MEASURE OF EFFECTIVENESS OF THE MINIMIZATION MEASURES OF RMP PROTOCOL

TITLE: Knowledge survey of educational materials in patients treated with Lemtrada® (alemtuzumab)

COMPOUND: Alemtuzumab

STUDY NAME: Lemtrada® EU-RMP Survey in patients

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 of educational materials in patients treated with Lemtrada®
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 objective of the survey is to assess descriptively the knowledge of treated patients about the key educational messages concerning autoimmune conditions and serious infections, and adherence to monitoring, to ensure the safe use of Lemtrada®. **Research questions:** • Has the patient received the Patient Guide and Patient Alert Card? • What is the knowledge of patients about the Patient Guide and Patient Alert Card? • What is the knowledge of patients about the risks associated with the use of Lemtrada®? • What is the knowledge of patients about risk minimization activities to be undertaken?
Countries of study	The survey will be conducted 18 months and 3 years following the launch of Lemtrada® in at least 5 countries, including launch in at least 2 of the highly populated EU countries (DE, FR, UK, IT, ES), with adequate translations in local languages.
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2 LIST OF ABBREVIATIONS

RMP	Risk Management Plan
PC	Patient Card
PL	Package Leaflet
PG	Patient Guide
HCP	Healthcare Professional
EMA	European Medicines Agency
PSP	Patient Support Programme
SmPC	Summary Of Medical Product Characteristics
MAH	Market Authorisation Holder
MS	Multiple Sclerosis
ITP	Immune Thrombocytopenic Purpura

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 patients and management of the questionnaire.

The survey is sponsored by Genzyme, a Sanofi company.

4 ABSTRACT

Title

A Cross Sectional Survey assessing the effectiveness of minimization measures of a risk management plan (RMP): Knowledge survey of educational materials in patients treated with Lemtrada®

Rationale and background

The Lemtrada® risk management plan (RMP) includes risk minimisation measures and education tools to support the safe use of the product. The patient educational materials (Patient Guide (PG) and Patient Alert Card (PC)) form one of the core elements of risk minimization targeted at patients. The primary objectives of the educational materials are to ensure early detection of events to mitigate severity and sequelae of autoimmune disease through education, and facilitating periodic monitoring, communicate risks (e.g. secondary autoimmune disease and serious infections), and need and importance of periodic monitoring, to patients and prescribers and to inform about benefit-risk decisions before each treatment course.

Research question and objectives

The objective of the survey is to assess the knowledge of patients regarding the key educational messages concerning autoimmune conditions and serious infections, and adherence to monitoring which support safe use of Lemtrada®. Research questions relate to the extent of patients' knowledge about the Patient Guide and Patient Alert Card, knowledge of serious adverse events relating to Lemtrada® and knowledge of risk minimization activities to be performed.

Study design

The study is a cross-sectional survey conducted in two distinct waves (18 months and 3 years) conducted each time over a 6-week period. The surveys will be conducted both online using a structured questionnaire. Results will be analysed and reported to the European Medicines Agency (EMA).

Population

The population for this study will be a randomly generated sample of patients treated for MS with Lemtrada®. The selected countries will include at least 2 of the highly populated EU countries (DE, FR, UK, IT, ES). The registered patient population will be described in terms of age and basic disease history and compared in each participating country with the known MS population statistics.

Variables

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

1) Whether the patient has received the Patient Guide and Patient Alert Card
2) Whether the patient carries the Patient Alert Card with them and whether the patient understands the purpose of the Patient Alert Card
3) The patient's understanding of the risks associated with use of the product
4) The patient's knowledge of the risk minimization activities to be undertaken: the type of monitoring required (e.g. blood and urine, self-monitoring) and the frequency and length of time monitoring required.

Data Sources

Data regarding the known MS population statistics for participating countries will be supplied by EU SA/GZ marketing. All other data will be collected via patient self-report in the questionnaire.

Study size

The survey will be conducted in 200 patients. Additionally, 200 patients (excluding those who completed the first round) will be invited to complete the second round questionnaire.

Data analysis

Descriptive analyses only will be performed. Sub-populations will be analyzed to identify patient groups that may require further education efforts.

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
-	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/Package Leaflet.

Description of Lemtrada® Risk Management Plan

The Lemtrada® risk management plan (RMP) includes additional risk minimisation measures and tools to support the safe use of the product. The patient educational materials (Patient Guide (PG) and Patient Alert Card (PC)) form one of the core elements of risk minimization targeted at patients.

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.

Patients will receive the PL, PG, and PC in hard copy at the time they have been confirmed to receive Lemtrada®. Additionally, the educational materials (PL, PG, and PC) will be available on Lemtrada® MS web portals of participating countries (e.g. the MS One to One web-portal) to provide electronic access to Health Care Professionals (HCPs) who prescribe the product, and to patients who have been prescribed the treatment. It is important to note that access to the Lemtrada® specific part of the web-portal is intended for patients treated with Lemtrada® only. In addition patients accessing the web-portal and/or enrolling into the programme will certify they are on treatment by entering a code number which can be found in the MS One to One Lemtrada® handbook provided to them by their HCP. As a consequence only patients (and not members of the general public) will be able to access the materials.

Patient Guide (PG)

The PG provides:

- Summary on risks of delayed side effects of certain autoimmune conditions and risk of serious infections
- Summary on recommended monitoring (duration and details of testing)
- Summary of symptoms to monitor and actions to be taken (carry card, contacting their doctor if they have symptoms, keeping up with their tests for the duration).

Patient Alert Card (PC)

Patients will use the PC to carry with them the key information for their safety and adherence to monitoring. The PC covers the following information:

- The ability (and need) to show the card to HCPs who are treating them for any condition
- Knowledge of side effects to be aware of and associated symptoms:
    - Autoimmune Conditions
        - Immune Thrombocytopenic Purpura – ITP
        - Kidney problems
        - Thyroid Disorder
    - Serious infections
- Importance of monitoring until four years after last course of treatment

It provides patients with a quick reference guide for risks as listed above including problems of the thyroid gland.

Relevant published research

This study will assess the knowledge of treated patients 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 information relating to patients' understanding of the risk messages that are discussed in the patient educational materials (PG and PC) for Lemtrada® prescribed for MS. It will evaluate the knowledge of patients prescribed Lemtrada®.

8 RESEARCH QUESTIONS:

1. Have patients received the Patient Guide and Patient Alert Card?

2. What is the knowledge of patients about the Patient Guide and Patient Alert Card?

    a. Do patients understand the purpose of the Patient Guide?

    b. Do patients understand the purpose of the Patient Alert Card?

3. What is the understanding of patients about serious adverse reactions related to Lemtrada®?

    a. Immune Thrombocytopenic Purpura (ITP)

    b. Kidney Disorders

    c. Thyroid Disorders

    d. Serious Infections

4. What is the patient's knowledge of the risk minimization activities to be undertaken?

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

    b. Frequency and length of time monitoring is required.

8.1 PRIMARY OBJECTIVE

The objective of the survey is to assess descriptively the knowledge of treated patients with regard to the educational materials and adherence to monitoring, 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 additional risk minimization (as described in the Patient Guide and Patient Alert Card) of patients treated with Lemtrada.

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

The study is cross-sectional and will use a convenience sample of patients prescribed Lemtrada. Data will be collected in two distinct waves (Wave 1 and Wave 2) conducted each time over a 6-week period. The surveys will be conducted using structured questionnaires, both online and on paper, 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 5 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

- Patient has been diagnosed with multiple sclerosis (MS)
- Patient has been prescribed at least one dose of Lemtrada®
- Patient supplies informed consent by ticking a box on the website.

9.2.2.2 Exclusion criteria

- Applies in Wave 2 only: Patient completed the survey in Wave 1

- Patient has not been prescribed Lemtrada®

9.2.3 Analysis populations

The survey is expected to include approximately two thirds female patient respondents because the male to female ratio for the disease is 0.5 (that is, 2 women for every man) [2].

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

9.2.4 Modalities of recruitment

9.2.4.1 Physician selection

Not applicable.

9.2.4.2 Patient selection

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

- Recruitment via online panels – panels exist for MS patients and will be used as the first recruitment approach;
- Telephone recruitment;
- Snowballing – we will ask respondents to suggest other potential respondents that may be interested in participating.

The prescription of therapies is under the responsibility of the patient's physician only.

9.3 VARIABLES

Knowledge is defined as awareness and understanding of important risk minimization information contained in the PL, PG and PC. Important risk information measured:

- Awareness of the patient guide and patient alert card and of the purpose of the patient guide and patient alert card.

- Knowledge of side effects to be aware of, and associated symptoms

- Awareness of the importance of monitoring until four years after last course of treatment

Knowledge will be measured via self-report using a questionnaire (see Annex 1). The questionnaire will comprise questions with single and multiple-choice responses (as appropriate). The questionnaire has been user tested by people with MS (described below).

Potential confounding factors

1. Length of time since first prescription of medication: it is possible that patients may only read the PL at first prescription and knowledge may decline over time. Self-reported length of time since first prescription of medication will be included as a variable for sub-group analysis.

2. Exposure to the information: patients who have received but not read the PG and PC may not have the same knowledge or demonstrate the same risk minimization behaviour as those who have read the information. The questionnaire will include a variable relating to whether the RMP materials have been read.

9.4 DATA SOURCES

Data regarding the known MS population statistics for participating countries will be supplied by EU SA/GZ marketing. All other data will be collected via patient 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 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 2150 Lemtrada® patients in the countries where the study is planned to be conducted, and taking into account an expected response rate of approximately 10%, the survey will be administered in a random selection of 200 patients.

9.5.2 Sample size

It is planned to recruit 200 patients in Wave 1 and 200 patients in Wave 2, from at least 5 countries including at least 2 highly populated EU countries (DE, FR, UK, IT, ES).

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

Patient 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.

Lemtrada patients 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 and survey consent page will be displayed. Patients 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.

Following receipt of consent, the patient 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 patient is ineligible (e.g. has not taken 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.

Eligible patients will move through the questionnaire measuring knowledge. Following completion of the questionnaire the patient will be thanked for their participation and shown the correct answers to all questions.

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

- Wave 2 only: Whether patient took part in Wave 1
- Country
- Age
- Treatment start date
- MS diagnosis date
- Gender
- Knowledge relating to Lemtrada® risk management

MS population data

- Age
- Year of MS diagnosis
- Gender

9.6.3 Site / Physician questionnaire

Not applicable.

9.6.4 Screening log (if applicable)

Not applicable.

9.6.5 Patient data

Patient data

- Age: Self-reported
- Treatment start date: Self-reported
- MS diagnosis date: Self-reported
- Gender: Self-reported

- Knowledge relating to Lemtrada® risk management: Self-reported

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

The analysis will be descriptive (e.g. frequency distributions for each item).

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: country, having read the RMP materials (ever (yes/no) and time since the RMP materials were read (in the last 6, 12 or 18 months)), time since prescription with Lemtrada®.

9.7.3 Interim analysis

No interim analysis is planned for this registry. 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 patients (without input from physicians), using a secure system.

Data will be anonymised 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. gender or age). 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 and behavior, 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.

Responsibilities of MAH/MAH REPRESENTATIVE

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

The MAH/MAH REPRESENTATIVE is responsible for:

- Local submission(s) complying with data protection rules,
- Any other local submission(s).

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 study 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 with closed questions 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.

2. World Health Organisation, Atlas of Multiple Sclerosis Resources in the World, 2008.

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	V12	July 2013	Patient Guide
4	V10	July 2013	Patient Alert card