NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY (PASS) PROTOCOL

A NON-INTERVENTIONAL POST-AUTHORISATION SAFETY STUDY TO INVESTIGATE DRUG UTILISATION AND SAFETY MONITORING PATTERNS FOR LEMTRADA (ALEMTUZUMAB)

COMPOUND: Alemtuzumab

PRIME STUDY NUMBER: DUT0008

PROTOCOL VERSION 3.1: December 2023

The Study will be conducted by Parexel International hereinafter referred also as the "Study Management".

NAMES AND ADDRESSES OF

STUDY MANAGEMENT	Name: Address: Tel: E-mail:	Katja M Hakkarainen, PhD Parexel International, Gothenburg, Sweden REDACTED REDACTED
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PASS Information

Title	A non-interventional post-authorisation safety study to investigate drug utilisation and safety monitoring patterns for LEMTRADA (alemtuzumab)
Protocol version identifier	Version 3.1
Date of last version of protocol	December 2023
EU PAS register number	EUPAS42540
Active substance	Alemtuzumab (GZ402673): ATC L04AA34
Medicinal product	Lemtrada
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003718
Marketing authorisation holder(s)	Sanofi Belgium
Joint PASS	NO

Research question and Objectives	The overall goal of this study is to assess compliance with risk minimisation measures implemented after the Article 20 procedure for LEMTRADA (procedure number: EMEA/H/A-31/1483/C/3718/0028) e.g., newly revised indication, newly added contraindications and newly added safety monitoring recommendations for LEMTRADA The objectives are as follows: **1a)** to measure the proportion of patients who meet the newly restricted indication on initiating their first course of LEMTRADA after implementation of the revised European Union Summary of Product Characteristics (EU SmPC) January 2020. **1b)** to measure the proportion of LEMTRADA courses, first or continuing, that are not contraindicated after implementation of the revised EU SmPC January 2020. **2a)** to measure the proportion of LEMTRADA courses that receive cardiac monitoring and blood testing prior to infusion, cardiac monitoring during course, and platelet testing during course as specified in the newly revised EU SmPC. **2b)** to measure percentage adherence, at the patient level, to long-term monitoring for full blood counts (FBC), serum creatinine, serum transaminases, urinalysis with microscopy (all monthly) and thyroid function (every three months) as specified in the newly revised EU SmPC.
Country(-ies) of study	Czech Republic, UK, Germany, Belgium
Authors	REDACTED Director Pharmacoepidemiology, Sanofi, REDACTED REDACTED REDACTED

Marketing authorisation holder(s)

Marketing authorization holder(s)	Sanofi Belgium Leonardo Da Vincilaan 19 B-1831 Diegem Belgium
MAH/MAH REPRESENTATIVE contact person (Qualified Person Pharmacovigilance, QPPV)	REDACTED Senior Medical Advisor -- QPPV deputy for Specialty care Business Unit QPPV office -- Sanofi R&D- Global Pharmacovigilance REDACTED REDACTED REDACTED

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2. LIST OF ABBREVIATIONS

AE	Adverse Events
AI	Autoimmune
AIM-IMA	L'Agence Intermutualiste - Het InterMutualistisch Agentschap (Belgian Social Security database)
ATC	Anatomical Therapeutic Chemical
BMSD network	Big MS Data Network
BP	Blood Pressure
CI	Confidence Intervals
CED	Cohort Entry Date
CNK	National Code Number
Covid-19	Coronavirus disease 2019
CRF	Case Report Form
DUS	Drug Utilisation Study
DMT	Disease modifying therapy
ECG	Electrocardiogram
EC	European Commission
eCRF	Electronic Case Report Form
EPR	Electronic Patient Record
EUReMS	European Register for Multiple Sclerosis
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EU SmPC	European Union Summary of Product Characteristics
FBC	Full Blood Count
GDPR	General Data Protection Regulation
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HE-DMT	Highly Efficacious DMT

HIV	Human Immunodeficiency Virus
HR	Heart rate
ICD	International Classification of Diseases
MAH	Marketing Authorisation Holder
MD	Medical Doctor
MRI	Magnetic Resonance Imaging
MS	Multiple Sclerosis
MSDS-3D	Multiple Sclerosis Documentation System-3D
OP	Operating Protocol
PASS	Post-authorisation safety study
PRAC	Pharmacovigilance Risk Assessment Committee
SWiM	Synthesis without meta-analysis
ReMuS	Czech Multiple Sclerosis Registry
RMP	Risk Management Plan
RRMS	Relapsing-Remitting Multiple Sclerosis
SmPC	Summary of Product Characteristics
SAP	Statistical Analysis Plan
TREAT-MS	Long-Term study foR obsErvAtion of Treatment with alemtuzumab in active relapsing-remitting MS
UK	United Kingdom
WCP	Welsh Clinical Portal

3. RESPONSIBLE PARTIES

3.1 RESPONSIBILITIES OF THE DATABASE COLLABORATOR:

1 To contribute 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 (OP) 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 the OPs.

7 To participate in the meetings and other activities necessary for the good conduct of the study.

8 To participate in the feasibility analysis and review of final study reports.

List of database collaborators at protocol stage:

Belgium*	AIM-IMA (L'Agence Intermutualiste – Het InterMutualistisch Agentschap) Av. De Tervueren, 188/A, B-1150 Brussels, www.aim-ima.be Contact: Birgiet Gielen
United Kingdom	University Hospital of Wales, 4th Floor, B-C Link Corridor, Main Hospital Building, Heath Park, Cardiff, CF14 4XN Principal Investigator: Prof Neil Robertson Cambridge University Hospitals, Department of Clinical Neurosciences, University of Cambridge, England Principal Investigator: Dr. William Brown Derriford Hospital/ Plymouth University, Room N13, ITTC Building, Plymouth Science Park, Davy Road, PL68BX Principal Investigator: Prof Jeremy Hobart
Germany	Non-interventional long-Term study foR obsErvAtion of Treatment with alemtuzumab in active relapsing-remitting MS (TREAT-MS) (1)

Czech Republic	The Czech Multiple Sclerosis Registry (ReMuS) IMPULS Endowment Fund, Katerinska 30, 120 00 Prague 2, Czechia Principal Investigator: Dana Horakova Department of Neurology and Center of Clinical Neuroscience, First Faculty of Medicine, Charles University in Prague and General University Hospital, Prague, Czechia

* Involvement of the data source in Belgium stopped in January 2023. Further information provided in section 9.5.2.

3.2 RESPONSIBLITIES OF THE STUDY MANAGEMENT

1. To write the OPs specific to each database.
2. To coordinate the implementation of the study in the various databases, with consideration to local administrative, legal and technical environment.
3. To plan and run feasibility analysis.
4. To define with database providers the practical modalities of participation to 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 prepare statistical methods and computer software needed for data analysis.
7. To train database scientists on tasks related to data handling, cleaning and analyses.
8. To organise meetings between the database providers, the Marketing Authorisation Holder (MAH) and the Study Management for discussing study progress and results.
9. To prepare study reports intended for submission to the Regulator.
10. To regularly inform the MAH on study advancement and issues to be addressed.
11. To organise meetings between the database providers, the MAH and the Study Management for discussing study progress and results.

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 GROUP

An external scientific study committee is not set up for this study. Instead, a study group, comprised of Study Management, MAH representation and the principal investigators of each data source will be established. The remit of the Study Group will be to discuss the results of the feasibility analysis and whether study progression would be prudent. In the case of study progress, the study group will discuss annual accrual, final analyses, final report and publishing.

4 ABSTRACT

Version and date: Version 3.1, December 2023

Author: Sanofi, 450 Water St, Cambridge, MA 02141, USA

Title: A non-interventional post-authorisation safety study to investigate drug utilisation and safety monitoring patterns for LEMTRADA (alemtuzumab)

Rationale and background:

LEMTRADA was subject to a European Medicines Agency Article 20 procedure (EMEA/H/A-31/1483/C/3718/0028) initiated in 2019, following findings of serious safety concerns from post -marketing data. During the procedure, new and cumulative safety data were assessed. Subsequently, changes to the European Union (EU) summary of product characteristics (SmPC) label were implemented. The indication has been revised and additional safety information has been included under "Contraindications" and "Special warnings and precautions for use" sections of the EU SmPC.

Research question and objectives:

This non-interventional drug utilisation study will assess compliance with the therapeutic indication, contraindications, and implementation of measures to minimise the risk of cardiovascular and cerebrovascular adverse events and immune-mediated adverse reactions that have been incorporated into the newly revised EU SmPC (January 2020).

The objectives are as follows:

1a) To measure the proportion of patients who meet the newly restricted indication on initiating their first course of LEMTRADA after implementation of the revised EU SmPC January 2020.

1b) To measure the proportion of LEMTRADA courses, first or continuing, that are not contraindicated after implementation of the revised EU SmPC January 2020.

2a) To measure the proportion of LEMTRADA courses that receive cardiac monitoring and blood testing prior to infusion, cardiac monitoring during course, and platelet testing during course as specified in the newly revised EU SmPC.

2b) To measure adherence, at the patient level, to long-term monitoring of full blood counts (FBC), urinalysis with microscopy, serum creatinine, serum transaminases (all monthly), and thyroid function (every three months) as specified in the newly revised EU SmPC.

Study design:

Cohort design based on use of secondary data.

Population:

Patients treated with LEMTRADA, or monitored, under the revised EU SmPC (January 2020 and subsequent versions).

Variables:

If sample sizes permit, utilisation and monitoring patterns by main strata will be examined: age, gender and calendar year of cohort entry, within each country.

Data Sources:

Multiple sclerosis (MS) registry data from Czech Republic, administrative data from Belgium, hospital chart data from the UK, and secondary data use from a cohort study in Germany. The Belgian data source contributed data for analyses up to the interim report of 2022. Results of these analyses will be included in the interim report of 2023 and the final report of 2024, but no new analysis will be carried out.

Study size:

This is a descriptive study. There are no formal hypothesis tests and thus traditional sample size calculations to estimate power are not appropriate. Instead, the focus is on obtaining a sample that is representative of the main usage countries, to achieve geographical diversity where practicable and to allow some precision in calculation of descriptive proportions. A feasibility analysis was carried out in 2022 to investigate numbers of eligible patients and ability to measure variables as required for the successful conduct of the study across all data sources.

Data analysis:

In each individual data source, descriptive proportions will be calculated as follows:

- Prescribed in accordance with the newly revised indication (objective 1a): numerator = number of patients with revised indication, denominator=all patients initiating their first course of LEMTRADA after implementation of the revised EU SmPC January 2020.
- New or continuing user with no contraindications at time of course initiation post EU SmPC change (objective 1b): numerator=number of courses without contraindications, denominator=all LEMTRADA courses post EU SmPC change.
- Receive advised cardiac monitoring (electrocardiogram (ECG), heart rate (HR), blood pressure (BP)) and blood testing prior to, along with HR/BP and platelet testing during LEMTRADA course (objective 2a): numerator=number of courses with each unique test prior to and during infusion, denominator=all LEMTRADA courses post EU SmPC change.
- Percentage adherence to each test will be calculated, at the patient level, to monthly monitoring for up to 48 months since last infusion for FBCs, serum creatinine, serum transaminases and urinalysis with microscopy, and monitoring every three months for

thyroid function (objective 2b): numerator=number of specific tests received, denominator=number of testing periods required.

Milestones

- Report on feasibility analysis **Q3 2021**
- Annual interim progress report **Q4 2021**
- Full feasibility report **Q2 2022**
- Annual interim progress report **Q4 2022**
- Annual interim progress report **Q4 2023**
- Final report of study results **Q3 2024**

5 AMENDMENTS AND UPDATES

Protocol history: The first version of the protocol that was approved by the PRAC was V1.4 (May 2021). A first protocol amendment occurred in 2022 and resulted in the second approved protocol, which was numbered V1.6 (June 2022). The second protocol amendment occurred in 2023 and resulted in protocol V3.0 (July 2023). Minor edits to V3.0 were added on foot of PRAC request and the latest version is labelled as V3.1 (December 2023)[1].

Protocol Amendments Summary of Changes Table

Item	Description	Reason for amendment	Sections	Date
1	Addition of EUPAS Register number.	Update of information.	PASS information	June 2022
2	Removal of the Danish Multiple sclerosis Registry.	No patient treated with LEMTRADA since January 2020.	3.1; 4; 9.2; 9.2.2; 9.3; 9.4; 9.4.1; 9.7.2; 9.9; 9.10; 10.1; 17	June 2022
3	Addition of the Czech Multiple Sclerosis Registry.	Replacement of the Danish Multiple Sclerosis Registry.	3.1; 4; 9.2; 9.2.2; 9.3; 9.4; 9.4.1; 9.7.2, 9.9; 9.10; 10.1; 17	June 2022
4	Change of milestones dates.	Revision of timelines following unforeseen delays in 2021: and the addition of a full feasibility report in Q2 2022.	4; 6; 9.8; 9.10; 12.1	

[1] Note that there is no protocol V2.0.

Item	Description	Reason for amendment	Sections	Date
		Removal of operational steps in the milestones section of the protocol e.g., construction of databases. Achieving working database structure is not a direct regulatory commitment, rather it is a marker of internal progress towards formal regulatory commitments. The MAH removed working database milestones from Sections 4 and 6 in order to list only milestones of regulatory importance.		June 2022
5	Removed Gantt Chart.	The Gantt 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.	Appendix 3	June 2022
6	Study Management was revised to Parexel throughout the document and document ownership assigned to Sanofi only.	Due to a change of CRO.	Title page; 3; 4; 9.7; 12.1	July 2023 Version 3.0
7	Updated details for the German data source with details on TREAT-MS.	To provide updated information.	3.1; 9.5.3	July 2023 Version 3.0
8	Explanation throughout the document to describe the	The Belgian data source opted to no longer participate in the study	3.1; 4; 9.2; 9.5.2	July 2023 Version 3.0

Item	Description	Reason for amendment	Sections	Date
	withdrawal of the data source from Belgium.	after the 2022 annual interim report. Explanation has been added to the protocol that no new analyses will be carried out on the Belgian data, but the 2022 annual interim analysis will be included in the 2023 annual report and the final report in 2024.		
9	Updated operational definitions for the proxy for history of stroke in Belgium.	Appendix 1 has been revised to provide up-to-date proxy for history of stroke used in Belgium.	Appendix 1	July 2023 Version 3.0
10	Cohort 2a: Updated monitoring period for prior and during the treatment course.	As on the first day of the course (i.e. index date), there may be both tests prior and during first infusion (e.g., in case of BP and HR monitoring), the index date will contribute to both the monitoring period prior and during the LEMTRADA course.	9.1; 9.3; 9.8.2	July 2023 Version 3.0
11	Cohort 2b: Addition of new sensitivity analysis based on anchoring on the last test date.	Minor changes to analysis plan.	9.8.2 and 9.8.4	July 2023 Version 3.0
12	Removed sensitivity analyses for 7-day window on monthly testing and 15-day window for testing every three months.	Minor changes to analysis plan.	9.8.2	July 2023 Version 3.0

Item	Description	Reason for amendment	Sections	Date
		This was tested in the feasibility analysis and found not to be appropriate.		
13	Information on the LEMTRADA treatment plan was added to the background.	For clarification.	Section 7.1	July 2023 Version 3.0
14	The definition of cohort entry date (CED) was added and the definition of index date was harmonised throughout the protocol.	For clarification.	Section 9.1; 9.8.2	July 2023 Version 3.0
15	Permanent cardiac monitoring added as proxy variable for ECG data for ReMuS.	In the ReMus database, use of intensive care monitors will be used as proxy for ECG monitoring when no ECG monitoring test is identified prior to the course.	Section 9.3 Table 4	July 2023 Version 3.0
16	Note added that HR and BP data are reported together as vital signs in the German data source.	Clarification.	Table 4	July 2023 Version 3.0
17	Addition of sensitivity analysis for objective 2b.	The sensitivity analysis will use monitoring windows counting from the last available testing date to consider real-world situations.	Section 9.8.4	July 2023 Version 3.0

Item	Description	Reason for amendment	Sections	Date
18	Revised text on the feasibility analysis to reflect that the feasibility activities have been completed.	To clarify that the MAH has submitted the results of a feasibility analysis in Q3 2021 and in Q2 2022 (i.e. a completed activity).	Section 9.8.2; 9.9, 9.10	July 2023 Version 3.0
19	Addition of sensitivity analysis for objective 2a.	To provide the proportion of courses with a monitoring test prior to index date, excluding the index date, for the tests that contribute to both the prior period and to the during infusion period (in case of BP and HR monitoring).	Section 9.1; 9.8.4	December 2023 Version 3.1
20	Updated exclusion criteria.	As no consent is required in the UK or any of the other data sources, updated exclusion criteria as "None".	Section 9.2.3	December 2023 Version 3.1
21	Added additional information on TREAT-MS.	For clarification.	Section 9.3	December 2023 Version 3.1
22	Table 3 and as Table 4 updated for Germany TREAT-MS. Table 4 updated for Czech Republic.	Clarify the details collected by CRF in TREAT-MS study. To clarify that monitoring data in primary care are not systematically collected in ReMuS.	Section 9.3	December 2023 Version 3.1

Item	Description	Reason for amendment	Sections	Date
23	Patient consent details for UK updated as no consent is required in UK.	Patient consent details for UK updated as per the current process in UK.	Section 9.4	December 2023 Version 3.1
24	For ReMuS, further information on monitoring in primary care was added.	For clarification.	Section 9.5.1 and 9.11	December 2023 Version 3.1
25	Updated to provide clarification around enrolment in TREAT-MS study. Additionally, cross reference made to newly added Appendix 4 which provides a list of TREAT-MS variables.	For clarification.	Section 9.5.3	December 2023 Version 3.1
26	For the UK data source, added information on common data collection tool and updated information on hard copy notes and quality assessment.	For clarification.	Section 9.5.4	December 2023 Version 3.1
27	Added Table 5 “Sample size per data source for interim analysis 2023”.	To provide updated information based on the most recent interim analysis.	Section 9.6	December 2023 Version 3.1
28	Footnote 3 added for monitoring of BP and HR and footnote 4 added for blood and urinalysis monitoring in TREAT-MS.	To provide clarification on the data available for assessment of adherence to BP, HR, blood and urinalysis monitoring prior to the course in TREAT-MS.	Section 9.8.2	December 2023 Version 3.1

Item	Description	Reason for amendment	Sections	Date
29	Updated text on heterogeneity assessment for appropriateness of meta-analysis.	For clarification.	Section 9.8.3	December 2023 Version 3.1
30	Updated details on selection bias and generalizability	For selection bias, to clarify that no distortion in an association between an exposure and an outcome can occur due to differential selection of patients, since this is a not a comparative study. For generalizability, to clarify that the results are generalizable to the included sites.	Section 9.11	December 2023 Version 3.1
31	List of relevant variables in TREAT-MS was added as Appendix 4.	To provide an overview of variables available in the TREAT-MS study that can be used for the current study.	Section 16	December 2023 Version 3.1
32	Minor editorial and formatting changes were made. Consistency errors detected were corrected and references and abbreviations were updated. Numbering of few sections, tables and appendices were updated.	To enhance clarity.	Throughout the document	December 2023 Version 3.1

6 MILESTONES

Milestone	Planned date
Report on feasibility analysis	Q3 2021
Annual interim progress report 2021	Q4 2021
Full feasibility report	Q2 2022
Annual interim progress report 2022	Q4 2022
Annual interim progress report 2023	Q4 2023
Final report of study results	Q3 2024

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

LEMTRADA (alemtuzumab) is a recombinant humanised monoclonal antibody for the treatment of patients with relapsing-remitting multiple sclerosis (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. The LEMTRADA treatment plan consists of two LEMTRADA treatment courses administered one year apart, with up to two additional treatment courses if needed, administered at least 12 months after the prior treatment course. The first LEMTRADA treatment course consists of five LEMTRADA infusions delivered daily over five days. The following treatment courses consist of three LEMTRADA infusions delivered daily over three days. 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 Expanded Disability Status Scale (EDSS) scores.(2-4) However, LEMTRADA is associated with serious risks, including risk of cardiovascular events (temporally related to infusion), serious infections, and autoimmune-mediated conditions.

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 European Medicines Agency (EMA) Pharmacovigilance Risk Assessment Committee (PRAC). The procedure concluded that LEMTRADA is associated with new and emerging safety events including both cardiovascular and additional autoimmune (AI) events. PRAC advised changes to the European Union (EU) summary of product characteristics (SmPC) indication, the list of contraindications and safety monitoring recommendations, to best ensure patient safety.

The newly restricted indication is as follows:

- Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or
- Patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year, and with one or more Gadolinium enhancing lesions on brain magnetic resonance imaging (MRI) or a significant increase in T2 lesion load as compared to a previous recent MRI.

The newly revised list of contraindications is as follows:

- Hypersensitivity to alemtuzumab or any of the excipients;
- Human Immunodeficiency Virus (HIV);
- Severe active infection until complete resolution;
- Uncontrolled hypertension;
- History of arterial dissection of the cervicocephalic arteries;
- History of stroke;
- History of angina pectoris or myocardial infarction;

- Known coagulopathy, on anti-platelet or anti-coagulant therapy;
- Other concomitant AI diseases (apart from MS).

The newly advised monitoring recommendations are as follows:

- Monitoring of cardiovascular function (electrocardiogram (ECG), heart rate (HR), blood pressure (BP)) before infusion and during (HR/BP) LEMTRADA infusion. This recommendation also includes platelet count measurement prior to infusion and during the infusion, on days three and five for the first course and on day three of any subsequent course.
- Thyroid function tests continue to be recommended every three months post-infusion, while serum transaminases have been added to full blood counts (FBC), serum creatinine, and urinalysis with microscopy are all advised for monthly monitoring for 48 months post last infusion.

7.2 RATIONALE

Given the serious and unpredictable nature of both previously and newly identified adverse events associated with LEMTRADA, and that effective risk minimisation is key to support a positive benefit-risk balance, a drug utilisation study will be conducted to assess the implementation of risk minimisation measures in routine clinical practice.

8 RESEARCH QUESTION AND OBJECTIVES

The overall goal of this drug utilisation study is to describe how LEMTRADA is prescribed and how safety monitoring is implemented in routine clinical care. The EU SmPC contains a newly restricted indication, additional contraindications and additional monitoring requirements all intended to minimise the risk of cardiovascular and cerebrovascular adverse events (temporally related to infusions) and immune-mediated adverse reactions associated with exposure to LEMTRADA. This is a descriptive study, there is no *a priori* hypothesis to be tested.

8.1 PRIMARY OBJECTIVES

The primary objectives are as follows:

1a) To measure the proportion of patients who meet the newly restricted indication on initiating their first course of LEMTRADA after implementation of the revised EU SmPC in January 2020.

1b) To measure the proportion of LEMTRADA courses, first or continuing, that are not contraindicated after implementation of revised EU SmPC in January 2020.

8.2 SECONDARY OBJECTIVES

The secondary objectives are as follows:

2a) To measure the proportion of LEMTRADA courses that receive cardiac monitoring and blood testing prior to infusion, cardiac monitoring during the course, and platelet testing during the course as specified in the newly revised EU SmPC.

2b) To measure adherence, at the patient level, to long-term monitoring of FBCs, urinalysis with microscopy, serum creatinine, serum transaminases (all monthly) and thyroid function (every three months) as specified in the newly revised EU SmPC.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This post-authorisation safety study (PASS) is a non-interventional, non-comparative study that uses a cohort study design, based on use of routine health care data.

We will use data from four separate data sources. A local operating protocol (OP), derived from this master protocol for the entire study, will be applied to each data source individually. Then, aggregate results from each data source for the primary and secondary Objectives will be summarised using tables and figures.(5) Quantitative combination will be carried out through meta-analysis if levels of heterogeneity allow.

This multi-database approach is now well established in the area of drug safety research.(6-8) The approach is advantageous for three reasons. First, LEMTRADA utilisation is expected to be low (see Section 9.11), and so the approach is beneficial in that it facilitates examination of more data than are available in one single data source. Second, it may be inappropriate to pool individual patient data from various countries given heterogeneity arising from organisation of health systems, national prescribing guidelines, and differences in the delivery of care.(9) Third, the approach circumvents concerns about combining individual patient data from differing jurisdictions, which may breach data privacy laws.(10)

The cohort entry date (CED) is the date a patient is included in one of the study cohorts (please note there are different cohorts for different objectives, as described in Table 1) and is defined at the patient level. Each cohort will have different definitions of CED (described below and in Table 1). The index date is the date of LEMTRADA course initiation. A patient may have several index dates during the study if they have more than one treatment course. A treatment course is considered a new use course if it is the first ever use of LEMTRADA for a patient post SmPC change (2020) and a treatment course is considered a continuing use course if the patient has had at least one prior LEMTRADA course or infusion.

The primary objective 1a will assess patients' indications using all available baseline data on the CED, which is defined as the date of the first LEMTRADA treatment course after implementation of the revised EU SmPC January 2020. For cohort 1a, patients are required to be new users (first ever use after implementation of the revised EU SmPC January 2020). The index date for new users will correspond to the date of first (new) course LEMTRADA initiation post implementation of the newly revised SmPC (i.e. CED).

The primary objective 1b will assess patients' contraindications using all available data on the index date. Patients enter the cohort (CED) on the date of the first LEMTRADA treatment course initiation after implementation of the revised EU SmPC (January 2020). The course may be new or continuing. Contraindications will be assessed for each treatment course at each index date.

The rationale for including first ever users to address adherence to the indication (objective 1a) is that patients who met the indication prior to EU SmPC change in 2020 were indicated for full LEMTRADA treatment which is two courses. Thus, even if the second course was to occur post SmPC change, the patient would be receiving treatment based on the original indication. Given

that LEMTRADA is a highly effective disease modifying therapy, the patients who had highly active disease at the first infusion may not have highly active disease at the point of second infusion 12 months later. The new-user design avoids this issue by enrolling only patients required to meet the new indication.

The rationale for including both new and continuing users in addressing adherence to contraindications (objective 1b) is that all patients, regardless of new or continuing use, should not have any contradictions to treatment. This approach is conservative as some clinicians may opt to continue treating a continuing patient who had a comorbidity at the first infusion if they and the patient believe the benefit of treatment outweighs this newly specified contraindication.

For objective 1a, the indication will be measured at one point in time for each patient on the CED. For objective 1b, the presence of contraindications will be measured at each index date. As mentioned above, a patient may have more than one index date requiring a repeated measurement of contraindications at the start of each course that is administered after the SmPC change in 2020.

Objective 2a will assess implementation of infusion-related monitoring prior and during LEMTRADA courses (new or continuing). Same as for objective 1b, patients enter the cohort (CED) on the date of the first LEMTRADA treatment course initiation, either new or continuing, post the newly revised EU SmPC. For each treatment course, patient data will be assessed for monitoring prior to index date and patients will be followed from the index date onwards to assess whether recommended monitoring occurred during the course. On the first day of the course (i.e. index date) there may be tests that contribute to both the prior period and to the during infusion period (in case of BP and HR monitoring). This is because data on the time of the test and/or infusion are not available and therefore, for tests with the same date as index date, it is unknown if the test occurred before or during the infusion. Therefore, the index date will contribute to both the monitoring period prior to and during the LEMTRADA course. A sensitivity analysis will be performed to provide the proportion of courses with a monitoring test prior to index date, excluding the index date, for the tests that contribute to both the prior period and to the during infusion period (in case of BP and HR monitoring).

Objective 2b will assess the implementation of long-term safety monitoring for all patients' treatment courses (new or continuing). For the cohort of objective 2b, the CED is defined as:

- 16 January 2020 for MS patients who had a LEMTRADA treatment course before the SmPC change (16 January 2020), but for whom the required 48 months post-infusion monitoring ends after the SmPC change (i.e. a LEMTRADA treatment course between 16 February 2016 and 15 January 2020).

or,

- The date of the first LEMTRADA course on or after 16 January 2020 for MS patients who had no LEMTRADA treatment course between 16 February 2016 and 15 January 2020.

On the index date for each treatment course, patients will be followed to assess whether monthly and monitoring every three months occurred thereafter. Patients whose prior courses require post-infusion monitoring after the EU SmPC change will also be included.

The study design for objectives 2a and 2b is a cohort study, as patients will be followed forwards from the index date to assess monitoring during the infusion and thereafter.

Table 1. Study Design

Cohort	Entry Criteria	CED	Index date/Assessment period
1a)	Patients receiving a new use treatment course of LEMTRADA after the SmPC change.	The CED is defined as the date of the first LEMTRADA treatment course on or after 16 January 2020; this first course is a new course.	The index date is the date of LEMTRADA course initiation. The indication is only assessed at the index date of the new LEMTRADA course (i.e. CED).
1b)	Patients receiving a new or continuing use treatment course of LEMTRADA after the SmPC change	The CED is defined as the date of the first LEMTRADA treatment course on or after 16 January 2020.	The index date is the date of LEMTRADA course initiation. Contraindications will be assessed at the index date for each treatment course.
2a)	Patients receiving a new or continuing use treatment course of LEMTRADA after the SmPC change	The CED is defined as the date of the first LEMTRADA treatment course on or after 16 January 2020.	The index date is the date of LEMTRADA course initiation. Monitoring is assessed prior and during each LEMTRADA course.
2b)	Patients receiving a new or continuing use treatment course of LEMTRADA after the SmPC change; OR, Patients having received a treatment course after 16 February 2016, and having part of the 48-month long follow-up taking place after the SmPC change.	The CED is defined as: - 16 January 2020 for MS patients who had a LEMTRADA treatment course before 16 January 2020, but for whom the required 48 months post-infusion monitoring ends after the SmPC change (i.e. a LEMTRADA treatment course between 16 February 2016 and 15 January 2020); or, - The date of the first LEMTRADA course on or after 16 January 2020 for MS patients who had no LEMTRADA treatment course	The index date is the date of LEMTRADA course initiation. Long-term monitoring is assessed after each index date for each treatment course.

		between 16 February 2016 and 15 January 2020.	

9.2 SETTING

Data from four separate data sources will be used: Czech Republic, Belgium, the UK and Germany. Patients will be treated in routine care and will not receive any additional monitoring/intervention due to this study. The Belgian data source opted to no longer participate in the study in January 2023. Therefore, no new analyses will be carried out with the Belgian data. However, the analysis reported in the 2022 annual interim analysis will be included in the 2023 annual report and the final report in 2024.

9.2.1 Study duration

Prescribing patterns and safety monitoring in data accrued from January 2020 until Q1 2024, or the latest available data in each data source, will be assessed.

9.2.2 Inclusion criteria

The source population is MS patients receiving LEMTRADA as part of routine care in four European countries. All patients receiving courses of LEMTRADA under the newly revised SmPC will be included. For objective 1a, this will include only patients who received their first ever course of LEMTRADA after the implementation of the newly revised SmPC (Table 1). For all other objectives (objectives 1b, 2a and 2b), this can include first courses of LEMTRADA and continuing courses (2^{nd}, 3^{rd}, etc) provided the course occurs after the implementation of the newly revised SmPC (Table 1). For objective 2b, patients who had a treatment course before the EU SmPC change but who require post-infusion monitoring after the EU SmPC change, will also be included. In population level administrative data sources (Belgium), all patients must have at least a 15-month look back data prior to CED to ascertain new or continuing use of LEMTRADA. In chart review data, previous medication history or physician recorded new use will be used. Included patients will not be restricted by age or sex.

9.2.3 Exclusion criteria

None.

9.3 VARIABLES

Exposure and cohort entry: the exposure is an infusion of LEMTRADA. Information on LEMTRADA exposure will be extracted based on National Code Number (CNK) codes in Belgian data. From medical chart data, notes on drugs prescribed will be used to measure the exposure. Data on exposure are also recorded in the MS registries. The index date will be defined as the date of LEMTRADA course initiation (starting day of infusion course, either new or continuing), which must occur after implementation of the newly revised SmPC. For objective 1a, patients will be included if identified as a first ever user of LEMTRADA, defined as no previous use of LEMTRADA at any time recorded in the patients MS treatment history or

physician recorded new use from hospital chart data (minimum 15-month look back period required for Belgium). For all other objectives (objectives 1b, 2a and 2b), patients will be included if they are a new or a continuing user. Continuing use will be defined as having had at least one previous course of LEMTRADA at any time recorded in the patients MS treatment history or the patient's medical chart (a minimum 15-month look back period required for Belgium).

Outcome variables: the definitions of outcome variables in this study are presented below in Table 2. Of note, in Belgian data, proxy definitions will be used to measure the indication and contraindications.

The indication consists of a two part definition: 1) patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT) or 2) patients with rapidly evolving severe RRMS defined by two or more disabling relapses in one year, and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.(11)

In Belgian data, information on previous DMTs and relapse (12) will be used to measure part 1 of the indication. Because MRI results are not available in Belgian data, assessing the second part of the indication is not possible. For measurable contraindications, data on medication use and hospital services will be used to construct proxy variables. These data are readily available in the Belgian data source. Please see Appendix 1 for details.

In the German data source, the long-Term study foR obsErvAtion of Treatment with alemtuzumab in active relapsing-remitting MS (TREAT-MS), MRI data are collected if an MRI took place at the screening visit and/or at the day of the first LEMTRADA infusion (pooled together as "baseline" data). Additionally, the MRI results, if available, provide the number of gadolinium-enhancing lesions observed in one MRI. Thus, given the recency of MRI data, they would have been unlikely to have been used by clinicians for deciding to treat with LEMTRADA. This is in contrast to the UK and Czech Republic, where data on all MRIs that occurred in a 1 or 2-year period prior to CED (i.e., in the 12 or 24 months prior to initiation of LEMTRADA) were recorded and results from a recent MRI could be compared to a prior MRI. In TREAT-MS, the severity of the relapses prior to CED is not collected. Therefore, data on the number of relapses (rather than the severity) are used for the indication.

Furthermore, in the Czech Multiple Sclerosis Registry (ReMuS), instead of an ECG, patients could be set under permanent cardiac monitoring, similarly to standard procedures in Intensive Care Units or during general anaesthesia. If for a LEMTRADA course, no ECG monitoring test is identified prior to the course, the use of intensive care monitors is verified and recorded. Permanent cardiac monitoring starting with the first LEMTRADA infusion is considered equivalent to an ECG prior to LEMTRADA infusion, which will be used as proxy for ECG monitoring when no ECG monitoring test is identified prior to the course.

End of follow-up: patients will be followed until the end of study (Q1 2024), end of data collection in each data source or death/emigration as recorded in each data source, whichever occurs earliest. In medical chart data from Czech Republic, UK and Germany, end of follow-up is measured through recording of death or moving out of the area, and in the case of Germany,

through recording of discontinuation of the TREAT-MS study (described in Section 9.5.3). This is ascertained through active tracing procedures in each data source. In the Belgian data source, dates of death/emigration are available through linkage or updates from civil registry systems. The follow-up and monitoring times for each objective is described in Section 9.8.

Other variables: data on age, sex, course number and calendar year of index date will be used to stratify analyses.

Table 2: Core risk minimisation measures: indication, contraindication and monitoring

Objectives	As outlined in label	How to define in registry/chart data
1a Indication	Patients with highly active disease despite a full and adequate course of treatment with at least one DMT or Patients with rapidly evolving severe relapsing remitting MS defined by two or more disabling relapses in one year, and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	Data on relapses, prior medication history and MRI findings and/or MS type/diagnosis are available in the Czech, UK and German data sources allowing measurement of the indication. In Belgian data, a proxy definition will be used that will rely on prior DMT use and occurrence of relapses to capture the first part of the indication. The proxy will be defined as follows: One prior platform DMT + evidence of disease activity via measurement of relapse; Or, One prior highly efficacious DMT. Data on prior medication use in the Belgian data source are complete and reliable. Relapses will be detected using an algorithm that relies on prescribing data for corticosteroids. This algorithm has been found to have 96% (87-99%) positive predictive value and 47% (38-57%) sensitivity in Canadian health insurance claims data.(12) See Appendix 1 for further details on proxy definition.
1b Contraindication	1. Hypersensitivity to alemtuzumab or any excipients 2. HIV 3. Severe active infection until complete resolution 4. Uncontrolled hypertension 5. History of arterial dissection of the cervicocephalic arteries 6. History of stroke	Contraindications will be gathered from data recorded in medical charts in Czech Republic, UK and Germany. In the case of Belgian data, the proxy definitions for contraindications are outlined in Appendix 1**.** The following methods/codes for contraindication identification include and are not limited to:

	7. History of angina pectoris or myocardial infarction 8. Known coagulopathy, on anti-platelet or anti-coagulant therapy 9. Other concomitant AI diseases (apart from MS)	1. Not measurable in Belgian data, expected to be rare. 2. Recorded comorbidity: HIV (ICD-10 B20) or presence of anti-retroviral medications. 3. Hospital admission lasting at least 48 hours and/or oral and/or IV antibiotic/antiviral/antifungal prescribed during stay (ATC codes for drugs provided in SAP) 4. Not measurable in Belgian data (no BP readings prior to infusion and proxies based on prescriptions are inadequate as patients may be controlled). 5. Recorded comorbidities: arterial dissection of cerebral artery (ICD10 I77.71), arterial dissection of vertebral artery (ICD10 I77.74), arterial dissection of other precerebral arteries (ICD10 I77.75). Not measurable in Belgian data. 6. Recorded comorbidity: all strokes (ICD10 I60-I63) 7. Recorded comorbidity: Angina (ICD10 I20), Myocardial infarction (ICD10 I21-I23) 8. Recorded comorbidity: Coagulation defects (ICD10 D65-D69) or use of the following: Anti-platelet drugs [glycoprotein IIb/IIIa inhibitors (e.g., Abciximab, Eptifibatide, Orbofiban, Roxifiban, Tirofiban); ADP receptor/P2Y12 inhibitors (e.g., Clopidogrel, Prasugrel, Ticlopidine, Cangrelor, Elinogrel, Ticagrelor); prostaglandin analogues (e.g., Beraprost, Iloprost, Prostacyclin, Treprostinil); COX inhibitors (e.g., Acetylsalicylic acid, aspirin); thromboxane inhibitors (e.g., Dipyridamole + aspirin, Picotamide, Terbogrel, Terutroban); phosphodiesterase inhibitors (e.g., Cilostazol, Dipyridamole, Triflusal)]; anticoagulants [vitamin K antagonists

		(e.g., Warfarin, Acenocoumarol, Coumatetralyl, Dicoumarol, Ethyl biscoumacetate, Phenprocoumon, Diphenadione); factor Xa inhibitors (Heparin group / glycosaminoglycans / bind antithrombin: e.g., Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin, Fondaparinux, Danaparoid, Dermatan sulfate, Sulodexide); direct Xa inhibitors (e.g., Apixaban, Betrixaban, Edoxaban, Rivaroxaban); direct thrombin IIa inhibitors (e.g., Hirudin, Bivalirudin, Desirudin, Argatroban, Dabigatran, Efegatran); antithrombin III]; thrombolytic drugs / fibrinolytics [e.g., Alteplase, Reteplase, Tenecteplase, Saruplase, Urokinase, Anistreplase, Monteplase, Streptokinase, Brinase, Fibrinolysin]. ATC codes for drugs provided in SAP. 9. Recorded AI disease: please see rationale for list in attached Appendix 2
2a and 2b Monitoring if treated with LEMTRADA after new label	***Prior to Infusion*** Baseline ECG, vital signs including HR and BP Perform laboratory tests (FBC with differential, serum creatinine, serum transaminases, urinalysis with microscopy, and test of thyroid function). ***During Infusion*** HR and BP Platelets on days three and five of the first course (day three only for any subsequent course)	***Prior to infusion*** Data on ECG, HR and BP will be measured separately between the index date and 30 days prior to the index date (index date included), for each course. The test dates closest to course start date will be taken. Data on all blood and urine tests will be measured separately: FBC, serum transaminases, serum creatinine, thyroid function and urinalysis between the index date and 30 days prior to and including the index date, for each course. ***During infusion*** HR and BP measured separately on each day of course (index onwards). Platelets measured on

	Post-Infusion Monthly: FBC, serum creatinine, serum transaminases, and urinalysis with microscopy Every three months: Thyroid function tests.	day 3 and day 5 of the first course and day 3 of any subsequent course. ***Post-Infusion*** Evidence of monthly monitoring defined as: Evidence that each test is carried out within the designated testing period e.g., index date +30 days ± 15 days. Evidence of monitoring every three months defined as: Evidence that a thyroid function test is carried out within the designated testing period e.g., index date +90 days ± 30 days

AI=autoimmune; ATC=Anatomical Therapeutic Chemical; BP=blood pressure; DMT=disease modifying therapy, ECG=electrocardiogram; FBC= full blood count; HR=heart rate; HIV=human immunodeficiency virus; ICD=International Classification of Diseases; IV=intravenous; MS=multiple sclerosis; SAP=Statistical Analysis Plan; UK=United Kingdom

Table 3: Feasibility of each data source in meeting objectives 1a (indication) and 1b (contraindication). Grey sections indicate not measurable

	Type of data	Indication	Contraindication	Notes
Czech Republic	MS patient registry and patient chart data	Yes Data on previous treatments, MRI and relapse history directly available in MS registry data	Hypersensitivity to alemtuzumab or excipients	Contraindications and MRI data recorded in patient charts; manual extraction required
			HIV	
			Severe active infections until complete resolution	
			Uncontrolled hypertension	
			History of arterial dissection of the cervicocephalic arteries	
			History of stroke	
			History of angina pectoris or myocardial infarction	
			Known coagulopathy, on anti-platelet or anti-coagulant therapy	
			Other concomitant AI diseases (apart from MS)	
Belgium	Administrative health data/insurance claims	Yes – a proxy for part 1 of indication[2]. See notes.	Hypersensitivity to alemtuzumab or excipients	Proxy definition for part 1 of indication (See Table 2 and Appendix 1)
			HIV	

[2] Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT)

			Severe active infections until complete resolution	Proxy definitions for contraindications (See Table 2 and Appendix 1) Drugs codes in AIM-IMA using CNK codes (see Appendix 1 for more information on this coding system)
			Uncontrolled hypertension	
			History of arterial dissection of the cervicocephalic arteries	
			History of stroke	
			History of angina pectoris or myocardial infarction	
			Known coagulopathy, on anti-platelet or anti-coagulant therapy	
			Other concomitant AI diseases (apart from MS)	
UK Data for Plymouth, Cambridge and Cardiff	Patient charts	Yes Data on previous treatments, MRI and relapse history available	Hypersensitivity to alemtuzumab or excipients	Data on HIV is not required to be declared by patients.
			HIV	
			Uncontrolled hypertension	
			Severe active infections until complete resolution	
			History of arterial dissection of the cervicocephalic arteries	
			History of stroke	
			History of angina pectoris or myocardial infarction	
			Known coagulopathy, on anti-platelet or anti-coagulant therapy	
			Other concomitant AI diseases (apart from MS)	

Germany	Patient charts	Yes Data on highly active disease status, previous treatments, and relapse history are collected in the TREAT-MS CRF. MRI data are collected for MRIs that possibly took place at the screening visit and/or at the day of first LEMTRADA infusion. Therefore, MRI data are not available in TREAT-MS for the entire baseline period (12 or 24 months) and is anticipated to unavailable for many patients.	Hypersensitivity to alemtuzumab or excipients HIV Severe active infections until complete resolution Uncontrolled hypertension History of arterial dissection of the cervicocephalic arteries History of stroke History of angina pectoris or myocardial infarction Known coagulopathy, on anti-platelet or anti-coagulant therapy Other concomitant AI diseases (apart from MS)	There is a detailed CRF for the TREAT-MS study which is completed using data from hospital charts or other medical information available to treating physicians as per TREAT-MS protocol. The CRF collects information on two contraindications for LEMTRADA by targeted questions, including: - Is there hypersensitivity to the active substance or any of the other ingredients? - Is there an infection with HIV? Furthermore, pre-existing conditions, and test results (e.g., HIV test, test of various infections, serology) are collected. Additionally, adverse event data collected between TREAT-MS enrolment and the initiation of a continuing course are used to indicate a contraindication for a subsequent course.

AI= Autoimmune; BP=blood pressure; CRF=case report form; CNK=National Code Number; ECG=electrocardiogram; FBC= full blood count; HR=heart rate; HIV=human immunodeficiency virus; MRI=Magnetic Resonance Imaging; MS=Multiple sclerosis; MSDS-3D=Multiple Sclerosis Documentation System-3D

Table 4: Feasibility of each data source in meeting objective 2a (monitoring prior to and during infusion) and objective 2b (long-term monitoring). Grey sections indicate not measurable.

	Type of data	Monitoring Prior to infusion	Monitoring during infusion	Long-term monitoring post-infusion	Notes
Czech Republic	MS registry and patients charts	ECG	HR	FBC (monthly)	All data are available in patient charts, when monitoring occurred at the MS centre. For long-term monitoring, patients may be monitored in primary care, which usually occurs if they live further away from the MS centre. These monitoring data in primary care are not collected in ReMuS, and cannot be included in this PASS. In the ReMuS database cardiac monitoring using intensive care monitors was used as proxy for ECG monitoring when no ECG monitoring test was identified prior to the course.
		HR	BP	Serum creatinine (monthly)	
		BP	Platelets (Days 3 and 5)	Serum transaminase (monthly)	
		FBC		Thyroid Function (every three months)	
		Serum creatinine		Urinalysis with microscopy (monthly)	
		Serum transaminase			
		Thyroid Function			
		Urinalysis with microscopy			
Belgium	Administrative health data	ECG	HR	FBC (monthly)	Data on ECG, HR, BP and urinalysis tests are not identifiable in the IAM-IMA database. Coding available as INAMI codes. Different sets of codes exist for the inpatient and outpatient setting. See Appendix 1 for further details on this coding system.
		HR		Serum creatinine (monthly)	
		BP	BP	Serum transaminase (monthly)	
		FBC		Thyroid Function (every three months)	
		Serum creatinine	Platelets (Days 3 and 5)	Urinalysis with microscopy (monthly)	
		Serum transaminase			

		Thyroid Function			
		Urinalysis with microscopy			
UK	Patient charts	ECG	HR	FBC (monthly)	Data are obtained from patient charts and electronic files. Data expected to be 100% complete. The UK does not routinely carry out urinalysis with microscopy.
		HR		Serum creatinine (monthly)	
		BP	BP	Serum transaminase (monthly)	
		FBC		Thyroid Function (every three months)	
		Serum creatinine	Platelets (Days 3 and 5)	Urinalysis with microscopy (monthly)	
		Serum transaminase			
		Thyroid Function			
		Urinalysis with microscopy			
Germany	Patient charts	ECG	HR	FBC (monthly)	The detailed CRF (held in MSDS-3D) for the TREAT-MS study collects data from patient charts on targeted fields on blood count, thyroid function, creatinine, urinalysis, and other laboratory tests in the period prior to infusion, during infusion and throughout the post-infusion follow-up period. Data on HR and BP prior to course (measured on index date) are reported together as vital signs; i.e. if vital signs are measured, it is considered that both HR and BP are tested. Furthermore, for each infusion day, HR and BP are collected. The collection of ECG data is not facilitated in the TREAT-MS CRF.
		HR		Serum creatinine (monthly)	
		BP	BP	Serum transaminase (monthly)	
		FBC		Thyroid Function (every three months)	
		Serum creatinine	Platelets (Days 3 and 5)	Urinalysis with microscopy (monthly)	
		Serum transaminase			
		Thyroid Function			

					The collection of platelet testing data during the infusion is not facilitated in the TREAT-MS CRF.

BP=blood pressure; CRF=case report form; ECG=electrocardiogram; FBC= full blood count; HR=heart rate; HIV=human immunodeficiency virus; MS=Multiple sclerosis; MSDS-3D=Multiple Sclerosis Documentation System-3D; UK=United Kingdom

9.4 CONSENT

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

Germany

There is no additional patient consent necessary for this study, as this is covered within the framework of consenting to participate in the TREAT-MS study. The collection, transmission, storage, and evaluation of patients' personal information within the research project will take place according to the applicable German data protection provisions.

UK

Patient consent is not required as the study is based on secondary use of de-identified data.

Czech Republic

There is no additional patient consent necessary for this study because patient consent when entering the ReMuS covers all data used in this study and because this study is based on secondary use of anonymised data.

Belgium

Patient consent is not required as this project is based on secondary use of anonymised data that are held in administrative databases or registers.

9.5 DATA SOURCES OVERVIEW

This study relies on the use of routine care data. In Czech Republic, data will come from the national Czech MS registry with chart review. In Belgium, administrative data from a national Belgian data source are used. In Germany, secondary data from the TREAT-MS cohort study will be used. Lastly, in the UK, data extracted from patients' charts at three academic-clinical MS centres in England and Wales (the University Hospital of Wales in Cardiff, Cambridge University Hospitals in Cambridge, and Derriford Hospital/Plymouth University in Plymouth) will be used.

Data sources were selected for inclusion based on preliminary assessment of:

- countries with high frequency use;
- feasibility of acquiring data for the purposes of this study e.g., on indication and contraindication;
- data sources with a history of high data quality or a history of LEMTRADA research (1, 3);
- estimated numbers of patients forecasted to be exposed to LEMTRADA after the Article 20 procedure.

The feasibility of each data source as they pertain to meeting the primary and secondary objectives is outlined in Table 3 and Table 4. A feasibility analysis was submitted in 2022 and endorsed in April 2023 (EMEA/H/C/ANX/010.5).

The Marketing Authorisation Holder (MAH) investigated the use of MS registry data *via* the Big MS Data network and other independent channels, such as the UK MS registry. However, given the granularity of the variables required for this study (e.g., accurate capture of the indication),

complete recording of comorbidities, and long-term monitoring, registry data were not appropriate data sources in the absence of prescription or hospital data linkages. Additionally, small numbers of exposed patients precluded the use of registers where linkages did exist (e.g., Sweden and Wales). Other MS registry consortiums exist, including the European Register for Multiple Sclerosis (EUReMS). Data from some of these registries in EUReMS, including Czech Republic, the UK, and Germany are included in this protocol. Other countries in EUReMS were not appropriate for reasons discussed above, such as small numbers of exposed patients after 2020 (Sweden, Denmark) or absence of linked data (UK registry).

9.5.1 Secondary Data: Czech MS Registry

The ReMuS is the Czech national MS registry. It started in January 2013 and has been collecting data from 15 MS referral centres across the Czech Republic. Only patients followed in these centres are allowed to be prescribed with DMT, and as such registry completeness for highly efficacious DMT (HE-DMT) treated patients is very high. More details about the ReMuS can be found in Horakova et al. (13)

The ReMuS collects data on MS patients, characteristics of MS, MS treatments and socioeconomic status. Other medical data unrelated to MS (e.g., comorbidities) are collected in patient charts, but are not directly available in the ReMuS, hence chart review is used to supplement registry data for Drug Utilisation Study (DUS) objectives relating to contraindications and monitoring. Data is entered in the database by trained staff, using ReMuS standard procedures. The same procedures and reference manual are used in each of the 15 participating centres.

When a patient goes for the first time to one of the 15 MS centres, he or she is asked about his/her full medical history. MS patients treated with DMT have per standard of care, check-ups at the MS centre approximately every six months. At each visit, MS data are updated as needed. Patient charts are also updated with health issues unrelated to MS since the last visit. The Czech Republic health care system is based on compulsory state-owned health insurance, which reimburses health care costs. Hence, data on medical conditions and their treatment are well recorded in patient files since these data are needed for reimbursement purposes. Comorbidities are recorded in patient charts using International Classification of Diseases (ICD)-10 codes or plain text, and comedications using Anatomical Therapeutic Chemical (ATC) codes or plain text. If the patient visited his/her MS hospital for reasons other than their routine MS check-up visits, all related information will also be registered in the patient chart. Similarly, all data on MRI and monitoring tests required for treating patients with LEMTRADA are recorded and extracted by neurologists from patient charts. Type of test (ECG, FBC, etc.) and dates of monitoring tests are available in patients' charts. The medical history recorded in the patient chart is therefore a mix of information provided by the patient and the doctors. Of note, in the Czech Republic, patients may be monitored in primary care, which usually occurs if they live further away from the MS site. Generally, patients treated with Lemtrada visit the MS centre every 3-6 months and the expectation is that for that visit, a blood test also occurs at the hospital. In between visits, testing may be performed in primary care closer to the place of residence of the patients. These results can be emailed through to the neurologist, so these data may be available in patient charts. Long-term monitoring data from primary care are thus not systematically collected in ReMuS data for this study. As such, the results of this analysis may be an underrepresentation of the actual long-term monitoring that is performed in the Czech Republic.

9.5.2 Secondary Data: Belgian AIM-IMA database

Since 2008, the Belgian social security agencies have merged their data in a single national database that is managed by the AIM-IMA, a consortium body of social security agencies.(14)

This national database contains data on basic demographics, prescriptions, identifiable by CNK codes and date of prescribing, laboratory exams ordered from hospital/primary care, contacts with GPs, hospital stays and any other medical events that are reimbursable. All events and drugs relevant to this DUS are fully reimbursable in Belgium and thus, data on all are expected to be complete. The database is regularly updated with death/emigration data from existing linkages with civil registry systems. The database has been used in a prior pharmacoepidemiology study and is currently used to investigate the safety of MS treatments AUBAGIO and LEMTRADA.(15) The AIM-IMA opted to no longer participate in the study in January 2023. No new analyses will be carried out with Belgian data. However, the analyses from the 2022 annual interim report will be included in both the annual interim report in 2023 and the final report in 2024.

9.5.3 Secondary use of data from an ongoing cohort study: Germany TREAT-MS

The TREAT-MS study is a non-interventional long-term, multi-centre, cohort study that documents patients with RRMS treated with LEMTRADA.(15) The protocol aimed to recruit 1600 patients from across 400 MS centres in all parts of Germany (Appendix 3). The sites included different types of centres including neurologists and physicians in neurology departments or outpatient clinics as well as private neurologists in specialized MS centres. As such, the study population includes a broad “typical” alemtuzumab patient population as treated under real-life conditions in Germany.(16) The latest published interim analysis informs that as of February 2020, 883 patients were included in the cohort, recruited by 118 physicians.(16) The recruitment period was from 2013 to 2020, with last patient first visit in December 2020, after which the total study population consisted of over 900 patients. Included patients continue to receive indicated courses after this time and follow-up continues for up to 60 months for each patient.

The primary goal of the TREAT-MS study is to determine and assess the implementation of the LEMTRADA Risk Management Plan (RMP) in routine clinical practice. Therefore, the study database contains information for MS disease characteristics that inform on the indication, contraindications as well as monitoring pre, during and post-infusion. The objectives of the TREAT-MS study thus overlap with the objectives of the current DUS. Thus, the data collected in the TREAT-MS study can be used as a secondary source of data to satisfy the completion of the DUS. (17)

Details on data collection and storage can be found in the TREAT-MS protocol (Appendix 3). Briefly, data are entered to the electronic case report form (eCRF) with the guidance of the Multiple Sclerosis Documentation System (MSDS 3D) LEMTRADA TREAT-MS module.(18) Baseline data are collected up to six weeks prior to LEMTRADA administration, which include current and retrospective data on the patient and MS. Thereafter, follow-up data are collected as per routine care for up to a maximum of 60 months after first administration of LEMTRADA.

The structured CRF collects data on medical history, type of MS, number of relapses in the 2 years prior to enrollment, prior treatments for MS, contraindications, and examinations prior to,

during, and after treatment with LEMTRADA (e.g., blood count, urinalysis, thyroid function). A list of TREAT-MS variables used for the objectives of the DUS is provided in Appendix 4.

The prospective data collection started in December 2014 and will be completed in 2026.

The planned period of observation for patients in the TREAT-MS study is 4 years after the last treatment phase with LEMTRADA. The patient data are documented at regular intervals by the physician directly into the eCRF via MSDS-3D, ensuring high data quality, completeness, anonymity and the data protection.(19, 18) All data are labelled with a code (a pseudo identifier) that does not permit identification of the patient. This code is an individual patient number, which each patient receives upon admission to the study and which allows data from a single patient to be linked across pages, visits, and data sets in the MSDS 3D. The visits are based on routine clinical practice. (19)

9.5.4 Chart review: UK

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.

Each of the three UK centres has their own software for the management of data related to MS patients: PatientCare in Cardiff, iMED in Plymouth, and EPIC electronic patient record (EPR) in Cambridge. Thus, in order to facilitate the analysis of data from the three centres (and consider them as a single data source), a common data collection tool hereafter named ‘Clinical tool’ has been created to compile the data from the three centres into one database with a harmonized structure.

Demographic data on LEMTRADA exposed patients will be extracted from patient charts along with date of prescribing. Data on indication and contraindications will be available in charts. Data on long-term monitoring is expected to be complete. Tests ordered and carried in neurology clinics will be in patient charts. In Plymouth, data on most investigations originate from available electronic software, including iSoft, iCM, and sometimes MAXIMS. Exceptions are data on ECG, platelets, HR, and BP, which are obtained from hard-copy paper notes. The hard copy notes are entered manually by the healthcare professionals managing MS patients into the Clinical tool. The accuracy of entries is reviewed periodically when subsequently updating patients’ test results. Testing data are accessed either via primary care or hospital systems – depending on who has completed the test. In Cardiff, data on most investigations (Table 2) originate from the Welsh Clinical Portal (WCP) and include investigations in all care settings, as WCP is a national Wales NHS records system and includes any test that are ordered through primary or secondary (inpatient and outpatient) NHS care. In Cambridge, all data on investigations originate from EPIC (software for data management of EPRs in Cambridge, in use since 2015). Data on date of death will be available via active tracing of patients as part of routine care and with additional checks for completion of the study.

Results from each local database will be sent to lead principal investigator for combination in the Clinical Tool. Aggregate results for the collaboration will then be sent to the Study Management for combination with data from other sources. Quality assessment will be done which may consist of identifying missing data and checking for implausible values or dates.

9.6 STUDY SIZE

This is a descriptive study. There are no formal hypothesis tests and thus traditional sample size calculations to estimate power are not appropriate. Instead, the focus is on obtaining a sample that is representative of the main usage countries, and achieves, to the extent possible, geographical representation. This approach was selected for two reasons:

1) to optimise precision around calculated proportions
2) to provide interpretable utilisation patterns in the countries with most exposed patients.

Data from four countries will be included. Within each country variable numbers of patients treated with LEMTRADA during the study period are anticipated. In the original study protocol, the overall sample sizes were expected to range from 5 newly treated patients to 53 newly treated patients and to range from 6 continuing users to 74 continuing users. The numbers of patients observed in the interim analysis of 2023 is provided in **Table 5**. Examples of 95% Confidence Interval (CI) around sample proportions are given in Table 6.

Ideally the sample size will allow for stratification of study results by age and gender. However, the feasibility of this approach will depend on numbers included in the study. Data privacy practices vary by country and generally dictate that cell sizes of <3 or <5 are not reportable because patients become potentially identifiable in such cell counts. For example, consider a female aged x years who has MS and a rare comorbidity in country y. This person is now theoretically identifiable. Zero cells can be reported.

The sample sizes forecast in the original protocol were anticipatory and depended on forecasts of LEMTRADA from 2020 onwards. It was expected that the number of patients exposed to LEMTRADA after the Article 20 procedure would be low (as presented in Table 2 of 'Response to reviewers' document dated 30 November 2020). This was expected for two reasons:

1) the restricted indication post Article 20 procedure,
2) the Covid-19 pandemic which will reduce utilisation due to reduced hospital resources and concerns about immunosuppression.

Table 5: Sample size per data source for interim analysis 2023

Objective	Cohort entry criterion	AIM-IMA	ReMuS	UK centres	TREAT-MS	TOTAL
1a) Revised indication	Patients newly treated with LEMTRADA after 01/2020	27	63	16	8	114
1b) Revised contraindications	Patients treated with LEMTRADA after 01/2020	87	107	69	72	335
2a) Monitoring prior and during course	Patients treated with LEMTRADA after 01/2020	87	107	69	72	335

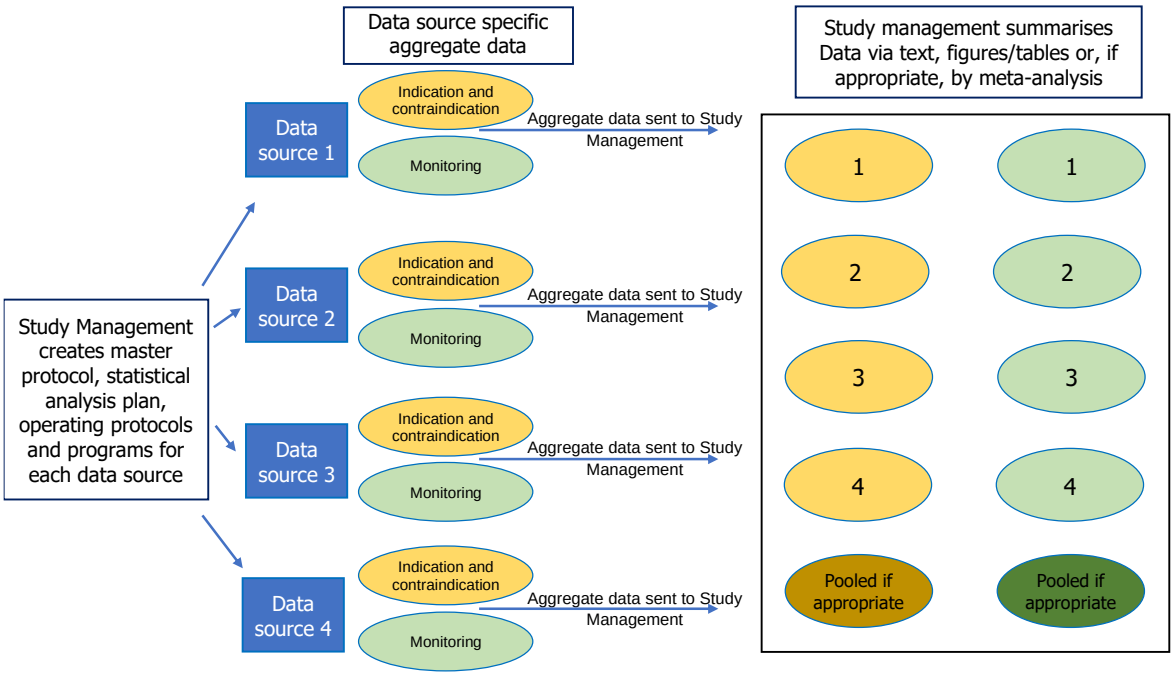
Objective	Cohort entry criterion	AIM-IMA	ReMuS	UK centres	TREAT-MS	TOTAL
2b) Monitoring after course (long-term)	Patients treated with LEMTRADA after 01/2016 and with defined safety screening window on 01/2020	529	209	447	791	1976

9.7 DATA MANAGEMENT

The Study Management will coordinate the development of the statistical analysis plan, the local OPs and the programmes applied to each data source. Given the differing nature of each data source contributing to the study, the data management procedures will be data source specific and will thus be detailed in each local OP.

Data handling and analyses procedures will be conducted within each data source, so that no individual data will be transferred to the Study Management or any other recipient. Once analyses are conducted within each data source as per the OP, summary tables will be sent from each data source to the Study Management (Figure 1**).** Data will be in aggregate format (e.g., tabular, and thus non-identifiable).

Figure 1: Study coordination by the study management and data flow.



9.7.1 Data collection schedule

There is no data collection schedule as patients' data will be recorded in local software/local files as part of routine care. Data will be extracted at various points over study duration.

9.7.2 Data collected

This study relies on data collected as part of routine care. The key outcome variables required for this study are outlined in Table 2. Data on age and sex will be available in each data source.

The procedure in each data source will be based on this master protocol, amended to accommodate local data with four OPs. Based on OPs, working databases will be created in which all data related to LEMTRADA-treated patients will be stored and updated. Programming scripts will be written specific to the format of key variable measurement in each data source; in this way, all data items relevant to this drug utilisation study will be captured. All analyses for this study are descriptive. The descriptive analyses will be outlined in scripts and implemented to achieve the same calculations in each database. Once descriptive analyses are run, these aggregate tables will be sent to the study management. There will be no transfer of individual patient data. In the final report, the study management will combine the aggregated quantitative data from each data source. As a first step, quantitative results will be summarised by using tables and figures (see Section 9.8.3). If heterogeneity allows, results may be combined quantitatively using a meta-analytic approach (see details in Section 9.8.3).

9.8 DATA ANALYSIS

9.8.1 Primary analysis

Analysis approach:

We will use data from four separate data sources. A local OP, derived from this master protocol, will be applied to each data source. Then, aggregate results from each data source for the primary and secondary objectives will be combined to achieve an overall summary of results using tables and figures.(4) Quantitative combination will be carried out through meta-analysis if levels of heterogeneity allow (see Section 9.8.3).

Please see Table 6 below for examples of data and precision for objectives (1a and 1b).

Objective 1a:

For objective 1a, the proportion of MS patients who have a new use course of LEMTRADA on or after 16 January 2020 and who were prescribed in accordance with the newly revised indication will be calculated as follows:

- numerator = number of patients with revised indication at the CED
- denominator = number of patients with a first ever course of LEMTRADA in the study period

Objective 1b:

On the index date of either a new or a continuing (see Section 9.3 for definitions of new and continuing use) LEMTRADA course after the EU SmPC change in January 2020, the following will be calculated:

- numerator=number of courses without any contraindications at the index date.
- denominator=number of courses, either newly treated or continuing treatment in the study period.

Proportions will be stratified by new and continuing use, and course number. Proportions will also be assessed at the patient level (as opposed to course level). The numerator will be number of patients who had all courses without a contraindication. The denominator will be number of patients receiving a LEMTRADA course in the study period.

Table 6: Example results for Objectives 1a and 1b

	Country X Proportion (95% CI)	Country Y Proportion (95% CI)
Correct indication	N= 5	N= 53
	4/5 = 90% (28.4 – 99.5)	40/53 = 76% (61.7 – 86.2)
No contraindications	N= 6	N= 74
	4/6 = 66.7% (22.2 – 95.7)	63/74 = 85.1% (75.0 – 95.3)

To note, this is example data only. 95% Confidence Interval (CI) is calculated using the exact method. N=relevant denominator for each objective. Proportions underneath each N indicate example numerators meeting correct indication and having no contraindications.
For description of indication: N=number of first ever users with correct indication, denominator is number of first ever treated patients after EU SmPC change. For description of contraindications: N=number of courses without a contraindication, denominator is number of courses, whether new or continuing use, after EU SmPC change.

9.8.2 Secondary analysis

Objective 2a: Cohort entry and follow-up:

The index date will be defined as the date of LEMTRADA course initiation, which must occur after implementation of the newly revised SmPC. Each course will be identified as a new use course or a continuing course, see Section 9.3 for definitions of new and continuing use. On the index date, the following proportions will be calculated:

- Cardiac monitoring prior to infusion
  - Numerator=number of courses that had ECG, BP, and HR monitoring (separately) between the index date and 30-day period prior to index date[3]. The test dates closest to course start date will be taken.
  - Denominator=number of courses in the study period.
- Blood and urinalysis monitoring prior to infusion.
  - Numerator=number of courses that had evidence for FBC, serum transaminases, serum creatinine, urinalysis with microscopy and test of thyroid function (all separately) between the index date and 30-day period prior to index date[4].
  - Denominator=number of courses in study period. Proportions will be stratified on new and continuing use as well as course number. See Table 7 for example table shells.

A period of 30 days was selected to construct the testing period prior to infusion based on knowledge of clinical practice and the time usually taken for tests to be administered and results received in order to prepare for infusion.

[3] In TREAT-MS, the monitoring of BP and HR prior to course is checked at index date only; there is no look-back period.

[4] In TREAT-MS, for the new courses, blood and urinalysis monitoring prior to infusion is collected at screening and/or at index date. The screening visit occurs at least 6 weeks prior to the first infusion. For continuing courses, this is collected throughout the follow-up and thus, the 30-day period will apply.

Between the index date and index date + 5 days for new courses or + 3 days for continuing courses (index date included), the following proportions will be calculated:

- Cardiac monitoring (HR and BP) during infusion.
    - Numerator=number of courses with evidence for HR and BP on each day for the first course (or first three days for subsequent courses).
    - Denominator=number of courses in study period.
- Platelets on day three and day five of infusion if the first course, otherwise day three for subsequent courses.
    - Numerator=number of infusion courses with evidence for platelet count on days three and five of first course and on day three of continuing courses.
    - Denominator=number of infusion courses in study period.

Proportions will be stratified on new and continuing use as well as course number. See Table **8** for example table shells.

To capture monitoring during the infusion, follow-up must be sufficient for monitoring to occur. The follow-up time for each patient will be described and patients excluded from the analysis at the point that follow-up ends.

In a supportive analysis, average adherence to pre-infusion monitoring and during infusion monitoring at the patient level will also be calculated.

Table 7: Percentage adherence to monitoring prior to infusion course in each data source

	N	ECG	HR	BP	FBC	Serum Creatinine	Serum transaminases	Thyroid function	Urinalysis with microscopy
UK	X	X%	X%	X%	X%	X%	X%	X%	X%
Germany	X	X%	X%	X%	X%	X%	X%	X%	X%
Belgium	X	X%	n/a	n/a	X%	X%	X%	X%	X%
Czech Republic	X	X%	X%	X%	X%	X%	X%	X%	X%
Pooled*	X	X%	X%	X%	X%	X%	X%	X%	X%

*Pooling of results across data sources only if heterogeneity allows
BP=blood pressure; ECG=electrocardiogram; FBC= full blood count; HR=heart rate; UK=United Kingdom

Table 8: Percentage adherence to monitoring during infusion course in each data source

	N	HR	BP	Platelets on day 3	Platelets on day 5
UK	X	X%	X%	X%	X%
Germany	X	X%	X%	X%	X%
Belgium	X	n/a	n/a	X%	X%
Czech Republic	X	X%	X%	X%	X%
Pooled*	X	X%	X%	X%	X%

*Pooling of results across data sources only if heterogeneity allows. Platelets not measurable on day 5 for second, third etc courses.
BP=blood pressure; HR=heart rate; UK=United Kingdom

Objective 2b: Cohort entry and follow-up

From the index date, patients will be followed forwards so that the following patient level adherence percentages can be calculated:

- Percentage adherence to monthly FBC, serum transaminases, serum creatinine, and urinalysis with microscopy monitoring e.g., the number of each specific test carried out within designated testing periods (e.g., index +30 days ±15 days) divided by the total number of testing periods for each patient. Adherence to safety monitoring will be calculated for each test and for each patient and then the average for each test across all patients will be presented in each data source (see Table 9for example table shells).
- Percentage adherence to thyroid monitoring every three months e.g., the number of tests carried out within designated testing periods (e.g., index +90 days ±30 days) divided by the total number of tri-monthly testing periods for each patient. Adherence to thyroid monitoring will be calculated for each patient and then the average across all patients will be presented in each data source (see Table 9for example table shells).

To verify that the designated testing periods (±15 days for monthly tests and ±30 days for tests every three months) are appropriate, the distribution of days around the intended testing day was tested in the feasibility analysis.

To capture monitoring post-infusion, follow-up must be sufficient for monitoring to occur. The follow-up time for each course will be described and patients excluded from the analysis at the point that follow-up ends. Patients will be followed until 48 months after the last infusion, receipt of another LEMTRADA course, the end of study (Q1 2024), end of data in each data source or death/emigration as recorded in each data source, whichever occurs earliest.

Follow-up time will reset at the point of an additional course. For example, if a patient receives a course in May 2020 and a course in May 2021, their follow-up for first course will run from May 2020 to May 2021. Then, their index date will change to May 2021 and follow-up for monitoring will continue anchored on new index date for course 2. Adherence will be stratified by course number so that an understanding of continued monitoring can be gained.

For patients initiated on treatment prior to 2020, such as continuing users, follow-up for adherence to monitoring will begin from SmPC change (January 2020) onwards, anchored on the original index date.

Table 9: Percentage adherence to long-term monitoring after infusion in each data source

		Monthly					Every three months
	N	**FBC**	**Serum Creatinine**	**Serum transaminases**	**Thyroid function**	**Urinalysis with microscopy**	**Thyroid function**
UK	X	X%	X%	X%	X%	n/a	X%
Germany	X	X%	X%	X%	X%	X%	X%
Belgium	X	X%	X%	X%	X%	X%	X%
Czech Republic	X	X%	X%	X%	X%	X%	X%
Pooled*	X	X%	X%	X%	X%	X%	X%

*Pooling of results across data sources only if heterogeneity allows
FBC= Full Blood Count; UK=United Kingdom

As described above, adherence will be calculated at the patient level, across all courses. Percentage adherence will be calculated on the continuous scale and the full distribution of adherence will be presented as the main results, as highlighted in Table **7** to Table **9**.

To gain further understanding of monitoring patterns the following analyses will be run:

- Adherence will be stratified by new and continuing use;
- Adherence will be stratified by course number;
- Categorical thresholds will be defined for adherence (all objectives). For example, if a patient receives ≥80% of recommended monitoring they could be classified as adherent. The percentage of patients meeting other arbitrary thresholds for adherence e.g., thresholds ranging from ≥60% to ≥95% will be calculated. These thresholds will be further defined in the statistical analysis plan.

The main analysis will measure adherence to monitoring using a 15-day tolerance window for monthly testing and a 30-day tolerance window for testing that occurs every three months. These windows were chosen to reflect the real-world provision of care and to accommodate the deviations in monitoring that occur as part of routine practice. The feasibility analysis included sensitivity analyses using a 7-day window for the monthly testing and a 15-day window for the testing that occurs every three months (as described in Protocol V1.6, June 2022). These analyses were found to not be appropriate and were therefore removed from the protocol.

9.8.3 Combination of results

All data source specific results will be summarised using tables and figures. The Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline (SWiM) to guide this approach to summarising results will be used.(5)

Heterogeneity is expected for various reasons. First, based on knowledge that the use of HE-DMT is varied in Europe.(9) Second, the way in which outcome variables are constructed and measured

in each contributing data source will differ for example based on coding systems used. Heterogeneity will be assessed qualitatively by examining the patterns in proportions across each data source and, potentially, quantitatively by using the heterogeneity test (Cochran's chi square test).(20) If it is deemed appropriate to report a meta-analysis, a random effects model will be considered to accommodate heterogeneity, along with appropriate data transformations to avoid problems relating to variance of extreme proportions.(21, 22) If a meta-analysis is reported, guidance will be provided on interpretation of the results in the presence of heterogeneity.

9.8.4 Other Analyses (Subgroup/Stratified and Sensitivity Analyses)

For all objectives we will carry out the following subgroup/stratified analyses, where cell size permits:

- Stratified by age group and gender.
    - Age groups to be defined during full feasibility analysis.
- Stratified by the year of index date.
    - For objective 2b, analyses will be stratified by calendar year that monitoring is intended to occur (2020, 2021, 2022, 2023 and (Q1) 2024) to understand how the Covid-19 pandemic may have impacted monitoring. The analysis should consider the year of infusion.
- For objectives 1b, 2a, and 2b, analyses will be stratified by new or continuing use.
- For objectives 1b, 2a, and 2b, analyses will be stratified by course number (first, second, third, etc).
- For objective 1b, analyses will be stratified by individual contraindications.
- For objective 2b, analyses will be stratified by time period.
- For objective 2a, a sensitivity analysis will evaluate the proportion of courses with monitoring tests at least 1 day prior to index date (i.e. period excluding index date). This analysis will be done for each monitoring test that is recommended per SmPC both prior to the course initiation and during the course (i.e. HR and BP). The results will provide a more conservative estimate by considering patients with a test only at index date as not adherent for prior testing.
- For objective 2b, sensitivity analysis will be carried out counting from the last available testing date instead of the index date for the window when the subsequent test is expected.

9.9 FEASIBILITY ANALYSIS

The number of LEMTRADA patients included in this drug utilisation study is anticipated to be low. This is a result of two factors. First, utilisation of the drug reduced in Europe after the initiation of the Article 20 procedure in 2019 (please refer to Table 2 in 'Response to reviewers' document dated 30 November 2020). Second, we anticipate that the Covid-19 pandemic will result in lower utilisation due to limited availability of medical facilities, local restrictions on movement and concerns about severely immunocompromised patients (please refer to Table 2 in 'Response to reviewers' document dated 30 November 2020).

A feasibility analysis was submitted as described in Protocol V1.6, June 2022. It was endorsed in April 2023. The MAH has submitted the results of this feasibility analysis in Q3 2021 and in Q2 2022. The full feasibility analysis addressed the technical details of how to:

1) Operationally define the indication, contraindications and monitoring as required in each data source;
2) Gain a deeper understanding of heterogeneity across each data source;
3) Assess numbers treated in each data source;
4) Enumerating the quantity of missing data for age and sex, found to be negligible;
5) The distribution of test dates around the intended testing day was documented and reflected the appropriateness of ±15 days and ±30 days testing windows.

9.10 QUALITY CONTROL

Local procedures in each data source will include checking electronic files, maintaining security and data confidentiality, following analysis plans as outlined in OP, and performing quality control checks of all programmes as outlined in OP. In addition, the Study Management will produce standard descriptive procedures, outlined in each OP, to be applied on data sets for identifying missing and erroneous data and verify the consistency of the dataset. For instance, variables with values exceeding typical ranges will be flagged (e.g., testing that appears beyond the level of too low or too high plausibility).

With regards to missing data, in the feasibility analysis (2022), no missing data for age and sex were identified in the included data sources (the Czech Republic, UK, and Belgium). It is expected that missing data for age and sex will be very rare for Germany as well.

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 study 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.

9.11 LIMITATIONS OF THE RESEARCH METHODS

The central limitation of this study is anticipated low numbers of exposed patients due to 1) the Article 20 procedure and subsequent EU SmPC change in January 2020 and 2) the Covid-19 global pandemic (please refer to Table 2 in ‘Response to reviewers’ document dated 30 November 2020). A feasibility analysis was submitted in 2022 to ascertain numbers of newly prescribed LEMTRADA courses in 2020 and 2021 (Section 9.9). Section 9.6 above provides the most recent patient counts in interim analysis 2023.

As highlighted in Table 3 and Table 4, each data source contributes in different ways to meeting the study objectives. For example, from medical chart data in the Czech Republic, UK, and Germany, data on cardiac monitoring, blood testing, and the indication and contraindication can be collected, although the data also have some limitations as detailed below. In the Belgian data source, data on ECGs and blood monitoring are not available. HR and BP are rolled into one variable called “cardio-monitoring”. In Belgian data, a proxy definition will be used for the

indication which may lead to some misclassification (Appendix 1). Namely, the first part of the indication is measurable in Belgian data[5], but the second part of the indication is not due to the lack of available data on MRI results[6]. Proxy definitions will also be required for contraindications in Belgian data. While validation studies do not exist for the exact proxies we propose in Belgian data; the method of using pharmacy data and hospital service data to detect cardiovascular, other chronic disease and other comorbidities is widely performed, demonstrates good validity and is a generally accepted method of detecting comorbidities.(23-26)

Some contraindications will not be measurable or may be only partially measurable. For example, HIV is not required to be reported by patients in the UK. Uncontrolled hypertension will not be measurable in Belgian data because blood pressure data are not available. Using proxies based on anti-hypertensive use would be inappropriate because it would not be known whether hypertension was controlled or not.

For TREAT-MS, we currently do not have information on the extent of missing data for laboratory tests. Crude, preliminary data indicate that approximately half of the patients in TREAT-MS do not have MRI data at baseline. Future analyses and reports will further evaluate the extent of missing data in the German data.

For ReMuS, some patients who live far away from their MS clinical centre may receive routine long-term monitoring via their local primary care service; however, the magnitude of this is not quantifiable. Data from primary care are not systematically collected in this study, which may lead to underestimations for adherence for long-term monitoring.

We expect heterogeneity in the results between each data source based on existing knowledge of how DMT are used in Europe.(9) This can be viewed as a strength of the study as it will demonstrate how the drug is used in routine care across various health systems. Heterogeneity may also arise from how variables are defined in each data source. For example, proxy definitions for contraindications will be used in Belgian data, while they are recorded directly in medical chart data.

Selection bias is not expected to be problematic given that this is not a comparative study, and therefore no distortion in an association between an exposure and an outcome can occur due to differential selection of patients. In terms of generalizability, the study results will be applicable to patients from the countries and sites (UK) that contributed to the study, and countries that use LEMTRADA in a similar way. As a reference, we plan to compare age and sex for the cohorts included in this study to previous studies, such as the ongoing LEMTRADA PASS study (OBS13434) and clinical trial data. These comparisons will be presented in the final report and in the interim analyses. However, there are several reasons to expect some differences in demographics. First, the indication for LEMTRADA in the DUS will be different to the indication for previous studies resulting in a different patient population exposed to LEMTRADA before and after January 2020. Second, geographical differences may have an impact. For example, this study refers to patients in European countries only, whereas LEMPASS includes patients from all over

[5] Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT)

[6] Patients with rapidly evolving severe relapsing-remitting multiple sclerosis defined by two or more disabling relapses in one year, and with one or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI

the world (although European patients can be stratified out). Third, patients in clinical trials are generally different in terms of age and comorbidities to patients included in real-world studies. An alternative approach for characterising the included population will be to compare demographic data for the cohorts in this DUS to demographic data maintained in ongoing patient support programmes.

10 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in accordance with the guidelines for Good Pharmacoepidemiology Practice (GPP) published by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Society of Pharmacoepidemiology.(27, 28)

10.1 DATA PROTECTION

All personal data collected related to participants, Investigators, or any person involved in the study shall be treated in compliance with all applicable laws and regulations including the GDPR (General Data Protection Regulation). Data collected must be adequate, relevant and not excessive, in relation to the purposes for which they are collected. Each category of data must be properly justified and in line with the study objective. In data sources where consent is required, the participant must be informed that his/her personal study-related data will be used by the Sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant.

No individual data will be transmitted to the Study Management or the MAH.

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 (GVP) practices modules VI and VIII and as also referenced in ENCePP guidelines for GPP. (28-30)

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 DISSEMINATION AND PUBLICATIONS

In accordance with the 2010 EU pharmacovigilance legislation, the protocol of this study was entered into the publicly available EU PAS register once PRAC approval is given. Updates to the study protocol in case of substantial amendments and the final study report will also be entered in the register.

A feasibility report was submitted to the Regulator in Q2 2022 (Section 9.9). Thereafter, an annual interim progress report was submitted in Q4 2022 and another interim progress report will be submitted in Q4 2023, detailing accrual and interim analyses. The final report will be submitted in Q3 2024.

The study group will be comprised of Parexel, 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 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 and reference the study and 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.

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13 APPENDIX 1

Appendix 1 Table 1: A list of proxy definitions for indication and contraindications in Belgian database.

Core Variable	Definition	Proxy	Notes/Coding
Indication	*Part 1 of indication* Patients with highly active disease despite a full and adequate course of treatment with at least one DMT or *Part 2 of indication* Patients with rapidly evolving severe relapsing remitting MS 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.	*Part 1:* One prior platform DMT + evidence of disease activity via measurement of relapse. or One prior highly efficacious DMT Part 2: *Part 2 will not be addressed due to a lack of MRI result data*	Drug use data is complete in the Belgian data source and is given by use of CNK codes. See description of Belgian health service and resultant coding below this table. Platform DMT defined as: Dimethyl fumarate, Glatiramer acetate, Interferon beta 1-a, Interferon beta 1-b, Peginterferon beta 1-a, Teriflunomide Highly Efficacious DMT defined as: defined as any of the following: Cladribine, Fingolimod, Mitoxantrone, Natalizumab, Ocrelizumab, Rituxumab Relapse defined as follows: The prescription of high doses of CS treatment over short periods (e.g., 500 mg/d for 5 days, sometimes with hospitalisation) may be used as proxy indicator for relapses. These proxy indicators are based on knowledge that MS relapses are typically treated with high doses CS administered as IV or taken orally. High doses 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 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 (Marriott et al., 2018, Thrower, 2009, Le Page et al., 2015, Van Le et al., 2019) and discussions with neurologists. Inclusion:

			1. high dose methylprednisolone during a short period, i.e. IV 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.(De Keyser et al., 1999) If high dose 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 immunoglobulins; This algorithm has been demonstrated to have 96% (87-99%) positive predictive value and 47% (38-57%) sensitivity in Canadian health insurance claims data (Marriott et al., 2018).
Contraindication	Hypersensitivity to alemtuzumab or excipients	*Not measurable*	
Contraindication	HIV carriage, or AIDS, or past anti-HIV therapy	Anti-retroviral drugs	Drugs in the following categories: • Nucleotide/nucleoside reverse transcriptase inhibitors • Non-nucleoside reverse transcriptase inhibitors • Protease inhibitors • Post-attachment inhibitors • CCR5 inhibitors • Fusion inhibitors
Contraindication	Uncontrolled hypertension	*Not measurable*	
Contraindication	History of arterial dissection of the cervicocephalic arteries	*Not measurable*	

Contraindication	History of MI/angina	Use of specific drug treatments, imaging, testing, procedures and monitoring and hospitalisation. See text below this table that describes coding system for therapies, tests, procedures, monitoring in full.	Use of treatments used in the acute phase of MI: antiplatelets/nitrates/betablocker AND Troponin test OR coronary angiography OR percutaneous coronary angioplasty AND >ECG over 7 days OR ECG OR 2-D Cardiac Sonography AND Hospital stay >2 days OR ICU admission for at least 1 day. An example of coding given in Table 2 of Appendix 1 (below)
Contraindication	History of stroke	Dispensing of medications, medical procedures and hospitalisations that would signal either a haemorrhagic stroke, or a ischaemic stroke. See text below this table that describes coding system for therapies, tests, procedures, monitoring in full.	<u>Haemorrhagic stroke</u> Anti-haemorrhagic agents/idarucizumab OR parenteral nicardipine AND cerebral angiography/interventional neuroradiology procedure OR neurosurgery AND Hospital stay >2 days <u>Ischaemic Stroke</u> Antithrombotic agents, enzymes OR cerebral angiography/interventional neuroradiology procedure OR transoesophageal ecography, HOLTER AND Hospital stay >2 days An example of tabular algorithms given in Tables 3 and 4 of Appendix 1 (below)
Contraindication	Severe active infection until complete resolution	E.g. Hospital stay and use of IV/oral antibiotics, anti-viral and anti fungal drugs, laboratory	<u>Exact algorithm will depend on infection types but will typically adhere to the following logic</u>

		searches for infectious agents in blood and sputum, need of respiratory assistance, stay in ICU	IV/IM major antibiotherapy, systemic anti-viral therapies, systemic anti fungal therapies, anti-tuberculosis therapies, Therapies specific to opportunistic infections (e.g., Pneumocystis jirovecii) AND Hospital stay >2 days In some instances, testing and interventional events will be used as part of the algorithm Search for sepsis (blood culture aerobic and anaerobic), meningitis, pyelonephritis, search of bacteria, viruses, and fungal infestation in excretions and fluids (e.g., sputum, spinal fluid); search for specific infectious agents such as mycoplasma, legionella; test for antibiotic resistance, respiratory assistance An example algorithm for aspergillosis is given in Table 5 of Appendix 1 (below).
Contraindication	Known coagulopathy, on anti-platelet or anti-coagulant therapy	Use of specific drugs	Anti-platelet drugs [glycoprotein IIb/IIIa inhibitors (e.g., Abciximab, Eptifibatide, Orbofiban, Roxifiban, Tirofiban); ADP receptor/P2Y12 inhibitors (e.g., Clopidogrel, Prasugrel, Ticlopidine, Cangrelor, Elinogrel, Ticagrelor); prostaglandin analogues (e.g., Beraprost, Iloprost, Prostacyclin, Treprostinil); COX inhibitors (e.g., Acetylsalicylic acid, aspirin); thromboxane inhibitors (e.g., Dipyridamole + aspirin, Picotamide, Terbogrel, Terutroban); phosphodiesterase inhibitors (e.g., Cilostazol, Dipyridamole, Triflusal)]; anticoagulants [vitamin K antagonists (e.g., Warfarin, Acenocoumarol, Coumatetralyl, Dicoumarol, Ethyl biscoumacetate, Phenprocoumon, Diphenadione); factor Xa inhibitors (Heparin group / glycosaminoglycans / bind antithrombin: e.g., Bemiparin, Certoparin, Dalteparin, Enoxaparin, Nadroparin, Parnaparin, Reviparin, Tinzaparin, Fondaparinux, Danaparoid, Dermatan sulfate, Sulodexide); direct Xa inhibitors (e.g., Apixaban, Betrixaban, Edoxaban, Rivaroxaban); direct thrombin IIa inhibitors (e.g., Hirudin, Bivalirudin, Desirudin, Argatroban, Dabigatran, Efegatran); antithrombin III]; thrombolytic drugs / fibrinolytics [e.g., Alteplase, Reteplase, Tenecteplase, Saruplase, Urokinase, Anistreplase, Monteplase, Streptokinase, Brinase, Fibrinolysin].

			ATC/CNK codes outlined in SAP
Contraindication	Other concomitant AI diseases (apart from MS)	Proxy definitions will rely on drug use of therapies typically used in the management of identified AI conditions (Appendix 2). As a second step, patients who meet the proxy definition for AI conditions will have their full history extracted from the AIM-IMA database and reviewed by specialists to make a final decision on whether an AI condition other than MS was present. For example, organ transplant will be excluded.	The main therapies will include, but not be limited to, the following therapies used chronically, i.e. continuously for three months or more in the patients history prior to LEMTRADA exposure 1. Azathioprine, Cyclophosphamide, Methotrexate, Mycophenolate, Ciclosporin, lefluonomide, sulphasalazine, hydroxychloroquine, 6-mercaptopurine, 5-aminosalicylates, mesalamine; 2. Anti-TNF-alfa; etanercept, adalibumab, certolizumab, golimumab, infliximab 3. Anti-IL1, 6, 12/23, 23, 17, 5, 4; 4. Other immunosuppressants (generic names): Abatacept, Rituximab, Belimumab, Vedolizumab, Tofacitinib, baricitinib, apremilast, toculizumab, sarilumab 5. Chronic use of steroids (e.g., use for ≥3 months) Other diseases can be identified by specific therapies eg use of insulin as first anti-diabetic drug starting before age 30 years for Type 1 Diabetes, or use of propylthiouracil or thyroid hormones for AI thyroid disease. Some diseases will have specific algorithms eg Guillan Barre disease which requires hospitalisation, lumbar puncture, use of intravenous immunoglobulins and often, respiratory assistance. Other conditions eg acquired haemophilia A may not be identifiable via drug use.

Notes: While validation studies do not exist for the exact proxies we propose in Belgian data; the method of using pharmacy data to detect cardiovascular, other chronic disease and other comorbidities is widely performed, demonstrates good validity and is a generally accepted method of detecting comorbidities.(23-26)
AI = Auto immune; AIDS=Acquired Immune Deficiency Syndrome; ATC=Anatomical Therapeutic Chemical; CNK=National Code Number; CS=corticosteroid; DMT=disease modifying therapy; ECG=electrocardiogram; HR=heart rate; BP=blood pressure; HIV= human immunodeficiency virus; ICU=intensive care unit; IV=intravenous; IM=intramuscular; IL=Interleukin; MS=Multiple sclerosis; MI=myocardial infarction; MRI=Magnetic resonance imaging; SAP=Statistical Analysis Plan, TNF=tumor necrosis factor

AIM-IMA (social security) administrative database in Belgium

In Belgium, registration with the national social security system is compulsory by law. Few (less than 1%) people residing in Belgium are not registered in this system (e.g., staff members of international, multilateral organisations). The database registers all therapies, tests, examinations and medical interventions reimbursed to patients residing in Belgium. The AIM-IMA is complete from 2008 onwards. There is a lag-time of 1 to 2 years for complete data availability. The AIM-IMA codification procedures are defined by the Belgian National Institute for Health and Disability Insurance (RIZIV/INAMI), the Belgian governmental institution in charge of regulations for the medical and drug sectors. The AIM-IMA does not register diagnoses and results of tests and examination. Vital status (alive, death and immigration) of all subjects is updated every 6 months via an automated linkage process to the national population registry.

For each test and medical intervention, there is a unique so-called "INAMI code" that corresponds to a reimbursement price. These codes are organised by systems (e.g., exams for cardiology) and functions (e.g., laboratory tests).

Each reimbursed drug is recorded with WHO ATC and INAMI codes. Unlike ATC codes, INAMI codes are unique to each brand name. In addition, there is a specific code, referred to as the CNK code, denoting the chemical compound of the active substance(s), the route of administration, dosage, packaging, and brand name. A same drug with same brand name, dose and mode of administration will have different CNK codes if commercialised with different packaging, e.g., a box of XXXX® with 28 tabs 10 mg and a box with 84 tabs will have same ATC and INAMI codes, but different CNK codes. CNK codes are attributed by the Belgian Pharmaceutical Association on the basis of information provided by MAHs. The INAMI and CNK codes provide more information than ATC codes, and thus for a given ATC code with 7 digits (the maximum level of detail for ATC), there may be more than one INAMI code, and for each one INAMI code, there can be more than one CNK code. Each therapeutic item reimbursed has its CNK code registered with the date of reimbursement, which generally corresponds to the day of dispensing in primary care or hospital pharmacies. Examples of AIM-IMA data for DMT are displayed in Appendix 1 Table 6 with codes and basic information on each drug and packaging. Search for drugs in the AIM-IMA database may thus use ATC codes with 1 to 7 digits (least detailed), INAMI codes (high detail level) and CNK codes (most detailed level), depending on search question.

Use of AIM-IMA data for identifying contraindications to LEMTRADA

The following procedures are proposed:

1. For each patient registered in the AIM-IMA database and included in the DUS for examining presence of contraindications to LEMTRADA usage, the AIM-IMA database will be searched for proxy indicators of contraindications. Proxy indicators consist of combination(s) of codes (INAMI, CNK, ATC) standing for therapies, tests, examinations, and medical interventions and the relevant dates attached to each code. Each patient will be required to have at least one year of look back data prior to date of entry to the study to allow data capture.

2. Once anonymised patients with the proxy contraindication have been identified in the database, their full coding history will be downloaded. This coding history will then be translated to a treatment/medical history narrative understandable to clinicians.
3. The medical history will be revised by specialised medical doctors (MDs) who will confirm the likelihood of a contraindication. The review team will include senior MDs specialised in infectious diseases, cardiology and internal medicine (for auto immune and chronic inflammatory diseases). Members of the team as well as the Parexel coordinator of the study must comply with medical confidentiality. The review process will take place in AIM-IMA premises at fixed dates, and under supervision of a member staff of the AIM-IMA. This step is of particular importance for identification of auto immune (AI) conditions.

Appendix 1 Table 2: An outline of algorithm to identify myocardial infarction (MI)/angina in Belgian AIM-IMA database with corresponding coding.

Drugs (at least one of the following)	
Name	**ATC code**
clopidogrel highly specific at one shot dose of 300 mg	B01AC04
prasugrel	B01AC22
ticagrelor	B01AC24
eptifibatide	B01AC16
isosorbide dinitrate	C01DA08
metoprolol*	C07AB02 C07FX03 C07FB13 C07FB02 C07FX05 C07CB02 C07BB52 C07BB02 C07AB03 C07FB03 C07CB03
atenolol*	C07CB53 C07BB03 C07DB01 C07AB11 C07AB07 C07FX04 C07FB07
bisoprolol*	C07BB07 C09BX02 C09BX04 C09BX05
AND	
Medical tests and interventions (at least one of the following)	
Name	**INAMI code**
troponins	542334 542345 542356 542360
coronary angiography	453574 453585

percutaneous coronary angioplasty Stenting	453596 453600 464170 464181 464192 464203 589013 589024 589050 589061 589094 589105
AND	
Medical examination (at least one of the following)	
>2 ECG over 7 days	475834 475845
Cardiomonitoring	212015 212026 212041 214012 214023 214045 214060 460465
2-D cardiac sonography	460423 469232 460412 460423 460434 460445 460456 460460 469243
AND	
Hospital stay > 2 days	AIM-IMA algorithm for hospital episodes

* blocking agents most used in the context of acute coronary syndrome

Appendix 1 Table 3: An outline of algorithm to identify haemmorhagic stroke in Belgian AIM-IMA database. Specific lists of codes provided in SAP.

Drug (at least one)	**ATC Code (or CNK)**
antihemorrhagics	B02
idarucizumab specific antidote of dabigatran	V03AB37
nicardipine if parenteral (IV)	(ATC: C08CA04) for IV --> CNK: 0743-021
antithrombotic agents	B01A
AND	
Medical tests and interventions (at least one)	
Name	**INAMI/RIZIV code**
Cerebral angiography/interventional neuroradiology	454016 454020 454031 454042 454053 454064 454075 454086 465076 465010 465021 465032 465043 465054 465065 465080
Neurosurgery	
Trépanation pour drainage d'abcès intracrânien	230296 230311
Trépano-ponction cérébrale	477724 477746
Trépanation pour ventriculographie directe	230333
Trépanation décompressive ou pour drainage	230355
Intervention chirurgicale pour drainage ventriculo souscutané	230370
Cure chirurgicale d'un ou plusieurs hématomes intracrâniens extracérébraux par simple trépanation (élargie à la pince gouge ou couronne tréphine) quel que soit le nombre de trous de trépan	230392

Cure chirurgicale d'un ou plusieurs hématomes intracrâniens extracérébraux par grand volet de trépanation	230414
Cure chirurgicale d'un ou plusieurs hématomes intracérébraux par grand volet de trépanation	230436
Trépanation pour drainage d'abcès intracrânien	230300
Trépano-ponction cérébrale	230322
Trépanation pour ventriculographie directe	230344
Trépanation décompressive ou pour drainage	230366
Intervention chirurgicale pour drainage ventriculo souscutané	230381
Cure chirurgicale d'un ou plusieurs hématomes intracrâniens extracérébraux par simple trépanation (élargie à la pince gouge ou couronne tréphine) quel que soit le nombre de trous de trépan	230403
Cure chirurgicale d'un ou plusieurs hématomes intracrâniens extracérébraux par grand volet de trépanation	230425
Cure chirurgicale d'un ou plusieurs hématomes intracérébraux par grand volet de trépanation	230440
AND	
Hospital stay	
Hospital stay > 2 days	AIM-IMA algorithm for hospital episodes

Appendix 1 Table 4: An outline of algorithm to identify ischaemic stroke in Belgian AIM-IMA database. Specific lists of codes provided in SAP

ATC codes	**ATC or INAMI**
Antithrombotic agents, enzymes	B01AD
Cerebral angiography/interventional neuroradiology	454016 454020 454031 454042 454053 454064 454075 454086 465010 465021 465032 465043 465054 465065 465076 465080
Transoesophageal echography, HOLTER	460574 460585 461252 461263 469674 469685 469836 469840
AND	
Hospital stay	
Hospital stay > 2 days	AIM-IMA algorithm for hospital episodes

Appendix 1 Table 5: An outline of algorithm to identify Aspergillosis infection in Belgian AIM-IMA database.

Aspergillus infestation	INAMI code
Test/exam	
Search for aspergillus antigens in broncho-alveolar aspiration liquid	552064
Medications	
	ATC codes
Amphotericine B Abelcet 100	J02AA01
Amphotericine B Ambisome	J02AA01
CANCIDAS 70 mg	J02AX04
CANCIDAS 50 mg	J02AX04
CASPOFUNGINE ACCORD 50 mg	J02AX04
CASPOFUNGINE ACCORD 70 mg	J02AX04
CASPOFUNGIN TEVA 50 mg	J02AX04
CASPOFUNGIN TEVA 70 mg	J02AX04
CASPOFUNGIN SANDOZ 50 mg	J02AX04
CASPOFUNGIN SANDOZ 70 mg	J02AX04
CASPOFUNGINE MYLAN 70 mg	J02AX04
CASPOFUNGINE MYLAN 50 mg	J02AX04

Appendix 1 Table 6: An outline of ATC, INAMI and CNK codes in AIM-IMA database for identifying disease modifying therapies in the treatment of MS.

Drug	Brand names in Belgium	ATC	INAMI code	CNK	Description	Date of reimbursement
Interferon β 1A	AVONEX PEN 30 µg/0,5 ml	L03AB07	01102261	3019-155	60 µg/mL; 120 injectable solution in 4 injection pens	01/07/2013
Interferon β 1A	AVONEX PEN 30 µg/0,5 ml	L03AB07	01102261	7702-749	60 µg/mL; 120 injectable solution in 4 injection pens	01/07/2013
Interferon β 1A	REBIF 22 microgram/0,5 ml	L03AB07	00813887	2686-418	44 µg/mL; 12 doses; 4 cartridges	01/04/2010
Interferon β 1A	REBIF 22 microgram/0,5 ml	L03AB07	00813887	0796-573	44 µg/mL; 12 doses; 4 cartridges	01/04/2010
Interferon β 1A	REBIF 44	L03AB07	00447008	1724-582	88 µg/mL; 12x6 mL pre-filled syringes	01/09/2003
Interferon β 1A	REBIF 44	L03AB07	00447008	0774-356	88 µg/mL; 12x6 mL pre-filled syringes	01/09/2003
Interferon β 1A	REBIF 44 microgram/0,5 ml	L03AB07	00813988	2686-392	88 µg/mL; 12 doses; 4 cartridges	01/04/2010
Interferon β 1A	REBIF 44 microgram/0,5 ml	L03AB07	00813988	0796-581	88 µg/mL; 12 doses; 4 cartridges	01/04/2010
Interferon β 1A	REBIF	L03AB07	00221177	1485-986	44 µg/mL; 12x6 mL pre-filled syringes	01/12/1999
Interferon β 1A	REBIF	L03AB07	00221177	0761-536	44 µg/mL; 12x6 mL pre-filled syringes	01/12/1999
Interferon β 1B	BETAFERON 250 µg/ml (kit)	L03AB08	00679000	2446-789	250 µg/mL; 18 mL injectable solution; 15 injectable doses + 15 syringes	01/05/2008
Interferon β 1B	BETAFERON 250 µg/ml (kit)	L03AB08	00679000	0788-877	250 µg/mL; 18 mL injectable solution; 15 injectable doses + 15 syringes	01/05/2008
Interferon β 1B	BETAFERON 250 µg/ml (kit)	L03AB08	01459872	3666-229	250 µg/mL; 15x6 mL injectable solution	01/12/2017
Interferon β 1B	BETAFERON 250 µg/ml (kit)	L03AB08	01459872	7721-285	250 µg/mL; 15x6 mL injectable solution	01/12/2017
Interferon β 1B		L03AB08	00254321		0.25 mg/mL; 30 mL injectable solution; 15 doses + 15 syringes	No longer reimbursed since 01/04/2012
Interferon β 1B		L03AB08	00718204		250 µg/mL; 18 mL injectable solution; 15 injectable doses + 15 syringes	No longer reimbursed since 01/02/2016
Peginterferon β 1A	PLEGRIDY 125 µg	L03AB13	01285046	3275-278	125 µg; 2 pre-filled syringes of 0.5 ml	01/08/2018

Peginterferon β 1A	PLEGRIDY 125 µg	L03AB13	01285046	7713-035	125 µg; 2 pre-filled syringes of 0.5 ml	01/08/2015
Peginterferon β 1A	PLEGRIDY 125 µg	L03AB13	01285147	3275-286	125 µg; 2 pre-filled syringes of 0.5 ml	01/08/2015
Peginterferon β 1A	PLEGRIDY 125 µg	L03AB13	01285147	7713-043	125 µg; 2 pre-filled syringes of 0.5 ml	01/08/2015
Peginterferon β 1A	PLEGRIDY	L03AB13	01284844	3275-302	63 µg + 94 µg; 2 pre-filled syringes	01/08/2015
Peginterferon β 1A	PLEGRIDY	L03AB13	01284844	7713-019	63 µg + 94 µg; 2 pre-filled syringes	01/08/2015
Peginterferon β 1A	PLEGRIDY	L03AB13	01284945	3275-294	2 injection pens	01/08/2015
Peginterferon β 1A	PLEGRIDY	L03AB13	01284945	7713-027	2 injection pens	01/08/2015
Glatiramer acetate		L03AX13	00406285		20 mg/mL; 28 vials	No longer reimbursed since 01/01/2009
Glatiramer acetate	COPAXONE 20 mg/ml	L03AX13	00517938	2173-870	20 mg/mL; 28 pre-filled syringes	01/02/2005
Glatiramer acetate	COPAXONE 20 mg/ml	L03AX13	00517938	0778-472	20 mg/mL; 28 pre-filled syringes	01/02/2005
Glatiramer acetate	COPAXONE 40 mg/ml	L03AX13	01305456	3263-514	40 mg/mL; 12 pre-filled syringes	01/01/2016
Glatiramer acetate	COPAXONE 40 mg/ml	L03AX13	01305456	7714-561	40 mg/mL; 12 pre-filled syringes	01/01/2016
Teriflunomide	AUBAGIO 14 mg	L04AA31	01187642	7708-381	14mg; 28 tablets pack	01/10/2014
Teriflunomide	AUBAGIO 14 mg	L04AA31	01541747	4180-238	14mg; 28 tablets pack	01/07/2020
Teriflunomide	AUBAGIO 14 mg	L04AA31	01541747	7727-738	14mg; 28 tablets pack	01/07/2020
Dimethyl fumarate	TECFIDERA 120 mg	L04AX07	01286359	3236-080	120mg; 14 capsules pack	01/09/2015

Dimethyl fumarate	TECFIDERA 120 mg	L04AX07	01286359	7713-209	120mg; 14 capsules pack	01/09/2015
Dimethyl fumarate	TECFIDERA 240 mg	L04AX07	01286460	3236-106	240mg; 56 capsules pack	01/09/2015
Dimethyl fumarate	TECFIDERA 240 mg	L04AX07	01286460	7713-217	240mg; 56 capsules pack	01/09/2015
Dimethyl fumarate	SKILARENCE 120 mg	L04AX07	01490165	3780-467	120mg; 90 capsules pack	01/12/2018
Dimethyl fumarate	SKILARENCE 120 mg	L04AX07	01490165	7723-794	120mg; 90 capsules pack	01/12/2018
Dimethyl fumarate	SKILARENCE 30 mg	L04AX07	01490166	3780-459	30mg; 42 capsules pack	01/12/2018
Dimethyl fumarate	SKILARENCE 30 mg	L04AX07	01490166	7723-745	30mg; 42 capsules pack	01/12/2018
Mitoxantrone	MITOXANTRONE ACCORD 2 mg/ml	L01DB07	01288985	7713-399	2 mg/mL; 5 mL drip to dilute	01/10/2015
Mitoxantrone	MITOXANTRONE ACCORD 2 mg/ml	L01DB07	01289086	7713-407	2 mg/mL; 10 mL drip to dilute	01/10/2015
Mitoxantrone	MITOXANTRONE SANDOZ 2 mg/ml	L01DB07	00664448	0787-804	2 mg/mL; 5 mL drip to dilute	01/09/2013
Mitoxantrone	MITOXANTRONE SANDOZ 2 mg/ml	L01DB07	00664650	0787-812	2 mg/mL; 5x10 mL drip to dilute	01/09/2013
Mitoxantrone		L01DB07	00106292		2 mg/mL; 10 mL drip to dilute	No longer reimbursed since 01/05/2012
Mitoxantrone		L01DB07	00106191		2 mg/mL; 125 mL drip to dilute	No longer reimbursed since 01/12/2007
Mitoxantrone		L01DB07	00531779		2 mg/mL; 12.5 mL drip to dilute	no information
Mitoxantrone		L01DB07	00531880		2 mg/mL; 10 mL drip to dilute	no information
Fingolimod	GILENYA 0,5 mg	L04AA27	00995864	0753-160	0.5 mg; 28 capsules pack	01/02/2012

Fingolimod	GILENYA 0,25 mg	L04AA27	01541286	7726-433	0.25 mg; 28 capsules pack	01/12/2019
Fingolimod	GILENYA 0,5 mg	L04AA27	01541598	7727-472	0.5mg; 28 capsules pack	01/06/2020
Natalizumab	TYSABRI 300 mg	L04AA23	00651516	0787-317	20 mg/mL; 15 mL drip to dilute	01/12/2007
Cladribine	LEUSTATIN	L01BB04	00214915	0760-520	1 mg; 7x10mL drip to dillute	01/06/1999
Cladribine	LITAK 2 mg/ml	L01BB04	00960300	0755-124	2 mg/mL; 5mL injectable solution	01/10/2011
Cladribine	MAVENCLAD 10 mg	L04AA40	01459885	7722-937	1 mg; 1 cp	01/08/2018
Alemtuzumab	LEMTRADA 12 mg	L04AA34	01201079	7709-090	12 mg; 1.2 mL drip to dilute	01/01/2015
Alemtuzumab		L04AA34	00571892		30 mg/mL; 3x1mL drip to dilute	no information
Rituxumab	MABTHERA 100 mg	L01XC02	00226635	0763-177	10 mg/mL; 2x10mL drip to dilute	01/08/2000
Rituxumab	MABTHERA 500 mg	L01XC02	00226736	0763-169	10mg/mL; 50mL drip to dilute	01/08/2000
Rituxumab	MABTHERA 1400 mg	L01XC02	01197948	7708-944	120mg/mL; 11,7 drip to dilute	01/12/2014
Rituxumab	TRUXIMA 500mg	L01XC02	01429457	7721-004	10 mg/mL; 50mL drip to dilute	01/11/2017
Rituxumab	MABTHERA 1600 mg	L01XC02	01459717	7722-135	120mg/mL; 13,4mL drip to dilute	01/04/2018
Rituxumab	TRUXIMA 100 mg	L01XC02	01459764	7722-002	10mg/mL; 2x10mL drip to dilute	01/03/2018
Rituxumab	RIXATHON 100 mg	L01XC02	01459890	7723-349	10mg/mL; 2x10mL drip to dilute	01/10/2018
Rituxumab	RIXATHON 500 mg	L01XC02	01459891	7723-331	10mg/mL; 50mL drip to dilute	01/10/2018
Rituxumab	TRUXIMA 500mg	L01XC02	01541656	7727-746	10mg/mL; 50mL drip to dilute	01/07/2020
Rituxumab	TRUXIMA 100 mg (Abacus)	L01XC02	01541886	7728-256	10mg/mL; 2x10mL drip to dilute	01/09/2020
Ocrelizumab	OCREVUS 300 mg	L04AA36	01510398	7724-305	30mg/mL; 10mL drip to dilute	01/03/2019

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Appendix 2.1 LIST OF AUTOIMMUNE CONDITIONS

One of the contraindications on the newly revised SmPC is "other concomitant autoimmune (AI) disease". To measure whether patients have "other AI disease" a framework defining diseases that this term may encompass is needed.

We reviewed the epidemiology of AI disease in both a general population and the MS population to construct a broad list of AI conditions. (1-8)

We aimed to make this list as comprehensive and general as possible, and so have not restricted the list by frequency or seriousness of disease. We added to this list a number of rare/serious AI conditions that are listed as safety concerns in the current Risk Management Plan for LEMTRADA (e.g., acquired haemophilia A, IgA nephropathy, anti-glomerular basement membrane disease/Goodpasture Syndrome and hemophagocytic lymphohistiocytosis), or have been subject to discussion with regulatory bodies.

Connective tissue disorders

- Ankylosing spondylitis (M45.*)
- Dermatomyositis/polymyositis (M33.*)
- Polymyalgia rheumatica (M35.3)
- Rheumatoid arthritis (M05.*)
- Sjogren's Syndrome (M35.0*)
- SLE (M32.8)
- Systemic sclerosis (M34.*)
- Wegener's granulomatosis (Granulomatosis with polyangiitis) (M31.3*)
- Churg-Strauss syndrome (M30.1)
- Cutaneous leukocytoclastic angiitis
- Essential cryoglobulinemic vasculitis (D89.1)
- Henoch-Schönlein purpura (D69.0)
- Microscopic polyangiitis (M31.7)
- Kawasaki disease (M30.3)
- Polyarteritis nodosa (M30.0)
- Giant cell (temporal) arteritis (M31.6)
- Raynaud (I73.*)
- Takayasu arteritis (M31.4)
- Behcet's syndrome (M35.2)
- Relapsing polychondritis (M94.1)
- Reactive arthritis (M02.3*)

Endocrine

- Adrenocortical insufficiency (E27.4)
- Type 1 Diabetes (E10)
- Hashimoto's Disease and Grave's disease (E06.3, E05.00)

Gastrointestinal

- Autoimmune hepatitis (K75.4)
- Celiac Disease (K90.0)
- Inflammatory Bowel Disease (Crohn's and UC) (K50.* and K51.*)
- Primary Biliary Cirrhosis (K74.3)

Hair and skin

- Alopecia areata (L63.*)
- Phemphigoid/pemphigus (L10.9)
- Psoriasis (L40.0, L40.1, L40.2, L40.3, L40.4, L40.8)
- Vitiligo (L80.0)

Other

- Guillain Barre Syndrome (G61.0)
- Pernicious anaemia (D51.0)
- Autoimmune hemolytic anaemia (D59.1)
- Idiopathic thrombocytopenic purpura (D69.3)
- Acquired haemophilia A
- IgA nephropathy (N02.8)
- Anti-Glomerular basement membrane disease/Goodpasture Syndrome (M31.0)
- Hemophagocytic lymphohistiocytosis (D76.1)
- Myocarditis
- Acute disseminated encephalomyelitis (G04.00)
- IPEX: immune dysregulation, polyendocrinopathy, enteropathy, X-linked
- Thrombotic Thrombocytopenic Purpura (D69.3)
- Rheumatic fever and rheumatic heart disease (I01.*)
- Myasthenia Gravis/Lambert-Eaton syndrome* (G70.0*/G70.80 and G70.81)
- Sarcoidosis (D86.*)

Notes on the above list:
1) chronic gastritis is excluded because it may be mixed with other non-AI forms of gastritis e.g., *H. Pylori* infections.
2) In a sensitivity analysis, thyroid disease will be examined by using ICD-10 code E06.*

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15 APPENDIX 3

Protocol – TREAT-MS

TREAT-MS

ALEMTL07122

Non-interventional Long-term Observational Study of Treatment with LEMTRADA® in active, relapsing-remitting MS

Patient management and monitoring under conditions of routine practice

Observation plan
Version 3.0 dated 28/08/18

Sanofi-Aventis Deutschland GmbH
Sanofi Genzyme

Observation plan

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GLOSSARY

(s)AESI		(Severe) Adverse Event of Special Interest
CGI-S		Clinical Global Impressions Severity Scale
DGN		*Deutsche Gesellschaft für Neurologie* (German Neurological Association)
DMT		*Krankheitsmodifizierende Therapie* (disease modifying therapy)
DMP		Data management plan
DMSG		*Deutsche Multiple Sklerose Gesellschaft* (German Multiple Sclerosis Association)
DVP		Data validation plan
EDSS		Expanded Disability Status Scale
EuroQoL		EQ-5D – Health-related quality of life
GA		Glatiramer acetate
IFN		Interferon beta
ITP		idiopathic thrombocytopenic purpura
IVIg		Intravenous immunoglobulins
KIS		Clinically isolated syndrome
KKNMS		*Krankheitsbezogenes Kompetenznetz Multiple Sklerose* (Disease-related Competence Network for Multiple Sclerosis)
MRT		*Magnetresonanztomographie* (Magnetic Resonance Imaging, MRI)
MS		Multiple Sclerosis
MSDS^{3D}		Multiple Sclerosis data management system
PRIMUS		Patient-Reported Indices for Multiple Sclerosis
NIS		Non-interventional study
PEI		Paul Ehrlich Institute
PPMS		Primary Progressive Multiple Sclerosis
RMS		Relapsing forms of multiple sclerosis
RRMS		Relapsing-remitting MS
SAP		Statistical analysis plan
SDMT		Symbol Digit Modality Test
SPMS		Secondary progressive MS
STROBE		Strengthening the Reporting of Observational Studies in Epidemiology
TSH		Thyroid-stimulating hormone
ADR		Adverse Drug Reaction
VfA		*Verband der forschenden Arzneimittelhersteller* (Association of Research-based Pharmaceutical Companies)
WPAI		Work Productivity and Activity Impairment Questionnaire

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1. BACKGROUND

Manifestation

Multiple sclerosis (MS) is an immune-mediated chronic inflammatory disease of the central nervous system, characterised histopathologically by different degrees of demyelination and axonal damage.[1,2] MS is the most common neurological disease causing permanent disability and early retirement in the young adults.[1]
The clinical course of the disease is variable and cannot be predicted for the given individual. In about 85% of the persons affected the disease is manifested as relapsing-remitting MS (RMS or RRMS). In these cases, clearly distinguishable exacerbations occur at irregular intervals, separated by phases free of symptoms or with few symptoms.[2] Untreated RRMS advances to the secondary progressive form (SPMS) after about 10 years in at least 50% of patients.

Treatment options

At this time, MS is incurable. The approved medications for long-term disease modifying therapy (DMT) make it possible to decrease attacks, retard disease progression and thus achieve reduced rates of disability in some patients. For disease-modifying treatment of RRMS, the 2012 DGN/KKNMS guidelines recommend beta-interferon Ia or Ib (IFN, for intramuscular or subcutaneous injection) or glatiramer acetate (GA, subcutaneous injection), and only with certain limitations, azathioprine (oral therapy: limited approval, poor data situation, risk of cancer in long-term therapy) as well as immunoglobulins (intravenous therapy).[3] Since October 2013 teriflunomide (Aubagio®) has been available as an additional alternative.

LEMTRADA® (alemtuzumab) as a new treatment option for active RRMS

- LEMTRADA® (alemtuzumab) (ATC-Code: L04AA34) is a selective immunosuppressant and has been approved by the European Medicines Agency (EMA) since September 2013 in Germany for treating adult patients with relapsing-remitting MS defined according to clinical findings or imaging.

LEMTRADA® (alemtuzumab) is a monoclonal antibody that is administered intravenously. It binds to CD52, an antigen expressed in large amounts on T- and B-

lymphocytes and also occurs to a smaller degree also on the cell surface of natural killer cells, monocytes and macrophages. The mechanism by which LEMTRADA® exerts its therapeutic effect on MS has not yet been fully explained. However, research points in the direction of immunomodulatory effects due to the depletion and repopulation of lymphocytes, including[8,9,10]

- Changes in the number, fractions and properties of some lymphocyte subgroups after treatment
- Elevated fractions of regulatory T-cell subgroups
- Increased fractions of memory T and B lymphocytes
- Transient effects on components of innate immunity (e.g., neutrophils, macrophages, natural killer cells)

The selective depletion of the circulating B and T cells by LEMTRADA® and the subsequent repopulation might be responsible for the therapeutic effect.

The safety and effectiveness of LEMTRADA® (alemtuzumab) were investigated in 3 randomised, observer-blinded clinical studies with active comparator in patients with RRMS (Study 1: Phase II - CAMMS223 [4];. Study 2: Phase III - CARE-MS I [5]; Study 3: Phase III - CARE-MS II [6]).

In line with the effect on the exacerbation rate, supporting analyses from Study 1 (CAMMS323) show that patients treated with LEMTRADA® 12 mg/day experienced significantly fewer severe exacerbations compared with IFNB-1a (61% decrease, p = 0.0056) and significantly fewer exacerbations when treated with steroids (58% decrease, p < 0.0001).

Supporting analyses from Study 2 (CAMMS32400507) showed that patients treated with LEMTRADA® 12 mg/day compared with IFNB-1a had significantly fewer severe exacerbations (48% decrease, p = 0.0121) and significantly fewer exacerbations when treated with steroids (56% decrease, p < 0.0001) or requiring hospitalisations (55% decrease, p < 0.0045).

A prolonged reduction in disability (Sustained Reduction in Disability, SRD) was shown in Study 3: After 3 years, LEMTRADA® reduced the risk of 6-month accumulation of disability (Sustained Accumulation of Disability, SAD) by 76% (Hazard Ratio: 0.24 [95% CI: 0.110; 0.545], p < 0.0006) and reduced the annual exacerbation rate by 67% (incidence density rate: 0.33 [95% CI: 0.196; 0.552], p < 0.0001) compared with subcutaneously administered IFNB-1a. Over 2 years of follow-up LEMTRADA®

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12 mg/day compared with subcutaneously administered IFNB-1a led to significantly lower EDSS values (improved compared with baseline) ($p < 0.0001$). After 5 years, LEMTRADA® reduces the risk of an SAD by 69% (Hazard Ratio: 0.31 [95% CI: 0.161; 0.598], $p = 0.0005$) and reduces the annual exacerbation rate by 66% (incidence density rate: 0.34 [95% CI: 0.202; 0.569], $p < 0.0001$) compared with subcutaneously administered IFNB-1a.

Thus the efficacy of LEMTRADA® (alemtuzumab) in RRMS patients with an EDSS of less than 3 (CARE-MS I) and less than 5 (CARE-MS II) was demonstrated impressively. The most important clinical results of the two Phase III studies are represented in the table below.[7]

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	Study 1		Study 2	
Study title	CAMMS323 (CARE-MS I)		CAMMS32400507 (CARE-MS II)	
Clinical endpoints	**LEMTRADA 12 mg (N=376)**	**IFNB-1a SC (N=187)**	**LEMTRADA 12 mg (N=426)**	**IFNB-1a SC (N=202)**
Relapse rate[1] Annual relapse rate (ARR) (95% CI)	0,18 (0.13; 0.23)	0.39 (0.29; 0.53)	0,26 (0.21; 0.33)	0,52 (0.41; 0.66)
Incidence density ratio (95% CI) Risk reduction	0.45 (0.32; 0.63) 54.9 (p<0.0001)		0.51 (0.39; 0.65) 49.4 (p<0.0001)	
Disabilities[2] (Sustained accumulation of disability [SAD] over 6 months[1]) Confirmed patients with SAD over 6 months (95% CI)	8.0% (5.7; 11.2)	11.1% (7.3; 16.7)	12.7% (9.9; 16.3)	21.1% (15.9; 27.7)
Risk ratio (hazard ratio; 95% CI)	0.70 (0.40; 1.23) (p=0.22)		0.58 (0.38; 0.87) (p=0.0084)	
Relapse-free patients after 2 years (95% CI)	77.6% (72.9; 81.6) (p<0.0001)	58.7% (51.1; 65.5)	65.4% (60.6; 69.7) (p<0.0001)	46.7% (39.5; 53.5)
Change in EDSS from baseline after 2 years; Estimate (95% CI)	-0,14 (-0.25; -0.02) (p = 0.42)	0,14 (-0.29; 0.01)	0,17 (-0.29; -0.05) (p<0.0001)	0,24 (0.07; 0.41)
MRT endpoints (0-2 years)				
Mean percent change in the volume of the T2 lesion	-9,3 (-19.6; -0.2) (p = 0.31)	-6,5 (-20.7; 2.5)	-1,3 (p = 0.14)	-1,2
Patients with new or enlarging T2 lesions over 2 years	48.5 % (p = 0.035)	57.6%	46.2% (p<0.0001)	67.9%
Patients with gadolinium-enhancing lesions over 2 years	15.4% (p = 0.001)	27.0%	18.5% (p<0.0001)	34.2%
Patients with new T1 hypointense lesions over 2 years	24.0% (p = 0.055)	31.4%	19.9% (p<0.0001)	38.0%
Mean percent change in brain atrophy	-0.867 (p<0.0001)	-1.488	-0.615 (p = 0.012)	-0.810

[1] Co-primary endpoints: ARR and SAD. The study was considered as being successful if at least one of the two co-primary endpoints was reached.

[2] The time to occurrence of SAD was defined as an increase by at least 1 point on the Kurtzke expanded disability status scale (EDSS) beginning with a baseline EDSS value of ≥ 1.0 (increase by 1.5 points in patients with a baseline EDSS value of 0), lasting for over 6 months.

In summary, LEMTRADA® (alemtuzumab) improved the clinical course of MS by decreasing the disease activity (among other things, reduced number of

exacerbations), slowed the progression of the disability and reduced the number of cerebral lesions in the magnetic resonance tomography (MRT) scans.
A total of 1,188 patients with RRMS treated with LEMTRADA® (either 12 mg or 24 mg) formed the safety population in a pooled analysis of controlled clinical trials that provided 2,363 patient-years of safety observation and a median follow-up time of 24 months.
The most significant adverse effects are autoimmunity, infusion-associated reactions (IAR) and infections.
The most common adverse effects under LEMTRADA® (in ≥ 20% of patients) are rash, headache, fever and respiratory infections.[7]

Up to one third of all patients are at risk of developing antibody-mediated autoimmune diseases, especially in the first four years after the final infusion. These include:

- Thyroid disorders
- Idiopathic thrombocytopenic purpura (ITP, immune thrombocytopenia)
- Nephropathies, including Goodpasture syndrome (anti-GBM disease: Auto-antibodies against the basal membrane of the blood vessels, especially in the area of the renal glomeruli and the pulmonary alveoli)

These diseases can usually be treated effectively. Nevertheless these events can be serious and lead to morbidity and/or mortality; they may also not be manifested until many years after treatment.

Currently there are no known surrogate markers that can predict a higher individual risk for developing these secondary autoimmune diseases.

Early diagnosis offers the best chance of successful treatment. To monitor the patients for early signs of autoimmune disease, according to the Summary of Product Characteristics, the blood count and renal function as well as thyroid function should be checked before the beginning of treatment with LEMTRADA® or at regular intervals during the treatment, and for 48 months after the last phase of treatment with LEMTRADA®, blood count and renal function should be checked monthly and additionally thyroid function should be checked every three months. In addition, the treating physician should pay close attention to signs and symptoms.
Furthermore, pregnancy should be prevented for up to four months following a treatment phase.

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Overview of laboratory tests during LEMTRADA® therapy

Disease	Measure	Time	
Idiopathic thrombocytopenic purpura (ITP)	Complete blood count with differential count	Before the beginning of treatment with LEMTRADA®	Monthly up to 48 months after the last infusion
Nephropathies, including Goodpasture syndrome	Serum creatinine	Before the beginning of treatment with LEMTRADA®	Monthly up to 48 months after the last infusion
Nephropathies, including Goodpasture syndrome	Urinalysis with microscopic sediment analysis	Before the beginning of treatment with LEMTRADA®	Monthly up to 48 months after the last infusion
Thyroid disorders	Thyroid function tests (e.g., TSH)	Before the beginning of treatment with LEMTRADA®	Every 3 months up to 48 months after the last infusion

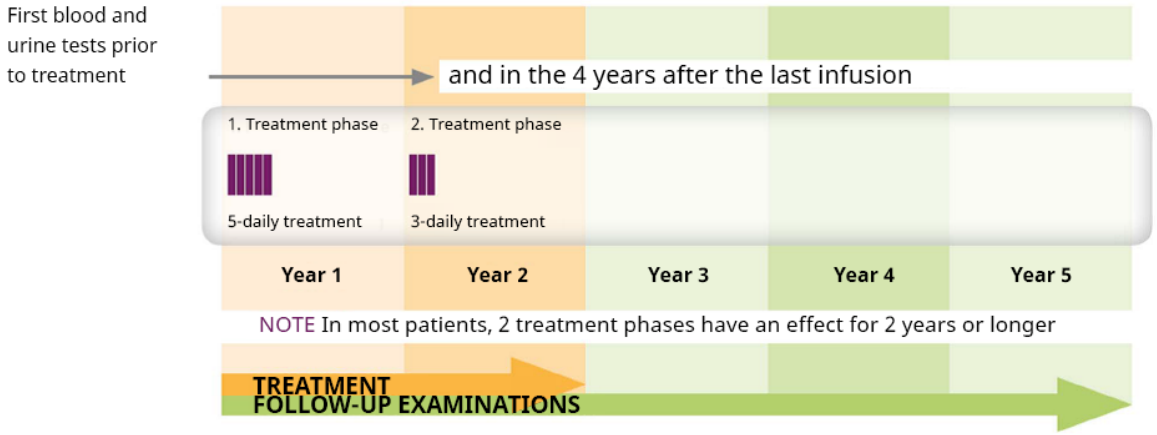
LEMTRADA® is administered as a solution for infusion in two phases on 5 successive days (at the beginning of treatment) and 3 successive days (from the end of the second treatment phase). There is a one-year treatment-free interval between the first and second treatment phases. According to the Summary of Product Characteristics (as of July 2018), up to 2 additional treatment phases can be considered as needed.

According to the Summary of Product Characteristics, the patients should be pre-treated on each of the first 3 days after each of the treatment phases immediately before the administration of LEMTRADA®. In addition, pre-treatment with antihistamines and/or antipyretics before administration of LEMTRADA® should be considered. Oral prophylaxis against herpes infections should be performed in all patients.

Since LEMTRADA® (alemtuzumab) is an immunomodulating medication, it is recommended that the patient should have met the regional immunisation requirements at least 6 weeks before initiation of treatment with LEMTRADA®. Patients who have no history of chickenpox and have not been immunised against the varicella zoster virus (VZV) should be tested for antibodies to VZV before the beginning of the

Observation plan

treatment phase with LEMTRADA®. VZV vaccination of antibody-negative patients 6 weeks before the beginning of treatment with LEMTRADA® should be considered.



Risk Management Plan

As part of the Risk Management Plan (RMP), a guideline has been developed for prescribing physicians and other specialist medical staff involved in the care of patients treated with LEMTRADA®. This is intended to provide more specific information about the possible serious risks associated with treatment with LEMTRADA®. In addition, the regular monitoring needed to provide for clinical vigilance should also be clarified. Sanofi has made guidelines available for patients as well as for physicians and other specialist medical staff.

The multidimensional Multiple Sclerosis Documentation System (MSDS^{3D}) of the MSDS Project Group in Dresden is used for documenting the patient data in accordance with the Risk Management Plan and SPC.[11] This system is a software package that permits standardised management and documentation of the patient and can serve as a data input system for various databases.

Database, data processing and data sharing for the MSDS^{3D}-TREAT module

Collection in the TREAT-MS study can take place as local documentation with the MSDS^{3D}-TREAT module or by means of an internet-based WEB-TREAT eCRF system.

- The patient data to be documented with the internet-based WEB-TREAT eCRF system are obtained in pseudonymised form within the framework of the

TREAT-MS study. The patient data are provided with a code (pseudonym). This is a non-descriptive identifier for a patient. Only the physicians and persons authorised by the project manager who are involved in conducting the research project have access to this code.

- The patient data collected with the MSDS^{3D}-TREAT module system will initially be stored locally within the framework of the TREAT-MS study and sent in pseudonymised form for evaluation and further processing to the MSDS^{3D} registry server of the MedicalSyn GmbH. The data collected are stored throughout the project period both locally in the project centres by means of the MSDS^{3D}-TREAT module and on the MSDS^{3D} registry server of the MedicaSyn GmbH within the framework of the TREAT-MS study.

As soon as the patient's consent for storing the data collected in the MSDS^{3D}-TREAT module (separate patient information and consent form) is available, the data obtained within the framework of the TREAT-MS study are incorporated into the MSDS^{3D}-TREAT database. The MSDS^{3D}-TREAT database is made available by MedicalSyn GmbH Stuttgart on behalf of Carl Gustav Carus Management GmbH Dresden, implementing body Dresden University Hospital, Clinic for Neurology, Centre for Clinical Neurosciences.

The data in the TREAT-MS study server are provided with a code (pseudonym). This is a non-descriptive identifier for a patient. Only the physicians and persons authorised by the project manager who are involved in conducting the research project have access to this code.
Additional patient-related information (age, sex, medical history, diagnosis, history of current illness, clinical course and treatment data) are likewise provided with this code and stored and managed on the MSDS^{3D}-TREAT study server. In this way, protection of the samples from loss, destruction, alteration and access by unauthorised persons is guaranteed.

Confidentiality of data

The collection, transmission, storage and evaluation of patients' personal information within the research project will take place according to the applicable German data

Observation plan

protection provisions. The prerequisite for this is the voluntary consent of the study participants within the framework of consenting to participate in the TREAT-MS study.
The medical data collected from study participants must be treated in the strictest confidence and may not be divulged to third parties.
Confidentiality is guaranteed by the use of codes. All patients are encoded with an alphanumeric code (pseudonymised).
The data to be evaluated are provided with this code only and stored in a data sheet on an MSDS^{3D}-TREAT study server with access limited to the MSDS^{3D} Developer Group of the Department for Neurology and MS Research at the University of Dresden Hospital. Only authorised persons have access to the original data.

Data collected within the framework of this project can be viewed for checking or inspection by the independent ethics committee.

2. OBSERVATION METHOD

This non-interventional study (NIS) is an open-label, uncontrolled, multi-centre, prospective study that documents in accordance with the provisions of the German Drugs Act (AMG §67(6)) patients with relapsing-remitting MS treated with LEMTRADA® (alemtuzumab).

The planned period of observation of the patients is 4 years after the last treatment phase with LEMTRADA® (alemtuzumab), to cover the complete implementation of the RMP. The observation ends at the latest on 31/12/2025 even if the patient has received the 3rd or 4th treatment phase with LEMTRADA® (alemtuzumab). The patient data are documented at regular intervals via the multidimensional Multiple Sclerosis Documentation System (MSDS-3D). The required visits are based on the LEMTRADA® Risk Management Plan (RMP) according to the Summary of Product Characteristics and routine clinical practice.

Within the framework of the NIS, the treating physician will not be given any targets in terms of diagnosis, therapy or follow-up examinations. Thus only parameters relating to diagnosis and therapy which the investigator has already obtained in routine practice or which are available to him from other sources (e.g., from hospital reports) will be documented. In addition, at the beginning of treatment and at regular intervals thereafter, the treating physician will be asked for his assessment of the state of health and the disease-related quality of life of the patient.

The patients will be asked to complete questionnaires at the beginning of treatment and at regular intervals thereafter:

- Satisfaction with treatment
- Cognition
- State of health
- Health-related quality of life
- Ability to work

In addition to the prospective data capture, patient data will be also be used, within this non-interventional study, which had already been entered in a local version of the MSDS already available to the treating physician since the market launch of LEMTRADA® on 01/10/2013. The prerequisite for this data sharing within the framework of this non-interventional study is the explanation given to and written

consent from the patient. In this case the patients will only be asked to complete the relevant questionnaires after entry into the study. The analysis of these questionnaires will take place separately from the prolectively obtained questionnaire data.

3. QUERIES

The present prospective non-interventional study will collect data on unselected adult patients with active, relapsing-remitting multiple sclerosis who are being treated with LEMTRADA®.

The goals of the studies are as follows:

- Determining and assessing the implementation of the LEMTRADA® Risk Management Plan (RMP) in routine clinical practice
- Fulfilment of the requirements arising from the RMP for early detection of suspected cases of newly occurring autoimmune diseases during LEMTRADA® treatment.
- Evaluation of the infusion phases and possible infusion reactions.
- Identifying and evaluating the patients with more than 2 treatment phases
- Benefits of treatment in subgroups of patients
- Determination of the EDSS over the period of observation
- Evaluation of patient satisfaction
- Description of patients' quality of life
- Description of cognition over the period of observation
- Description of ability to work over the period of observation
- Detection of exacerbations and their severity
- Compiling AE/SAE and AESI/SAESI
- General description of the use of LEMTRADA® under routine practice conditions

4. NUMBER AND SELECTION OF STUDY SITES

The study data are to be collected in about 400 sites throughout Germany. Neurologists and physicians in neurology departments or outpatient clinics as well as private neurologists in specialised MS centres may participate. A total of 1600 patients will be included.

5. PATIENT POPULATION

Within the framework of this non-interventional study it will be possible to document adult patients where the treating physician has already made a decision to initiate treatment with LEMTRADA® within the framework of the approval (see enclosed SPC). In such instances the therapy decision is independent of participation in the documentation.

The written consent from the patient must have been given before the beginning of documentation in the MSDS^{3D}. If the data are already available in a local MSDS^{3D} version, the patient's written consent must have been given before these data are forwarded within the framework of this non-interventional study. The decision for treatment with LEMTRADA® is made independently of the documentation.

Exclusion criteria are not defined since an unselected patient population is to be included (under routine practice conditions). However, obstacles may arise that can interfere with participation in the observational study or the regular monitoring visits, for example motor limitations, vision limitations, cognitive disorders. In addition, the recommendations of the SPC should be observed:

- Contraindications: Hypersensitivity to the active substance, HIV infection
- The safety and efficacy of LEMTRADA® in children and adolescents aged between 0 and 18 years have not been confirmed
- No patients above 55 years of age were included in the clinical trials

6. OBSERVATION CRITERIA

The investigation will be performed in each patient at the times listed in the table. The following parameters will be included (insofar as they are routinely recorded, or last available value):

Nicht-Interventionelle Studie (AWB gemäß §67 (6) AMG)
mit LEMTRADA® (alemtuzumab) - TREAT-MS (ALEMTL07122)

Observation plan

	Baseline*	Treatment* 1. Infusion 2. Infusion (possibly additional**)	Follow-up examinations: month after initiation of treatment											
			1	2	3	4	5	6	7	8	9	10	11	12
			13	14	15	16	17	18	19	20	21	22	23	24
			25	26	27	28	29	30	31	32	33	34	35	36
			37	38	39	40	41	42	43	44	45	46	47	48
			49	50	51	52	53	54	55	56	57	58	59	60
Patient information - Availability of the patient's informed consent form	x													
Sociodemographic information														
Age, sex	x													
Information on MS														
Medical history (including)														
- Diagnosis	x													
- Date of first diagnosis (RRMS)	x													
- Number of relapses in the last and penultimate years	x													
- Concomitant diseases including fatigue and depression	x													
- Prior basic therapy for MS, reason for termination of therapy	x													
Relapses*** during the observation period														
- Number	x		x	x	x	x	x	x	x	x	x	x	x	x
- Number treated with cortisone	x		x	x	x	x	x	x	x	x	x	x	x	x
EDSS (Expanded Disability Status Scale)	x				x			x			x			x
SDMT (Symbol Digit Modality Test)	x							x						x
PRIMUS (Patient Reported Indices for Multiple Sclerosis)	x							x						x
EuroQol (EQ-5D)	x							x						x
Responding to treatment/clinical assessment														
CGI (Clinical Global Impression Scale)														
- Information by doctor	x							x						x
- Information by patient	x							x						x
Economic parameters														
WPAI (Work Productivity and Activity Impairment Scale)	x							x						x
Examinations prior to and during treatment with LEMTRADA®**														
Pre-existing diseases	x													
Physical examination	x	x												
Complete and differential blood count	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Serum creatinine level		x	x	x	x	x	x	x	x	x	x	x	x	x
Urine examination (including microscopy)		x	x	x	x	x	x	x	x	x	x	x	x	x
Thyroid function (TSH)	x	x			x			x			x			x
Vaccination status	x													
Infections	x													
HIV infection	x													
Tuberculosis test	x													
Hepatitis B and Hepatitis C test	x													
Varicella zoster virus test	x													
JC test	x													
Contraception/exclusion of an existing pregnancy****	x	x												
Adverse events since the start of treatment**		x	x	x	x	x	x	x	x	x	x	x	x	x
MRI (New T2 or Gd+ lesions)	x		in case MRI examinations were routinely performed											
** Additional screening may be documented for further LEMTRADA treatments														

* Baseline at least 6 weeks before the first infusion if immunisations are still to be performed
** In the case of clinically relevant deviating from values recorded before commencement of the treatment, and if pregnancy is detected, an AE form must be completed and sent to the Pharmacovigilance Agency (pregnancy must be noted in free text on the AE form) as soon as the study physician learns about it.
*** If exacerbations occur with high intensity and thus outside of the usual courses of illness, an AE form must be completed and sent to the Pharmacovigilance Agency as soon as the study doctor learns of it.

Observation plan

**** To be queried before the respective treatment phase. Pregnancy must be prevented for 4 months after a treatment phase.
# If more than two treatment phases: If, according to the Summary of Product Characteristics, a 3rd/4th treatment phase takes place, the documentation of the infusions and an associated preliminary examination in MSDS3D is carried out. The observation is extended accordingly and ends 48 months after the last treatment phase, but at the latest on 31/12/2025.

If applicable (e.g., M12/2nd infusion) the questionnaires should be completed **before** the infusion with LEMTRADA®.

If, according to the Summary of Product Characteristics, a third/fourth treatment phase is started beyond the two treatment phases, this can be documented as additional causal MS therapy, including an additional preliminary examination in MSDS3D. If a disease-modifying treatment (DMT) is started after the 2nd treatment phase, this can also be documented in the MSDS[3D].

Expanded Disability Status Scale (EDSS)[12,13]

The EDSS is a method of quantifying the disability of patients with MS and monitoring changes in the degree of disability over time. The EDSS measures the disability in 8 function systems: Bowel and bladder function, vision and brain function (pyramidal, cerebellar, brain stem, sensory). The EDSS scale extends from 0 to 10 in steps of 0.5 representing higher degrees of disability

Symbol Digit Modality Test (SDMT)[14]

The Symbol Digit Modality Test (SDMT) was developed by WECHSLER (1945). It displays the numbers from 1 to 9, which are assigned to nine symbols. The test subject is to briefly memorise this assignment . In a row with a random succession of symbols, the test subject is supposed to assign as many numbers as possible to the corresponding symbols and write down the respective solution. 90 seconds are allowed for this; the study subject can look back at the specified assignment at any time. The number of correctly assigned digits gives the test result. The SDMT combines visual commitment to memory, retrieval and response to a graphic symbol. It is a test of persistent attention and concentration (cognition).

Clinical Global Impression-Severity (CGI-S)[15]

The treating physician's clinical overall assessment of disease severity during the observation period will be documented with the CGI-S. An assessment of the disease severity from the patient's viewpoint will be similarly documented.

Observation plan

EQ-5D – health-related quality of life (EuroQoL)

The EuroQoL questionnaire consists of six questions and is used for determining the health-related quality of life. The first five questions (EQ-5D self-classifier) are descriptive in nature and relate to issues such as mobility, self-care, general activities, pain and physical complaints as well as anxiety and depression. The five different dimensions reflect the principal aspects of quality of life, the different weightings of which lead to different qualities of life.

The sixth question relates to the current state of health of the respondent (visual analogue scale - VAS). The respondent should mark the current assessment of his/her own health on a thermometer scale from 0 to 100.

Patient-Reported Indices for Multiple Sclerosis (PRIMUS)[16]

The PRIMUS patient questionnaire is used to determine the health-related quality of life and has 3 independent scales: Symptoms, activity status and quality of life. The questionnaire consists of 8 questions on symptoms, 15 questions on activity status and 22 questions relating to the quality of life. The questions are simply answered yes or no.

Work Productivity and Activity Impairment Questionnaire (WPAI)[17]

The patient questionnaire covers the effects of health problems on the ability to work and pursue normal activities. Health problems include all physical and psychological problems. The questionnaire has 6 questions.

7. SURVEY PERIOD AND SEQUENCE

The retrolective data collection is to commence in Germany in October 2013 with the approval of LEMTRADA®. The prospective data collection was started in Germany in December 2014 and will be completed in 2026 with the issue of the final report . In addition, regular interim evaluations of the data collection are planned.

If the maximum number of patients is reached before the end of the scheduled period, the recruitment can be ended prematurely. Patients will be observed under LEMTRADA® treatment for up to a total of 60 months.

- Guidance by the Ethics Committee: July 2014
- Retrolective inclusion period October 2013 to June 2014*

Observation plan

- Prospective inclusion period December 2014 to December 2020
- Patient documentation until: December 2025
- Closure of database: March 2026
- Draft final report: October 2026
- Publication of results Q2/2028

* Monitoring of retrolectively included LEMTRADA® patients according to the existing RMP, from the time of entry into the study plus questionnaires

8. GUIDANCE BY ETHICS COMMITTEE

The documents of this NIS (observation plan, patient questionnaire, patient information and consent form) will be presented to the Ethics Committee of Dresden Technical University for guidance by the research director in accordance with the Professional Code for Physicians.

9. RESPONSIBILITIES OF THE PARTICIPANTS

9.1 Research director

The research director advises the sponsor on the design and execution of the project, the evaluation of the results and on the preparation of the publication(s) after the results are made available.

9.2 Study sites

The responsible physician at the site serves as the contact person for answering logistical questions, in case of questions about the documentation (especially the undesirable effects) and for other quality examination measures.

9.3 Sponsor and contract research institution

The Medical Department of Sanofi-Aventis Deutschland GmbH is the sponsor of the NIS. It is responsible for preparing the study documents (observation plan, electronic documentation system, etc.), the registration of the project in the relevant databases, the submission of the documents to the ethics committee on behalf of the scientific director and the quality assessment measures.

The documentation folders are distributed on the instructions of the Department of Medicine by employees of Sanofi-Aventis Deutschland GmbH. The Project Management prepares the observation plan and the patient documentation forms. The NIS Management coordinates the shipping, contract data, fees and the quality assurance measures. Sanofi-Aventis Deutschland GmbH is responsible for preparing the Data Management Plan (DMP, including the Data Validation Plan DVP) and analysis plan, the data input, data analysis, preparation of the final report and a summary of the results in English.

10. PERFORMANCE OF THE NIS AT THE STUDY SITE

10.1 Distribution of the documents

Each participating site will be provided with a folder containing the following documents by an employee of Sanofi-Aventis Deutschland GmbH at the beginning of the study:

- NIS contract (between Sanofi-Aventis Deutschland GmbH and the site)
- Results of ethics committee consultation
- Observation plan
- LEMTRADA® Summary of Product Characteristics and materials for the RMP
- Patient identification list (to be archived by the responsible physician)
- For each patient, 1 patient information brochure (for the patient) and 1 patient consent form (in duplicate, one for the patient and one for the physician). The physician must keep his/her copy of the patient consent form on file for 10 years.
- Documentation materials for 3 patients (patient questionnaires: questionnaires for assessing the severity of the disease, EuroQoL (EQ-5D), PRIMUS, WPAI, SDMT)
- 3 AE report forms per folder

10.2 Obtaining patient consent

Each patient to be documented will be informed by the treating physician about the objective and performance of the non-interventional, observational study, including the data collection. For patients prepared to participate, the consent is documented by the signature of the patient on the patient consent form. One copy remains with the patient

and the other with the physician. The patient will be informed that he/she may withdraw consent at any time without incurring any disadvantages. In addition, the patient is informed that the treatment with LEMTRADA® and the follow-up examinations as part of the follow-up observation can be performed by neurologists/physicians in various neurology departments and/or outpatient clinics, and the **documenting physician** will receive these data upon request.

10.3 Patient identification list

A patient identification list is to be maintained at each study site. It is the prerequisite for the pseudonymised questionnaire at the site to be able to be assigned to the individual patient (for example, in case of questions).

10.4 Completion of the patient documentation form

During the investigation period, the MSDS^{3D} documentation form containing the information mentioned in section 6 will be completed promptly after the outpatient examination.

The questionnaires provided for the treating physician are completed by the physician directly in the MSDS^{3D}.

The questionnaires intended for the patient will be provided as PDF files (printable version) and as a paper version. The questionnaires should be completed in black ball-point pen if at all possible. Free text may only be entered in the boxes provided.

At the participating sites the paper questionnaires completed by the patients are mailed to the contract research institution for data input and assessment.

The patients will be asked to fill out the EuroQoL (EQ-5D) and the PRIMUS for health-related quality of life, a questionnaire for evaluating the severity of the disease, the SDMT for evaluating attention and the WPAI for evaluating fitness for work. The maximum time allowed for completing these is 35 minutes.

10.5 Monitoring patient information and monitoring card

Each patient will receive a patient card and a monitoring card as a reminder for the necessary regular checks of blood and urine values, kidney and thyroid function (before the beginning of treatment, and after the beginning of treatment blood values and kidney function monthly, with thyroid function additionally every 3 months.).

Observation plan

The monitoring card will be handed out to the patient by the treating neurologist at the beginning of the study. Dates of laboratory follow-up with neurologist / family practitioner will be noted on the card. The cards will be viewed regularly by the neurologist to check whether the patient has followed the schedule for check-up visits. To remind the patient in the most effective way about the monthly monitoring, the MS team ("MS navigators") is available. This service is also available to the patient upon written request. Documents for this service are located under the "MS navigators" tab in the documentation folder.

Upon admission to this study the patient will receive an individual patient number, which can be entered onto the monitoring card. With reference to this individual patient number, the data sets in the MSDS^{3D} can be examined both by the physician responsible for the treatment (infusing physician/infusion centre) and the physician responsible for the follow-up examinations according to the RMP, as long as they are registered in the system. The documentation of the patient data can only be done by the documenting physician.

11. QUALITY ASSESSMENT

The non-interventional study will be established by employees of Sanofi-Aventis Deutschland GmbH in accordance with the VFA recommendations[18] for performing an NIS. In this process the participating physician will be informed about the goals, background and procedures of the non-interventional study. The employees and the project management of Sanofi-Aventis Deutschland GmbH will be available to answer questions.

By signing the contract the treating physician declares his consent to make all data available to the sponsor for checking. It is planned that quality assessment measures will be performed on site during the observation period at about 5% of the participating centres by comparing individual data from the electronic documentation forms (MSDS^{3D}) with the entries in the patient files (and vice-versa). The centres will be randomly selected.

Observation plan

12. APPLICATION FOR AND REGISTRATION OF THE NIS

This observational study will be announced according to § 67 (6) AMG (German Drugs Act) to the Paul Ehrlich Institute (PEI), the German Association of Statutory Health Insurance Physicians (KBV),the umbrella group Central Federal Association of Health Insurance Funds, as well as the Association of Private Health Insurance Funds e. V. (PKV).

In addition to the name of the preparation, the notice will include the place, time, objective and observation plan of the observational study. Participating physicians will be listed by name with complete address, physician number and mention of the fees actually paid to them (KBV, SpiBU, PKV).

The competent higher federal authorities will be sent a final report by e-mail within one year after completion of data collection.

13. DATA PROTECTION

13.1 Patient information and consent

The patients must be informed about participation in the TREAT-MS NIS and must have understood its content and significance. For this purpose the patients will be given the patient information leaflet. The patients must sign the respective informed consent statement and data protection declaration. One copy will remain with the physician and the patient will retain another copy.

13.2 Data protection

The electronic documentation form and the questionnaires completed by the patient are provided with a code number (pseudonymisation of the data). The name of the patient will only be recorded on the patient informed consent form, one copy of which will be given to the patient and one to the research physician, and on the patient identification list. The patient identification list, which makes it possible to link the study-related data to the patient, will remain in the practice.

The pseudonymised data is stored on the MSDS^{3D}-Study server of MedicalSyn GmbH Stuttgart. The analysis of the data will be performed by the evaluating contract research institution in compliance with the data protection provisions. The participating

patients will receive appropriate explanations in the patient information brochure and will consent to this procedure in writing on the patient informed consent form.

14. DATA MANAGEMENT AND STATISTICAL EVALUATION

14.1 Data Management

Details on data management, including data validation, will be described in a separate document, the Data Management Plan (DMP), including the Data Validation Plan (DVP).

14.2 Target parameters

The present prospective study will collect data on adult patients with relapsing-remitting MS being treated with LEMTRADA®:

Observation goals:

- Determining and assessing the implementation of the LEMTRADA® Risk Management Plan (RMP) in routine clinical practice (monitoring adherence)
- Fulfilment of the requirements arising from the RMP for early detection of suspected cases of newly occurring autoimmune diseases during LEMTRADA® treatment.
- Evaluation of the infusion phases and possible infusion reactions.
- Identifying and evaluating the patients with more than 2 treatment phases
- Benefits of treatment in subgroups of patients
- Determination of the EDSS over the period of observation
- Evaluation of patient satisfaction
- Description of patients' quality of life
- Description of cognition over the period of observation
- Description of ability to work over the period of observation
- Detection of exacerbations and their severity
- Detection of AESI (adverse events of special interest)
- General description of the use of LEMTRADA® under routine practice conditions

Observation plan

14.3 Justification of sample size

On the basis of 1600 LEMTRADA® patients, the fraction of patients with premature discontinuation of the RMP can be determined by a 95% confidence interval whose length does not exceed 5 percentage points. In subgroups containing at least 25% of the total random sample, this fraction can be determined by a 95% confidence interval whose length is less than 10 percentage points.
Undesirable events with an incidence of at least 0.00187 (1:534) will be observed with 95% certainty at least once in the random sample of 1600 LEMTRADA® patients.

14.4 Statistical evaluation

The statistical evaluation of all data recorded will be performed descriptively. On the basis of a previously established statistical analysis plan (SAP) drafted by the contract research institute Winicker Norimed GmbH and examined by Sanofi, the data will be evaluated and the results evaluated by tabular and graphical means. For the fraction of patients with premature discontinuation of the RMP, 95% confidence intervals were determined according to the method of Clopper and Pearson. The effect of subgroup membership on this discontinuation rate will be examined in logistical regressions.
In general, for continuous variables the number of patients, mean value, standard deviation, the number of patients, mean value, standard deviation, the five-number summary (minimum, lower quartile, median, upper quartile, maximum) and optionally additional suitable percentiles are determined for constant variables. For categorical variables, the absolute frequencies and percentage frequencies are indicated.
For mean values and estimated probabilities and, insofar as is reasonable for other parameters as well, 95% confidence intervals are determined. The evaluations will also be performed for subgroups defined in advance in the SAP. Depending on the number of subgroups established in the analysis plan, the confidence interval will be increased if necessary.
The evaluations of the questionnaires used, SDMT (attention), EQ-5D and PRIMUS (health-related quality of life), CGI-S (physician version)/ patient and WPAI questionnaires (assessment of ability to work) will be performed according to validated and published algorithms.
The statistical evaluations of the data are exploratory in nature.

On the basis of the tables and graphs, the Winicker Norimed GmbH contract research institute will prepare a final report and a summary of the results in English.

15. PUBLICATION

The results of this study will be published. This will take place in a well-respected, peer-reviewed medical journal. The publication(s) will be prepared based on the final report. The physicians participating in this study will be informed about the results of the investigation by the corresponding publication(s).

The authors named in publications may include all persons who have made a substantial contribution to (1) design, data collection or analysis, interpretation of data; (2) preparation of the manuscript or substantial intellectual comments on the manuscript, and (3) finalisation and approval of the final manuscript.

16. ARCHIVING

All relevant documents of the non-interventional study will be archived for at least 10 years. The participating physician will only store the patient identification list and the patient consent declaration, likewise for at least 10 years.

17. ADVERSE EVENTS

17.1 General

LEMTRADA® is a product under special observation, and therefore during the observation period it is fundamentally necessary to record and document adverse events, regardless of whether a correlation with LEMTRADA® is seen. The following adverse events must be documented as individual instances on the (S)AE form:

- Any adverse event that has a fatal outcome, is life-threatening by nature, or leads to hospitalisation
- Any adverse event found on the list in the appendix

In addition, all suspected cases of adverse drug effects are to be documented as individual cases on the (S)AE form, thus all adverse events in which the physician or

the patient sees a link to LEMTRADA® or another medicinal product from Sanofi, Sanofi-Aventis, Winthrop, Zentiva or Genzyme.

In the patient questionnaires, an adverse event should always be considered and documented on the (S)AE form if a deterioration in the patient's condition was noted (e.g., hospitalisation)).

The data documentation can, for example, be done by an MS nurse. The medical evaluation/validation of whether an adverse event is actually involved is an obligation of the treating physician, who can best assess the individual patient and his/her medical history (e.g., laboratory values classified as adverse events depending on their clinical relevance). For each reported adverse event, the treating physician should provide an assessment of whether there is any indication of a link to the product. He is also responsible for sending the information to Sanofi via the IT system.

For each reported case, the doctor should provide an assessment as to whether there is any indication of a link to the product.
Because the frequency with which MS relapses occur is an efficacy criterion in this non-interventional study, the occurrence of MS relapses is only documented additionally as an adverse event on the AE/SAE form if the relapses occur outside the usual course of the disease.
If a side effect occurs that is related to a medicinal product other than the Sanofi, this must be reported as stipulated in the reporting obligations of the German Physicians' Professional Code of Practice to the Drug Commission of the German Medical Association (AKdÄ), the Federal Institute for Drugs and Medical Devices (BfArM) or the respective pharmaceutical company. This information is not reported additionally to Sanofi.
Adverse events (AE/SAE) verified by the treating physician which occur within the observation period of this NIS must be reported immediately (but at the latest within 24 hours) to the pharmacovigilance (drug safety) unit of Sanofi-Aventis Deutschland GmbH (see below), regardless of whether or not a causal link to the use of **LEMTRADA®** is suspected.

Observation plan

17.2 Definition of terms

An **adverse event (AE)** is defined as any adverse and unexpected event in research subjects or users in a study or examination, regardless of whether there is a link to the research product. This includes any disease or injury or unfavourable clinical symptoms (including clinically relevant changes in laboratory test values) occurring or worsening after taking or using the medicinal product, regardless of whether there is presumed to be a causal link to the .medicinal product. (Section 3 of the German GCP Ordinance [GCP-V])

The observation period for detecting **adverse events** is defined as the time period between the first use of **LEMTRADA®** and 48 months after the patient's last infusion cycle that was documented within the framework of this observational study.

A **serious adverse event (SAE)** regardless of the dose and manifestation,

- is any event with a **fatal outcome** or immediately **life-threatening character** (life-threatening means that the patient is in immediate danger of losing his or her life, but not that the patient might have died if the event were more severe).
- any event that—without planning and unpredictably – requires **hospital admission** or prolongation of the hospital stay.
- any event that causes **persistent incapacity**, inability to work or substantial disruption of the patient's ability to conduct normal life functions (a significant disruption is present when the patient is substantially incapacitated by the event in his or her ability to manage normal activities of daily life).
- any event that corresponds to **congenital malformation** or another birth defect.
- events that require medical intervention to prevent **permanent injury**, a fatal outcome or **hospitalisation**.

Documentation of AE/SAE takes place in the LEMTRADA® module of the data sheet system MSDS^{3D}-TREAT-MS of MedicalSyn GmbH Stuttgart, which provides the database system on behalf of Carl Gustav Carus Management GmbH Dresden. The AE/SAE form is stored as both a paper-based form in the MSDS3D system and as an electronic Case Reporting Form (eCRF). AE/SAE reports recorded via the MSDS3D eCRF will be sent automatically by e-mail to the Sanofi-Aventis / Genzyme Pharmacovigilance Department. Hard copy documents must be FAXED to the

Observation plan

Pharmacovigilance Department at Sanofi-Aventis/Genzyme. The data are pseudonymised and can be traced back to the patient by the doctor upon enquiry from Pharmacovigilance via the contract number and patient identification list.

Adverse drug effects (UAW)

Adverse drug effects (side effects) of medications intended for use in humans are harmful and unintended reactions to the medication. This means that a causal link between the medication and the event at least cannot be ruled out. Adverse drug effects are basically independent of the appropriate use of the medicinal product. Therefore the definition of this term excludes consequences of, for example, overdosage, abuse, misuse, inappropriate use or administration errors.

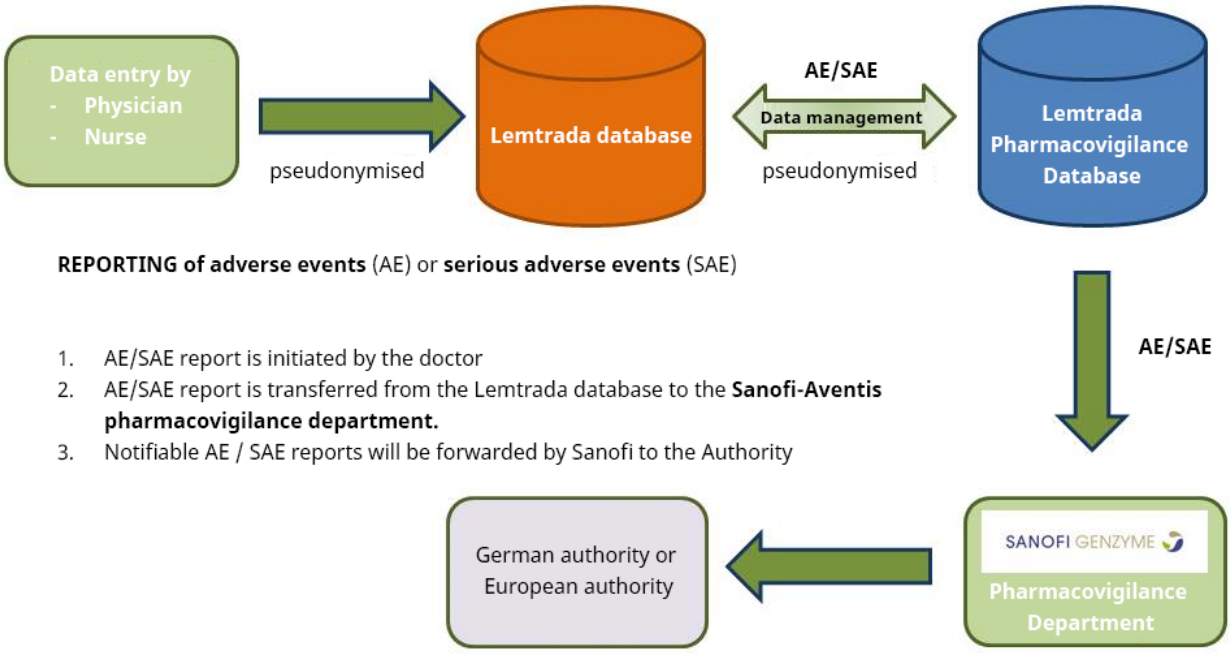


Fig.: Pharmacovigilance process TREAT-MS

Observation plan

Adverse drug effects / adverse events / serious adverse events are to be documented on the “AE/SAE reporting form” and transmitted immediately (but at the latest within 24 hours after notification) by fax of e-mail to the following locations:

Pharmacovigilance
Sanofi-Aventis Deutschland GmbH
Industriepark Höchst, Bldg K703
65926 Frankfurt am Main
Arzneimittelsicherheit@sanofi.com
Fax: 069 305 177 66
Call centre: 0180 222 2010 (0.06 €/call (German landline); max. 0.42 €/min (wireless mobile))

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19. ANNEX A: LIST OF ADVERSE EVENTS OF PARTICULAR MEDICAL SIGNIFICANCE

Pregnancy	
Symptomatic overdosage	
Malignant diseases	
Cervical dysplasia	
Other autoimmune diseases	
Infusion-related reactions	Symptom/Finding
	Anaphylactic reactions
Infections	Symptom/Finding
	Opportunistic infections
	Disseminated infections
Diseases of the blood and lymphatic system	Symptom/Finding
	Leukocytopenia
	Lymphocytopenia
	Thrombocytopaenia
	### ITP
	Agranulocytosis
	Anaemia
Liver diseases	Symptom/Finding
	Transaminase elevation
Nervous system disease	Symptom/Finding
	### PML
Kidney disease	Symptom/Finding
	Glomerulonephritis
	### Nephropathies, e.g., Goodpasture Syndrome

special attention

16 APPENDIX 4

List of used variables in TREAT-MS

Note: List may not be exclusive, is at high level, and does not provide the operation definitions.

Variable in TREAT-MS, used in this PASS	Timing of measurement, used in this PASS	Naming and use of the variable in this DUS PASS
Visit date	Each visit	Data collection for each objective
Date of infusion performed with 100 mL LEMTRADA solution	At date of the first LEMTRADA infusion of a course	Defining exposed patients, index dates, and the LEMTRADA courses
Sociodemographic information		
Birth year	Baseline	Patient characteristics
Gender		
Objective 1a: indication		
MS type (RRMS/ SPMS/ PPMS/ CIS/ undetermined)	Screening visit	MS type RRMS
Active RRMS (yes/no)	Baseline	Highly active disease
Number of relapses in the last 12 months and 24 months	Baseline	Relapses
Any prior MS treatment: therapy name with start and end date	Baseline	Prior DMTs
MRI • Was MRI performed? • With contrast agent? • Number of gadolinium-enhancing lesions	At the screening visit and/or at the day of the first LEMTRADA infusion	MRI status
Objective 1b: contraindications		
Pre-existing diseases* by name with start date	Baseline	All contraindications
Is there hypersensitivity to the active substance or any of the other ingredients?	Baseline	Hypersensitivity
Is there an infection with the HIV?	Baseline	HIV
Infection status with fields to report if a test was performed and if the results were positive for:	Baseline	Severe active infections

Variable in TREAT-MS, used in this PASS	Timing of measurement, used in this PASS	Naming and use of the variable in this DUS PASS
• HIV • Hepatitis B • Hepatitis C • HPV • JCV antibody status • Chest x-ray • TB		
Adverse events* • Name/description of adverse events • Adverse event start and stop date • Related to LEMTRADA	During of LEMTRADA infusion At each follow-up visit	Hypersensitivity Severe active infections
Objective 2a: monitoring prior to LEMTRADA		
Were the patient's vital signs checked during the infusion?	At date of the first LEMTRADA infusion of a course	HR, BP
Has a blood count performed (yes/no)	Baseline At date of the first LEMTRADA infusion of a course	FBC
GOT and GPT	Baseline At date of the first LEMTRADA infusion of a course	Transaminases
Clinical examination / thyroid state	Baseline At date of the first LEMTRADA infusion of a course	Thyroid function test
Serum creatinine	Baseline At date of the first LEMTRADA infusion of a course	Creatinine
Urine status	At date of the first LEMTRADA infusion of a course	Urinalysis
Objective 2a: monitoring during LEMTRADA		
Were the patient's vital signs checked during the infusion?	On each day of a LEMTRADA infusion	HR, BP
Objective 2b: long-term monitoring		
Blood count performed (yes/no)	At each follow-up visit	FBC
GOT and GPT	At each follow-up visit	Transaminases
Clinical examination / thyroid state	At each follow-up visit	Thyroid function test
Serum creatinine	At each follow-up visit	Creatinine

Variable in TREAT-MS, used in this PASS	Timing of measurement, used in this PASS	Naming and use of the variable in this DUS PASS
Urine status	At LEMTRADA infusion	Urinalysis

BP=blood pressure; CIS= clinically isolated syndrome; DMTs=disease modifying therapy; DUS=drug utilisation study; FBC=full blood count; GOT= glutamate oxaloacetate transaminase; GPT=glutamate pyruvate transaminase; HIV= human immunodeficiency virus; HPV=human papilloma virus; HR=heart rate; JPV=John Cunningham Virus; MRI=magnetic resonance imaging; MS=multiple sclerosis; PASS=post-authorisation safety study; PPMS=primary-progressive multiple sclerosis; RRMS=relapsing-remitting multiple sclerosis; SPMS=secondary-progressive multiple sclerosis; TB=tuberculosis.

*Pre-existing diseases and adverse events are coded with Medical Dictionary for Regulatory Activities (MedDRA) Lowest Level Term (LLT) codes. The dates of all variables are available through the visit date.

17 APPENDIX 5

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 (https://www.encepp.eu/standards_and_guidances/checkListProtocols.shtml), 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 DRUG UTILISATION AND SAFETY MONITORING PATTERNS FOR LEMTRADA (ALEMTUZUMAB)

EU PAS Register® number: EUPAS42540
Study reference number (if applicable): DUT0008 and VV-PV-0404767

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				All in section 4 & 6 & 12
1.1.1 Start of data collection[7]	☒	☐	☐	
1.1.2 End of data collection[8]	☒	☐	☐	

[7] 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.
[8] Date from which the analytical dataset is completely available.

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
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:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	7 & 8 & 9
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)	☒	☐	☐	
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 Sections 7.1 and 7.2 2.1.2 in Sections 8.1 and 8.2 2.1.3 in Sections 9.2, 9.2.2 and 9.11 2.1.4 and 2.1.5 in Section 8 and 9.6

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
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	9.1, 9.2 & 9.5
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.8.1 & 9.8.2
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))	☐	☒	☐	
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:

Rates of occurrence or measures of association are not relevant for this study. As outlined in section 9.8 we will report proportions of patients with the correct indication, without contraindications and with cardiac monitoring prior to and during LEMTRADA infusion. Adherence at the patient level will be measured for objective 2b.

Section 4: Source and study populations		**Yes**	**No**	**N/A**	**Section Number**
4.1	Is the source population described?	☒	☐	☐	9.2, 9.2.2 & 9.11
4.2	Is the planned study population defined in terms of:				Section 9 See notes
	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 in each data source included

Comments:

4.2.1 in Section 9.2.1 4.2.2 in Section 9.2.2 4.2.3 in Section 9.5 4.2.4 in Section 7.1 and 9.2.2 4.2.5 in Section 9.3

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
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?	☐	☒	☐	
5.4	Is intensity of exposure addressed? (e.g., dose, duration)	☐	☒	☐	
5.5	Is exposure categorised based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6	Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement		**Yes**	**No**	**N/A**	**Section Number**
6.1	Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	8.1, 8.2, 9.8.1 & 9.8.2

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	9.3, Table 2 and Appendix 1 for Belgian data
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)	☒	☐	☐	See comments
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)	☒	☐	☐	Relevant if adherence to monitoring is of interest to HTA

Comments:

This is a drug utilisation study: "outcomes" as laid out in table 1 are not typical of epidemiological studies. Proxy definitions for indication and contraindication will be used in Belgian data. A discussion of validity and their definitions is provided in Table 2 and Appendix 1.

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g.,confounding by indication)	☐	☐	☒	See notes
7.2 Does the protocol address selection bias? (e.g., healthy user/adherer bias)	☒	☐	☐	9.11 See notes
7.3 Does the protocol address information bias? (e.g., misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.11 See notes

Comments:

7.1 This is a descriptive study so traditional confounding is not examined (i.e. imbalance on one variable between two study groups). Instead, the results will be stratified on key variables eg age, sex and calendar year. This is outlined in Section 9.8.4.

7.2 The definition of selection bias in ENCePP guidelines is "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". We have addressed the generalizability of the population in section 9.11. Bias such as healthy user bias or similar is not relevant for this study given that there is no comparative arm.

7.3 Information bias: misclassification is discussed in limitations section 9.11.

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, subgroup analyses, anticipated direction of effect)	☒	☐	☐	9.8.4 See comments

Comments:

Section 9.8.4 outlines various subgroup analyses that will be run to gain an understanding of how utilisation and monitoring will occur according to various strata e.g., age, sex, country, number of courses. The protocol does not use language pertaining to "effect modification" to describe these analyses.

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, 9.5, and Tables 3 – 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, 9.5, and Tables 3 – 4
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.5
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)	☒	☐	☐	9.5.1 – 9.5.4
9.2.2 Outcomes? (e.g., date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.5.1 – 9.5.4 and Tables 3 – 4
9.2.3 Covariates and other characteristics? (e.g., age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	9.5.1 – 9.5.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g., WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Tables 3 – 4
9.3.2 Outcomes? (e.g., International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Tables 3 – 4
9.3.3 Covariates and other characteristics?	☐	☐	☒	See notes
9.4 Is a linkage method between data sources described? (e.g., based on a unique identifier or other)	☒	☐	☐	9.5.1 – 9.5.4 and Tables 3 – 4

Comments:

9.3.3 Coding for covariates is not required because age and sex are not typically “coded”. All other covariates for stratified analyses (9.8.4) will be derived variables.

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	9.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.6
10.3 Are descriptive analyses included?	☒	☐	☐	9.8
10.4 Are stratified analyses included?	☒	☐	☐	9.8.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.8.4 See notes

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
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
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.8.4

Comments:

10.5 This is a descriptive study so traditional confounding is not examined (i.e. imbalance on one variable between two study groups). Instead, the results will be stratified on key variables eg age, sex and calendar year. This is outlined in Section 9.8.4

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 information technology (IT) environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.7 & 9.10
11.2 Are methods of quality assurance described?	☒	☐	☐	9.10
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3.4 and 12

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	9.11 See notes
12.1.2 Information bias?	☒	☐	☐	
12.1.3 Residual/unmeasured confounding? (e.g., anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☐	☒	☐	
12.2 Does the protocol discuss study feasibility? (e.g., study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	9.9

Comments:

12.1.3 This is a descriptive study so traditional confounding is not examined (i.e. imbalance on one variable between two study groups). Instead, the results will be stratified on key variables eg age, sex and calendar year. This is outlined in Section 9.8.4

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	9.4

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

Comments:

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

18 APPENDIX 6

List of stand-alone documents

None