MEASURE OF EFFECTIVENESS OF THE MINIMIZATION MEASURES OF RMP PROTOCOL

TITLE: Knowledge survey to assess the effectiveness of educational materials among healthcare professionals who prescribe Lemtrada®(alemtuzumab)

COMPOUND: Alemtuzumab

STUDY NAME: Lemtrada® EU-RMP Survey in HCPs

The Study is conducted by Genzyme, a Sanofi Company, Atlantis Healthcare (2nd Floor, Building 5, Chiswick Park, 566 Chiswick High Road, London W4 5YA) and IPSOS (3 Thomas More Square, London E1W 1YW)

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Protocol Agreement Form

Not applicable.

PASS Information

Title	Knowledge survey to assess the effectiveness of educational materials among healthcare professionals who prescribe Lemtrada®(alemtuzumab)
Protocol version identifier	1.7
Date of last version of protocol	30th November 2016
EU PAS register number	Not applicable
Active substance	Alemtuzumab
Medicinal product	Lemtrada®
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003718
Marketing authorisation holder(s)	Genzyme Therapeutics, Ltd
Joint PASS	Not applicable
Research question and objectives	The overall objective of the survey is to assess descriptively the knowledge level of HCPs with regard to educational messages and thus the effectiveness of the educational materials to support the safe use of Lemtrada®. Research questions: 1. What is the prescriber's understanding and awareness of the risks associated with use of Lemtrada®? 2. What is the prescriber's knowledge of the key safety messages in the content of the HCP guide and HCP checklist? 3. What is the prescriber's knowledge and understanding of the risk minimization activities to be undertaken in relation to Lemtrada®?
Countries of study	The survey will be conducted in two distinct waves, 18 months and 3 years after launch of Lemtrada® in at least 5 countries, including launch in at least 2 of the most populated EU countries (DE, FR, UK, IT, ES), with adequate translations in local languages.
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2 LIST OF ABBREVIATIONS

AE	Adverse Event
EU	European Union
HCP	Healthcare Professional
MG	Medication Guide
MS	Multiple Sclerosis
PC	Patient Card
PIL	Patient Information Leaflet
RMP	Risk Management Plan
SmPC	Summary of Product Characteristics

3 RESPONSIBLE PARTIES

Atlantis Healthcare will be involved in the preparation of the protocol and its amendments and will develop the survey and analyse the results.

IPSOS will be involved with the recruitment of HCPs and management of the questionnaire.

The survey is sponsored by Genzyme, a Sanofi company.

4 ABSTRACT

Title

Knowledge survey to assess the effectiveness of educational materials among healthcare professionals who prescribe Lemtrada® (alemtuzumab).

Rationale and background

The Lemtrada® risk management plan (RMP) includes additional risk minimisation measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimization. The HCP educational pack consists of the Summary of Product Characteristics (SmPC), HCP materials and patient materials. The core elements of the HCP educational materials are an HCP guide and checklist. These are aimed at ensuring early detection of key symptoms indicative of adverse events (AEs), communication of risks of symptoms and the importance of periodic monitoring, and to inform about benefit-risk decisions before each treatment course.

The risk management knowledge of HCPs prescribing Lemtrada® will assess the effectiveness of the RMP in HCPs. Very little published research exists relating to the evaluation of RMPs, however, the methods of extant published literature have been used to guide proposals wherever possible.

Research question and objectives

The objective of the survey is to assess descriptively the knowledge of HCPs prescribing Lemtrada® about the key items of the educational materials and therefore the effectiveness of these materials to support the safe use of Lemtrada®. Research questions relate to the extent of the HCP's understanding and awareness of the risks associated with use of the product, the key safety messages in the content of the HCP guide and HCP checklist and knowledge of risk minimization activities to be undertaken.

Study design

The study is a cross-sectional survey conducted in two distinct waves (18 months and 36 months) after the launch of the product in at least 2 highly populated EU countries. Each wave will be conducted over a 6-week period. The surveys will be conducted online using a structured questionnaire. Results will be analysed and reported to the European Medicines Agency (EMA).

Population

A randomly generated sample of HCPs involved in the treatment of multiple sclerosis (MS) patients with Lemtrada®. The selected countries will include at least 2 of the highly populated EU

countries (DE, FR, UK, IT, ES). It is important that HCPs have prescribed Lemtrada® to at least one of their patients in the last 6 months.

Variables

The following elements will be collected and assessed at each wave:

1. The prescriber's understanding and awareness of the risks associated with use of the product
2. The prescriber's knowledge of the key points in the content of the HCP guide and HCP checklist
3. The prescriber's knowledge of the risk minimization activities to be undertaken

Data Sources

Data regarding the known distribution of neurologists and MS sub-specialists for participating countries will be supplied by EU SA/GZ marketing. All other data will be collected via HCP self-report in a questionnaire.

Study size

The survey will be administered in a random selection of 60 - 70 HCPs. Additionally, 60 - 70 HCPs (excluding those who completed the first round) will be invited to complete the second round questionnaire.

Data analysis

Descriptive analyses only will be performed. Additional sub analyses may be conducted to further investigate any findings.

Milestones

The survey will be conducted in 2 waves at 18 months and at 3 years after launch of Lemtrada® in at least 5 countries including launch in at least 2 highly populated EU countries (DE, FR, UK, IT, ES).

5 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	DD Month YYYY	Text	Text	Text
2	DD Month YYYY	Text	Text	Text
3	DD Month YYYY	Text	Text	Text

6 MILESTONES

Milestone	Planned date
Start of data collection Wave 1	December 2015
End of data collection Wave 1	January 2016
Interim Report 1	March 2016
Start of data collection Wave 2	May 2017
End of data collection Wave 2	June 2017
Final report of study results	September 2017

7 RATIONALE AND BACKGROUND

BACKGROUND

Safety hazards

Not applicable– this is a survey evaluating the effectiveness of a risk management plan.

Safety profile

For the safety profile of alemtuzumab please refer to the SmPC.

Description of Lemtrada® Risk Management Plan

The Lemtrada® risk management plan (RMP) includes risk minimisation measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimization.

The primary objectives of the educational materials are to:

- Ensure early detection of events to mitigate the severity and sequelae of autoimmune disease through education, and facilitating periodic monitoring.
- Communicate risks (e.g. secondary autoimmune disease), and the need and importance of periodic monitoring, to patients and prescribers.
- Inform about benefit-risk decisions before each treatment course.

Prescribing Healthcare professionals (HCPs) will receive all educational materials in hard copy for their own use. The HCP educational pack consists of the Summary of Product Characteristics (SmPC), HCP materials and patient materials. The HCP materials consist of an HCP guide, and HCP checklist (one per HCP). HCPs should also be familiar with the patient education package: patient alert card (PC), patient guide (PG) and package leaflet (PL).

Additionally, the educational materials (HCP guide, HCP checklist, and SmPC) will be available on the MS One to One website to provide electronic access to HCPs who prescribe the product.

The survey will focus on the HCP-focused materials (HCP guide, HCP checklist).

HCPs use these materials to ensure they understand and communicate to patients adequately about the following items:

Autoimmune conditions, including:

- Immune Thrombocytopenic Purpura (ITP)
- Nephropathies including anti-Glomerular Basement Membrane (anti-GBM) disease,
- Thyroid disorders

Additional items that HCPs need to be aware of:

- It is important that HCPs are aware of patients' risks of developing these autoimmune conditions, and the necessary monitoring procedures (blood and urine testing, watching for signs and symptoms) that must take place. HCPs need to be aware of the blood and urine tests that should be conducted before treatment initiation and continued for 48 months after last infusion. They should be aware of the need to counsel the patient on the risks and how to detect any signs or symptoms. This should be part of a benefit-risk discussion prior to Lemtrada® treatment.
- In addition, HCPs responsible for managing the patient's pregnancy must be aware of the increased risks of thyroid disorders due to the patient's Lemtrada® treatment, and consequences of untreated thyroid disorders for the baby.
- HCPs should be aware of the patient education materials and patient compliance tools, and how to access them.
- HCP should follow the recommended patient's screening, vaccination and pretreatment programs.

Relevant published research

This study will assess the knowledge of HCPs who prescribe Lemtrada® about the items of the educational materials and thus the effectiveness of these materials to ensure the safe use of Lemtrada®.

This is the first study to assess the effectiveness of the Lemtrada® RMP. Historically, there have been few published studies reporting the effectiveness of risk management interventions.[1]

RATIONALE

This RMP assessment of effectiveness survey will provide the first information relating to HCPs' understanding of the risk messages that are discussed in the education guide and SmPC for Lemtrada® prescribed for MS. It will evaluate the HCP prescribers' knowledge of RMP materials. There are limited published studies reporting HCPs' knowledge of tools used in risk management plans. The findings of this study may make an important contribution to the understanding of the effectiveness of the RMP strategy and the safe prescription of Lemtrada®.

8 RESEARCH QUESTION AND OBJECTIVES

Research questions

1. What is the prescriber's understanding and awareness of the risks associated with use of Lemtrada®?
2. What is the prescriber's knowledge of the key safety messages in the content of the HCP guide and HCP checklist?
3. What is the prescriber's knowledge and understanding of the risk minimization activities to be undertaken in relation to Lemtrada®?

8.1 PRIMARY OBJECTIVE

The objective of the study is to assess descriptively knowledge of HCPs who prescribe Lemtrada® with regard to the items of the educational materials and thus the effectiveness of these materials to ensure the safe use of Lemtrada®

8.2 SECONDARY OBJECTIVES

Not applicable.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is an international survey, recruiting from at least 5 countries across the EU. Information will be collected regarding the knowledge relating to risk minimization (as described in the HCP guide and checklist) of HCPs involved in the treatment of MS using Lemtrada®

It is not an interventional study to evaluate the impact of a predefined therapy or procedure.

The study is a cross-sectional survey conducted in two distinct waves 18 months apart conducted each time over a 6-week period. The surveys will be conducted online or by alternative methods, using structured questionnaires, comprising of questions where the response format is either the selection of a single response or selection of a number of responses as appropriate. Results will be analysed and reported to the European Medicines Agency (EMA).

9.2 SETTING

The study will be conducted in selected European countries including launch in at least 2 of the most populated EU countries (DE, FR, UK, IT, ES), with adequate translations in local languages. Web and telephone recruitment will be used. Collection of survey data will take place online.

9.2.1 Duration of the study

The duration of the study will be 96 weeks.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

- HCP is a neurologist/ MS specialist
- HCP has prescribed Lemtrada® to at least one patient within the past 6 months
- HCP supplies informed consent by ticking a box on the website.

Exclusion criteria

- HCP has not prescribed Lemtrada® within the past 6 months
- Wave 2 only: Participation in the questionnaire in Wave 1

9.2.3 Analysis populations

All surveys returned with at least one response completed will be analysed.

9.2.4 Modalities of recruitment

9.2.4.1 Physician selection

The survey will be conducted in at least 5 countries of the EU. HCPs involved in the treatment of multiple sclerosis (MS) patients receiving Lemtrada® will be invited to take part.

For the selection of HCPs free found recruitment will be used. Multiple approaches will be used and will include:

- Recruitment via online panels – panels exist for HCPs and will be used as the first recruitment approach;
- Telephone recruitment – hospital/center contact information will be used in order to identify appropriate HCPs for the study;
- Snowballing – we will ask respondents to suggest other potential respondents that may be interested in participating.

The registered HCP population will be described in terms of age, type of hospital, large/medium cities, urban/rural location and compared in each participating country with the known distribution of neurologists and MS sub specialists to ensure representativeness.

HCPs will provide informed consent and data will be anonymous for the Marketing Authorization Holder (MAH).

60 - 70 Lemtrada® prescribing HCPs will be invited to participate in the first round survey in order to obtain a representative sample size from each country. A further 60 - 70 Lemtrada® prescribing HCPs (excluding those who completed the first round) will be invited to complete the second round questionnaire. At each time point a follow-up reminder email will be sent two weeks after initial invitation to try to ensure adequate recruitment.

9.3 VARIABLES

Knowledge is defined as awareness and understanding of important risk minimization information contained in the HCP guide and HCP checklist.

The following elements will be collected and assessed at each wave:

1. Physician characteristics including:

    a) Country

b) Type of hospital

c) Speciality

d) Total number of MS patients under treatment

e) Number of patients prescribed Lemtrada®

f) Time since last prescription of Lemtrada®

2. The prescriber's knowledge of the existence of:

a) the HCP guide

b) the HCP checklist

c) the SmPC

d) the Patient Guide

e) the Patient Alert Card

f) the Package Leaflet

3. The prescriber's understanding and awareness of the risks associated with use of the product:
   a) Immune Thrombocytopenic Purpura (ITP)
   b) Kidney Disorders
   c) Thyroid Disorders
   d) Thyroid Disorders in pregnancy

4. Knowledge of the key points in the content of the HCP guide, and HCP checklist:

a) Contraindications

b) Lists of tests to be conducted for the initial screening of the patient

c) Vaccination, pre-treatment courses

d) Monitoring activities for the autoimmune events

e) Special warnings on fertility, contraception, pregnancy and breast feeding

5. The prescriber's knowledge of the risk minimization activities to be undertaken

   a) Type of monitoring required (blood and urine, self-monitoring)

   b) Required time period for monitoring

   c) If ITP or anti-GBM or Thyroid disorder is suspected, the HCPs should know that appropriate medical intervention should be promptly initiated, including immediate referral to a specialist

If all questions on the pre-defined topics have been answered correctly, the knowledge level will be considered to be adequate, but it will not be required to answer all questions correctly. For example, each outcome topic will cover approximately three questions. If the HCP answers the first question incorrectly they will be given the opportunity to answer two further questions before that topic can be deemed incorrect. A perfect knowledge level will be assumed when all questions have been answered correctly. If HCPs do not answer all three questions correctly, they will be deemed to have imperfect knowledge. HCPs will be shown all correct answers at the end of the survey.

Knowledge will be measured via self-report using an online questionnaire, which HCPs will complete. The questionnaire will measure knowledge using questions with single choice or multiple-choice responses (as appropriate).

Potential confounding factors

1. Some HCPs may only have small numbers of patients eligible to be prescribed Lemtrada® Approximate number of patients treated with Lemtrada® will be recorded and included as a variable for sub-group analysis.
2. Length of time since last prescription of Lemtrada® to a patient will be recorded and included as a variable for sub-group analysis.

9.4 DATA SOURCES

Data regarding the known distribution of neurologists and MS sub specialists for participating countries will be supplied by EU SA/GZ marketing. All other data will be collected via HCP self-report in the questionnaire.

The questionnaire will be developed by psychologists with experience of developing questionnaires. Before implementation, the questions will be user-tested in a small sample of HCPs who treat patients with MS to ensure the questions and translations are understood and adequate.

9.5 STUDY SIZE

9.5.1 Determination of sample size

Since this study will not use inferential statistics, a formal power calculation has not been undertaken. Based on an estimation of 360 Lemtrada® prescribers in the countries where the study is planned to be conducted, and taking into account an expected response rate of approximately 15 - 20%, the survey will be administered in a random selection of 60 - 70 HCPs.

9.5.2 Sample size

It is planned to recruit 60 - 70 HCPs.

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

HCP data

Data will be collected online at 18 months and 3 years after launch of Lemtrada® in the participant countries. Recruitment will take place over a 6-week period in each wave.

Physicians who were recruited via methods as described previously will be sent an invitation email. The email will contain a link to the online study questionnaire and an email address to contact the research team if further information about the study is required. The invitation email and questionnaire will be translated into the local languages of participating countries.

On following the link within the invitation email, the information sheet will be displayed. HCPs will also be provided with an email address to make contact with the research team in the event of having questions prior to consent into the study. The information sheet and consent statement will emphasize that answers are anonymous and confidential. Following receipt of consent, the HCP will be able to move into the pages of the online questionnaire. In order to minimize missing data, it will be mandatory to answer all questions within the questionnaire.

The first page of the questionnaire will relate to the eligibility criteria. If any of the answers indicate that the HCP is ineligible (e.g. has not prescribed a single dose of Lemtrada®), they will be taken to a page thanking them for their participation and explaining that they are not eligible to take part.

Following completion of the questionnaire the HCP will be taken to a page thanking them for their participation.

All survey tools (the text of the invitation email, information sheet, consent wording and questionnaire items) are available in Annex 1.

MS population data

Known MS population statistics for participating countries will be supplied by EU SA/GZ marketing.

9.6.2 Data collected

Online questionnaire

- Country of practice
- Work setting (public/private; university/community hospital)
- Prescribed at least one dose of Lemtrada® within the past 6 months
- Knowledge relating to Lemtrada® risk management

9.6.3 Site / Physician questionnaire

Not applicable.

9.6.4 Screening log (if applicable)

Not applicable.

9.6.5 Patient data

Not applicable.

9.6.6 Procedure for withdrawal of patients from study follow-up schedule

Not applicable.

9.6.7 Logistic aspects

Not applicable.

9.7 DATA ANALYSIS

9.7.1 Primary analysis

Descriptive analyses only (e.g. frequency distributions for each item) will be performed on the overall population of participating prescribers.

9.7.2 Secondary analysis

The analysis will be descriptive.

1. Where knowledge is found to be <100% a more detailed analysis will be conducted (e.g. to identify specific areas where knowledge is low).
2. Responses in sub-groups compared to the rest of the sample. Sub-groups to be analysed are:
    - Number of eligible patients HCPs treat with Lemtrada®
    - Length of time since last prescription
    - University or community hospital
    - General neurologist or MS sub specialist
    - Country

9.7.3 Interim analysis

No interim analysis is planned for this survey. A report per wave is planned.

9.8 QUALITY CONTROL

9.8.1 Data collection, validation and data quality control at MAH/MAH representative level

Data will be collected electronically directly from HCPs using a secure system.

Data will be anonymized and stored on a password protected computer in a locked office. The data will be stored electronically in this way for 5 years (from completion of Wave 2) and then erased.

Analysis will be undertaken using the statistical software package SPSS by qualified research personnel employed by Atlantis Healthcare.

All data will be self-reported, and there will be no opportunity to verify source data.

9.8.2 Data quality control at site level

Not applicable.

9.9 LIMITATIONS OF THE RESEARCH METHODS

All data supplied will be self-report, and it will not be possible to objectively verify information (e.g. work setting).

The study uses descriptive statistics only. Therefore it is not possible to determine whether findings are statistically significant or could be due to chance. However, given that the main objective is to measure knowledge, descriptive statistics are sufficient.

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

Not applicable.

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.2.1 Ethical principles

This study will be conducted in accordance with the principles laid by the 18th World Medical Assembly (Helsinki, 1964) and all subsequent amendments.

10.2.2 Laws and regulations

Each participating country should locally ensure that the survey is performed in accordance with local regulations including local data protection regulations.

10.2.3 Data protection

The patient's personal data which may be included in the MAH/MAH representative database shall be treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the patients, the MAH/MAH representative shall take all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

10.2.4 Insurance

Not applicable. This is a survey using a mandatory template, not a treatment study.

10.2.5 Secrecy agreement

Not applicable

10.2.6 Record retention

It is recommended that Atlantis Healthcare and IPSOS shall arrange for the retention of study documentation for at least five years. In addition Atlantis Healthcare and IPSOS will comply with specific local regulations/ recommendations with regards to patient record retention.

However, applicable regulatory requirements should be taken into account in the event that a longer period is required.

10.2.7 Discontinuation of the study

The MAH/MAH representative can decide at any time and for any reason to discontinue the study.

10.2.8 MAH/MAH representative audits and inspections by competent authorities

Atlantis Healthcare agrees to allow the MAH/MAH representative auditors/Competent Authorities inspectors to have direct access to his/her study records for review, being understood that this personnel is bound by professional secrecy, and as such will not disclose any personal identity or personal medical information. Access to the source document will not be allowed (because no ICF is signed).

Atlantis Healthcare will make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents.

The confidentiality of the data verified and the protection of the patients should be respected during these inspections.

Any result and information arising from the inspections by the competent authorities will be communicated by Atlantis Healthcare to the MAH/MAH representative.

Atlantis Healthcare shall take appropriate measures required by the MAH/MAH representative to take corrective actions for all problems found during the audit or inspections.

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable – this is a survey and will not generate adverse events.

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorisation of the MAH/MAH REPRESENTATIVE conducting the study.

12.2 PUBLICATIONS

There are no plans to publish the data from this survey.

13 REFERENCES

1. Andrews E, Gilsenan A, Cook S. Therapeutic risk management interventions: feasibility and effectiveness. Journal of the American Pharmacists Association 2004;44:491-500.

ANNEXES

Numbered list of literature or electronic references of documents referred to in the protocol. Sufficient information should be provided to allow retrieval of the document.

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	2.0	20 August 2015	Questionnaire User Testing report
2	2.0	24 August 2015	Questionnaire
3	V11	July 2013	HCP guide
4	V12	July 2013	HCP checklist
5	V12	July 2013	Patient Guide
6	V10	July 2013	Patient Alert Card