NON-INTERVENTIONAL POST AUTHORIZATION 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 1.4: May 20 2021

The Study will be conducted by [redacted]

NAMES AND ADDRESSES OF

STUDY MANAGEMENT	Name: Address: Tel: E-mail:	[redacted]
MAH EPIDEMIOLOGY REPRESENTATIVE	Name: Address: Tel: E-mail:	[redacted]
MAH REPRESENTATIVE PHARMACOVIGILANCE	Name: Address: Tel: Email	[redacted]

PASS Information

Title	A non-interventional post-authorisation study to investigate drug utilization and safety monitoring patterns for Lemtrada (alemtuzumab)
Protocol version identifier	Version 1.4
Date of last version of protocol	May 20 2021
EU PAS register number	Study will be registered on receipt of PRAC approval
Active substance	Alemtuzumab (GZ402673): ATC L04AA34
Medicinal product	Lemtrada
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003718
Marketing authorization holder(s)	Sanofi Belgium
Joint PASS	NO

Research question and objectives	The overall goal of this study is to assess compliance with risk minimization 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 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, serum creatinine, serum transaminases, urinalysis with microscopy (all monthly) and thyroid function (three-monthly) as specified in the newly revised EU SmPC
Country(-ies) of study	Denmark, UK, Germany, Belgium
Authors	[redacted]

Marketing authorization 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]

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2. LIST OF ABBREVIATIONS

AIM-IHA	L'Agence Intermutualiste - Het InterMutualistisch Agentschap (Belgian Social Security database)
BMSD network	Big MS Data Network
BP	Blood Pressure
CI	Confidence Intervals
ECG	Electrocardiogram
EMA	European Medicines Agency
EU	European Union
FBC	Full Blood Count
HR	Heart rate
MAH	Marketing Authorization Holder
MS	Multiple Sclerosis
MSDS-3D	Multiple Sclerosis Documentation System-3D
OP	Operating Protocol
PI	Principal Investigator
PRAC	Pharmacovigilance Risk Assessment Committee
SmPC	Summary of Product Characteristics

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 with the Study Management.
5. To organise training of staff in accordance with the Study Management.
6. To produce the working databases and analysis databases according to procedures outlined in operating protocols.
7. To participate in the meetings and other activities necessary for the good conduct of the study.
8. To participate in the feasibility analysis and review of final study reports.

List of database collaborators at protocol stage:

Denmark	The Danish Multiple Sclerosis Registry Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark PI: Prof Melinda Magyari
Belgium	AIM-IMA (L'Agence Intermutualiste - Het InterMutualistisch Agentschap) Av. de Tervueren, 188/A, B-1150 Brussels, www.aim-ima.be Contact: Birgiet Gielen
UK	University Hospital of Wales, 4th Floor, B-C Link Corridor, Main Hospital Building, Heath Park, Cardiff, CF14 4XN PI: Prof Neil Robertson

	Cambridge University Hospitals, Department of Clinical Neurosciences, University of Cambridge, England PI: Prof Alasdair Coles Derriford Hospital/ Plymouth University, Room N13, ITTC Building, Plymouth Science Park, Davy Road, PL68BX PI: Prof Jeremy Hobart
Germany	MS Center Dresden, Center of Clinical Neuroscience, University Hospital Carl Gustav Carus, Dresden University of Technology, Fetscherstr. 74, 01307 Dresden, Germany PI: Prof Tjalf Ziemssen

3.2 RESPONSIBLITIES OF THE STUDY MANAGEMENT

1. To write operating protocols 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 Authorization 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.

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 1.4, May 20 2021

Authors: [redacted]

Title: A non-interventional post-authorization safety study to investigate drug utilization 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 utilization 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 (Jan 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 for full blood counts, urinalysis with microscopy, serum creatinine, serum transaminases (all monthly) and thyroid function (three-monthly) 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 (Jan 2020 and subsequent versions).

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

Data Sources:
MS registry data from Denmark, administrative data from Belgium, hospital chart data from the UK and Germany.

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 is planned in 2021 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:

- Are prescribed in accordance with the newly revised indication (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).
- Are a new or continuing user and do not have any contraindications at time of course initiation post EU SmPC change (numerator = number of courses without contraindications, denominator = all LEMTRADA courses post EU SmPC change)
- Receive advised cardiac monitoring (ECG/HR/BP) and blood testing prior to, HR/BP during, and platelet testing during LEMTRADA course (numerator = number of courses with each unique test prior to and during infusion, denominator = all LEMTRADA courses post EU SmPC change)

Additionally, percentage adherence to each test will be calculated, at the patient level, to monthly monitoring for up to 48 months since last infusion for full blood counts, serum creatinine, serum transaminases and urinalysis with microscopy, and tri-monthly monitoring for thyroid function (numerator = number of specific tests received, denominator = number of testing periods required).

Milestones

- Constitution of working database structure using data from 2020-2021 **Q2 2021**
- Report on feasibility analysis **Q3 2021**
- Annual Interim progress report **Q4 2021**
- Annual interim progress report **Q4 2022**
- Annual interim progress report **Q4 2023**
- Constitution of final analysis database structure using data from 2020 – 2024 **Q1 2024**
- Final report of study results **Q3 2024**

5 AMENDMENTS AND UPDATES

None

6 MILESTONES

Milestone	Planned date
Constitution of working database structure using data from 2020 - 2021	Q2 2021
Report on feasibility analysis	Q3 2021
Annual interim progress report 2021	Q4 2021
Annual interim progress report 2022	Q4 2022
Annual interim progress report 2023	Q4 2023
Constitution of final analysis database structure using data from 2020-2024	Q1 2024
Final report of study results	Q3 2024

7 RATIONALE AND BACKGROUND

7.1 BACKGROUND

LEMTRADA (alemtuzumab) is a recombinant humanized 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. LEMTRADA has been demonstrated to be a highly efficacious agent in the treatment of RRMS with data from clinical trials demonstrating reduced relapse rates, reduced disability, reduced brain volume loss and improved EDSS scores.[1-3] 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 events. PRAC advised changes to the EU 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 relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.

The newly revised list of contraindications is as follows:

- Hypersensitivity to alemtuzumab or any of the excipients
- 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 autoimmune diseases (besides 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 three monthly post infusion, while serum transaminases have been added to full blood counts (FBC), serum creatinine, urinalysis with microscopy, 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 utilization 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 utilization 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 OBJECTIVE

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 January 2020

1b) to measure the proportion of LEMTRADA courses, first or continuing, that are not contraindicated after implementation of revised SmPC 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 SmPC

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

9 RESEARCH METHODS

9.1 STUDY DESIGN

This 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 one overall master protocol for the entire study, will be applied to each data source individually. Then, aggregate results from each data source for objectives one and two will be summarized using tables and figures.[4] 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.[5-7] The approach is advantageous for three reasons. First, LEMTRADA utilization is expected to be low (see Section 9.10), 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 organization of health systems, national prescribing guidelines, differences in the delivery of care.[8] Third, the approach circumvents concerns about combining individual patient data from differing jurisdictions, which may breach data privacy laws.[9]

The primary objective (1a and 1b) will assess patients' indications and contraindications using all available baseline data on the index date. For objective 1a, the index date is the date that patients initiate their first course of LEMTRADA after implementation of the revised EU SmPC January 2020 (first ever use). For objective 1b, the index date is the date of LEMTRADA course post implementation of the newly revised SmPC for both new and continuing use.

The rationale for including first ever users to address adherence to the indication 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 on the basis of 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 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 index date. For objective 1b the contraindications will be measured at one point in time for each patient on the index date. However, a patient may have more than one index date requiring a repeated measurement of contraindications at each infusion after the SmPC change in 2020.

Objective 2a will assess implementation of infusion-related monitoring for all courses (new or continuing). On the index date, i.e. the date of LEMTRADA course, post the newly revised EU SmPC, patient data will be assessed for monitoring prior to infusion course. From the index date onwards, patients will be followed to assess whether recommended monitoring occurred during the course.

Objective 2b will assess the implementation of long-term safety monitoring for all patients (new or continuing). On the index date, i.e. the date of LEMTRADA course, post the newly revised EU SmPC, patients will be followed to assess whether monthly and tri-monthly monitoring occurred thereafter. Patients whose prior courses require post-infusion monitoring after the EU SmPC change will also be included.

The study design for objective 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.

9.2 SETTING

Data from four separate data sources will be used: Denmark, Belgium, the UK and Germany. Patients will be treated in routine care and will not receive any additional monitoring/intervention due to this study.

9.2.1 Study duration

Prescribing patterns and safety monitoring in data accrued from Jan 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 objectives 1a this will include patients receiving a first ever course of LEMTRADA. For all other objectives 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. 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 (Denmark and Belgium), all patients must have at least fifteen months look back data prior to cohort entry date 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

We will use two data sources in which patient consent will be required; patient charts from Germany and the UK. The process of consenting patients to the study will follow local procedures and local ethics guidelines. Patients will be excluded if they refuse to consent to the study (Section 10).

9.3 VARIABLES

Exposure and cohort entry: the exposure is an infusion of LEMTRADA. Information on LEMTRADA exposure will be extracted based on ATC code (L04AA34) in the Danish MS register and CNK codes in Belgian data. From medical chart data, notes on drugs prescribed will be used to measure the exposure. The index date will be defined as the date of LEMTRADA course (starting day of infusion course), 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 in at least fifteen months look back data (or physician recorded new use from hospital chart data). For all other objectives, patients will be included if they are a new or a continuing user. Continuing use will be defined as having had previous courses of LEMTRADA in the fifteen month (minimum) look back period and prior to new label, or physician record of nth course in medical chart data.

Outcome variables: the definitions of outcome variables in this study are laid out 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 relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI

or a significant increase in T2 lesion load as compared to a previous recent MRI.[19] In Belgian data, information on previous DMTs and relapse [20] 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 **Table 2** and **Appendix 1** for details.

End of follow-up: patients will be followed until the end of study (March 2024), end of data in each data source or death/emigration as recorded in each data source, whichever occurs earliest. In medical chart data from UK and Germany end of follow-up is measured through recording of death or moving out of the area and this is ascertained through active tracing procedures in each data source. In Belgian and Danish data sources, dates of death/emigration are available through linkage or updates from civil registry systems.

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

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

	Type of data	Indication	Contraindication	Notes
Denmark	MS registry linked to 1) national patient record 2) laboratory monitoring database	Yes Data on previous treatments, MRI and relapse history available from MS registry data	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 autoimmune diseases (besides MS)	Completeness of linkage – 100% Contraindications taken from linked data. • ICD-10 coding • ATC codes for dispensed prescriptions at the pharmacy or SKS codes for treatments at the hospital
Belgium	Administrative health data/insurance claims	Yes – a proxy for part 1 of indication[1]. See notes.	Hypersensitivity to alemtuzumab or excipients HIV	Proxy definition for part 1 of indication (See **Table 2** and Appendix 1)

[1] *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 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 autoimmune diseases (besides MS)	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)
UK Data for Plymouth and Cardiff	Patient charts	Yes Data on previous treatments, MRI and relapse history available	Hypersensitivity to alemtuzumab or excipients 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	Data on HIV is not required to be declared by patients.

			Known coagulopathy, on anti-platelet or anti-coagulant therapy	
			Other concomitant autoimmune diseases (besides MS)	
Germany	Patient charts	Yes Data on previous treatments, MRI and relapse history available	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 autoimmune diseases (besides MS)	

Table 1b - Feasibility of each data source in meeting objectives 2a (monitoring prior to and during infusion) and 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
Denmark	MS registry linked to 1) national patient record 2) laboratory monitoring database (LABKA)	ECG Heart Rate Blood Pressure FBC Serum creatinine Serum transaminase Thyroid Function Urinalysis with microscopy	Heart Rate Blood Pressure Platelets (Days 3 and 5)	FBC (monthly) Serum creatinine (monthly) Serum transaminase (monthly) Thyroid Function (tri-monthly) Urinalyis with microscopy (monthly)	Completeness of relevant linkage – 78% Data on thyroid function testing 100% complete. Data on ECG, HR and BP prior to and during infusion are not available. In LABKA: testing information is recorded in a uniform way according to the international NPU (Nomenclature, Properties and Units) coding system. The NPU code is the unique identification number for each single investigation. The NPU coding system provides a terminology for identification of clinical laboratory test values following the international recommendations for efficient electronic communication in clinical laboratories, and ensures that names and units are shown in a uniform manner.
Belgium	Administrative health data	ECG Heart Rate Blood Pressure FBC Serum creatinine Serum transaminase	Heart Rate Blood Pressure Platelets (Days 3 and 5)	FBC (monthly) Serum creatinine (monthly) Serum transaminase (monthly) Thyroid Function (tri-monthly) Urinalysis with microscopy (monthly)	Data on ECG prior to infusion is available. Data on HR and BP prior to and during infusion not available separately, but are available as “cardio-monitoring” 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.

		Thyroid Function Urinalysis with microscopy			
UK	Patient charts	ECG Heart Rate Blood Pressure FBC Serum creatinine Serum transaminase Thyroid Function Urinalysis with microscopy	Heart Rate Blood Pressure Platelets (Days 3 and 5)	FBC (monthly) Serum creatinine (monthly) Serum transaminase (monthly) Thyroid Function (tri-monthly) Urinalysis with microscopy (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.
Germany	Patient charts	ECG Heart Rate Blood Pressure FBC Serum creatinine Serum transaminase Thyroid Function	Heart Rate Blood Pressure Platelets (Days 3 and 5)	FBC (monthly) Serum creatinine (monthly) Serum transaminase (monthly) Thyroid Function (tri-monthly) Urinalysis with microscopy (monthly)	Data are obtained from patient charts and inputted into MSDS-3D. 85-100% complete

Table 2 - Core risk minimization measures: indication, contraindication and monitoring

Objective	*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 disease modifying therapy (DMT) or Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	Data on relapses, prior medication history and MRI findings are available in the Danish, 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.[20] 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.	Contraindications will be gathered from data recorded in medical charts in UK and Germany. In Denmark, data will be gathered from the linked National Patient Registry relying on ICD-10 codes and medications outlined below.

	5. History of arterial dissection of the cervicocephalic arteries. 6. History of stroke. 7. History of angina pectoris or myocardial infarction. 8. Known coagulopathy, on anti-platelet or anti-coagulant therapy. 9. Other concomitant autoimmune diseases (besides MS)	In Belgian data, proxy definitions will be required for measurable contraindications. These are outlined in **Appendix 1.** 1. Not measurable in Danish/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 oral and/or IV antibiotic/antiviral/antifungal prescribed during stay (ATC codes for drugs provided in SAP) 4. Not measurable in Danish/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 analogs (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 autoimmune disease: please see rationale for list in attached **Appendix 2.**
2a Monitoring if treated with Lemtrada after new label	***Prior to Infusion*** Baseline ECG, vital signs including heart rate (HR) and blood pressure (BP) Perform laboratory tests (full blood count (FBC) with differential, serum transaminases, serum creatinine, test of thyroid function and urinalysis with microscopy). ***During Infusion*** Heart rate 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, 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 the index date, for each course. ***During infusion*** HR and BP measured separately on each day of course (index+1 onwards). Platelets measured on day 3 and day 5 of the first course and day 3 of any subsequent course.

	Post-Infusion Monthly: Full blood count, serum transaminases, serum creatinine and urinalysis with microscopy Three-monthly: Thyroid function tests.	***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±15days Evidence of three-monthly monitoring defined as: Evidence that a thyroid function test is carried out within the designated testing period e.g., index date +90 days±30days

9.4 DATA SOURCES OVERVIEW

This study relies on the use of routine care data from the national Danish MS registry and administrative data from a national Belgian data source. Chart review in the UK and Germany will also 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 quality data or a history of LEMTRADA research[2, 10]; and 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 **Tables 1a and 1b.**

We investigated the use of MS registry data *via* the Big MS Data network, and also other independent channels, for example 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, for example EUReMS. We include data from some of the registries included in EUReMS e.g., Denmark, the UK, and Germany. Other countries included in EUReMS were not appropriate for reasons discussed above e.g., small numbers of exposed patients (Sweden, Czech Republic) or absence of linked data (UK registry).

9.4.1 Secondary Data: Danish MS Registry

The Danish MS Treatment Register (DMSTR) is a national patient registry, established in 1996.[11] The major strength of the DMSTR is that it is nationally complete. It contains data on demographics, treatments prescribed, identifiable by ATC code and date of prescribing and basic clinical information. It collects on-treatment follow-up data on relapses, progression (EDSS) and side effects during treatment. As patients are identified with a unique national personal identifier, it is possible to link data from the DMSTR with external registries, including the national patient registry which includes hospital diagnoses, dispensing data and the national civil status registry, collecting immigration/emigration data and vital statistics.[12]Clinical data recorded in the MS registry will give data relevant to the indication. Data from linked patient registries will give information on comorbidities/contraindications and laboratory monitoring. Data on thyroid function is expected to be complete in the national patient registry. Data on the remaining blood tests will be extracted *via* a linkage to the Clinical Laboratory Information System (LABKA).[13] This is a repository for laboratory testing data and holds data on more than 1700 different types of tests. Testing information is recorded in a uniform way according to the international NPU (Nomenclature, Properties and Units) coding system. The NPU code is the unique identification number for each single investigation. The NPU coding system provides a terminology for identification of clinical laboratory test values following the international recommendations for efficient electronic communication in clinical laboratories, and ensures that names and units are shown in a uniform manner.[13] Our contacts at the Danish MS registry estimate that linkage to

the LABKA database is available for 78% of MS registry patients.[14] Within each of the linked data sources, data on heart rate, blood pressure and electrocardiograph are not recorded.

9.4.2 Secondary Data: Belgian AIM-IMA database

Since 2008, the four 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.[15] 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 event that is 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.[16]

9.4.3 Chart review: Germany MSDS-3D

Primary data collection will be carried out by a network of neurological centers contributing to the Multiple Sclerosis Documentation System (MSDS-3D) software system in Germany.[17] The MSDS-3D was established in 2010. It is a tool that facilitates collection of demographic data, a structured history, clinical progress and treatment details, inclusive of LEMTRADA prescribing and date of prescription, in patients with MS. Additional primary data collection can be implemented, and data are entered according to the study protocol. The recording of all study variables is mandatory by the contributing physician ensuring high data quality and completeness. Anonymity and the data protection are guaranteed.[18] The Multiple Sclerosis Documentation System (MSDS-3D) software is currently used to collect data for TREAT-MS, a single-arm observational safety study for LEMTRADA.[10] Data on date of death/emigration are collectable in MSDS-3D. These data are collected via active tracing of patients as part of routine care and with additional checks for completion of the study.

9.4.4 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.

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, tests ordered from primary care will be recorded in a database of tests results maintained by iSoft. In Wales, there is a digital patient record where all patients test results, regardless of whether they have been ordered from primary or secondary care, are stored and data can be readily accessed. 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. Aggregate results for the collaboration will then be sent to the Study Management for combination with data from other sources.

9.5 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 optimize precision around calculated proportions to and 2) to provide interpretable utilization patterns in the countries with most exposed patients.

We will include data from four countries. Within each country we anticipate variable numbers of patients treated with LEMTRADA during the study period, ranging from 5 newly treated patients to 53 newly treated patients and ranging from 6 continuing users to 74 continuing users **(Table 2 in response to reviewers document dated November 30th 2020)**. Examples of 95% CI around sample proportions are given in **Table 3.**

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 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.

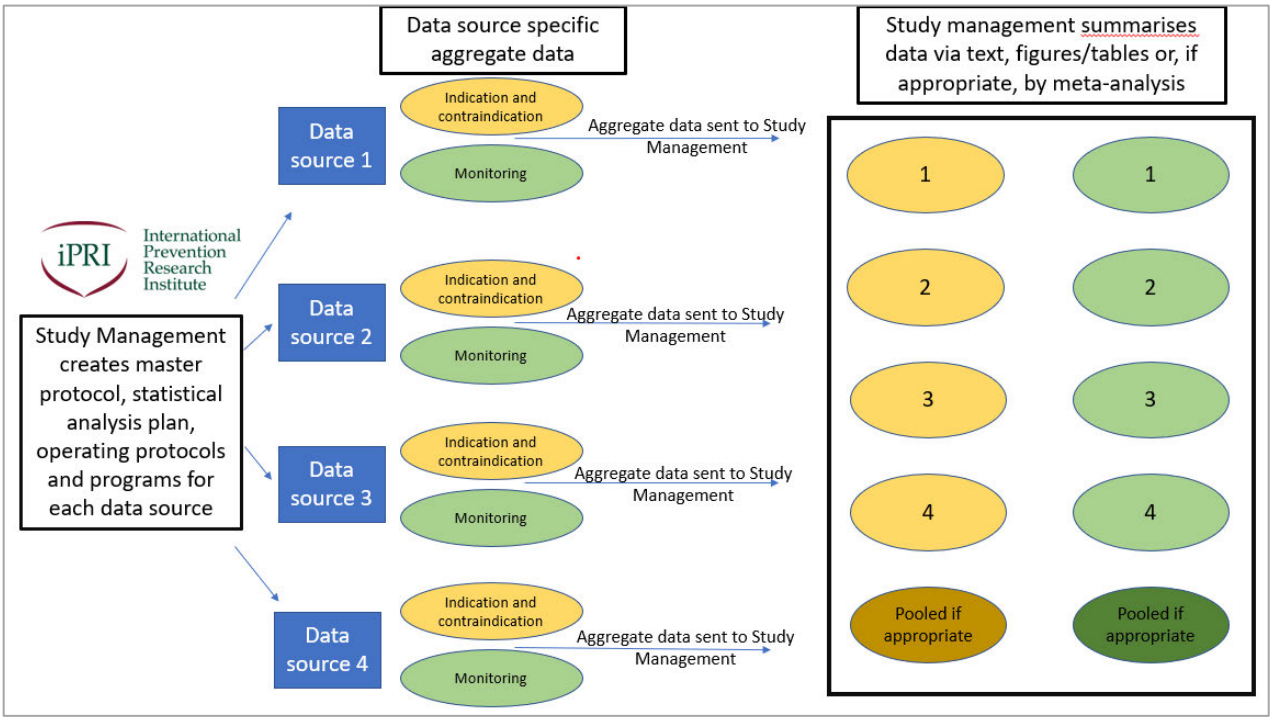
The above sample sizes are anticipatory and depend on utilization of LEMTRADA from 2020 onwards. We expect that the number of patients exposed to LEMTRADA after the Article 20 procedure will be low (as presented in Table 2 response to reviewers document dated November 30th 2020)**.** This will occur for two reasons: 1) the restricted indication post Article 20 procedure and 2) the Covid-19 pandemic which will reduce utilization due to reduced hospital resources and concerns about immunosuppression. Please see Section 9.8 Feasibility Analysis for further discussion.

9.6 DATA MANAGEMENT

The Study Management will coordinate the development of the statistical analysis plan, the local operating protocols (OP) and the programs 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 - A diagrammatic representation of study coordination by the study management and data flow.



9.6.1 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 (see milestones).

9.6.2 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 one master protocol, amended to accommodate local data with four operating protocols (OP). 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 summarized by using tables and figures (see Section 9.7.3). If heterogeneity allows, results may be combined quantitatively using a meta-analytic approach (see details in Section 9.7.3).

9.7 DATA ANALYSIS

9.7.1 Primary Analysis

Analysis approach:

We will use data from four separate data sources. A local OP, derived from a master protocol, will be applied to each data source individually. Then, aggregate results from each data source for objectives 1 and 2 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 9.7.3)

Objective 1a and 1b:

On the index date, defined as date of first ever LEMTRADA course after the EU SmPC change in January 2020, the proportion prescribed in accordance with the newly revised indication will be calculated as follows

- numerator = number of patients with revised indication at the index date
- denominator = number of patients with a first ever course of LEMTRADA in the study period
- See Table 3 for example data and precision.

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
- See Table 3 for example data and precision.
- 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 without a contraindication. The denominator will be number of patients receiving a LEMTRADA course in the study period.

Table 3 - 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)

*Example data only. 95% CI 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.

9.7.2 Secondary analysis

Objective 2a: Cohort entry and follow-up:

The index date will be defined as the date of LEMTRADA course, 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. 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, test of thyroid function and urinalysis with microscopy (all separately) between the index date and 30-day period prior to index date
    - Denominator = number of courses in study period
    - See table 4 for example table shells
    - Proportions will be stratified on new and continuing use, and course number.

Thirty 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.

Between the index date +1 and index date + 5 days, 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
    - See table 5 for example table shells
    - Proportions will be stratified on new and continuing use, and course number.

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 4 - Percentage adherence to monitoring prior to infusion course in each data source

	N	ECG	Heart Rate	Blood Pressure	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%
Denmark	X	n/a	n/a	n/a	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

Table 5 - Percentage adherence to monitoring during infusion course in each data source

	N	Heart Rate	Blood Pressure	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%
Denmark	X	n/a	n/a	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.

Objective 2b: Cohort entry and follow-up

From the index date, patients will be followed forwards so that the following percentage adherence at the patient level 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 +30days ±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 over all patients will be presented in each data source (Table 6 for example table shells).
- Percentage adherence to three monthly thyroid monitoring e.g., the number of tests carried out within designated testing periods (e.g., index +90days ±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 over all patients will be presented in each data source (Table 6 for example table shells)

To verify that the designated testing periods (e.g. ±15 days for monthly tests and ±30 days for three-monthly tests) are appropriate, the distribution of days around the intended testing day will be documented and reported. To accommodate potential changes in testing behaviour over time, and the large number of testing periods in this study, a number of testing periods will be chosen and the distribution of tests around that time presented for example, the example, tests at 1, 6, 12, 24, 36 and 48 months.

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 receipt of another LEMTRADA course, the end of study (March 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 i.e. continuing users, follow-up for adherence to monitoring will begin from SmPC change (January 2020) onwards, anchored on the original index date.

Table 6 - Percentage adherence to long term monitoring after infusion in each data source

		Monthly					Tri-monthly
	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%
Denmark	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

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 tables 3-6.

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 tri-monthly testing. 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. **Table 7** below demonstrates how a 7-day

tolerance window for monthly testing is a) not sensitive towards ranges of non-adherence and b) not accommodating of minor deviations from a monthly testing schedule.

Table 7 - A demonstration of 7-day and 15-day tolerance windows on calculating adherence to monthly monitoring in 7 potential real-world scenarios

Scenario	30±7 days from index date	30±15 days from index date
1. Adherent: tests are made every 1st of the month	19/36 tests = 53%	35/36 tests = 97%
2. Adherent: tests are made every 30 days from index date	35/36 = 97%	35/36 = 97%
3. Adherent: tests are made every 28 days from index date	17/36 = 47%	35/36 = 97%
4. Mostly adherent: tests are made every 31 days from index date	19/36 = 53%	34/36 = 94%
5. Mostly adherent: 1st test delayed by 15 days from index date subsequent tests are made every 30 days from first test	0/36 = 0%	35/36 = 97%
6. Non-adherent: tests are made 45 days from index date	11/36 = 31%	23/36 = 64 %
7. Non-adherent: tests are made 90 days from index date	11/36 = 31%	11/36 = 31%

Based on a hypothetical patient who receives first course on 1st Jan 2021 and is followed until 10th Dec 2023. Patient should be receiving monthly testing.

Examining scenarios 6 and 7: the 7-day tolerance window provides the same adherence estimates for a patient receiving one test every 45 days and a patient receiving one test every 3 months. Therefore, the 7-day tolerance window is not sensitive to ranges of non-adherence. In comparison, a tolerance window of 15 days correctly identifies the patient with one test every three months as having worse adherence to monitoring than the patient with testing every 45 days.

On the other hand, if a patient receives their monthly testing every 28 days, using a 7-day tolerance window would suggest that the patient is only adherent approximately half of the time, even though they are tested every month. Similarly, if a patient received their monthly testing every 31 days, a 7-day tolerance window would suggest that the patient is adherent approximately half of the time. If a patient delays their first testing date for example due to a vacation or other real life event such as a bereavement, and then all future testing is anchored on this new test date, the analysis using a 7 day tolerance window would never demonstrate any adherence to monitoring – even though the patient is tested regularly. In contrast, the 15-day tolerance window more accurately captures whether the patient is adherent to the monitoring schedule taking into account deviations that are likely to happen in routine care.
Based on this explanation, the main analysis will use a 15-day tolerance window for monthly testing and a 30-day tolerance window for tri-monthly testing. Seven-day and 15-day tolerance windows will be assessed in a sensitivity analysis with the above caveats on interpretation.

9.7.3 Combination of results

All data source specific results will be summarized using tables and figures. The Synthesis without meta-analysis (SWiM) in systematic reviews: reporting guideline (SWiM) to guide this approach to summarizing results will be used.[4]

Heterogeneity is expected for various reasons. First, based on knowledge that the use of HE-DMT is varied in Europe.[8] 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 by examining the proportions achieved in each data source and examining whether the confidence limits around proportions overlap. The I^2 test can be used to formally test for heterogeneity.[21] 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.[22, 23] If a meta-analysis is reported, guidance will be provided on interpretation of the results in the presence of heterogeneity.

9.7.4 Subgroup/stratified 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 index date year
- 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 (eg first, second, third etc).
- For objective 1b analyses will be stratified by individual contraindications, or grouped by organ/system class.
- Seven-day and 15-day tolerance windows for monthly and tri-monthly testing respectively.

9.8 FEASIBILITY ANALYSIS

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

The MAH will submit the results of a feasibility analysis in Q3 2021. The rationale for submitting a full feasibility analysis at this timepoint is that legal and administrative procedures must be put

in place to facilitate access to all data sources. Thereafter, quality checks must be applied, working databases must be established and then descriptive analyses can be run. See Appendix 3 for a Gantt chart that outlines the timeline for the full feasibility analysis. The purpose of the full feasibility analysis is twofold. First, to reflect numbers exposed to LEMTRADA in 2020 and the first half of 2021. The ability of the study to generate interpretable patterns will depend on the number of patients exposed to LEMTRADA post 2020. Second, to understand fully how each core variable can be practically/operationally measured in each data source and how definitions of each core variable may differ between data sources, it will be necessary to run data checks. For example, the application of proxy definitions in Belgian data must be tested.

Due to a data lag for the Danish and Belgian data sources utilization information for 2020-2021 may not be wholly available by Q3 2021. In this instance the MAH will make an estimate of utilization from internal data (Table 2 in response to reviewers document dated November 30th 2020). To test the application of proxy definitions, the most up to date available data will be used, augmented with data from 2019. The rationale is that this approach would boost numbers to test application of programs, but data from 2019 would not be used in a final analysis.

Thus, the full feasibility analysis will address 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. Currently this is expected be <1%. If missing data is thought to be problematic, approaches such as imputation will be considered to preserve the numbers of patients included.

5) The distribution of test dates around the intended testing day will be documented and reported to reflect the appropriateness of ±15 days and ±30 days testing windows.

9.9 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 programs 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.

As regards missing data, we expect to have no missing data for age and sex in medical chart data from the UK and Germany. Our prior experience of using Danish and Belgian data for other PASS studies suggests that missing data for age and sex will be very rare; <1%. Nonetheless, in

the full feasibility analyses we will quantify the extent of missing data and if necessary will explore imputing missing values to preserve numbers of patients enrolled in the study.[24]

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.

9.10 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 SmPC change in January 2020 and 2) the Covid-19 global pandemic (Table 2 in response to reviewers document dated November 30th 2020). We have planned a feasibility analysis in Q3 2021 to ascertain numbers of newly prescribed LEMTRADA courses in 2020 and the first half of 2021 (Section 9.8).

As highlighted in Tables 1a and 1b, each data source contributes in different ways to meeting the study objectives. For example, from medical chart data in the UK and Germany data on all cardiac monitoring, all blood testing, and the indication and contraindication can be collected. In the Belgian data source, data on ECGs and blood monitoring are 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[2], but the second part of the indication is not due to the lack of available data on MRI results[3]. Proxy definitions will also be required for contradictions 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.[25-28]

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 Danish or 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.

In Danish data, good data are available for the indication and contraindication but not ECG, heart rate or blood pressure. There may be up to 22% missing data for blood testing in Danish data. It is

[2] *Patients with highly active disease despite a full and adequate course of treatment with at least one disease modifying therapy (DMT)*
[3] *Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI*

expected that there may be up to 15% missing data for monitoring in German data. Missing data for laboratory tests in German and Danish data may contribute to some misclassification of adherence to monitoring – the quantity of missing data will inform the extent to which misclassification will occur. Missing data for monitoring would result in erroneous underestimation of appropriate monitoring.

We expect heterogeneity in the results between each data source based on existing knowledge of how DMT are used in Europe.[8] 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 arise from how variables are defined in each data source. For example, ICD codes for previous MI/stroke will exist in Danish data, while a proxy definition will be used in Belgian data, and a history of comorbidities will be used in medical chart data.

Selection bias is not expected to be problematic given that this is not a comparative study. In terms of generalizability, the study results will be applicable to patients from the countries 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, for example the ongoing LEMTRADA PASS study (OBS013434), TREAT-MS and clinical trial data. These comparisons will be presented in the final report and also 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 difference; for example TREAT-MS is for German patients only whereas LEMPASS includes patients from all over 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 characterizing the included population will be to compare demographic data for the cohorts in this DUS to demographic data maintained in ongoing patient support programs.

10 PROTECTION OF HUMAN SUBJECTS

This study will be conducted in accordance with the guidelines for Good Pharmacoepidemiology Practice published by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) and the International Society of Pharmacoepidemiology.[29, 30]

10.1 CONSENT

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

In **Germany,** the MSDS3D system documents that the patient has agreed to participate in the study and that patient consent has been obtained.

In the **UK**, patient consent is carried out at the local level (there are three participating academic centres). The lead PI for the study will apply to the National Health Service Ethics Committee for approval if deemed necessary, otherwise local ethical approval will be sought.

In **Germany and the UK,** it is the data source's responsibility to obtain informed consent from patients prior to inclusion in the study, and to record all data pertinent to the investigation. She/he will ensure that the information reported is precise and accurate. The patient will be fully informed of all pertinent aspects of the study. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

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

In **Denmark and Belgium**, as this project is based on secondary use of anonymized patient data that are held in administrative databases or registers, subject informed consent is not required.

10.2 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 (Global 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 practices modules VI and VIII and as also referenced in ENCEPP guidelines for good pharmacoepidemiological practice. [30-32]

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 will be 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 will be submitted to the Regulator in Q3 2021 (Section 9.8) followed by an interim report. Thereafter, annual interim progress reports will be submitted in Q4 2022 and Q4 2023 detailing accrual and interim analyses. The final report will be submitted in Q3 2024.

The study group for this study will be comprised of [redacted] 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 make reference to the study and the primary publication (i.e. the final study report). The final decision to publish any manuscript/abstract/presentation will be made by the Study Group after prior notice to the MAH allowing for its internal review and comments. All manuscript/abstract/presentations must be submitted for internal review by the MAH at least forty-five (45) calendar days in advance of submission. The MAH may request that the name and/or names of one or several of its employees appear or do not appear in such publication. Any publication in a peer reviewed journal will be disclosed onto the ENCePP site within 2 weeks of acceptation by journal.

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14 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 disease modifying therapy (DMT) or *Part 2 of indication* Patients with rapidly evolving severe relapsing remitting multiple sclerosis defined by 2 or more disabling relapses in one year, and with 1 or more Gadolinium enhancing lesions on brain MRI or a significant increase in T2 lesion load as compared to a previous recent MRI.	*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 corticosteroid (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 corticosteroids (CS) administered intravenously (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; 3. CS doses less than 50 mg per day (IV or oral). 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	n/a	This is 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 hospitalization. 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 Appendix 1 Table 2 (below)
Contraindication	History of stroke	Use of specific drug treatments, imaging, testing, procedures and monitoring and hospitalization.	<u>Hemorrhagic stroke</u> Anti-hemorrhagic agents/idarucizumab OR parenteral nicardipine AND

		See text below this table that describes coding system for therapies, tests, procedures, monitoring in full.	Brain computed tomography/MRI AND cerebral angiography AND interventional neuroradiology procedure OR neurosurgery AND Hospital stay >2days OR ICU admission for at least one day <u>Ischemic Stroke</u> Alteplase AND Brain computed tomography/MRI AND cerebral angiography AND interventional neuroradiology procedure AND ECG/HOLTER OR transesophageal sonography, AND Hospital stay >2days OR ICU admission for at least one day An example of tabular algorithms given in Appendix 1 Tables 3 and 4 (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 searches for infectious agents in blood and sputum, need of respiratory assistance, stay in ICU	<u>Exact algorithm will depend on infection types but will typically adhere to the following logic</u> 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 Appendix 1 Table 5 (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 analogs (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 autoimmune diseases (besides 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.[1-4]

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 INAMI-RIZIV, 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 subject 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 disease modifying therapies (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 contra-indications 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 contra-indications. 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 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 [redacted] coordinator of the study are all MDs who have to 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 AI conditions.

Myocardial infarction, myocardial ischemia, unstable angina pectoris=acute coronary syndrome	
Drugs	
ATC codes	**Name**
B01AC04	clopidogrel highly specific at one shot dose of 300 mg
OR/AND	
B01AC22	prasugrel
B01AC24	ticagrelor
B01AC16	eptifibatide
C01DA08	isosorbide dinitrate
C07AB02	metoprolol*
C07AB03	atenolol*
C07AB07	bisoprolol*
AND	
Medical tests and interventions	
Name	**INAMI code**
repeated (hours) troponins	542334, 542345, 542356, 542360
OR/AND	
coronary angiography	453143
OR/AND	
percutaneous coronary angioplasty Stenting	
AND	
Medical examination	
>2 ECG over 7 days	475834, 475845
OR/AND	
Cardiomonitoring	212015, 212026, 212041, 214012, 214023, 214045, 214060
OR/AND	
2-D cardiac sonography	460465, 460423
AND	
Hospital stay > 2 days	AIM-IMA algorithm for hospital episodes
OR/AND	
Stay in ICU for at least one day	
* blocking agents most used in the context of acute coronary syndrome	

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

Haemorrhagic stroke	
ATC codes	
ATC codes	**Name**
B02	antihemorrhagics
V03AB37	idarucizumab specific antidote of dabigatran
OR/AND	
C08CA04	nicardipine if parenteral (IV)
Medicines on admission as CAUSE of the haemorrhagic stroke (if medicines history is known), !!! MORE RELEVANT if immediately interrupted	
B01A	antithrombotic agents
B01AE07	dabigatran etexilate
B01AA	vitamin K antagonists
AND	
Medical tests and interventions	
Name	
brain computed tomography or/and brain magnetic resonance imaging (especially if repeated in a few days)	
AND	
Cerebral angiography	
AND	
Interventional neuroradiology procedure	
OR/AND	
Neurosurgery	
AND	
Hospital stay > 2 days OR/AND Stay in ICU for at least one day	AIM-IMA algorithm for hospital episodes

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

Ischemic stroke	
ATC codes	
ATC codes	**Name**
B01AD02	alteplase
AND	
Medical tests and interventions	
Name	
brain computed tomography or/and brain magnetic resonance imaging	
AND	
cerebral angiography	
AND/OR	
Interventional neuroradiology procedure	
AND	
Cardiac test, transoesophageal, HOLTER	
AND	
Hospital stay > 2 days	AIM-IMA algorithm for hospital episodes
OR/AND	
Stay in ICU for at least one day	

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

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

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

Drug	Brand names in Belgium	ATC	INAMI code	CNK	Description	Date of reimbursement
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

Drug	Brand names in Belgium	ATC	INAMI code	CNK	Description	Date of reimbursement
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

Drug	Brand names in Belgium	ATC	INAMI code	CNK	Description	Date of reimbursement
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

Drug	Brand names in Belgium	ATC	INAMI code	CNK	Description	Date of reimbursement
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

Drug	Brand names in Belgium	ATC	INAMI code	CNK	Description	Date of reimbursement
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

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

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15 APPENDIX 2

LIST OF AUTOIMMUNE CONDITIONS

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

We reviewed the epidemiology of autoimmune disease in both a general population and the MS population to construct a broad list of autoimmune 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 autoimmune conditions that are listed as safety concerns in the current Risk Management Plan for LEMTRADA (i.e. 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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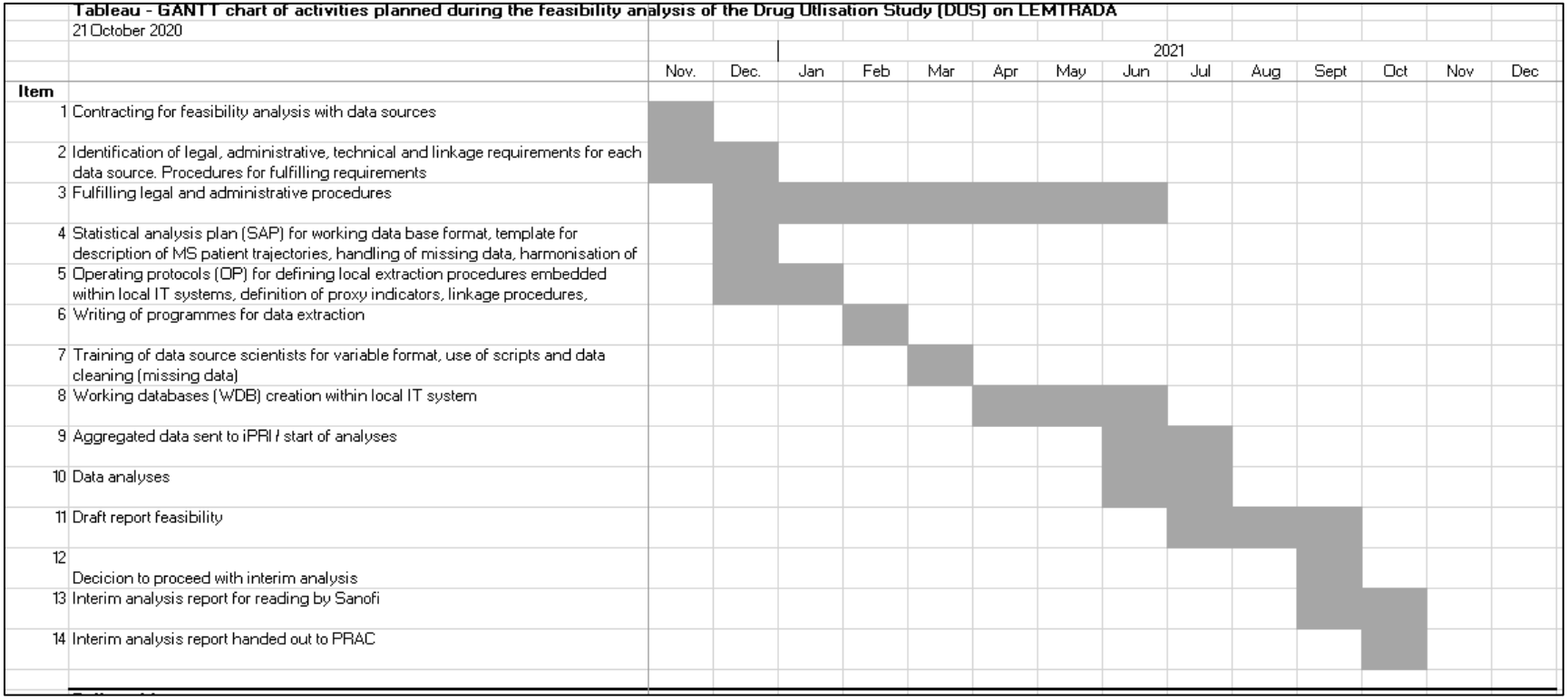
16 APPENDIX 3

Tableau - GANTT chart of activities planned during the feasibility analysis of the Drug Utlisation Study (DUS) on LEMTRADA

21 October 2020



17 APPENDIX 4

POINT BY POINT RESPONSE TO ISSUES HIGHLIGHTED IN SECTION 4.7.1 OF PRAC AR ON PROTOCOL V1.0

Appendix 4 Table 1 - Addressing issues with feasibility identified in PRAC assessment report

Identified Issue	Preliminary Feasibility Data	Full Feasibility analysis
Belgian database: 1. Proxy indication 2. Proxy contraindications 3. Nature of data - reimbursable events 4. Nature of linkages for Belgian data 5. Alternative data sources	Proxy definitions for the indication and contraindication are given in **Appendix 1**. All health events relevant to the DUS are fully reimbursable in Belgium and thus, missing data due to non-reimbursement is not a concern. This is reflected in section 9.4.2 of Protocol. There are no linkages specifically required for this study - data on vital status is updated automatically at designated timepoints.. We considered many potential data sources, some of which we deemed to have too small numbers of LEMTRADA-treated MS patients or do not collect most data relevant to the DUS or there were issues with access.	Operationalize each proxy definition. Example codelists for proxy definitions are given in Appendix 1. Final lists of codes for proxy definitions given in SAP.
Danish data 1. LABKA linkage and coverage	The Danish MS Treatment registry is linked to the national patient registry (collecting prescription data) and the national civil status registry (collecting immigration/emigration data and vital statistics).(1) A linkage to the LABKA database is also possible. This is a repository for laboratory testing data and holds data on more than 1700 different types of tests. Testing information is recorded in a uniform way according to the international NPU (Nomenclature, Properties and Units) coding	Assess whether linkage to LABKA exists for patients newly using LEMTRADA.

	system. The NPU code is the unique identification number for each single investigation. The NPU coding system provides a terminology for identification of clinical laboratory test values following the international recommendations for efficient electronic communication in clinical laboratories, and ensures that names and units are shown in a uniform manner.(2) Our contacts at the Danish MS registry estimate that linkage to the LABKA database is available for 78% of MS registry patients. Linkage between databases is achieved using a unique 10-digit personal identifier [Central Personal Register (CPR) number]. Linkages of population health databases are routinely carried out in Denmark.(3)	
UK and German data 1. New users 2. Long-term FU	New use of LEMTRADA post SmPC change (2020) is ascertained in medical charts by checking date of infusion. Prior usage is determined by the treating physician by checking the drug history of each patient in chart data (see section 9.3 and 9.2.2 of Protocol) In medical charts, date of death/emigration is available. Thus, it is known when to stop follow-up for monitoring (see section 9.3 of Protocol).	*No further action required*
Heterogeneity of data	Heterogeneity in the data is likely given that we are including data from four different countries, each with its' own type of social health care system. This is a strength of the study as it will enhance generalisablity. Heterogeneity in terms of how variables are defined may be introduced. For example, ICD codes for previous MI/Stroke will exist in Danish data, while a proxy definition will be used in Belgian data, and a history of comorbidities will be used in medical chart data.	Assess heterogeneity by looking at prevalence of comorbidities in the LEMTRADA population in each country, and the rate of testing. Attempt to understand emergent heterogeneity by understanding the underlying health system and the measurement of variables in each data base. We anticipate that heterogeneity may be high and thus we will present results separately for each country rather than meta-analyze.
Validation of variables	Appendix 1 details the proxy definitions in Belgian data and also outlines the coding systems used and the availability of drug data, testing, medical services etc on which to build proxy definitions. Steps to “validate” proxy definitions via consulting with local specialists and data experts are also outlined in Appendix 1.	
Estimation of missing data	Based on our prior experience in Belgian and Danish data for MS patients there are no missing data on age and sex. Occasionally, errors in the recording of these variables can occur. This is a rare event, affecting less than 0.1% of all patients included in data sources.	Evaluation of missing data for age and sex in full feas bility. This is expected to be negligible.

		If required, multiple imputation can be used to impute missing age or sex so that no patient is lost from the analysis.
Generalisability of study	*Cannot address at this stage*	Comparison of patient age and sex distributions in comparison to observational studies (eg LEMPASS OBS13434 and TREAT-MS) and clinical trials for LEMTRADA (eg CARE-MS). Note, however, the characteristics of patients included in this DUS may be different to the LEMPASS (obs013434) or clinical trials due to the changed indication and thus the changing profile of patients included.
Coding	We have listed the types of coding systems used in Danish and Belgian in Tables 1a and 1b in the Protocol.	Final codes lists for will be provided in the Operating Protocol which is required for execution of the feasibility analysis.
Numbers exposed to LEMTRADA	Actual and forecasted usage for 2020 are provided in response to reviewers document [dated 30th November 2020]. Forecasted data for 2021 are also provided. These data are based on internal sales and marketing data.	Exact enumeration of those exposed to LEMTRADA will be poss ble. Note there may be a lag in data in Belgian and Danish data sources, in which forecasted data for 2021 will be used to inform the numbers expected in the study. To aid running feasibility analyses, data from 2019 can be used for Danish and Belgian data. The logic is that this will provide more patients for testing operational definitions of variables.
Timelines for feasibility analysis	Please see Gannt chart (**Appendix 3**) which documents the steps to deliver the feasibility analysis in 2021	
Procedures to ensure data quality and reporting of accurate data	As stated in the protocol, local procedures will include checking electronic files, maintaining security and data confidentiality, following analysis plans, and performing quality-control checks of all programs.	Application of local procedures and study management procedures can occur. Issues with data quality can be reported on.

	Further to this, the Study Management will produce standard descriptive procedures, outlined in the operating protocol, 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 plaus bility. Identification of each key variable including defining end of follow-up time will be specified for each data source in the Operating Protocol. These definitions will include code lists where required. Please see amended sections 9.6 and 9.9 in Protocol	
Analysis of adherence	This is not technically related to feasibility, however we are addressing because was mentioned in section 4.7.1 of PAR. We will no longer use the days covered approach for adherence to laboratory monitoring. Please see section 9.7.2 which describes new method of calculating adherence.	
Confounding variables	We will stratify on age and sex where cell sizes allow (>=5). See notes above on missing data for age and sex. Please see section 9.7.4 which outlines all stratified analyses.	*No action required*

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18 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, 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: *Will be registered on receipt of PRAC approval*
Study reference number (if applicable):

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				All in

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1.1 Start of data collection[4]	☒	☐	☐	section 4 & 6.
1.1.2 End of data collection[5]	☒	☐	☐	
1.1.3 Progress report(s)	☒	☐	☐	
1.1.4 Interim report(s)	☒	☐	☐	Item 1.1.5 in Section 12
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 9.10 2.1.5 in Section 8

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 & 9.4

[4] 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.

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

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	9.7.1 & 9.7.2
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 9.7 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 & 9.10
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	Section 9 See notes
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 9.4 4.2.4 in Section 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
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 utilization study: "outcomes" as laid out in table 2 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)	☒	☐	☐	9.10 See notes
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	9.10 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 9.7.4 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 9.10. 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 limitations section 9.10

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, sub-group analyses, anticipated direction of effect)	☒	☐	☐	9.7.4 See comments

Comments:

Section 9.7.4 outlines various subgroup analyses that will be run to gain an understanding of how utilization 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:				

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	9.3, 9.4, and Table 1a-1b
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, 9.4, and Table 1a-1b
9.1.3 Covariates and other characteristics?	☒	☐	☐	9.3, 9.4
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)	☒	☐	☐	9.4.1 – 9.4.4
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	9.4.1 – 9.4.4 Tables 1a - 1b
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, lifestyle)	☒	☐	☐	9.4.1 – 9.4.4
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	Tables 1a - 1b
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	Tables 1a - 1b
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)	☐	☐	☐	9.4.1 – 9.4.4 Tables 1a - 1b

Comments:

9.3.3 Coding for covariates is not required because age and sex are not typically "coded". All other covariates for stratified analyses (9.7.4) 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?	☒	☐	☐	9.7
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	9.5
10.3 Are descriptive analyses included?	☒	☐	☐	9.7

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.4 Are stratified analyses included?	☒	☐	☐	9.7.4
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	9.7.4 See notes
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☐	☒	☐	
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	9.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	9.7.4

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 9.7.4

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 IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	9.6 & 9.9
11.2 Are methods of quality assurance described?	☒	☐	☐	9.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	3.4 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?	☒	☐	☐	
12.1.2 Information bias?	☒	☐	☐	9.10 See notes
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)	☒	☐	☐	9.8

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 9.7.4

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	10
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	10.2

Comments:

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

Comments:

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

Comments:

Name of the main author of the protocol: _____

Date: dd/Month/year

Signature: _____

19 APPENDIX 6

List of stand-alone documents

Response to reviewer document dated April 05 2021

Response to reviewer document dated May 19th 2021