES

3.1. RESPONSIBILITIES OF THE DATA source PROVIDER

1. To contribute to and collaborate with the study in accordance with the protocol.
2. To allow access to data sources relevant to the study.
3. To obtain ethical approval where necessary and adhere to legal requirements surrounding data protection.
4. To develop the operating protocol with the Study Management.
5. To organise training of staff in accordance with the Study Management.
6. To produce the working databases and analysis databases according to procedures outlined in operating protocols.
7. To participate in the meetings and other activities necessary for the good conduct of the study.
8. To participate in the feasibility study and review of final study reports.

List of collaborators at protocol stage:

Denmark	The Danish Multiple Sclerosis Registry Copenhagan University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark PI: Prof Melinda Magyari
Belgium	AIM-IMA (L'Agence Intermutualiste - Het InterMutualistisch Agentschap) Av. de Tervueren, 188/A, B-1150 Brussels, www.aim-ima.be Contact: Birgiet Gielen
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Czech Republic	The Czech Multiple Sclerosis Registry (ReMuS) IMPULS Endowment Fund, Katerinska 30, 120 00 Prague 2, Czechia PI: Dana Horakova Dpt. of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czechia
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Germany	The German Pharmacoepidemiological Research Database (GePaRD) Leibniz Institute for Prevention Research and Epidemiology – BIPS GmbH Achterstraße 30, 28359 Bremen, Germany PI: Prof Tania Schink

3.2. RESPONSIBLITIES OF THE STUDY MANAGEMENT

1. To write the study protocol.
2. To write operating protocols specific to each database.
3. To coordinate the implementation of the study in the various databases, with consideration to local administrative, legal and technical environment.
4. To define with database providers the practical modalities of participation in the study, including legal and financial aspects.
5. To monitor study progress, identify or predict problems and work with database providers to find suitable solutions.
6. To plan, supervise and report on the feasibility study.
7. To prepare statistical methods and computer software needed for data analysis.
8. To train database scientists on tasks related to data handling, cleaning and analyses.
9. To organise meetings between the database providers, the MAH and the Study Management for discussing study progress and results.
10. To prepare study reports intended for submission to the Regulator.
11. To regularly inform the MAH on study advancement and issues to be addressed.

3.3. RESPONSIBILITIES OF THE MAH

The MAH is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

3.4. RESPONSIBILITIES OF THE SCIENTIFIC STUDY COMMITTEE

The Scientific Committee will be responsible for reviewing central documents to the study, including the study protocol, the report on the interim analysis in 2022, and the final report in 2024. The Scientific Committee will guide the strategy for dissemination and publication of study results, as detailed in section 12. of the protocol.

The Scientific Committee members will be the same as for the External Comparison Cohort Study (ECCS) initiated in 2015 which is a sub-study of the EUPAS7346 on LEMTRADA.

The Scientific Committee will be composed of two neurologists, one epidemiologist experienced in pharmacoepidemiology and two biostatisticians experienced in pharmacoepidemiology.

The Members of the Scientific Committee will have no conflict-of-interest that could be associated with the study. Members of the Scientific Committee will not be involved in the study conduct or have any direct link with data sources used for the study.

4. ABSTRACT

Version and date: Version 1.5, June 2022

Author: [redacted]

Title: A non-interventional post-authorisation safety study to investigate the risk of mortality in patients treated with alemtuzumab relative to comparable patients using other disease modifying therapies: a cohort study

Rationale and background: Following a European Medicines Agency (EMA) Article 20 procedure (EMEA/H/A-31/1483/C/3718/0028) in 2019, an investigation into the risk of mortality in multiple sclerosis (MS) patients treated with LEMTRADA compared to a relevant MS patient population is required for years during which LEMTRADA has been in use.

Research objective/question: To ascertain whether MS patients treated with LEMTRADA have a higher risk of all-cause mortality than comparable MS patients treated with other highly efficacious disease modifying therapies (HE-DMT).

Study design: Observational comparative cohort study based on the secondary use of data held in MS registries, administrative databases and other data sources in Europe.

Population: MS patients treated with a HE-DMT in usual clinical practice in multiple European countries.

Variables: The outcome will be all-cause mortality. Exposure will be exposure to LEMTRADA vs. exposure to HE-DMT other than LEMTRADA. Patient characteristics and known predictors of mortality in MS patients (e.g. severity of MS, comorbidities) will be used to control for confounding.

Data: Individual level data of MS patients held in population-based MS patient registries, administrative and prescription registries, as well as chart review data will be used. Data from the date of LEMTRADA approval/reimbursement (2013-2015) until last available data in each data source will be used. There will be no transfer of individual or of identifiable data to any recipient.

Data sources:

- MS registries in Denmark, Sweden and Czech Republic
- Chart review in the United Kingdom
- Prescription and administrative data in Belgium and Germany

Sample size:

All MS patients treated with a HE-DMT will be included in the study. Expected estimates of precision surrounding the risk of mortality have been computed considering a median follow-up of six years, a mortality rate of 0.24 to 0.48 per 100 person-years in HE-DMT treated patients, relative risks ranging from 1.2 to 2.0 and a ratio of 1:4 between patients treated with LEMTRADA and patients treated with another HE-DMT. A HR of 1.5 with a 95% CI ranging from 1.00 to 2.25 could be possible with 1,000 LEMTRADA treated MS patients.

Data analysis: Statistical analyses will be performed separately in each data source. Within each data source, a propensity score (PS) will be used to control for confounding. Propensity score weighted Cox proportional hazards models will be used to calculate adjusted hazard ratios (aHRs) and corresponding 95% confidence intervals. The weighting approach will generate the average treatment effect among LEMTRADA treated MS patients. To provide overall results for the study, aHRs found in each data source will be pooled using appropriate meta-analytic methods to obtain a summary estimate for the risk of mortality.

Milestones

Feasibility study report **Q3 2022**

Progress report with interim analyses **Q2 2023**

Final analysis study report **Q3 2024**

5. AMENDMENTS AND UPDATES

Protocol Amendments: Summary of Changes

Section number and name	**Description of change**	**Brief Rationale**	**Version number and date**
na	Protocol revisions as part of initial approval procedure	Responding to PRAC requests for revisions to protocol prior to final approval	1.0 – 1.4 July 2020 – May 2021
Section 4: Abstract Section 6: Milestones	Removal of tasks not representing direct regulatory commitments.	Sequential steps towards delivering direct regulatory commitments were removed because they are a marker of internal progress towards a formal regulatory commitments (e.g., submission of feasibility report).	1.5 June 2022
	Feasibility report submission changed from Q4 2021 to Q3 2022	Feasibility report changed to accommodate availability of data.	
	Interim report submission changed from Q4 2022 to Q2 2023.	First interim report changed to accommodate availability of data.	
	Removal of interim report submission Q4 2023	Because the first interim report is moved to Q2 2023 the submission of two interim reports the same year (i.e., 2023) is not warranted as the differences between the two reports would be minimal.	
Section 9.8 Feasibility study	Dates for submission of interim analysis updated	See above	1.5 June 2022
	Removal of dates pertaining to feasibility analysis	See above	

	Removal of Gannt chart	The Gannt Chart has been removed because it served as a planning tool at the start of this project. Additions and revisions to the chart are out of scope to protocol amendments.	

6. MILESTONES

Feasibility study report	**Q3 2022**
Progress report with interim analyses	**Q2 2023**
Final analysis study report	**Q3 2024**

7. BACKGROUND AND RATIONALE

7.1. Background

Disease modifying therapies (DMT) are immunomodulatory drugs used in the treatment of multiple sclerosis (MS). DMT are classified in two broad categories, the platform-DMT (P-DMT) and the highly efficacious DMT (HE-DMT) (Appendix 1**)** (1, 2).

LEMTRADA® is a HE-DMT that received initial marketing authorisation by the European Medicine Agency (EMA) in September 2013[1]. The approved indication was: "treatment of adult patients with relapsing remitting multiple sclerosis (RRMS) with active disease defined by clinical or imaging features".

In 2019, LEMTRADA was subject to a European Commission (EC) triggered procedure under Article 20 of Regulation (EC) No 726/2004 in which new and cumulative safety data were assessed by the EMA pharmacovigilance risk assessment committee (PRAC)[2]. The procedure concluded that LEMTRADA is associated with new and emerging safety events; cardiovascular adverse events (temporally associated with infusion) and additional autoimmune events. The PRAC advised changes to the EU Summary of Product Characteristics indication, the list of contraindications and safety monitoring recommendations to best ensure patient safety.

An outstanding safety question from the procedure was the evaluation of the risk of fatal events associated with exposure to LEMTRADA. In the Article 20 Assessment report, mortality rates from clinical trials (0.17 per 100 patient-years) and post-marketing data (0.42 per 100 patient-years) were reviewed. However, these data were deemed insufficient to fully understand whether there may be an increased risk of mortality associated with exposure to LEMTRADA due to a lack of adequate comparative data.

Given this evidence gap, an investigation of the risk of mortality in patients treated with LEMTRADA compared to a relevant MS patient population is planned. This PASS protocol outlines the investigational plan to address this request. The study will utilise real-world data retrieved from multiple sources in Europe including MS patient registries, administrative health care databases and chart reviews. This will enable a direct comparison of the risk of fatal events in LEMTRADA exposed patients and risk of fatal events in a population of clinically comparable MS patients from the same data source.

This PASS protocol has been written with background knowledge from the External Comparison Cohort Study (ECCS) initiated in 2015 which is a sub-study of the EUPASS7346 on LEMTRADA.[3] The ECCS has been designed to assess the incidence of adverse events among LEMTRADA treated and MS patients treated with other DMT. In the ECCS study, data until the end of 2018-2019 provide an indication of prescription patterns for LEMTRADA:

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[1] Committee for Medicinal Products for Human Use (CHMP). Summary of opinion (initial authorisation). LEMTRADA (alemtuzumab). EMA/377379/2013, 27 June 2013.

[2] Pharmacovigilance Risk Assessment Committee (PRAC). Assessment report. Procedure under Article 20 of Regulation (EC) No 726/2004 resulting from pharmacovigilance data. LEMTRADA. EMA/682560/2019, 31 Oct 2019.

[3] The ECCS has been implemented in Denmark (Danish MS Registry) and in Belgium (Belgian MS Registry [BELTRIMS] and the Belgian social security database [AIM-IMA]).

- A peak in LEMTRADA prescriptions is noticeable in the year directly following LEMTRADA reimbursement with a stabilisation afterwards.
- For about one fifth of LEMTRADA recipients, this therapy was the first DMT ever received.
- Approximately 16% of LEMTRADA recipients were aged 50 years or more.
- Between 15% (in Denmark) and 37% (in Belgium) of LEMTRADA treated MS patients have an EDSS[4] of 4.0 or more at initiation of LEMTRADA.

Hence, there is a substantial proportion of young MS patients treated with LEMTRADA rapidly after MS diagnosis and a substantial proportion of older MS patients treated with LEMTRADA after a history of therapy with another DMT.

7.2. Rationale

LEMTRADA is a recombinant humanized monoclonal antibody for the treatment of patients with RRMS. LEMTRADA binds to CD52, a cell surface antigen present at high levels on T and B lymphocytes, and at lower levels on natural killer cells, monocytes, and macrophages. LEMTRADA is administered as two courses of 12 mg/day on five consecutive days at baseline and on three consecutive days 12 months later.

LEMTRADA has been demonstrated to be a highly efficacious agent in the treatment of RRMS with data from clinical trials demonstrating reduced relapse rates, reduced disability, reduced brain volume loss and improved EDSS scores (3-5). The efficacy of LEMTRADA in RRMS patients across multiple parameters of the disease is well established and maintained over long term follow-up (6-8). This level of efficacy is present across a wide range of patient populations, as evidenced by the consistency of findings across various subgroups including baseline EDSS score, disease activity level, age and history of prior DMT use in LEMTRADA clinical studies (4). However, LEMTRADA is associated with serious risks, including risk of cardiovascular events (with temporal relation to infusion), serious infections and autoimmune-mediated conditions (9).

Several other therapies are considered to be highly efficacious: natalizumab (TYSABRI®), fingolimod (GILENYA®), ocrelizumab (OCREVUS®), and cladribine (MAVENCLAD®). Of note there has also been significant off-label use of rituximab (anti-CD20) for the treatment of MS (10). All of these agents are associated with a risk of serious adverse events including fatal events (9, 11-15).

MS is a heterogeneous disease and selection of therapy is highly individualized. Important considerations should include clinical factors such as: disease severity and prognosis; comorbidities; prior therapy response or tolerability; as well as patient preferences including risk tolerance and important life factors such as employment status and family planning (1). Given the complex risk-benefit profiles for DMT there can be many patient-related factors that contribute to risks and safety outcomes for each drug. Thus, adequate comparative data is necessary for understanding the safety profiles of each DMT.

[4] Expanded Disability Status Scale: standard scale used by neurologists for evaluating the level of disability associated with MS disease. The scale ranges from 0 (no disability) to 9.5 (10 is equivalent to death due to MS).

In the context of these considerations it is unknown whether there is a difference in the occurrence of fatal events in LEMTRADA treated patients as compared to fatal events in clinically similar patients treated with other HE-DMT.

There are various sources of data inclusive of clinical trial data, extension studies, single arm observational studies and pharmacovigilance data that provide some information on mortality rates in LEMTRADA treated patients, albeit all with their own unique limitations.

Mortality rates observed in randomized trials with LEMTRADA and their follow-up studies (0.17 per 100 person-years) do not suggest an excess risk of mortality compared to published data on mortality in MS populations (4, 16-18). Similarly, early reports on LEMTRADA use in daily neurological practice in the United Kingdom did not allude to unexpected fatal outcomes (19). Two ongoing single arm safety studies for LEMTRADA report interim deaths. First, in TREAT-MS there have been two deaths in 779 patients as of 2018[5]. Second, in the ongoing PASS for LEMTRADA (GZ402673-OBS13434), there have been five deaths, as of March 2020, in 2,092 European MS patients, corresponding to a mortality rate of 0.10 per 100 person-years (95% CI: 0.03; 0.24)[6].

However, patient selection criteria for controlled trials, and lack of comparator arms in long-term follow-up from controlled trials and post-marketing observational studies limit the comparability of these data to other MS populations including those treated with other HE-DMTs.

A review of adverse events reported to the EMA database of suspected adverse reactions related to medicinal products (EudraVigilance) indicated that fatal events associated with LEMTRADA treatment were reported to occur more frequently than in randomised trials and early clinical series (20). But it is difficult to derive a reliable estimate of mortality rates from pharmacovigilance data based on spontaneous reports given the unknown rate of under or over reporting and lack of complete information in many reports. Moreover, the absence of data on adverse events occurring in comparable MS patients not receiving LEMTRADA limits the interpretation of spontaneous reports.

Thus, current data from multiple sources are not sufficient to understand whether LEMTRADA is causally associated with mortality.

The study outlined in this protocol proposes an observational cohort study intended to compare the risk of mortality in LEMTRADA treated MS patients with the risk of mortality in comparable MS patients, i.e., those treated with other HE-DMT. The data sources will consist of MS patient registries, prescription/administrative data and clinical chart data in European countries that hold data on patient characteristics, clinical parameters, therapies, vital status, as well as data on major potential confounders like cardiovascular or respiratory conditions and other co-morbidities.

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[5] https://onlinelibrary.ectrims-congress.eu/ectrims/2019/stockholm/279348/rocco.haase.treat-ms.study.of.real-world.effectiveness.of.alemtuzumab.in.rrms.html?f=listing%3D3%2Abrowseby%3D8%2Asortby%3D1%2Amedia%3D1, interim results of January 2014 to October 2018.

[6] EUPAS 7346 : http://www.encepp.eu/encepp/viewResource.htm?id=28499, update of March 2020.

8. RESEARCH QUESTION AND OBJECTIVES

8.1. Research question

What is the risk of mortality in MS patients treated with LEMTRADA as compared to MS patients treated with other HE-DMT?

8.2. Primary OBJECTIVE

To ascertain whether MS patients treated with LEMTRADA have a higher risk of all-cause mortality than comparable MS patients treated with other HE-DMT.

8.3. Secondary OBJECTIVE

To examine the cause of death in data sources where this information is available and when the number of cases for a specific cause is sufficient for formal examination. This objective will be exploratory as it is anticipated that availability and quality of cause-specific mortality data will be variable across data sources.

9. Research methods

9.1. Study design

9.1.1. General study design

This PASS is an observational comparative cohort study based on secondary use of data held in various European real-world data sources. The primary endpoint is all-cause mortality, and the secondary endpoint is cause-specific mortality. The study will compare mortality risk between MS patients treated with LEMTRADA and comparable MS patients treated with another HE-DMT.

Some drug safety studies especially those concerning rare events (e.g., mortality) and rare exposures (e.g., LEMTRADA) require more data than is available in any single observational database. Therefore, it has become common in drug safety research to use data from multiple data sources, usually from different countries (21-26).

The approach is to develop a master protocol and share this protocol across all contributing data sources. Each data source will be required to adapt the master protocol to their local data and to implement it in their own usual software. This will produce local effect estimates that will be ultimately combined by meta-analysis (27). This approach is akin to the Common Data Model (CMD) concept (23), whereby all datasets are formatted in one pre-defined manner and thus, one program can be run on all.

It is known that the format of several variables may differ across data sources. Whenever possible, the “statistical analysis plan” (SAP) and the operating protocols (OP) (i.e., how the SAP is applied in each data source) will aim at harmonising the format of variables used in analyses e.g., same categories implanted for categorising continuous variables.

9.1.2. Comparable MS patients

In studies of non-intended adverse events such as mortality, the risk of the outcome can be strongly correlated with the progression of the disease being treated. Therefore, it is important that the comparison treatment is for a similar indication and stage of disease as the treatment under study (28).

In 2013, the EMA approved LEMTRADA for adult patients with RRMS with active disease defined by clinical or imaging features[7]. Hence, LEMTRADA was the first HE-DMT approved by the EMA as a first line DMT. In this regard, LEMTRADA therapy could have been initiated shortly after diagnosis of highly active MS (i.e., as first line DMT), or after evidence that another DMT failed to control disease activity. In Q2 2019, the indication for LEMTRADA was restricted following the reporting of serious cardiovascular and immune mediated adverse events and the initiation of an Article 20 procedure (EMEA/H/A-31/1483/C/3718/0028). In January 2020, the EMA restricted the indication of LEMTRADA therapy to (i) MS patients with highly active disease, despite a full and adequate course of treatment with at least one disease modifying therapy, or (ii) patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI[8].

The other HE-DMT that are available on the market have similar indications to LEMTRADA: natalizumab (TYSABRI®), fingolimod (GILENYA®), ocrelizumab (OCREVUS®), mitoxantrone (NOVANTRONE®) and cladribine (MAVENCLAD®) (9, 11-15). Of note there is also off-label use of rituximab (anti-CD20) for the treatment of MS (10). The literature indicates earlier recourse to HE-DMT in the last decade, suggesting use of LEMTRADA and other HE-DMT at similar stages of disease (29-31).

By using an active comparator design, whereby the comparator population comprises patients treated with other HE-DMT, it is possible to better control for disease severity and prognosis at baseline. The aim is to achieve two treatment groups that have similar risk of the outcome related to their disease (28).

Apart from MS disease severity, which is addressable using an active-comparator design, the two treatment groups may be different in other ways that could potentially be associated with the outcome. For example, one treatment group could be older than the other, and thus more likely to die; or imbalanced in terms of other comorbidities for example cardiovascular conditions which have been cited as a leading cause of death in MS patients (32).

To deal with potential imbalance of measured confounders, a propensity score will be developed (Section 9.7.4) and used in weighted analyses (Section 9.7.6.3).

9.2. Setting

The study will include MS patients treated with a HE-DMT after the date of LEMTRADA approval/reimbursement in usual clinical practice in European countries.

[7] LEMTRADA Public Assessment Report 25/09/2013. EMA/563018/2013. Available from https://www.ema.europa.eu/en/documents/assessment-report/lemtrada-epar-public-assessment-report_en.pdf
[8] https://www.ema.europa.eu/en/medicines/human/EPAR/lemtrada#product-information-section.

9.2.1. Study duration

Cohort entry can occur from the date of LEMTRADA approval/reimbursement until six months prior to last available data in each data source. The date of approval/reimbursement varies from country to country; it ranges from 2013 to 2015 in the countries selected for this study. The last available data will range from 2021 to 2023 depending on the data source.

9.2.2. Eligibility criteria

9.2.2.1. Inclusion criteria

Eligible participants are MS patients who initiated LEMTRADA or other HE-DMT after the date of LEMTRADA approval/reimbursement. An MS diagnosis will be given by: presence in an MS registry/diagnosis of MS in MS registry data; ICD-10 code G35 in administrative data; or a recorded diagnosis of MS in medical charts. In administrative data without ICD-10 coding, only patients with treatment codes specific to LEMTRADA and other HE-DMT will be included in the study.

Included patients will have two-year look-back data at cohort entry to facilitate covariate assessment. This period of two years may change according to the results of the feasibility study (see section 9.8.).

9.2.2.2. Exclusion criteria

MS patients who do not consent to have their data used for research purposes will be excluded.

9.2.3. Cohort entry date

The cohort entry date will be defined as the date of first prescription of a HE-DMT after the date of LEMTRADA approval/reimbursement. Initiation or switching status will be determined by using at least two-year look-back data prior to cohort entry to establish prior DMT history. This period of two years may change according to the results of the feasibility study (see section 9.8.).

Cohort entry can occur at any point between LEMTRADA approval/reimbursement and up until six months prior to end of available data in each data source. This approach allows for at least six months follow-up for those who enter late in the study.

9.2.4. Analysis population(s)

All MS patients meeting eligibility criteria will be considered for inclusion in analyses.

9.2.5. Modalities of recruitment

This cohort study relies on secondary use of health-related data from European MS patient registries, administrative prescription databases and chart review. The study relies thus on health care data that are routinely collected for social security or epidemiological purposes.

9.3. Variables

9.3.1. Period of variable assessment

The data collection period for exposure and outcome variables will span from 2013-2015 (dependent on local date of LEMTRADA reimbursement) to 2021-2023 (dependent on timing of data updates in the local data sources). A time-lag in data availability in data sources, varying from few months to 24 months, needs to be taken into account. This means there will be seven to ten years of data across all sources to address the study objective.

Examination of medical history in the two years before cohort entry date will enable measurement of baseline variables for example past use of DMT prescriptions, relapses in the two years preceding cohort entry and comorbidities. This period of two years may change following the feasibility study.

9.3.2. Outcome variable

The outcome will be all-cause mortality, given by recorded date of death. Wherever available, the cause of death will also be accessed.

MS registries typically update vital status data via linkage with vital status registries. Prescription registries typically update vital status data through receiving regular information on births, deaths, emigrations, and immigrations from vital status registries.

In Belgium, Denmark and Sweden linkage with national vital status registries will be done using a unique national personal identifier. In the UK, Germany and Czech Republic, data sources are not directly linkable to vital status registries. The Czech Republic MS Registry is currently developing a linkage. The UK and Czech data sources have thus to perform active tracing of MS patients. Active tracing for vital status means to have direct contact with patients, their relatives or their GPs. In these data sources, updates of vital status of MS patients will need to be performed at a pre-determined time before using data for analyses. In German data, death is recorded as a reason for end of insurance or if the death occurred in a hospital.

Practical aspects for vital status updates are specific to each data source and will be detailed in Operating Protocols. A-priori, there is no indication from any data source that differential recording of mortality for any drug in particular could be expected.

The information hereafter summarises vital status registration in data sources.

In Sweden, vital status of patients will be recorded through linkage with the Swedish Cause of Death Register. The Swedish cause of death register is a high quality virtually complete register of all deaths that occurred in Sweden since 1952 (33).

In Denmark, deaths will be updated via linkage with the civil status registry. The Danish Civil Registration System keeps records on gender, date of birth, change of address, date of emigration and changes in vital status since 1968. Daily updated information on migration and vital status allows for nationwide cohort studies with virtually complete long-term follow-up on emigration and death (34).

In the Czech Republic, linkage of the national MS patient registry to the national death register is in development. Until then, active tracing will occur.

In the UK, active patient tracing is needed. A linkage to Office of National Statistics death data is available for the Welsh site (35). In other sites mortality is expected to be well recorded due to close monitoring of MS patients regularly attending MS clinics. Incident deaths will be verified by obtaining death certificate data.

In Germany, deaths registered within the GePaRD database originate from health insurance data and are recorded as a reason for end of insurance or if the death occurred in a hospital. Completeness and accuracy of vital registration have been validated against reference mortality index databases (36-38).

In Belgium, since 2002, the AIM-IMA databases are updated with data on births, vital status, emigration and immigration twice a year by linking with the central Population Register[9]. As a result, vital status update until June 30 of a reference year is available in March of the following year. Vital status update until December 31 of a reference year is available in June of the following year.

9.3.3. Exposure variable

The exposure variable used for the main statistical analyses will be LEMTRADA vs. other HE-DMT. In the comparison group of other HE-DMT, no distinction will be made between the various HE-DMT. This lack of distinction between HE-DMT does not apply to the baseline period, where number and type of prior DMT will be measured.

In the main statistical analysis, the treatment exposure variable will be handled as a time-dependent variable (39), which means that exposure to a HE-DMT will be determined from the date of initiation or the date of switch from LEMTRADA to another HE-DMT, and vice-versa.

Treatment initiation is defined as the documentation in medical charts that a HE-DMT was prescribed or delivered for the first time to a MS patients, or in a database evidence of new use using a two-year look-back period to establish prior medication history. This period of two years may change according to the results of the feasibility study (see section 9.8.).

Treatment switching is defined as the documentation in medical charts of the discontinuation of a treatment with a P- or HE-DMT and its replacement with another HE-DMT, or in a database as evidence of initiation of a new HE-DMT without continuing the prior DMT.

The administration schedule differs substantially between HE-DMT, for example fingolimod and cladribine are taken orally whereas LEMTRADA, ocrelizumab and natalizumab are given by intravenous infusion. Therefore, doses or days of administration will not be used to calculate exposure duration. Rather, exposure will be considered as having occurred if a prescription for a HE-DMT is found. Since dose and duration of use will not be taken into account, some exposure misclassification could occur.

Where possible, information on the exposure will be extracted based on ATC codes of HE-DMT described in Table 1. If other types of codification are used in data sources, an adequate bridging will be made, with the ATC codes in Table 1 as reference.

[9] Source: https://www.ima-aim.be

It is anticipated that capture of HE-DMT exposure will be complete and will not be prone to misclassification in any of the data sources expected to participate to the study.

Table 1 List of HE-DMT with their ATC codes

Description	Brand names	ATC code
Rituximab	MabThera®, Rixathon®, Riximyo®, Blitzima®, Ritemvia®, Rituneza®, Ruxience®[biosimilar], Truxima®[biosimilar]	L01XC02
Ocrelizumab	Ocrevus ®	L04AA36
Cladribine	Mavenclad ®	L04AA40
Mitoxantrone	Novantrone ®	L01DB07
Fingolimod	Gilenya ®	L04AA27
Natalizumab	Tysabri ®	L04AA23
Alemtuzumab	LEMTRADA ®	L04AA34

9.3.4. Follow-up time and exposure

Follow-up time will be calculated from the cohort entry date until last update of vital status in each administrative/MS registry data source, death, emigration, or end of data collection, whichever occurs first.

Various drug utilisation trajectories can be envisioned. Handling of switchers and attribution of fatal outcomes to LEMTRADA and other HE-DMT during follow-up will be based on examples of MS patient trajectories displayed in Figure 1.

In the main analysis, the classification of follow-up time into LEMTRADA vs. other HE-DMT category is based on a time-dependent approach in which the outcome is associated with the last HE-DMT (LEMTRADA or another HE-DMT) given to the patient. There will be no right censoring if a patient discontinues or interrupts treatment. If a switch to a P-DMT occurs, this switch will be ignored, follow-up will continue and will be attributed to the last HE-DMT (LEMTRADA or another HE-DMT). The group assignments and follow-up times for the different patients are shown in

Table 2.

The time-dependent exposure approach was selected to accommodate complex treatment trajectories in MS patients and to facilitate an optimally sized LEMTRADA treatment group. This approach has the best ability to capture actual exposure to LEMTRADA and to maximize statistical precision. Other ways to attribute exposure and follow-up can be derived from Figure 1. They are depicted in sensitivity analyses (see section 9.7.7.2.). These other ways have some disadvantages that are presented in Appendix 2. For example, they could lead to a reduction in statistical precision.

Figure 1. Examples of MS patient trajectories after prescription of HE-DMT. Outcomes are not displayed (LEM = LEMTRADA; HE= non-LEMTRADA HE-DMT; [=cohort entry; italicized letters are durations of treatment; pt = patient).

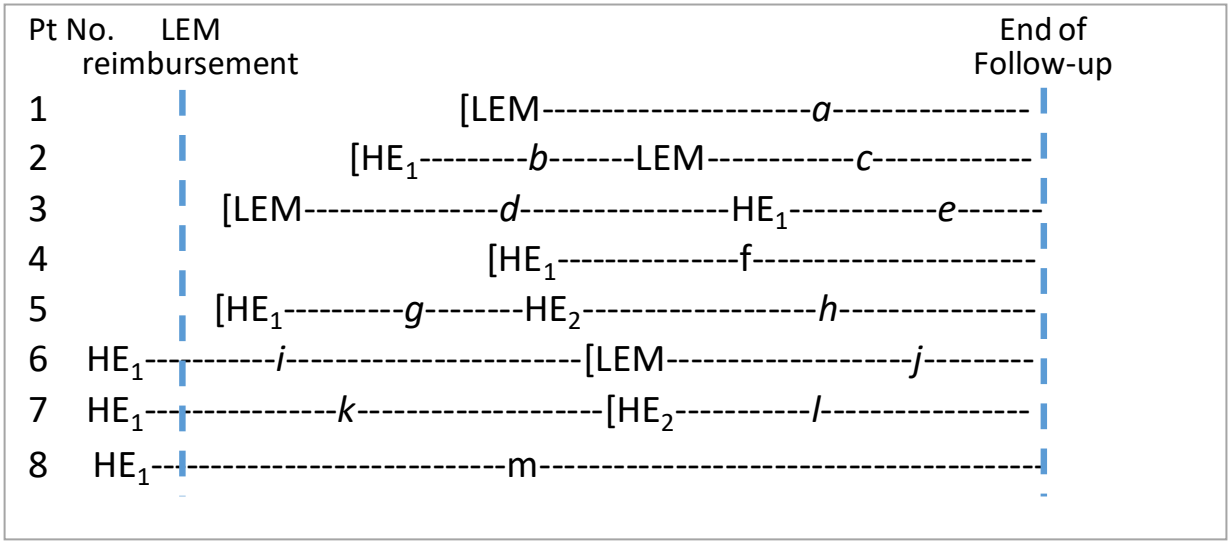


Table 2. Group assignment and follow-up time for outcome assessment according to main analysis

Patient number according to Figure 1	Group assignment	Follow-up time for outcome assessment
1	LEMTRADA	a
2	HE-DMT	b
2	LEMTRADA	c
3	LEMTRADA	d
3	HE-DMT	e
4	HE-DMT	f
5	HE-DMT	g*
5	HE-DMT	h*
6	LEMTRADA	j
7	HE-DMT	l
8	Excluded	

*(total time contributed to HE-DMT = g+h)

9.3.5. MS patients' characteristics variables

Variables will be related to MS patient's demographic characteristics, disease and treatment history, and covariates known to be associated with mortality risk of MS patients.

There may be key differences in baseline characteristics between LEMTRADA and non-LEMTRADA treated MS patients, for example age, MS disease severity or comorbidities that increase the risk of mortality. The literature shows that LEMTRADA is often used as a "rescue therapy" when other DMTs have failed to control the disease activity (as indicated by clinical measures and/or MRI) (40-42). These studies indicate that compared to other HE-DMT treated MS patients, LEMTRADA treated MS patients tend to have higher EDSS scores and long duration of the disease and history of one or more previous DMTs. On-going observational studies like the External Comparison Cohort Study (ECCS)[10] show that young MS patients can also be treated with LEMTRADA.

The active comparator design, using comparator drugs that have a similar indication to LEMTRADA helps to mitigate the impact of confounding by indication at baseline. Nonetheless, an imbalance in unmeasured disease-related or other characteristics between the two groups could lead to confounding, and may bias the relationship between exposure group and mortality, independently of the exposure (43). It is therefore important to obtain data on as many relevant covariates as possible to safeguard against unmeasurable confounding.

A large body of literature exists on risk factors for mortality in MS patients, which provides guidance about variables required to control for confounding (35, 44-48). These variables are listed below. The strategy for dealing with confounding is outlined in section 9.7.4. . We complemented this literature review by creating Directed Acyclic Graphs (DAGs). DAGs have been designed in function of knowns and unknowns on relationships between exposure, mortality and other variables (see Appendix 3). They represent how potential confounders could act on the relationship between the exposure and the outcome.

Because the exposure variable is time-dependent, core covariates will be measured each time a MS patient changes exposure group. In instances where a direct measure of the variable cannot be assessed, proxy measures will be considered if such an approach is possible. Proxy measures will be mainly used for EDSS and relapses in administrative data (see Appendix 4).

Measurement of variables will occur at cohort entry date and at each switch date between HE-DMTs. A two-year look-back period will be required as the covariate assessment period, not including the cohort entry date. This period of two years may change according to the results of the feasibility study (see section 9.8.).

Variables that are core to the successful conduct of the study are indicated by an asterisk (*). These core variables are those known to be associated with mortality among MS patients. Where multiple recordings of variables exist for each patient e.g. EDSS or BMI or smoking status, the value closest to the cohort entry date/switch date will be chosen.

[10] The External Comparative Cohort Study (ECCS) is an ongoing PAS study on alemtuzumab. It aims at comparing the incidence of a selection of adverse events among alemtuzumab treated MS patients vs. MS patients treated with other DMTs. Comparisons of incidence rates take into account numbers of clinical, laboratory and imaging tests experienced by each MS patient.

Baseline variables, assessed at cohort entry and at each switch to another HE-DMT:

- **Date of cohort entry***;
- **Sex***;
- **Age at cohort entry***;
- **Treatment history before cohort entry***: number and type of DMT (P-DMT or HE-DMT) received before cohort entry;
- **Year of MS diagnosis*** (year of first P- or HE-DMT prescription may be used as a proxy);
- Number of relapses in preceding year ;
- **Type of MS***: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), unknown; (35, 45, 47, 48);
- **Expanded Disability Status Scale (EDSS)*** (48);
- Time between MS diagnosis and EDSS 4 (assessed whenever EDSS 4 is reached); patients who did not reach EDSS 4 at the time of variable assessment will be identified as such (35);
- **Co-morbidities***: e.g., auto-immune diseases, cardiovascular disease, cancer, respiratory disease, urinary tract infection; (32, 44);
- Neuropsychological disorders: mood disorders (ICD-10 F30.* to F39.*), mental and behavioural disorders (F60.* to F69.*) and epilepsy (G40.*) (32, 49). Information on these disorders are rarely reported in data sources. However, these disorders may be captured via proxy variables such as psycho-tropic and anti-epileptic drugs received by MS patients (see prescribed medications below).
- **Hospital stays with number of stays and duration***;
- Prescribed medications other than DMT* e.g.:
    - Statins,
    - Anti-hypertensives*,
    - Anti-platelets*,
    - Proton pump inhibitors,
    - Immunosuppressants,
    - Anti-depressors*
    - Benzodiazepines*,
    - Anti-epileptic*,
    - Anti-diabetic*,
    - Prescribed nutritional supplements and vitamins.
- Indicator of socio-economic status (e.g., education level, deprivation index, area of residence);
- Smoking status (e.g., current smoker, past smoker, never smoker, unknown smoking status);
- Adiposity (e.g., body mass index);
- MRI:
  -MRI done before LEMTRADA or HE-DMT treatment;
  -Results of MRI exam;
- JCV status;
- Cerebrospinal fluid analyses.

9.4. Data sources

We will use data from countries that:

- have frequent use of LEMTRADA in order to increase the size of exposed cohort;
- represent as much geographical spread as is practicable;
- have data sources in which key variables can be measured.

We will use MS registry data from Denmark, Sweden and the Czech Republic. These registries are part of the Big MS Data (BMSD) network (50). This network encompasses data from six European MS registries and is a collaboration coordinated by Karolinksa Institute. The collaboration has close links with pharma companies and is currently being used to run other PAS studies in the area of MS[11]. The BMSD network undertook a quality approval process by the EMA, with an application submitted in October 2020. Submitted documentation included a presentation of the individual MS registries and BMSD as well as a description of similarities and differences between the registries including number of MS patients and coverage; data collection; serious adverse events; quality control; analysis methods; PASS (ongoing, planned and BMSD coordinated). Karolinksa Institute is currently developing a webpage for this consortium. A review paper outlining the details of the BMSD network is in development.

We also expect to use hospital chart data from three study sites in the UK (Cambridge, Plymouth and Cardiff) and administrative data from Germany (GePaRD database) and Belgium (AIM-IMA).

In Sweden, Denmark, Germany, Belgium and Czech Republic data for the study are those gathered from routine clinical care in MS patient registries or social security databases. In UK data sources, routine care data for the study are the notes, laboratory results and imaging results recorded in electronic patient files of each medical institution.

[11] The CONFIDENCE study: Safety and Effectiveness of Ocrelizumab under Real World Conditions: a Non-Interventional Post Authorization Safety Study in Patients Diagnosed with Relapsing or Primary Progressive Multiple Sclerosis. http://www.encepp.eu/encepp/viewResource.htm?id=33758

Table 3. Description of expected data sources

Country	Cumulative number of patients exposed to LEMTRADA	Date of LEMTRADA reimbursement	Description of Data Source
Sweden	~130	September 2013	National MS Patient registry that is linked to national registries for mortality, prescriptions, and hospital data
Denmark	~240	September 2013	National MS Patient registry that is linked to national registries for mortality, prescriptions, and hospital data
Czech Republic	~130 (May include some patients treated in trials)	January 2015	National MS patient registry – good follow-up and good data on death due to incentive-based data collection. Linkage to death register in development. Comorbidities will need to be added from files.
UK	~700 (Approx 50% prior to approval)	May 2014	Collaboration established for this project amongst three large UK MS academic clinical centres that will manually extract data from chart reviews.
Germany	~150 (counts ending in 2016)	October 2013	Administrative data: prescriptions, outpatient and inpatient services + diagnoses
Belgium	~500	January 2015	Administrative data: prescriptions, laboratory tests and some indicators of disability.

*****The presented numbers of exposed patients are based on numbers included to date. NA: not available.

9.4.1. Description of individual data sources

9.4.1.1. The Swedish Multiple Sclerosis Registry (SMSR)

The Swedish MS Registry (SMSR)[12] started in 1996 (51). It has been collecting DMT prescriptions data since 2001. The SMSR is used by all neurology departments, and by most neurologists in Sweden. There are around 14,500 MS patients alive and registered in the SMSR, which corresponds to approximately 80% coverage of the total Swedish MS patient population.

As patients are identified with a unique national personal identifier, it is possible to link data from the SMSR with external registries, including the National Cause of Death Registry and the National Patient Registry.

9.4.1.2. The Danish Multiple Sclerosis Registry (DMSR)

The Danish MS registry (DMSR)[13] was created in 1956 and collects data on all Danish MS patients since then (52). Registration of MS patients is compulsory in Denmark. Data on therapies are collected since 1996. The main goal of the DMSR is to track the impact and improve the quality of immunomodulatory and immunosuppressive treatments in patients with MS.

Each treatment site (e.g. hospital, MS referral centre, etc.) enters their data directly into the DMSR. The DMSR contains follow-up data on relapses, side effects, EDSS, and treatments. The database includes around 18,000 MS patients who are currently alive, of which about one third are treated with a DMT.

As patients are identified with a unique national personal identifier, it is possible to link data from the DMSR with external registries, including the national patient registry (collecting prescription data) and the national civil status registry (collecting immigration/emigration data and vital statistics) (53). The strength of the DMSR is that MS patient notification is nationwide and virtually complete. Its weakness is that follow-up usually stops when the patient discontinues treatment, however this is mitigated by follow-up continuing in linked data sources.

[12] http://www.neuroreg.se/en.html/multiple-sclerosis

[13] https://www.rigshospitalet.dk/english/departments/neuroscience-centre/department-of-neurology/research/the-danish-multiple-sclerosis-registry/about-the-registry/Pages/about-the-danish-multiple-sclerosis-registry.aspx)

9.4.1.3. The Czech Multiple Sclerosis Registry (CMSR)

The ReMuS is the Czech national MS registry that is operated by the Endowment Foundation Impuls[14] in cooperation with the Czech Neuroimmunological Society (54). The main goals of the ReMuS are:

- to describe the real prevalence and incidence of MS in the Czech Republic,
- to provide to the health authorities data about severity of MS, treatment allocation and employment and social situation of MS patients,
- to serve as a basis for research at national and international level.

The registry started in January 2013 and has been collecting data from 15 MS referral centres across the whole Czech Republic. The estimated number of patient records as of 2016 is 8,353. The software iMed has been used in all MS centres as a tool for data collection. Data is summarized centrally twice a year and summary output is provided publicly[15]. The number of LEMTRADA patients treated as part of routine care versus as part of LEMTRADA clinical trials will be investigated in feasibility study (see section 9.8.)

9.4.1.4. Academic clinical MS centres in England and Wales

A tripartite collaboration has been established for the purposes of this study across three academic-clinical MS centres in England and Wales. These institutions have sizeable MS practices, including regular use of LEMTRADA as a treatment option. Data on key comorbidities and drug utilization will be available from patient charts and patient notes. Variables needed for the study will be extracted from patient charts of eligible patients, and entered into a local database. Data from each local database will be sent to lead principal investigator (Prof Neil Roberston, Cardiff) to be combined into one dataset for analysis.

The tripartite collaboration in the UK involves medical institutions that have similar working patterns and operate within the National Health System (NHS). MS patients' management follows UK NHS recommendations and follow-up of MS patients (via active tracing) is similar in all three institutions. Data on MS patient's characteristics, clinical course (e.g., EDSS and relapses) and treatment received are collected in the same way. Therefore, the tripartite collaboration will be considered as a single source of data.

9.4.1.5. The German Pharmacoepidemiological Research Database (GePaRD)

Since 2004, the Leibniz Institute for Prevention Research and Epidemiology – BIPS has been working on the establishment and maintenance of the project-based German Pharmacoepidemiological Research Database (GePaRD)[16]. This database contains claims data from four statutory health insurance providers and covers about 20 million insured Germans since 2004 (~ 17% of the population of Germany). GePaRD data fairly represent the German general population with respect to age, sex, region of residence, overall hospitalisation rates, disease-specific admission rates (55) and medication dispensations (56). However, patients with middle to

[14] https://www.nfimpuls.cz/index.php/en/czech-ms-registry/about-the-registry

[15] https://www.nfimpuls.cz/index.php/en/czech-ms-registry/final-reports

[16] https://www.bips-institut.de/en/research/research-infrastructures/gepard.html

higher socioeconomic status may be overrepresented in GePaRD, since three of the four statutory health insurance providers are more likely to insure patients of middle to higher socioeconomic status (37).

GePaRD includes demographic characteristics for each person, information on drug prescriptions, outpatient/inpatient hospital contacts and diagnoses since 2004. Prescription data include reimbursable drugs and include dates of prescription, dates of delivery, and the amount of drug prescribed. All diagnoses are based on the German Modification of the International Classification of Diseases, 10th revision (ICD-10-GM).

This database is updated on an annual basis with anonymised and validated data. Of note, the entire process from data delivery to availability for studies can take up to two years. BIPS can be commissioned to carry out drug utilisation or drug safety studies that are requested by health authorities such as the EMA.

9.4.1.6. The Belgian Social Security Database (AIM-IMA)

The AIM-IMA (L'Agence Intermutualiste - Het InterMutualistisch Agentschap) is a non-for-profit organisation created in 2002[17]. The AIM-IMA mission is to analyse data collected by Belgian health insurance companies, in order to help improving health policy information (57). The completeness of the AIM-IMA is very high (nearly 100%) because first, by law people residing in Belgium must be registered to the Belgian social security and second, the reimbursement of drugs and medical activities is bound to data sent to the AIM-IMA.

The AIM-IMA databases include all individual data on reimbursement for prescriptions, laboratory exams, contacts with GPs and other specialists, in-hospital medical care and interventions for the entire Belgian population (11 million people) since 2008. However, diagnoses are not recorded. To circumvent this limitation, only patients who received a treatment having a brand name listed in Table 1 will be included in the study. Commercial names are recorded in the AIM-IMA database (i.e., the CNK codes that are specific to this database). Use of commercial names prevents inclusion of patients treated with these compounds but for another indication, for instance, CAMPATH®, which is alemtuzumab presentation for conditions other than MS.

Individuals are recognised by a unique personal identifier. This unique identifier allows the matching of the AIM-IMA database with other population databases like the cause of death registry and the national cancer registry.

The level of detail is the main asset of the database. Full data on prescriptions are available since 1 January 2008. There is a time-lag of one to two years between a prescription or health event and its availability on the AIM-IMA consolidated database. This database was used successfully in pharmacoepidemiological studies (21).

9.4.2. Study implementation in data sources

In each data source, a “working database” specific to the study will be created and hosted in the local IT system. All data relevant to the study derived from the local IT system will be stored in this working database. Resolution of anomalous data, variable recodifications, computations of exposure and follow-up times, and if needed, linkages with external databases will be performed

[17] www.aim-ima.be

within this working database. When all data handling procedures are terminated, the variables necessary for descriptive and statistical analyses will be transferred into an "analysis database" onto which statistical scripts will be applied. These scripts will produce results such as descriptive statistics and risk estimates in tabular format. These tables with aggregated results will be transferred to the Study Management where further analyses will be carried out using meta-analytic techniques.

All procedures specific to a data source that are needed for producing the working and analysis databases are detailed in an "Operating Protocol" (OP). A main goal of OPs is to harmonise as far as possible the most important variables to be included in analyses, in order to minimise heterogeneity between data sources. OPs will be developed in collaboration with each local data source to accommodate local variations in variable definitions, and ways to apply statistical scripts on datasets.

9.5. Study size

9.5.1. Background information

Sample size calculations require a mortality rate in the unexposed population. We outline below the mortality rates that we have reviewed before performing our calculations.

Mortality rates for MS populations, generated using MS registry data, are 2.5 to 3.5 higher than in general populations (47, 58-60). These data refer to a heterogeneous MS population; those treated with DMT and those not treated with DMT inclusive of those who may not attend neurology services regularly.

As regards mortality rates in DMT users: a study in US Veterans found that use of DMT was associated with a 42% reduced risk of mortality in comparison to never use of a DMT, after adjustment for age, sex and many other confounders (48). Articles reporting all-cause mortality rates in mainly DMT treated MS patients show rates of 0.32 per 100 patient-years in Denmark (from 1996 to 2015) (61) and of 0.24 to 0.37 per 100 patient-years in France (from 1976 to 2004 and 1990 to 2009) (47, 58).

The randomised trials on LEMTRADA enrolled MS patients 18 to 55 years of age and demonstrated mortality of 0.17 per 100 patient-years[18]. Unpublished interim data for an ongoing LEMTRADA PASS[19] reports five deaths in 2,092 LEMTRADA treated patients with 4,889.30 patient-years in Europe as of March 2020, giving a mortality rate of 0.10 deaths per 100 person-years (95% CI: 0.03; 0.24).

Based on a scarcity of data for mortality rates in HE-DMT users as an MS subgroup, we use the above rates along with unpublished data from an on-going PASS on another DMT, teriflunomide (Aubagio®)[20] to select a range of plausible morality rates for our computations. In the

[18] Pharmacovigilance Risk Assessment Committee (PRAC). LEMTRADA INN/active substance: alemtuzumab. PRAC assessment report, , 31 October 2019

[19] EUPAS 7346 : http://www.encepp.eu/encepp/viewResource.htm?id=28499

[20] EUPAS 19610: http://www.encepp.eu/encepp/viewResource.htm?id=26074

Teriflunomide PASS, all-cause mortality rates in HE-DMT treated patients in Denmark and France were 0.31 per 100 patient-years (based on 2014-2018 data).

9.5.2. Determination of sample size

All patients meeting inclusion criteria will be considered for inclusion in the study. Because sample size is a priori given for this study, we have estimated the precision of mortality risk using the following key assumptions and analysis choices:

- Mortality rate 1.2 to 2.0 times higher in LEMTRADA treated patients than in patients treated with other HE-DMT
- A ratio of exposed/unexposed of ¼ i.e. four patients treated with HE-DMT for one patient treated with LEMTRADA
- Median follow-up of six years. This value was chosen because median follow-up in the ECCS was around four years as of 2019, based on data collected between 2013-2015 and 2017-2018. The follow-up will be longer in the current study since MS patients will be followed from 2013-2015 until 2021-2023.
- Mortality rates in the HE-DMT group of 0.24, 0.36 or 0.48 per 100 person-years (see section 9.5.1.).
- Type I error (α risk) of 5% and 10% (two-sided).

The method for calculating precision is based on Rothman and Greenland (62). Sensitivity analyses show how precision changes with respect to study size, assumed mortality and relative risk of mortality between the two groups (Table 4 and Appendix 5).

Results in Table 4 indicate that if the mortality rate in HE-DMT treated MS patients was 0.24 per 100 person-years and if the relative risk of LEMTRADA vs. HE-DMT were 1.5, the 95% CI would range from 1.00 to 2.25 if 1,500 LEMTRADA treated patients were included. If the mortality rate in HE-DMT patients were 0.36 per 100 person-years, then the 95% CI would range from range from 1.00 to 2.25 with 1,000 LEMTRADA treated MS patients. The possibility to gather relevant data on 1,500 LEMTRADA treated MS patients is communicated in Table 3 and will be further evaluated during the feasibility study (see section 9.8.).

Appendix 5 presents results of alternative scenarios for variable levels of mortality risk and gives full details of calculations.

Table 4. Precision of mortality risk estimates associated with LEMTRADA treatment for given sample size and mortality rate in the group of MS patients treated with HE-DMT, for a type I error of 5 and 10%. (CI = confidence interval, RR = Relative Risk, PY=person-years)

Scenarios →		1	2	3	4	5	6
Mortality rate in comparison (non-LEM) group (deaths/100 PYs)		0.24	0.24	0.36	0.36	0.48	0.48
Median follow-up (years)		6	6	6	6	6	6
Number of LEM patients		1,000	1,500	1,000	1,500	1,000	1,500
Number of non-LEM patients		4,000	6,000	4,000	6,000	4,000	6,000
RR = 1.2	95% CI	0.70 – 2.05	0.77 – 1.86	0.77 – 1.86	0.84 – 1.72	0.82 – 1.75	0.88 – 1.64
	90% CI	0.77 – 1.88	0.83 – 1.73	0.83 – 1.73	0.89 – 1.62	0.87 – 1.65	0.93 – 1.56
RR = 1.5	95% CI	0.91 – 2.46	1.00 – 2.25	1.00 – 2.25	1.08 – 2.09	1.06 – 2.13	1.13 – 2.00
	90% CI	0.99 – 2.27	1.07 – 2.10	1.07 – 2.10	1.14 – 1.98	1.12 – 2.01	1.18 – 1.90
RR = 1.7	95% CI	1.06 – 2.73	1.16 – 2.50	1.16 – 2.5	1.24 – 2.33	1.22 – 2.38	1.29 – 2.23
	90% CI	1.14 – 2.53	1.23 – 2.35	1.23 – 2.35	1.31 – 2.21	1.29 – 2.25	1.35 – 2.14
RR = 2.0	95% CI	1.28 – 3.13	1.39 – 2.88	1.39 – 2.88	1.48 – 2.69	1.46 – 2.74	1.54 – 2.59
	90% CI	1.38 – 2.91	1.47 – 2.71	1.47 – 2.71	1.56 – 2.57	1.53 – 2.61	1.61 – 2.48

9.6. Data management

The data management procedures are specific to each data source and will thus be detailed in data source specific OPs. OPs will be finalised for each data source after completion of the first step of the feasibility study that will inform on available data and variable format (see section 9.8.). An essential goal of OPs will be to harmonise variable formats and handling of missing data across data sources, in order to reduce heterogeneity between data sources.

Each data source employs selected software for data management, sometimes locally developed and not commercially available. Statistical packages are usually R or SAS. These technical items will be described in OPs.

In general, local procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs. Each data source will maintain 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 authorised staff.

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

9.7. Data analysis

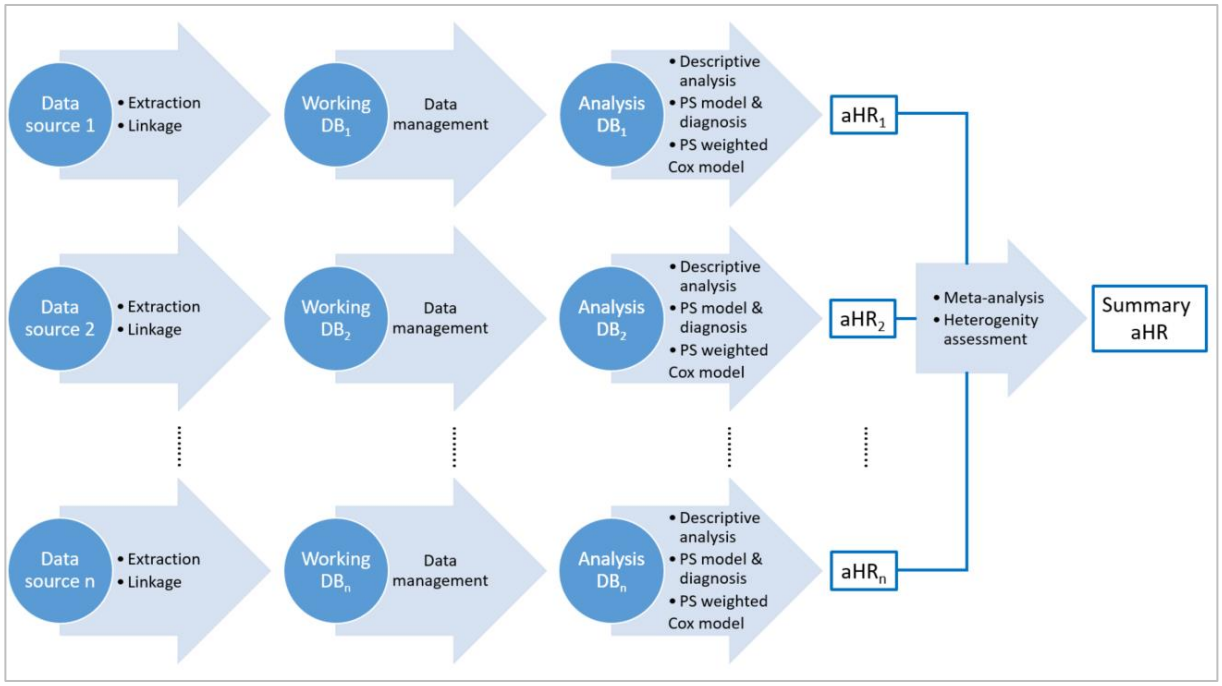
9.7.1. Patient data

The study is based on secondary use of patient data, i.e., data that are generally collected for administrative or routine care purposes.

9.7.2. Data flow

The data flow and analysis steps are summarised in **Figure 2**.

Figure 2. Data flow of the PAS study on LEMTRADA use and mortality risk.
DB: database; aHR = adjusted hazard ratio; PS = propensity score



In each data source, the data collection period regarding DMT use and vital status will span from the date of approval/reimbursement of LEMTRADA in the country until end of follow-up. Working and analysis databases will be created in each data source, and descriptive analyses, PS building and Cox Proportional Hazard model analyses will be conducted in each data source. These data source specific hazard ratios will then be meta-analysed to compute a summary hazard ratio (27).

Seven steps can be delineated for the data analysis process:

1. Descriptive analyses of exposure, confounding variables, and outcomes;
2. PS construction for predicting the likelihood of LEMTRADA treatment;
3. Analysis of PS density function and of covariate balance;
4. Statistical analyses of mortality risk of MS patients treated with LEMTRADA vs. MS patients treated with other HE-DMT;
5. Sensitivity analyses;
6. Meta-analysis of results on mortality risks with assessment of heterogeneity across data sources;
7. Estimation of the possible influence of unmeasured confounders.

During descriptive analyses and PS model construction (steps 1 to 3), no link will be made between exposure or covariates, and fatal outcomes.

9.7.3. Descriptive analyses

Because of the expected complexity of data at hand, descriptive analysis step will be required for defining the optimal way to construct propensity score (PS) models and perform subsequent analyses (63).

The descriptive analysis will be done for all eligible MS patients included in each data source and for each variable. This will allow specifying the group of patients receiving LEMTRADA or another HE-DMT in each data source, and will be done before PS modelling. The descriptive analysis will compare how variables are distributed between LEMTRADA and HE-DMT patients. The descriptive analysis will thus assess how LEMTRADA treated and HE-DMT treated compare to each other in terms of sex, age, disease duration, age at disease onset, EDSS at cohort entry date, relapse history, comorbidities, past therapies, follow-up duration and censored data (i.e. death, emigration or loss to follow-up). Particular attention will be devoted for finding out whether for some variable categories there would be zero LEMTRADA treated MS patients, while there would be HE-DMT treated MS patients, and vice-versa (64). Missing data will also be evaluated for each variable. Variability across data sources, in terms of variable availability and data format, will be examined. Whenever possible, harmonisation of variable format between data sources will be done.

Attention will be devoted to follow-up time between LEMTRADA treated and HE-DMT treated groups in order to detect the possibility of imbalance in outcome ascertainment between groups. Imbalance could occur for two reasons: 1) deaths occurring more in one group than another reflecting a true differential in mortality rates and a result that is valuable to report or 2) closer follow-up of MS patients in one group as compared to the other group, for instance, because health professionals are aware of hazards associated with a particular drug (detection bias). The later reason could lead to better detection of deaths in one group over the other leading to a biased result. This bias is however unlikely because of the seriousness of the outcome. In any event, detection bias will be minimized by ensuring that end of follow-up is recorded in the same way for each group, with extensive effort to update death data in each data source regularly and comprehensively.

Descriptive analyses will also appraise how LEMTRADA treated MS patients in routine care resemble MS patients included in phase III trials on LEMTRADA (age, MS type, EDSS, relapse history, disease duration, comorbidities and DMT prior to first LEMTRADA course).

Descriptive analyses will be based on data organised in tabular format (without individual or identifiable data) that will be sent by each data source to the Study Management. These tabular formats will be issued by the Study Management and will be standard for all data sources.

9.7.4. Propensity score model

A PS is a value ranging from zero to 1.0 which represents the probability of being exposed vs. being non-exposed to the treatment being evaluated. The exposure probability is based on variables measured at each initiation of LEMTRADA or another HE-DMT at cohort entry date. PS-based methods have the ability to inform on and control for confounding, in particular confounding by indication as long as data exist for all relevant confounders (65-67). PS modelling is recommended for confounder adjustment when the outcome is rare and that many factors may confound the exposure-outcome relationship (67-69).

Using the propensity score with the standardised mortality ratio-weighted estimator, allows to compare the risk of mortality in LEMTRADA treated MS patients to a population treated with HE-DMT other than LEMTRADA whose distribution of risk factors is similar to that of the LEMTRADA treated population. In this approach, the target of inference is the average treatment effect among LEMTRADA treated MS patients (ATT) (70).

We expect heterogeneity in data between data sources, as well as differences in availability of variables involved in confounding, both of which may contribute to heterogeneity in mortality risk estimates across data sources. PS models including all variables available in each data source will probably exert a better control of confounding, but probably also entail more heterogeneity. One way to minimize heterogeneity is to start with a parsimonious PS model including the same core variables in all data sources identified during literature review and assessment of confounding potential (see section 9.3.5. and Appendix 3). The primary PS model will be based on core variables and will be obtained through fitting a logistic regression model. Adding variables that are not found in all data sources to the PS model will be part of a sensitivity analysis.

The way the PS will be built, and the exact statistical analysis strategy described hereafter will depend on thorough descriptive analysis of data at hand (see sections 9.7.3. and 9.8.).

PS will be computed at each time point of relevance, i.e., at cohort entry date and at each subsequent switch to another HE-DMT. This rule also applies to MS patients that would switch from one HE-DMT other than LEMTRADA to another HE-DMT other than LEMTRADA (e.g., patient 5 on Figure 1). Hence there might be more than one PS attached to one MS patient.

After weighting (see section 9.7.5.), the balance of variables between the two groups will be evaluated through computation of standardised mean differences (65, 71). If for some variables, the balance is not optimal, improvements will be sought through careful examination of the PS models. PS models will then be re-specified for instance, through modification of covariate codification (66). Additionally, the PS density functions obtained for each data source will be graphically displayed, and PS distributions among LEMTRADA and other HE-DMT treated MS patients will be compared.

Non-overlapping regions between LEMTRADA treaa sensitivitryted and other HE-DMT treated patients will be detected. If non-overlapping (or poorly overlapping) regions are observed, the characteristics of MS patients populating these regions will be examined so that factors determining the "non-positivity" of LEMTRADA treated and non-LEMTRADA treated MS patients can be identified.

Exclusion of non-overlapping regions at both ends of the PS distribution addresses non-positivity, and is recommended as the default prior to any PS implementation (72). It also avoids having MS patients who had practically no chance to have received LEMTRADA (72-74). Therefore, the main analysis will be based on the primary PS model using all data after exclusion of non-overlapping regions. In sensitivity analyses, trimming of LEMTRADA treated MS patients with lowest PS (i.e. treated patients contrary to prediction) and non-LEMTRADA treated MS patients with highest PS (non-treated patients that should have been treated according to prediction) will be conducted following procedures outlined by Stürmer and colleagues (72, 75) (see section 9.7.7.2.).

High-dimensional PS (hd-PS) have probably the greatest potential for achieving optimal balance in covariates between groups being compared (76). However, their development requires availability of hundreds of variables related to the health status of MS patients. Such an amount of variables is common in some real-world data sources e.g., from health insurance claims data, or national patient registries. The hd-PS approach will be explored for feasibility in MS registries linked to national registries and administrative data sources. However, the hd-PS approach may not be possible in the UK due to limited number of variables in the medical chart, and in the Czech Republic MS Registry because data on MS patients are not linkable to other national registries.

9.7.5. Computation of PS weights

Data analysis methods based on PS weighting are often used for controlling the influence of confounding factors on the association between an exposure and an outcome in the setting of pharmacoepidemiology studies (67, 70). PS weighting has several advantages over traditional multivariable regression analyses like the ability to provide a global comparison of covariate distribution between groups being compared, and the possibility to clearly define the target population of inference (i.e., the population onto which study findings apply) (77).

We elected the standardised mortality ratio (SMR) method (or "weighting by odds" method) for computing weights. The method for computing PS weights has been selected considering that LEMTRADA is indicated for MS patients characterized by MS severity and progression. Thus, we aim to compare the risk of mortality in LEMTRADA treated MS patients to a population treated with another HE-DMT whose distribution of risk factors is similar to that of the LEMTRADA treated population. In this approach, the target of inference is the average treatment effect among LEMTRADA treated MS patients (ATT) (70).

Weighting in the LEMTRADA treated group is set to 1.0. Weighting in the comparison group is done using the odds of the PS attached to each MS patient included in comparison groups, i.e., PS/(1-PS). SMR weighting reweights the control patients to be representative of the treated population. SMR weighting thus results in an estimate of ATT. Approaches for dealing with potential extreme weights will be outlined in the SAP.

9.7.6. Statistical analysis

9.7.6.1. Mortality rates

In each data source, mortality rates will be calculated after the latest update of vital status. Crude mortality rates in the LEMTRADA and other HE-DMT treated groups will be calculated for all MS patients. Then, age and sex adjusted mortality rates will be computed. Mortality rates will be expressed as number of deaths per 1,000 patient-years with 95% CI. Comparisons between data sources will allow an appreciation of variability in mortality rates.

9.7.6.2. Survival curves

Data sources will transfer to the Study Management fully de-identified text files including individual data on age at cohort entry, sex, follow-up, and date of death or of last news. The Study Management will then draw Kaplan-Meier curves combining aggregated survival data from each data sources, so that an overall picture of crude survival data is obtained.

9.7.6.3. Cox proportional hazard model

Statistical analyses will be conducted in each data source in order to compute the risk of mortality using the PS weighted time-dependent Cox proportional hazard model. The proportional hazards assumptions underpinning Cox regression will be checked via visual inspection of Kaplan-Meier curves and on the visual inspection of Schoenfeld residuals. Cox model specifications will be the same across data sources. What may vary are the PS models and subsequent weighting owing to variations in data availability and variable codification across data sources. Hence, heterogeneity in PS model is susceptible to introduce heterogeneity in results across data sources.

Cox proportional hazards models will be used to generate hazard ratios (HR) and 95% confidence intervals (CI), computed using a robust variance estimator. Two Cox models will be performed with varying levels of adjustment. The rationale is to provide an indication of the ability to adjust for confounding. The first model will be adjusted for age and sex only. The second model will include the PS weighted population, age and sex.

9.7.6.4. Meta-analysis

Following the Council of International Organisation of Medical Sciences Working group X (CIOMS X) recommendations (27) a meta-analysis will be performed to combine all adjusted hazard ratios estimated in each data source and obtain a summary hazard ratio. Combination and interpretation of the summary hazard ratio will depend on heterogeneity of results across data sources.

Hazard ratios will be pooled together by the Study Management using a random-effects model (78), in order to account for the presence of heterogeneity across included data sources. This considers that the differences between sources are random. Also, 95% CI for the pooled hazard ratio will be calculated.

Heterogeneity will be assessed using Higgins' I^2 (79), will be informed by the Cochrane Handbook on Systematic Reviews (80), and will be interpreted according to Borenstein (81). If substantial or considerable heterogeneity is detected ($I^2 \geq 50\%$), potential sources of heterogeneity will be explored. Heterogeneity could be explained by the type of data (e.g. administrative database vs. MS registry), by differences in patient profiles (e.g. age, sex, EDSS, comorbidities) across databases and countries, and by variations in covariates in data source-specific PS models.

Results will be represented graphically with forest plots. Sensitivity analyses will be conducted, for example by removing one data source at a time in order to evaluate the influence of each data source on the overall result (i.e., "leave one out" analysis).

9.7.7. Primary analysis

9.7.7.1. Main analysis

The primary analysis will be based on a time-dependent approach using a weighted Cox proportional hazard model. Weights will be derived from the primary PS model fitted with core variables. Follow-up is determined as outlined in section 9.3.4. , Figure 1 and Table 2.

9.7.7.2. Sensitivity analyses

Nine sensitivity analyses are foreseen at this stage and are described below. More may be suggested by descriptive analyses and examination of PS density functions.

1. Analysis with asymmetrical trimming on both ends of PS distributions will be conducted following procedures outlined by Stürmer and colleagues (72, 75). This will exclude LEMTRADA treated and HE-DMT treated MS patients with PS exceeding cut-offs for trimming at both tails of PS distributions:
    - On highest PS distribution (i.e., MS patients most likely to be treated with LEMTRADA), cut-points for trimming will be based on the PS distribution of MS patients treated with a HE-DMT and will be 1%, 2.5% or 5%. The exact cut-points will be determined in the SAP.
    - On lowest PS distribution (i.e., MS patients less likely to be treated with LEMTRADA), cut-points for trimming will be based on the PS distribution of MS patients treated with LEMTRADA and will be 1%, 2.5% or 5%. The exact cut-points will be determined in the SAP.
2. Repeat of the main analysis using a type I error (α risk) of 10%, which will lead to narrower confidence intervals.
3. A sensitivity analysis with an intent-to-treat approach will be performed. In this analysis, patients will be attributed to the LEMTRADA group or to the HE-DMT group based on their treatment at the cohort entry date. Consequently, patients 1, 3 and 6 will be part of the LEMTRADA group while patients 2, 4, 5 and 7 will be part of the HE-DMT group (Figure 1). The follow-up time until the end of the study will be attributed to the treatment received at cohort entry date (Table 5). A more detailed comparison of the main analysis with this sensitivity analysis is displayed in Appendix 2.

Table 5. Group assignment and follow-up time for outcome assessment according to the ITT approach

Patient number according to Figure 1	Group assignment	Follow-up time for outcome assessment according to Figure 1
1	LEMTRADA	a
2	HE-DMT	b+c
3	LEMTRADA	d+e
4	HE-DMT	F
5	HE-DMT	g+h
6	LEMTRADA	J
7	HE-DMT	L

4. A sensitivity analysis will apply right-censoring at each treatment switch from one HE-DMT to another. Patients will be attributed to the LEMTRADA group or to the HE-DMT group as per the main analysis, but follow-up time will be censored at time of switching.

(Table 6). A more detailed comparison of the main analysis with this sensitivity analysis is displayed in Appendix 2.

Table 6. Group assignment and follow-up time for outcome assessment according to the first exposure only with right censoring analysis

Patient number according to Figure 1	Group assignment	Follow-up time for outcome assessment according to Figure 1
1	LEMTRADA	a
2	HE-DMT	b
3	LEMTRADA	d
4	HE-DMT	f
5	HE-DMT	g
6	LEMTRADA	j
7	HE-DMT	l

5. An analysis that considers fatal events occurring during the same follow-up duration in all data sources. Hence, the shortest follow-up duration in a data source will be applied to all other data sources. The resulting summary hazard ratio will be compared with the summary hazard ratio found in the main analysis.
6. Non-core variables (depending on available data in each data source) will be added in the logistic model for obtaining a calibrated PS model. Calibrated PS model can inform on whether factors not included in the primary PS model would affect PS weights and thus also risk estimates. These effects will be assessed at data source level. This will enable testing the robustness of PS models.
7. Some data sources may collect data on variables such as smoking status, adiposity, spinal fluid analysis, and MRI results. Their distribution in the LEMTRADA and the HE-DMT groups will be evaluated during the descriptive analysis. In case of proven imbalances in distribution, sensitivity analyses will be conducted by computing PS models with and without these variables. This would allow exploration of the impact of their inclusion in the PS model on results obtained in these data sources.
8. PS models constructed with data from MS patients without missing data in core variables will also be constructed.
9. Cohort entry date will be restricted to the period 2013 (date of LEMTRADA approval/reimbursement) until April 2019 in order to include MS patients exposed to LEMTRADA before the change in label in 2019. Follow-up of patients will continue until the date of last database update in 2023.

9.7.8. Secondary analysis

In secondary analyses we will investigate the cause of death in data sources where this information is available and when the number of cases for a specific cause is sufficient. Several key points need to be taken into account for an analysis focusing on causes of death:

- For 40 to 60% of MS patients who die, the cause of death is recorded as "multiple sclerosis" (45, 47, 82-87).
- Coding practices differ between countries and between health professionals (88), with for instance the trade-off for assigning the cause of death to "multiple sclerosis" or to another cause of death (89).

For these reasons, the results from the cause of death analysis may not be informative and will have to be considered with caution. Availability of cause of death will be assessed during the feasibility study (see section 9.8.).

9.7.9. Other analyses

A temporal analysis of fatal outcomes will be implemented as suggested by the PRAC. The PRAC Assessment Report on the Article 20 procedure for LEMTRADA raised the question of whether the number of fatalities stratified by age and disease severity within different time periods might exceed the expected rate. There is thus a need to examine whether rates of fatal events change with the year LEMTRADA treatment has been initiated.

There are two challenges to studying this. First, because the number of events over the study period will probably be low, stratifying by time period would result in even less events per time period. Second, patients treated with LEMTRADA from 2018-2019 onwards will have less available follow-up for an event to occur.

We will attempt to descriptively examine fatal events over time. If deemed feasible, we may consider a formal statistical analysis that incorporates time split into categories, informed by the descriptive analysis and other factors such as changes in label and release of newly marketed other HE-DMTs. This categorical time variable may be used for stratified analyses or as an interaction term with exposure in weighted Cox proportional hazards models. Time as a continuous variable may also be considered if the number of events allows it, and if categorisation is not reasonable.

9.8. Feasibility study

9.8.1. Rationale for feasibility study

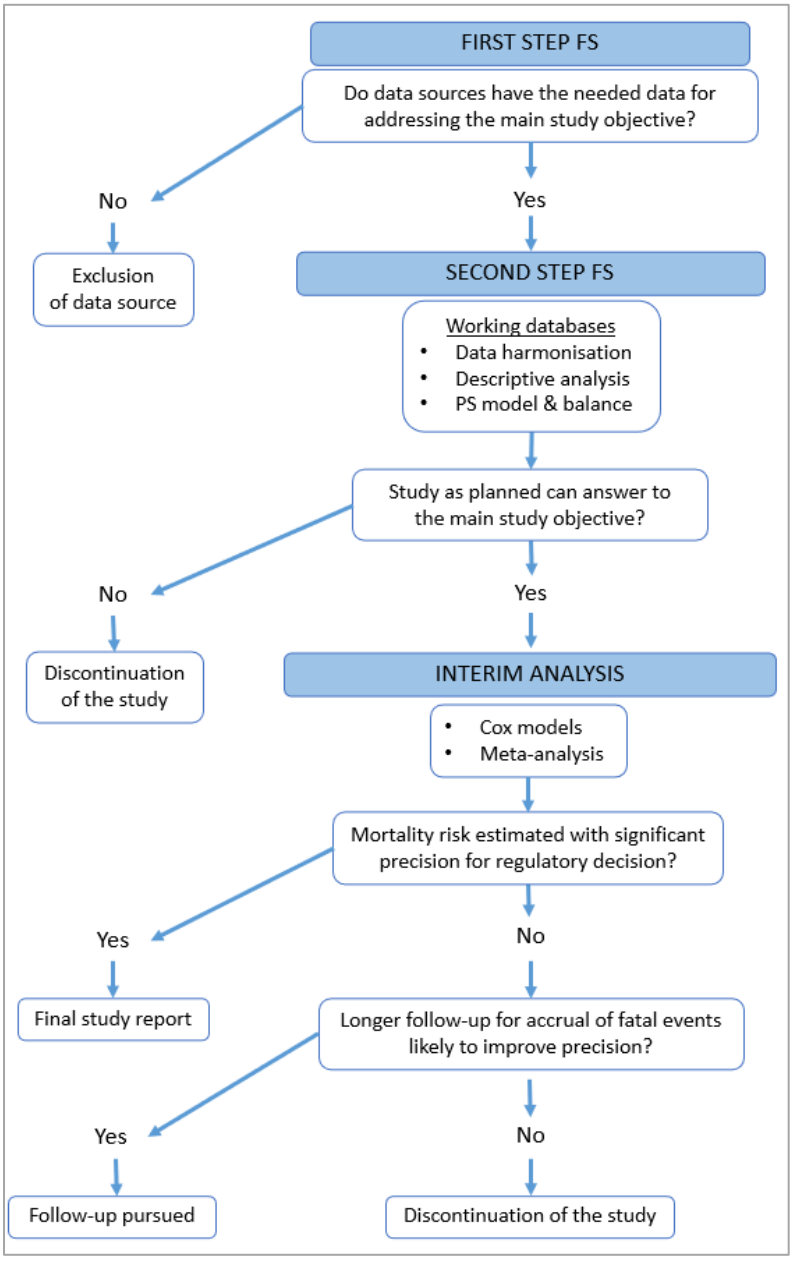
Uncertainties on four main aspects have been encountered at the time of protocol writing:

1. The all-cause mortality rate expected in MS patients treated with a HE-DMT is not well known, but is expected to be low across the study period.
2. The total number of exposed patients in each group is at present unknown, along with duration of follow-up in each group. How a two-year look-back period to determine prior medication use and baseline comorbidities might affect this number is unknown. Whether MS patients available in data sources are inclusive of both trial and routine care patients needs to be disentangled.
3. The availability and quality of data for core variables such as EDSS, MS type and comorbidities is at present unknown.
4. How MS patients treated with LEMTRADA will be comparable to MS patients treated with another HE-DMT is unclear. This is important in the context of achieving similar cohorts for making a valid comparison.

9.8.2. A feasibility study and interim analysis

To answer to the aforementioned questions, we propose a feasibility study organised in two successive steps. A first step will examine the availability of relevant data in each data source. Then, a second step will be dedicated to the creation of working databases with harmonisation of data and descriptive analyses. The feasibility study will identify data sources where the primary propensity score model with core variables can be fitted and will assess whether balanced cohorts can be achieved. If the feasibility study indicates that the main study objective can be addressed, a full ‘interim analysis” will be conducted (submission Q2 2023), and could be considered as the final analysis, if precision allows. The sequence of activities underpinning the feasibility study and interim/final analysis are summarised in Figure 3.

Figure 3. Summary steps and decision points for the feasibility study (FS) and interim analysis



9.8.3. First step of the feasibility study

The first step of the feasibility study will be an in-depth examination of data availability in each data source, which will aim at providing answers to the following questions;

1. Are the available data sufficient to answer the primary study objective?
    a. Based on number of patients treated in routine care in each group, median follow-up time and number of deaths, can we anticipate reasonable numbers of fatal events for the comparison? Does a two-year look-back period reduce the cohort size substantially? Is a one-year look-back better, considering the trade-off in terms of measuring prior medication use and baseline comorbidities?
    b. Are data available on core variables i.e., those that are important predictors of mortality?
2. What is the variability in data availability, quality and usability within and across data sources? Relative to a two-year look-back period, does a one-year look-back period provide similar recording of comorbidities?
3. Can balanced cohorts on all important confounders be developed in each data source?

To this end a detailed questionnaire will be sent to data sources (see Appendix 6), and virtual meetings will fine tune information gathered with questionnaires.

Questionnaires will inquire on:

1. Procedures in place for follow-up of MS patients included in study cohort,
2. Examination of whether core variables are available,
3. Examination of whether causes of death are available,
4. Assessment of data quality, with amount of missing data,
5. Administrative and legal procedures to be accomplished for assembling working databases.

Answers to questionnaires will evaluate the availability and quality of data within each data source especially for important predictors of mortality and confounding variables. Feasibility assessment for the entire study will be based on an indication that sufficient precision of mortality risk estimates can be expected based on numbers of MS patients in each treatment group, observed all-cause mortality rates and observed follow-up.

The first step will end up with decisions for launching works foreseen in step 2 of the feasibility study, i.e., creation of working databases, descriptive analyses and PS model in data sources. This second step will also allow finding optimal solutions for missing data and harmonisation of key variables and will assess whether balanced cohorts can be achieved.

9.8.4. Second step of the feasibility study

While administrative and legal procedures are in progress to secure access to data, the study coordination will work with local staff of each data source to prepare for the descriptive analysis once all authorisations have been received. Preparation actions will be detailed in the statistical analysis plan (SAP) and in "operating protocols" (OP). The SAP and OPs will take care of missing data handling and of variable harmonisation.

When all administrative procedures are accomplished, working databases will be created in IT systems of each data source and descriptive analyses will be conducted using these working databases, as outlined in the SAP.

The descriptive analysis will compare the characteristics of MS patients treated with LEMTRADA and MS patients treated with another HE-DMT (see section 9.7.3.). Then, a logistic model will be fitted to generate the propensity score. Assessment of propensity score balance will take place across the two groups.

Moreover, planned sensitivity analyses will investigate the numbers of LEMTRADA deaths that would be attributed to the previous HE-DMT treatment when ITT analysis is done, and reciprocally, the number of HE-DMT deaths that would be attributed to the previous LEMTRADA treatment.

The report on the second step will present two possible outcomes.

1. The study as planned is anticipated to not provide meaningful results due to at least one of several reasons including: not reaching study precision due to lack of outcomes despite continuing the study into 2023 across all data sources; exclusion of data sources due to data quality; suspected residual confounding, and/or lack of balance in confounding that cannot be addressed thus invalidating a comparative analysis. In any of these instances, discontinuation of study may be requested.
2. The interim analysis can address the main study objective on mortality risk associated with LEMTRADA treatment.

9.8.5. Interim analysis

Depending on the results of the step 2 of the feasibility study, interim analyses using all available data will take place in each data source, including:

1. The primary PS model will be fitted using the same core variables in all data sources, and then PS-weighted hazard ratios will be computed.
2. Investigation of heterogeneity across data sources.
3. Meta-analysis of HRs with sensitivity analyses to evaluate the influence of each data source on the overall result.

Data for the interim analysis will encompass the timeframe of 2013 to 2022 (depending on time-lag for data availability in each data source), which could provide up to eight years of follow-up time. We anticipate that these data will represent the majority of the evaluable LEMTRADA population due to low utilisation rates expected from 2019 onwards (restricted labelling related to the Article 20 procedure followed by the Covid-19 pandemic).

As outlined in Figure 3, a decision will need to be made as to whether the interim results could be potentially accepted as a full analysis or whether additional follow-up years should be permitted to accrue. This decision will be informed by two concepts.

First, the timing of deaths will be examined. Survival curves for each drug group (LEMTRADA vs HE-DMT) within each data source may inform on whether deaths in one exposure group were inclined to occur earlier after treatment start than in the other exposure group. In this setting, survival curves would diverge quickly in the first weeks after treatment start, and become parallel curves after longer follow-up. This scenario would indicate that additional follow-up may not be beneficial for accruing additional events.

Second, interpretation of interim analysis result is to be based on precision of mortality risk estimates reflected by the width of confidence intervals. It should not be based on statistical significance considerations on whether confidence intervals for hazard ratios include 1.0 or not. Interpretation based on precision avoids issues related to multiple testing, such as type I error inflation and overestimation of estimates (90). It also agrees with increasing thinking that interpretation of results of observational studies should no longer be based on hypothesis testing after setting an alpha level for decision making, but rather on precision of risk estimates (91, 92).

The sample size estimates in section 9.5.2 will be used as a guide for interpreting results of the interim analysis. At that stage, relevance of long-term follow-up will also be based on mortality rates in LEMTRADA and HE-DMT groups.

The report on the interim analysis will be available in Q2 2023.

9.9. Quality control

9.9.1. Data collection, validation, and data quality control at Study Management level

The Study Management will produce standard descriptive procedures to be applied on datasets for identifying missing and erroneous data and verify the consistency of the dataset. For instance, variables with values exceeding typical ranges and missing values will be flagged.

9.9.2. Data quality control at data source level

The Operating Protocols will detail the ways by which each data source will apply the standard descriptive procedures, in particular for spotting missing and erroneous data. Retrospective search for data will be allowed for data derived from medical charts, for instance, when time to EDSS 4.0 is known to have been collected in medical files but not registered in a data source.

Follow-up and outcome ascertainment modalities specific to each data source will be detailed in OPs. Follow-up completeness will be assessed for LEMTRADA and non-LEMTRADA groups, statistical description of follow-up duration as well as characteristics (age, sex, DMT taken) of MS patients with incomplete follow-up.

9.9.3. Handling of missing data

Descriptive analysis in each data source will examine frequency of missing data. Special attention will be devoted to core variables that will be used for the primary propensity score model.

Descriptive analyses will evaluate whether missing data are random processes or could be linked to key characteristics such as age (93).

Regarding the core variables with missing data, and dependent on the pattern of missingness observed, the general approach will be the use of multiple imputations (94), based on the R package Multivariate Imputation by Chained Equations (mice) (95, 96).

Regarding age and sex, it is known from previous studies done with data sources used in this PASS that MS patients with unknown age and sex are rare, i.e., less than 1% of all MS patients. Missing data on age and sex are usually random. When age or sex of patients will be missing, we will try to infer them from other variables (e.g. history of pregnancy) or from multiple imputation. If imputation is not possible, these MS patients will be excluded. In any case, few MS patients will have unknown age and/or sex which is not likely to affect study precision or bias results.

It is anticipated that the EDSS which is a key prognostic factor of survival in MS patients but also a key determinant of treatment may have a sizeable proportion of missing data, around 6% according to unpublished data from the Teriflunomide PASS. Imputation on EDSS at cohort entry date will rest on many other variables including age, sex, history of relapses, delay since MS diagnosis, comorbidities, and treatment history. For missing EDSS at treatment switch, we will use the "last observation carried forward" unless a proxy indicator for disability is available and informs that the EDSS may have changed. In the latter case, we will use the EDSS category corresponding to the proxy indicator category (see Appendix 4).

Of note, apart from the propensity score used for weighting, the main Cox model will include age, sex and treatment (LEMTRADA vs. other HE-DMT), so that no additional missing data are anticipated for variables in the main Cox model. In a sensitivity analysis, the main Cox model will be fitted with a new propensity score weight after discarding all observations with missing data in core variables.

9.10. Limitations of the research methods

9.10.1. Global study limitations

This study aims to investigate the risk of death associated with exposure to LEMTRADA relative to other HE-DMT. The main limitations are:

- The anticipated small number of fatal events, which may preclude reaching sufficient statistical precision.
- Imbalance in measured confounders and the potential influence of unmeasured confounder(s).

The feasibility study will allow an assessment of study precision and availability of data on important predictors of mortality and confounding variables. Also, it will inform on the possibility of obtaining balanced cohorts allowing valid comparisons between LEMTRADA and other HE-DMT treated groups. We will investigate how strong an unmeasured confounder must be for causing a spurious result (see section 9.10.5.4.).

9.10.2. Absence of similar examples in the literature

We did not find published literature investigating mortality associated with specific DMT. However, the methodological challenges in this study (e.g., low number of events, numerous confounders, complex exposure patterns, etc.) have been studied in other disease areas. Therefore, we have used some of these solutions (97-99).

9.10.3. Variability in data collection between data sources

Not all variables listed in section 9.3.5. related to MS patient's characteristics and disease history will be available in all data sources. Factors like adiposity, smoking and mood disorders are known risk factors for premature mortality in populations at large. Smoking and mood disorders are also associated with more aggressive MS disease (100). However, many data sources do not record (or have incomplete or inaccurate recording of) variables like smoking, adiposity, mood disorders or quality of life. In addition, no literature exists on possible associations between these variables and the type of DMT received. We are thus not aware whether variables like "smoking, "adiposity", "mood disorders", would be dissimilar between MS patients treated with LEMTRADA and MS patients treated with another HE-DMT, and thus could confound the relationship between treatment exposure and mortality.

We however thought that possible imbalance in mood disorder prevalence between groups being compared had to be addressed. Mood disorders are rarely captured by data sources such as administrative and disease registries. To circumvent this difficulty, prior or concomitant treatment with anti-depressants or benzodiazepines will be used as proxy of mood disorders.

There will be differences between data sources in available data and in data collection/recording procedures. For instance, depending on data source, initiation of HE-DMT will be captured as the date of prescription or of actual dispensing. The EDSS may be collected as a continuous variable, as a categorical variable, or as a proxy based on use of assistive devices. Consequently, there may be heterogeneity in results between data sources because of differences in confounder adjustment. However, statistical analysis plans and operating protocols implemented in Q2-Q3 2021 will aim at harmonizing variable codification and format across data sources. In addition, descriptive analyses within each data source, evaluation of the PS distribution and a leave-one-out analysis at the meta-analysis stage will be performed to first understand sources of heterogeneity and second to investigate the influence of heterogeneity on the summary risk estimate.

9.10.4. Criteria for MS diagnosis

MS diagnosis criteria may differ according to age of MS patients at cohort entry. While McDonald criteria (101) has been in use for two decades, older MS patients may have been diagnosed according to Poser or Schumacher criteria (102), which may impact on age at MS onset or at MS diagnosis. However, there is no a-priori to believe that changes in diagnosis criteria may introduce bias because first, the assessment of the disease severity at cohort entry date is independent of diagnosis criteria, and second, the selection of MS patients considers the age at first prescription of a HE-DMT.

9.10.5. Bias

This section presents several types of bias that could occur in the study. The biases potentially encountered include selection bias, information or detection bias and unmeasured confounding.

Quantitative bias analysis methods will be used to explore and quantify the impact of such biases on study results. The complexity of these methods ranges from simple, with sensitivity analyses, to more intricate with probabilistic and multiple bias modelling (103). In our case, we will perform sensitivity analyses and compute E-values (unmeasured confounding bias), considering limitations of the latter method.

9.10.5.1. Selection bias

According to the Good Pharmacoepidemiology Practice from the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) definition, selection bias entails the selective recruitment into the study of subjects that are not representative of the exposure or outcome pattern in the source population. In a scenario characterised by selection bias, more outcomes might be present in one group more than the other as a direct result of differential selection or retainment (e.g. more intense medical surveillance in one group over the other) as opposed to a truthful over-occurrence. Minimal selection bias is expected in this study as all MS patients initiating a HE-DMT after LEMTRADA approval/reimbursement within each data source will be considered for inclusion (ratios of recruitment given in sample size calculation).

In terms of generalisability, it is noted that not all countries in the EU will be represented and in some data sources not all patients within a country will be represented, for example the UK. Thus, the generated results will be applicable to countries included in this study and to countries that use LEMTRADA in a similar way.

9.10.5.2. Misclassification bias in exposure and confounders

The possible influence of misclassification of drug exposure will be addressed by the various sensitivity analyses. Consistent results across these analyses would indicate low risk of exposure misclassification.

Core variables defined in this protocol may be subject to misclassification but the misclassification will likely be non-differential. In other words, we expect any measurement error will occur to the same extent for the LEMTRADA and the other HE-DMT groups. Thus, the results will not be biased in favour of one group or another, but could be biased towards the null.

9.10.5.3. Misclassification bias in outcome ascertainment

Incomplete follow-up may introduce detection bias mainly if medical surveillance of MS patients differs between treatment groups (104, 105). For instance, health professionals could be more alert about vital status of LEMTRADA treated MS patients than of other HE-DMT treated MS patients. This contrast in surveillance may lead to mortality being observed more accurately or in a more timely way for LEMTRADA patients *versus* other HE-DMT patients (106). However, this bias is unlikely because of the seriousness of the outcome.

In Denmark, Belgium and Sweden, data sources on MS patients regularly link with national population registries that exhaustively record deaths and migrations of all people living in the country. When data proceed from MS patient's files, procedures in place for "active tracing" of MS patients will be assessed. The three centres in the UK have participated to randomised trials and other prospective studies and have thus great experience with active tracing. Data sources obtaining their data from health insurances (like in Germany) may have less complete data since these data sources do not link with national population registries. For example in Germany, death is recorded as a reason for end of insurance or if the death occurred in a hospital. Other data sources are informed on vital status of patients thanks to notifications by health professionals or relatives.

Detection bias would be introduced if active tracing was carried out to different levels of completeness for each treatment group. In this regard, active tracing of MS patients in both treatment groups until study end is crucial. As stated above, given the gravity of the outcome it is expected that surveillance for the outcome would be equal in both groups.

The Study Management will vet modalities for the tracing of MS patients and linkage with vital data statistics in each data source. In order to avoid information bias on the outcome, analyses will be carried out only after last vital status update.

9.10.5.4. Unmeasured confounding

An association between LEMTRADA use and mortality risk could be due to imbalance on confounders that were not measured and thus not included in the PS model. For instance, an unmeasured confounder could be smoking, if smoking was more or less prevalent in LEMTRADA treated MS patient than in HE-DMT treated MS patients. However, data on smoking are seldom available in population level data sources and when available they are sometimes incomplete or outdated.

One quantitative bias analysis method for assessing unmeasured confounding is based on the computation of the "E-value". The "E-value" represents the minimum strength of association, on the risk ratio scale, that an unmeasured confounder would need to have with both the treatment and outcome, conditional on the measured covariates, to explain away a treatment–outcome association (107). Hence, estimation of the "E-value" will provide a quantitative estimate of the association between an unmeasured confounder and mortality risk associated with LEMTRADA use that could lead to a change in study conclusions.

However, the E-value has known limitations (108-110). The interpretation of the E-value, namely for which thresholds is an E-value suggestive of residual confounding, or absence thereof, depends on the research context. Variables that could potentially confound mortality risk estimates are MS type, EDSS, MS duration. In contrast, thyroid disorders seem not associated with increased mortality (Marrie et al, 2016). The E-values will be calibrated for the study results, by calculating E-values corresponding to known confounders (MS type, EDSS or MS duration) and non-confounders (thyroid disorders), through analyses that do or do not adjust for each or combinations of these factors.

We plan to also report the E-value for the limit of the confidence interval closest to the null, as indicated by VanderWeele, Mathur (110). This would inform on the strength of association an unmeasured confounder would require to have in order to render the risk estimate statistically non-significant.

In addition to the computation of the E-value, sensitivity analyses will be performed to assess the effect of unmeasured confounding on the study result. First, a sensitivity analysis will be conducted in data sources collecting data on specific confounders (e.g. smoking, obesity) by including and excluding these variables in statistical models (calibrated PS models). Second, a sensitivity analysis will be conducted with trimming at both ends of the PS distribution. This method has been shown to reduce unmeasured confounding (75).

10. Protection of human subjects

This study will be conducted in accordance with the guidelines from ENCePP and the International Society of Pharmacoepidemiology (111, 112).

10.1. Consent

In each participating country, all necessary regulatory/ethics submissions will be performed in accordance with local regulations including local data protection regulations.

For the MS registry data from Denmark, Sweden and the Czech Republic explicit consent is not required due to secondary use of anonymized data. For administrative data from Belgium and Germany, explicit consent is not required due to secondary use of anonymized data. In the UK, patient consent is carried out at the local level (there are three participating academic centres). The lead PI for the study will apply to the National Health Service Ethics Committee for approval if deemed necessary, otherwise local ethical approval will be sought.

The Informed Consent Form and the Information Sheet used for obtaining the Patient's Informed Consent must be reviewed and approved by the Study Management.

10.2. Data protection

All data handling and hosting will be done in data sources. No individual data will be transmitted to the Study Management or the MAH. Transfer of data to the Study Management will be done as aggregated, de-identified data in tabular format. De-identification usually entails « age » being given by 5-year age group, and the date of death or of last news set on the mid-day of the month during which the event occurred.

For non-interventional studies that are based on use of secondary or routine health care data, reporting of adverse events/adverse drug reactions beyond the aim of the study is not required as laid out in the EMA guidelines for good pharmacovigilance practices modules VI and VIII and as also referenced in ENCEPP guidelines for good pharmacoepidemiological practice (13, 111, 113).

11. Management and reporting of adverse events/adverse reactions/other medically important events

For non-interventional studies that are based on use of secondary or routine health care data, reporting of adverse events/adverse drug reactions/other medically important events beyond the aim of the study is not required as laid out in the EMA guidelines for good pharmacovigilance practices modules VI and VIII and as also referenced in ENCEPP guidelines for good pharmacoepidemiological practice (13, 111, 113).

12. Plans for disseminating and communicating study results

In accordance with the 2010 EU pharmacovigilance legislation, the protocol of this study will be entered into the publicly available EU PAS register, once PRAC approval is given. A completed ENCePP Checklist for study protocols is included in Appendix 7. Updates to the study protocol in case of substantial amendments and the final study report will also be entered in the register.

A report on the interim analysis will be submitted to the Regulator in Q1 2022. Thereafter, annual reports will be submitted in Q4 2022 and Q4 2023 detailing accrual and including interim analyses. The final report will be submitted in Q3 2024.

The Study Group for this study will be comprised of the International Prevention Research Institute (Lyon, France) which is in charge of the PASS coordination, the heads of individual data sources and MAH representation. The study group will have full access to the final data allowing for appropriate analysis, interpretation and reporting of the study results. All reporting will be done in accordance with the advice of the Scientific Committee. All involved parties from individual data sources give full authority to the Study Group for primary presentation and/or primary publication (i.e the final study report) of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for sub-studies) must be approved by the Study Group, along with the guidance of the Scientific committee, and make reference to the study and the primary publication (i.e. the final study report). The final decision to publish any manuscript/abstract/presentation will be made by the Study Group after prior notice to the MAH allowing for its internal review and comments. All manuscript/abstract/presentations must be submitted for internal review by the MAH at least forty-five (45) calendar days in advance of submission. The MAH may request that the name and/or names of one or several of its employees appear or do not appear in such publication. Any publication in a peer reviewed journal will be disclosed onto the ENCePP site within 2 weeks of acceptation by journal.

13. References

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APPENDIX 1: DISEASE MODIFYING THERAPIES (DMT)

List of DMTs approved in Europe.

- The Platform DMT (P-DMT) include:
  - Dimethyl fumarate (Tecfidera®),
  - Glatiramer acetate (Copaxone®),
  - Interferon beta 1-a (Avonex®, Rebif®),
  - Interferon beta 1-b (Betaferon®, Extavia®),
  - Peginterferon beta 1-a (Plegridy®),
  - Teriflunomide (Aubagio®).

- The Highly Efficacious DMT (HE-DMT) include:
  - Cladribine (Mavenclad®),
  - Fingolimod (Gilenya®),
  - Mitoxantrone (Novantrone®),
  - Natalizumab (Tysabri®),
  - Alemtuzumab (LEMTRADA®),
  - Ocrelizumab (Ocrevus®),
  - Rituxumab (MabThera®, Rixathon®, Riximyo®, Blitzima®, Ritemvia®, Rituneza®, Ruxience®[biosimilar], Truxima®[biosimilar]).

The classification of P-DMT and HE-DMT in this PASS may differ from the classification encountered in some countries or adopted by some neurologists and scientists. DMT usually starts with a P-DMT.

APPENDIX 2: FOLLOW-UP SCENARIOS, PROS AND CONS

Scenarios	**1**		**2**		**3**	
	Time-dependent exposure Main analysis		Intent-to-treat (ITT)		Right-censoring analysis	
Patients	Exposure group	Follow-up	Exposure group	Follow-up	Exposure group	Follow-up
1	LEM	a	LEM	a	LEM	a
2	HE-DMT	b	HE-DMT	b + c	HE-DMT	b
	LEM	c	-	-	-	-
3	LEM	d	LEM	d + e	LEM	d
	HE-DMT	e	-	-	-	-
4	HE-DMT	f	HE-DMT	f	HE-DMT	f
5	HE-DMT	g	HE-DMT	g + h	HE-DMT	g
	HE-DMT	h	-	-	-	-
6	LEM	j	LEM	j	LEM	j
7	HE-DMT	l	HE-DMT	l	HE-DMT	l
8	Not eligible	-	Not eligible	-	Not eligible	-

Scenarios	**1**		**2**		**3**	
	Time-dependent exposure Main analysis		Intent-to-treat (ITT)		Right-censoring analysis	
Patients	Exposure group	Follow-up	Exposure group	Follow-up	Exposure group	Follow-up
	1/ Assumes effect of LEM stops after switch to another HE-DMT		1/ Pt 2: death during time c is attributed to HE_1, because HE-DMT index treatment carried forward. 2/ Pt 3: death during time e is attributed to LEM, because LEM index treatment carried forward.		1/ Pt 2: LEM exposure is ignored and thus death occurring during time c is also ignored. 2/ Pt 3: death after HE_1 is ignored. 3/ Loss of statistical precision because deaths occurring after switch are ignored.	

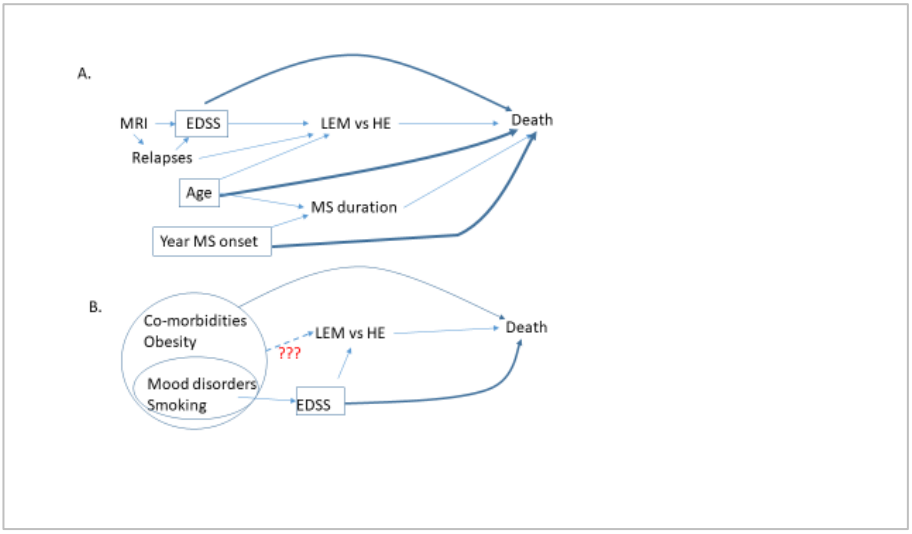
APPENDIX 3: DIRECTED ACYCLIC GRAPHS (DAG) FOR THE ASSOCIATION BETWEEN TREATMENT WITH LEMTRADA (LEM) OR ANOTHER HE-DMT (HE) AND MORTALITY

The DAGs have been designed in function of knowns and unknowns on relationships between exposure, mortality and other variables.

In DAG A, EDSS is a backdoor path and needs to be controlled for. MRI and relapses affect EDSS, and thus their influence on mortality is mediated via EDSS. The few available data in the literature do not support an association between relapses and risk of death.

In DAG A, treatment with LEMTRADA or another HE-DMT depends on MS patient age, and age at LEMTRADA treatment initiation is not similar to age at other HE-DMT treatment initiation. Age is thus a backdoor path that needs to be controlled for. MS duration is correlated with year at MS onset and patient age. Many studies have shown that recent MS onset is associated with better survival than onset many years prior. Hence, MS duration is also a mediator for year of MS onset. A priori, the logistic model for PS computations will include age at cohort entry and year of MS onset, but not MS duration. This a-priori will be verified during the descriptive analysis.

DAG B displays known risk factors for premature death. However, no literature exist informing on relationships between these variables and treatment with LEMTRADA or with another HE-DMT. The descriptive analysis will help shed light on these relationships. Of note, smoking and mood disorders exerts their influence on death through their negative influence on EDSS. But this is independent of their association with treatment.



Appendix 3 Figure: two directed acyclic graphs to depict confounding relationships between exposure drug groups and outcome mortality.

APPENDIX 4: VARIABLES THAT REQUIRE PROXY INDICATORS

Relapses

The treatment with high doses of corticosteroid (CS) over short periods (e.g., 5 days) may be used as proxy indicator for relapses. These proxy indicators are based on knowledge that MS relapses are typically treated with high doses corticosteroids (CS) administered intravenously (IV) or taken orally. Relapses may be clinical or radiological (i.e., based on MRI change). Proxy indicators specific to data sources will be formulated according to ways by which data on CS therapies and MRI imaging are collected by data sources (to be defined in Operating Protocols).

High doses of CS over a few days are often administered for acute conditions such as lumbago, lumbar hernia, sciatic, dentistry/stomatology on jaws (e.g., placement of dental implant). In these cases, however, daily CS doses rarely exceed 50 mg.

The inclusion/exclusion criteria hereafter are in the setting of MS patients treated with a DMT (hence there is no need for algorithms to find MS patients in data sources). These criteria have been derived from a paper by Quantum Black report for Sanofi-Genzyme, as well as from the literature (42, 114-116) and discussions with neurologists.

Inclusion:

1. high dose methylprednisolone during a short period, i.e., intravenous injection or oral intake of 500 mg/day or more for 3 to 5 days, or,
2. Methylprednisolone or prednisone per os 50 mg/day or more for 3 to 5 days, or,
3. Oral dexamethasone 16 mg per day for 5 consecutive days (117).

If CS are administered in 30 days following a first administration, it will be considered as the same relapse episode, and as a new relapse episode otherwise.

Exclusion:

1. CS in five days around the administration of a DMT;
2. CS around the time of IV administration of immuno-globulins;
3. CS doses less than 50 mg per day (IV or oral).

Searches in databases may be based on ATC codes or on local custom codes (e.g., CNK codes in the Belgian AIM-IMA).

ATC codes: H02AB02: Dexamethasone; H02AB04: Methylprednisolone; H02AB06: Prednisolone; H02AB07: Prednisone.

Expanded Disability Status Scale

The Expanded Disability Status Scale (EDSS) is the standard scale used by neurologists for evaluating the level of disability associated with MS disease. The scale ranges from 0 (no disability, normal neurological exam) to 9.5 (10 is equivalent to death due to MS).

Possible proxy indicators are:

- Acquisition or reimbursement of aids for disabled people (with dates), such as:
  - walking aids (cane, crutch, walker): EDSS 5 to <7
  - wheel chairs: EDSS 7 to < 9
  - medicalised beds and/or physiotherapy for bedridden patients: EDSS 9 or more.
- Information on ambulatory Status, e.g.,
  - Ambulatory without an assistive device: EDSS <5
  - Usually walks with an assistive device (cane, crutch, walker): EDSS 5 to <7
  - Usually uses wheelchair: EDSS 7 to <9
  - Usually confined to bed: EDSS 9 or more

The equivalence between proxy indicators and EDSS is based on Kurtzke (118).

EDSS is not captured in administrative data sources, such as the Belgian AIM-IMA or German BIPs data. Proxy indicators of EDSS in administrative data have been developed and we will investigate the use of these algorithms (116, 119).

In Belgian data, other proxy indicators may consist of walking and mobility aids such as wheel-chair (motorised or not), tripods, walking sticks, medicalised beds placed in homes of MS patients, and many other devices. All these aids are reimbursed for MS patients. Hence, according to dates of reimbursement of aids registered in the AIM-IMA database, one can have an indication of the disability level of a MS patient. The equivalence between the different aids against the EDSS values will be done with Belgian neurologists.

APPENDIX 5: ADDITIONAL COMPUTATIONS OF PRECISION FOR RISK ESTIMATES

Scenarios →	1	2	3	4	5	6	7	8	9	10	11	12
Mortality rate in comparison group (deaths/100 PYs)	0.24	0.24	0.24	0.24	0.36	0.36	0.36	0.36	0.48	0.48	0.48	0.48
Median follow-up (years)	6	6	6	6	6	6	6	6	6	6	6	6
RR LEM vs. Non LEM	1.5	2	1.5	2	1.5	2	1.5	2	1.5	2	1.5	2
Ratio exposed/ unexposed	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4	1/4
Number of LEM patients	1,000	1,000	1,500	1,500	1,000	1,000	1,500	1,500	1,000	1,000	1,500	1,500
Number of non-LEM patients	4,000	4,000	6,000	6,000	4,000	4,000	6,000	6,000	4,000	4,000	6,000	6,000
Risk time for LEM patients	6,000	6,000	9,000	9,000	6,000	6,000	9,000	9,000	6,000	6,000	9,000	9,000
Risk time for non-LEM patients	24,000	24,000	36,000	36,000	24,000	24,000	36,000	36,000	24,000	24,000	36,000	36,000
Number of expected deaths in LEM group	21.6	28.8	32.4	43.2	32.4	43.2	48.6	64.8	43.2	57.6	64.8	86.4

Scenarios →	1	2	3	4	5	6	7	8	9	10	11	12
Number of expected deaths in non-LEM group	57.6	57.6	86.4	86.4	86.4	86.4	129.6	129.6	115.2	115.2	172.8	172.8
Expected SE(ln(RR))	0.252	0.228	0.206	0.186	0.206	0.186	0.168	0.152	0.178	0.161	0.146	0.132
LCL of 95% CI	0.91	1.28	1.00	1.39	1.00	1.39	1.08	1.48	1.06	1.46	1.13	1.54
UCL of 95% CI	2.46	3.13	2.25	2.88	2.25	2.88	2.09	2.69	2.13	2.74	2.00	2.59
Ratio of UCL to LCL	2.69	2.45	2.24	2.08	2.24	2.08	1.93	1.82	2.01	1.88	1.77	1.68
LCL of 90% CI	0.99	1.38	1.07	1.47	1.07	1.47	1.14	1.56	1.12	1.53	1.18	1.61
UCL of 90% CI	2.27	2.91	2.10	2.71	2.10	2.71	1.98	2.57	2.01	2.61	1.90	2.48
Ratio of UCL to LCL	2.29	2.11	1.97	1.84	1.97	1.84	1.74	1.65	1.80	1.70	1.61	1.54

Details of calculation for scenario 1

In scenario 1, we assume:

- A mortality rate among non-LEMTRADA users of 0.24 per 100 person-years
- A median follow-up of six years
- A relative risk of mortality in LEMTRADA users of 1.5
- A ratio of four non- LEMTRADA users for one LEMTRADA user

With this hypothesis, if 1,000 LEMTRADA users are included in the study, then 4,000 non-LEMTRADA users will be available.
This will represent $1{,}000 \times 6 = 6{,}000$ person-years under LEMTRADA and $4{,}000 \times 6 = 24{,}000$ PY under non- LEMTRADA . By applying mortality rates to person-years at risk, we can compute expected numbers of death in each group:

$$Deaths_{NonLEM} = Rate_{NonLEM} \times PY_{NonLEM}$$

$$= {}^{0.24}/_{100} \times 24{,}000 = 57.6$$

$$Deaths_{LEM} = Rate_{NonLEM} \times RR_{LEMvsNonLEM} \times PY_{LEM}$$
$$= {}^{0.24}/_{100} \times 1.5 \times 6{,}000 = 21.6$$

The standard error of the log relative risk is computed as:

$$SE(\ln_{RR}) = \sqrt{\frac{1}{Deaths_{LEM}} + \frac{1}{Deaths_{NonLEM}}}$$
$$= \sqrt{\frac{1}{21.6} + \frac{1}{57.6}} = 0.252$$

The 95% confidence limits of the RR are then computed as:

$$95\%\ CI = \exp\left(\ln_{LEMvsNonLEM} \pm 1.96 \times SE(\ln_{RR})\right)$$
$$= \exp(\ln(1.5) \pm 1.96 \times 0.252)$$
$$= \begin{cases} 0.91\ for\ the\ lower\ limit \\ 2.46\ for\ the\ upper\ limit \end{cases}$$

The 90% confidence limits of the RR are calculated similarly:

$$95\%\ CI = \exp\left(\ln_{LEMvsNonLEM} \pm 1.64 \times SE(\ln_{RR})\right)$$
$$= \exp(\ln(1.5) \pm 1.64 \times 0.252)$$
$$= \begin{cases} 0.99\ for\ the\ lower\ limit \\ 2.27\ for\ the\ upper\ limit \end{cases}$$

APPENDIX 6: FEASIBILITY QUESTIONNAIRE

Objective of the feasibility analysis

The objective of the PAS study is to ascertain whether multiple sclerosis patients treated with LEMTRADA have a higher risk of all-cause mortality than comparable multiple sclerosis patients treated with other highly efficacious disease modifying therapies (HE-DMT) .

The objective of the feasibility analysis is to gather information from data sources for assessing whether all elements necessary for fulfilling the PAS study objective are actually or potentially available in each data source.

The feasibility analysis will collect standard information from all participants. The needed information is outlined in the remaining of this document. The information is organised by section, each section capturing information on a key component.

We highly appreciate your contribution to the feasibility analysis.

Answers should be given in the attached Xcel file and returned to philippe.autier@i-pri.org.

When we will have received your answers, we may organise a vidioconference with you in order to discuss items for which more details or precisions would be needed.

Identification	
Name of Institution or Register	
Country	
Date of Answer	
Name of persons completing the survey	

Section 1: MS patients

Lemtrada was approved for marketing by the European Medicine Agency on 12 September 2013.

Questions	Answers
In which month and year Lemtrada was reimbursed in your country? (month/year)	
In your data source, how many MS patients have been ever treated with Lemtrada? (number)	
When was this number updated for the last time? (month/year)	

Section 2: Outcome

Death from all cause is the main outcome of the study.
Death events of interest are those occurring between the cohort entry date until end of follow-up.
The cohort entry date is the date of first prescription of a HE-DMT after the date of LEMTRADA approval/reimbursement in a country (see annex for a list of DMT).

Questions	Answers
In the data source you manage, are death events,	
1/ routinely recorded in the data source you manage? (yes/no)	
2/ obtained through linkage with another data source? (yes/no)	
If yes, which data source ?	
* State owned (national) population register	
* State owned (national) patient register	
* Health insurance bodies (private or public)	
3/ obtained through contacts with municipalities where MS patients reside (yes/no)	
4/ obtained from MS patient's relatives or GPs (yes/no)	
5/ Other, please explain:	
What is the usual time lag for obtaining updates on death events? (months)	
In the last 5 years, has there been an evaluation of the completeness of mortality statistics of your data source? (yes/no)	
If yes, in what year ?	
If yes, what was the result of the evaluation ?	
How complete is the recording of death events? (100% O ; 90 to 99% O; Less than 90% O)	

Section 3: Follow-up

Follow-up begins at cohort entry date and continues until the earliest of: death; emigration; end of study period whichever occurs first.
For each MS patient, follow-up time will be calculated from the cohort entry date until last update of vital or emigration status of all MS patients registered in each data source.
Achievement of complete follow-up of MS patients included in the study cohort is a crucial aspect of the study.
Incomplete follow-up may introduce bias on vital status [1], mainly if follow-up would differ between MS patients treated with LEMTRADA-treated and MS patients treated with other HE-DMT [2].

Questions	Answers
In the data source you manage, how follow-up of MS patients until study end will be done?	
1/ through linkage with another data source? (yes/no)	
If yes, which data source?	
* State owned population register	
* State owned patient register	
* Health insurance bodies (private or public)	
* Other: explain	
2/ obtained via active contact tracing via regular contacts with patients themselves, their relatives, their GPs, or the municipality of residence, using mail and/or phone calls?	
Please explain:	
In which year active tracing was established for the first time?	
For which other study(ies) did you perform active tracing?[2]	
3/ obtained only via contacts with patients (eg, medical visits)? (yes/no)	

[2] **Please provide literature citation of studies you were involved in that were based on active tracing.**

Section 4: Treatment variables

Measurement of exposure to HE-DMT will occur from cohort entry to end of follow-up.
The cohort entry date will be defined as the date of first prescription of a HE-DMT after the date of LEMTRADA approval/reimbursement in a country.

Questions	Answers
In the data source you manage, the dates associated with HE-DMT relate to:	
Prescription (yes)/no)	
or Dispensing (yes)/no)	
First and last prescription/dispensing of a specific HE-DMT? (yes)/no)	
Dates of every prescription/dispensing are recorded? (yes)/no)	
Do you have dates of each Lemtrada infusion? (yes)/no)	
If no, how Lemtrada treatment courses are recorded?	

Section 5: Patient characteristics and cofunders

Measurement of patient characteristics and confounder variables will occur at cohort entry date.
In addition, some confounding variables will be time-updated when a switch between HE-DMTs occurs.
The cohort entry date will be defined as the date of first prescription of a HE-DMT after the date of LEMTRADA approval/reimbursement in a country.
Core variables for the study are indicated by an asterisk (*).
These variables are those known to be associated with mortality among MS patients.
Where multiple recordings of variables exist for each patient eg EDSS or BMI or smoking status, the value closest to the cohort entry date/switch date will be chosen.
Could you report in the Xcel form how there variables are recorded and in which format. An estimation of missing data for core variables is also requested.

Questions	Recorded in database Y/N	Approximate % of missing data	Comments
Baseline variables, assessed at cohort entry:			
• **Date at cohort entry***			
• **Sex***			
• **Age at cohort entry***: this variable will be derived from year of birthdate and data at cohort entry. When age at cohort entry will be computed, birthdate will be removed from the database.			
• **Treatment history before cohort entry***: number and type of platform (P) or high-efficacious (HE) DMT received before cohort entry (see annex for a list of DMT);			
• **Year of MS diagnosis*** (year of first P- or HE-DMT prescription may be used as a proxy)			
• Number of relapses in preceding year (see annex for proxy measures of relapses).			
• Type of MS*: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), unknown; [3-6].			
• **Expanded Disability Status Scale (EDSS)*** [5] or suitable proxy indicator*. Possible proxy indicators are:			
▪ acquisition or reimbursement of aids for disabled people (with dates), such as walking aids (cane, crutch, walker), wheel chairs, medicalised beds.			
▪ Information on ambulatory Status, e.g.,			
- Ambulatory without an assistive device			
- Usually walks with an assistive device (cane, crutch, walker)			
- Usually uses wheelchair			
- Usually confined to bed.			
• **Co-morbidities***:			
o cardiovascular disease			
o cancer			
o respiratory disease			
o urinary infection (except cystitis)			
o major auto-immune disease: such as sclerodermy, SLE auto-immune, glomerulonephritis, rheumatoid arthritis			
o Thyroid disorder			
o Pneumomia			
o Sepsis			
o Renal failure			
• **Neuropsychological disorders:**			
o Mood disorders			
o Epilepsy (seizure episodes)			
Note: these disorders may be captured via knowledge of psycho-tropic and anti-epileptic drugs received by MS patients (see prescribed medications below).			
• Hospital stays with number of stays and duration*;			
• **Prescribed medications other than DMT**			
o Statins,			
o Anti-hypertensives,*			
o Anti-platelets*,			
o Proton pump inhibitors,			
o Immunosuppressants*,			
o Cortico-steroids,*			
o Anti-depressors,*			
o Benzodiazepins,*			
o Anti-epileptic,*			
o Anti-diabetic,*			
o Prescribed nutritional supplements and vitamins.			
• Indicator of socio-economic status (eg, education level, deprivation index, area of residence);			
• Smoking status (e.g., current smoker, past smoker, never smoker, unknown smoking status);			
• Adiposity (e.g., body mass index).			
• Pregnancy:			
o Pregnancy statuts with dates			
o Pregancy plans			
• MRI:			
o MRI done before Lemtrada or HE-DMT treatment			
o Result of MRI exam			
• JVC status:			
Variables to be assessed at each switch from one HE-DMT to another HE-DMT after the cohort entry date:			
• **Date of switch to another HE-DMT***;			
• Number of relapses in preceding year ;			
• **Type of MS if change in MS type around the time of HE-DMT switch***: relapsing remitting (RRMS), secondary progressive (SPMS), primary progressive (PPMS), unknown; [3-6].			
• **Expanded Disability Status Scale (EDSS)*** [5] or suitable proxy indicator* (see annex Proxy measures of relapses);			

Section 6: Administrative procedures

Contracting procedures data sources are expected to star in January 2021. The following questions are about the types and duration of procedures necessary to accomplish and their approximate duration before being able to assemble the full data set in the local IT system in order to perform statistical analyses.

Questions	Answers
Contractual processes between the data source and the [redacted] (thick box)	
The [redacted] will propose and agreement and have it concluded with the data source O	
The [redacted] will propose and agreement and have it concluded with the institution supervising the data source O	
The data source will issue its own agreement that will be concluded with the [redacted] O	
How long would it take for having contracts agreed and signed by the data source? (months)	
Authorisations and clearances	
1. Governing instance of the data source,[3] (yes/no)	
if yes, how long (months)	
2. Governing instance of other data source(s)[3] (yes/no)	
(eg, for linkage with vital status registry)	
if yes, how long (months)	
3. Social security institution owning the data (yes/no)	
if yes, how long (months)	
4. Private health insurance owning the data (yes/no)	
if yes, how long (months)	
5. Governmental body supervising the data source (yes/no)	
if yes, how long (months)	
6. Ethics committee (yes/no)	
if yes, how long (months)	
7. Institutional Review Board (yes/no)	
if yes, how long (months)	
8. Personal data protection committee (yes/no)	
if yes, how long (months)	
9. Small cell analysis expertise (yes/no)	
if yes, how long (months)	
10. Other: (yes/no)	
if yes, how long (months)	
How long would it take for having the entire procedure completed? (months)	
Which step(s) could significantly delay the effective study start? Explain:	
When statistical analyses will be done, is there a need for an authorisation prior to sending aggregated data and results to the study coordination ([redacted])? (yes/no)	
if yes, how long (months)	

[3] **Head(s) of the institution owning a data source.**

APPENDIX 7: ENCEPP CHECKLIST

ENCePP Checklist for Study Protocols (Revision 4)

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

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

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

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

Study title:
A NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY TO INVESTIGATE THE RISK OF MORTALITY IN PATIENTS TREATED WITH ALEMTUZUMAB (LEMTRADA®) RELATIVE TO COMPARABLE PATIENTS USING OTHER DISEASE MODIFYING THERAPIES: A COHORT STUDY

EU PAS Register® number:
Not yet registered – will register once PRAC approval is obtained

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				4 & 6 & 12
1.1.1 Start of data collection[21]	☒	☐	☐	
1.1.2 End of data collection[22]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	
1.1.5 Registration in the EU PAS Register®	☒	☐	☐	
1.1.6 Final report of study results.	☒	☐	☐	

Comments:

All listed items in Abstract (section 4) and Section 6, except 1.1.5
1.1.5 (registration in EU PAS register only) in Section 12

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	7 & 8 & 9
2.1.2 The objective(s) of the study?	☒	☐	☐	
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

2.1.1 in Section 7
2.1.2 in Section 8.2 & 8.3
2.1.3 in Sections 9.2, 9.2.4 and 9.7.4

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	9.1.1

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

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1.1
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.6.1
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	9.7.6.3
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	11

Comments:

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

Comments:

4.2.1 in Section 9.2.1
4.2.3 in Section 9.4
4.2.4 in Section 9.2.4
4.2.5 in Section 9.3.4

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorising exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	9.3.3
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☐	☒	☐	
5.3 Is exposure categorised according to time windows?	☒	☐	☐	Figure 1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☐	☒	☐	9.3.3
5.5 Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	9.7.7.2 & Figure 3
5.6 Is (are) (an) appropriate comparator(s) identified?	☒	☐	☐	9.1.2

Comments:

5.5 addressed in Section 9.3.3 which describes exposure definition and also in Section 9.5.8.2 which describes sensitivity analyses around exposure definition.

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

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	9.1.2 9.3.5, 9.7.4, 9.10.5
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	9.10.5.1
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10.5.2, 9.10.5.3

Comments:

Confounding is addressed in several sections: 9.1.2 (Comparable MS patients), 9.3.5 (Variables for the study), 9.7.4 (Propensity Score Model), 9.10.5 (unmeasured confounding)

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.9

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3.3 & 9.4
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	9.3.2
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3.5
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	9.3.3
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.3.2
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.3.5

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	9.3.3
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☐	☒	☐	Date of death
9.3.3 Covariates and other characteristics?	☐	☒	☐	9.3.5 Additional lists of codes to be developed for SAP
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☒	☐	☐	9.4

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7.3
10.4 Are stratified analyses included?	☒	☐	☐	9.7.9
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.9.3
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.7.2

Comments:

Sections 9.7.2 outlines the various stages in the statistical analyses plan from descriptive analyses to inform propensity score development to the final outcome model.

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3.4 & 12

Comments:

The role of the Scientific Committee is outlined in Section 3.4 and Section 12

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.10.5.1
12.1.2 Information bias?	☒	☐	☐	9.10.5.2-9.10.5.3
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	9.10.5.4
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.8

Comments:

Misclassification of exposure and confounders in Section 9.8.2 Misclassification of outcome in Section 9.8.3

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10.1
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

APPENDIX 8: LIST OF STAND-ALONE DOCUMENTS

n/a