POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

FINAL REPORT WAVE 1 AND WAVE 2

TITLE: Knowledge survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA® (alemtuzumab)

COMPOUND: ALEMTUZUMAB

SHORT TITLE: LEMTRADA® EU-RMP Survey in Patients

The Study is conducted by Genzyme, a Sanofi Genzyme Company, and Ipsos (3 Thomas More Square, London E1W 1YW), hereinafter referred also as the "MAH/MAH REPRESENTATIVE".

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PASS Information

Title	Knowledge Survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA (alemtuzumab)
Version identifier of the final study report	Version 1
Date of last version of the final study report	N/A
EU PAS register number	Study not registered
Active substance	Alemtuzumab
Medicinal product	LEMTRADA
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003178
Marketing authorization holder(s)	Sanofi Belgium
Joint PASS	No
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: 1. Has the patient received the Patient Guide (PG) and Patient Alert Card (PC)? 2. What is the knowledge of patients about the PG and PC? 3. What is the knowledge of patients about the risks associated with the use of LEMTRADA? 4. What is the knowledge of patients about risk minimization activities to be undertaken?
Countries of study	The first wave of the survey was conducted in the United Kingdom (UK), Germany, Italy, Spain, Denmark, and Norway. The second wave of the survey was conducted in the UK, Germany, Italy, Spain, Greece, Belgium and the Netherlands.

Marketing authorization holder(s)

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The Coordinating Investigator's and Company responsible medical officer's signed approvals of the report are kept by the company.

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The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

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Not applicable.

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Not applicable.

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2 OTHER RESPONSIBLE PARTIES

Ipsos has been involved in the preparation of the protocol and its amendments and has developed the survey and analysed the results. Ipsos was also responsible for the recruitment of patients and management of the questionnaire.

The survey was sponsored by Sanofi Genzyme.

3 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection Wave 1	December 2015	March 2016	The change from the planned start date 18 months after launch was due to delays in contracting, compliance, and local approvals.
End of data collection Wave 1	January 2016	July 2016	--
Interim Report 1 (Wave 1 results)	March 2016	November 2016	--
Start of data collection Wave 2	End of May 2017	October 2017	--
End of data collection Wave 2	September 2017	January 2018	--
Results Wave 2	November 2017	November 2018	--
Final report Wave 1 and 2 results	November 2017	November 2018	--

4 LIST OF ABBREVIATIONS

AE:	adverse event
EMA:	European Medicines Agency
EU:	European
MAH:	Marketing Authorization Holder
MS:	multiple sclerosis
PASS:	Post Authorization Safety Study
PC:	Patient Alert Card
PG:	Patient Guide
RMP:	risk management plan

5 INTRODUCTION

This report presents a concise overview of the combined results of Wave 1 and Wave 2 of the Knowledge survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA® (alemtuzumab).

The LEMTRADA risk management plan (RMP) includes risk minimization measures and tools to support the safe use of the product. The patient educational materials comprising the Patient Guide (PG) and Patient Alert Card (PC) form one of the core elements of risk minimization. The objective of the patient educational materials are to ensure early detection of key symptoms indicative of adverse events (AEs) to mitigate the severity and sequelae of autoimmune disease through education, and facilitating periodic monitoring, to communicate risks of signs and symptoms and the importance of periodic monitoring, and to inform about benefit-risk decisions before each treatment course.

Patients should have received the PG and PC from their HCP in hard copy at the time they were confirmed to receive LEMTRADA. Additionally, the patient educational materials are available on a Multiple Sclerosis (MS) One to One website to provide electronic access patients who have been prescribed treatment.

5.1 METHODOLOGY

To define the familiarity of patients with the educational materials, the sponsor has performed an international, cross-sectional survey, recruiting from a total 9 countries across the EU. The study was conducted in 2 distinct waves (Wave 1 and Wave 2) at approximately 18 months and 36 months after the launch of LEMTRADA in 2 highly populated EU countries (Germany and Spain). The objective of the survey was to assess the knowledge and adherence of patients treated with LEMTRADA with regard to the topics covered in the LEMTRADA educational materials (PC, PG), and thus the effectiveness of these materials to ensure the safe use of LEMTRADA.

Research questions were related to the extent of the patients' awareness and purpose of the PG and PC, knowledge of side effects to be aware of, and associated symptoms and action to be taken should they occur, and awareness of the importance of monitoring until 4 years after last course of treatment. The survey was conducted online using a structured questionnaire. A convenience (ie, non-random) sample of MS patients treated with LEMTRADA was selected, and data was collected via patient self-report. A threshold of 70% was defined as 'adequate' knowledge.

The first wave of the survey (Wave 1) was conducted with 201 patients recruited from Italy (n=49 [24%]), Germany (n=46 [23%]), Spain (n=44 [22%]), Norway (n=32 [16%]), the UK (n=22 [11%]), and Denmark (n=8 [4%]). Results were analyzed and were reported to the European Medicines Agency (EMA) within procedure PSUSA/00010055/201609. The second wave of the survey (Wave 2) was conducted in the same manner as for Wave 1 with 200 patients recruited from Italy (n=53 [27%]), Spain (n=45 [23%]), the UK (n=43 [22%]), Germany (n=32 [16%]), Belgium (n=12 [6%]), Greece (n=11 [6%]), and the Netherlands (n=4 [2%]). Participants in Wave

1 were excluded from participating in Wave 2. Reports of the Wave 1 and Wave 2 survey can be found in Annex 1 of this report.

5.2 DATA COLLECTED

The Questionnaire collected data concerning patient characteristics, including:

- Patient's country, age, gender, year of first LEMTRADA infusion, year of MS diagnosis
- Patient's receipt and understanding of the purpose of the patient educational materials
- How long ago the patient read the PG and the amount of PG read
- Whether the doctor/nurse discussed the PG prior to the first LEMTRADA infusion
- Patient's understanding of SAEs signs and symptoms, and action to be taken if they occur
- Patient's knowledge of the risk minimization activities to be undertaken

No identifiable data regarding patients were collected.

5.3 DIFFERENCES IN QUESTIONNAIRES AND SCORING

The protocol was amended once in between the two waves (Protocol version identifier 1.8, 08 May 2017; see Annex 1) to reformat to current Sanofi standards and to add a threshold of 70% to define 'adequate' knowledge. In addition, some of the Wave 1 responses were rephrased or deleted, and some questions were added in Wave 2.

6 RESULTS

6.1 DEMOGRAPHIC RESULTS

Over the 2 waves, the survey was conducted in a total of 401 (201 Wave 1, 200 Wave 2) patients from Belgium, Denmark, Germany, Greece, Italy, the Netherlands, Norway, Spain, and the UK. The population surveyed was generally consistent between Wave 1 and Wave 2 (common demographics questions on both surveys). The majority (52% Wave 1, 60% Wave 2) were female patients. Most participants (80% Wave 1, 73% Wave 2) were age 45 years or younger. Most patients in Wave 1 (83%) received a diagnosis of MS between 2010 and 2016, and the average number of months since the first LEMTRADA infusion was 13.6. Most patients in Wave 2 (57%) had been diagnosed with MS less than 5 years from the survey, and 46% received their first LEMTRADA infusion in 2016.

6.2 PRIMARY ANALYSIS

6.2.1 Awareness of Patient Educational Materials

The majority of patients in both Waves reported that they had received the PC and the PG (Table 1, Q9, Q11). Of those patients who had received the PG, 97% in Wave 1 and 94% in Wave 2 reported reading at least half of it (Q14). In Wave 2, most (75%) had read the PG more than 3 months ago (Q14a; question was not asked in Wave 1). More patients in Wave 2 (64%) than in Wave 1 (25%) knew the purpose of the PC (Q10); likewise, more patients in Wave 2 (78%) than in Wave 1 (32%) knew the purpose of the PG (Q12). Most patients in both waves (92% Wave 1, 88% Wave 2) who had received the PG also reported having the guide explained to them by their doctor or nurse before their first infusion (Q11a).

As an additional exploratory question, Wave 2 asked if patients had suggestions for improving the PG (Table 1, Q14b; question was not asked in Wave 1). The most popular suggestion was to add more pictures (41%) followed by adding more detailed information in general (37%) and covering topics other than side effects, such as quality of life (29%).

Table 1 - Knowledge about Patient Guide and Patient Educational Materials across waves

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.9 Have you received and reviewed the Patient Alert Card?	Yes	155 (77%)	131 (66%)
	No	32 (16%)	58 (29%)
	Don't remember	14 (7%)	11 (6%)

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.10 Purpose of the Patient Alert Card?[a]	Correct answer	38 (25%)	84 (64%)
	2/3 responses selected	33 (21%)	NA
	1/3 responses selected	79 (51%)	NA
	Don't know/not sure	5 (3%)	1 (1%)
Q.11 Have you received and reviewed the Patient Guide?	Yes	164 (82%)	137 (69%)
	No	26 (13%)	53 (27%)
	Don't remember	11 (6%)	10 (5%)
Q.12 Purpose of the Patient Guide?[b]	Correct answer	52 (32%)	107 (78%)
	2/3 responses selected	35 (21%)	NA
	1/3 responses selected	77 (47%)	NA
	Don't know/not sure	5 (3%)	1 (1%)
Q.14 How much of the Patient Guide have you read?[b]	All of it	82 (50%)	87 (64%)
	More than half of it	56 (34%)	25 (18%)
	About half of it	21 (13%)	17 (12%)
	Less than half of it	4 (2%)	5 (4%)
	None of it	1 (1%)	3 (2%)
Q.14a How long ago did you read the Patient Guide?[b]	<1 week ago	NA	2 (1%)
	Between 1-2 weeks ago	NA	9 (7%)
	Between 2-4 weeks ago	NA	14 (10%)
	Between 1-3 months ago	NA	9 (7%)
	>3 months ago	NA	100 (75%)
Q.11a Did your doctor/nurse discuss the PG with you before your first infusion of LEMTRADA?[b]	Yes	150 (92%)	121 (88%)
	No	9 (6%)	11 (8%)
	Don't know	5 (3%)	5 (4%)
	No	NA	15 (20%)
Q.14b Do you have any suggestions to improve the PG?[b]	More detailed information in general	NA	50 (37%)
	Less detailed information in general	NA	15 (11%)
	More pictures	NA	55 (41%)
	Less pictures	NA	2 (1%)
	Covering topics other than side effects, such as QoL	NA	69 (29%)
	More practical	NA	39 (20%)
	Other	NA	6 (4%)

NA = Not asked in the questionnaire

a Answered by respondents who have received and reviewed the Patient Alert Card

b Answered by respondents who have received and reviewed the Patient Guide

6.2.2 Knowledge about SAEs and signs and symptoms related to LEMTRADA

Patient knowledge of the serious adverse events and signs and symptoms of important risks with LEMTRADA was surveyed in both Wave 1 and Wave 2. Percentages of 'correct' answers are provided in Table 2.

Of note, in Wave 1, for most questions a list of possible responses was provided and patients had to choose all of the correct responses to score a 'complete answer'. This resulted in the fact that questions could be answered partially, as explained in the Comments column.

Responses for all of the questions on SAEs and signs and symptoms of risks were below the adequacy level of 70% in both waves, although patients in Wave 2 had higher scores than patients in Wave 1. This may be because the questions in Wave 2 contained part of the correct answer, and patients then had to choose from 3 options to complete the answer instead of choosing multiple options as mentioned above.

Table 2 - Knowledge about SAEs and signs and symptoms related to LEMTRADA (Responses by Patients Who Reported Receiving and Reviewing the Patient Guide)

Question (abbreviated)	Correct answers		
	Wave 1	Wave 2	Comments
Q15: Symptoms of bleeding disorder	12 (7%)	108 (54%)	In Wave 1, 5 topics had to be selected to answer completely (7% of patients); 11% selected at least 4/5 topics and 23% selected 3/5; 58% selected 2/5 or 1/5 or 0/5 responses.
Q17: Symptoms of kidney problems or anti-GBM disease	44 (27%)	112 (56%)	In Wave 1, 2 topics had to be selected to answer completely (27% of patients); 46% selected 1/2 topics and 27% selected 0/2.
Q19: Symptoms of overactive thyroid	15 (9%)	126 (63%)	In Wave 1, 5 topics had to be selected to answer completely (9% of patients); 26% selected at least 4/5 or 3/5 topics and 65% selected 2/5 or 1/5 or 0/5 responses.
Q20: Symptoms of underactive thyroid	17 (10%)	112 (56%)	In Wave 1, 4 topics had to be selected to answer completely (10% of patients); 37% selected at least 3/4 or 2/4 topics and 52% selected 1/4 or 0/4 responses.

6.2.3 Knowledge of risk-minimization activities

On patient knowledge of the actions that should be taken upon noticing symptoms associated with side effects or severe reactions to LEMTRADA, the correct response option for all questionnaire items – 'See your doctor immediately' – received the highest proportion of responses within each item in both Wave 1 and Wave 2 (bleeding disorder: 41% Wave 1, 84% Wave 2; kidney disorder: 45% Wave 1, 78% Wave 2; thyroid disorder: 43% Wave 1, 77% Wave 2) (Table 3). However, in Wave 1 all correct responses were <70% compared with Wave 2 where they were all >70%. In addition, nearly one-third of patients in Wave 1 identified 'waiting' (an incorrect answer) as a valid option following the appearance of symptoms of a bleeding, kidney, or thyroid disorder.

With regard to the appearance of new, recurring, or worsening symptoms, the correct response option for all questionnaire items – 'Call your doctor right away' – again received the highest proportion of responses within each item in both Wave 1 and Wave 2 (new symptoms: 41% Wave 1, 79% Wave 2; recurring symptoms: 36% Wave 1, 67% Wave 2; worsening symptoms: 48% Wave 1, 78% Wave 2) (Table 3). However, again, in Wave 1 all correct responses were <70% compared with Wave 2 where the frequency of correct responses were close to or above 70%. Few respondents indicated it is valid to 'take no action' for new symptoms, although approximately one quarter to one-third of patients in Wave 1 indicated it is valid to 'continue to monitor your symptoms for another week' when experiencing new, recurring, or worsening symptoms.

Table 3 - Knowledge of risk-minimization activities

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.16 If you have symptoms of a bleeding disorder, what action should you take?	Wait until the bleeding stops	52 (32%)	NA
	Tell a doctor at your next scheduled visit	45 (28%)	21 (11%)
	Contact your doctor immediately ✓	**66 (41%)**	**167 (84%)**
	Make an appointment to see your doctor within the next 4 weeks	NA	10 (5%)
	None	NA	1 (1%)
Q.18 If you have symptoms of a kidney disorder, what action should you take?	Wait to see if the symptoms resolve	49 (30%)	9 (5%)
	Tell a doctor at your next scheduled visit	40 (25%)	21 (11%)
	Contact your doctor immediately ✓	**74 (45%)**	**155 (78%)**
	Drink extra fluids	NA	15 (8%)
Q.21 If you have symptoms of a thyroid disorder, what actions should you take?	Wait to see if the symptoms resolve	35 (22%)	8 (4%)
	Tell a doctor at your next scheduled visit	58 (36%)	34 (17%)
	Contact your doctor immediately ✓	**70 (43%)**	**153 (77%)**
	Eliminate all carbohydrates from your diet for at least 4 weeks	NA	5 (3%)
Q.25 What should you do if you experience signs or symptoms that you have not experienced before?	Take no action	16 (10%)	NA
	Continue to monitor your symptoms for another week	55 (34%)	NA
	Continue to monitor your symptoms for another month	26 (16%)	NA
	Contact your doctor immediately ✓	**66 (41%)**	**157 (79%)**
	Wait 4 weeks to see if the symptoms resolve	NA	7 (4%)
	Tell your doctor at your next scheduled visit	NA	33 (17%)
	Find a patient contact group on the Internet	NA	3 (2%)
Q.25b What should you do if you experience signs or symptoms that you have had before, then disappeared and have now come back?	Take no action	15 (9%)	NA
	Continue to monitor your symptoms for another week	57 (35%)	NA
	Continue to monitor your symptoms for another month	33 (20%)	NA
	Contact your doctor immediately ✓	**58 (36%)**	**134 (67%)**
	Wait 4 weeks to see if the symptoms resolve	NA	14 (7%)
	Tell your doctor at your next scheduled visit	NA	50 (25%)
	Find a patient contact group on the Internet	NA	2 (1%)

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.25c What should you do if you experience signs or symptoms that you had all the time and have now become worse?	Take no action	10 (6%)	NA
	Continue to monitor your symptoms for another week	44 (27%)	NA
	Continue to monitor your symptoms for another month	31 (19%)	NA
	Contact your doctor immediately ✓	**78 (48%)**	**156 (78%)**
	Wait 4 weeks to see if the symptoms resolve	NA	10 (5%)
	Tell your doctor at your next scheduled visit	NA	33 (17%)
	Find a patient contact group on the Internet	NA	1 (1%)

✓ Correct answer

Patient knowledge of the frequency of required periodic monitoring and their duration after their last LEMTRADA infusion was surveyed in both Wave 1 and Wave 2. Percentages of 'correct' answers are provided in Table 4.

Responses for all of these questions were below the adequacy level of 70% in both waves, although patients in Wave 2 had higher scores than patients in Wave 1. With regard to blood and urine tests after an infusion of LEMTRADA, 39% of patients in Wave 1 and 66% of patients in Wave 2 answered correctly. However, 25% of patients in Wave 1 and 3% of patients in Wave 2 believed blood and urine tests should be done more frequently than the requirement (weekly instead of monthly). Similarly, for testing thyroid function, 14% of patients in Wave 1 and 49% of patients in Wave 2 answered correctly. However, 80% and 45%, respectively, selected the more frequent testing options (weekly, monthly, or every 2 months instead of every 3 months).

Patient responses about how long it is necessary to continue having blood and urine tests for auto-immune conditions (bleeding, kidney, and thyroid disorders) show that 14% of patients in Wave 1 and 56% of patients in Wave 2 are aware that testing should be continued for 4 years after the last course of treatment. All other patients in both waves believed that testing should be continued for a shorter time frame (6 weeks–2 years) after the last course of treatment with LEMTRADA.

Table 4 - Patient Knowledge of frequency of required periodic monitoring and their duration after last infusion

Question (abbreviated)	Correct answers		
	Wave 1	Wave 2	Comments
Q.14c After an infusion of LEMTRADA, how often should you have blood and urine tests	63 (39%)	131 (66%)	In Wave 1, an additional 25% of patients selected a more stringent answer (weekly instead of monthly). In Wave 2, an additional 3% of patients selected a more stringent answer (weekly instead of monthly).
Q.23 After an infusion of LEMTRADA, how often should you have thyroid function tests	22 (14%)	98 (49%)	In Wave 1, an additional 80% of patients selected a more stringent answer (weekly, monthly, or every 2 months instead of every 3 months). In Wave 2, an additional 45% of patients selected a more stringent answer (weekly, monthly, or every 2 months instead of every 3 months).
Q.24 For how long is it necessary to have blood and urine tests for auto-immune conditions (bleeding, kidney and thyroid disorders	22 (14%)	111 (56%)	

6.3 SUMMARY OF SECONDARY ANALYSES

Although there were some slight differences, subgroup comparisons were generally consistent between Wave 1 and Wave 2.

Subgroup comparisons by time since first infusion or how long ago the PG was read were consistent with the primary analysis results. There were no apparent trends within groups with regard to receipt of the patient educational materials, knowledge on symptoms of the most important side effects (overall <70% for both waves), knowledge of risk minimization activities (overall >70% for Wave 2 but <70% for Wave 1), and knowledge of timing of monitoring tests (<70% for both waves). The scores for receipt of the PC and PG over the years since first infusion suggested that distribution of materials has not reduced over the years. Having read all of the PG or at least a substantial amount of it correlated with higher levels of knowledge for most comparisons.

For subgroup comparison by country, in both waves patients from the UK had among the highest scores for receiving, reading, and understanding the purpose of the PC and PG. Consistent with the primary analysis, scores for knowledge on symptoms of side effects were low (<70%) for all countries with few exceptions; patients from the UK were most knowledgeable about signs and symptoms as shown by higher proportions of complete answers in both waves. Overall, there were no apparent trends among countries except that in Norway in Wave 1 and Belgium in Wave 2 consistently had among the lowest scores.

7 DISCUSSION

7.1 KEY RESULTS

In both waves, the findings of this survey indicate that patients received and read the PC and PG. In Wave 1 and Wave 2 (respectively), 77% and 66% reported receiving and reviewing the PC, and 82% and 69% reported receiving and reviewing the PG. In Wave 1 and Wave 2, 50% and 64%, respectively reported reading at least half of the PG, and 92% and 88% reported that their doctor/nurse discussed the PG with them before the first infusion of LEMTRADA. The PG thus seems a well-established tool to facilitate discussion between patients and HCPs. However, for those who did not receive or did not remember receiving the PG, it may be that a nurse/HCP may have gone through the PG with the patient but did not give it to them. Although patients should receive it, all patients could have been exposed to the content of the PG at some point before receiving LEMTRADA. Nevertheless, the MAH is committed to continue to stress the importance of these materials to HCPs in their contact with the patients.

Patient knowledge was lower than the 70% limit for acceptability in knowledge on symptoms of side effects related to LEMTRADA, but in all cases patients in Wave 2 scored higher than those in Wave 1. Patient knowledge of the actions that should be taken upon noticing symptoms was better than knowledge of the symptoms themselves, although scores for patients in Wave 1 were still well below 70% (range: 36%–48%). By comparison, scores for the risk minimization activities in Wave 2 ranged from 67% to 84%. There are several items that may have influenced both the Wave 1 and Wave 2 survey results that merit discussion.

Many of the questions in Wave 1 asked patients to select from a list of possible responses, and patients had to choose all of the correct responses to score a ‘complete answer’. This was recognized as a difficult task to perform from memory, especially for a lay person with no medical knowledge, and in the amended protocol for Wave 2, patients were asked to select the response that completed the question in the best way, which may explain why scores in Wave 2 were higher than those in Wave 1.

Although the protocol amendment improved the way questions were asked, it may be that some possible answers still confused respondents. In both waves, some of the alternative answers were very similar. For example, for the questions about the appropriate action if a patient experiences a new, recurring, or worsening symptom, the correct answer was, ‘Contact your doctor immediately’ and was selected by the majority of patient in both Wave 1 and Wave 2. However, an alternative answer in Wave 1 was, ‘Continue to monitor your symptoms for another week’, and this was selected by about one-third of Wave 1 patients. An alternative answer in Wave 2 was, “Tell your doctor at your next scheduled visit’, and this was selected by approximately 20% of Wave 2 patients. It may be that many patients do not want to ‘bother’ their doctors, and for them this answer is quite reasonable. Few respondents incorrectly indicated it was valid to wait to see if the symptoms resolve, which is encouraging. Even if patients do not know exactly what to watch for in case of, eg, thyroid disorder, they seem to know that if they experience new/worsening symptoms they should go to their doctor as soon as possible, which means that the main objective

of patient risk minimization materials is working. As long as patients check new symptoms with an HCP (who holds the responsibility of recognizing symptoms of adverse reactions), worsening can be prevented and the objective to ensure early detection of events to mitigate the severity and sequelae of autoimmune disease can be considered met.

In addition, while patient knowledge to questions about the frequency of required periodic monitoring was <70% in both waves, patients in both waves responded with more stringent answers than the 'correct' ones. For example, regarding how often should patients have blood and urine tests after an infusion of LEMTRADA, 39% of patients in Wave 1 selected the correct answer (monthly), but an additional 25% of patients selected a more stringent answer (weekly instead of monthly). In Wave 2, 66% of patients selected the correct answer and an additional 3% selected the more stringent answer (weekly instead of monthly). Although knowledge of the frequency of the specific tests is below 70%, knowledge of the timing of each of the specific tests separately is less important than overall awareness that monthly testing is required. Furthermore, most patients are accustomed to monthly blood and urine tests without knowing exactly which tests are ordered by their HCP at each visit.

Patient knowledge that blood and urine tests for autoimmune conditions (bleeding, kidney, and thyroid disorders) should be continued for 4 years following final course of treatment with LEMTRADA was also suboptimal, with 56% of patients scoring correctly. Approximately 86% of patients in Wave 1 and nearly 45% of patients in Wave 2 thought that testing should be continued 2 years or less (6 weeks, 6 months, or 2 years). This finding suggests that this may be an area where knowledge could be improved among patients. Also, HCPs should also be counseling patients on the importance of follow-up for 4 years.

A mitigating factor is that questions were to be answered without having the educational materials at hand. In addition to the fact that recalling all details from memory might already be difficult in the general population, MS is a disease in which many patients suffer from cognitive problems, including memory loss.

7.2 SUBGROUP ANALYSES

Subgroup comparisons by time since first infusion or how long ago the PG was read were consistent with the primary analysis results. There were no apparent trends within groups with regard to receipt of the patient educational materials, knowledge on symptoms of the most important side effects (overall <70%), knowledge of risk minimization activities (overall >70%), and knowledge of timing of monitoring tests (overall <70%). The scores for receipt of the PC and PG over the years since first infusion, suggesting that distribution of materials has not reduced over the years.

Having read all of the PG or at least a substantial amount of it correlated with higher levels of knowledge. However, regarding patient knowledge of the actions that should be taken upon noticing new, returning, or worsening symptoms, there seemed to be no consistent pattern among groups no matter how much of the PG was read. Those who reported reading all of the PG scored (Wave 1 and Wave 2, respectively) 55% and 83% for new symptoms, 46% and 63% for returning symptoms, and 61% and 80% for worsening symptoms.

For subgroup comparison by country, in both waves patients from the UK had among the highest scores for receiving, reading, and understanding the purpose of the PC and PG. Consistent with the primary analysis, scores for knowledge on symptoms of side effects were low (<70%) for all countries with few exceptions. Overall, there were no apparent trends among countries except that in Norway in Wave 1 and Belgium in Wave 2 consistently had among the lowest scores. However, Belgium has an interesting program (LemMon patient support program). After informed consent, the patient is registered in the program and a visiting nurse comes to the patient's home for monthly blood sampling. The blood is analyzed in a central lab and results are published on a platform that can be accessed by neurologists, who receive email alerts when results are posted. Therefore, the patient is not involved at all in knowing when to call or what tests are being performed, which could explain the lower knowledge among Belgian patients.

7.3 STRENGTHS AND LIMITATIONS

The strength of this comprehensive survey include the number of patients included (N=401), the wide distribution in a total of 9 EU countries over 2 waves (Germany, Italy, Spain, UK, Denmark, Norway, Greece, Belgium, and the Netherlands), and the wide range of questions presented to participants, which describe the most important aspects of LEMTRADA risk management knowledge for patients.

Limitations of this survey include the wording of survey questions that may have misled patients to provide answers that were later deemed 'incorrect' or 'incomplete' (when the patient may in reality have a good understanding of individual signs and symptoms). Limitations also include the use of a cross-sectional design which made it difficult to determine whether the patient educational materials increased knowledge, or whether increased knowledge among those who had received and reviewed the materials was the result of another factor, such as conscientiousness or motivation. A convenience sample (non-randomized) was used, rather than a random sample, and included only patients from the EU, which means that the findings may not be representative of the whole population of patients taking LEMTRADA, thereby limiting the generalizability of the results. Some of the subgroup analyses numbers were small and comparisons were limited to descriptive observations. Also, all data were self-reported, and there was no opportunity to verify source data.

Another potential limitation is that questions were to be answered without using the educational materials. In practice, patients should be encouraged to have the educational materials on hand or be reminded how to access these materials through the MS One to One site, and encouraged to reference the materials as needed. The MAH is still working on improving our reach to both patients and HCPs, eg, via digital initiatives.

8 CONCLUSION

The survey findings indicated that the majority of patients acknowledged the receipt of the PC and PG and that these numbers seem stable across the years in which patients began infusions of LEMTRADA. Almost all patients who reported receiving the materials, read at least half of them. Patient knowledge about the purposes of the educational materials was overall moderate to adequate. Patients' overall score was <70% for the symptoms associated with the most important adverse reactions to LEMTRADA and frequency of monitoring for specific conditions. It is encouraging that although the knowledge on specific SAEs may be lacking, patients were knowledgeable about risk minimization measures for various signs and symptoms. For example, the results of this survey suggest that patients will contact their HCP as soon as possible in case of new/worsening symptoms. However, few patients were aware that blood/urine monitoring should continue for 4 years following the final course of LEMTRADA, which highlights a need for HCPs to reinforce this message.

The survey results may be influenced by the design of the study, in that patients were not shown the educational materials nor were allowed to reference them during the survey.

Useful actions to improve patient knowledge include ensuring that all patients have access to materials that they can read, and encouraging them to keep and refer to the materials as needed. Other methods for improving patient knowledge might include reinforcing to HCPs the need to go through the materials with them to emphasize and reiterate information, and that this process be repeated with patients periodically to ensure the information remains up to date and the patient remains aware of the importance of having adequate knowledge. Finally, patients should be reminded that the educational materials (PG and PC) are available on the MS One to One web site.

To further strengthen the LEMTRADA risk minimization approach, the MAH continues its efforts to ensure that all patients are reached and commits to stressing the importance of these materials to HCPs who are in contact with the patients. The MAH is still working on improving our reach to both patients and HCPs, eg, via digital initiatives.

ANNEXES

List of stand-alone documents

Annex 1

Number	Document reference number	Date	Title
1	Post Authorization Safety Study (PASS) Interim Report (Wave 1)	09 November 2016	Knowledge Survey to assess the effectiveness of educational materials among healthcare professionals who prescribe LEMTRADA® (alemtuzumab)
2	Post Authorization Safety Study (PASS) Report (Wave 2)	13 November 2018	Knowledge Survey to assess the effectiveness of educational materials among healthcare professionals who prescribe LEMTRADA® (alemtuzumab)

SANOFI GENZYME

POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

TITLE: Knowledge Survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA® (alemtuzumab)

COMPOUND: ALEMTUZUMAB

STUDY NUMBER: N/A

SHORT TITLE: LEMTRADA EU-RMP SURVEY IN PATIENTS

The Study is conducted by Genzyme, a Sanofi Genzyme Company, and Ipsos (3 Thomas More Square, London E1W 1YW), hereinafter referred also as the "MAH/MAH REPRESENTATIVE".

Version number:	7		
Date:	13 November 2018	Total number of pages:	55

PASS Information

Title	Knowledge survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA (alemtuzumab)
Version identifier of the final study report	Version 1
Date of last version of the final study report	30 November 2015 (Wave 1) No report has been issued before for Wave 2
EU PAS register number	Study not registered
Active substance	Alemtuzumab
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 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: 1. Has the patient received the Patient Guide (PG) and Patient Alert Card (PC)? 2. What is the knowledge of patients about the PG and PC? 3. What is the knowledge of patients about the risks associated with the use of LEMTRADA? 4. What is the knowledge of patients about risk minimization activities to be undertaken?
Countries of study	The first wave of the survey was conducted in the United Kingdom (UK), Germany, Italy, Spain, Denmark, and Norway. The second wave of the survey was conducted in the UK, Germany, Italy, Spain, Greece, Belgium and the Netherlands.

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	Sanofi Belgium Leonardo Da Vincilaan 19 B-1831 Diegem Belgium
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TABLE OF CONTENTS

1 ABSTRACT

Title

Knowledge survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA (alemtuzumab)

Keywords

LEMTRADA, audit, risk minimization materials, effectiveness

Rationale and background

The LEMTRADA risk management plan (RMP) includes risk minimization measures and education tools to support the safe use of the product. The patient educational materials comprising the 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, to communicate risks (eg, secondary autoimmune disease), and the 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 this survey is to assess descriptively the knowledge and adherence of treated patients with regard to the topics covered in the LEMTRADA educational materials, and thus the effectiveness of these materials to ensure the safe use of LEMTRADA. The specific research questions address patients' knowledge about the PG and PC, their knowledge of serious adverse events (SAEs) relating to LEMTRADA, and their knowledge of risk minimization activities to be performed.

Study design

This was an international, cross-sectional survey, conducted in 2 distinct waves (Wave 1 and Wave 2) at 18 months and 36 months after the launch of the product in 2 highly populated EU countries (Germany and Spain). Wave 1 results were analyzed and were reported to the European Medicines Agency (EMA) within procedure PSUSA/00010055/201609. The start of data collection for Wave 2 was October 2017; end of data collection for Wave 2 was February 2018. This report describes Wave 2 of the survey

Setting

- Site and patient selection: A convenience (ie, non-random) sample of patients treated for multiple sclerosis (MS) with LEMTRADA, recruited from the UK, Germany, Italy, Spain, Greece, Belgium, and the Netherlands.

- Data regarding the known MS population statistics for participating countries were supplied by the Marketing Authorization Holder (MAH). All other data were collected via patient self-reporting in a structured online questionnaire.

Patients and study size, including dropouts

The sample size was based on an estimate of 2150 LEMTRADA patients in the countries where the study was planned. A 10% response rate was expected, which was equivalent to approximately 200 patients.

Variables and data sources

- Variables and evaluation criteria: The following elements were collected and assessed:
  1. Whether the patient received the PG and PC
  2. Whether the patient carries the PC with them and whether the patient understands the purpose of the PC
  3. The patient's understanding of the risks associated with use of LEMTRADA
  4. The patient's knowledge of the risk minimization activities to be undertaken
- Data regarding the known MS population statistics for participating countries were supplied by the MAH. All other data were collected via patient self-reporting in a structured online questionnaire.
- Data analyses: Descriptive analyses were performed. For all analyses, a threshold of 70% was defined as 'adequate' knowledge.

Results

The survey was conducted in 200 patients from 7 countries (UK, Germany, Italy, Spain, Greece, Belgium, and the Netherlands). Nearly two-thirds of the patients (60%) were female. The majority of patients (73%) were age 45 years or younger. Most patients (57%) had been diagnosed with MS less than 5 years ago, and 46% received their first LEMTRADA infusion within 2 years of the survey.

Key results from this survey include the following:

- The majority of patients recalled having received the PC (66%) and the PG (69%). Patient understanding of the purpose of the PC was 64% while the knowledge level concerning the purpose of the PG was 78%. Most patients (88%) who had received the PG also reported having the guide explained to them by their doctor or nurse before their first infusion.
- Knowledge about the specific symptoms related to relevant medical conditions was <70%. Fifty-four percent of the patients provided a correct answer for the question on bleeding disorders, 56% for kidney disorders, and 63% for overactive thyroid disorder, and 56% for underactive thyroid disorder.
- Patient knowledge of risk minimization activities was adequate:

- The correct response option for all questionnaire items – 'See your doctor immediately' – received the highest proportion of responses within each item (bleeding disorder, 84%; kidney disorder, 78%; thyroid disorder, 77%).
- Few respondents incorrectly indicated it was valid to make an appointment to see the doctor within the next 4 weeks (bleeding disorder, 5%) or wait to see if the symptoms resolve (kidney disorder, 5%; thyroid disorder, 4%).
- With regard to new signs/symptoms, knowledge on the appropriate action to be taken was 79%; for recurring signs/symptoms, 67% would take the appropriate action; for worsening signs/symptoms, 78% would take the appropriate action.
- Correct knowledge of the specific timepoints at which monitoring activities for autoimmune events should be conducted was lower (<70%).

Discussion

Patient knowledge of risk minimization activities was adequate (≥70%), although patients' overall score was <70% on knowledge on specific SAEs associated with LEMTRADA. A potential explanation for less than adequate responses on specific risks may be that patients were asked to answer the questions for the survey without referring to the PG or the PC.

While patient knowledge on specific symptoms was less than adequate, patients had sufficient knowledge on what actions to take in case of signs of a medical condition. For example, results suggest that patients will contact their HCP as soon as possible in case of new/worsening symptoms, which puts in perspective the lower results of the knowledge of SAEs/signs and symptoms. Even if patients do not know exactly what to look out for in case of, eg, thyroid disorder, they do know that if they experience new/worsening symptoms they should go to their doctor as soon as possible. As long as patients check new symptoms with an HCP (who holds the responsibility of recognizing symptoms of adverse reactions), worsening can be prevented and the objective to ensure early detection of events to mitigate the severity and sequelae of autoimmune disease can be considered met.

Useful actions to improve patient knowledge include ensuring that all patients have access to materials that they can read, and encouraging them to keep and refer to the materials as needed. Other methods for improving patient knowledge includes a qualified HCP to go through the materials with them to reinforce and reiterate information, and that this process must be repeated with patients periodically to ensure the information remains up to date and the patient remains aware of the importance of having adequate knowledge. Finally, patients should be reminded that the educational materials (PG and PC) are available on the MS One to One web site.

Conclusion

Cognitive impairment is frequent among patients with RRMS (1). Overall, the survey indicated that less than 70% of patients recalled receiving or reading the patient educational materials and patients had trouble recalling the specific signs of the SAE and frequency of monitoring for specific conditions. However, patients were knowledgeable about risk minimization measures for various signs and symptoms. These results may be influenced by the design of the study, in that patients were not shown the educational materials nor allowed to reference them during the

survey. In practice, patients must be encouraged to access, reference, and read the materials as often as necessary. Thus, the survey results emphasize the importance of distribution of the patient educational materials as well as the need for patients to read and discuss them with their HCP. To further strengthen the LEMTRADA risk minimization approach, the MAH continues its efforts to ensure that all patients are reached and commits to stressing the importance of these materials to HCPs in contact with the patients.

Study Personnel

The MAH and Company responsible medical officer's signed approvals of the report are kept by the Company.

This report was prepared by: Sandy Buckley (PRA medical writer), Anne Katrine Andreasen (EU medical lead), Jeri Nijland (EU regulatory), Emmanuelle Hoogewys-Cynober (Risk Management Expert).

The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

2 LIST OF ABBREVIATIONS

anti-GBM:	anti-Blomerular Basement Membrane
EU:	European
MS:	multiple sclerosis
PASS:	Post Authorization Safety Study
PC:	Patient Alert Card, Patient Alert Card
PG:	Patient Guide, Patient Guide
PL:	Package Leaflet
SmPC:	Summary of Product Characteristics

3 RESPONSIBLE PARTIES

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4 OTHER RESPONSIBLE PARTIES

Ipsos has been involved in the preparation of the protocol and its amendments and has developed the survey and analyzed the results as well as the recruitment of patients and management of the questionnaire.

The survey was sponsored by Sanofi Genzyme.

5 MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection Wave 1	December 2015	March 2016	The change from the planned start date 18 months after launch was due to delays in contracting, compliance, and local approvals.
End of data collection Wave 1	January 2016	July 2016	--
Interim Report 1 (Wave 1 results)	March 2016	November 2016	--
Start of data collection Wave 2	May 2017	October 2017	--
End of data collection Wave 2	June 2017	February 2018	--
Results Wave 2	September 2017	November 2018	--
Final report Wave 1 and 2 results		November 2018	--

6 RATIONALE AND BACKGROUND

6.1 BACKGROUND

Safety profile

For the safety profile of LEMTRADA, please refer to the current version of the Summary of Product Characteristics (SmPC)/Package Leaflet (PL).

Description of LEMTRADA Risk Management Plan

The LEMTRADA RMP includes risk minimization 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 (eg, secondary autoimmune disease), and the need and importance of periodic monitoring, to patients and prescribers.
- Inform about benefit-risk decisions before each treatment course.

Apart from the PL, patients should have received the PG and PC from their prescriber in hard copy at the time they were confirmed to receive LEMTRADA.

Additionally, the educational materials (PG and PC) and PL are available on the MS One to One web site to provide electronic access patients who have been prescribed treatment.

Of note, access to the LEMTRADA-specific part of the web-portal was intended for patients treated with LEMTRADA only. Patients accessing the web portal and/or enrolling into this program certified that they were on treatment by entering a code number found in the MS One to One LEMTRADA handbook provided to them by their HCP.

Patient Guide (PG)

The PG provides:

- Summary of risks of autoimmune side effects and serious infections
- Summary of recommended monitoring (duration and details of testing)
- Summary of symptoms to monitor and actions to take (carry the PC, contact their doctor if they have symptoms, keep up with their tests for the duration)

Patient Alert Card (PC)

Patients are to use the PC to carry with them the key information for their safety and adherence to monitoring. The PC provides patients with a quick reference guide and covers:

- The need to show the card to HCPs who treat them for any condition
- Knowledge of side effects to be aware of and associated symptoms:
  - Autoimmune conditions (immune thrombocytopenic purpura [ITP], kidney problems, thyroid disorders)
  - Serious infections
- Importance of monitoring until 4 years after last course of treatment.

Relevant published research

This study assessed 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 educational materials. Historically, there have been few published studies reporting the effectiveness of risk management interventions (2).

6.2 RATIONALE

This RMP assessment of effectiveness survey of patient educational materials provides information relating to patients' understanding of the risk messages that are discussed in the PG and PC for LEMTRADA prescribed for MS. It evaluates the patients' knowledge of RMP materials.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTIONS[1]

1. Have patients received the PG and PC?
2. What is the knowledge of patients about the PG and PC?
   a) Do patients understand the purpose of the PG?
   b) Do patients understand the purpose of the PC?
3. What is the understanding of patients about SAEs signs and symptoms related to LEMTRADA?
   a) Bleeding disorders
   b) Kidney disorders/ anti-Glomerular Basement Membrane (anti-GBM) disease
   c) Thyroid disorders
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.

7.2 OBJECTIVES

7.2.1 Primary objectives

The objective of the study was to assess descriptively the knowledge of patients treated with LEMTRADA regarding the educational materials and adherence to monitoring and thus the effectiveness of these materials to ensure the safe use of LEMTRADA.

7.2.2 Secondary objectives

Not applicable.

[1] The questionnaire included the following questions, which were not listed in the protocol:
- "How much of the PG have they read and how long ago was this?"
- "Symptoms to be monitored and action to be taken if they occur"

In addition, a research question about serious infections was included in the protocol but not asked in the questionnaire.

8 AMENDMENTS AND UPDATES

The protocol was amended once (Protocol version identifier 1.18, 08 May 2017; Annex 1) to reformat to current Sanofi standards and to add a threshold of 70% to define 'adequate' knowledge.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This was an international, cross-sectional survey conducted in 2 distinct waves (Wave 1 and Wave 2), 18 months apart. Online and snowballing recruitment (Section 9.3.3) were used. Information was collected regarding knowledge relating to risk minimization (as described in the PG and PC) of patients receiving treatment with LEMTRADA for MS. Survey data was collected online using structured questions where the response format was the selection of either a single response or multiple choice responses as appropriate.

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

9.2 SETTING

The study was to be conducted in selected European countries after launch of LEMTRADA in at least 2 of the most populated EU countries (Denmark, France, UK, Italy, Spain), with adequate translations in local languages.

The first wave of the survey (Wave 1) was conducted in the UK, Germany, Italy, Spain, Denmark, and Norway. Start of data collection for Wave 1 was March 2016 (Section 5). Results were analyzed and were reported to the European Medicines Agency (EMA) within procedure PSUSA/00010055/201609.

The second wave of the survey (Wave 2) was conducted the UK, Germany, Italy, Spain, Greece, Belgium, and the Netherlands. The start of data collection for Wave 2 was October 2017; end of data collection for Wave 2 was February 2018 (Section 5).

Results for Wave 2 are presented in this report and will be reported to the EMA.

9.3 PARTICIPANTS

9.3.1 Eligibility criteria

Patients were eligible to be included in the study only if all of the following criteria applied:

I 01. Patient has been diagnosed with MS.

I 02. Patient has been prescribed at least 1 dose of LEMTRADA.

I 03. Patient has supplied informed consent by ticking a box on the survey website.

Patients were excluded from the study if any of the following criteria applied:

E 01. Patient has participated in Wave 1 of the survey.

E 02. Patient has not been prescribed LEMTRADA.

9.3.2 Analysis population

All surveys returned with at least 1 question completed were analyzed.

9.3.3 Modalities of patient recruitment

Patients with MS in the selected EU countries who were receiving LEMTRADA were invited to take part. The prescription of therapies was under the responsibility of the patient's physician only.

Multiple approaches were used to recruit the patients:

- Recruitment via online panels – existing panels for MS patients were used as the first recruitment approach
- Telephone recruitment
- Snowballing – respondents were requested to suggest other potential respondents that might be interested in participating.

Patients provided informed consent and the data was anonymised for the MAH.

The Wave 2 target sample size was 200 patients.

9.4 VARIABLES

Knowledge was defined as awareness and understanding of important risk minimization information contained in the PG and PC. 'Adequate' knowledge was defined as 70% or more correctly answered questions. Important risk information measured was:

- Awareness of the PG and PC and of the purpose of the PG and PC
- Knowledge of side effects to be aware of, and associated symptoms and action to be taken should they occur
- Awareness of the importance of monitoring until 4 years after last course of treatment

Patients were shown all correct answers at the end of the survey.

9.4.1 Potential confounding factors

1. Length of time since first prescription of LEMTRADA. It is possible that patients may have read the PG and PC only at first prescription and knowledge may have declined over time. Self-reported length of time since first prescription of medication was included as a variable for subgroup analysis.
2. Exposure to the information. Patients who received but did not read the PG and PC may not have the same knowledge or demonstrate the same risk minimization behavior as those who did read the information. The questionnaire included a variable relating to whether the educational materials had been read.

9.5 DATA SOURCES AND MEASUREMENT

The MAH supplied known MS population statistics in the participating countries. All other data were collected via the patient self-reporting in the questionnaire.

The questionnaire was developed by psychologists with experience in developing questionnaires. Before implementation, the questions were user-tested in a small sample of patients with MS to ensure the questions were understood and adequate.

9.6 BIAS

All data were self-reported, and there was no verification of source data. A convenience sample (rather than a random sample) was used, and therefore the results may not be generalizable to the overall population of patients taking LEMTRADA.

9.7 SAMPLE SIZE

A formal power calculation was not undertaken. The sample size was based on an estimate of 2150 LEMTRADA patients in the countries where the study was planned. A 10% response rate was expected, which was equivalent to approximately 200 patients.

Initially, the survey link was clicked 88,202 times in total. A total of 85,078 potential patients were not eligible as they did not have a diagnosis of MS. An additional 776 were not eligible as they were not treated with LEMTRADA, leaving 2348 potential eligible patients. These 2348 patients quit before completing the survey, leaving no patients that were eligible.

As the first screening did not yield the desired sample size, a second supplier was brought in who prescreened respondents before providing them with the link. This resulted in a base of 382 potential respondents, of whom 82 did not meet all eligibility criteria, 48 and were over quota, and 52 did not complete the survey, resulting in a total of 200 respondents who completed the survey.

9.8 DATA TRANSFORMATION

9.8.1 Data collection schedule

Per protocol, data were collected online 18 months after the start of Wave 1 (Section 5), approximately 3 years after launch of LEMTRADA in the participating countries. Wave 2 recruitment took place over a 6-week period.

LEMTRADA patients who were recruited via methods described in Section 9.3.3 were sent an invitation email. The email contained a link to the online study questionnaire and an email address to contact the research team if further information about the study was required prior to consent. The invitation email and questionnaire were translated into the local languages of participating countries.

On following the link within the invitation email, the information sheet was displayed. The information sheet and consent statement emphasized that answers were anonymous and confidential. Following receipt of consent, the patient was able to move into the pages of the online questionnaire.

The first page of the questionnaire was related to the eligibility criteria. If any of the answers indicated that the patient was ineligible (eg, had not taken a single dose of LEMTRADA) they were taken to a page thanking them for their participation and explaining that they were not eligible to take part.

Following completion of the questionnaire, the patient was taken to a page thanking them for their participation.

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

9.8.2 Data collected – Online questionnaire

The following data were collected within the questionnaire.

Online questionnaire

- Country
- Age
- Gender
- Year of first LEMTRADA infusion
- Year of MS diagnosis
- Receipt of PC and PG
- Understanding of the purpose of PC and PG
- How long ago patient read PG

- Amount of PG the patient read
- Whether doctor/nurse discussed PG prior to first LEMTRADA infusion
- Understanding of SAEs signs and symptoms, and action to be taken if they occur
- Knowledge relating to LEMTRADA risk minimization activities to be undertaken

Patient data

No identifiable data regarding patients were collected.

9.9 STATISTICAL METHODS

9.9.1 Primary analysis

Descriptive analyses only (eg, frequency distributions for each item) were performed on the overall population of participating patients. The response on knowledge was considered satisfactory if patients provided ≥70% of correct answers.

9.9.2 Secondary analysis

The analysis was descriptive only. Subgroups compared were:

- Country
- Time since first infusion of LEMTRADA
- How long ago PG was read
- How much of the PG was read

9.10 QUALITY CONTROL

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

Data were collected electronically directly from patients (without input from physicians) using a secure system.

Data were 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.

All data were self-reported; there was no verification of source data.

10 RESULTS

10.1 PARTICIPANTS

Table 1 summarizes the key demographic characteristics. Questionnaires were completed by 200 patients across 7 countries. Patients were from Italy (n=53 [27%]), Spain (n=45 [23%]), the UK (n=43 [22%]), Germany (n=32 [16%]), Belgium (n=12 [6%]), Greece (n=11 [6%]), and the Netherlands (n=4 [2%]). Nearly two-thirds of the respondents (60%) were female patients. The majority (73%) was age 45 years or younger. Most (57%) had been diagnosed with MS less than 5 years ago, and 46% received their first LEMTRADA infusion within 2 years of the survey.

Table 1 - Demographic characteristics of the patient sample (N=200)

Category	Response option	n (%)
Country	UK	43 (22%)
	Germany	32 (16%)
	Italy	53 (27%)
	Spain	45 (23%)
	Greece	11 (6%)
	Belgium	12 (6%)
	The Netherlands	4 (2%)
Gender	Female	119 (60%)
	Male	81 (41%)
Age	18-25 years	19 (10%)
	26-35 years	53 (27%)
	36-45 years	71 (36%)
	46-55 years	43 (22%)
	56-65 years	11 (6%)
	66 years or above	3 (2%)
MS years of diagnosis	<5 years	114 (57%)
	5-10 years	48 (24%)
	>10 years	38 (19%)
First LEMTRADA infusion	<2013	2 (1%)
	2013	4 (2%)
	2014	13 (7%)
	2015	38 (19%)
	2016	92 (46%)

Category	Response option	n (%)
	2017	50 (25%)
	Do not know	1 (1%)

MS = multiple sclerosis; UK = United Kingdom

10.2 MAIN RESULTS

10.2.1 Primary analysis

10.2.1.1 Receipt of the patient educational materials

Table 2 summarizes the responses regarding receipt of patient educational materials. The majority of patients (66%) reported they received the PC. Among them, 64% provided the correct answer in response to the purpose of the PC. Of note, 14% of patients said it was to provide safety information, which, in addition to the 'correct' answer, is an important response.

More than two-thirds (69%) of patients reported having received a PG for LEMTRADA. Among them, 78% of patients correctly answered that the purpose of the PG (n=137) was both 'to make you aware of the monitoring schedule' and 'to show you how to recognize symptoms that might be related to possible side effects of LEMTRADA'. Notably, 11% of patients did select the latter answer, which again is an important response.

Most patients (n=121, 88%) who had received the PG also reported having the guide explained to them by their doctor or nurse before their first infusion; 8% of patients said this did not happen, and 4% did not know.

Table 2 - Knowledge about PC and PG

Questionnaire item	Response option	n (%)
Q.9 Have you ever received a PC for LEMTRADA? (N=200)	Yes	131 (66%)
	No	58 (29%)
	Don't know	11 (6%)
Q.10 What is the purpose of the PC?[a] (N=131)	To show a doctor or HCP involved in your medical care that you have been treated with LEMTRADA	28 (21%)
	To give you important safety information you need to be aware of when receiving treatment LEMTRADA	18 (14%)
	Both of the above ✓	84 (64%)
	Don't know/not sure	1 (1%)

Questionnaire item	Response option	n (%)
Q.11 Have you ever received a PG for LEMTRADA? (N=200)	Yes	137 (69%)
	No	53 (27%)
	Don't know	10 (5%)
Q.12 What is the purpose of the PG?[b] (N=137)	To make you aware of the monitoring schedule	14 (10%)
	To show you how to recognize symptoms that might be related to possible side effects of LEMTRADA	15 (11%)
	Both of the above ✓	107 (78%)
	Don't know/not sure	1 (1%)
Q.11a Did your doctor/nurse discuss the PG with you before your first infusion of LEMTRADA? (N=137)[b]	Yes	121 (88%)
	No	11 (8%)
	Don't know	5 (4%)

PC = Patient Alert Card; PG = Patient Guide

a All respondents who have ever received a PC for LEMTRADA

b All respondents who have ever received a PG for LEMTRADA

✓ Correct answer

10.2.1.2 Use of the PG

Table 3 describes the use of the PG by patients who reported having received the PG. About 94% of patients said that they had read about half or more of PG. The majority (75%) had read the PG more than 3 months ago.

When asked if patients had suggestions for improving the PG, the most popular suggestion was to add more pictures (41%) followed by adding more detailed information in general (37%) and covering topics other than side effects, such as quality of life (29%).

Table 3 - Use of the PG

Questionnaire item	Response option	n (%)
Q.14 People differ in the amount of information they read about their medicines. How much of the PG have you read?[a] (N=137)	All of it	87 (64%)
	More than half of it	25 (18%)
	About half of it	17 (12%)
	Less than half of it	5 (4%)
	None of it	3 (2%)
Q.14a How long ago did you read the PG?[b] (N=134)	<1 week ago	2 (1%)
	Between 1-2 weeks ago	9 (7%)
	Between 2-4 weeks ago	14 (10%)
	Between 1-3 months ago	9 (7%)
	>3 months ago	100 (75%)
Q.14b Do you have any suggestions to improve	More detailed information in general	50 (37%)

Questionnaire item	Response option	n (%)
the PG?[b] (N=134)	Less detailed information in general	15 (11%)
	More pictures	55 (41%)
	Less pictures	2 (1%)
	Covering topics other than side effects, such as QoL	69 (29%)
	More practical	39 (20%)
	Other	6 (4%)

PG = Patient Guide; QoL = quality of life

a All respondents who have ever received a PG for LEMTRADA

b All respondents who have ever received a PG for LEMTRADA except the ones who did not read any of the PG

10.2.1.3 Knowledge about SAEs and signs and symptoms related to LEMTRADA

Table 4 summarizes patient responses to questionnaire items assessing knowledge of signs and symptoms associated with side effects and adverse reactions to LEMTRADA.

With regard to patients' knowledge on bleeding disorder signs and symptoms, 54% provided the correct answer. The patients that answered incorrectly selected only 1 of the 3 options that – when taken all together – made up the correct answer (8%, 14%, and 24% of total).

Knowledge on kidney problems and anti-GBM disease signs and symptoms was correctly answered by 56% of patients. A total of 26% incorrectly chose 'all' options (including the correct options), 10% incorrectly answered 'diarrhoea', and 8% incorrectly answered 'depression'.

With regard to knowledge on an overactive thyroid signs and symptoms, 63% answered correctly. Fourteen percent incorrectly answered 'depression and nausea', 12% 'swelling of the legs and depression', and 12% answered that 'none of the above' mentioned options was correct.

When assessed for knowledge on underactive thyroid signs and symptoms, 56% of patients gave the correct answer. Eighteen percent thought the correct answer was not given at all, 15% incorrectly answered 'depression and nausea', and 12% answered 'bruising easily and nausea'.

Table 4 - Understanding of patients about SAEs to LEMTRADA

Questionnaire item	Response option	n (%)
Q.15 Which of the symptoms listed below could show a bleeding disorder? (N=200)	Bruising easily	16 (8%)
	Small red, pink or purple spots on the skin	48 (24%)
	Bleeding from a cut that is harder to stop as well as bleeding from gums or nose that takes longer than usual to stop	28 (14%)
	All of the above ✓	108 (54%)
Q.17 Apart from red or dark yellow/brown urine, what are further signs and symptoms of kidney problems or anti-GBM disease? (N=200)	Diarrhoea	20 (10%)
	Swelling in the legs or feet ✓	112 (56%)
	Depression	16 (8%)
	All of the above	52 (26%)
Q.19 Apart from excessive sweating and nervousness, which of the following symptoms could be further signs of an over-active thyroid? (N=200)	Swelling of the legs and depression	23 (12%)
	Unexplained weight loss, eye swelling and fast heartbeat ✓	126 (63%)
	Depression and nausea	28 (14%)
	None of the above	23 (12%)
Q.20 Apart from unexplained weight gain and feeling cold, which of the following could be further signs of an underactive thyroid? (N=200)	Depression and nausea	29 (15%)
	Bruising easily and nausea	23 (12%)
	Swelling in the legs or feet, worsening tiredness, and newly occurring constipation ✓	112 (56%)
	None of the above	36 (18%)

SAE = serious adverse event
✓ Correct answer

10.2.1.4 Knowledge of risk-minimization activities

Table 5 summarizes patient knowledge of the actions that should be taken upon noticing symptoms. The correct response option for all questionnaire items – 'See your doctor immediately' – received the highest proportion of responses within each item (bleeding disorder, 84%; kidney disorder, 78%; thyroid disorder, 77%). However, more than 10% of patients identified 'make an appointment to see their doctor at the next scheduled visit' (an incorrect response option) as a valid option following the appearance of symptoms of a bleeding disorder (11%), kidney disorder (11%), and thyroid disorder (17%). Few respondents indicated it is valid to make an appointment to see the doctor within the next 4 weeks (bleeding disorder, 5%) or wait to see if the symptoms resolve (kidney disorder, 5%; thyroid disorder, 4%).

With regard to the appearance of new signs or symptoms, 79% would contact their doctor immediately, and 17% would tell their doctor at the next scheduled visit. For signs or symptoms that patients had, then disappeared, and have now come back, 67% would contact their doctor immediately, and 25% would tell their doctor at the next scheduled visit. Finally, if patients experienced worsening signs or symptoms that they have had all the time, 78% would contact

their doctor immediately, and 17% would tell their doctor at the next scheduled visit. Few respondents indicated it is valid to 'wait 4 weeks to see if the symptoms resolve' when experiencing new symptoms (4%), a return of symptoms (7%), or a worsening of symptoms (5%).

Table 5 - Patient understanding of appropriate action after symptoms

Questionnaire item	Response option	n (%)
Q.16 If you have symptoms of a bleeding disorder, what action should you take? (N=200)	Make an appointment to see your doctor within the next 4 weeks	10 (5%)
	Tell your doctor at your next scheduled visit	21 (11%)
	Contact your doctor immediately ✓	167 (84%)
	None	2 (1%)
Q.18 If you have symptoms of a kidney disorder, what action should you take? (N=200)	Wait to see if the symptoms resolve	9 (5%)
	Tell your doctor at your next scheduled visit	21 (11%)
	Drink extra fluids	15 (8%)
	Contact your doctor immediately ✓	155 (78%)
Q.21 If you have symptoms of a thyroid disorder, what actions should you take? (N=200)	Wait to see if the symptoms resolve	8 (4%)
	Tell your doctor at your next scheduled visit	34 (17%)
	Contact your doctor immediately ✓	153 (77%)
	Eliminate all carbohydrates from your diet for at least 4 weeks	5 (3%)
Q.25 What should you do if you experience signs or symptoms that you have not experienced before? (N=200)	Wait 4 weeks to see if the symptoms resolve	7 (4%)
	Tell your doctor at your next scheduled visit	33 (17%)
	Contact your doctor immediately ✓	157 (79%)
	Find a patient contact group on the Internet	3 (2%)
Q.25b What should you do if you experience signs or symptoms that you have had before, then disappeared and have now come back? (N=200)	Wait 4 weeks to see if the symptoms resolve	14 (7%)
	Tell your doctor at your next scheduled visit	50 (25%)
	Contact your doctor immediately ✓	134 (67%)
	Find a patient contact group on the Internet	2 (1%)
Q.25c What should you do if you experience signs or symptoms that you had all the time and have now become worse? (N=200)	Wait 4 weeks to see if the symptoms resolve	10 (5%)
	Tell your doctor at your next scheduled visit	33 (17%)
	Contact your doctor immediately ✓	156 (78%)
	Find a patient contact group on the Internet	1 (1%)

✓ Correct answer

Patient knowledge of the frequency of required periodic monitoring and their duration after last infusion is shown in Table 6. Sixty-six percent of patients correctly identified that they should be receiving monthly blood and urine tests after an infusion of LEMTRADA, although 33% of patients thought the tests should be done less frequently (every 2 to 6 months) and 3% thought they should be done more frequently (weekly). With regard to testing thyroid function, almost half

(49%) of the patients correctly answered 'every 3 months', while another 45% and 7% of patients responded that it should be done more frequently (weekly, monthly, or every 2 months) or less frequently (every 6 months), respectively.

Patient responses about how long it is necessary to continue having blood and urine tests for autoimmune conditions (bleeding, kidney, and thyroid disorders) show that most patients (56%) are aware that testing should be continued for 4 years after the last course of treatment with LEMTRADA. All other patients believed that testing should be continued for a shorter time (6 weeks–2 years) after the last course of treatment with LEMTRADA.

Table 6 - Patient knowledge of frequency of required periodic monitoring and their duration after last infusion

Questionnaire item	Response option	n (%)
Q.14c After an infusion of LEMTRADA, how often should you have blood and urine tests? (N=200)	Weekly	6 (3%)
	Monthly ✓	131 (66%)
	Every 2 months	35 (18%)
	Every 3 months	21 (11%)
	Every 6 months	7 (4%)
Q.23 After an infusion of LEMTRADA, how often should you have thyroid function tests? (N=200)	Weekly	4 (2%)
	Monthly	51 (26%)
	Every 2 months	33 (17%)
	Every 3 months ✓	98 (49%)
	Every 6 months	14 (7%)
Q.24 For how long is it necessary to have blood and urine tests for auto-immune conditions (bleeding, kidney and thyroid disorders)? (N=200)	For 6 weeks after the last course of treatment with LEMTRADA	22 (11%)
	For 6 months after the last course of treatment with LEMTRADA	37 (19%)
	For 2 years after the last course of treatment with LEMTRADA	30 (15%)
	For 4 years after the last course of treatment with LEMTRADA ✓	111 (56%)

✓ Correct answer

10.2.2 Secondary analysis

10.2.2.1 Subgroup analysis: Country

Table 7 shows the patient responses to each questionnaire item by country.

Receipt and review of PC

More than 70% of patients in the UK, Spain, Belgium, and the Netherlands recalled having received the PC; countries where <70% patients recalled receiving the PC were Germany (69%), Greece (45%), and Italy (30%). Of the patients who recalled receiving the PC, the countries where patients reported sufficient knowledge of the purpose of the PC were Italy (81%) and Spain (79%).

Receipt and review of PG

With regard to the PG, more than 70% of patients in the UK, Germany, Spain, Greece, and the Netherlands recalled having received the PG; countries where <70% patients recalled receiving the PG were Belgium (58%) and Italy (30%). When assessed for the purpose of the PG, countries where patients scored higher than 70% included Spain (88%), UK (84%), and Greece and Italy (75% each). Of those patients that indicated that they had received the PG, more than 80% of patients in each country reported that the doctor/nurse discussed the PG before the first infusion of LEMTRADA (81%-100%).

Of patients who reported receiving the PG, more patients in Spain (85%) and Belgium (86%) than in other countries reported they had read all of it. However, more than 80% of patients in each country reported that they had read at least half of the PG (including all of it). More patients in each country reported that they had read the PG more than 3 months ago (range: 43%-100%), while few patients reported having read the PG more recently.

With regard to suggestions to improve the PG: Of patients who reported receiving the PG, more than half of German patients (52%) suggested to 'add more detailed information in general' to the PG, whereas 'covering topics other than side effects' was the most common suggestion for Belgian (71%), Italian (56%), and UK patients (47%). The majority of Spanish (59%) and Dutch (67%) patients indicated that they would like to see more pictures in the PG.

Symptoms of side effects

Consistent with the primary analysis, scores for knowledge on symptoms of side effects were low (<70%) for all countries with a few exceptions. For bleeding disorders, only Italian patients had an adequately high number of correct scores (72%). For kidney disorders, patients in all 7 countries scored from 27% to 69%. For overactive thyroid, patients from the UK (77%), the Netherlands (75%), and Spain (71%) scored adequately high; while only patients in the Netherlands (75%) scored adequately high for underactive thyroid.

Understanding of appropriate action after symptoms

Consistent with the primary analysis, patient knowledge of the actions that should be taken upon noticing symptoms was better than knowledge of the symptoms themselves. The correct answer in all cases was to contact the doctor immediately. Patients in all countries scored >70% except for Belgium (50%) and the Netherlands (50%) for bleeding disorders; Belgium (50%) and the Netherlands (50%) for kidney disorders; and Germany (63%) and Belgium (50%) for thyroid disorders.

Knowledge on how often blood and urine tests should be conducted following a LEMTRADA infusion was at an adequately high level for UK (86%), Greece (82%), Germany (72%), and Spain (71%). Patients in all countries scored <70% on knowledge of how often thyroid function tests should be conducted following a LEMTRADA infusion, and on how long blood and urine tests for autoimmune conditions (bleeding, kidney and thyroid disorders) should be conducted after the last course of LEMTRADA treatment.

Also consistent with the primary analysis, patient knowledge of the actions that should be taken upon noticing new, returning, or worsening symptoms was better than knowledge of the symptoms themselves. The correct answer in all cases was to contact the doctor immediately. Patients in all countries scored >70% except for Belgium (33%) for new symptoms; Germany (63%), the Netherlands (50%), UK (42%), and Belgium (33%) for returning symptoms; and UK (58%) and Belgium (42%) for worsening symptoms.

Table 7 - Subgroup analysis: Country

PC								
	Response option	**UK (n=43)**	**Germany (n=32)**	**Italy (n=53)**	**Spain (n=45)**	**Greece (n=11)**	**Belgium (n=12)**	**Netherlands (n=4)**
Q9 Received PC (N=200)	Yes	37 (86%)	22 (69%)	16 (30%)	38 (84%)	5 (45%)	9 (75%)	4 (100%)
	No	5 (12%)	7 (22%)	34 (64%)	6 (13%)	4 (36%)	2 (17%)	--
	Don't know	1 (2%)	3 (9%)	3 (6%)	1 (2%)	2 (18%)	1 (8%)	--
	Response option	**UK (n=37)**	**Germany (n=22)**	**Italy (n=16)**	**Spain (n=38)**	**Greece (n=5)**	**Belgium (n=9)**	**Netherlands (n=4)**
Q10 Purpose PC (N=131)[a]	Correct answer	24 (65%)	8 (36%)	13 (81%)	30 (79%)	3 (60%)	5 (56%)	1 (25%)
	Incorrect answer	13 (35%)	14 (63%)	2 (19%)	8 (21%)	2 (40%)	4 (44%)	3(75%)
PG								
	Response option	**UK (n=43)**	**Germany (n=32)**	**Italy (n=53)**	**Spain (n=45)**	**Greece (n=11)**	**Belgium (n=12)**	**Netherlands (n=4)**
Q11 Received PG (N=200)	Yes	37(86%)	25 (78%)	16 (30%)	41(91%)	8 (73%)	7 (58%)	3 (75%)
	No	4 (9%)	4 (13%)	34 (64%)	4 (9%)	3 (27%)	4 (33%)	--
	Don't know	2 (5%)	3 (9%)	3 (6%)	--	--	1 (8%)	1 (25%)
	Response option	**UK (n=37)**	**Germany (n=25)**	**Italy (n=16)**	**Spain (n=41)**	**Greece (n=8)**	**Belgium (n=7)**	**Netherlands (n=3)**
Q12 Purpose PG (N=137)[b]	Correct answer	31 (84%)	17 (68%)	12 (75%)	36 (88%)	6 (75%)	4 (57%)	1 (33%)
	Incorrect answer	6 (16%)	8 (32%)	4 (25%)	5 (12%)	2 (25%)	3 (43%)	2 (67%)

Table 7 - Subgroup analysis: Country (continued)

	Response option	UK (n=37)	Germany (n=25)	Italy (n=16)	Spain (n=41)	Greece (n=8)	Belgium (n=7)	Netherlands (n=3)
Q11a Did doctor/nurse discuss PG before first LEMTRADA infusion (N=137)[b]	Yes	32 (86%)	23 (92%)	13 (81%)	35 (85%)	8 (100%)	7 (100%)	3 (100%)
	No	3 (8%)	2 (8%)	2 (13%)	4 (10%)	--	--	--
	Don't remember	2 (5%)	--	1 (6%)	2 (5%)	--	--	--
Q14 How much of PG did you read (N=137)[b]	All of it	21 (57%)	11 (44%)	8 (50%)	35 (85%)	4 (50%)	6 (86%)	2 (67%)
	> half of it	9 (24%)	9 (36%)	4 (25%)	2 (5%)	1 (13%)	--	--
	~ half of it	6 (16%)	3 (12%)	1 (6%)	3 (7%)	2 (25%)	1 (14%)	1 (33%)
	< half of it	--	--	3 (19%)	1 (2%)	1 (13%)	--	--
	None of it	1 (3%)	2 (8%)	--	--	--	--	--
	Response option	**UK (n=36)**	**Germany (n=23)**	**Italy (n=16)**	**Spain (n=41)**	**Greece (n=8)**	**Belgium (n=7)**	**Netherlands (n=3)**
Q14a How long ago did you read PG? (N=134)[c]	<1 week	2 (1%)	--	--	1 (2%)	--	1 (14%)	--
	1-2 weeks	3 (8%)	3 (13%)	1 (6%)	1 (2%)	1 (13%)	--	--
	2-3 weeks	7 (19%)	4 (17%)	--	--	--	3 (43%)	--
	1-3 months	3 (8%)	2 (9%)	1 (6%)	3 (7%)	--	--	--
	>3 months	23 (64%)	14 (61%)	14 (88%)	36 (88%)	7 (88%)	3 (43%)	3 (100%)
Q14b Suggestions to improve PG (N=134)[c]	>Detailed information in general	8 (22%)	12 (52%)	4 (25%)	20 (49%)	2 (25%)	3 (43%)	1 (33%)
	<Detailed information in general	5 (14%)	3 (13%)	3 (19%)	2 (5%)	1 (13%)	--	1 (33%)
	>Pictures	11 (31%)	12 (52%)	1 (6%)	24 (59%)	2 (13%)	4 (57%)	2 (67%)
	<Pictures	2 (6%)	--	--	--	--	--	--
	Covering topics other than side effects	17 (47%)	11 (48%)	9 (56%)	22 (54%)	4 (50%)	5 (71%)	1 (33%)
	>Practical	10 (28%)	7 (30%)	2 (13%)	14 (34%)	3 (38%)	2 (29%)	1 (33%)
	Other	2 (6%)	2 (9%)	--	2 (5%)	--	--	--

Table 7 - Subgroup analysis: Country (continued)

	Response	UK (n=43)	Germany (n=32)	Italy (n=53)	Spain (n=45)	Greece (n=11)	Belgium (n=12)	Netherlands (n=4)
Q15 Symptoms of bleeding disorder (N=200)	Correct answer	24 (56%)	11 (34%)	38 (72%)	24 (53%)	5 (45%)	4 (33%)	2 (50%)
	Incorrect answer	19 (44%)	21 (66%)	15 (28%)	21 (47%)	6 (55%)	8 (67%)	2 (50%)
Q16 Actions if symptoms of bleeding disorder (N=200)	>Practical	37 (86%)	25 (78%)	50 (94%)	38 (84%)	9 (82%)	6 (50%)	2 (50%)
	Other	6 (14%)	7 (22%)	3 (6%)	7 (16%)	2 (18%)	6 (50%)	2 (50%)
Q17 Signs/ symptoms kidney problems/ anti-GBM disease (N=200)	Correct answer	25 (58%)	22 (69%)	23 (43%)	30 (67%)	3 (27%)	7 (58%)	2 (50%)
	Incorrect answer	18 (42%)	10 (31%)	30 (57%)	15 (33%)	8 (73%)	5 (43%)	2 (50%)
Q18 Actions if symptoms kidney disorder (N=200)	Correct answer	37 (86%)	24 (75%)	40 (75%)	37 (82%)	9 (82%)	6 (50%)	2 (50%)
	Incorrect answer	6 (14%)	8 (25%)	13 (25%)	8 (18%)	2 (18%)	6 (50%)	2 (50%)
Q19 Symptoms overactive thyroid (N=200)	Correct answer	33 (77%)	21 (66%)	25 (47%)	32 (71%)	7 (64%)	5 (42%)	3 (75%)
	Incorrect answer	10 (23%)	11 (34%)	28 (53%)	13 (29%)	4 (36%)	7 (58%)	1 (25%)
Q20 Symptoms underactive thyroid (N=200)	Correct answer	27 (63%)	16 (50%)	29 (55%)	27 (60%)	4 (36%)	6 (50%)	3 (75%)
	Incorrect answer	16 (37%)	16 (50%)	24 (45%)	18 (40%)	7 (64%)	6 (50%)	1 (25%)
Q21 Actions if symptoms thyroid disorder (N=200)	Correct answer	33 (77%)	20 (63%)	45 (85%)	38 (84%)	8 (73%)	6 (50%)	3 (75%)
	Incorrect answer	10 (23%)	12 (37%)	8 (15%)	7 (16%)	3 (27%)	6 (50%)	1 (25%)
Q14c How often blood and urine tests (N=200)	Correct answer	37 (86%)	23 (72%)	22 (42%)	32 (71%)	9 (82%)	6 (50%)	2 (50%)
	Incorrect answer	6 (14%)	9 (28%)	31 (58%)	13 (29%)	2 (18%)	6 (50%)	2 (50%)
Q23 How often thyroid function tests (N=200)	Correct answer	27 (63%)	9 (28%)	36 (68%)	18 (40%)	5 (45%)	2 (17%)	1 (25%)
	Incorrect answer	16 (37%)	23 (72%)	17 (32%)	27 (60%)	6 (55%)	10 (83%)	3 (75%)

Table 7 - Subgroup analysis: Country (continued)

	Response	UK (n=43)	Germany (n=32)	Italy (n=53)	Spain (n=45)	Greece (n=11)	Belgium (n=12)	Netherlands (n=4)
Q24 For how long blood/ urine tests for auto-immune conditions (N=200)	Correct answer	29 (67%)	12 (38%)	29 (55%)	30 (67%)	3 (27%)	6 (50%)	2 (50%)
	Incorrect answer	14 (33%)	20 (62%)	24 (45%)	15 (33%)	8 (73%)	6 (50%)	2 (50%)
Q25 Actions for new signs/ symptoms (N=200)	Correct answer	31 (72%)	23 (72%)	51 (96%)	36 (80%)	8 (73%)	4 (33%)	4 (100%)
	Incorrect answer	12 (28%)	9 (28%)	2 (4%)	9 (20%)	3 (27%)	8 (67%)	--
Q25b Actions for recurrent signs/ symptoms before (N=200)	Correct answer	18 (42%)	20 (63%)	48 (91%)	33 (73%)	9 (82%)	4 (33%)	2 (50%)
	Incorrect answer	25 (58%)	12 (37%)	5 (9%)	12 (27%)	2 (18%)	8 (67%)	2 (50%)
Q25c Actions for worsened signs/symptom (N=200)	Correct answer	25 (58%)	25 (78%)	52 (98%)	36 (80%)	9 (82%)	5 (42%)	4 (100%)
	Incorrect answer	18 (42%)	7 (22%)	1 (2%)	9 (20%)	2 (18%)	7 (58%)	--

a All respondents who have ever received a PC for LEMTRADA

b All respondents who have ever received a PG for LEMTRADA

c All respondents who have ever received a PG for LEMTRADA except the ones who did not read any of the PG

10.2.2.2 Subgroup analysis: Time since first infusion of LEMTRADA

Table 8 shows the patient responses to each questionnaire item assessed against the time when patients received their first infusion of LEMTRADA. In this subgroup, 1 patient reported "don't know" the time since first infusion of LEMTRADA and is not included in the discussion below.

Receipt and review of PC

The highest percentages of patients who recalled receiving the PC had their first LEMTRADA dose in 2014 (85%) and 2013 (75%); all other groups scored <70%. However, of the patients who received the PC, the only group who knew its purpose was patients who received their first LEMTRADA dose in 2017 (73%).

Receipt and review of PG

With regard to the PG, most patients who recalled receiving the PG received their first LEMTRADA dose in 2014 (92%) and 2013 (75%); all other groups scored <70%. When assessed for the purpose of the PG, all groups scored >70% except for those who received their first LEMTRADA dose in 2014 (67%). Of those patients that indicated that they had received the PG,

more than 70% of patients in all groups reported that the doctor/nurse discussed the PG before the first infusion of LEMTRADA.

Of patient who reported receiving the PG, only patients who received their first LEMTRADA dose after 2017 (81%) reported they had read all of it. The majority of patients in each group reported that they had read the PG more than 3 months ago (range 72%-100%). The rest of the groups scored <70% (of note, the score for the <2013 group was 100% but only 1 patient was in that group). However, more than 80% of patients in each group reported that they had read at least half of the PG.

With regard to suggestions to improve the PG: Of patients who reported receiving the PG, there were no clear trends in the responses, and no one suggestion was selected by >70% of any group. Overall, the greatest number of responses were about covering topics other than side effects (5 groups responding with 40%-67%), more pictures (4 groups responding with 28%-49%), and adding more detail in general (4 groups responding with 25%-48% not counting the groups with n=1).

Symptoms of side effects

Consistent with the primary analysis, the percentages for knowledge on symptoms of side effects varied but were <70% for all with few exceptions. For bleeding disorders, no group scored >70%. For kidney disorder, the only group that scored >70% were those who received their first LEMTRADA dose in 2013 (75%). For overactive thyroid, the groups who scored >70% were those who received their first LEMTRADA dose in 2014 (85%) and 2013 (75%). Finally, for underactive thyroid, the only group who scored more than 70% was those who received their first LEMTRADA dose in 2013 (75%).

Understanding of appropriate action after symptoms

Consistent with the primary analysis, patient knowledge of the actions that should be taken upon noticing symptoms was better than knowledge of the symptoms themselves. The correct answer in all cases was to contact the doctor immediately. Patients in all groups scored >70% except for those who received their first LEMTRADA dose in 2014 (69%) for bleeding disorders; those who received their first LEMTRADA dose in 2014 (69%) for kidney disorders; and 2015 (68%) for thyroid disorders.

Patient knowledge of the frequency of required periodic monitoring and their duration after last infusion was <70% for all groups with few exceptions.

Also consistent with the primary analysis, patient knowledge of the actions that should be taken upon noticing new, returning, or worsening symptoms was better than knowledge of the symptoms themselves. The correct answer in all cases was to contact the doctor immediately. Patients in all countries scored >70% except for those who received their first LEMTRADA dose in 2014 (69%) for new symptoms; and those who received their first LEMTRADA dose in 2015 (68%) and 2014 (62%) for worsening symptoms.

Table 8 - Subgroup analysis: Time since first infusion of LEMTRADA

	Response	<2013 (N=2)	2013 (N=4)	2014 (N=13)	2015 (N=38)	2016 (N=92)	2017 (N=50)	Don't know (N=1)
Q9 Received PC (N=200)	Yes	1 (50%)	3 (75%)	11 (85%)	26(68%)	57 (62%)	33 (66%)	--
	No	1 (50%)	1 (25%)	2 (15%)	9 (24%)	29 (32%)	16 (32%)	--
	Don't know	--	--	--	3 (8%)	6 (7%)	1 (2%)	1 (100%)
	Response	**<2013 (N=1)**	**2013 (N=3)**	**2014 (N=11)**	**2015 (N=26)**	**2016 (N=57)**	**2017 (N=33)**	**Don't know (N=0)**
Q10 Purpose PC (N=131)[a]	Correct answer	--	1 (33%)	7 (64%)	17 (65%)	35 (61%)	24 (73%)	--
	Incorrect answer	1 (100%)	2 (67%)	4 (36%)	9 (35%)	22 (39%)	9 (27%)	--
	Response	**<2013 (N=2)**	**2013 (N=4)**	**2014 (N=13)**	**2015 (N=38)**	**2016 (N=92)**	**2017 (N=50)**	**Don't know (N=1)**
Q11 Received PG (N=200)	Yes	1 (50%)	3 (75%)	12 (92%)	26 (68%)	62 (67%)	32 (64%)	1 (100%)
	No	1 (50%)	1 (25%)	1(8%)	11 (29%)	24 (26%)	15 (30%)	--
	Don't know	--	--	--	1 (3%)	6 (7%)	3 (6%)	--
	Response	**<2013 (N=1)**	**2013 (N=3)**	**2014 (N=12)**	**2015 (N=26)**	**2016 (N=62)**	**2017 (N=32)**	**Don't know (N=1)**
Q12 Purpose PG (N=137)[b]	Correct answer	--	2 (67%)	10 (83%)	21 (81%)	49 (79%)	25 (78%)	--
	Incorrect answer	1 (100%)	1 (33%)	2 (17%)	5 (19%)	13 (21%)	7 (22%)	1 (100%)
Q11a Did doctor/ nurse discuss PG before first LEMTRADA infusion (N=137)[b]	Yes	1 (100%)	3 (100%)	11 (92%)	23 (88%)	58 (94%)	24 (75%)	1 (100%)
	No	--	--	1 (8%)	1 (4%)	6 (6%)	5 (16%)	--
	Don't remember	--	--	--	2 (8%)	--	3 (9%)	--
Q14 How much of PG did you read (N=137)[b]	All of it	1 (100%)	1 (33%)	7 (58%)	13 (50%)	39 (63%)	26 (81%)	--
	> half of it	--	1 (33%)	2 (17%)	7 (27%)	12 (19%)	3 (9%)	--
	~ half of it	--	1 (33%)	1 (8%)	3 (12%)	8 (13%)	3 (9%)	1 (100%)
	< half of it	--	-	1 (8%)	2 (8%)	2 (3%)	--	--
	None of it	--	--	1 (8%)	1 (4%)	1 (2%)	--	--
Q14a How long ago did you read the PG (N=134)[c]	<1 week	--	--	--	--	1 (2%)	1 (3%)	--
	1-2 weeks	--	-	2 (18%)	--	5 (8%)	2 (6%)	--
	2-3 weeks	--	--	1 (9%)	4 (16%)	6 (10%)	3 (9%)	--
	1-3 months	--	-	--	2 (8%)	5 (8%)	2 (6%)	--
	>3 months	1 (100%)	3 (100%)	8 (73%)	19 (76%)	44 (72%)	24 (75%)	1 (100%)

	Response	<2013 (N=1)	2013 (N=3)	2014 (N=12)	2015 (N=26)	2016 (N=62)	2017 (N=32)	Don't know (N=1)
Q14b Any suggestions to improve PG (N=134)[c]	>Detailed information in general	1 (100%)	--	5 (45%)	6 (24%)	29 (48%)	8 (25%)	1 (100%)
	<Detailed information in general	--	1 (33%)	2 (18%)	6 (24%)	3 (5%)	3 (9%)	--
	>Pictures	--	--	4 (36%)	12 (48%)	30 (49%)	9 (28%)	--
	<Pictures	--	--	--	--	1 (4%)	1 (2%)	--
	Covering topics other than side effects	1 (33%)	--	2 (67%)	6 (55%)	10 (40%)	30 (49%)	21 (66%)
	>Practical	1 (33%)	--	1 (33%)	2 (18%)	8 (32%)	22 (36%)	6 (19%)
	Other	--	--	-	1 (9%)	2 (8%)	2 (3%)	1 (3%)
	Response	**<2013 (N=2)**	**2013 (N=4)**	**2014 (N=13)**	**2015 (N=38)**	**2016 (N=92)**	**2017 (N=50)**	**Don't know (N=1)**
Q15 Symptoms of bleeding disorder (N=200)	Correct answer	1 (50%)	2 (50%)	3 (23%)	23 (61%)	50 (54%)	29 (58%)	--
	Incorrect answer	1 (50%)	2 (50%)	10 (77%)	15 (39%)	42 (46%)	21 (42%)	1 (100%)
Q16 Actions if symptoms of bleeding disorder (N=200)	Correct answer	1 (50%)	4 (100%)	9 (69%)	29 (76%)	79 (86%)	44 (88%)	1 (100%)
	Incorrect answer	1 (50%)	--	4 (31%)	9 (24%)	13 (14%)	6 (12%)	--
Q17 Signs/ symptoms kidney problems/anti-GBM disease (N=200)	Correct answer	1 (50%)	3 (75%)	9 (69%)	23 (61%)	44 (48%)	31 (62%)	1 (100%)
	Incorrect answer	1 (50%)	1 (25%)	4 (31%)	15 (39%)	48 (52%)	19 (38%)	--
Q18 Actions if symptoms kidney disorder (N=200)	Correct answer	1 (50%)	3 (75%)	9 (69%)	29 (76%)	72 (78%)	40 (80%)	1 (100%)
	Incorrect answer	1 (50%)	1 (25%)	4 (31%)	9 (24%)	20 (22%)	10 (20%)	--
Q19 Symptoms overactive thyroid (N=200)	Correct answer	--	3 (75%)	11 (85%)	24 (63%)	58 (63%)	29 (58%)	1 (100%)
	Incorrect answer	2 (100%)	1 (25%)	2 (15%)	14 (37%)	34 (37%)	21 (42%)	--
Q20 Symptoms underactive thyroid (N=200)	Correct answer	2 (100%)	3 (75%)	8 (62%)	21 (55%)	49 (53%)	29 (58%)	--
	Incorrect answer	--	1 (25%)	5 (38%)	17 (45%)	43 (47%)	21 (42%)	1 (100%)

	Response	<2013 (N=2)	2013 (N=4)	2014 (N=13)	2015 (N=38)	2016 (N=92)	2017 (N=50)	Don't know (N=1)
Q21 Actions if symptoms thyroid disorder (N=200)	Correct answer	2 (100%)	3 (75%)	10 (77%)	26 (68%)	75 (82%)	37 (74%)	--
	Incorrect answer	--	1 (25%)	3 (23%)	12 (32%)	17 (18%)	13 (26%)	1 (100%)
Q14c How often blood and urine tests (N=200)	Correct answer	--	2 (50%)	9 (69%)	31 (82%)	57 (62%)	31 (62%)	1 (100%)
	Incorrect answer	2 (100%)	2 (50%)	4 (31%)	7 (18%)	35 (38%)	19 (38%)	--
Q23 How often thyroid function tests (N=200)	Correct answer	--	3 (75%)	6 (46%)	18 (47%)	45 (49%)	26 (52%)	--
	Incorrect answer	2 (100%)	1 (25%)	7 (54%)	20 (53%)	47 (51%)	24 (48%)	1 (100%)
Q24 For how long blood and urine tests for auto-immune conditions necessary (N=200)	Correct answer	--	3 (75%)	9 (69%)	20 (53%)	48 (52%)	31 (62%)	--
	Incorrect answer	2 (100%)	1 (25%)	4 (31%)	18 (47%)	44 (48%)	19 (38%)	1 (100%)
Q25 Actions for new signs/ symptoms (N=200)	Correct answer	2 (100%)	3 (75%)	9 (69%)	28 (74%)	76 (83%)	38 (76%)	1 (100%)
	Incorrect answer	--	1 (25%)	4 (31%)	10 (26%)	16 (17%)	12 (24%)	--
Q25b Actions for recurrent signs/ symptoms before (N=200)	Correct answer	2 (100%)	4 (100%)	8 (62%)	22 (58%)	64 (70%)	33 (66%)	1 (100%)
	Incorrect answer	--	--	5 (38%)	16 (42%)	28 (30%)	17 (34%)	--
Q25c Actions for worsened signs/symptom (N=200)	Correct answer	2 (100%)	3 (75%)	8 (62%)	26 (68%)	75 (82%)	41 (82%)	1 (100%)
	Incorrect answer	--	1 (25%)	5 (38%)	12 (32%)	17 (18%)	9 (18%)	--

a All respondents who have ever received a PC for LEMTRADA

b All respondents who have ever received a PG for LEMTRADA

c All respondents who have ever received a PG for LEMTRADA except the ones who did not read any of the PG

10.2.2.3 Subgroup analysis: How long ago was the PG read?

Table 9 shows the patient responses to each questionnaire item assessed against how long ago the PG was read by respondents that indicated that they had received the PG (N=134). In this subgroup analysis, given that 100/134 respondents were in one group who responded that they had read the PG (>3 months ago), no useful conclusions can be drawn. No trends were apparent.

Table 9 - Subgroup analysis: How long ago was the PG read?

	Response	<1 week (N=2)	1-2 weeks (N=9)	2-4 weeks (N=14)	1-3 months (N=9)	>3 months (N=100)
Q9 Received PC (N=134)	Yes	2 (100%)	7 (78%)	13 (93%)	9 (100%)	89 (89%)
	No	--	2 (22%)	1 (7%)	--	6 (6%)
	Don't know	--	--	--	--	5 (5%)
	Response	**<1 week (N=2)**	**1-2 weeks (N=7)**	**2-4 weeks (N=13)**	**1-3 months (N=9)**	**>3 months (N=89)**
Q10 Purpose PC (N=120)[a]	Correct answer	1 (50%)	2 (29%)	7 (54%)	6 (67%)	65 (73%)
	Incorrect answer	1 (50%)	5 (71%)	6 (46%)	3 (33%)	24 (27%)
	Response	**<1 week (N=2)**	**1-2 weeks (N=9)**	**2-4 weeks (N=14)**	**1-3 months (N=9)**	**>3 months (N=100)**
Q11 Received PG (N=137)	Yes	2 (100%)	9 (100%)	14 (100%)	9 (100%)	100 (100%)
	No	--	--	--	--	--
	Don't know	--	--	--	--	--
Q12 Purpose PG (N=134)[b]	Correct answer	1 (50%)	3 (33%)	9 (64%)	5 (56%)	86 (86%)
	Incorrect answer	1 (50%)	6 (67%)	5 (36%)	4 (44%)	14 (14%)
Q11a Did doctor/ nurse discuss PG before first LEMTRADA infusion (N=137)[b]	Yes	2 (100%)	9 (100%)	13 (93%)	8 (89%)	87 (87%)
	No	--	--	1 (7%)	--	9 (9%)
	Don't remember	--	--	--	1 (11%)	4 (4%)
Q14 How much of PG did you read (N=137)[b]	All of it	2 (100%)	3 (33%)	6 (43%)	3 (33%)	73 (73%)
	> half of it	--	6 (67%)	5 (36%)	4 (44%)	10 (10%)
	~ half of it	--	--	3 (21%)	2 (22%)	12 (12%)
	< half of it	--	--	--	--	5 (5%)
	None of it	--	--	--	--	--

	Response	<1 week (N=2)	1-2 weeks (N=9)	2-4 weeks (N=14)	1-3 months (N=9)	>3 months (N=100)
Q14b Any suggestions to improve PG (N=134)[c]	>Detailed information in general	2 (100%)	4 (44%)	6 (43%)	5 (56%)	33 (33%)
	<Detailed information in general	--	4 (44%)	4 (29%)	1 (11%)	6 (6%)
	>Pictures	2 (100%)	3 (33%)	11 (79%)	5 (56%)	34 (34%)
	<Pictures	--	--	1 (7%)	1 (11%)	--
	Covering topics other than side effects	2 (100%)	1 (11%)	6 (43%)	4 (44%)	56 (56%)
	>Practical	1 (50%)	1 (11%)	5 (36%)	--	32 (32%)
	Other	--	--	1 (7%)	--	5 (5%)
Q15 Symptoms of bleeding disorder (N=200)	Correct answer	1 (50%)	2 (22%)	3 (21%)	3 (33%)	62 (62%)
	Incorrect answer	1 (50%)	7 (78%)	11 (79%)	6 (67%)	38 (38%)
Q16 Actions if symptoms of bleeding disorder (N=200)	Correct answer	1 (50%)	2 (22%)	8 (57%)	5 (56%)	94 (94%)
	Incorrect answer	1 (50%)	7 (78%)	6 (43%)	4 (44%)	6 (6%)
Q17 Signs/ symptoms kidney problems/anti-GBM disease (N=200)	Correct answer	1 (50%)	2 (22%)	7 (50%)	7 (78%)	67 (67%)
	Incorrect answer	1 (50%)	7 (78%)	7 (50%)	2 (22%)	33 (33%)
Q19 Symptoms overactive thyroid (N=134)	Correct answer	--	5 (56%)	8 (57%)	7 (78%)	81 (81%)
	Incorrect answer	2 (100%)	4 (44%)	6 (43%)	2 (22%)	19 (19%)
Q20 Symptoms underactive thyroid (N=134)	Correct answer	1 (50%)	2 (22%)	6 (43%)	6 (67%)	68 (68%)
	Incorrect answer	1 (50%)	7 (78%)	8 (57%)	3 (33%)	32 (32%)
Q21 Actions if symptoms thyroid disorder (N=134)	Correct answer	1 (50%)	4 (44%)	6 (43%)	6 (67%)	87 (87%)
	Incorrect answer	1 (50%)	5 (56%)	8 (57%)	3 (33%)	13 (13%)

	Response	<1 week (N=2)	1-2 weeks (N=9)	2-4 weeks (N=14)	1-3 months (N=9)	>3 months (N=100)
Q14c How often blood and urine tests (N=134)	Correct answer	1 (50%)	4 (44%)	8 (57%)	8 (89%)	82 (82%)
	Incorrect answer	1 (50%)	5 (56%)	6 (43%)	1 (11%)	18 (18%)
Q23 How often thyroid function tests (N=134)	Correct answer	--	3 (33%)	4 (29%)	2 (22%)	57 (57%)
	Incorrect answer	2 (100%)	6 (67%)	10 (71%)	7 (78%)	43 (43%)
Q24 For how long blood and urine tests for auto-immune conditions necessary (N=134)	Correct answer	--	4 (29%)	3 (33%)	76 (76%)	66 (76%)
	Incorrect answer	9 (100%)	10 (71%)	6 (67%)	24 (24%)	21 (24%)
Q25 Actions for new signs/ symptoms (N=134)	Correct answer	1 (50%)	3 (33%)	6 (43%)	6 (67%)	88 (88%)
	Incorrect answer	1 (50%)	6 (67%)	8 (57%)	3 (33%)	12 (12%)
Q25b Actions for recurrent signs/ symptoms before (N=134)	Correct answer	1 (50%)	3 (33%)	6 (43%)	5 (56%)	69 (69%)
	Incorrect answer	1 (50%)	6 (67%)	8 (57%)	4 (44%)	31 (31%)
Q25c Actions for worsened signs/symptom (N=134)	Correct answer	1 (50%)	4 (44%)	6 (43%)	6 (67%)	85 (85%)
	Incorrect answer	1 (50%)	5 (56%)	8 (57%)	3 (33%)	15 (15%)

a All respondents who have ever received a PC for LEMTRADA
b All respondents who have ever received a PG for LEMTRADA
c All respondents who have ever received a PG for LEMTRADA except the ones who did not read any of the PG

10.2.2.4 Subgroup analysis: How much of the PG was read?

Table 10 shows the patient responses to each questionnaire item according to whether or not they indicated having read all of the PG by respondents that indicated that they had received the PG (n=134).

Receipt and review of PG

The majority (87/134 [60%]) of patients reported reading all of it, and of those, 82% reported knowledge of the purpose of the PG. All except those who reported reading none of the PG reported that the doctor/nurse discussed the PG before the first infusion of LEMTRADA. Eighty-four percent of those who reported reading all of the PG also reported they read it more than 3 months ago.

With regard to suggestions to improve the PG: Of patients who reported receiving the PG, there were no clear trends in the responses, and no one suggestion was selected by >70% of any group. Overall, the greatest number of responses were about covering topics other than side effects (5 groups responding with 40%-56%), more pictures (4 groups responding with 20%-47%), and adding more detail in general (4 groups responding with 18%-43%).

Symptoms of side effects

Consistent with the primary analysis, the percentages for knowledge on symptoms of side effects varied but were <70% for all with few exceptions. For bleeding disorders and kidney disorders, no group scored >70%. For overactive thyroid, the only group who scored >70% were those who reported reading all of the PG (79%) and those who read less than half of it (80%). Finally, for underactive thyroid, the only group who scored more than 70% was those who read less than half of the PG (80%).

Understanding of appropriate action after symptoms

Consistent with the primary analysis, patient knowledge of the actions that should be taken upon noticing symptoms was better than knowledge of the symptoms themselves. The correct answer in all cases was to contact the doctor immediately. Patients in all groups scored >70% for knowledge of the actions that should be taken for any of the disorders except for those who reported reading more than half of the PG (56% for each).

Patient knowledge of the frequency of required periodic monitoring and their duration after last infusion was disparate. Patients in all groups scored >70% on knowledge of how often blood and urine tests should be conducted following a LEMTRADA infusion. Patients in all groups scored <70% on knowledge of how often thyroid function tests should be conducted following a LEMTRADA infusion. Knowledge on how long blood and urine tests for auto-immune conditions (bleeding, kidney and thyroid disorders) should be conducted after the last course of LEMTRADA treatment was acceptable only for those who read all of the PG (76%) and those who reported reading none of it (100%).

Regarding patient knowledge of the actions that should be taken upon noticing new, returning, or worsening symptoms, there seemed to be no consistent pattern among groups no matter how much of the PG was read. Those who reported reading all of the PG scored 83% for new symptoms, 63% for returning symptoms, and 80% for worsening symptoms.

Table 10 - Subgroup analysis: Comparing those who have read all of the PG vs those who have read some

	Response	All of it (N=87)	> Half of it (N=25)	~ Half of it (N=17)	< Half of it (N=5)	None of it (N=3)
Q9 Received PC (N=137)	Yes	81 (93%)	23 (92%)	14 (82%)	2 (40%)	2 (67%)
	No	5 (6%)	2 (8%)	1 (6%)	1 (20%)	1 (33%)
	Don't know	1 (1%)	--	2 (12%)	2 (40%)	--

	Response	All of it (N=81)	> Half of it (N=23)	~ Half of it (N=14)	< Half of it (N=2)	None of it (N=2)
Q10 Purpose PC (N=131)[a]	Correct answer	55 (68%)	12 (52%)	12 (86%)	2 (100%)	--
	Incorrect answer	26 (32%)	11 (48%)	2 (14%)	--	2 (100%)
	Response	**All of it (N=87)**	**> Half of it (N=25)**	**~ Half of it (N=17)**	**< Half of it (N=5)**	**None of it (N=3)**
Q12 Purpose PG (N=134)[b]	Correct answer	71 (82%)	16 (64%)	13 (76%)	4 (80%)	3 (100%)
	Incorrect answer	16 (18%)	9 (36%)	4 (12%)	1 (20%)	--
Q11a Did doctor/ nurse discuss PG with you before first infusion of LEMTRADA? (N=137)[b]	Yes	76 (87%)	24 (96%)	15 (88%)	4 (80%)	2 (67%)
	No	8 (9%)	1 (4%)	--	1 (20%)	1 (33%)
	Don't remember	3 (3%)	--	2 (12%)	--	--
Q14a How long ago did you read the PG? (N=134)[c]	<1 week 1-2 weeks	2 (2%)	--	--	--	--
	2-3 weeks	3 (3%)	6 (24%)	--	--	--
	1-3 months	6 (7%)	5 (20%)	3 (18%)	--	--
	>3 months	3 (3%)	4 (6%)	2 (12%)	--	--
Q14b Any suggestions to improve PG? (N=134)[c]	>Detailed information in general	37 (43%)	9 (36%)	3 (18%)	1 (20%)	--
	<Detailed information in general	5 (6%)	6 (24%)	3 (18%)	1 (20%)	--
	>Pictures	37 (43%)	9 (36%)	8 (47%)	1 (20%)	--
	<Pictures	--	2 (8%)	--	--	--
	Covering topics other than side effects	49 (56%)	11 (44%)	7 (41%)	2 (40%)	--
	>Practical	30 (34%)	5 (20%)	3 (18%)	1 (20%)	--
	Other	5 (6%)	1 (4%)	--	--	--
Q15 Symptoms of bleeding disorder? (N=137)	Correct answer	52 (60%)	10 (40%)	7 (41%)	2 (40%)	2 (67%)
	Incorrect answer	35 (40%)	15 (60%)	10 (59%)	3 (60%)	1 (33%)

	Response	All of it (N=87)	> Half of it (N=25)	~ Half of it (N=17)	< Half of it (N=5)	None of it (N=3)
Q16 Actions if symptoms of bleeding disorder (N=137)	Correct answer	78 (90%)	14 (56%)	14 (82%)	4 (80%)	3 (100%)
	Incorrect answer	9 (10%)	11 (44%)	3 (18%)	1 (20%)	--
Q17 Signs/ symptoms kidney problems/anti-GBM disease? (N=137)	Correct answer	59 (68%)	12 (48%)	11 (65%)	2 (40%)	2 (67%)
	Incorrect answer	28 (32%)	13 (52%)	6 (35%)	3 (60%)	1 (33%)
Q18 Actions if symptoms kidney disorder? (N=137)	Correct answer	78 (90%)	14 (56%)	14 (82%)	5 (100%)	3 (100%)
	Incorrect answer	9 (10%)	11 (44%)	3 (18%)	--	--
Q19 Symptoms overactive thyroid? (N=137)	Correct answer	69 (79%)	17 (68%)	11 (65%)	4 (80%)	3 (100%)
	Incorrect answer	18 (21%)	8 (32%)	6 (35%)	1 (20%)	--
Q20 Symptoms underactive thyroid? (N=137)	Correct answer	58 (67%)	13 (52%)	8 (47%)	4 (80%)	2 (67%)
	Incorrect answer	29 (33%)	12 (48%)	9 (53%)	1 (20%)	1 (33%)
Q21 Actions if symptoms thyroid disorder? (N=137)	Correct answer	73 (84%)	14 (56%)	13 (76%)	4 (80%)	2 (67%)
	Incorrect answer	14 (16%)	11 (44%)	4 (24%)	1 (20%)	1 (33%)
Q14c How often blood and urine tests? (N=137)	Correct answer	66 (76%)	19 (76%)	13 (76%)	5 (100%)	3 (100%)
	Incorrect answer	21 (24%)	6 (24%)	4 (24%)	--	--
Q23 How often thyroid function tests? (N=137)	Correct answer	47 (54%)	11 (44%)	5 (29%)	3 (60%)	2 (67%)
	Incorrect answer	40 (46%)	14 (56%)	12 (71%)	2 (40%)	1 (33%)
Q.24 For how long blood and urine tests for auto-immune conditions necessary? (N=137)	Correct answer	66 (76%)	8 (32%)	7 (41%)	3 (60%)	3 (100%)
	Incorrect answer	21 (24%)	17 (68%)	10 (59%)	2 (40%)	--
Q25 Actions for new signs/symptoms? (N=137)	Correct answer	72 (83%)	13 (52%)	14 (82%)	5 (100%)	3 (100%)
	Incorrect answer	15 (17%)	12 (48%)	3 (18%)	--	--

	Response	All of it (N=87)	> Half of it (N=25)	~ Half of it (N=17)	< Half of it (N=5)	None of it (N=3)
Q25b Actions for recurrent signs/ symptoms before (N=137)	Correct answer	55 (63%)	14 (56%)	10 (59%)	5 (100%)	2 (67%)
	Incorrect answer	32 (37%)	9 (44%)	7 (41%)	--	1 (33%)
Q25c Actions for worsened signs/symptom (N=137)	Correct answer	70 (80%)	15 (60%)	12 (71%)	5 (100%)	2 (67%)
	Incorrect answer	17 (20%)	10 (40%)	5 (29%)	--	1 (33%)

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11 DISCUSSION

The LEMTRADA RMP includes risk minimization measures and education tools to support the safe use of the product. The patient educational materials comprising the Patient Guide (PG) and Patient Alert Card (PC) form one of the core elements of risk minimization targeted at patients. The PC is a liaison tool to inform any HCPs who are treating patients receiving LEMTRADA. The PG provides a summary of risks of autoimmune side effects and serious infections as well as recommended monitoring and actions to take.

The objective of this LEMTRADA EU-RMP Survey in patients was to assess descriptively the knowledge and adherence of patients treated with LEMTRADA with regard to the topics covered in the LEMTRADA educational materials (PC, PG), and thus the effectiveness of these materials to ensure the safe use of LEMTRADA.

The survey was conducted in 200 patients of which 60% were female. The majority (73%) was age 45 years or younger. Most (57%) had been diagnosed with MS less than 5 years ago, and 46% received their first LEMTRADA infusion within 2 years of the survey. Patients were from Italy (n=53 [27%]), Spain (n=45 [23%]), the UK (n=43 [22%]), Germany (n=32 [16%]), Belgium (n=12 [6%]), Greece (n=11 [6%]), and the Netherlands (n=4 [2%]).

For all analyses, a threshold of 70% was defined as an 'adequately' high level of knowledge.

11.1 PRIMARY ANALYSIS

Key insights from the primary analysis of this survey include the following:

The majority of patients recalled having received the PC (66%) and the PG (69%). Patient understanding of the purpose of the PC (64%) was just below the adequacy level that was set at 70% in the protocol; of note, 14% of patients said it was to provide safety information, which, in addition to the 'correct' answer, is an important response. The knowledge level concerning the purpose of the PG was overall adequate (78%). However, as the full answer for each of the documents consisted of 2 items which could also be chosen separately, patients correctly indicated at least 1 of the 2 correct items in 21% and 14% of cases concerning the PC's purpose, and 10% and 11% of the PG's purpose.

Most patients (88%) who had received the PG also reported having the guide explained to them by their doctor or nurse before their first infusion. The PG thus seems a well-established tool to facilitate discussion between patients and HCPs. However, for those who did not receive or did not remember receiving the PG, it may be that a nurse/HCP may have gone through the PG with the patient but did not give it to them. Therefore, all patients could have been exposed to the content of the PG at some point before receiving LEMTRADA. Nevertheless, Sanofi Genzyme is committed to continue to stress the importance of these materials to HCPs in their contact with the patients.

Knowledge about the important risks was <70%. Fifty-four percent of the patients provided a correct answer for signs and symptoms of bleeding disorders, 56% for kidney disorders, and 63% for overactive thyroid disorder, and 56% for underactive thyroid disorder.

Patient understanding of the action to take upon noticing symptoms associated with side effects or severe reactions to LEMTRADA was moderate to adequate. The correct response option for all questionnaire items – 'See your doctor immediately' – received the highest proportion of responses within each item (bleeding disorder, 84%; kidney disorder, 78%; thyroid disorder, 77%). Few patients incorrectly indicated it was valid to make an appointment to see the doctor within the next 4 weeks (bleeding disorder, 5%) or wait to see if the symptoms resolve (kidney disorder, 5%; thyroid disorder, 4%), which is encouraging.

With regard to new signs/symptoms, knowledge on the appropriate action of seeing their doctor immediately was 79%; for recurring signs/symptoms, 67% responded correctly; for worsening signs/symptoms, 78% responded correctly. These results of knowing the correct action in response to new, recurring, or worsening symptoms adds an important perspective to the low results of the previous section (knowledge of SAEs/signs and symptoms). Even if patients do not know exactly what to watch for in case of, eg, thyroid disorder, they know that if they experience new/worsening symptoms they should go to their doctor as soon as possible, which means that the main objective of patient risk minimization materials is working. As long as patients check new symptoms with an HCP, who holds the responsibility of recognizing symptoms of adverse reactions, worsening will be prevented and the objective to ensure early detection of events to mitigate the severity and sequelae of autoimmune disease will be considered met.

Compared with knowing the correct action in case of experiencing adverse symptoms, knowledge of the specific timepoints at which monitoring activities should be conducted was lower (<70%). Overall, 66% of patients correctly identified that they should be receiving monthly blood and urine tests after an infusion of LEMTRADA, although 33% of patients thought the tests should be done less frequently (every 2 to 6 months) and 3% thought they should be done more frequently (weekly). With regard to tests for thyroid function, 49% of patients correctly answered 'every 3 months', while another 45% and 7% of the patients responded that they should be done more frequently (weekly, monthly, or every 2 months) or less frequently (every 6 months), respectively. Although knowledge of the frequency of the specific tests is below 70%, knowledge of the timing of each of the specific tests separately is less important than overall awareness that monthly testing is required. Furthermore, most patients are accustomed to monthly blood and urine tests without knowing the exact tests ordered by their HCP at each visit.

Patient knowledge that blood and urine tests for autoimmune conditions (bleeding, kidney, and thyroid disorders) should be continued for 4 years following final course of treatment with LEMTRADA was also suboptimal, with 56% of patients scoring correctly. Nearly 45% of patients thought that testing should be continued 2 years or less (6 weeks, 6 months, or 2 years). This finding suggests that this may be an area where knowledge could be improved among patients. Also, HCPs should also be counseling patients on the importance of followup for 4 years.

11.2 SECONDARY ANALYSES BY SUBGROUP

Subgroup comparisons by time since first infusion or how long ago the PG was read were consistent with the primary analysis results. There were no apparent trends within groups with regard to receipt of the patient educational materials, knowledge on symptoms of the most important side effects (overall <70%), knowledge of risk minimization activities (overall >70%), and knowledge of timing of monitoring tests (overall <70%). The scores for receipt of the PC and PG over the years since first infusion suggested that distribution of materials has not declined over the years.

Having read all of the PG or at least a substantial amount of it correlated with higher levels of knowledge. However, regarding patient knowledge of the actions that should be taken upon noticing new, returning, or worsening symptoms, there seemed to be no consistent pattern among groups no matter how much of the PG was read. Those who reported reading all of the PG scored 83% for new symptoms, 63% for returning symptoms, and 80% for worsening symptoms.

Subgroup comparison by country showed that patients from Italy were more likely than patients from other countries to answer that they had not received the PC or the PG (30% for each). Interestingly, of the patients who recalled receiving the PC, Italy was one of only 2 countries where patients reported an adequately high level of knowledge of the purpose of the PC (Italy, 81%; Spain, 79%). When assessed for the purpose of the PG, Italy was one of only 4 countries with the correct response: Spain (88%), UK (84%), and Greece and Italy (75% each). Since in the primary analysis, 88% of patients who had received the PG also reported having the guide explained to them by their doctor or nurse before their first infusion, it appears that the majority of patients could have been exposed to the content of the PG at some point before receiving LEMTRADA. Nevertheless, results show that HCPs should be encouraged to give patients both the PC and the PG, to explain the materials well, and to encourage their patients to read the PG in full. Patients from Belgium (n=12) consistently had among the lowest scores compared with the other countries for knowledge of risks and appropriate monitoring activities; however, the small number of patients in this group may have affected the comparison. However, Belgium has an interesting program (LemMon patient support program). After informed consent, the patient is registered in the program and a visiting nurse comes to the patient's home for monthly blood sampling. The blood is analyzed in a central lab and results are published on a platform that can be accessed by neurologists, who receive email alerts when results are posted. Therefore, the patient is not involved at all in knowing when to call or what tests are being performed, which explains the lower knowledge among Belgian patients.

11.3 STRENGTHS AND LIMITATIONS

The strength of this comprehensive survey include the number of patients included (N=200) recruited from 7 different countries including 2 of the most populated countries in which LEMTRADA has been launched. The survey included 60% female patient respondents which closely mirrors the sex distribution for the disease (2/3 female, 1/3 male) (3).

Limitations of this survey include the use of a cross-sectional design which made it difficult to determine whether receiving and reading the patient educational materials actually increased

knowledge or whether increased knowledge among those who had received and reviewed the materials was the result of another factor, such as conscientiousness or motivation. A convenience sample (non-randomized) was used, rather than a random sample, and included only patients from the EU, which means that the findings may not be representative of the whole population of patients taking LEMTRADA, thereby limiting the generalizability of the results. Some of the subgroup analyses numbers were small and comparisons were limited to descriptive observations.

Another potential limitation is that questions were to be answered without having the educational materials at hand. In addition to the fact that recalling all details from memory might already be difficult in the general population, MS is a disease in which many patients suffer from cognitive problems, including memory loss (1).

This suggests that the responses to the present survey may be limited by cognitive impairment amongst the patients, including the fact that some patients may have forgotten receiving the materials and/or the content of the materials. In practice, patients should be encouraged to have the educational materials on hand or be reminded how to access these materials through the MS One to One site, and encouraged to reference the materials as needed.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The Wave 2 survey findings indicated that 66% of patients acknowledged the receipt of the PC and 69% of the PG. Almost all patients who reported receiving the materials read at least half of them. Patient knowledge about the purposes of the educational materials was overall moderate to adequate. Patients' overall score was <70% for the symptoms associated with the most important adverse reactions to LEMTRADA and frequency of monitoring for specific conditions, and only 56% were aware that blood/urine monitoring should continue for 4 years following the final course of LEMTRADA, which highlights a need for HCPs to reinforce this message. It is encouraging that although the knowledge on symptoms related to specific SAEs may be lacking, patients will contact their HCP as soon as possible in case of new (79%), recurring (67%), or worsening (78%) symptoms.

The survey results may be influenced by the design of the study, in that patients were not shown the educational materials nor allowed to reference them during the survey.

Useful actions to improve patient knowledge include ensuring that all patients have access to materials that they can read, and encouraging them to keep and refer to the materials as needed. Other methods for improving patient knowledge includes a qualified HCP to go through the materials with them to reinforce and reiterate information, and that this process must be repeated with patients periodically to ensure the information remains up to date and the patient remains aware of the importance of having adequate knowledge. Finally, patients should be reminded that the educational materials (PG and PC) are available on the MS One to One web site.

To further strengthen the LEMTRADA risk minimization approach, the MAH continues its efforts to ensure that all patients are reached and commits to stressing the importance of these materials to HCPs who are in contact with the patients. The MAH is still working on improving our reach to both patients and HCPs, eg, via digital initiatives.

14 REFERENCES

1. Sumowski JF, Benedict R, Enzinger C, Filippi M, Geurts JJ, Hamalainen P, et al. Cognition in multiple sclerosis: State of the field and priorities for the future. Neurology. 2018;Feb 6;90(6):278-288.

2. Andrews E, Gilsenan A, Cook S. Therapeutic risk management interventions: feasibility and effectiveness. J Am Pharm Assoc. 2004;44:491-500.

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

ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	4.0	04 May 2017	HCP and Patient Questionnaire
2	1.8	08 May 2017	Epidemiology Study Protocol Measure of Effectiveness of the Minimisation Measures of RMP Protocol

Annex 2 Administrative and Legal Considerations

Ethical Considerations

Ethical principles

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

Laws and regulations

This study was conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the study was performed, as well as any applicable guidelines.

Each participating country locally ensured that all necessary regulatory submissions (eg, IRB/IEC) were performed in accordance with local regulations including local data protection regulations.

Regulatory authorities' submissions by country are presented

Data Protection

The patient's personal data and Investigator's personal data which were to be included in the Company's databases were treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Record Retention

The Investigator was responsible for the retention of the study documentation until the end of the study. In addition, the Investigator had to comply with specific local regulations and recommendations regarding patient record retention.

The Company Audits and Inspections by Competent Authorities (CA)

The Investigator agreed to allow the Company's auditors and Competent Authorities' inspectors to have direct access to records of the study for review, it being understood that all personnel with access to patients' records are bound by professional secrecy and as such, could not disclose any personal identity or personal medical information.

The Investigator had to make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as notification from the authorities for an inspection was received by the Investigator, he/she had to inform the

Company and authorize the Company to participate in this inspection. The confidentiality of the data to verify and the protection of the patients must be respected during these inspections. Any results or information arising from the inspections by the Competent Authorities were to be immediately communicated by the Investigator to the Company. The Investigator had to take appropriate measures required by the Company to ensure corrective actions for all problems found during audits and inspections.

Ownership of Data and Use of Study Results

Unless otherwise specified by local laws and regulations, the Company retains ownership of data, results, reports, findings, and discoveries related to the study. Therefore, the Company reserves the right to use the data from the present study for any purpose, including to submit them to the Competent Authorities of any country.

The Study Committee, if any involved in the study, has full access to the final data base allowing for appropriate academic analysis and reporting of the study results.

SANOFI GENZYME

EPIDEMIOLOGY STUDY PROTOCOL

MEASURE OF EFFECTIVENESS OF THE MINIMISATION MEASURES OF RMP PROTOCOL

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

Study type:	Knowledge survey
Company:	Sanofi
Version Number/Status:	1.8
Study number:	Using the ClubNet numbering system

This study will be conducted in accordance with Sanofi standard operating procedures for GPE epidemiologic studies

Date: May 8, 2017, 2017 Total number of pages 25

PASS information:

Title:	Knowledge survey of educational materials in patients treated with Lemtrada (alemtuzumab)
Protocol version identifier	1.8
Date of last version of protocol	February 27, 2017
EU PAS register number (if applicable)	n.a.
Active substance	Alemtuzumab
Medicinal product	Lemtrada®
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003718
Marketing authorization holder(s)	Genzyme Therapeutics, Ltd.
Joint PASS	No
Research questions and objective(s):	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 minimisation activities to be undertaken?
Country(-ies) 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.
Author	t.b.d.

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	Genzyme Therapeutics, Ltd 4620 Kingsgate Cascade Way Oxford Business Park South Oxford OX4 2SU United Kingdom
MAH contact person	Femke Sanders Project manager Regulatory Affairs Europe, MS / Neurology Genzyme Europe B.V. Gooimeer 10 1411 DD Naarden The Netherlands Tel: +31 35 6991215 Fax: +31 35 6991444 email: femke.sanders@genzyme.com

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LIST OF ABBREVIATIONS

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

1 RESPONSIBLE PARTIES

Ipsos, together with Sanofi Genzyme, will be involved in the preparation of the protocol and its amendments and will develop the survey and analyse the results.

Ipsos will also be involved with the recruitment of patients and management of the questionnaire.

The survey is sponsored by Sanofi Genzyme.

2 SYNOPSIS

Title

A Cross Sectional Survey assessing the effectiveness of minimisation 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 minimisation 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 PG and PC, knowledge of serious adverse events (SAEs) relating to Lemtrada and knowledge of risk minimisation activities to be performed.

Study design

The study is a cross-sectional survey conducted in two distinct waves (18 months and 3 years after the launch of the product in at least 2 highly populated European Union (EU) countries). 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 multiple sclerosis (MS) with Lemtrada. The selected countries will include at least 2 of the highly populated European Union (EU) countries (DE, FR, UK, IT, ES). The registered patient population will be described in terms of age, year of first diagnosis and gender 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 PG and PC

2) Whether the patient carries the PC with them and whether the patient understands the purpose of the PC

3) The patient's understanding of the risks associated with use of the product

4) The patient's knowledge of the risk minimisation 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 the MAH. 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. The response on knowledge will be considered satisfactory if participants provide >70% of correct answers.

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 European Union (EU) countries (DE, FR, UK, IT, ES).

3 AMENDMENTS AND UPDATES

Number	Date	Section of study protocol	Amendment or update	Reason
1	Feb 27, 2017	All	New format	New format
2	Date	Text	Text	Text
…	Date	Text	Text	Text

4 MILESTONES

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

5 RATIONALE AND BACKGROUND

Not applicable – this is a survey evaluating the effectiveness of minimisation measures of a RMP.

BACKGROUND

Safety profile

For the safety profile of Lemtrada, please refer to the SmPC/Package Leaflet (PL).

Description of Lemtrada Risk Management Plan

The Lemtrada RMP includes additional risk minimisation measures and tools to support the safe use of the product. The patient educational materials (PG and PC) form one of the core elements of risk minimisation 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 healthcare 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 disorders
    - 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.

6 RESEARCH QUESTION AND OBJECTIVES

1. Have patients received the PG and PC?

2. What is the knowledge of patients about the PG and PC?

    a. Do patients understand the purpose of the PG?

    b. Do patients understand the purpose of the PC?

3. What is the understanding of patients about SAEs related to Lemtrada?

    a. ITP

    b. Kidney disorders (anti-GBM disease)

    c. Thyroid disorders

    d. Serious infections.

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

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

    b. Frequency and length of time monitoring is required.

A) 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.

B) SECONDARY OBJECTIVES

Not applicable.

7 RESEARCH METHODS

7.1 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 minimisation (as described in the PG and PC) 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 uses a convenience sample of patients prescribed Lemtrada. Data will be collected in two distinct waves 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 EMA.

7.2 SETTING

The study will be conducted in selected European countries, with adequate translations in local languages. Web and telephone recruitment will be used. Collection of survey data will take place online.

7.2.1 Duration of the study

The duration of the study will be 96 weeks.

7.2.2 Eligibility criteria

7.2.2.1 Inclusion criteria

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

7.2.2.2 Exclusion criteria

- Patient completed the survey in Wave 1
- Patient has not been prescribed Lemtrada.

7.2.3 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.

7.2.3.1 Physician selection

Not applicable.

7.2.3.2 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.

7.3 VARIABLES

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

- Awareness of the PG and PC and of the purpose of the PG and PC
- 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 minimisation behaviour as those

who have read the information. The questionnaire will include a variable relating to whether the RMP materials have been read.

7.4 DATA SOURCES

Data regarding the known MS population statistics for participating countries will be supplied by the MAH. 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.

8.5 STUDY SIZE

8.5.1 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 2,150 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.

8.5.2 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).

7.6 DATA MANAGEMENT

7.6.1 Data collection schedule

Patient data

Data will be collected online at 18 months and 3 years after launch of Lemtrada in the participant countries.

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 element 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 the MAH.

7.6.2 Data collected

Online questionnaire

- 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.

7.6.3 Site / Physician questionnaire

Not applicable.

7.6.4 Screening log (if applicable)

Not applicable.

7.6.5 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.

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

Not applicable.

7.6.7 Logistic aspects

Not applicable.

7.7 ANALYSIS

7.7.1 Primary analysis

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

7.7.2 Secondary analysis

1. The analysis will be descriptive. Where it is found to be <70%, more in-depth analysis will be considered (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.

7.7.3 Interim analysis

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

7.8 QUALITY CONTROL

7.8.1 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 IBM statistical software package by qualified research personnel employed by Ipsos.

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

7.8.2 Data quality control at site level

Not applicable.

7.9 LIMITATIONS OF THE RESEACH 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, descriptive statistics are sufficient.

7.10 OTHER ASPECTS

Not applicable.

8 PROTECTION OF HUMAN SUBJECTS

8.1 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).

8.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

8.2.1 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.

8.2.2 Laws and regulations

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

8.2.3 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.

8.2.4 Insurance

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

8.2.5 Secrecy agreement

Not applicable.

8.2.6 Record retention

It is recommended that Ipsos shall arrange for the retention of study documentation for at least five years. In addition, 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.

8.2.7 Discontinuation of the study

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

8.2.8 MAH/MAH representative audits and inspections by competent authorities

Ipsos 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).

Ipsos 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 Ipsos to the MAH/MAH representative.

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

9 MANAGEMENT OF REPORTING ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable – this is a survey with closed questions and will not generate AEs.

10 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

10.1 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.

10.2 PUBLICATIONS

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

11 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.

12 ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	3.0	5 April 2017	Questionnaire User Testing report
2	3.0	5 April 2017	Questionnaire
3	V12	July 2013	Patient Guide
4	V10	July 2013	Patient Alert card

Lemtrada RMP

Questionnaires

United Kingdom
Germany
Italy
Spain
Greece
Denmark
Norway
Belgium
The Netherlands

Version 4.0
4 May 2017

Contents

Notes

- Throughout, text which is intended for participants is featured in black, whereas notes for Sanofi Genzyme/Ipsos are featured in *[blue]. Blue notes should be removed from final documents for patients/HCPs.*
- Prior to distributing the questionnaires in non-English speaking countries, the Medical Director or his/her representative of the local market must check that translated copies have used appropriate language.

Considerations

- We do not want the patient or healthcare professional (HCP) to refer to the Patient Card (PC)/Patient Information Leaflet (PIL)/Patient Education Guide/Summary of Product Characteristics (SmPC) when they answer the questions: we have tried to avoid this through the wording of the introductions. Time taken from beginning to end of the questionnaire will be recorded, but is not included in the protocol.
- Participants will be given a link or information should they wish to report adverse events (AEs).
- At the end of the survey (patient and HCP) we propose that the participant should be shown the correct answers to all the questions.

Requirements (from synopsis documents)

HCP

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

1. Physician characteristics including:
    a) Country
    b) Affiliation: Type of hospital (in-out-patient)/private practice
    c) Speciality
    d) Multiple sclerosis (MS) experience (number of treated patients)
    e) Number of patients prescribed Lemtrada
    f) Time since last prescription of Lemtrada.

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

    a) HCP Guide

    b) HCP Checklist

    c) SmPC

    d) Patient Guide

    e) Patient Alert Card

    f) 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) Tests to be conducted for the initial screening of the patient
    c) Vaccination, pre-treatment courses
    d) Monitoring activities for 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.

Patient

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

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.

Knowledge is defined as awareness and understanding of important risk minimization information contained in the patient guide and patient alert card. Important risk information measured:

- Knowledge 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. 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).

Sample

	UK	Germany	Italy	Spain	Denmark	Norway	Greece	Belgium	The Netherlands
MS patients	**200 across all markets**								
Neurologists / MS specialists	**75 Lemtrada prescribers across all markets**								

UK approval numbers required for all sections of questionnaire.

<Display on a separate screen before the patient information page>

1. Which country do you live in?

[Eligibility criteria]

Germany	
UK	
Italy	
Spain	
Denmark	
Norway	
Belgium	
The Netherlands	
Greece	
Other	*[INELIGIBLE]*

Pre-Screener questions - [DO NOT show this on screen]

PS1. Have you been diagnosed with any of the following diseases by a doctor?

Multiple response	Diabetes	[Terminate] IF NOT selected with multiple sclerosis]
	Parkinson's disease	[Terminate] IF NOT selected with multiple sclerosis]
	Rheumatoid arthritis	[Terminate] IF NOT selected with multiple sclerosis]
	Multiple sclerosis	**[continue, if selected alone or with any of the other responses]**

	Psoriasis	[Terminate] IF NOT selected with multiple sclerosis]
EXCLUSIVE	None of the above	[Terminate]

PS2. You mentioned that you've been diagnosed with Multiple sclerosis, are you **currently** taking any of the following medications?

Multiple response rotate	Metformin	[Terminate] if NOT selected with Lemtrada]
	Aubagio	[Cannot be selected with Lemtrada. If selected alone or with any other drug divert to Aubagio patient survey after Q26a has been answered]
	Lemtrada	[continue to ps3]
	Tysabri	[Terminate] if NOT selected with Lemtrada]
	Remicade	[Terminate] if NOT selected with Lemtrada]
EXCLUSIVE Do not rotate	None of the above	[Terminate]

[Only ask those who select Lemtrada at PS2 or Aubagio alone or Aubagio + any other drug (except Lemtrada)]

26a. Please enter the name of the MS charity you would like to donate your [insert incentive amount] below. [open end]

For those who selected Aubagio alone, Aubagio + any other drug (except Lemtrada) at PS2 take to patient invitation email screen on Aubagio survey.

Patient invitation email

Lemtrada▼ (alemtuzumab) RMP questionnaire

Dear patient,

Subject header: Invitation related to your Lemtrada®▼ (alemtuzumab) medication

We are inviting you to take part in a survey related to your medication Lemtrada, a treatment for multiple sclerosis (MS). The purpose of the survey is to help us to better understand the effectiveness of the patient education materials. It will take about 15 minutes to complete.

[Show to UK only]

▼Lemtrada is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects, you may get. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this document. You can also report side effects directly via the national reporting system to: www.mhra.gov.uk/yellowcard
By reporting side effects, you can help provide more information on the safety of this medicine.

[Show to all markets]
For more information, and to take part in the survey, please follow this link <insert link to patient information page country page Q2>.

Patient Information page

What's involved in taking part?

We are inviting you to take part in a survey. The questions in the survey are to gather information on what you remember about the Patient Alert Card and Patient Information Leaflet for Lemtrada. The goal is to see how clear the information is in these educational materials. We kindly ask you not to look at into the Patient Alert Card and Patient Information Leaflet when answering the questions. Do not worry if you can't remember everything! We will use the answers to update the educational materials if they are not clear enough. [SHOW TO UK ONLY] **Throughout the survey we will refer to Lemtrada by its generic name - alemtuzumab**

The survey will take about 15 minutes to complete.

This survey is being conducted to meet a regulatory obligation from the European Medicine Agency. The survey is being run by a company called Ipsos, on behalf of the pharmaceutical company that markets Lemtrada [show to all other markets] alemtuzumab [show to UK only]. All information that you provide will be confidential and every precaution will be taken to protect your privacy. Your answers will not be identifiable, and data shared with the pharmaceutical company will be in aggregated form. Ipsos is obliged to pass on to the pharmaceutical company any information about adverse events of medication. If any of your survey answers indicate a possible adverse event, you will be asked to give permission for Ipsos to pass this information to the pharmaceutical company.

If you have any questions about the survey please contact europe.online@ipsos.com.

I would like to take part. <link to patient consent page>

Patient Consent page

Thank you for deciding to participate in this survey to assess information provided about Lemtrada (alemtuzumab) conducted by Ipsos and sponsored by the manufacturer of Lemtrada. This survey is likely to produce information that may help us improve the information and support provided to the patients. We would like to reassure you that:

- We will comply with all UK laws protecting your personal data and the British Healthcare Business Intelligence Association guidelines and with the highest ethical standards. [Show to UK only]
- Your responses will be collated with other respondents and presented to the sponsor in aggregated or anonymised form.
- Different patients sometimes respond in different ways to the same medicine, and some side effects may not be discovered until many people have used a medicine over a period of time. For this reason, we are obliged to pass on to our client, who is a manufacturer of medicines, details of any side effects related to their own products that are mentioned during the survey. This information will also be passed on to the European Medicines Agency. Although your answers will be treated in confidence, should you indicate a side effect with Lemtrada (alemtuzumab), we would need to report this along with your contact information, so that they can learn more about the safety of their medicines.

[Show to UK only]

Lemtrada is subject to additional monitoring. This will allow quick▼ identification of new safety information. You can help by reporting any side effects you may get. If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this document. You can also report side effects directly via the national reporting system to: www.mhra.gov.uk/yellowcard

By reporting side effects, you can help provide more information on the safety of this medicine.

- We are required to inform you that Market Research Agencies are required to report adverse events to pharmacovigilance, including exposure to pregnancy/lactation, suspected transmission of infectious agents, technical issue/quality, drug interaction and special situations such as overdose, abuse, misuse, incorrect administration, medication error, occupational exposure, and lack of efficacy that are mentioned during the discussion of a product from the company that sponsor the research.

[SHOW TO ITALY ONLY]

- Although everything said will remain confidential, if during the survey you indicate any adverse (or the aforementioned situations) event occurred to you, we will need to report this even if it has already been reported by you/your physician/directly to the company or the Italian regulatory authorities (we remind you that you can report using the AIFA web site http://www.agenziafarmaco.gov.it/it/content/modalit%C3%A0-di-segnalazione-delle-sospette-reazioni-avverse-ai-medicinali). In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event/drug exposed pregnancy/product complaint. Everything else you say during the course of the interview will continue to remain confidential.

- In such a situation you have the option to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the survey will continue to remain confidential, and you will still have the option to remain anonymous if you wish.

[DO NOT SHOW TO GERMANY]

- If you agree to waive the confidentiality given to you, then your name and contact details will be forwarded to the sponsor's Pharmacovigilance department for the express and sole purpose of follow-up of such report(s). If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

[SHOW TO GERMANY ONLY]

- If you agree to waive the confidentiality given to you, due to German Data protection laws you will need to contact the sponsor's Pharmacovigilance department to provide the details for the express and sole purpose of follow-up of such report(s). In this event you will be re-contacted in order to be provided with the details. If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

[SHOW TO ALL MARKETS]

Please indicate if you are willing to waive your confidentiality if an adverse event is identified during the course of this survey.

- I agree to waive my confidentiality for the express and sole purpose of follow-up of adverse events mentioned by me during this survey. In this event I understand that I will be re-contacted to be provided with the details.

- I do not agree to waive my confidentiality for the express and sole purpose of follow-up of adverse events mentioned by me during this survey and choose to stay anonymous.

SINGLE CODE
CONTINUE

- Your responses will be otherwise confidential and will not be used for any other purposes or disclosed to any third party without your approval except in cases where the manufacturer of the medicine is obliged to share the results with national and international regulatory agencies and government bodies responsible for the safety of medications.
- We remind you that you may at all times request a copy of your personal information, have it corrected and object to its processing by contacting europe.online@ipsos.com.
- You have the right to withdraw your participation at any time during this survey.

Please indicate whether you have read and understood the survey information provided above:

Code	Type	Response	Answer
	Single response check-box	Yes, I have read the information provided above and the purpose of the survey and steps are clear to me.	✓
		No [patient selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	

Please confirm your agreement to participate in the current survey:

Code	Type	Response	Answer
	Single response check-box	Yes, I agree to participate in this survey	✓
		No, I do not agree to take part in the survey [patients selecting this option will not be directed to the survey pages and will be directed to a "termination" page with appropriate text]	

PS3. Do you remember completing a similar survey about Lemtrada (alemtuzumab) in 2016?

code	*Type*	*Response*	*Answer*
	Single response	Yes	TERMINATE
		No	
		Don't know	

Start the survey! <link to patient questionnaire>

Patient questionnaire

Survey relating to patient information about Lemtrada▼

[show to all other markets] **(alemtuzumab)** ▼ [show to UK only]

Please read each question carefully and indicate your response in the boxes provided. The questionnaire will take approximately 15 minutes to complete. Please complete the questionnaire in one sitting. [SHOW TO UK ONLY] **Throughout the survey we will refer to Lemtrada by its generic name – alemtuzumab.**

Introduction questions

Programming note: Screener questions

Today's date: <Make it autofill for online surveys>

Please give us some information about yourself and your medication so that we can make sure you are eligible to take part in the survey.

P1. Have you ever been diagnosed with multiple sclerosis (MS) by a doctor? ***[eligibility criteria]***

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	INELIGIBLE

2. Have you been prescribed Lemtrada [show to all other markets] alemtuzumab [show to UK only]? *[eligibility criteria]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	INELIGIBLE

3. Have you had your first Lemtrada [show to all other markets] alemtuzumab [show to UK only] infusion yet? *[eligibility criteria]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	INELIGIBLE

4. *<IF participant answers "yes" to question 3>* When did you have your first Lemtrada [show to all other markets] alemtuzumab [show to UK only] infusion? *[potential confounding factor] [Year range is 2013-2017]*

code	*Type*	*Response*	*Answer*
	Date	Before 2013	
		2013	
		2014	
		2015	
		2016	
		2017	
		Do not know	

Questions about you

5. In which year were you first diagnosed with MS?

code	*Type*	*Response*	*Answer*
	Date	YYYY	

6. Please tell us your current age (in years). [AGE RANGE IN YEARS MUST BE > ANSWER IN Q6]

code	*Type*	*Response*	*Answer*
	Single response	18-25	
		26-35	
		36-45	
		46-55	
		56-65	
		66 or above	

7. What is your gender?

code	*Type*	*Response*	*Answer*
	Single response	Male	
		Female	

Questions about Lemtrada ▼ [show to all other markets] (alemtuzumab) ▼ [show to UK only] information

Patient Alert Cards and Patient Guides are supplied to patients prescribed Lemtrada [show to all other markets] alemtuzumab [show to UK only]. We want to find out how useful they are at telling people about Lemtrada [show to all other markets] alemtuzumab [show to UK only].

About the Patient Alert Card

8. Have you ever received a Patient Alert Card for Lemtrada [show to all other markets] alemtuzumab [show to UK only]? *[potential confounding factor] [include an image of the front of the patient card supplied in the relevant country[1]]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No [patients selecting this option will be directed to question 10]	
		Do not know	

9. *<IF participant answers "yes" to question 8>* What is the purpose of the Patient Alert Card? *[knowledge: patient card]*

code	*Type*	*Response*	*Answer*
	Single response	To show a doctor or healthcare professional involved in your medical care that you have been treated with Lemtrada [show to all other markets] alemtuzumab [show to UK only]	
		To give you important safety information you need to be aware of when receiving treatment with Lemtrada [show to all other markets] alemtuzumab [show to UK only]	
		Both of the above	✓
		None of the above	
		Do not know/not sure	

[1] Image of Patient Card needs to be customised per country (i.e. in the correct language)

About the Patient Guide

10. Have you ever received a Patient Guide for Lemtrada [show to all other markets] alemtuzumab [show to UK only]? *[potential confounding factor] [include an image of the front of the patient guide supplied in the relevant country[2]]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	
		No [Go to "about Lemtrada" text/Q14]	
		Do not know [Go to "about Lemtrada" text/Q14]	

10a. Did your doctor/nurse discuss the Patient Guide with you before your first infusion of Lemtrada [show to all other markets] alemtuzumab [show to UK only]?

code	*Type*	*Response*	*Answer*
	Single response	Yes	
		No	
		Do not remember	

11. *<IF participant answers "yes" to question 10>* What is the purpose of the Patient Guide? *[knowledge: patient guide]*

code	*Type*	*Response*	*Answer*
	Single response	To make you aware of the monitoring schedule	
		To show you how to recognize symptoms that might be related to possible side effects of Lemtrada [show to all other markets] alemtuzumab [show to UK only]	
		Both of the above	✓
		To instruct you how to administer the infusion	
		Do not know / not sure	

12. *<IF participant answers "yes" to question 10>* People differ in the amount of information they read about their medicines. How much of the Patient Guide have you read? *[potential confounding factor]*

code	*Type*	*Response*	*Answer*
	Single response	All of it	
		More than half of it	
		About half of it	
		Less than half of it	
		None of it	

[2] Image of Patient Card needs to be customised per country (i.e. in the correct language)

About the Lemtrada [show to all other markets] alemtuzumab [show to UK only] materials

13. How long ago did you read the Lemtrada [show to all other markets] alemtuzumab [show to UK only] patient guide? *[potential confounding factor]*

code	*Type*	*Response*	*Answer*
	single response	Less than a week ago	
		Between 1-2 weeks ago	
		Between 2-4 weeks ago	
		Between 1-3 months ago	
		More than 3 months ago	

13a. Do you have any suggestions to improve the Patient Guide? (you can choose more than one answer). [Codes 1 and 2 can't be selected together and codes 3 and 4 can't be selected together]

code	*Type*	*Response*	*Answer*
	Multi response	More detailed information in general	
		Less detailed information in general	
		More pictures	
		Less pictures	
		Covering topics other than (serious) side effects, such as quality of life	
		More practical	
		Other (please specify)	

Questions about Lemtrada [show to all other markets] alemtuzumab [show to UK only]

Please answer these questions based on what you remember from the information you received. Do not worry if you can't remember everything - we want to see how clear the information you were given is. Remember that this survey is anonymous and it will not be possible to link the answers to you. We will use the answers we get from this survey to make changes to the information if it is not clear enough.

After completing this survey, you will be shown the correct answers for all of the following questions.

14. After an infusion of Lemtrada [show to all other markets] alemtuzumab [show to UK only], how often should you have blood and urine tests? *[knowledge – importance of monthly monitoring]*

Code	*Type*	*Response*	*Answer*
	Single response	Weekly	
		Monthly	✓
		Every 2 months	
		Every 3 months	
		Every 6 months	

15. Bleeding disorder can be a side effect of Lemtrada [show to all other markets] alemtuzumab [show to UK only]. Which of the symptom(s) listed below could show a bleeding disorder? *[knowledge: immune thrombocytopenic purpura (ITP)]*

Code	*Type*	*Response*	*Answer*
	Single response	Bruising easily	
		Small red, pink or purple spots on the skin	
		Bleeding from a cut that is harder to stop as well as bleeding from gums or nose that takes longer than usual to stop	
		All of the above	✓

15a. Bleeding disorders are important to recognise. Which, if any, of the following images represent symptom of bleeding disorder?

Picture A [click here to see picture A]

Picture B [click here to see picture B]

Picture C [click here to see picture C]

16. If you have symptoms of a bleeding disorder, what actions should you take?

Code	*Type*	*Response*	*Answer*
	Single response	Make an appointment to see your doctor within the next 4 weeks	
		Tell your doctor at your next scheduled visit	
		Contact your doctor immediately	✓
		None	

17. Apart from red or tea coloured urine, what are further signs and symptoms of kidney problems or anti-GBM disease? *[knowledge – kidney disorders]*

Code	Type	*Response*	Answer
	Single response	Swelling in the legs or feet	✓
		Diarrhoea	
		Depression	
		All of the above	

18. If you have symptoms of a kidney disorder, what actions should you take? *[knowledge – kidney disorders]*

Code	*Type*	*Response*	*Answer*
	Single response	Wait to see if the symptoms resolve	
		Tell your doctor at your next scheduled visit	
		Drink extra fluids	
		Contact your doctor immediately	✓

<Intro Screen> People who have had a Lemtrada [show to all other markets] alemtuzumab [show to UK only] infusion may develop symptoms of a thyroid disorder which can be an under-active thyroid or over-active thyroid.

19. Apart from excessive sweating and nervousness, which of the following symptoms could be further signs of an **over-active** thyroid? *[knowledge – under-active thyroid]*

Code	Type	*Response*	Answer
	Single response	Swelling of the legs and depression	
		Unexplained weight loss, eye swelling and fast heartbeat	✓
		Depression and nausea	
		None of the above	

20. Apart from unexplained weight gain and feeling cold, which of the following could be further signs of an **under-active** thyroid? *[knowledge – under-active thyroid]*

Code	Type	Response	Answer
	Single response	Depression and nausea	
		Bruising easily and nausea	
		Swelling in the legs or feet, worsening tiredness, and newly occurring constipation	✓
		None of the above	

21. If you have symptoms of a thyroid disorder, what actions should you take? *[knowledge – thyroid disorder]*

Code	*Type*	*Response*	*Answer*
	Single response	Wait to see if the symptoms resolve	
		Tell your doctor at your next scheduled visit	
		Contact your doctor immediately	✓
		Eliminate all carbohydrates from your diet for at least 4 weeks	

22. After an infusion of Lemtrada [show to all other markets] alemtuzumab [show to UK only], how often should you have thyroid function tests? *[knowledge – importance of monthly monitoring]*

Code	*Type*	*Response*	*Answer*
	Single response	Weekly	
		Monthly	
		Every 2 months	
		Every 3 months	✓
		Every 6 months	

23. For how long is it necessary to have blood and urine tests for auto-immune conditions (bleeding, kidney and thyroid disorders)? *[knowledge – importance of monitoring for 4 years after the last course of treatment]*

Code	*Type*	*Response*	*Answer*
	Single response	For 6 weeks after the last course of treatment with Lemtrada [show to all other markets] alemtuzumab [show to UK only]	
		For 6 months after the last course of treatment with Lemtrada [show to all other markets] alemtuzumab [show to UK only]	
		For 2 years after the last course of treatment with Lemtrada [show to all other markets] alemtuzumab [show to UK only]	
		For 4 years after the last course of treatment with Lemtrada [show to all other markets] alemtuzumab [show to UK only]	✓

24. What should you do if you experience signs or symptoms that you have not experienced **before?**

Code	*Type*	*Response*	*Answer*
	Single response	Wait 4 weeks to see if the symptoms resolve	
		Tell your doctor at your next scheduled visit	
		Contact your doctor immediately	✓
		Find a patient contact group on the Internet	

24a. What should you do if you experience signs or symptoms that you have **had before, then disappeared and have now come back?**

Code	*Type*	*Response*	*Answer*
	Single response	Wait 4 weeks to see if the symptoms resolve	
		Tell your doctor at your next scheduled visit	
		Contact your doctor immediately	✓
		Find a patient contact group on the Internet	

24b. What should you do if you experience signs or symptoms that you **had all the time and have now become worse?**

Code	*Type*	*Response*	*Answer*
	Single response	Wait 4 weeks to see if the symptoms resolve	
		Tell your doctor at your next scheduled visit	
		Contact your doctor immediately	✓
		Find a patient contact group on the Internet	

[ASK THOSE WHO ANSWER 'DON'T KNOW' AT PS4]

25. Do you remember completing a similar survey about Lemtrada (alemtuzumab) in 2016?

code	*Type*	*Response*	*Answer*
	Single response	Yes	TERMINATE
		No	
		Don't know	

<Completion page>

You have now finished the survey.

Thank you very much for taking part! Click here to see the correct responses. <link to page of correct responses>

Lemtrada RMP

Questionnaires for healthcare professionals

United Kingdom
Germany
Italy
Spain
Greece
Denmark
Norway
Belgium
The Netherlands

UK approval number required for each section of questionnaire

<Programming note: please show this question on a separate screen before HCP information page>

1. Which country are you working in? *[eligibility criteria]*

Germany	
UK	
Italy	
Spain	
Denmark	
Norway	
Belgium	
The Netherlands	
Greece	
Other	***[INELIGIBLE]***

Pre-screening questions [do not show on screen]

PS1. What is your primary medical specialty? Please select one

single response	Endocrinologist	[Terminate]
	Diabetes specialist	[Terminate]
	Neurologist	[continue]
	MS specialist	[continue]
	Oncologist	[Terminate]
EXCLUSIVE	None of the above	[Terminate]

PS2. Which patients represent the majority of your case load? Please select one.

single response	Diabetes patients	[Terminate]

	MS patients	[continue]
	Dementia /Alzheimer's patients	[Terminate]
	Cancer patients	[Terminate]
	Patients with thyroid disorders	[Terminate]
EXCLUSIVE	None of the above	[Terminate]

PS3. Which of the following medications do you prescribe to your MS patients [if selected in QPS2].

Multiple response rotate	Lemtrada	**[continue to Lemtrada invite email text screen]**
	Avonex	[Terminate] – if NOT selected with Lemtrada]
	Rebif	[Terminate] – if NOT selected with Lemtrada]
	Tecfidera	[Terminate] – if NOT selected with Lemtrada]
	Aubagio	**[If selected with Lemtrada continue to Lemtrada invite email text screen]** **[If selected with another drug apart from Lemtrada or selected alone go to Q30]**
EXCLUSIVE do not rotate	None of the above	[Terminate]

HCP invitation email

LEMTRADA▼ (alemtuzumab) RMP questionnaire

Subject header: Survey relating to RMP information for Lemtrada®▼ (alemtuzumab)

Dear Doctor,

We are inviting you to take part in a survey to evaluate the efficacy of risk management information provided for Lemtrada (alemtuzumab). The survey is for healthcare professionals who have prescribed Lemtrada (alemtuzumab).

It will take about 15 minutes to complete. We will use the information provided by doctors to determine whether the existing provision of risk information is sufficient.

We are required to pass on to our client details of adverse events that are mentioned during the course of market research. Although what you say will of course be treated in confidence, should you raise during the discussion an adverse event (AE) in a specific patient or groups of patient, we will need to report this even it has already been reported by you directly to the company or to the regulatory authorities. [SHOW TO UK ONLY] using the MHRA's "Yellow Card" system.

In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that AE. Everything else you say during the course of the interview will continue to remain confidential, and you will still have the option to remain anonymous if you so wish.

[SHOW TO UK ONLY]

▼Lemtrada is subject to additional monitoring. This will allow quick identification of new safety information. Adverse Events should be reported. Reporting forms and information can be found at:

www.mhra.gov.uk/yellowcard

Adverse events should also be reported to Sanofi Genzyme Tel: 00 44 (0)1865 405 200

HCP information page

This survey is being conducted to meet a regulatory obligation from the European Medicines Agency (EMA). The purpose of the survey is to evaluate effectiveness of education materials provided for Lemtrada (alemtuzumab) ▼. [SHOW TO UK ONLY] **Throughout the survey we will refer to Lemtrada by its generic name – alemtuzumab.**

The survey is being run by a company called Ipsos, on behalf of Sanofi Genzyme, the manufacturer of Lemtrada alemtuzumab [SHOW 'alemtuzumab' TO UK ONLY]. Your answers will not be identifiable, and data shared with the pharmaceutical company will be in aggregated form.

The survey will take about 15 minutes to complete.

If you have any questions about the survey please contact europe.online@ipsos.com.

I would like to take part in the survey. <insert link to HCP consent page>

HCP consent page

Thank you for deciding to participate in this survey to assess risk information provided about Lemtrada [show to all other markets], alemtuzumab [Show to UK only], conducted by Ipsos and sponsored by Sanofi Genzyme, the manufacturer of Lemtrada [show to all other markets], alemtuzumab [Show to UK only], This survey is likely to produce results that may benefit patients. We would like to reassure you that:

- We will comply with all UK laws protecting your personal data and the British Healthcare Business Intelligence Association guidelines and with the highest ethical standards. [SHOW TO UK ONLY]
- Your responses will be collated with other respondents and presented to the sponsor in aggregated or anonymised form.
- I agree that if an AE related to the commissioning company's own products in a specific patient has been mentioned in the survey, the company will need to report this (even if it has already been reported by me directly to the company or the regulatory authorities). I understand that if I decide to disclose my personal details in association with any AE report, this information will be disclosed to the commissioning company.

[SHOW IN A BOX TO UK ONLY]

Lemtrada is subject to additional monitoring. This will allow quick identification of new safety information. Adverse Events should be reported. Reporting forms and information can be found at:

www.mhra.gov.uk/yellowcard

Adverse events should also be reported to Sanofi Genzyme Tel: 00 44 (0)1865 405 200

[SHOW TO ITALY ONLY]

- Although everything said will remain confidential, if during the survey you indicate any adverse (or the aforementioned situations) event occurred to you, we will need to report this even if it has already been reported by you/directly to the company or the Italian regulatory authorities (we remind you that you can report using the AIFA web site http://www.agenziafarmaco.gov.it/it/content/modalit%C3%A0-di-segnalazione-delle-sospette-reazioni-avverse-ai-medicinali). In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that AE/drug exposed pregnancy/product complaint. Everything else you say during the course of the interview will continue to remain confidential.

[SHOW all markets – except GERMANY AND ITALY]

- In such a situation you have the option to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the survey will continue to remain confidential, and you will still have the option to remain anonymous if you wish.

- If you agree to waive the confidentiality given to you, then your name and contact details will be forwarded to the sponsor's Pharmacovigilance department for the express and sole purpose of follow-up of such report(s). If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

[SHOW TO GERMANY ONLY]

- If you agree to waive the confidentiality given to you, due to German Data protection laws you will need to contact the sponsor's Pharmacovigilance department to provide the details for the express and sole purpose of follow-up of such report(s). In this event you will be re-contacted in order to be provided with the details. If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

- Are you happy to proceed with the interview on this basis? Please indicate your response by selecting the appropriate option below.

  I would like to proceed and give permission for my contact details to be passed on to the Drug Safety department of the company if an adverse event / product complaint is mentioned by me during the survey. Please tick the box ☐
  [Proceed]

  I would like to proceed but do not wish for my contact details to be passed on to the Drug Safety department of the company if an adverse event / product complaint is mentioned by me during the survey. Please tick the box ☐
  [Proceed]

  I do not want to proceed and wish to end the interview here [Thank and close] Please tick the box ☐

  - We remind you that you may at all times request a copy of your personal information, have it corrected and object to its processing by contacting europe.online@ipsos.com.
  - You have the right to withdraw from the survey at any time during this survey.

Please indicate whether you have read and understood the survey information provided:

Code	*Type*	*Response*	*Answer*
	Single response check-box	Yes, I have read the information provided above and the purpose of the survey and steps are clear to me.	✓

		No [HCP selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	

Please confirm your agreement to participate in this survey:

Code	*Type*	*Response*	*Answer*
	Single response check-box	Yes, I agree to participate in this survey	✓
		No, I do not agree to take part in the survey [HCPs selecting this option will not be directed to the survey pages and will be directed to a "termination" page with appropriate text]	

Begin the survey. <link to HCP questionnaire>

HCP questionnaire

Survey to assess knowledge relating to Lemtrada [show to all other markets] (alemtuzumab) [show to UK only]

This is a questionnaire about your knowledge relating to Lemtrada [show to all other markets] alemtuzumab [Show to UK only].

Please read each question carefully and indicate your response in the boxes provided. The questionnaire will take approximately 15 minutes to complete. Please complete the questionnaire in one sitting.

About you

1. What is your specialist area? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Single response exclusive	Neurologist	
		MS specialist	
		Other	INELIGIBLE

2. When did you qualify as a medical doctor? *[subsample analysis] [year range = [1970-2017]*

Code	*Type*	*Response*	*Answer*
	Date	YYYY	

3. When did you qualify as a specialist neurologist[3]? *[subsample analysis] [year range = [1970-2017]*

Code	*Type*	*Response*	*Answer*
	Date	YYYY	

4. How many MS patients in total do you treat within a typical year? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Single response	Up to 10	
		11 - 50	
		51-99	
		100+	

[3] Local medical director should ensure that terminology is appropriate for their market.

5. Have you ever prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only]? *[eligibility criteria]*

Code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No [HCP selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	INELIGIBLE

6. When did you last initiate Lemtrada [show to all other markets] alemtuzumab [Show to UK only]? Choose the answer that is most accurate. *[potential confounding factor]*

Code	*Type*	*Response*	*Answer*
	Single response	Within the last week	
		Within the last month	
		Within the last 3 months	
		More than 3 months ago	
		More than 6 months ago [HCP selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	INELIGIBLE

7. Approximately how many patients have you treated with Lemtrada [show to all other markets] alemtuzumab [Show to UK only]?

Code	*Type*	*Response*	*Answer*
	Single response	0-10 patients	
		10-25 patients	
		25-50 patients	
		>50 patients	

8. How many prescriptions for Lemtrada [show to all other markets] alemtuzumab [Show to UK only] do you write each month? [*potential confounding factor]*

Code	*Type*	*Response*	*Answer*
		0-2 prescriptions per month	
	Single response	2-4 prescriptions per month	
		4-8 prescriptions per month	
		More than 8 prescriptions per month	

9. Do you work in a public (state funded) or private healthcare system? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Single response	Public healthcare only	
		Private healthcare only	
		Both public and private healthcare	

10. What percentage of your professional time is spent in the following settings? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Multi response	___% in an MS clinic in university hospital	
		___% in an MS clinic in community hospital	
		___% in a General neurology in university hospital	
		___% in a General neurology in community hospital	
		___% in an Office-based setting [*ask in France, Germany, Italy, Spain*]	

Information about Lemtrada (alemtuzumab) [show to all other markets] [show to UK only]

The Lemtrada [show to all other markets] alemtuzumab [Show to UK only] risk management plan (RMP) includes educational materials as the core element of risk minimisation tools. You have received some materials about Lemtrada [show to all other markets] alemtuzumab [Show to UK only] the HCP Guide, the HCP Checklist and the SmPC as well as educational materials targeted to patients which should have been given to them by you. We want to find out how useful these materials are for communicating risk management information about Lemtrada [show to all other markets] alemtuzumab [Show to UK only].

The following questions relate to your knowledge about Lemtrada [show to all other markets] alemtuzumab [Show to UK only].

Please answer the questions based on what you remember.

After completing this survey, you will be shown the correct answers for all of the following questions.

About the HCP and Patient Educational Materials

11. Have you received the HCP Guide? *[knowledge: HCP guide]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	
		Do not remember	

12. How much of the HCP Guide have you read? *[behaviour: HCP Guide]*

code	*Type*	*Response*	*Answer*
	Single response	All of it	
		More than half of it	
		About half of it	
		Less than half of it	
		None of it	

13. Have you received and reviewed the HCP Checklist? *[knowledge: HCP checklist]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	
		Do not remember	

14. How often do you use the HCP Checklist? *[knowledge: HCP checklist]*

code	*Type*	*Response*	*Answer*
	Single response	Always	
		Usually	
		Sometimes	
		Hardly	
		Never	

15. Have you reviewed the Summary of Product Characteristics (SmPC)? *[knowledge: SmPC]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	
		No	
		Can't remember	

[ASK THOSE WHO SELECT CODE 1 "YES" OR 3 "CAN'T REMEMBER"]

15a. How often do you review the Summary of Product Characteristics (SmPC)?

code	*Type*	*Response*	*Answer*
	Single response	Always	
		Usually	
		Sometimes	
		Rarely	

16. Which patient educational materials are available for patients prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only]? *[Knowledge – patient guide, patient alert card, package leaflet]*

code	*Type*	*Response*	*Answer*
	Single response	Patient Guide and Patient Alert Card	✓
		Patient Alert Card and special women's brochure	
		Patient Guide and special women's brochure	
		None of the above	

16a. Did you review any of the *patient* materials yourself, before you gave them to patients?

code	*Type*	*Response*	*Answer*
	Single response	Yes	
		No	

About Lemtrada ▼ [show to all other markets] (alemtuzumab) ▼ [show to UK only]

17. At first prescription of Lemtrada [show to all other markets] alemtuzumab [Show to UK only], patients need to be informed on nephropathies (including anti-GBM disease) and thyroid disorders. Which potential risks need to be discussed as well? *[knowledge: risks associated with the product]*

code	*Type*	*Response*	*Answer*
	Single response	Immune thrombocytopenic purpura [ITP], active infections and depression	
		Pregnancy & contraception (if applicable) and depression	
		Immune thrombocytopenic purpura [ITP], active infections and pregnancy & contraception (if applicable)	✓
		Pregnancy & contraception (if applicable), active infections and gastro-intestinal issues	

18. In which patients with the following condition(s) is Lemtrada [show to all other markets] alemtuzumab [Show to UK only] contraindicated? *[knowledge: key points in the HCP guide and checklist - contraindications]*

code	*Type*	*Response*	*Answer*
	Single response	Human immunodeficiency virus (HIV) and ischemic heart disease	
		Human immunodeficiency virus (HIV) and hypersensitivity to the active substance or any of the excipients	✓
		Human immunodeficiency virus (HIV) and depression	
		Ischemic heart disease and depression	

19. Which of the following treatments is to be used cautiously due to potential combined effects on the patient's immune system with Lemtrada [show to all other markets] alemtuzumab [Show to UK only]? *[knowledge: key points in the HCP guide and checklist - contraindications]*

code	*Type*	*Response*	*Answer*
	Single response	Selective serotonin reuptake inhibitors (SSRIs) and immunosuppressive therapy	
		Selective serotonin reuptake inhibitors (SSRIs) and antineoplastic therapy	
		Antineoplastic therapy and antiviral therapies	
		Immunosuppressive therapy and antineoplastic therapy	✓

20. According to the HCP guide and checklist, serum creatinine and complete blood count with differential should be conducted before first prescription of Lemtrada [show to all other markets]

alemtuzumab [Show to UK only]; what other tests are required? *[knowledge: key points in the HCP guide and checklist - tests to be conducted for the initial screening of the patient]*

code	*Type*	*Response*	*Answer*
	Single response	Urinalysis with microscopy and thyroid function tests such as TSH	✓
		Urinalysis with microscopy and urine protein creatinine test	
		Urine protein creatinine test and thyroid function tests such as TSH	
		Thyroid function tests such as TSH and cholesterol	

21. How long after the patient's last vaccination should you wait before administering Lemtrada [show to all other markets] alemtuzumab [Show to UK only]? *[knowledge- key points in the HCP guide and checklist - vaccinations]*

code	*Type*	*Response*	*Answer*
	Single response	2 weeks	
		4 weeks	
		6 weeks	✓
		6 months	

22. When do you need to check serum creatinine? *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single response	Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 3 months until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and monthly until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	✓
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 8 weeks until last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only] or as indicated by clinical signs and symptoms.	
		These tests do not need to be carried out	

23. When do you need to check complete blood count with differential? *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single response	Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and monthly until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	✓
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 3 months until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Every 8 weeks until last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only] or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out	

24. When do you need to conduct urinalysis with microscopy? *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single response	Monthly from the start of treatment until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and monthly until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	✓
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 3 months until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 8 weeks until last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only] or as indicated by clinical signs and symptoms	

25. When do you need to conduct liver function tests? *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single response	Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and monthly until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only]	
		Every 3 months until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Every 8 weeks until last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only] or as indicated by clinical signs and symptoms.	
		These tests do not need to be carried out [exclusive]	✓

26. When do you need to conduct thyroid function tests [such as TSH]? *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single response	Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and monthly until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 3 months until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	✓
		Every 8 weeks until last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only]or as indicated by clinical signs and symptoms.	
		These tests do not need to be carried out	

27. When do you need to conduct urine protein creatinine ratio tests? *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single response	Before the patient is prescribed Lemtrada [show to all other markets] alemtuzumab [Show to UK only]	
		Monthly until 48 months after last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only] and every 3 months until 48 months after last infusion of	

		Lemtrada [show to all other markets] alemtuzumab [Show to UK only].	
		Every 8 weeks until last infusion of Lemtrada [show to all other markets] alemtuzumab [Show to UK only] or as indicated by clinical signs and symptoms.	
		These tests do not need to be carried out	✓

28. How long should women of childbearing potential use effective contraceptive measures? *[knowledge: special warnings on fertility, contraception and breastfeeding]*

code	*Type*	*Response*	*Answer*
	Single response	During treatment and for at least 5 days following each treatment	
		During treatment and for at least 30 days following each treatment	
		During treatment and for at least 4 months following each treatment	✓
		During treatment and for at least 48 months after each treatment	

29. What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)? *[knowledge: key points in the HCP guide and checklist –appropriate medical intervention]*

code	*Type*	*Response*	*Answer*
	Single response	Obtain a complete blood count and if thrombocytopenia is confirmed, refer to a specialist (haematologist) immediately	✓
		Obtain a complete blood count and if thrombocytopenia is confirmed, repeat thrombocyte counts within 1 week	
		Ask patient to self-monitor symptoms until their next scheduled appointment when a complete blood count will be obtained	

30. What should you do if your monitoring results lead you to suspect nephropathy? *[knowledge: key points in the HCP guide and checklist- appropriate medical intervention]*

code	*Type*	*Response*	*Answer*
	Single response	Refer the patient to a specialist (nephrologist) immediately	✓
		Ask the patient to come in as soon as possible, conduct urine tests and keep monitoring the patient yourself	
		Wait until the patient's next scheduled appointment to confirm any change in serum creatinine level from baseline	
		None of the above	

31. What counselling should you provide patients treated with Lemtrada [show to all other markets] alemtuzumab [Show to UK only]? *[knowledge: key points in the HCP guide]*

Code	*Type*	*Response*	*Answer*
	Single response	Coping with MS, importance of contraception and depression prevention	
		Coping with MS, importance of contraception and risks and importance of monthly monitoring appointments	✓
		Only the importance of monthly monitoring appointments	
		None of the above	

Ask i**f selected Aubagio + Lemtrada or Aubagio + another drug or selected Aubagio alone at PS3.**

32. At the beginning of this survey, you mentioned that you prescribe Aubagio [SHOW TO OTHER MARKETS] teriflunomide [SHOW TO UK ONLY]. If you would like to take a similar survey about Aubagio [SHOW TO OTHER MARKETS] teriflunomide [SHOW TO UK ONLY], please click here. <link to Aubagio HCP survey>

You have now finished the survey.

Thank you very much for taking part! Click here to see the correct responses. <link to page of correct responses>

SANOFI GENZYME

POST AUTHORIZATION SAFETY STUDY (PASS) INTERIM REPORT

TITLE: Knowledge Survey to assess the effectiveness of educational materials among patients prescribed LEMTRADA® (alemtuzumab)

COMPOUND: ALEMTUZUMAB

STUDY NUMBER: N/A

Short title: LEMTRADA EU-RMP Survey in Patients

The Study is conducted by Sanofi Genzyme, Atlantis Healthcare and IPSOS, hereinafter referred also as the "MAH/MAH REPRESENTATIVE".

Version Number:	6.0		
Date:	November 09, 2016	Total number of pages:	68

PASS Information

Title	Knowledge survey of educational materials in patients treated with LEMTRADA
Version identifier of the final study report	1.7
Date of last version of the final study report	30th November 2015
EU PAS register number	Not available
Active substance	Alemtuzumab
Medicinal product	LEMTRADA
Product reference	EU/1/13/869/001
Procedure number	EMEA/H/C/003718
Marketing authorization 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 (PG) and Patient Alert Card (PC)? • What is the knowledge of patients about the PG and PC? • 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?
Country(-ies) of study	This first wave of the survey was conducted in United Kingdom, Germany, Italy, Spain, Denmark and Norway.
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Marketing authorization holder(s)

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TABLE OF CONTENTS

1 ABSTRACT

Title

Knowledge survey of educational materials in patients treated with LEMTRADA

Keywords

LEMTRADA, audit, risk minimisation materials, effectiveness

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 minimisation targeted at patients. The primary objectives of the educational materials are to ensure early detection of adverse events of interest to mitigate severity and sequelae potentially related to LEMTRADA or to such immunomodulatory agents through education, and facilitating periodic monitoring, communicate risks (e.g. secondary autoimmune disease and serious infections) to patients and prescribers and to inform about benefit-risk decisions before each treatment course.

Research question and objectives Study

The objective of this 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. The research questions include the extent of patients' knowledge about the PG and PC, knowledge of serious adverse events relating to LEMTRADA and knowledge of risk minimisation activities to be performed.

Study Design

A cross-sectional survey conducted in two distinct waves at 18 months and 36 months after the launch of the product in at least 2 highly populated EU countries (Germany and Spain). The first wave was conducted in Germany, Italy, Spain, UK, Denmark, and Norway. Data collection took place over an 11-week period and the survey was conducted online using a structured questionnaire. Results have been analysed and reported to the European Medicines Agency (EMA). This report describes Wave 1 of the survey. Wave 2 will be conducted three years after the launch of LEMTRADA, in 2017.

Setting

- Site and patient selection: The population for this study was a convenience (non-randomised) sample of patients treated for MS with LEMTRADA.
- Recruitment via online panels (panels exist for MS patients and were used as the first recruitment approach) and snowballing (we asked respondents to suggest other potential respondents interested in participating).

- Data collection: Data was collected via patient self-report in the questionnaire.
- Overall participation status: Patients were from Denmark (n=8, 4%), Italy (n=49, 24%), Germany (n=46, 23%), Norway (n=32, 16%), Spain (n=44, 22%), and UK (n=22, 11%)
- Patients were not given the PC and PG to help them answer questions; instead they were asked to recall receiving and reading the PC and PG

Patients and study size, including dropouts

The survey was conducted in 201 patients.

Variables and data sources

- Variables and evaluation criteria: The following elements were collected and assessed:

  1) Whether the patient has received the PG and PC

  2) Whether the patient carries the PC with them and whether the patient understands the purpose of the PC

  3) The patient's understanding of the risks associated with use of LEMTRADA

  4) The patient's knowledge of the risk minimisation 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, and symptoms to be monitored and action to be taken if they occur.

- Data analyses: Descriptive analyses were performed. Sub-populations were analysed to identify patient groups that may require further education efforts.

Results

Demographics and Country Differences

There were 201 participants in total. More than half (52%) of the participants were female and almost 70% were aged 26-45 years (26-35 36%; 36-45 33%). Very few were 56 years or older (6%). Individuals were from Denmark (n=8, 4%), Italy (n=49, 24%), Germany (n=46, 23%), Norway (n=32, 16%), Spain (n=44, 22%), and UK (n=22, 11%). The sample of patients representing each country in this survey were mostly in line with the estimated populations of patients with MS in Europe. Germany has the largest MS patient population on Lemtrada, followed by the UK, Spain and Italy. As expected Norway and Denmark have the smaller populations. This means the UK is somewhat underrepresented..

Overall, patients from the UK were more knowledgeable about signs and symptoms of a kidney disorder ($p = .079$). However, there were no other between-country differences in symptom knowledge (bleeding disorder, over-active thyroid, under-active thyroid). Danish patients, who

also had the second highest proportion of correct answers for the purpose of the PG (p = .041) and purpose of the Patient Alert Card (p = .02), had the highest proportion of correct answers for what to do if you notice symptoms of a bleeding disorder (83% correct), kidney disorder (83% correct), or thyroid disorder (83% correct), as well as what action to take if you experience new symptoms (67% correct), returned symptoms (50% correct), or worsening symptoms (83% correct). They also had the best recollection of the fact that blood and urine tests should be continued for four years following the final course of treatment (67% correct), and that blood/urine and thyroid tests should be conducted monthly (50% correct) and 3-monthly (33% correct), respectively (though the latter two were non-significant). On the other hand, Norwegian patients were the group that was most consistently incorrect; they had the lowest proportions of correct scores across almost all questionnaire items. For example, only 4% of Norwegian patients recalled that blood/urine tests are required for four years and between 0 to 4% of patients correctly identified that one should 'call your doctor right away' if they develop new, returned, or worsened symptoms. This finding of poor knowledge among Norwegians may relate to the fact that they were the group least likely to have read the entire PG (only 8% read 'all of it' and 29% read 'less than half'').

Knowledge of Symptoms

Signs and symptoms associated with serious adverse reactions to LEMTRADA emerged as an area where patients appeared to have insufficient knowledge, though this is not surprising given the difficulty to achieve a 'complete' answer for questions 15 and 19 in particular. For knowledge of signs/symptoms of ITP (question 15), 7% of patients scored completely by selecting 5/5 symptoms, while a further 34% scored either 3/5 or 4/5 symptoms. For understanding of signs/symptoms of kidney disorders (question 17), 27% scored completely by selecting 2/2 symptoms, and a further 46% scored partially completely. For knowledge of over-active thyroid (question 19), 9% scored completely by selecting 5/5 symptoms, and a further 26% had partially complete answers. For knowledge of under-active thyroid (question 20), 10% had complete answers by selecting 4/4 symptoms, while a further 37% had partially complete answers. Evidently, the proportion of participants scoring completely decreased as the complexity of the question increased.

Knowledge of Action to be Taken

Patients appeared to have better knowledge about the action that should be taken following the appearance of signs/symptoms associated with the above conditions as well as the actions that should be taken following appearance of other symptoms, than they did for symptom knowledge. This is not surprising as there is less room for error in these questions. Forty-one percent, 45%, and 43% of respondents correctly chose 'see your doctor immediately' for action to take after symptoms of bleeding disorder, kidney disorder, and thyroid disorder, respectively. Meanwhile 41%, 36%, and 48% correctly chose 'call your doctor right away' for action to take after experiencing new, returned, or worsening symptoms, respectively. Up to one-third of patients saw waiting until symptoms resolve or subside as a valid option following the appearance of symptoms of a bleeding disorder (32%), kidney disorder (30%), and thyroid disorder (22%). Up to 10% of patients saw 'take no action' as a valid option following the appearance of new symptoms (10%), returned symptoms (9%), and worsening symptoms (6%). An additional 16% saw 'continue to monitor your symptoms for another month' as a valid option following

development of new symptoms, while 20% and 19% selected this answer for returned symptoms and worsening symptoms, respectively.

Knowledge of Frequency of Monitoring

In terms of understanding of the frequency of monitoring, 39% were correct for the frequency of blood/urine tests for bleeding disorders and kidney problems, however only 14% were correct for the frequency of blood tests for thyroid function and only 14% recalled that blood and urine tests must be continued for four years following the last course of treatment.

Receipt/Reading of Materials – Group Differences

Over 75% of patients recalled receiving the PC and over 80% of patients recalled receiving the PG. Over 70% said they had received both, and 11% said they had received neither. Subgroup analyses involved a comparison of patients who had received both RMP materials (PC and PG, n = 146) versus just one (just PG, n = 21). Those who had received both materials were significantly more likely to have read all of the PG. Those receiving only the PG were significantly more likely to know action to be taken following development of thyroid symptoms (trend to significance), however this is not a surprising finding given that the PC does not explain thyroid symptoms or what to do if patients experience them. However, the frequency of blood and urine tests is something that is mentioned on the PC, yet patients receiving this as well as the PG were significantly less likely to be correct on this question. All other findings were non-significant.

A comparison of those who had read all of the PG versus those who had not read all of it revealed that those who read all were significantly more likely to know the purpose of the PC ($p < .000$), to have a HCP discuss the PG with them ($p = .019$), to know the purpose of the PG, ($p < .000$), to know the symptoms of kidney problems ($p < .000$) and an over-active thyroid ($p = .051$), and to know the action that should be taken following development of bleeding disorder symptoms ($p = .005$), new symptoms ($p < .000$), returned symptoms ($p = .004$) and worsening symptoms ($p = .001$). This suggests that reading the entire PG has positive implications for patient knowledge.

Time Since First Infusion – Group Differences

Other subgroup analyses revealed that across the sample, those prescribed LEMTRADA between 7 to 12 months ago were more knowledgeable about signs and symptoms of a kidney disorder (48% complete), while those prescribed the medication more than 37 months ago were most knowledgeable about symptoms of an under-active thyroid (40% complete). Patients who had been prescribed LEMTRADA 7 to 12 months ago were significantly more likely than those who had been prescribed LEMTRADA at other times to answer correctly for what to do following development of kidney symptoms (58%), returned general symptoms (55%), and existing symptoms that are worsening (61%).

Discussion

It is important to note that Lemtrada is prescribed to patients with highly active MS. Not seldomly they have received several medications before. These are seriously ill patients and loss of cognitive function is a known symptom of MS, with 40% already showing some cognitive

dysfunction at the start of their disease. The results of this survey should be seen in this light. The questions were asked from recollection and the recollection of an MS patient cannot be judged in the same way as a recollection from a healthy human being. Results show that despite over 75% of patients acknowledging the receipt of the PC and over 80% of patients acknowledging the receipt of the PG, patient knowledge about the purposes of the educational materials is moderate, and most patients do not have complete knowledge of signs and symptoms associated with serious adverse reactions to LEMTRADA. However, it is important to note that the criteria set out for a complete answer to some questions was almost unattainable for a lay person. For example, it is reasonable to expect that few patients would be able to select all five correct symptoms of Immune Thrombocytopenic Purpura from memory when they are non-healthcare professionals and, as aforementioned, may also be suffering from cognitive issues related to their MS. Patients appeared more knowledgeable about the action that should be taken following the appearance of signs/symptoms associated with the above conditions as well as the actions that should be taken following appearance of symptoms in general. That said, between 20-40% of patients saw taking no action, waiting, and monitoring symptoms before contacting a doctor as the correct thing to do. However, there may be good reason for monitoring symptoms; MS patients experience a lot of transient symptoms and have likely become accustomed to monitoring all symptoms to see if they resolve themselves before they alert their doctor. A small proportion of patients were aware that blood/urine monitoring should continue for four years following the final course of LEMTRADA. These data highlight areas where knowledge among patients could be improved.

Subgroup analyses showed that patients from the UK were most knowledgeable about the purpose of the educational materials, and were most likely to have read all of the PG, while patients from Denmark appeared most knowledgeable about action to be taken following appearance of signs/symptoms of severe adverse reactions as well as the frequency and length of time that monitoring is required. On the other hand, patients from Norway were consistently less knowledgeable.

Comparisons also revealed that reading all of the PG led to significantly better knowledge and understanding in many areas. This suggests that one of the most useful actions that could be done to improve patient knowledge is to a) ensure that all patients have access to materials that they can read, and b) ensure that as many patients as possible read all of the PG, as opposed to half of it for example. Other methods for improving patient knowledge could include ensuring that all patients have a healthcare professional go through the materials with them to reinforce and reiterate information, or perhaps there could be alternative, more engaging methods of getting the information across to patients, for example the MS ONE to ONE website and the Mobile phone application ‘Lemcheck’ which is currently being rolled out in European countries. The application is based on the educational materials and can serve as an information and reminder tool.

Marketing Authorization Holder(s)

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The Coordinating Investigator's and Company responsible medical officer's signed approvals of the report are kept by the Company.

This report was prepared by:

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The Company Internal Staff

The Company was responsible for providing adequate resources to ensure the proper conduct of the study.

The Company was responsible for local submission(s) complying with data protection rules and any other local submission(s) required.

2 LIST OF ABBREVIATIONS

Anti-GBM: anti-glomerular basement membrane

HCP: Health Care Professional

ITP: Immune Thrombocytopenic Purpura

MAH: Marketing Authorisation Holder

MS: Multiple Sclerosis

Ns: non-significant

PASS: Post authorization safety study

PC: Patient Alert Card

PG: Patient Guide

PL: Patient Leaflet

RMP: Risk Management Plan

SmPC: Summary of product characteristics

3 INVESTIGATORS

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4 OTHER RESPONSIBLE PARTIES

Atlantis Healthcare has been involved in the preparation of the protocol and its amendments and has developed the survey and analysed the results.

IPSOS was involved with the recruitment of patients and management of the questionnaire.

The survey was sponsored by Sanofi Genzyme.

5 MILESTONES

Milestone	Planned date	Actual date
Start of data collection Wave 1	December 2015	17 March 2016
End of data collection Wave 1	January 2016	13 July 2016
Interim Report 1 (Wave 1 results)	March 2016	09 November 2016
Start of data collection Wave 2	May 2017	TBC
End of data collection Wave 2	June 2017	TBC
Final report of study results (wave 1 and 2 results)	September 2017	TBC

6 RATIONALE AND BACKGROUND

6.1 BACKGROUND

Safety profile

For the safety profile of alemtuzumab, reference is made to the current version of the SmPC/Package Leaflet.

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. The patient educational materials Patient Guide (PG) and Patient Alert Card (PC) form one of the core elements of risk minimisation targeted at patients.

The primary objectives of the educational materials were to:

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

Patients received the Patient Leaflet (PL), PG, and PC from their prescriber in hard copy at the time they were confirmed to receive LEMTRADA. Additionally, the educational materials (PL, PG, and PC) were available on LEMTRADA MS web portals of some of the 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 had been prescribed the treatment. It is important to note that access to the LEMTRADA specific part of the web-portal was intended for patients treated with LEMTRADA only. In addition, patients accessing the web-portal and/or enrolling into the programme certified that they were on treatment by entering a code number 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) were able to access the materials.

Patient Guide (PG)

The PG provides:

- Summary on risks of auto-immune side effects 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 should use the PC to carry with them the key information for their safety and adherence to monitoring. The PC covers the following information:

- The need to show the card to HCPs who are treating them for any condition
- Knowledge of auto-immune side effects to be aware of and associated symptoms:
    - Autoimmune Conditions
        - Immune Thrombocytopenic Purpura – ITP
        - Kidney problems (nephropathies, including anti-glomerular basement membrane [anti-GBM] disease)
        - 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 assessed 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 has been 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]

6.2 RATIONALE

The results of this RMP assessment of effectiveness survey provides 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 has evaluated the knowledge of patients prescribed LEMTRADA.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTIONS

1. Have patients received the PG and PC?

2. What is the knowledge of patients about the PG and PC?

    a. Do patients understand the purpose of the PG?

    b. Do patients understand the purpose of the PC?

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 minimisation activities to be undertaken?

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

    b. Frequency and length of time monitoring is required.

    c. Symptoms to be monitored and action to be taken if they occur

7.2 OBJECTIVES

7.2.1 Primary Objectives

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.

7.2.2 Secondary Objectives

Not applicable.

8 AMENDMENTS AND UPDATES

None.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is an international, cross-sectional survey, that will be conducted in two distinct waves (Wave 1 and Wave 2), 18 months apart. Information on the knowledge relating to risk minimisation (as described in the PG and PC of patients treated with LEMTRADA was collected for the first wave.

The study is cross-sectional and uses a convenience (i.e. non-randomised) sample of patients who were prescribed LEMTRADA. The surveys are conducted using structured questionnaires comprising questions where the response format is either the selection of a single response or selection of a number of responses as appropriate. Results for wave 1 have been analysed and will be reported to the European Medicines Agency (EMA).

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

9.2 SETTING

The first wave of the study was conducted in Denmark, UK, Norway, Spain, Germany and Italy with adequate translations in local languages. Recruitment via online panels and snowballing was used. Collection of survey data took place online.

Duration of the study

Start of data collection for Wave 1 was 21 months after the launch of LEMTRADA in two of the most populated EU countries (Germany and Spain) (March 2016). The end of data collection for Wave 2 will be June 2017.

9.3 PATIENTS

Eligibility criteria

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.

Exclusion criteria

- Patient has not been prescribed Lemtrada®

Analysis populations

The survey was 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 were analysed.

Modalities of recruitment

Patient selection

For the selection of patients free found recruitment was used. Multiple approaches were used including:

- Recruitment via online panels – panels exist for MS patients and were used as the first recruitment approach;
- Snowballing – we asked respondents to suggest other potential respondents interested in participating.

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

9.4 VARIABLES

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

- Awareness of the PG and PC and of the purpose of the PG and PC
- Knowledge of side effects to be aware of, and associated symptoms and action to be taken should they occur
- Awareness of the importance of monitoring until four years after last course of treatment

Potential confounding factors

1. Length of time since first prescription of medication: it is possible that patients may only have read the PL at first prescription and knowledge may have declined over time. Self-reported length of time since first prescription of medication was included as a variable for subgroup 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 minimisation behaviour as those who had read the information. The questionnaire will include a variable relating to whether the RMP materials had been read.

3. Cognitive issues in MS. Studies show that as many as 63% of patients with MS can have significant cognitive impairment, including impairment in information processing speed, executive functions, verbal fluency, verbal episodic memory, working memory and visuospatial construction (). This means that the repsonses to the present survey may be confounded by cognitive impairment amongst the participants.

9.5 DATA SOURCES AND MEASUREMENT

Data was collected via patient self-report in the questionnaire.

The questionnaire was developed by psychologists with experience of developing questionnaires. Before implementation, the questions were user-tested in a small sample of patients with MS to ensure the questions are understood and adequate.

9.6 BIAS

All data supplied was self-report, and it is not possible to objectively verify information (e.g. gender or age). A convenience sample was used, which may be subject to bias, therefore the results may not be generalisable.

9.7 STUDY SIZE

Determination of sample size

A formal power calculation was not undertaken. Based on an estimation at the start of the study of 2150 LEMTRADA patients in the countries where the study was planned to be conducted, and taking into account an expected response rate of approximately 10%, the survey was administered in a random selection of 200 patients.

Sample size

201 patients were recruited and provided complete data. 71,329 potential participants clicked the survey link, however it should be noted that many would not have qualified for the survey on the basis of the inclusion criteria and therefore would have been taken immediately to the completion page.

9.8 DATA TRANSFORMATION

Data collection schedule

Patient data

LEMTRADA patients who were recruited via methods as described previously, were sent an invitation email. The email contained a link to the online study questionnaire and an email address

to contact the research team if further information about the study was required. The invitation email and questionnaire was translated into the local languages of participating countries.

On following the link within the invitation email, the information sheet and survey consent page was displayed. Patients were also 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 was able to move into the pages of the online questionnaire. In order to minimise missing data, it was mandatory to answer all questions within the questionnaire.

The first page of the questionnaire related to the eligibility criteria. If any of the answers indicated that the patient was ineligible (e.g. has not taken a single dose of LEMTRADA) they were taken to a page thanking them for their participation and explaining that they are not eligible to take part.

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

MS population data

Known MS population statistics for participating countries were supplied by the MAH.

Data collected

Online questionnaire

- Country
- Age
- Treatment start date
- MS diagnosis date
- Gender
- Knowledge relating to LEMTRADA risk management

MS population data

- Age
- Year of MS diagnosis
- Gender

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

9.9 STATISTICAL METHODS

9.9.1 Primary analysis

The analyses were descriptive.

9.9.2 Secondary analysis

1. Responses in subgroups compared to the rest of the sample. Subgroups analysed were: 1) country, 2) time since prescription with LEMTRADA, 3) having received both RMP materials or just one, and 4) having read all of the PG or not. Time since RMP materials were read could not be analysed as this data was not collected in wave 1. For analyses 3, those recalling receipt of *both* RMP materials (PC plus PG; n=146) were compared to those recalling receipt of *one of* the RMP materials (the PG only n=21). Patients who recalled only receiving the patient alert card (n=12) and patients who recalled receiving neither (n=22) did not complete the majority of the questionnaire and so a comparison involving these patients was not possible. For analyses 4, those who read all of the PG (n = 82) (i.e. they rated ‘all of it’) were compared to those who did not read all of the PG (n=82) i.e. they rated ‘more than half of it’, ‘about half of it’, ‘less than half of it’, or ‘none of it’ to question 14.

2. While descriptive statistics are the main analyses, statistical significance values have been provided as Chi-square tests were performed on categorical data for subgroup analyses.

9.9.3 Interim analysis

No interim analysis was planned for this registry. A report per wave is planned and the final report will involve combined analyses of wave 1 and wave 2.

9.9.4 Main summary measures

Knowledge was described using frequencies and percentages.

9.9.5 Main statistical methods

Descriptive analyses were performed. Chi-square tests were performed to detect statistically significant differences between sub-groups in the secondary analysis.

9.10 QUALITY CONTROL

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

Data was collected electronically directly from patients (without input from physicians), using a secure system.

Data was 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 was undertaken using the statistical software package SPSS 19.0 by qualified research personnel employed by Atlantis Healthcare.

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

10 RESULTS

10.1 DEMOGRAPHIC CHARACTERISTICS

Table 1 summarises key demographic characteristics of the sample, and Table 2 covers key clinical characteristics of the sample. There were 201 participants in total, with individuals from Denmark (n=8, 4%), Germany (n=46, 23%), Italy (n=49, 24%), Norway (n=32, 16%), Spain (n=44, 22%) and UK (n=22, 11%). More than half (52%) were female and just over one third were aged 26-35 (36%). Most patients received a diagnosis of MS in the last six years. The average number of months since the first infusion was 13.6 (see Table 2).

Table 1 - Demographic Characteristics of Patient Sample (n=201)

		n (%)
Country	Denmark	8 (4)
	United Kingdom	22 (11)
	Norway	32 (16)
	Spain	44 (22)
	Germany	46 (23)
	Italy	49 (24)
Gender	Female	104 (52)
	Male	97 (48)
Age	18-25	22 (11)
	26-35	73 (36)
	36-45	66 (33)
	46-55	29 (14)
	56-65	9 (5)
	66 or above	2 (1)
Diagnosed with MS	1980-1989	5 (3)
	1990-1999	6 (3)
	2000-2009	23 (11)
	2010-2016	167 (83)

Table 2 - Clinical Characteristics of Patient Sample

		n (%)
Time since first infusion	Mean (SD, Range)	13.6 (11, 0-39)

(months)	0-6 months	91 (45)
	7-12 months	35 (17)
	13-18 months	21 (10)
	19-24 months	21 (10)
	25-30 months	13 (7)
	31-36 months	14 (7)
	37+ months	6 (3)

10.2 PRIMARY ANALYSES: DESCRIPTIVE STATISTICS

10.2.1 Receipt of patient educational materials

Table 3 shows that the majority of participants had received the PC (77%) and the PG (82%). A proportion reported not receiving the PC (16%) or the PG (13%) and a small proportion could not remember whether they had or had not received the materials. Twelve patients (6%) reported only receiving the alert card and not the guide, 21 (10%) reported receiving the guide and not the alert card, and 22 (11%) reported receiving neither. The 34 participants who had received neither materials or just the alert card were taken to the completion page in the survey and therefore did not complete it. Most patients (n=150, 92%) who had received the PG had also had the guide explained to them by their doctor or nurse before their first infusion (Table 4). Of those who had received the PG, 82 (50%) had read all of it, 56 (34%) had read more than half, 21 (13%) had read about half, and very few had read less than half (n=4, 2%) or none (n=1, 1%) (see Table 5).

Table 3 - Have Patients Received the PC and PG?

	Response Option	n (%)
Patient Alert Card (Q9)	Yes	155 (77)
	No	32 (16)
	Don't know	14 (7)
Patient Guide (Q11)	Yes	164 (82)
	No	26 (13)
	Don't know	11 (6)
Receipt of materials	Neither	22 (11)
	Only the PC	12 (6)
	Only the PG	21 (10)
	Both	146 (73)

Table 4 - Did your HCP Discuss the Patient Guide and Alert Card with you?

	Response Option	n (%)

Patient Guide (Q11a) (n = 164)*	Yes	150 (92)
	No	9 (6)
	Don't know	5 (3)

* n = 164 participants who answered "yes" to Q11 (Have you received a patient guide for Lemtrada?)

Table 5 - How Much of the Guide Have Patients Read?

	Response Option	n (%)
Amount Read (Q14) (n = 164)*	All of it	82 (50)
	More than half of it	56 (34)
	About half of it	21 (13)
	Less than half of it	4 (2)
	None of it	1 (1)

* n = 164 participants who answered "yes" to Q11 (Have you received a patient guide for Lemtrada?)

10.2.2 Patient understanding about education materials purpose

Most patients remembered the purpose of the PC was 'to show a doctor or Healthcare professional involved in your medical care' (66%) or 'to give you important safety information you need to be aware of when receiving treatment with alemtuzumab' (63%) (see Table 6). Twenty-five percent of respondents selected all three reasons to hold an PC and therefore scored 'completely'. Twenty-one percent had partially complete answers and 51% had incomplete answers as they either selected only one correct response option or they selected options 1 and 3.

Table 6 - Do Patients Understand the Purpose of the PC?

	Response Option	n (%)
Purpose of Patient Alert Card (Q10) (n = 155)*	To show a doctor or Healthcare professional involved in your medical care	102 (66)
	To give you important safety information you need to be aware of when receiving treatment with Lemtrada	98 (63)
	To alert all emergency and healthcare professionals that you have been treated with Lemtrada	69 (45)
	Don't know/not sure	5 (3)
Complete answer	*3/3 responses selected (to show a doctor + to give important safety information + to alert all emergency and healthcare professionals)*	38 (25)

Partially complete answer	*2/3 responses selected (1,2 or 2,3)*	33 (21)
Incomplete answer	*1/3 responses selected (1, or 2, or 3) or responses 1,3 selected*	79 (51)

* n = 155 participants who answered "yes" to Q9 (Have you received a Patient Alert Card for Lemtrada?)

For the following analysis, only patients who had received and read some of the PG (n=164) were included in the analyses. Most patients thought the purpose of the PG was 'to give you important safety information you need to be aware of when receiving treatment with LEMTRADA' (70%) (see Table 7). Overall, 32% of patients answered completely by selecting the 3 purposes of the PG. Twenty-one percent were had partially complete answers however almost half (47%) had incomplete answers as they selected either one or none of the desired response options, indicating sub-optimal knowledge of the purpose of the PG.

Table 7 - Do Patients Understand the Purpose of the Patient Guide? (n = 164*) **

	Response Option	n (%) answering yes
Purpose of Patient Guide (Q12)	To show a caregiver	75 (46)
	To give you important safety information you need to be aware of when receiving treatment with Lemtrada	114 (70)
	To make you aware of the needed monitoring schedule	87 (53)
	To show you how to recognize symptoms that might be related to possible side effects of Lemtrada	80 (49)
	Don't know/not sure	5 (3.0)
Complete answer	*3/3 responses selected (to give important safety information + to make you aware of the needed monitoring schedule + to show you how to recognize symptoms)*	52 (32)
Partially complete answer	*2/3 responses selected (1,2 or 2,3)*	35 (21)
Incomplete answer	*1/3 or 0/3 responses selected*	77 (47)

* n = 164 participants who answered "yes" to Q11 (Have you received a patient guide Lemtrada?)
** Completeness of answers is irrespective of additional responses selected by participants

10.2.3 Patient knowledge about serious adverse reactions and signs and symptoms related to LEMTRADA

Table 8 summarises patient responses to questionnaire items assessing knowledge of signs and symptoms associated with side effects and adverse reactions to LEMTRADA.

With regard to immune thrombocytopenic purpura (ITP), the most frequent response was 'bruising easily' (58%). A correct response option 'Bleeding from gums or nose that takes longer than usual to stop' received the fewest selections, with just over one-quarter of patients (29%) identifying it as a sign or symptom. Over one-quarter of patients incorrectly identified cold sores (34%) and itchy skin (38%) as being signs or symptoms of ITP. Only 12 patients (7%) selected all five correct response options and therefore had a complete answer. A total of 56 patients (34%) had partially complete answers, while 95 (58%) had incomplete answers (meaning they selected two or less of the correct response options).

With regard to signs or symptoms of a kidney disorder or anti-GBM disease, most (61%) were aware that 'red or tea coloured urine' is a sign or symptom, whereas less than half correctly identified the other correct sign/symptom of 'swelling in the legs or feet' (39%). On the other hand, almost one half (43%) incorrectly identified 'diarrhoea'. Overall, the proportion of patients selecting the two correct response options, and therefore scoring a complete answer, was 27%. Seventy-five (46%) patients scored partially correctly, and 44 (27%) scored incompletely for this question.

Looking at patient knowledge of signs or symptoms of thyroid disorders, 15 (9%) selected all signs and symptoms of an over-active thyroid, therefore scoring completely. Fourty-two (26%) scored partially completely, though for this question most respondents (65%) had incomplete answers.

For an underactive thyroid, only 17 (10%) were able to select all signs and symptoms of an under-active thyroid and therefore have complete answers. Sixty-one (37%) had partially complete answers, and the majority had incomplete answers (n=85, 52%). Almost half (47.9%) believed 'depression' is a sign of an over-active thyroid, and 47 (28.8%) believed bruising easily is a sign of an under-active thyroid. Interestingly, 'newly occurring constipation' – one of the correct response options for signs of an under-active thyroid – was selected least (n= 28, 17.2%).

Table 8 - The Understanding of Patients About Serious Adverse Reactions to Lemtrada (n = 163*) **

	Response Option	n (%) selecting answer
Knowledge of signs/symptoms of immune thrombocytopenic purpura (ITP) (Q15)	Cold sores (oral herpes)	55 (34)
	Itchy skin	62 (38)
	Bruising easily	95 (58)
	Coughing up blood	83 (51)
	Small red, pink, or purple spots on the skin	78 (48)
	Bleeding from a cut that is harder to stop	58 (36)
	Bleeding from gums or nose that takes longer than usual to stop	47 (29)

Q15 Complete answer	*5/5 responses selected (bruising easily + coughing up blood + spots + bleeding from a cut + bleeding from gums or nose)*	12 (7)
Q15 Partially complete answer	*4/5 responses selected*	18 (11)
	3/5 responses selected	38 (23)
Q15 Incomplete answer	*2/5 or 1/5 or 0/5 responses selected*	95 (58)
Knowledge of signs/symptoms of kidney disorders or anti-GBM disease (Q17)	Red or tea coloured urine	100 (61)
	Diarrhoea	70 (43)
	Coughing up blood	69 (42)
	Swelling in the legs or feet	63 (39)
	Rash	35 (22)
Q17 Complete answer	*2/2 responses selected (red or tea coloured urine + swelling in the legs or feet)*	44 (27)
Q17 Partially complete answer	*1/2 responses selected*	75 (46)
Q17 Incomplete answer	*0/2 responses selected*	44 (27)
Knowledge of signs or symptoms of an over-active thyroid (Q19)	Excessive sweating	78 (48)
	Nervousness	87 (53)
	Depression	78 (48)
	Unexplained weight loss	83 (51)
	Eye swelling	44 (27)
	Fast heartbeat	54 (33)
	Swelling of the legs	21 (13)
Q19 Complete answer	*5/5 responses selected (excessive sweating + nervousness + unexplained weight loss + eye swelling + fast heartbeat)*	15 (9)
Q19 Partially complete answer	*4/5 or 3/5 responses selected*	42 (26)
Q19 Incomplete answer	*2/5 or 1/5 or 0/5 responses selected*	106 (65)
Knowledge of signs or symptoms of an under-active thyroid (Q20)	Unexplained weight gain	83 (51)
	Feeling cold	72 (44)
	Swelling in the legs or feet	67 (41)
	Worsening tiredness	89 (55)
	Bruising easily	47 (29)
	Newly occurring constipation	28 (17)

Q20 Complete answer	*4/4 responses selected (unexplained weight gain + feeling cold + worsening tiredness + newly occurring constipation)*	17 (10)
Q20 Partially complete answer	*3/4 or 2/4 responses selected*	61 (37)
Q20 Incomplete answer	*1/4 or 0/4 responses selected*	85 (52)

* n = 163 respondents who have read the PG
** Completeness of answers is irrespective of additional responses selected by participants

10.2.4 Patient knowledge of risk-minimisation activities

Table 9 summarises patient knowledge of the actions that should be taken upon noticing symptoms. The correct response option for all questionnaire items – 'See your doctor immediately' – received the highest proportion of responses within each item. However, a significant proportion identified 'waiting' (an incorrect response option) as a valid option following the appearance of symptoms of a bleeding disorder (32%), kidney disorder (30%), and thyroid disorder (22%).

With regard to the appearance of symptoms in general, few respondents indicated it is valid to 'take no action' for new symptoms (10%), returned symptoms (9%) or a worsening of symptoms (6%). However, approximately one quarter to one-third of respondents indicated it is valid to 'continue to monitor your symptoms for another week' when experiencing new symptoms (34%), a return of symptoms (35%), or a worsening of symptoms (27%).

Table 9 - Patient Understanding of Appropriate Action After Symptoms (n = 163)*

	Response Option	n (%)
What action should you take if you have symptoms of a bleeding disorder? (Q16)	Wait until the bleeding stops Tell a doctor at your next scheduled visit See your doctor immediately *(correct answer)*	52 (32) 45 (28) 66 (41)
What action should you take if you have symptoms of a kidney disorder? (Q18)	Wait to see if the symptoms resolve Tell a doctor at your next scheduled visit See your doctor immediately *(correct answer)*	49 (30) 40 (25) 74 (45)
What action should you take if you have symptoms of a thyroid disorder? (Q21)	Wait to see if the symptoms resolve Tell a doctor at your next scheduled visit See your doctor immediately *(correct answer)*	35 (22) 58 (36) 70 (43)

What action should you take if you experience symptoms you have not experienced before? (Q25a)	Take no action	16 (10)
	Continue to monitor your symptoms for another week	55 (34)
	Continue to monitor your symptoms for another month	26 (16)
	Call your doctor right away *(correct answer)*	66 (41)
What action should you take if you experience a return of symptoms? (Q25b)	Take no action	15 (9)
	Continue to monitor your symptoms for another week	57 (35)
	Continue to monitor your symptoms for another month	33 (20)
	Call your doctor right away *(correct answer)*	58 (36)
What action should you take if you experience a worsening of symptoms? (Q25c)	Take no action	10 (6)
	Continue to monitor your symptoms for another week	44 (27)
	Continue to monitor your symptoms for another month	31 (19)
	Call your doctor right away *(correct answer)*	78 (48)

* n = 163 respondents who have read the PG

Table 10 summarises patient knowledge of frequency of required periodic monitoring and their duration after last infusion. Sixty-three patients (39%) correctly identified that they should be receiving monthly blood and urine tests after an infusion of alemtuzumab, though approximately half of the sample also believed blood and urine tests should be done weekly (25%) or every 2 months (25%). With regard to testing thyroid function, the largest proportion of patients incorrectly reported that they should be having tests monthly (35%), while the correct answer 'every 3 months' was selected by only 22 (14%) patients.

Patient responses about how long it is necessary to continue having blood and urine tests for auto-immune conditions (bleeding, kidney, and thyroid disorders) show that only 22 patients (14%) are aware that testing should be continued for four years after the last course of treatment. The majority of patients (42%) reported that testing should be continued for only six months following treatment, while 57 (35%) reported that testing should be continued for 6 weeks, and 16 (10%) believed it should be continued for two years.

Table 10 - Patient Knowledge of frequency of required periodic monitoring and their duration after last infusion

	Response Option	n (%)
Frequency of blood and urine tests (Q22)	Weekly	40 (25)
	Monthly *(correct answer)*	63 (39)
	Every 2 months	40 (25)
	Every 3 months	13 (8)
	Every 6 months	7 (4)
Frequency of thyroid function tests (Q23)	Weekly	31 (19)
	Monthly	57 (35)
	Every 2 months	43 (26)
	Every 3 months *(correct answer)*	22 (14)
	Every 6 months	10 (6)
For how long should you have blood and urine tests for auto-immune conditions (Q24)	For 6 weeks after the last course of treatment with LEMTRADA	57 (35)
	For 6 months after the last course of treatment with LEMTRADA	68 (42)
	For 2 years after the last course of treatment with LEMTRADA	16 (10)
	For 4 years after the last course of treatment with LEMTRADA *(correct answer)*	22 (14)

10.3 SECONDARY ANALYSES

For subgroup analyses Chi-square tests were performed and significance values have been reported.

10.3.1 Subgroup Analyses: Country

Table 11 shows the participant responses to each questionnaire item by country. Looking at receipt of and knowledge about the patient education materials themselves, there were no significant differences between countries in terms of whether or not patients had received a PC ($p = .307$), whether or not patients had received a PG ($p = .194$).

Those who had not received the PG, those who were not sure they had received the guide, and those who had not read the guide were excluded from all subsequent subgroup analyses.

There was no significant difference between the countries in relation to whether or not a doctor/nurse had discussed the PG with them ($p = .224$. There was, however, a significant

difference in knowledge of the purpose of the alert card (p = .02), knowledge of the purpose of the PG (p = .041), and the amount of the PG read (p = .002) between countries.

Looking at understanding of the purpose of the PC, patients from the UK were more likely to have complete answers (56%) compared to patients from Denmark (33%), Spain (24%), Italy (24%), Germany (18%), and Norway (9%). This was the same for knowledge of the purpose of the PG, where patients from the UK were again more likely have a complete answer (53%) than patients from Denmark (50%), Spain (38%), Germany (30%), Italy (29%) and Norway (8%). With regard to the amount of the PG read, patients from the UK were most likely to have read all of the guide (74%), compared to 68% of Italian patients, 56% of Spanish patients, 50% of Danish patients, 40% of German patients, and only 8% of Norwegian patients.

With regard to knowledge of signs and symptoms, there were no significant difference between countries in terms of their knowledge of bleeding disorder symptoms (p = .137), symptoms of an over-active thyroid (p = .292) and symptoms of an under-active thyroid (p = .263). There was a trend towards significance in knowledge of symptoms of a kidney disorder (p = .079), with UK patients being most likely (47%) to be complete in their answers.

With regard to taking action following symptoms, there were significant differences in knowledge of what to do across countries for symptoms of bleeding disorders (p = .035), kidney disorders (p = .008) and thyroid disorders (p = .043). Patients from Denmark were consistently most likely to answer these questions correctly, with almost all patients answering correctly for bleeding disorders (83%), kidney disorders (83%) and thyroid disorders (83%). Spanish and Italian patients were next most likely, with approximately half of patients scoring correctly for bleeding disorders (Spain - 50%, Italy – 49%), kidney disorders (Spain - 50%, Italy – 54%) and thyroid disorders (Spain – 53%, Italy – 51%). The country that consistently had the fewest correct responses for these three questions was Norway.

There were no significant differences in the cross country understanding about the frequency with which patients should get blood/urine (p = .963) and thyroid tests (p = .599). However, there was a significant difference in the cross country understanding of the length of time blood/urine tests are required after the last course of treatment (p = .002). Patients from Denmark were most likely (67%) to answer correctly i.e. that testing is required for four years. Only 4% of Norwegian patients and 6% of Spanish patients scored correctly.

Lastly, Table 11 shows responses to questionnaire items concerning what action should be taken following the appearance of symptoms. Results show significant cross country differences for action after new symptoms (p = .000), returned symptoms (p = .004) and worsening symptoms (p = .000). Specifically, Danish patients were more likely to score correctly and identify that one should ‘call your doctor right away’ following new symptoms (67%), returned symptoms (50%) and worsening symptoms (83%). In comparison, the next highest scoring country was Italy where correct scores were 59% for new symptoms, 49% for returned symptoms, and 59% for worsening symptoms, and the country with the fewest correct scores was Norway with 4% scoring correctly for action following new symptoms, zero scoring correctly for the item on returned symptoms, and 4% scoring correctly for the item assessing action to be taken after noticing worsening symptoms.

Table 11 - Subgroup Analyses: Country Differences in Responses[1]

			Denmark (n=8)	UK (n=22)	Norway (n=32)	Spain (n=44)	Germany (n=46)	Italy (n=49)
Q9. Received Patient Alert Card (n = 201)	Yes	n (%)	6 (75)	18 (82)	22 (69)	29 (66)	39 (85)	41 (84)
	No	n (%)	1 (13)	3 (14)	9 (28)	10 (23)	5 (11)	4 (8)
	Don't know	n (%)	1 (13)	1 (5)	1 (3)	5 (11)	2 (4)	4 (8)
		p-value			.307			
Q10. Purpose of Patient Alert Card (n = 155)	Complete Answer	n (%)	2 (33)	10 (56)	2 (9)	7 (24)	7 (18)	10 (24)
		p-value			**.02**			
Q11. Received Patient Guide (n = 201)	Yes	n (%)	6 (75)	19 (86)	24 (75)	34 (77)	40 (87)	41 (84)
	No	n (%)	0	3 (14)	7 (22)	8 (18)	3 (7)	5 (10)
	Don't know	n (%)	2 (25)	0	1 (3)	2 (5)	3 (7)	3 (6)
		p-value			.194			
Receipt of materials (n = 167)	Just PG	n (%)	1 (17)	2 (11)	4 (17)	7 (21)	5 (12)	2 (5)
	All	n (%)	5 (83)	17 (89)	20 (83)	27 (79)	37 (88)	40 (95)
		p-value			.433			

[1] Chi-square analyses for all questions had at least 1 cell with an expected count less than 5. This suggests there is less power to detect a difference in groups and results should be interpreted with some caution.

			Denmark (n=8)	UK (n=22)	Norway (n=32)	Spain (n=44)	Germany (n=46)	Italy (n=49)
Q11a. Did doctor/ nurse discuss patient guide?	Yes	n (%)	6 (100)	17 (90)	20 (83)	30 (88)	37 (93)	40 (98)
	No	n (%)	0	1 (5)	3 (13)	4 (12)	1 (3)	0
	Don't know	n (%)	0	1 (5)	1 (4)	0	2 (5)	1 (2)
(n = 164)		p-value			.224			
Q.12 Purpose of patient guide (n=164)	Complete Answer	n (%)	3 (50)	10 (53)	2 (8)	13 (38)	12 (30)	12 (29)
		p-value			**.041**			
Q14. Amount of patient guide read	Less ½	n (%)	0	0	0	2 (6)	1 (3)	1 (2)
	½	n (%)	0	1 (5)	7 (29)	2 (6)	7 (18)	4 (10)
	More ½	n (%)	3 (50)	4 (21)	15 (63)	11 (32)	15 (38)	8 (20)
	All	n (%)	3 (50)	14 (74)	2 (8)	19 (56)	16 (40)	28 (68)
		p-value			**.002**			
Q15. Symptoms of bleeding disorder	Complete Answer	n (%)	0	3 (16)	0	5 (15)	1 (3)	3 (7)
		p-value			.137			
(n = 163)								

			Denmark (n=8)	UK (n=22)	Norway (n=32)	Spain (n=44)	Germany (n=46)	Italy (n=49)
Q16. Action if symptoms of bleeding disorder (n = 163)	Correct Answer	n (%)	5 (83)	7 (37)	6 (25)	17 (50)	11 (28)	20 (49)
		p-value				.035		
Q17. Symptoms of kidney problems (n = 163)	Complete answer	n (%)	1 (17)	9 (47)	2 (8)	8 (24)	10 (26)	14 (34)
		p-value				.079		
Q18. Action if symptoms of kidney disorder (n = 163)	Correct Answer	n (%)	5 (83)	8 (42)	3 (13)	17 (50)	19 (49)	22 (54)
		p-value				.008		
Q19. Symptoms of over-active thyroid (n = 163)	Complete answer	n (%)	1 (17)	4 (21)	0	3 (9)	3 (8)	4 (10)
		p-value				.292		
Q20. Symptoms of under-active thyroid (n = 163)	Complete answer	n (%)	1 (17)	4 (21)	0	2 (6)	5 (13)	5 (12)
		p-value				.263		

			Denmark (n=8)	UK (n=22)	Norway (n=32)	Spain (n=44)	Germany (n=46)	Italy (n=49)
Q21. Action if symptoms of thyroid disorder (n = 163)	Correct Answer	n (%)	5 (83)	6 (32)	6 (33)	18 (53)	14 (36)	21 (51)
		p-value				.043		
Q22. Frequency of blood, urine tests (n = 163)	Correct answer	n (%)	3 (50)	7 (37)	8 (33)	14 (41)	14 (36)	17 (42)
		p-value				.963		
Q23. Frequency thyroid tests (n = 163)	Correct answer	n (%)	2 (33)	4 (21)	2 (8)	4 (12)	5 (13)	5 (12)
		p-value				.599		
Q24. Time blood, urine tests required (n = 163)	Correct answer	n (%)	4 (67)	3 (16)	1 (4)	2 (6)	5 (13)	7 (17)
		p-value				.002		
Q25a. Action if new symptoms appear (n = 163)	Correct answer	n (%)	4 (67)	9 (47)	1 (4)	16 (47)	12 (30)	24 (59)
		p-value				.000		
Q25b. Action if symptoms return	Correct answer	n (%)	3 (50)	8 (42)	0	13 (38)	14 (36)	20 (49)
		p-value				.004		

(n = 163)								
Q25c. Action if symptoms worsen (n = 163)	Correct answer	n (%)	5 (83)	9 (47)	1 (4)	20 (59)	19 (49)	24 (59)
		p-value				.000		

10.3.2 Subgroup Analyses: Time since first infusion of LEMTRADA

Table 12 shows the participant responses to each questionnaire item according to time since first infusion of LEMTRADA. Looking at receipt of and understanding of the purpose of the patient education materials themselves, there were no significant differences between groups in terms of whether or not patients had received a PC (p = .337) or PG (*p* = .817), and whether or not a doctor/nurse had discussed the PG with them (p = .720). There were also no significant differences in knowledge of the purpose of the alert card (p = .843), knowledge of the purpose of the PG (p = .228), and the amount of the PG read (p = .764).

With regard to knowledge of signs and symptoms, there were no significant difference between groups in terms of their understanding of bleeding disorder symptoms (p = .281). There was a trend towards significance for understanding of symptoms of an over-active thyroid (p = .087). There were significant differences in understanding of symptoms of kidney problems (p = .017) and symptoms of an under-active thyroid (p = .008). Specifically, those who had their first infusion of LEMTRADA 7-12 months ago were most likely (49%) to have complete answers for the symptoms of kidney disorder (red or tea coloured urine and swelling in the legs and feet). And those who had their first infusion of LEMTRADA more than 37 months ago were most likely (40%) likely to have complete answers for the symptoms of an under-active thyroid (unexplained weight gain, feeling cold, swelling in the legs or feet, worsening tiredness, newly occurring constipation). This was followed by those who had their first infusion 7-12 months ago, where 26% of participants had complete answers.

With regard to taking action following symptoms, there was no significant difference in knowledge of what to do for symptoms of bleeding disorders (p = .326) or thyroid disorders (p = .156). However, there was a significant difference for knowledge of what action should be taken following symptoms of kidney disorders (p = .004), with those who had their first infusion of LEMTRADA 7-12 months ago most likely to score completely (58%). This was followed by the group who had their first infusion of LEMTRADA 19-24 months ago.

There were no significant between-group differences in patients' understanding about the frequency with which they should get blood/urine tests for bleeding and kidney disorders (p = .761) and for thyroid function (p = .131), and there was no significant difference in the understanding of the length of time blood/urine tests for bleeding, kidney, and thyroid disorders are required after the last course of treatment (p = .311).

Table 12 also shows responses to questionnaire items concerning what action should be taken following the appearance of symptoms. Results show no significant difference between patients in terms of their understanding of action that should be taken following the appearance of new symptoms (p = .088). However, significant differences appeared for understanding of action that should be taken following returned symptoms (p = .036) and worsening symptoms (p = .052). Specifically, those who had their first infusion of LEMTRADA 7-12 months ago were most likely to score correctly for returned symptoms (54.8%) and worsening symptoms (61.3%) by selecting 'call your doctor right away'. Those least likely to score correctly were those who had their first infusion of LEMTRADA 31-36 months ago.

Table 12 - Subgroup analyses: Time since first infusion of LEMTRADA – group differences[2]

			0-6 months (n=91)	7-12 months (n=35)	13-18 months (n=21)	19-24 months (n=21)	25-30 months (n=13)	31-36 months (n=14)	37+ months (n=6)
Q9. Received Patient Alert Card (n = 201)	Yes	n (%)	65 (71)	28 (80)	17 (81)	16 (76)	12 (92)	11 (79)	6 (100)
		p-value				.337			
Q10. Purpose of Patient Alert Card (n=155)	Complete answer	n (%)	13 (20)	11 (39)	5 (29)	5 (31)	1 (8)	1 (9)	2 (33)
		p-value				.843			
Q11. Received Patient Guide (n=201)	Yes	n (%)	71 (78)	31 (86)	17 (81)	16 (76)	12 (92)	12 (86)	5 (83)
		p-value				.817			
			0-6 months (n=91)	7-12 months (n=35)	13-18 months (n=21)	19-24 months (n=21)	25-30 months (n=13)	31-36 months (n=14)	37+ months (n=6)

[2] Chi-square analyses for all questions had at least 1 cell with an expected count less than 5. This suggests there is less power to detect a difference in groups and results should be interpreted with some caution.

Recepit of materials (n = 167)	Just PG	n (%)	12 (16)	4 (12)	2 (12)	2 (12)	0	1 (8)	0
	All	n (%)	61 (84)	28 (88)	15 (88)	14 (88)	12 (100)	11 (92)	5 (100)
		p-value				.725			
Q11a. Did doctor/nurse discuss patient guide? (n=164)	Yes	n (%)	66 (93)	27 (87)	16 (94)	14 (88)	12 (100)	10 (83)	5 (100)
		p-value				.720			
Q.12 Purpose of patient guide (n=164)	Complete answer	n (%)	24 (34)	13 (42)	5 (29)	6 (38)	1 (8)	1 (8)	2 (40)
		p-value				.225			
Q14. Amount of guide read (n=164)	All	n (%)	37 (53)	19 (61)	7 (41)	7 (44)	7 (58)	3 (25)	2 (40)
		p-value				.764			
Q15. Symptoms of bleeding disorder (n=163)	Complete answer	n (%)	7 (10)	2 (7)	0	3 (19)	0	0	0
		p-value				.281			
Q16. Action if symptoms of bleeding disorder (n=163)	Correct answer	n (%)	31 (44)	15 (48)	7 (41)	7 (44)	2 (17)	2 (17)	2 (40)
		p-value				.326			

		0-6 months (n=91)	7-12 months (n=35)	13-18 months (n=21)	19-24 months (n=21)	25-30 months (n=13)	31-36 months (n=14)	37+ months (n=6)

Q17. Symptoms of kidney problems (n=163)	Complete answer	n (%)	12 (17)	15 (48)	5 (29)	6 (38)	3 (25)	1 (8)	2 (40)
		p-value				.028			
Q18. Action if symptoms of kidney disorder (n=163)	Correct answer	n (%)	37 (52)	18 (58)	7 (41)	9 (56)	1 (8)	1 (8)	1 (20)
		p-value				.004			
Q19. Symptoms of over-active thyroid (n=163)	Complete answer	n (%)	3 (4)	5 (16)	2 (12)	2 (13)	1 (8)	0	2 (40)
		p-value				.087			
Q20. Symptoms of under-active thyroid (n=163)	Complete answer	n (%)	3 (4)	8 (26)	1 (6)	2 (13)	1 (8)	0	2 (40)
		p-value				.008			
Q21. Action if symptoms of thyroid disorder (n=163)	Correct answer	n (%)	32 (46)	15 (48)	8 (47)	9 (56)	1 (8)	3 (25)	2 (40)
		p-value				.156			

		0-6 months (n=91)	7-12 months (n=35)	13-18 months (n=21)	19-24 months (n=21)	25-30 months (n=13)	31-36 months (n=14)	37+ months (n=6)

Q22. Frequency of blood, urine tests (n=163)	Correct answer	n (%)	30 (43)	12 (39)	6 (35)	7 (44)	2 (17)	4 (33)	2 (40)
		p-value				.761			
Q23. Frequency thyroid tests (n=163)	Correct answer	n (%)	6 (9)	7 (23)	4 (24)	4 (25)	1 (8)	0	0
		p-value				.131			
Q24. Time blood, urine tests required (n=163)	Correct answer	n (%)	7 (10)	7 (23)	2 (12)	4 (35)	0	1 (8)	1 (20)
		p-value				.311			
Q25a. Action if new symptoms appear (n=163)	Correct answer	n (%)	33 (47)	17 (55)	5 (29)	5 (31)	2 (17)	2 (17)	2 (40)
		p-value				.088			
Q25b. Action if symptoms return (n=163)	Correct answer	n (%)	27 (39)	17 (55)	5 (29)	5 (31)	1 (8)	1 (8)	2 (4)
		p-value				**.036**			
Q25c. Action if symptoms worsen (n=163)	Correct answer	n (%)	39 (56)	19 (61)	6 (35)	7 (44)	3 (25)	2 (17)	2 (40)
		p-value				**.052**			

10.3.3 Subgroup Analyses: Having received patient guide only or all RMP materials

Table 13 shows participant responses to each questionnaire item according to whether or not they have received only the patient guide or all RMP materials. Looking at knowledge of the purpose of the PG across the two groups, there were no significant differences for the purpose of the PG ($p = .522$), despite that those receiving both RMP materials being significantly more likely to have read all of the PG ($p<.05$).

With regard to understanding about signs and symptoms, there were no significant difference between the two groups in terms of their understanding of bleeding disorder symptoms ($p = .462$), symptoms of kidney problems ($p = .499$), symptoms of an over-active thyroid ($p = .594$) and symptoms of an under-active thyroid ($p = .367$). With regard to taking action following symptoms, there were trends toward significant differences in knowledge of what to do for symptoms of kidney disorders ($p = .079$), symptoms of bleeding disorders ($p = .095$), and symptoms of thyroid disorders ($p = .056$). For these questions, those who had received only the PG (as opposed to both the guide and the alert card) were more likely to have complete scores for understanding of action following kidney disorder symptoms (62% versus 43% complete), bleeding disorder symptoms (57% versus 39% complete) and thyroid disorder symptoms (62% versus 41% complete).

In terms of patients' understanding of the frequency with which they should have thyroid function blood tests, there was no significant difference in the proportion of correct responding from those who had versus hadn't received both educational materials ($p = .326$), though this is to be expected given that the ideal frequency of thyroid function blood tests is not mentioned on the PC. There was also no significant difference in understanding of how long one should continue to monitor themselves following final course of treatment ($p = .142$), however this is an unexpected finding as an aim of the PC (in addition to the guide) is to educate patients on the importance of continued monitoring. There was an unexpected significant difference in understanding of the frequency of blood/urine tests ($p = .006$), with patients who had received only the PG being more likely to score correctly (67%) than those who had received the alert card in addition to the guide (35%). It should be taken into account though that the group sizes were small in this analyses.

In terms of understanding of the action that should be taken following the appearance of symptoms, there were no significant between-group differences concerning understanding of action should be taken if new symptoms appear ($p = .310$), old symptoms return ($p = .489$), or if symptoms worsen ($p = .453$).

Table 13 - Subgroup Analyses: Comparing those who have received patient guide only and those who have received all RMP materials[3]

			Received PG only (n=21)		Received All (n = 146)
Q.12 Purpose of patient guide (n=164)	Complete answer	n (%)	7 (33)		45 (31)
		p-value		.522	
Q.14 Amount read (n = 164)	All	n (%)	7 (33)		75 (52)
	More than half		8 (38)		48 (34)
	About half		3 (14)		18 (13)
	Less than half		2 (10)		2 (1)
	None		1 (5)		0 (0)
		p-value		**.010**	
Q15. Symptoms of bleeding disorder (n = 167)	Complete answer	n (%)	2 (10)		10 (7)
		p-value		.462	
Q16. Action if symptoms of bleeding disorder (n = 166)	Correct answer	n (%)	12 (57)		57 (39)
		p-value		.095	
Q17. Symptoms of kidney problems (n = 166)	Complete answer	n (%)	5 (24)		39 (27)
		p-value		.499	

[3] Chi-square analyses for some questions had at least 1 cell with an expected count less than 5. This suggests there is less power to detect a difference in groups and some results should be interpreted with caution.

			Received PG only (n=21)		Received All (n = 146)
Q18. Action if symptoms of kidney disorder (n = 166)	Correct answer	n (%)	13 (62)		62 (43)
		p-value		.079	
Q19. Symptoms of over-active thyroid (n = 166)	Complete answer	n (%)	2 (10)		13 (9)
		p-value		.594	
Q20. Symptoms of under-active thyroid (n = 166)	Complete answer	n (%)	3 (14)		14 (10)
		p-value		.367	
Q21. Action if symptoms of thyroid disorder (n = 166)	Correct answer	n (%)	13 (62)		59 (41)
		p-value		**.056**	
Q22. Frequency of blood, urine tests (n = 166)	Correct answer	n (%)	14 (67)		51 (35)
		p-value		**.006**	
Q23. Frequency thyroid tests (n = 166)	Correct answer	n (%)	4 (19)		19 (13)
		p-value		.326	
Q24. Time blood, urine tests required (n = 166)	Correct answer	n (%)	5 (24)		18 (12)
		p-value		.142	

			Received PG only (n=21)		Received All (n = 146)
Q25a. Action if new symptoms appear (n = 166)	Correct answer	n (%)	10 (48)		57 (39)
		p-value		.310	
Q25b. Action if symptoms return (n = 166)	Correct answer	n (%)	7 (33)		53 (37)
		p-value		.489	
Q25c. Action if symptoms worsen (n = 166)	Correct answer	n (%)	11 (52)		70 (48)
		p-value		.453	

10.3.4 Subgroup Analyses: Having read or not read the Patient Guide

Table 14 shows participant responses to each questionnaire item according to whether or not they have read all of the PG. Looking at understanding of the purpose of the PC across the two groups, those who had read all of the PG were significantly more likely to score completely for this question (39% complete versus 12% complete, $p < .000$), showing that those who read all of the PG may be more knowledgeable about the three main purposes of the PC. Results also show a significant difference for question 11a, which suggests that those who had read all of the PG were significantly more likely to have had an HCP discuss the PG with them (98%) than those who have not read all the PG (85%, $p = .019$). This suggests that having an HCP discuss the guide may be a motivating factor for patients to then read the PG in full.

There was also a significant difference for understanding of the three main purposes of the PG ($p < .000$); not surprisingly, those who read all of the PG had a clearer understanding of its purposes (45% scored completely) than those who did not read all of it (18% scored completely).

With regard to understanding about signs and symptoms and action to take following the appearance of signs and symptoms, there was no significant difference between the two groups in terms of their understanding of bleeding disorder symptoms ($p = .185$), however there was a significant difference for understanding of what to do when experiencing bleeding disorder symptoms; those who had read the full PG were more likely to select the correct answer ‘see your doctor immediately’ (51% versus 30%, $p = .005$).

For kidney problems, there was a significant difference for understanding of symptoms; those who had read the PG in its entirety were more likely to have a complete answer (40%) than those who had not read the PG in full (13%, $p < .000$). This was not associated with significantly greater

understanding of what to do upon experiencing symptoms of kidney disorder; those who had read the PG were only slightly more likely to answer correctly (51%) than those who had not read the PG in full (39%), though this finding did approach significance (p = .079).

For understanding of thyroid disorders, there were trends towards significance for understanding of symptoms of both an under-active and over-active thyroid. Those who had read the entire PG were more likely than those who had not read the entire PG to score completely for symptoms of an under-active thyroid (15% complete versus 6% complete, p = .061) and an over-active thyroid (15% complete versus 5% complete, p = .051). However, there was no significant difference between groups in terms of what to do following symptoms of thyroid disorder (49% versus 38%, p = .104).

Looking at frequency of testing, there were no significant between-group differences for understanding of the frequency of blood/urine tests for bleeding and kidney disorders (39% versus 39%, p = .564), blood tests for thyroid function (15% versus 13%, p = .500), and length of time that blood/urine tests are required (17% versus 11%, p = .184).

For action following the appearance of symptoms, those who had read all of the PG were more likely to be correct (by selecting 'call your doctor right away') for new symptoms (55% versus 27%, p < .000), returned symptoms (46% versus 26%, p = .004), and worsening symptoms (61% versus 35%, p = .001).

Table 14 - Subgroup Analyses: Comparing those who have read all of the Patient Guide versus those who have read some

			Read all of the PG* (n = 82)		Have not read all of the PG** (n = 82)
Q.10 Purpose of Patient Alert Card (n = 143)	Complete answer	n (%)	29 (39)		8 (12)
		p-value		.000	
Q.11a Did HCP discuss the patient guide with you? (n = 164)	Yes	n (%)	80 (98)		70 (85)
		p-value		.019	
Q.12 Purpose of patient guide (n = 164)	Complete answer	n (%)	37 (45)		15 (18)
		p-value		.000	
Q15. Symptoms of bleeding disorder (n = 164)	Complete answer	n (%)	8 (10)		4 (5)
		p-value		.185	

			Read all of the PG* (n = 82)		Have not read all of the PG** (n = 82)
Q16. Action if symptoms of bleeding disorder (n = 164)	Correct answer	n (%)	42 (51)		25 (30)
		p-value		.005	
Q17. Symptoms of kidney problems (n = 164)	Complete answer	n (%)	33 (40)		11 (13)
		p-value		.000	
Q18. Action if symptoms of kidney disorder (n = 164)	Correct answer	n (%)	42 (51)		32 (39)
		p-value		.079	
Q19. Symptoms of over-active thyroid (n = 164)	Complete answer	n (%)	1 (13)		4 (5)
		p-value		.051	
Q20. Symptoms of under-active thyroid (n = 166)	Complete answer	n (%)	12 (15)		5 (6)
		p-value		.061	
Q21. Action if symptoms of thyroid disorder (n = 164)	Correct answer	n (%)	40 (49)		31 (38)
		p-value		.104	
Q22. Frequency of blood, urine tests (n = 164)	Correct answer	n (%)	32 (39)		32 (39)
		p-value		.564	
Q23. Frequency thyroid tests (n = 166)	Correct answer	n (%)	12 (15)		11 (13)
		p-value		.500	

			Read all of the PG* (n = 82)		Have not read all of the PG** (n = 82)
Q24. Time blood, urine tests required (n = 164)	Correct answer	n (%)	14 (17)		9 (11)
		p-value		.184	
Q25a. Action if new symptoms appear (n = 164)	Correct answer	n (%)	45 (55)		22 (27)
		p-value		.000	
Q25b. Action if symptoms return (n = 164)	Correct answer	n (%)	38 (46)		21 (26)
		p-value		.004	
Q25c. Action if symptoms worsen (n = 164)	Correct answer	n (%)	50 (61)		29 (35)
		p-value		.001	

* Patients who reported reading 'all of it' (Question 14

** Patients who reported reading 'more than half of it', 'about half of it', 'less than half of it', and 'none of it'

11 DISCUSSION

11.1 MAIN FINDINGS

11.1.1 Demographic Characteristics

The sample consisted of 201 patients of which fifty-two percent were female. Given that usually 2/3 of MS populations are female this suggests that there could have been some bias in the recruitment or that Lemtrada is more often prescribed to men than to women. Italy had the largest representation of patients, with 24% of the sample coming from Italy, and Denmark had the smallest representation with only 4% of patients in the sample. Germany has the largest MS patient population on Lemtrada, followed by the UK, Spain and Italy. As expected Norway and Denmark have the smaller populations. This means the UK is somewhat underrepresented.83% of the patients in the sample were diagnosed with MS since 6 years or less. Time since first infusion ranged from 0-39 months, with the largest group (45%) of patients having had their first infusion in the last months. This is in line with expectations given that the product is still being launched in many countries.

11.1.2 Receipt of Patient Education Materials

The large majority of patients had recalled to have received the PC (77%) and the PG (82%), suggesting that although there is room for improvement the materials reach the patients in most cases. It is important to note that these data may not reflect the true proportion of patients receiving the PC and PG; MS is a disease in which a majority of patients suffer from cognitive problems, including memory loss, suggesting that some patients may indeed have forgotten receiving the materials and/or the content of the materials.. Studies show that approximately 63% of patients can suffer from cognitive impairment (Planche, et al., 2015).

Patients from Germany, Italy, and the UK were more likely than patients from other countries to answer they had received the PC and PG (all > 80%, *ns*). There was no difference in receipt of materials depending on time since first infusion, suggesting that the percentage of patients receiving the materials has remained stable over time. Most of the sample (73%) had received *both* materials, however a notable proportion did not recall to have received anything (11%), just the PC (6%), or just the PG (10%). Most patients who had received the PG (n = 164) also mentioned to have the guide explained to them by their doctor or nurse before their first infusion (92%). Of those who had received the PG, 82 (50%) had read all of it, 56 (34%) had read more than half, 21 (13%) had read about half, and very few had read less than half (2%) or none (1%). The fact that 97% reported reading at least half of the material seems to indicate the patients see it as important to read the materials. Subgroup analyses revealed that patients from the UK were most likely to have read all of the guide (74%), while patients from Norway had read the least (29% had read half or less). Those who had received both the PC and PG were significantly more likely to have read all of the PG, suggesting that receiving both materials may be a motivating factor to read the entire PG, or that the HCPs treating these patients better emphasize the need to read the materials. Lastly, analyses showed a significant difference for those who had versus had

not read all of the PG; those who had read all of it were significantly more likely to have had a HCP discuss the PG with them (98% versus 85%, p = .019), which suggests that having a HCP discuss the guide may be another motivating factor for patients to then read the PG in full.

11.1.3 Patient understanding about education materials purpose

Patient understanding of the purpose of the PC appears incomplete, with only 25% recognizing all 3 correct answers: 'To show a doctor or Healthcare professional involved in your medical care' and 'To give you important safety information you need to be aware of when receiving treatment with Lemtrada' and 'To alert all emergency and healthcare professionals that you have been treated with Lemtrada'. An additional twenty-one percent identified 2 of 3 correct answers. Interestingly, those who had read all of the PG (n = 82) were significantly more likely to also know the three main purposes of the PC. The descriptive results suggest that the proportion of patients with complete answers (25%) was low because many selected only one of three options, particularly 'To show a doctor or healthcare professional involved in your medical care' which was selected by 66% of the sample. It is not surprising that participants favored this response option given that the PC has in large, bold font 'Please show this card to all emergency and healthcare providers'. Patients may also have misunderstood the question and not realised that they could have, and indeed needed to have, selected more than one reason to carry a PC in order to have a complete answer. Furthermore, the strong similarity between response options 1 and 3 – the only difference is that one includes alerting 'emergency' professionals as well as healthcare professionals – may have been interpreted by patients as a 'trick question' and hence they selected one or the other response option but not both. Clearly, the structure and wording of the survey should be revised in Wave 2 of the study to ensure maximum clarity for patients.

Patient understanding of the purpose of the PG also appeared low, though the same factors explained above may also have been at play with this question. Only 32% of patients had a complete answer by selecting all three desired responses: 'To give you important safety information you need to be aware of when receiving treatment with Lemtrada' and 'To make you aware of the needed monitoring schedule' and 'To show you how to recognize symptoms that might be related to possible side effects of Lemtrada'. Unsurprisingly, those who read all of the PG had a clearer understanding of its purposes (45% scored completely) compared to those who did not read all of it (18% scored completely). Analyses also revealed that patients from the UK were most likely to know all 3 purposes of the PC (56% complete answers) and PG (53% complete answers). This may be explained by the finding that patients from the UK were also most likely to have read all of the PG, and hence may have a stronger or clearer understanding of its purpose. This may also be partly explained by UK HCPs better explaining the educational materials to their patients than healthcare professionals in other countries. Overall, results show that HCPs should be encouraged to give both materials and explain them well to their patients and encourage them to read the PG in full.

11.1.4 Patient knowledge about serious adverse reactions and signs and symptoms related to LEMTRADA

Patient understanding of signs and symptoms associated with side effects and severe adverse reactions to LEMTRADA was interpreted based only on the number of 'correct' response options

they selected. 'Incorrect' response options selected were not taken into account as the objective of the educational materials is not to ensure that patients can list by heart all symptoms related to bleeding disorders, kidney problems, and thyroid problems without error. The objective is that they are educated enough to have a general idea of the symptoms and to know how to act if they experience them. For this set of questions, an incomplete answer was one where the patient selected less than 50% of the 'correct' response options. Knowledge of signs and symptoms associated with side effects and severe adverse reactions varied according to the disorder in question. For knowledge of signs and symptoms associated with ITP, a combined total of 34% had partially complete answers (3/5 or 4/5 symptoms selected) and 7% had complete answers (5/5 symptoms selected), however the majority (58%) had incomplete answers (2/5, 1/5 or 0/5 symptoms selected). Knowledge of signs and symptoms of an over-active thyroid were similar, with 26% having partially complete answers (3/5 or 4/5 symptoms selected), 9% having complete answers (5/5 symptoms selected), and the majority (65%) having incomplete answers (2/5, 1/5, or 0/5 symptoms selected). For knowledge of signs and symptoms of an under-active thyroid, 37% had partially complete answers (2/4 or 3/4 symptoms selected), 10% had complete answers (4/4 symptoms selected), and again the majority (52%) had incomplete answers (1/4 or 0/4 symptoms selected). Knowledge of signs and symptoms of kidney disorders or anti-GBM disease was superior to knowledge of ITP, and over-active and under-active thyroids. Here 46% had partially complete answers (1/2 selected), 27% had complete answers (2/2 selected), and less than one third (27%) had incomplete answers (0/2 selected).

Interestingly, there was a relationship between the complexity of the question and the likelihood of scoring complete answers.; more patients were correct or complete in their responses when the number of 'correct' responses was two (knowledge of kidney disorders), compared to when the number of 'correct' responses was higher e.g. four (knowledge of under-active thyroid) or five (knowledge of over-active thyroid and ITP). This is not surprising given that there is more room for error when the number of correct response options increases. The relatively poor scores may be explained by the criteria set out for a 'complete' answer, especially when it involves the selection of four or more symptoms; the criteria were very strict given that the respondent is a lay person rather than a healthcare professional. Furthermore, patients were asked about material that they may have received and read months or even years ago. On top of this, patients with MS may have cognitive issues (Planche, et al., 2015) that further diminish their likelihood of achieving a 'complete' answer. These points highlight further potential flaws in the question structure and overall complexity of the survey. The criteria for what constitutes an adequate knowledge level for a patient, i.e. a non-healthcare professional, should be further refined before wave 2 of the study.

Subgroup analyses showed that patients from the UK were most knowledgeable about signs and symptoms as shown by highest proportions of complete answers (however, these were statistically non-significant). This may relate to the finding that patients from the UK were second most likely behind Italians (ns) to have received *both* the PG and the PC, that they were most likely to have read all of the PG, and that they were most knowledgeable about the purpose of the PG. These factors may explain why patients from the UK have superior understanding about signs and symptoms to be aware of.

Those who had read the PG in its entirety were significantly more likely to have a complete answer for symptoms of kidney problems (40%) than those who had not read the PG in full

(13%). Those who had read the entire PG were also more likely to select all symptoms of an under-active thyroid (15% complete versus 6% complete) and an over-active thyroid (15% complete versus 5% complete). This suggests that reading all of the PG seems to lead to better knowledge, and therefore the materials meet their purpose.

As expected, receiving the PC in addition to the PG did not lead to significantly better knowledge of symptoms of thyroid disorders as this is not discussed in the PC. However, symptoms of bleeding disorders and kidney problems are summarized on the card, yet those receiving the PC did not have better knowledge of these symptoms than those receiving only the PG. This finding may be due to the small sample of patients that received both the PG and the PC, or alternatively it may be because the PG is the educational material that is more often referred to and read by patients while the PC is used by patients just as an alert for healthcare professionals.

Those who had their first LEMTRADA infusion between 7-12 months ago were most knowledgeable about signs and symptoms of a kidney disorder, while those who had their first infusion more than 37 months ago were most knowledgeable about symptoms of an under-active thyroid. This may relate to the fact that thyroid adverse events peak around 37 months after the infusion, and therefore these patients may be more alert to this than those who have recently started LEMTRADA.

11.1.5 Patient knowledge of risk-minimisation activities

Patient understanding of the action to take upon noticing symptoms associated with side effects or severe reactions to LEMTRADA was moderate. The correct answer ‘See your doctor immediately’ received the highest proportion of selections across questions that relate to action that should be taken if you have symptoms of a bleeding disorder (41%), kidney disorder (45%), and thyroid disorder (43%). The same was the case for answers relating to action to take upon noticing other symptoms, where the correct answer ‘Call your doctor right away’ again received the highest proportion of selections for questions relating to the experience of new symptoms (41%), returned symptoms (36%), and worsening symptoms (48%). However, a relevant proportion of patients identified watching and waiting as valid options following the appearance of symptoms of a bleeding disorder (32% selected ‘wait until the bleeding stops’), kidney disorder (30% selected ‘wait to see if the symptoms resolve’), and thyroid disorder (22% selected ‘wait to see if the symptoms resolve’). Furthermore, ‘take no action’ or ‘continue to monitor your symptoms for another month’ was selected by a significant proportion of the sample for new symptoms (total 26%), returned symptoms (total 29%) and worsening symptoms (total 25%).

There are several possible explanations for why so many patients considered watching and waiting as feasible options following the appearance of signs and symptoms. First, patients may have been very practical in their responses – a sensible option when one is bleeding is to ‘wait until the bleeding stops’ before physically seeing a doctor (question 16). Therefore, the wording of these response options may have been confusing for patients and hence may need further refinement before wave 2 of the study. Second, telling a doctor about thyroid symptoms at the next scheduled visit (selected by 36% of respondents) may seem appropriate to a patient if they prioritise MS symptoms and other symptoms that may require more immediate medical attention. Third, MS patients frequently experience symptoms and must decide how they will deal with

each. For a patient who experiences many symptoms, it may be feasible to monitor symptoms for a time and indeed it may seem unnecessary to 'call a doctor right away' upon experiencing a new, returned, or worsening symptom.

Subgroup analyses for this group of questions revealed that patients who had read the PG in full were more likely to know what should be done following development of bleeding disorder symptoms and kidney disorder symptoms, but not thyroid disorder symptoms. This latter finding may have occurred for a reason mentioned above – that all patients, whether they read the PG or not, see thyroid symptoms as less serious than bleeding symptoms or kidney symptoms and therefore do not see a reason to contact their doctor immediately. Whether this perceived hierarchy of symptoms is at play for patients or not is something that would need to be investigated further in wave 2 of this study. Patients who read the PG were also significantly more likely to select 'call your doctor immediately' (correct answer) for what to do following development of new symptoms, returned symptoms, or worsening symptoms. This suggests that reading the PG in full may encourage patients to be more vigilant about symptoms and to involve their healthcare professional whenever an unexpected symptom arises.

As expected, receiving the PC in addition to the PG did not lead to significantly better knowledge of action to be taken following development of thyroid symptoms, as this is not discussed in the PC. However, those receiving the PC as well as the PG were also less likely to report the appropriate action following the development of bleeding disorder symptoms and symptoms of kidney problems, and this is surprising given that the PC specifically mentions that patients should 'call your doctor right away to report these symptoms'. Of course, the small sample size in the group not receiving both materials should be taken into account when interpreting findings and forming conclusions. However, these findings taken at face value suggest that the addition of the PC may not better patient knowledge about action to take following bleeding disorder and kidney symptoms, or the importance of monthly monitoring. This suggests that this information could be made clearer on the PC so that patients are more likely to retain this knowledge.

Analyses also showed that patients who had their first infusion of LEMTRADA 7-12 months ago were significantly more likely to answer correctly for what to do following kidney symptoms (58%), returned general symptoms (55%), and worsening symptoms (61%), while those who had their first infusion 37 months ago or more were more likely to be correct for action to be taken following under-active thyroid symptoms (40%). This may reflect the finding that thyroid disorders tend to develop some years after LEMTRADA initiation, therefore this group of patients may have more knowledge relating to thyroid symptoms.

Lastly, from a country perspective, Danish patients had the highest proportion of correct answers for what to do following symptoms of a bleeding disorder (83% correct), kidney disorder (83% correct), or thyroid disorder (83% correct), as well as what action to take if you experience new symptoms (67% correct), returned symptoms (50% correct), or worsening symptoms (83% correct). The findings may be explained by the fact that 100% of Danish patients who received the PG also had a healthcare professional discuss it with them, and that they were also the only country where 100% of patients had read more than half or all of the PG. This suggests that Danish patients may have answered correctly because they had the support of a healthcare professional and because they read the majority of the PG.

Looking at the proportion of correct responding across the whole sample for the frequency of tests to be conducted, findings were unexpectedly low for thyroid tests (14% correct). It seems that most patients assumed 'monthly' was the correct frequency for thyroid tests, as well as blood/urine tests, as this option was selected by 35% of patients. This finding is not particularly concerning as patients sticking to monthly thyroid function tests would be being even more careful than is required.

Knowledge that tests should be continued for four years following final course of treatment with LEMTRADA was also suboptimal, with 14% of patients scoring correctly. It is concerning that 86% of the sample reported that testing only needs to be conducted for 2 years or less (2 years – 10%; 6 months – 42%; 6 weeks – 35%) rather than 4 years. This finding suggests that this is an area where knowledge must be improved among patients. The PC and PG should repeat and reinforce this message as much as possible so that patients are more likely to retain the knowledge.

Interestingly, knowledge of the frequency of blood/urine tests for bleeding and kidney disorders was better than knowledge of other tests, but still poor (at 39% correct). The PC reiterates that patients should have monthly blood/urine tests, so it could be expected that those receiving the PC in addition to the PG may have superior knowledge on this topic; however, those receiving the PC as well as the PG had worse knowledge of this than those receiving only the PG.

Country analyses revealed that Danish patients were significantly more likely to correctly report that blood and urine tests should be continued for four years following the final course of treatment, and that blood/urine and thyroid function blood tests should be conducted monthly and 3-monthly, respectively (both ns). Again this suggests that Danish patients may have a higher chance of answering correctly either because they have read the materials or because their HCP has discussed the materials with them.

11.1.6 Other Findings

Across all the findings, Norwegian patients were the group that was most consistently incorrect or incomplete in their responses; they had the lowest proportions of correct/complete scores across almost all questionnaire items. For example, only 4% of Norwegian patients correctly reported that blood/urine tests are required for four years, and between 0% to 4% of patients correctly identified that one should 'call your doctor right away' if they develop new, returned, or worsened symptoms. It should be noted that there were small numbers in some country groups, however Norway (n = 24) had a greater representation than both the UK (n = 19) and Denmark (n = 6). The finding of more incorrect responding among Norwegians may instead relate to the fact that they were the group with the highest proportion of patients starting infusions *at least* 25 months ago (31%) (therefore their knowledge may be fading), the group most likely to report *not* having received the PC (28%) or the PG (22%), the group least likely to report having a discussion with a doctor or nurse about the guide (83%), the group least likely to have read the entire PG (8%), and the group least likely to know the 3 key reasons why patients are given the PC (9%) and the PG (8%). It also cannot be ruled out that patients from Norway do not have higher levels of cognitive impairment that influence their likelihood of scoring complete answers. Together, these factors may have contributed to Norwegians patients' poor performance in the survey. They suggest that

knowledge and understanding could be improved among Norwegians by ensuring as many as possible have access to the materials as well as doctors or nurses that can discuss the materials with them and encourage them to read the materials in full.

11.2 STRENGTHS AND LIMITATIONS

The strengths of the survey include the number of patients included (n = 201). The study used a cross-sectional design, and therefore we are not able to determine whether reading the materials causes better knowledge or whether increased knowledge among those who had received and reviewed the materials is the result of another factor. The sample was a convenience sample (i.e. not randomly selected) and focused on European patients, therefore the findings may not be generalisable to all patients taking LEMTRADA. Some of the subgroup analyses numbers were small (e.g. Norway and UK sample sizes; sample of patients receiving both educational materials) therefore the results may be due to chance.

12 OTHER INFORMATION

None.

13 CONCLUSION

Results show that, while there is still room for improvement in terms of the reach of patient educational materials, the large majority (>75%) of patients acknowledge receipt of the PC and the PG, and the numbers are the same whether the patient began infusions of LEMTRADA recently or some years ago. Furthermore, most of the materials, when received, are read by patients. However, patient knowledge about the purposes of the education materials is moderate, and most patients do not have complete knowledge of signs and symptoms associated with serious adverse reactions to LEMTRADA. That said, criteria set out for a complete answer to some questions could be seen as difficult for a lay person with no medical knowledge to achieve, therefore the low proportions of complete answers for some questions should have been expected. It is not surprising that very few patients were able to select all five correct symptoms of immune thrombocytopenic purpura from memory. There are clearly some flaws with the wording of questions, similarity in response options, and overall complexity of the survey that may need to be revised before wave 2 of the study. It may make sense to re-think how patient responses are scored as complete/partially complete/incomplete prior to wave 2 of the study.

Patients appeared more knowledgeable in some areas, for example the action that should be taken following the appearance of signs/symptoms as well as the actions that should be taken following appearance of other symptoms. That said, a significant proportion of patients seem to see taking no action, waiting, and monitoring symptoms before contacting a doctor as the right thing to do. And only a small proportion of patients were aware that blood/urine monitoring should continue for 4 years following the final course of LEMTRADA. These data highlight areas where knowledge among patients could be improved. Patients from the UK and Denmark appeared most knowledgeable. On the other hand, patients from Norway were consistently less knowledgeable than patients from other countries, suggesting that reasons for any deficits in Norway should be further investigated and improved. Comparisons also revealed a reasonably clear relationship between reading all of the PG and better knowledge and understanding. This suggests that one of the most useful things that could be done to improve patient knowledge is to a) ensure that all patients have access to materials that they can read, and b) ensure that as many patients as possible read all of the PG, as opposed to half of it for example. Other methods for improving patient knowledge could include ensuring that all patients have a healthcare professional go through the materials with them to reinforce and reiterate information and encourage them to read materials, and that this process is repeated with patients periodically. Alternatively, it may be worth investigating more engaging methods of getting important information across to patients, for example the MS ONE to ONE website and the mobile phone application ‘Lemcheck’ which is currently being enrolled in European countries. The application is based on the educational materials and can serve as an information and reminder tool.

14 REFERENCES

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ANNEXES

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

Annex 2 Supportive Documents

Protocol

Add a copy of the protocol + amendments or only final amended protocol.

Study Report Approval

Add a copy of the Company's approval of the study report.

Annex 3 Administrative and Legal Considerations

Ethical Considerations

Ethical principles

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

Laws and regulations

This study was conducted in compliance with all international guidelines, and national laws and regulations of the country(ies) in which the study was performed, as well as any applicable guidelines.

Each participating country locally ensured that all necessary regulatory submissions (eg, IRB/IEC) were performed in accordance with local regulations including local data protection regulations.

Regulatory authorities' submissions by country are presented

Data Protection

The patient's personal data and Investigator's personal data which were to be included in the Company's databases were treated in compliance with all local applicable laws and regulations.

When archiving or processing personal data pertaining to the Investigator and/or to the patients, the Company took all appropriate measures to safeguard and prevent access to this data by any unauthorized third party.

Record Retention

The Investigator was responsible for the retention of the study documentation until the end of the study. In addition, the Investigator had to comply with specific local regulations and recommendations regarding patient record retention.

The Company Audits and Inspections by Competent Authorities (CA)

The Investigator agreed to allow the Company's auditors and Competent Authorities' inspectors to have direct access to records of the study for review, it being understood that all personnel with access to patients' records are bound by professional secrecy and as such, could not disclose any personal identity or personal medical information.

The Investigator had to make every effort to help with the performance of the audits and inspections, giving access to all necessary facilities, data, and documents. As soon as notification from the authorities for an inspection was received by the Investigator, he/she had to inform the

Company and authorize the Company to participate in this inspection. The confidentiality of the data to verify and the protection of the patients must be respected during these inspections. Any results or information arising from the inspections by the Competent Authorities were to be immediately communicated by the Investigator to the Company. The Investigator had to take appropriate measures required by the Company to ensure corrective actions for all problems found during audits and inspections.

Ownership of Data and Use of Study Results

Unless otherwise specified by local laws and regulations, the Company retains ownership of data, results, reports, findings, and discoveries related to the study. Therefore, the Company reserves the right to use the data from the present study for any purpose, including to submit them to the Competent Authorities of any country.

The Study Committee, if any involved in the study, has full access to the final data base allowing for appropriate academic analysis and reporting of the study results.

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)

Version Number:	1.7		
Date:	30 November 2015	Total number of pages:	31

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Other experts/consultants

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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Marketing authorisation holder(s)

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1 TABLE OF CONTENTS

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

Lemtrada® RMP Questionnaires – Germany, Italy, Spain, Denmark, Norway

Contents

Notes

- Throughout, text which is intended for participants is featured in black, whereas notes for Genzyme/AH are featured in *[blue]. Blue notes should be removed from final documents for patients/HCPs.*
- Prior to distributing the questionnaires in non-English speaking countries, the Medical Director or his/her representative of the local market must check that translated copies have used appropriate language.

Considerations

- We do not want the patient or HCP to refer to the patient card/PIL/Patient education guide/SPC when they answer the questions: we have tried to avoid this through the wording of the introductions. Time taken from beginning to end of the questionnaire will be recorded, but is not included in the protocol.
- Participants will be given a link or information should they wish to report adverse events.
- At the end of the survey (patient and HCP) we propose that the participant should be shown the correct answers to all the questions

Requirements (from synopsis documents)

HCP

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

1. Physician characteristics including:
    a) Country
    b) Affiliation: Type of hospital (in-out-patient)/ private practice
    c) Speciality
    d) MS experience (number of treated patients)
    e) Number of patients prescribed Lemtrada®
    f) Time since last prescription of Lemtrada®

2. The prescriber's knowledge of the existence of the :
    a) HCP guide

b) HCP checklist

c) SmPC

d) Patient Guide

e) Patient Alert Card

f) 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) Tests to be conducted for the initial screening of the patient
   c) Vaccination, pre-treatment courses
   d) Monitoring activities for 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

Patient

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

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

Knowledge is defined as awareness and understanding of important risk minimization information contained in the patient guide and patient alert card. Important risk information measured:

- Knowledge 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. 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).

Sample

	UK	Germany	Italy	Spain	Denmark	Norway
MS patients	200 across all markets					
Neurologists / MS specialists	60 Lemtrada prescribers across all markets					

Patient invitation email

Lemtrada ®▼ (alemtuzumab) RMP questionnaire

Dear patient,

Subject header: Invitation related to your Lemtrada® ▼ (alemtuzumab) medication

We are inviting you to take part in a survey related to your medication Lemtrada®, a treatment for multiple sclerosis (MS). The purpose of the survey is to help us to better understand the effectiveness of the patient education materials. It will take about 15 minutes to complete.

Different patients sometimes respond in different ways to the same medicine, and some side effects may not be discovered until many people have used a medicine over a period of time. For this reason, we are now required to pass on to our client, who is a manufacturer of medicines, details of any side effects related to their own products that are mentioned during the course of market research. Although what you say will, of course, be treated in confidence, should you indicate during the session a side effect when you, or someone you know, became ill after taking one of our client's medicines, we will need to report this, so that they can learn more about the safety of their medicines.

For more information, and to take part in the survey, please follow this link <insert link to country page QP0>.

<Display on a separate screen before the patient information page>

P0. Which country do you live in?

[Eligibility criteria]

Germany	
Italy	
Spain	
Denmark	
Norway	
Other	*[INELIGIBLE]*

Patient Information page

What's involved in taking part?

We are inviting you to take part in a survey. The questions in the survey are to gather information on what you remember about the patient alert card and patient information leaflet for Lemtrada ®.The goal is to see how clear the information is in these educational materials. We kindly ask you not to look at into the patient alert card and patient information leaflet when answering the questions. Don't worry if you can't remember everything! We will use the answers to update the educational materials if they are not clear enough.

The survey will take about 15 minutes to complete.

This survey is being conducted to meet a regulatory obligation from the European Medicine Agency (EMA). The survey is being run by a company called IPSOS, on behalf of the pharmaceutical company that markets Lemtrada®. All information that you provide will be confidential and every precaution will be taken to protect your privacy. Your answers will not be identifiable, and data shared with the pharmaceutical company will be in aggregated form. IPSOS is obliged to pass on to the pharmaceutical company any information about adverse events of medication. If any of your survey answers indicate a possible adverse event you will be asked to give permission for IPSOS to pass this information to the pharmaceutical company.

When you reach the end of this survey, there are some extra/optional questions which will take about 20 minutes to complete. When you have completed this main survey, you will be shown a link and then can decide if you want to complete these additional questions.

If you have any questions about the survey please contact europe.online@ipsos.com

I would like to take part. <link to patient consent page>

Patient Consent page

Thank you for deciding to participate in this survey to assess information provided about Lemtrada®. conducted by IPSOS and sponsored by the manufacturer of Lemtrada®. This survey is likely to produce information that may help us improve the information and support provided to the patients. We would like to reassure you that:

- Your responses will be collated with other respondents and presented to the sponsor in aggregated or anonymised form.

- Different patients sometimes respond in different ways to the same medicine, and some side effects may not be discovered until many people have used a medicine over a period of time. For this reason, we are obliged to pass on to our client, who is a manufacturer of medicines, details of any side effects related to their own products that are mentioned during the survey. This information will also be passed on to the European Medicines Agency (EMA). Although your answers will be treated in confidence, should you indicate a side effect with Lemtrada®, we would need to report this along with your contact information, so that they can learn more about the safety of their medicines.

- We are required to inform you that Market Research Agencies are required to report adverse events to pharmacovigilance, including exposure to pregnancy / lactation, suspected transmission of infectious agents, technical issue / quality, drug interaction and special situations such as overdose, abuse, misuse, incorrect administration, medication error, occupational exposure, and lack of efficacy that are mentioned during the discussion of a product from the company that sponsor the research.

[SHOW TO ITALY ONLY]

- Although everything said will remain confidential, if during the survey you indicate any adverse (or the aforementioned situations) event occurred to you, we will need to report this even if it has already been reported by you/your physician/ directly to the company or the Italian regulatory authorities (we remind you that you can report using the AIFA web site http://www.agenziafarmaco.gov.it/it/content/modalit%C3%A0-di-segnalazione-delle-sospette-reazioni-avverse-ai-medicinali). In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event/drug exposed pregnancy/product complaint. Everything else you say during the course of the interview will continue to remain confidential.

- In such a situation you have the option to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the survey will continue to remain confidential, and you will still have the option to remain anonymous if you wish.

- If you agree to waive the confidentiality given to you, then your name and contact details will be forwarded to the sponsor's Pharmacovigilance department for the express and sole purpose of follow-up of such report(s).If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

[SHOW TO GERMANY ONLY]

- If you agree to waive the confidentiality given to you, due to German Data protection laws you will need to contact the sponsor's Pharmacovigilance department to provide the details for the express and sole purpose of follow-up of such report(s). In this event you will be re-contacted in order to be provided with the details. If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

[SHOW TO ALL MARKETS]
Please indicate if you are willing to waive your confidentiality if an adverse event is identified during the course of this survey.

- I agree to waive my confidentiality for the express and sole purpose of follow-up of adverse events mentioned by me during this survey. In this event I understand that I will be re-contacted to be provided with the details and I will be responsible for contacting the sponsoring pharmaceutical company

- I do not agree to waive my confidentiality for the express and sole purpose of follow-up of adverse events mentioned by me during this survey and choose to stay anonymous

SINGLE CODE
CONTINUE

- Your responses will be otherwise confidential and will not be used for any other purposes or disclosed to any third party without your approval except in cases where the manufacturer of the medicine is obliged to share the results with national and international regulatory agencies and government bodies responsible for the safety of medications.
- We remind you that you may at all times request a copy of your personal information, have it corrected and object to its processing by contacting europe.online@ipsos.com.

- You have the right to withdraw your participation at any time during this survey

Please indicate whether you have read and understood the survey information provided above:

Code	Type	Response	Answer
	Single response check-box	Yes, I have read the information provided above and the purpose of the survey and steps are clear to me.	✓
		No [patient selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	

Please confirm your agreement to participate in the current survey:

Code	Type	Response	Answer
	Single response check-box	Yes, I agree to participate in this survey	✓
		No, I do not agree to take part in the survey [patients selecting this option will not be directed to the survey pages and will be directed to a "termination" page with appropriate text]	

Start the survey! <link to patient questionnaire>

Patient questionnaire

Survey relating to patient information about Lemtrada®.

Please read each question carefully and indicate your response in the boxes provided. The questionnaire will take approximately 15 minutes to complete. Please complete the questionnaire in one sitting.

Introduction questions

Programming note: Screener questions

Today's date: <Make it autofill for online surveys>

Please give us some information about yourself and your medication so that we can make sure you are eligible to take part in the survey.

P1. Have you ever been diagnosed with multiple sclerosis (MS) by a doctor? *[eligibility criteria]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	INELIGIBLE

2. Have you been prescribed Lemtrada®?*[eligibility criteria]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No	INELIGIBLE

3. Have you had your first Lemtrada® infusion yet? *[eligibility criteria]*

code	*Type*	*Response*	*Answer*
	single response	Yes	✓
		No	INELIGIBLE

4. When did you have your first Lemtrada® infusion? *[potential confounding factor]*

code	*Type*	*Response*	*Answer*
	Date	MM/YYYY	
		Don't know	

5. *<in Wave 2 only>* We did the same survey about Lemtrada® 18 months ago. Did you take part in that survey? *[eligibility criteria]*

code	*Type*	*Response*	*Answer*
	Single response	Yes	INELIGIBLE
		No	✓

Questions about you

6. In which year were you first diagnosed with multiple sclerosis?

code	*Type*	*Response*	*Answer*
	Date		
		YYYY	

7. Please tell us your age (in years)

code	*Type*	*Response*	*Answer*
	Single response	18-25	
		26-35	
		36-45	
		46-55	
		56-65	
		66 or above	

8. What is your gender?

code	*Type*	*Response*	*Answer*
	single response	Male	
		Female	

Questions about Lemtrada® information

Patient alert cards and patient guides are supplied to patients prescribed Lemtrada®. We want to find out how useful they are at telling people about Lemtrada®.

About the patient alert card

9. Have you ever received a patient alert card for Lemtrada®? *[potential confounding factor] [include an image of the front of the patient card supplied in the relevant country[1]]*

code	*Type*	*Response*	*Answer*
	single response	Yes	✓
		No [patients selecting this option will be directed to question 11]	
		Don't know	

10. *<If participant answers "yes" to question 9>* What is the purpose of the patient alert card? You can choose more than one answer. *[knowledge: patient card]*

code	*Type*	*Response*	*Answer*
	multi-response	To show a doctor or Healthcare professional involved in your medical care	✓
		To give you important safety information you need to be aware of when receiving treatment with Lemtrada®	✓
		To alert all emergency and healthcare professionals that you have been treated with Lemtrada	✓
	exclusive	Don't know/not sure	

11. Have you ever received a patient guide for Lemtrada®? *[potential confounding factor] [include an image of the front of the patient guide supplied in the relevant country[2]]*

code	*Type*	*Response*	*Answer*
	single response	Yes	✓
		No <Patients who select this should go to completion page>	
		Don't know	

11a. Did your doctor/nurse discuss the patient guide with you before your first infusion of Lemtrada?

code	*Type*	*Response*	*Answer*
	single response	*Yes*	
		No	
		Don't remember	

12. *<If participant answers "yes" to question 11 >* What is the purpose of the patient guide? You can choose more than one answer. *[knowledge: patient guide]*

[1] Image of patient card needs to be customised per country (i.e. in the correct language)
[2] Image of patient card needs to be customised per country (i.e. in the correct language)

code	*Type*	*Response*	*Answer*
	multi-response	To show to a caregiver	
		To give you important safety information you need to be aware of when receiving treatment with Lemtrada®	✓
		To make you aware of the needed monitoring schedule	✓
		To show you how to recognize symptoms that might be related to possible side effects of Lemtrada®	✓
	exclusive	Don't know/not sure	

14. *<If participant answers "yes" to question 11>* People differ in the amount of information they read about their medicines. How much of the patient guide have you read? *[potential confounding factor]*

code	*Type*	*Response*	*Answer*
	single response	All of it	
		More than half of it	
		About half of it	
		Less than half of it	
		None of it	

About Lemtrada®

Please answer these questions based on what you remember from the information you received. Don't worry if you can't remember everything - we want to see how clear the information you were given is. Remember that this survey is anonymous and it will not be possible to link the answers to you. We will use the answers we get from this survey to make changes to the information if it is not clear enough.

After completing this survey, you will be shown the correct answers for all of the following questions.

15. Bleeding can be a side effect of Lemtrada® - which 5 of the symptoms listed below could show a bleeding disorder? *[knowledge: immune thrombocytopenic purpura (ITP)]*

Code	*Type*	*Response*	*Answer*
	Multi response	Cold sores (oral herpes)	
		Itchy skin	
		Bruising easily	✓*
		Coughing up blood	✓
		Small red, pink or purple spots on the skin	✓
		Bleeding from a cut that is harder to stop	✓
		Bleeding from gums or nose that takes longer than usual to stop	✓

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

16. If you have symptoms of a bleeding disorder, what actions should you take?

Code	*Type*	*Response*	*Answer*
	Single response	Wait until the bleeding stops	
		Tell a doctor at your next scheduled visit	
		See your doctor immediately	✓

17. What are the signs and symptoms of kidney problems or anti-GBM disease? You can choose more than one answer. *[knowledge – kidney disorders]*

Code	Type	*Response*	Answer
	Multi response	Red or tea coloured urine	✓
		Diarrhoea	
		Coughing up blood	✓
		Swelling in the legs or feet	✓
		Rash	

18. If you have symptoms of a kidney disorder, what actions should you take? *[knowledge – kidney disorders]*

Code	*Type*	*Response*	*Answer*
	Single response	Wait to see if the symptoms resolve	
		Tell a doctor at your next scheduled visit	
		See your doctor immediately	✓

<Intro Screen> People who have had a Lemtrada® infusion may develop symptoms of a thyroid disorder which can be an under-active thyroid or over-active thyroid.

19. Which of the following symptoms could be a sign of an **over-active** thyroid? You can choose more than one answer. *[knowledge – over-active thyroid]*

Code	Type	*Response*	Answer
	Multi response	Excessive sweating	✓
		Nervousness	✓
		Depression	
		Unexplained weight loss	✓
		Eye swelling	✓
		Fast heartbeat	✓
		Swelling of the legs	

20. Which of the following could be a sign of an **under-active** thyroid? You can choose more than one answer. *[knowledge – under-active thyroid]*

Code	Type	Response	Answer
	Multi response	Unexplained weight gain	✓
		Feeling cold	✓
		Swelling in the legs or feet	
		Worsening tiredness	✓
		Bruising easily	
		Newly occurring constipation	✓

21. If you have symptoms of a thyroid disorder, what actions should you take? *[knowledge – thyroid disorder]*

Code	*Type*	*Response*	*Answer*
	Single response	Wait to see if the symptoms resolve	
		Tell a doctor at your next scheduled visit	
		See your doctor immediately	✓

22. After an infusion of Lemtrada, how often should you have blood and urine tests? *[knowledge – importance of monthly monitoring]*

Code	*Type*	*Response*	*Answer*
	Single response	Weekly	
		Monthly	✓
		Every 2 months	

		Every 3 months	
		Every 6 months	

23. After an infusion of Lemtrada, how often should you have thyroid function tests? *[knowledge – importance of monthly monitoring]*

Code	*Type*	*Response*	*Answer*
	Single response	Weekly	
		Monthly	
		Every 2 months	
		Every 3 months	✓
		Every 6 months	

24. For how long is it necessary to have blood and urine tests for auto-immune conditions (bleeding, kidney and thyroid disorders)? *[knowledge – importance of monitoring for 4 years after the last course of treatment]*

Code	*Type*	*Response*	*Answer*
	Single response	For 6 weeks after the last course of treatment with Lemtrada	
		For 6 months after the last course of treatment with Lemtrada	
		For 2 years after the last course of treatment with Lemtrada	
		For 4 years after the last course of treatment with Lemtrada	✓

25a. What should you do if you experience signs or symptoms that you have **not experienced before**?

Code	*Type*	*Response*	*Answer*
	Single response	Take no action	
		Continue to monitor your symptoms for another week	
		Continue to monitor your symptoms for another month	
		Call your doctor right away	✓

25b. What should you do if you experience signs or symptoms that you have **had before, then disappeared and have now come back**?

Code	*Type*	*Response*	*Answer*
	Single response	Take no action	
		Continue to monitor your symptoms for another week	
		Continue to monitor your symptoms for another month	
		Call your doctor right away	✓

25c. What should you do if you experience signs or symptoms that you **had all the time and have now become worse**?

Code	*Type*	*Response*	*Answer*
	Single response	Take no action	
		Continue to monitor your symptoms for another week	

		Continue to monitor your symptoms for another month	
		Call your doctor right away	✓

<Completion page>

You have now finished the survey.

Thank you very much for taking part! Click here to see the correct responses. <link to page of correct responses>

There is a second part to this survey, which will take about 20 minutes to complete. If you would like to take part in this, please indicate below.

code	*Type*	*Response*	*Answer*
	Single response	Yes – I would like to do the second part of this survey	✓
		No	Thank and close

HCP invitation email

LEMTRADA ®▼ (alemtuzumab) RMP questionnaire

Subject header: Survey relating to RMP information for Lemtrada®▼ (alemtuzumab)

Dear Doctor,

We are inviting you to take part in a survey to evaluate the efficacy of risk management information provided for Lemtrada®. The survey is for healthcare professionals who have prescribed Lemtrada®.

It will take about 15 minutes to complete. We will use the information provided by doctors to determine whether the existing provision of risk information is sufficient.

We are required to pass on to our client details of adverse events that are mentioned during the course of market research. Although what you say will of course be treated in confidence, should you raise during the discussion an adverse event in a specific patient or groups of patient, we will need to report this even it has already been reported by you directly to the company or to the regulatory authorities. In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the interview will continue to remain confidential, and you will still have the option to remain anonymous if you so wish.

For more information, and to take part in the survey, please follow this link <insert link to country page Q1>.

<Programming note: please show this question on a separate screen before HCP information page>

1. Which country are you working in? *[eligibility criteria]*

Germany	
Italy	
Spain	
Denmark	
Norway	
Other	*[INELIGIBLE]*

HCP information page

This survey is being conducted to meet a regulatory obligation from the European Medicines Agency (EMA). The purpose of the survey is to evaluate effectiveness of education materials provided for Lemtrada®.

The survey is being run by a company called Ipsos, on behalf of Genzyme, the manufacturer of Lemtrada. Your answers will not be identifiable, and data shared with the pharmaceutical company will be in aggregated form.

The survey will take about 15 minutes to complete.

If you have any questions about the survey please contact europe.online@ipsos.com

I would like to take part in the survey. <insert link to HCP consent page>

HCP consent page

Thank you for deciding to participate in this survey to assess risk information provided about Lemtrada®, conducted by Ipsos and sponsored by Genzyme, the manufacturer of Lemtrada®. This survey is likely to produce results that may benefit patients. We would like to reassure you that:

- Your responses will be collated with other respondents and presented to the sponsor in aggregated or anonymised form.
- I agree that if an adverse event related to the commissioning company's own products in a specific patient has been mentioned in the survey, the company will need to report this (even if it has already been reported by me directly to the company or the regulatory authorities). I understand that if I decide to disclose my personal details in association with any adverse event report, this information will be disclosed to the commissioning company.

[SHOW TO ITALY ONLY]

- Although everything said will remain confidential, if during the survey you indicate any adverse (or the aforementioned situations) event occurred to you, we will need to report this even if it has already been reported by you/your physician/ directly to the company or the Italian regulatory authorities (we remind you that you can report using the AIFA web site http://www.agenziafarmaco.gov.it/it/content/modalit%C3%A0-di-segnalazione-delle-sospette-reazioni-avverse-ai-medicinali). In such a situation you will be asked whether or not you are willing to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event/drug exposed pregnancy/product complaint. Everything else you say during the course of the interview will continue to remain confidential.

- In such a situation you have the option to waive the confidentiality given to you under the Market Research Codes of conduct specifically in relation to that adverse event. Everything else you say during the course of the survey will continue to remain confidential, and you will still have the option to remain anonymous if you wish.

- If you agree to waive the confidentiality given to you, then your name and contact details will be forwarded to the sponsor's Pharmacovigilance department for the express and sole purpose of follow-up of such report(s).If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

[SHOW TO GERMANY ONLY]

- If you agree to waive the confidentiality given to you, due to German Data protection laws you will need to contact the sponsor's Pharmacovigilance department to provide the details for the express and sole purpose of follow-up of such report(s). In this event you will be re-contacted in order to be provided with the details. If you do not agree, then we will forward the report(s) to the sponsor's Pharmacovigilance department, but your anonymity remains unaffected – and you will not be contacted again regarding such report(s). You are able to participate in this research regardless of whether or not you are willing to waive your confidentiality in relation to any adverse events mentioned.

- Are you happy to proceed with the interview on this basis? Please indicate your response by selecting the appropriate option below.
  I would like to proceed and give permission for my contact details to be passed on to the Drug Safety department of the company if an adverse event / product complaint is mentioned by me during the survey. Please tick the box ☐
  [Proceed]

  I would like to proceed but do not wish for my contact details to be passed on to the Drug Safety department of the company if an adverse event / product complaint is mentioned by me during the survey. Please tick the box ☐
  [Proceed]

  I do not want to proceed and wish to end the interview here
  [Thank and close] Please tick the box ☐

- We remind you that you may at all times request a copy of your personal information, have it corrected and object to its processing by contacting europe.online@ipsos.com.
- You have the right to withdraw from the survey at any time during this survey.

Please indicate whether you have read and understood the survey information provided:

Code	*Type*	*Response*	*Answer*
	Single response check-box	Yes, I have read the information provided above and the purpose of the survey and steps are clear to me.	✓
		No [HCP selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	

Please confirm your agreement to participate in this survey:

Code	*Type*	*Response*	*Answer*
	Single response check-	Yes, I agree to participate in this survey	✓

	box	No, I do not agree to take part in the survey [HCPs selecting this option will not be directed to the survey pages and will be directed to a "termination" page with appropriate text]	

Begin the survey. <link to HCP questionnaire>

HCP questionnaire

Survey to assess knowledge relating to Lemtrada®

This is a questionnaire about your knowledge relating to Lemtrada®.

Please read each question carefully and indicate your response in the boxes provided. The questionnaire will take approximately 15 minutes to complete. Please complete the questionnaire in one sitting.

About you

4. What is your specialist area? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Multi response	Neurologist	
		MS specialist	
	exclusive	Other	INELIGIBLE

5. "How many MS patients in total do you treat within a typical year? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Single response	Up to 10	
		11 - 50	
		51-99	
		100+	

6. Have you ever prescribed Lemtrada®? *[eligibility criteria]*

Code	*Type*	*Response*	*Answer*
	Single response	Yes	✓
		No [HCP selecting this option will not be directed to the survey and will be directed to a "termination" page with appropriate text]	INELIGIBLE

7. When did you last initiate Lemtrada®? Choose the answer that is most accurate. *[potential confounding factor]*

Code	*Type*	*Response*	*Answer*
	Single response	Within the last week	
		Within the last month	
		Within the last 3 months	
		More than 3 months ago	
		More than 6 months ago [HCP selecting this option will not be directed to the survey and will be directed to a	INELIGIBLE

		"termination" page with appropriate text]	

8. Approximately how many patients have you treated with Lemtrada?

Code	*Type*	*Response*
	Single response, open end.	*[numerical answer]*

9. Do you work in a public (state funded) or private healthcare system? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Single response	Public healthcare only	
		Private healthcare only	
		Both public and private healthcare	

10 . In which of the following settings have you prescribed Lemtrada? *[subsample analysis]*

Code	*Type*	*Response*	*Answer*
	Multi response	MS/neurology clinic in a University hospital	
		MS/neurology clinic in a Community hospital	
		Office-based specialist [only show to Germany, Italy, Spain]	

10a. . How many prescriptions for Lemtrada® do you write each month? *[potential confounding factor]*

Code	*Type*	*Response*	*Answer*
		Less than five prescriptions per month	
	Single response	5-10 prescriptions per month	
		11-20 prescriptions per month	
		More than 20 prescriptions per month	

Information about Lemtrada®

The Lemtrada risk management plan includes educational materials as the core element of risk minimisation tools. You will have received some materials about Lemtrada®: the Health Care Professional Guide, the Health Care Professional checklist and the Summary of Product Characteristics (SmPC). We want to find out how useful these materials are for communicating risk management information about Lemtrada®.

The following questions relate to your knowledge about Lemtrada®. Please answer the questions based on what you remember.

After completing this survey, you will be shown the correct answers for all of the following questions.

About the Health Care Professional and Patient Educational Materials

11. Have you received and reviewed the Health Care Professional Guide? *[knowledge: HCP guide]*

code	*Type*	*Response*	*Answer*
	single response	Yes	✓
		No	
		Don't remember	

12. Have you received and reviewed the Health Care Professional checklist? *[knowledge: HCP checklist]*

code	*Type*	*Response*	*Answer*
	single response	Yes	✓
		No	
		Don't remember	

13. Have you received and reviewed the Summary of Product Characteristics (SmPC)? *[knowledge: SmPC]*

code	*Type*	*Response*	*Answer*
	single response	Yes	✓
		No	
		Don't remember	

14 What patient educational materials are available for patients prescribed Lemtrada®? *[Knowledge – patient guide, patient alert card, package leaflet]*

code	*Type*	*Response*	*Answer*
	multi-response	Patient Guide	✓
		Patient Alert Card	✓
		Patient Checklist	
		Package Leaflet	✓

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

About Lemtrada®

15. What potential risk needs to be discussed at first prescription of Lemtrada® with a patient? Select as many as apply. *[knowledge: risks associated with the product]*

code	Type	Response	Answer
	Multi response	Nephropathies including anti-GBM disease	✓*
		Thyroid disorders	✓
		Immune thrombocytopenic purpura [ITP]	✓
		Active Infections	✓
		Pregnancy & Contraception (if applicable)	✓
		Depression	
		Gastro-intestinal issues	

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

16. Lemtrada is contraindicated in patients with the following conditions. Select as many that apply. *[knowledge: key points in the HCP guide and checklist - contraindications]*

code	Type	Response	Answer
	Multi response	Human immunodeficiency virus (HIV)	✓
		Ischemic heart disease	
		Depression	
		Hypersensitivity to the active substance or any of the excipients	✓

17. Lemtrada is contraindicated in patients prescribed the following treatments Select as many that apply. *[knowledge: key points in the HCP guide and checklist -contraindications]*

code	Type	Response	Answer
	Multi response	Selective serotonin reuptake inhibitors (SSRIs)	
		Immunosuppressive therapy	✓
		Antineoplastic therapy	✓
		Antiviral therapies	

18. According to the HCP guide and checklist what tests should be conducted before first prescription of Lemtrada®? *[knowledge: key points in the HCP guide and checklist - tests to be conducted for the initial screening of the patient]*

code	Type	Response	Answer
	Multi response	Serum creatinine	✓*
		Complete blood count with differential	✓
		Urinalysis with microscopy	✓
		Liver function tests	
		Thyroid function tests such as TSH	✓
		Urine protein creatinine test	

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

19. How long after the patient's last vaccination should you wait before administering Lemtrada®? *[knowledge- key points in the HCP guide and checklist - vaccinations]*

code	*Type*	*Response*	*Answer*
	Single response	2 weeks	
		4 weeks	
		6 weeks	✓
		8 weeks	
		Don't know	

20. When do you need to check serum creatinine? Select as many as apply. *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Multi-response	Before the patient is prescribed Lemtrada	✓
		Monthly until 48 months after last infusion of Lemtrada	✓
		Every 3 months until 48 months after last infusion of Lemtrada	
		Every 8 weeks until last infusion of Lemtrada or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out [exclusive]	

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

21. When do you need to check complete blood count with differential? Select as many as apply. *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Multi-response	Before the patient is prescribed Lemtrada	✓
		Monthly until 48 months after last infusion of Lemtrada	✓
		Every 3 months until 48 months after last infusion of Lemtrada	
		Every 8 weeks until last infusion of Lemtrada or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out [exclusive]	

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

22. When do you need to conduct urinalysis with microscopy? Select as many as apply. *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	multi response	Before the patient is prescribed Lemtrada®	✓
		Monthly until 48 months after last infusion of Lemtrada®	✓
		Every 3 months until 48 months after last infusion of Lemtrada®	
		Every 8 weeks until last infusion of Lemtrada® or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out [exclusive]	

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

23. When do you need to conduct liver function tests? Select as many as apply. *[knowledge: monitoring activities for the autoimmune events]*

code	*Type*	*Response*	*Answer*
	Single-response	Before the patient is prescribed Lemtrada®	
		Monthly until 48 months after last infusion of Lemtrada®	

		Every 3 months until 48 months after last infusion of Lemtrada®	
		Every 8 weeks until last infusion of Lemtrada® or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out [exclusive]	✓

24. When do you need to conduct thyroid function tests [such as TSH]? Select as many as apply.
[knowledge: monitoring activities for the autoimmune events]

code	*Type*	*Response*	*Answer*
	multi response	Before the patient is prescribed Lemtrada®	✓
		Monthly until 48 months after last infusion of Lemtrada®	
		Every 3 months until 48 months after last infusion of Lemtrada®	✓
		Every 8 weeks until last infusion of Lemtrada® or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out [exclusive]	

*[*all items must be selected to be recognised as a correct answer i.e. a single missing item constitutes an incorrect answer]*

25. When do you need to conduct urine protein creatinine ratio tests? Select as many as apply.
[knowledge: monitoring activities for the autoimmune events]

code	*Type*	*Response*	*Answer*
	Single-response	Before the patient is prescribed Lemtrada®	
		Monthly until 48 months after last infusion of Lemtrada®	
		Every 3 months until 48 months after last infusion of Lemtrada®	
		Every 8 weeks until last infusion of Lemtrada® or as indicated by clinical signs and symptoms	
		These tests do not need to be carried out [exclusive]	✓

26. How long should women of childbearing potential use effective contraceptive measures?
[knowledge: special warnings on fertility, contraception and breastfeeding]

code	*Type*	*Response*	*Answer*
	Single-response	During treatment and for at least 5 days following each treatment	
		During treatment and for at least 30 days following each treatment	
		During treatment and for at least 4 months following each treatment	✓
		During treatment and for at least 48 months after each treatment	

27. What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)?
[knowledge: key points in the HCP guide and checklist –appropriate medical intervention]

code	*Type*	*Response*	*Answer*
	Single-response	Obtain a complete blood count immediately and refer to a specialist immediately if onset is confirmed	✓
		Obtain a complete blood count immediately and continue to treat the patient myself if onset confirmed	
		Ask patient to self-monitor symptoms until their next scheduled appointment when a complete blood count will be obtained	

28. What should you do if your monitoring results lead you to suspect nephropathy? *[knowledge: key points in the HCP guide and checklist- appropriate medical intervention]*

code	*Type*	*Response*	*Answer*
	Single-response	Refer the patient to a specialist immediately	✓
		Ask the patient to come in as soon as possible, conduct urine tests and keep monitoring the patient myself.	
		Wait until the patient's next scheduled appointment when any change in serum creatinine level from baseline can be confirmed	

29. What counselling should you provide patients treated with Lemtrada? *[knowledge: key points in the HCP guide]*

code	*Type*	*Response*	*Answer*
	Multi-response	Coping with MS	
		Importance of contraception	✓
		Risks and importance of monthly monitoring appointments	✓
		None	

You have now finished the survey.

Thank you very much for taking part! Click here to see the correct responses. <link to page of correct responses>