POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

FINAL REPORT WAVE 1 AND WAVE 2

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

COMPOUND: Alemtuzumab

STUDY NAME: LEMTRADA® EU-RMP Survey in HCPs

The Study is conducted by Genzyme, a Sanofi 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 healthcare professionals who prescribe 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)	Genzyme Therapeutics Ltd
Joint PASS	No
Research question and objectives	The overall objective of the survey is to assess descriptively the knowledge level of Healthcare Professional (HCPs) with regard to educational messages and thus the effectiveness of the educational materials to support the safe use of LEMTRADA. Research questions: 1. What is the HCP's understanding and awareness of the risks associated with use of LEMTRADA? 2. What is the HCP's knowledge of the key safety messages in the content of the HCP guide and HCP checklist? 3. What is the HCP's knowledge and understanding of the risk minimization activities to be undertaken in relation to LEMTRADA?
Country(-ies) 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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Study Personnel

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.

Names and affiliations of Principal Investigators

Not applicable.

National coordinators

Not applicable.

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ANNEX 1

1 RESPONSIBLE PARTIES

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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 HCPs 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
anti-GBM:	anti-Glomerular Basement Membrane
EMA:	European Medicines Agency
EU:	European
HCP:	Healthcare Professional
ITP:	immune thrombocytopenic purpura
MAH:	Marketing Authorization Holder
MS:	multiple sclerosis
PASS:	Post Authorization Safety Study
RMP:	risk management plan
SmPC:	Summary of Product Characteristics
UK:	United Kingdom

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 healthcare professionals who prescribe LEMTRADA® (alemtuzumab).

The LEMTRADA risk management plan (RMP) includes risk minimization measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimization; as an example, the Healthcare Professional (HCP) educational pack comprises the Summary of Product Characteristics (SmPC), HCP materials, and patient materials. The objective of the HCP educational materials are to ensure early detection of key symptoms indicative of adverse events (AEs), to communicate risks of signs and symptoms and the importance of periodic monitoring, and to inform about benefit-risk decisions before each treatment course.

HCPs who may prescribe LEMTRADA receive all educational materials in hard copy. Additionally, the HCP educational materials are available on a Multiple Sclerosis (MS) One to One website to provide electronic access to HCPs who prescribe the product. HCPs also should be familiar with the Patient Educational Materials: Patient Guide and Patient Alert Card.

5.1 METHODOLOGY

To define the familiarity of the HCPs 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 including 2 highly populated EU countries (Germany and Spain). The objective of the survey was to assess the effectiveness of the educational materials to support the safe use of LEMTRADA by measuring HCP knowledge about the key items presented in the educational materials.

Research questions were related to the extent of the HCP's understanding and awareness of the risks associated with use of the product, the key safety messages in the content of the HCP guide and HCP checklist, and knowledge of risk minimization activities to undertake. The survey was conducted online using a structured questionnaire. A convenience (ie, non-random) sample of HCPs involved in the treatment of MS patients with LEMTRADA was selected, and data was collected via HCP self-report. A threshold of 70% was defined as 'adequate' knowledge.

The first wave of the survey (Wave 1) was conducted with 74 HCPs recruited from Germany (n=20, 27%), Italy (n=20, 27%), Spain (n=15, 20%), UK (n=15, 20%), Denmark (n=1, 1%) and Norway (n=3, 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 75 HCPs recruited from the UK (n=15, 20%), and Germany, Italy, Spain, Greece, Belgium and the Netherlands (n=10, 13% from each country). Participants in Wave 1 were excluded from participating in Wave 2. Reports of the Wave 1 and Wave 2 surveys can be found in Annex 1 of this report.

5.2 DATA COLLECTED

The Questionnaire collected data concerning HCP characteristics, including:

- HCP's specialty, work setting, and activity with LEMTRADA patients
- HCP's knowledge of HCP and patient educational materials
- HCP's understanding and awareness of the risks associated with use of the product
- HCP's knowledge of the key points in the content of the HCP guide and checklist with respect to
  - contraindications
  - tests to be conducted for the initial screening of the patient
  - vaccination precautions
  - monitoring activities for the autoimmune events
  - special warnings on contraception, pregnancy, and breast feeding
- HCP's knowledge of the risk minimization activities to be undertaken including type, duration, and frequency of monitoring required and appropriate interventions for suspected immune thrombocytopenic purpura (ITP) or anti-Glomerular Basement Membrane (anti-GBM) or thyroid disorder

No identifiable data regarding patients or HCPs were collected.

5.3 DIFFERENCES IN QUESTIONNAIRES AND SCORING

The protocol was amended once (Protocol version identifier 1.8, 27 February 2017; see **Error! Reference source not found.**) to facilitate the interpretation of the data. The following changes were made:

- Based on the results from Wave 1, the wording of some of the questions was updated for Wave 2 to ensure that for all questions only 1 answer could be chosen, instead of multiple answers that were to be selected in some questions in the Wave 1 survey.
- In Wave 2, some questions were omitted and some were newly introduced.
- A threshold of 70% was defined as 'adequate' knowledge.

6 RESULTS

6.1 DEMOGRAPHIC RESULTS

Over the 2 waves, the survey was conducted in 149 HCPs 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 (58% Wave 1, 60% Wave 2) considered themselves an MS specialized neurologist. Most participants (66% Wave 1, 67% Wave 2) treated at least 100 patients with MS in a typical year, and most (62% Wave 1, 64% Wave 2) had initiated LEMTRADA with a patient within the last month.

6.2 PRIMARY ANALYSIS

6.2.1 Awareness of HCP and Patient Educational Materials

The majority of HCPs who participated in both Waves reported that they had received and reviewed the HCP educational materials (Table 1, Q11, Q12, Q13). In Wave 2, 83% reported reading more than half of the HCP guide, 83% reported they always or usually use the HCP checklist, and 63% reported they always or usually review the SmPC (Q12a, Q12b, Q13a; question was not asked in Wave 1).

With regard to Patient Educational Materials, the majority of HCPs were aware of the availability of the Patient Guide and the Patient Alert Card (Table 1, Q14). Few responded that none of the mentioned materials were available. In addition, in Wave 2 the majority (80%) of HCPs confirmed that they had reviewed the Patient Educational Materials themselves before giving them to patients (Q14a; question was not asked in Wave 1).

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

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.11 Have you received and reviewed the HCP Guide?	Yes	56 (76%)	59 (79%)
	No	6 (8%)	4 (5%)
	Don't remember	12 (16%)	12 (16%)
Q.12a How much of the HCP Guide have you read?[a]	All of it	NA	33 (56%)
	More than half of it	NA	16 (27%)
	About half of it	NA	9 (15%)
	Less than half of it	NA	1 (2%)
Q.12 Have you received and reviewed the HCP Checklist?	Yes	56 (76%)	56 (75%)
	No	6 (8%)	4 (5%)
	Don't remember	12 (16%)	15 (20%)
Q.12b How often do you use the HCP Checklist?[b]	Always	NA	25 (45%)
	Usually	NA	21 (38%)
	Sometimes	NA	6 (11%)
	Hardly	NA	4 (7%)
	Never	NA	0
Q.13 Have you received and reviewed the SmPC?	Yes	66 (89%)	60 (80%)
	No	2 (3%)	4 (5%)
	Don't remember	6 (8%)	11 (15%)
Q.13a Since you started prescribing LEMTRADA, how often do you review the SmPC?[c]	Always	NA	12 (20%)
	Usually	NA	26 (43%)
	Sometimes	NA	16 (27%)
	Rarely	NA	6 (10%)
Q.14 What patient educational materials are available for patients prescribed LEMTRADA?[d]	**Patient Guide + Patient Alert Card ✓**	42 (57%)	**61 (81%)**
	Patient Alert Card + special women's brochure	NA	8 (11%)
	Patient Guide + special women's brochure	NA	3 (4%)
	None of the above	NA	3 (4%)
	Patient Guide	62 (84%)	NA
	Patient Alert Card	57 (77%)	NA
	Patient Checklist	43 (58%)	NA
	Package Leaflet	57 (77%)	NA
Q.14a Did you review any of the patient materials yourself, before you gave them to patients?	Yes	NA	60 (80%)
	No	NA	15 (20%)

HCP = Healthcare Provider; NA = Not asked in the questionnaire; SmPC = Summary of Patient Characteristics
a Answered by respondents who have received and reviewed the HCP Guide
b Answered by respondents who have received and reviewed the HCP Checklist
c Answered by respondents who have received and reviewed the SmPC
d This is a multiple choice question in Wave 1 and therefore the total is >100%.
✓ Correct answer (Wave 2)

6.2.2 Knowledge of the key points of the educational materials

HCP knowledge of the key points of the educational materials was surveyed in both Wave 1 and Wave 2. Percentages of 'correct' answers are provided in Table 2. Note that for the purpose of this report, some alternative 'correct' answers were considered as an 'acceptable' answer, as explained in the Comments column. The table is divided in 3 sections: acceptable responses in both waves, acceptable responses in either Wave 1 or Wave 2, and unacceptable responses in both waves.

Topics where HCP knowledge was high in both Wave 1 and Wave 2 included knowledge of contraindicated conditions (Q16) and contraindicated treatments (Q17), the appropriate medical intervention if the patient had suspected ITP (Q27), and the need to counsel patients on the essential topics (Q29).

There was a difference between waves in scores for the majority of questions, with the scores only acceptable for one of the waves. These questions include risks to be discussed at first prescription of LEMTRADA (Q15), tests to be conducted before prescribing LEMTRADA (Q18), required wait period following vaccination (Q19), monitoring activities for autoimmune events (Q20, Q21, Q22, Q24), timing for the use of contraception in women of childbearing potential (Q26), and appropriate medical intervention for suspected nephropathy (Q28).

Responses to the time to conduct liver function tests (Q23) or urine protein creatinine ratio tests (Q25) were unacceptable in both waves.

It is difficult to assess whether HCPs in either Wave 1 or Wave 2 had better knowledge than those in the other wave because of the way the questions were structured in each wave. For example, in Q15, Wave 1 required that 5 of 5 topics had to be selected to score 'completely correct'. A total of 58% of Wave 1 HCPs answered completely, but 82% selected at least 4 of the 5 correct topics, which is consistent with the Wave 2 score of 85%. In Q18, 59% Wave 1 HCPs answered correctly, and an additional 28% selected 3/4 of the topics, bringing the total (87%) well above the Wave 2 score of 59%.

Table 2 - Knowledge About Key Points of the Educational Materials (Responses by HCPs Who Reported Receiving and Reviewing All HCP Educational Materials

Question (abbreviated)	Correct answers		
	Wave 1	Wave 2	Comments
Acceptable responses in both Wave 1 and Wave 2 (≥70% correct)[a]			
Q16: Contraindicated conditions	85%	85%	
Q17: Contraindicated treatments	72%	71%	
Q27: What to do if a patient has suspected immune thrombocytopenic purpura	91%	87%	
Q29: Counseling for patients treated with LEMTRADA	80%	91%	
Acceptable responses in either Wave 1 or Wave 2[b]			
Q15: Risks to be discussed at first prescription of LEMTRADA	58%	85%	In Wave 1, 5 topics had to be selected to answer completely (58% of HCPs), but 82% selected at least 4 out of the 5 topics.
Q18: Tests to be conducted before prescribing LEMTRADA	59%	59%	In Wave 1, 4 correct topics had to be selected out of 6 possible choices; an additional 28% selected 3 of the 4 correct topics. In Wave 2, the remainder of respondents selected a response option that contained only 1 of the 2 correct tests, incorrectly identifying urine protein creatinine test or cholesterol.
Q19: Required wait period following vaccination	72%	65%	In Wave 1, '6 weeks OR 8 weeks' was the correct answer. In Wave 2, 40% selected '6 weeks', which was the correct answer, but an additional 25% selected '6 months', indicating 65% of HCPs would wait at least 6 weeks.
Q20: When to check serum creatinine levels	54%	76%	In Wave 1, 2 topics had to be selected to answer completely (54% of HCPs), but 77% selected one correct answer (before prescribing) and 77% selected another correct answer (monthly until 48 months following treatment). Of note, serum creatinine was part of the correct answer of earlier question Q18 for Wave 1.
Q21: When to check complete blood count with differential	61%	68%	In Wave 1, 2 topics had to be selected to answer completely (61% of HCPs), but 81% selected one correct answer (before prescribing) and 72% selected another correct answer (monthly until 48 months following treatment). Of note, complete blood count was part of the correct answer of earlier question Q18 for Wave 1.

Question (abbreviated)	Correct answers		
	Wave 1	Wave 2	Comments
Q22: When to check urinalysis with microscopy	47%	49%	In Wave 1, 2 topics had to be selected to answer completely (47% of HCPs), but 70% selected one correct answer (before prescribing) and 58% selected another correct answer (monthly until 48 months following treatment). Of note, urinalysis was part of the correct answer of earlier question Q18 for Wave 1. In Wave 2, an additional 21% responded that monthly urinalysis until 48 months was required, but failed to recall that this was also required prior to prescription.
Q24: When to check thyroid function tests	46%	55%	In Wave 1, 2 topics had to be selected to answer completely (46% of HCPs); 85% selected one correct answer (before prescribing) and 54% selected another correct answer (every 3 months until 48 months following treatment). An additional 30% selected a more stringent answer (monthly until 48 months after the last infusion); combining the 'correct' response with the more stringent one demonstrates that 76% of Wave 1 HCPs understand thyroid function tests should be conducted at least every 3 months. Of note, thyroid function was part of the correct answer of earlier question Q18 for Wave 1. In Wave 2, an additional 36% of HCPs selected a more stringent answer (monthly instead of every 3 months until 48 months after the last infusion); combining the 2 responses demonstrates that 91% of Wave 2 HCPs understand thyroid function tests should be conducted at least every 3 months.
Q26: Use of contraception in women of childbearing potential	70%	57%	While 70% was the cut-off, this can be considered sub-optimal knowledge given the seriousness of the topic. However, an additional 19% of the HCPs in Wave 1 and 21% of HCPs in Wave 2 selected the more stringent answer (48 months – instead of 4 months – after each treatment), which is a longer period than required and may reflect an HCP's scientific opinion to tell patients to wait until the "at risk" period of autoimmune disease is over.
Q28: What to do if a patient has suspected nephropathy	80%	53%	In Wave 2, 47% selected an alternative answer that included 'refer/send the patient to nephrologist immediately' plus some extra features that may be appealing to HCPs, such as asking the patient to come in as soon as possible and conducting urine tests; combining the 2 responses demonstrates that nearly all of HCPs understand that patients with suspected nephropathy should be referred to a nephrologist immediately.
Unacceptable in either Wave			
Q23: When to conduct liver function tests	22%	28%	No liver function testing is required, but most HCPs (77% Wave 1, 73% Wave 2) seemed to err on the side of caution and mentioned that periodic testing is required.

Question (abbreviated)	Correct answers		
	Wave 1	Wave 2	Comments
Q25: When to conduct urine protein creatinine ratio tests	28%	27%	No urine protein creatinine ratio testing is required, but most HCPs (76% Wave 1, 60% Wave 2) seemed to err on the side of caution and mentioned that periodic testing is required.

HCP = Healthcare Provider

a Per protocol, acceptable = 70% correct

b Additional answers as noted in the Comment were considered as contributing to an 'acceptable' answer for the purposes of this report.

6.2.3 Summary of secondary analyses

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

For subgroup comparison by country, in both waves HCPs from the UK scored lower than HCPs from other countries on several topics, but the topics were different between the 2 waves. In Wave 1, HCPs from the UK scored lower than HCPs from other countries on potential risks to be discussed at first prescription, conditions where LEMTRADA is contraindicated, wait period after patient vaccination, when to check serum creatinine and when to conduct urinalysis with microscopy, and what to do if there is suspected nephropathy. In Wave 2, UK HCPs scored lower than HCPs from other countries on awareness of the available educational materials including the patient materials, treatments in which LEMTRADA is contraindicated, and the frequency and duration of monitoring tests.

In both waves, more MS specialized neurologists (74% Wave 1, 87% Wave 2) recalled having received and reviewed the HCP educational materials than did general neurologists (or neurologist with a sub specialism other than MS as surveyed in Wave 2) (55% Wave 1, 67% Wave 2), suggesting either that the materials are more likely to reach MS specialist neurologists than general neurologists, or that MS specialist neurologists are more likely to have reviewed the materials. However, with few exceptions, there were only minor or no differences between the 2 groups in nearly all secondary comparisons.

In Wave 1, there was a trend for LEMTRADA prescription: HCPs who had initiated LEMTRADA in a patient within the last month were more likely to report having received and reviewed the materials (74%) than those who had not initiated LEMTRADA within the last month (54%). However, in Wave 2 there was no discernable overall pattern for initiating LEMTRADA within the past week (76%), within the last month not including the first week (83%), between 1 and 3 months ago (68%), or more than 3 months ago (90%).[1]

Awareness of the Patient Educational Materials among HCPs who had received and reviewed all the HCP educational materials was 65% in Wave 1 and 90% in Wave 2.

[1] In Wave 2, responses for HCP guide, HCP checklist, and SmPC were compiled separately. The percentages reported here are an average of the responses for each item.

7 DISCUSSION

7.1 KEY RESULTS

In both waves, the findings of this survey indicate that HCPs received and read the HCP guide, HCP checklist, and the SmPC, and they were familiar with the Patient Guide and Patient Alert Card. In Wave 1 and Wave 2 (respectively), 76% and 79% reported receiving and reviewing the HCP guide, 76% and 75% reported receiving and reviewing the HCP checklist, and 89% and 80% reported receiving and reviewing the SmPC. In Wave 2, when HCPs were asked to estimate how much of the materials they had read, 83% reported reading more than half of the HCP guide, 83% reported they always or usually use the HCP checklist, and 63% reported they always or usually reviewed the SmPC. This demonstrates that these materials have a well-established place in the HCPs' practice for risk minimization activities. With regard to patient educational materials, 79%[2] and 81% (Wave 1, Wave 2, respectively) of HCPs were aware of the available patient materials, and 80% of HCPs in Wave 2 reported to have read them before giving them to patients.

HCPs were aware of the most important risks and were aware of how to counsel their patients on essential topics. Questions on which HCPs scored ≥70% were rather similar between Wave 1 and Wave 2. Those topics in Wave 1 included contraindicated conditions and treatments, the required wait period following vaccination, the appropriate medical intervention if the patient has suspected ITP, and the need to counsel patients on the importance of contraception and risks and the importance of keeping monthly monitoring appointments. Those topics in Wave 2 included risks to be discussed at first prescription of LEMTRADA, contraindicated conditions and treatments, when to check serum creatinine levels, the appropriate medical intervention if the patient has suspected ITP, and the need to counsel patients on the importance of contraception and risks and the importance of keeping monthly monitoring appointments.

HCP knowledge was lower than the 70% limit for acceptability in certain areas and again there were similarities between Wave 1 and Wave 2. Those topics in Wave 1 included risks to be discussed at first prescription of LEMTRADA, tests to be conducted before first prescription of LEMTRADA, timing for the use of contraception for women of childbearing potential, knowledge of time-points at which monitoring activities for autoimmune events should be conducted, and and knowledge of tests included in the risk management plan. Those topics in Wave 2 included the required wait period following vaccination, the appropriate medical intervention for suspected nephropathy, timing for the use of contraception for women of childbearing potential, when to check complete blood count with differential, knowledge of time-points at which monitoring activities for autoimmune events should be conducted, and knowledge of tests included in the risk management plan.

[2] Average of Wave 1 scores for receiving and reviewing the HCP guide, HCP checklist, and SmPC.

It is difficult to assess whether HCPs in either Wave 1 or Wave 2 had better knowledge than those in the other wave because of the way the questions were structured in each wave. As already mentioned, for some Wave 1 questions more than 1 answer was required, so that HCPs could get partial credit for an answer. For example, in Q15 (Risks to be discussed at first prescription of LEMTRADA), 58% of HCPs in Wave 1 selected all 5 of the correct answers, but 82% selected at least 4 out of 5 of the correct answers, which is consistent with the Wave 2 score of 85%. In Q18 (Tests to be conducted before prescribing LEMTRADA), 59% of HCPs in Wave 1 selected all 4 of the correct answers, and an additional 28% selected 3/4 of the answers, bringing the total (87%) well above the Wave 2 score of 59%.

There are several items that may have influenced both the Wave 1 and Wave 2 survey results that merit discussion.

As mentioned above, many of the questions in Wave 1 asked HCPs to select from multiple choices, and there may have been more than 1 correct choice. All of the correct choices had to be selected to score the answer as 'completely correct'. This was recognized as a difficult task to perform from memory, and in the amended protocol for Wave 2, HCPs were asked to select only 1 response that answered the question in the best way.

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, in Q28 (what to do if the HCP suspects that a patient has nephropathy), the correct answer was, 'Refer the patient to a specialist (nephrologist) immediately' and was selected by 80% of HCPs in Wave 1 but only 53% of HCPs in Wave 2. However, an alternative answer, 'Ask the patient to come in as soon as possible, conduct urine tests and if suspected nephropathy refer/send the patient to nephrologist immediately', holds not only the correct answer but extra features (asking the patient to come in as soon as possible and conducting urine tests) that may be appealing or even standard practice for some HCPs. In fact, this alternative answer was selected by 20% of HCPs in Wave 1 and 47% of HCPs in Wave 2. Therefore, even though each answer was selected by <70% of HCPs, combining the correct answer and the cautious but incorrect answer resulted in all HCPs in both waves reporting that they would refer the patient to a specialist. In fact, many subgroups also scored high on this particular alternative answer, sometimes even higher than on the correct answer, which supports the speculation that the presentation of the answer may have been confusing.

In several cases, some of the alternative answers in both waves were more stringent than the 'correct' answer, which could mean that HCPs were using or responding with more caution than required. In addition to the possibility of HCPs erring on the side of caution when responding to the questions, it may be that some HCPs have adapted their own monitoring schedules and conduct tests more often than what was considered as 'correct' in the survey. Indeed, the majority of HCPs provided answers that were correct OR more cautious (ie, more often testing). For example, an HCP who reports performing thyroid tests monthly (an 'incorrect' survey response) is responding in a more thorough manner than one who reports performing thyroid tests every 3 months (the 'correct' survey response). Therefore, although their behavior is clinically sound, the responses would be interpreted as 'incorrect'. Similarly, regarding the length of time that women of childbearing potential should use effective contraceptive measures (Q26), 70% of HCPs in Wave 1 and 57% of HCPs in Wave 2 correctly selected this answer. However, another

19% in Wave 1 and 21% in Wave 2 thought contraception should be used for at least 48 months following each treatment, which is a more stringent answer.

Also, the lower scores about timing of clinical assessments might be explained by the role of support staff having logistical responsibilities, like scheduling follow-up testing. Sometimes LEMTRADA treatment is given in expert centers far away from patients' homes. MS specialists and neurologists have in some cases arranged with the patients' general practitioner or a local neurologist to perform the monitoring tests locally, and this will influence the routine knowledge of the prescribing HCPs and therefore their responses to the pertinent questions. Finally, infusion clinics often employ MS nurse specialists and/or other support staff with specific responsibilities. In well-organized clinics the neurologist prescribes a LEMTRADA monitoring package but not the individual tests. The nurses and/or support staff are highly involved and in some places take care of ordering the clinical tests, which in this particular case with LEMTRADA follow a pre-defined schedule.

The HCP population was heterogeneous (eg, area of specialty, work setting, experience with LEMTRADA, etc). Some of these HCPs – particularly the general neurologists – would be responsible for a wide range of patients with many different diagnoses and medication risks; those HCPs may not be able to easily recall all potential risks to be discussed and time points of tests to be conducted without having to refer to the educational materials or other resources.

Lastly, the HCPs were asked to answer the survey without referring to the actual materials, which may not reflect actual daily clinical practice where they may even be encouraged to reference and review the materials during patient care.

7.2 SUBGROUP ANALYSES

The descriptive subgroup comparisons were generally consistent with the primary analysis results in demonstrating that review of all HCP educational materials leads to improved knowledge, further supporting the efficacy of the materials. Ensuring that all HCPs receive the materials and reinforcing the importance of the HCP educational materials may increase knowledge in all areas. There were, however, a few interesting differences within subgroups.

In Wave 1, there was a trend for LEMTRADA prescription: HCPs who had initiated LEMTRADA in a patient within the last month were more likely to report having received and reviewed the materials (74%) than those who had not initiated LEMTRADA within the last month (54%). This finding may reflect greater recollection of the materials among those who have accessed them more recently, meaning that those HCPs who selected 'no' or 'don't remember' to receiving and reviewing the materials may have received or reviewed them too long ago to properly recall. However, in Wave 2 there was no discernable overall pattern for initiating LEMTRADA within the past week (76%), within the last month not including the first week

(83%), between 1 and 3 months ago (68%), or more than 3 months ago (90%).[3] If one supposes that HCPs who most recently prescribed LEMTRADA might have accessed the educational materials more recently and therefore would have a greater recollection of the materials, then this finding is surprising.

Subgroup comparisons also indicated that MS specialized neurologists had more knowledge about the HCP educational materials than did general neurologists. However, in nearly all secondary comparisons, there were only minor or no differences between the 2 groups. Despite the fact that fewer general neurologists reported having received and reviewed the HCP educational materials, it may be that those who did receive the materials used them more often, demonstrating that the materials do fulfill their purpose.

HCPs based in community hospitals were more knowledgeable about LEMTRADA contraindications and specific tests and monitoring activities than those based in university hospitals. This finding may be because doctors in university hospitals are more likely to refer patients back to community hospitals following LEMTRADA infusions. Community-based HCPs may use the educational materials more frequently as part of their monitoring responsibilities and therefore would be more familiar with the contraindications and monitoring activities.

Lastly, the descriptive subgroup comparisons showed one surprising trend among countries. The results warrant mention here as use of LEMTRADA is highest in UK compared to other countries involved in the survey. HCPs from the UK had the poorest knowledge in the following topics: (Wave 1) potential risks to be discussed at first prescription, where LEMTRADA is contraindicated, wait period after patient vaccination, when to check serum creatinine and when to conduct urinalysis with microscopy, and what to do if there is suspected nephropathy; (Wave 2) awareness of the available materials, including the patient materials, potential risks to be discussed at first prescription, treatments where LEMTRADA is contraindicated, when to check serum creatinine and when to conduct complete blood count with differential, and knowledge of the type of counseling to be provided to LEMTRADA patients. This trend may be at least partly due to the active role MS nurses play in the UK clinics in patient treatment, preparation, and education. In larger centers, MS nurses may be tasked with patient counseling and logistics, and/or staff physicians may delegate such tasks to junior physicians.

7.3 STRENGTHS AND LIMITATIONS

The strengths of this comprehensive survey in both Wave 1 and Wave 2 include the potential reach of HCPs for recruitment (there were more than 600 clicks on each survey's website link), the large number of unique responses (N=149), 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 prescription. The completion rate was high: in Wave 1, all

[3] In Wave 2, responses for HCP guide, HCP checklist, and SmPC were compiled separately. The percentages reported here are an average of the responses for each item.

eligible HCPs completed the survey (100%), and in Wave 2, only 4 HCPs who began the survey quit without completing (95%).

Limitations of this survey include the wording of survey questions that may have misled HCPs to provide answers that were later deemed 'incorrect' or 'incomplete' (when the HCP may in reality have sound clinical knowledge). The use of a cross-sectional design made it difficult to determine whether the HCP 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, motivation, or greater experience with the drug. In addition, the survey targeted only the prescribing HCP and therefore in some cases may not have reached the population directly involved in the patient treatment, preparation, and education who may be accessing the educational materials most often. Especially in larger centers, MS nurses or junior physicians may play a dominant role in the actual treatment logistics, and therefore they would be the ones who are using the educational materials most often. Lastly, because of the (relatively) low number of participants enrolled in the survey, statistical analyses could not be performed, allowing only for descriptive results. All data were self-reported, and there was no opportunity to verify source data. Finally, a convenience sample (non-randomized) was used, rather than a random sample, which means that the findings may be subject to bias, thereby limiting the generalizability of the results to the overall population of HCPs prescribing LEMTRADA. However, it should be noted that a random sample is not possible given that there is not a database of names and addresses of LEMTRADA HCPs that could be accessed in order to randomly select HCPs.

The caveat of a relatively small number of physicians and the fact that the participants were asked to answer the questions without referring to the educational materials should be considered when interpreting the results of the study.

8 CONCLUSION

The survey findings suggest that the HCP educational materials are effective in ensuring HCPs prescribing LEMTRADA have an adequate knowledge of risk minimization activities. A total of 76% and 79% (Wave 1, Wave 2, respectively) reported receiving and reviewing the HCP guide, 76% and 75% reported receiving and reviewing the HCP checklist, and 89% and 80% reported receiving and reviewing the SmPC. Of these (Wave 2), 83% reported reading more than half of the HCP guide, 83% reported they always or usually use the HCP checklist, and 63% reported they always or usually reviewed the SmPC when dealing with alemtuzumab (eg, when prescribing or consulting patients). This demonstrates that these materials have a well-established place in the HCPs' practice for risk minimization activities. In addition, 79% and 81% (Wave 1, Wave 2, respectively) of HCPs were aware of the available patient materials, and 80% of HCPs in Wave 2 reported to have read them before giving them to patients.

There appears to be a link between use of the materials and the knowledge on LEMTRADA and its risks. The overall results show adequate knowledge and behavior of the HCPs around identification of potential serious adverse events and behavior when symptoms occur, based on a 70% threshold for correct responses. This suggests that the materials are effective in ensuring the safe use of LEMTRADA.

However, there is room for improvement in some areas of HCP knowledge. Therefore, the need remains to ensure not only that all HCPs who prescribe LEMTRADA, and support staff who are responsible for monitoring, receive the HCP educational materials but that they understand the importance of them as well.

Overall, the MAH considers that the results of the Wave 1 and Wave 2 HCP knowledge and understanding survey confirm that the educational materials are overall effective in supporting HCP knowledge relating to the safe use of LEMTRADA. No changes to the RMP are warranted based on these results.

ANNEXES

List of stand-alone documents

Annex 1

Number	Document reference number	Date	Title
1	Post Authorization Safety Study (PASS) Interim Report (Wave 1), v6.0	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), v1.0	13 November 2018	Knowledge Survey to assess the effectiveness of educational materials among healthcare professionals who prescribe LEMTRADA® (alemtuzumab)

POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

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

COMPOUND: Alemtuzumab

STUDY NAME: LEMTRADA® EU-RMP Survey in HCPs

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

Version Number:	1.0		
Date:	13 November 2018	Total number of pages:	77

PASS Information

Title	Knowledge Survey to assess the effectiveness of educational materials among healthcare professionals who prescribe 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)	Genzyme Therapeutics Ltd
Joint PASS	No
Research question and objectives	The overall objective of the survey is to assess descriptively the knowledge level of Healthcare Professional (HCPs) with regard to educational messages and thus the effectiveness of the educational materials to support the safe use of LEMTRADA. Research questions: 1. What is the HCP's understanding and awareness of the risks associated with use of LEMTRADA? 2. What is the HCP's knowledge of the key safety messages in the content of the HCP guide and HCP checklist? 3. What is the HCP's knowledge and understanding of the risk minimization activities to be undertaken in relation to LEMTRADA?
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
MAH/MAH REPRESENTATIVE contact person	Jeri Nijland Regulatory Affairs Senior Associate, neurology, GRA EU Paasheuvelweg 25, 1105 BP, AMSTERDAM The Netherlands +31 (0) 20 245 3693 +31 (0) 6 1083 5854 Jeri.Nijland@sanofi.com

TABLE OF CONTENTS

1 ABSTRACT

Title

Knowledge Survey to assess the effectiveness of educational materials among healthcare professionals who prescribe LEMTRADA (alemtuzumab)

Keywords

LEMTRADA, audit, risk minimization materials, effectiveness

Rationale and background

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

The risk management knowledge survey assesses the effectiveness of the educational materials for HCPs as part of the RMP amongst HCPs who have prescribed LEMTRADA. Very little published research exists relating to the evaluation of RMPs, however, the methods of existent published literature were used to guide proposals wherever possible.

Research question and objectives

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

Study Design

This was an international, cross-sectional survey, recruiting from 9 countries across the EU. The study was 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 second wave of the survey (Wave 2) was conducted in the UK, Germany, Italy, Spain, Greece, Belgium, and the Netherlands. HCPs were recruited over a 6-week period. The start of data collection for Wave 2 was October 2017; end of data collection for Wave 2 was January 2018.

Setting

- Site and patient selection: A convenience (ie, non-random) sample of HCPs involved in the treatment of multiple sclerosis (MS) patients with LEMTRADA, recruited from Germany, Italy, Spain, Greece, Belgium, and the Netherlands
- Data collection: EU Sanofi Genzyme marketing supplied data regarding the distribution of neurologists and MS subspecialists in the participating countries. All other data was collected via the HCP self-reporting in a structured online questionnaire.

Patients and study size, including dropouts

The sample size was based on an estimate of 360 LEMTRADA HCPs in the countries where the study was planned. A 15% to 20% response rate was expected, which was equivalent to 60 to 70 HCPs.

Variables and data sources

- Variables and evaluation criteria: The following elements were collected and assessed quantitatively:
  1. The HCP's understanding and awareness of the risks associated with use of the product
  2. The HCP's knowledge of the key points in the content of the HCP guide and HCP checklist
  3. The HCP's knowledge of the risk minimization activities to be undertaken
- Data analyzes: Descriptive analyzes were performed. For all analyzes, a threshold of 70% was defined as 'adequate' knowledge.

Results

The survey was conducted in 75 HCPs from 7 countries (UK, Germany, Italy, Spain, Greece, Belgium, and the Netherlands). Forty-five (60%) HCPs were MS specialists. The majority of HCPs (n=50; 67%) treated at least 100 patients with MS in a typical year. Forty HCPs (64%) had initiated LEMTRADA treatment with at least 1 patient within the last month.

Key results from this survey include the following:

- The majority (>75%) of HCPs recalled receiving and reviewing the HCP materials package, including the HCP Guide, HCP checklist, SmPC, and Patient Guide and Patient alert card. In general, the HCPs' understanding and awareness about the risks associated with the use of LEMTRADA was satisfactory, and within only few areas were the number of correct answers considerably <70%.
- A total of 85% of HCPs were aware of the important risks – specifically immune thrombocytopenic purpura (ITP), nephropathies, thyroid conditions, and pregnancies – and contraindications in relation to LEMTRADA treatment.

- Ninety-one percent of HCPs indicated that they were aware of the need to counsel patients on coping with MS, the importance of contraception, and the risks and importance of monthly monitoring appointments.
- HCP knowledge of risk minimization activities for the important risks varied:
  - Knowledge of appropriate intervention if the patient had suspected ITP was 87%.
  - Knowledge of appropriate intervention for suspected nephropathy was 53%; however, an additional 47% of HCPs selected an alternative answer that contained the correct response – 'refer the patient to a nephrologist' – among some other interventions.
  - A total of 57% of HCPs were aware of the need for women of childbearing potential to use contraception for at least 4 months following each infusion course (5%, 16% and 21% of HCPs reported that contraception should be used during treatment and for at least 5 days, 30 days, and 48 months following treatment, respectively).
  - Correct knowledge of the specific timepoints at which monitoring activities for autoimmune events should be conducted was lower (<70%).

Discussion

HCP knowledge was mostly sufficient (≥70%), although there were some areas in which the number of correct answers was lower (<70%). Potential explanations for less than adequate responses include the following:

- The HCP population was heterogeneous (eg, area of [sub-]specialty, work setting, experience with LEMTRADA, etc.), so that it may be that some HCPs have adapted their own monitoring schedules, may be responsible for a wide range of patients with many different diagnoses and medication risks, or may have arranged with the patients' general practitioner or local neurologists to perform the tests.
- The HCPs had to answer the survey questions without referring to the actual materials, which may not reflect actual practice where they can reference and review the materials at any time to check the proper risk minimization measures.
- In many clinics, nurses and/or support staff are highly involved, taking care of ordering the paraclinical examinations, making sure patients show up in a timely manner, and doing some of the patient counseling. In those clinics it is not important for the doctors to keep track of specific timepoints but to act on test results and symptoms when needed.
- The wording of the questions presented to the HCPs may have been confusing for certain questions. In some cases where responses were deemed 'incorrect' according to the survey, HCPs were in fact answering cautiously and reporting, for example, that they would test more frequently than was required for a correct answer, or selecting an response that contained the correct answer plus some extra features that may be appealing to HCPs.

Conclusion

The survey findings suggest that the HCPs prescribing LEMTRADA have an adequate knowledge of risk minimization activities. There appears to be a link between use of the materials and the knowledge on LEMTRADA and its risks, as comparison of subgroups indicated that HCPs who had received and reviewed all HCP materials, compared with those who had not reviewed the materials or did not recall receiving them, had greater knowledge of essential topics on which to counsel patients and on important risk minimization activities. The MAH considers that the results of the Wave 2 HCP knowledge and understanding survey confirm that the educational materials are overall effective in supporting HCP knowledge relating to the safe use of LEMTRADA. No changes to the RMP are warranted based on these results.

Study Personnel

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: 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.

Names and affiliations of Principal Investigators

Not applicable.

National coordinators

Not applicable.

2 LIST OF ABBREVIATIONS

AE:	adverse event
anti-GBM:	anti-Glomerular Basement Membrane
CBC:	complete blood count
EU:	European
HCP:	Healthcare Professional
HIV:	human immunodeficiency virus
ITP:	immune thrombocytopenic purpura
MAH:	Marketing Authorization Holder
MS:	multiple sclerosis
Q:	question
RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
TSH:	thyroid stimulating hormone
UK:	United Kingdom

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. Ipsos was also responsible for the recruitment of HCPs 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	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	--

6 RATIONALE AND BACKGROUND

6.1 BACKGROUND

Safety profile

For the safety profile of alemtuzumab reference is made to the current version of the Summary of Product Characteristics (SmPC). Of note, in the most recent version of the SmPC, several revisions have been made compared to the version valid at the time of the survey. None of these revisions significantly impacted the safety topics covered in the survey.

Description of LEMTRADA Risk Management Plan

The LEMTRADA RMP includes risk minimization measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimization.

The primary objectives of the educational materials are to:

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

HCPs receive all educational materials in hard copy. The HCP educational package consists of the SmPC, HCP materials, and patient materials. The HCP materials consist of an HCP Guide and an HCP Checklist (one per HCP). HCPs also should be familiar with the Patient Educational Materials: Patient Guide and Patient Alert Card.

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

The HCP survey focused on the HCP materials. HCPs use these materials to ensure they understand and communicate to patients adequately about the following risks:

- Serious infections (not a part of the survey, which was conducted at time when the previous version of the HCP educational materials was available; the currently available educational materials have been updated with serious infections)
- Autoimmune conditions, including:
  - ITP
  - Nephropathies including anti-Glomerular Basement Membrane (anti-GBM) disease
  - Thyroid disorders

- Additional items that HCPs need to be aware of:
  - Patients' risks of developing the aforementioned autoimmune conditions and the necessary monitoring procedures (blood and urine testing, watching for signs and symptoms). Patient counseling should be part of a benefit-risk discussion prior to LEMTRADA treatment and should include the risk for autoimmune conditions, the need for monitoring for these risks, and how to detect any signs or symptoms.
  - Patient educational materials and how to access them.
  - The HCP should follow the recommended patient screening, vaccination, and pretreatment programs.

Relevant published research

This study assesses the knowledge of HCPs who prescribe LEMTRADA about the items of the educational materials and thus the effectiveness of these materials to ensure the safe use of LEMTRADA.

This is the first study to assess the effectiveness of the LEMTRADA RMP educational materials. Historically, there have been few published studies reporting the effectiveness of risk management interventions. A recent study showed greater knowledge of the risks of treatment among HCPs who had received an educational plan than those who had not (1). The methods of existing published literature were used to guide proposals wherever possible (2).

6.2 RATIONALE

This RMP assessment of effectiveness survey of HCP educational materials provides information relating to HCPs' understanding of the risk messages that are discussed in the education guide and SmPC for LEMTRADA prescribed for MS. It evaluates the HCPs' knowledge of RMP materials. The findings of this study may make an important contribution to the understanding of the effectiveness of the RMP strategy and the safe prescription of LEMTRADA.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTIONS

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

7.2 OBJECTIVES

7.2.1 Primary objectives

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

7.2.2 Secondary objectives

Not applicable.

8 AMENDMENTS AND UPDATES

The protocol was amended once between Wave 1 and Wave 2 (Protocol version identifier 1.8, 27 February 2017; see Annex 1) to reformat to current Sanofi standards. In addition, the following changes were made:

- Based on the results from Wave 1, the wording of some of the questions was updated for Wave 2 to ensure that for all questions only 1 answer could be chosen, instead of multiple answers to be selected in some questions in the Wave 1 survey.
- Some questions used in Wave 1 were omitted and some were newly introduced in Wave 2.
- A threshold of 70% was defined as '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 HCP guide and checklist) of HCPs involved in the treatment of MS using LEMTRADA. Survey data was collected online using structured questions where the response format was the selection of either multiple choice responses (in Wave 1 only) or a single response (in both Waves), as appropriate.

All survey tools (Questionnaire including 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. HCPs were recruited from these countries over an 11-week period. Start of data collection for Wave 1 was 21 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. HCPs were recruited over a 6-week period. The start of data collection for Wave 2 was October 2017; end of data collection for Wave 2 was January 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

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

I 01. HCP is a neurologist/ MS specialist.

I 02. HCP has prescribed LEMTRADA to at least 1 patient within the past 6 months.

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

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

E 01. HCP has not prescribed LEMTRADA within the past 6 months.

E 02. HCP has participated in Wave 1 of the survey.

9.3.2 Analysis populations

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

9.3.3 Modalities of HCP recruitment

HCPs in the selected EU countries involved in the treatment of MS patients receiving LEMTRADA were invited to take part.

Multiple approaches were used to recruit the HCPs:

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

HCPs provided informed consent and the data was anonymised for the Marketing Authorization Holder (MAH).

The Wave 2 target sample size was 75 LEMTRADA-prescribing HCPs.

9.4 VARIABLES

Knowledge was defined as awareness and understanding of important risk minimization information contained in the HCP educational materials (HCP guide, HCP checklist, and SmPC). 'Adequate' knowledge was defined as 70% or more HCPs correctly answered questions.

9.4.1 Data elements collected

The following elements were collected and assessed:

1. HCP characteristics including:
   a) Country
   b) Type of hospital
   c) Specialty
   d) Total number of MS patients under treatment

e) Number of patients prescribed LEMTRADA
f) Time since last prescription of LEMTRADA

2. The HCP's knowledge of the existence of:
   a) the HCP guide
   b) the HCP checklist
   c) the SmPC
   d) the Patient Guide
   e) the Patient Alert Card
3. The HCP's understanding and awareness of the risks associated with use of the product:
   a) ITP
   b) Kidney disorders
   c) Thyroid disorders
4. Knowledge of the key points in the content of the HCP guide, and HCP checklist:
   a) Contraindications
   b) Lists of tests to be conducted for the initial screening of the patient
   c) Vaccination
   d) Monitoring activities for the autoimmune events
   e) Special warnings on contraception and pregnancy
5. The HCP's knowledge of the risk minimization activities to be undertaken:
   a) Type of monitoring required (blood and urine, self-monitoring)
   b) Required duration and frequency for monitoring
   c) If ITP or anti-GBM or thyroid disorder is suspected, the HCPs should know that appropriate intervention should be promptly initiated, including immediate referral to a specialist, when needed

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

9.4.2 Potential confounding factors

1. Some HCPs may see only a small number of patients who are eligible to be prescribed LEMTRADA. Approximate number of patients ever treated with LEMTRADA were recorded and included as a variable for subgroup comparisons.
2. Length of time since last prescription of LEMTRADA to a patient was recorded and included as a variable for subgroup comparisons.

9.5 DATA SOURCES AND MEASUREMENT

9.5.1 Data sources

EU Sanofi Genzyme marketing supplied data regarding the distribution of neurologists and MS subspecialists in the participating countries. All other data was collected via the HCP self-reporting in the questionnaire.

The questionnaire was developed by psychologists with experience in developing questionnaires. Before implementation, the questions were pre-tested in a small sample of HCPs who treat patients with MS to ensure the appropriateness of the questions.

9.6 BIAS

All data were self-reported, and there was no opportunity to verify 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 HCPs prescribing LEMTRADA.

9.7 SAMPLE SIZE

A formal power calculation was not undertaken. The sample size was based on an estimate of 360 LEMTRADA HCPs in the countries where the study was planned. A 15% to 20% response rate was expected, which was equivalent to 60 to 70 HCPs.

Seventy-five HCPs were recruited and provided complete data. The survey link was clicked 668 times in total. A total of 280 potential participants were not eligible as their primary medical specialty was not "neurologist" or "MS neurologist". A further 207 potential participants were not eligible as the majority of their patients were not MS patients. Of the remaining 181 eligible potential participants, 22 did not meet other eligibility criteria (Section 9.3.1), 80 were over quota, and 4 did not complete the survey.

9.8 DATA TRANSFORMATION

9.8.1 Data collection schedule

Per protocol, data were collected online 18 months after 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.

HCPs who were recruited via methods as described in Section 9.3 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 HCP 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 HCP was ineligible (eg, had not prescribed 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 HCP was taken to a page thanking them for their participation.

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

9.8.2 Data collected

The following data was collected within the questionnaire.

Online questionnaire

- Country of practice
- Specialist area (general neurologist, MS specialised neurologist, or neurologist with sub specialism other than MS)
- Medications prescribed to MS patients
- Years in practice as a medical doctor and as a specialist
- Work setting (private/public healthcare or both) and time spent in various settings
- Number of MS patients seen in a year
- Prescription of at least 1 dose of LEMTRADA
- Length of time since last LEMTRADA initiation
- Number of patients ever treated with LEMTRADA
- Number of prescriptions for LEMTRADA written each month
- Whether HCPs had read and reviewed the HCP Guide/Checklist/SmPC and how much of each they have read
- How often the HCPs use/review the HCP Guide/Checklist/SmPC
- Knowledge of which patient educational materials are available to LEMTRADA patients
- Whether HCPs had reviewed any of the patient materials themselves before giving them to patients
- HCP knowledge relating to LEMTRADA Risk Management

Patient and HCP data

No identifiable data regarding patients or HCPs were collected.

9.9 STATISTICAL METHODS

9.9.1 Primary analysis

Descriptive analyzes only (eg, frequency distributions for each item) were performed on the overall population of participating HCPs.

9.9.2 Secondary analysis

The analysis was descriptive only. Subgroups compared were:

- Number of eligible patients HCPs treat with LEMTRADA
- Length of time since last prescription
- University or community hospital
- General neurologist or MS sub specialist
- Country

9.9.3 Interim analysis

No interim analysis was planned for this study. A report describing Wave 1 was prepared in 2016.

9.9.4 Main summary measures

Knowledge was described using frequencies and percentages. 'Adequate' knowledge was defined as 70% or more HCPs correctly answered questions.

9.9.5 Main statistical methods

Descriptive analyzes were performed. No statistical analysis was done.

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 HCPs 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 was self-reported; there was no opportunity to verify source data.

10 RESULTS

10.1 PARTICIPANTS

Table 1 summarises key characteristics of the sample. Questionnaires were completed by 75 HCPs across 7 countries. The distribution of HCPs across the countries was similar (n=10), with the exception of the UK (n=15).

Forty-five (60%) HCPs were MS specialists. The majority of HCPs (n=50; 67%) treated at least 100 patients with MS in a typical year. Forty HCPs (64%) had initiated LEMTRADA treatment with at least 1 patient within the last month.

Table 1 - Demographic characteristics of the HCP sample (N=75)

Category	Response option	n (%)
Country	UK	15 (20%)
	Germany	10 (13%)
	Italy	10 (13%)
	Spain	10 (13%)
	Greece	10 (13%)
	Belgium	10 (13%)
	Netherlands	10 (13%)
Specialist area	General neurologist	28 (37%)
	MS specialised neurologist	45 (60%)
	Neurologist with sub specialism other than MS	2 (3%)
Years in practice as a medical doctor	0 to 5 years	2 (3%)
	6 to 10 years	10 (13%)
	11 to 20 years	34 (45%)
	21 to 30 years	22 (29%)
	31 years or more	7 (9%)
Years in practice as a neurologist	0 to 5 years	15 (20%)
	6 to 10 years	22 (29%)
	11 to 20 years	26 (35%)
	21 to 30 years	9 (12%)
	31 years or more	3 (4%)

Category	Response option	n (%)
Healthcare system	Public healthcare only	52 (69%)
	Private healthcare only	12 (16%)
	Both public and private healthcare	11 (15%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic	23%
	MS clinic in a community hospital	22%
	Neurology clinic (other than MS) in an university hospital/specialty clinic	21%
	Neurology clinic (other than MS) in a community hospital	30%
	Office-based specialist	5%
Number of MS patients seen in a typical year	Up to 10 patients	--
	11-50 patients	4 (5%)
	51-99 patients	21 (28%)
	100-250 patients	29 (39%)
	>250 patients	21 (28%)
Number of patients treated with LEMTRADA	0-10 patients	48 (64%)
	11-25 patients	15 (20%)
	26-50 patients	9 (12%)
	>50 patients	3 (4%)
Last initiation of LEMTRADA	Within last week	11 (25%)
	Within last month	29 (39%)
	Within last 3 months	25 (33%)
	More than 3 months ago	10 (13%)
Number of prescriptions each month	<5	52 (70%)
	5-10	17 (23%)
	11-20	3 (4%)
	>20	2 (3%)

HCP = Healthcare Provider; MS = multiple sclerosis; UK = United Kingdom

10.2 MAIN RESULTS

10.2.1 Primary analysis

10.2.1.1 Knowledge about HCP and Patient Educational Materials

The majority of HCPs (79%) reported that they had received and reviewed the HCP educational materials (Table 2). Among them, 83% reported reading more than half of the HCP guide, 83%

reported they always or usually use the HCP checklist, and 63% reported they always or usually reviewed the SmPC.

With regard to Patient Educational Materials, the majority of HCPs (81%) were aware of the availability of the Patient Guide and the Patient Alert Card which was the correct answer (Table 2). The remaining 19% percent incorrectly answered that the available materials were either the "Patient Alert Card and special women's brochure" or the "Patient Guide and special women's brochure", or that none of the mentioned materials were available. The majority (80%) of HCPs confirmed that they had reviewed any of the Patient Educational Materials themselves before giving them to patients.

Table 2 - Knowledge about HCP Guide and Patient Educational Materials

Questionnaire item	Response option	n (%)
Q.11 Have you received and reviewed the HCP Guide? (N=75)	Yes	59 (79%)
	No	4 (5%)
	Don't remember	12 (16%)
Q.12a How much of the HCP Guide have you read?[a] (N=59)	All of it	33 (56%)
	More than half of it	16 (27%)
	About half of it	9 (15%)
	Less than half of it	1 (2%)
Q.12 Have you received and reviewed the HCP Checklist? (N=75)	Yes	56 (75%)
	No	4 (5%)
	Don't remember	15 (20%)
Q.12b How often do you use the HCP Checklist?[b] (N=56)	Always	25 (45%)
	Usually	21 (38%)
	Sometimes	6 (11%)
	Hardly	4 (7%)
	Never	--
Q.13 Have you received and reviewed the SmPC? (N=75)	Yes	60 (80%)
	No	4 (5%)
	Don't remember	11 (15%)
Q.13a Since you started prescribing LEMTRADA, how often do you review the SmPC? (N=60)[c]	Always	12 (20%)
	Usually	26 (43%)
	Sometimes	16 (27%)
	Rarely	6 (10%)
Q.14 What patient educational materials are available for patients prescribed LEMTRADA?	**Patient Guide + Patient Alert Card ✓**	**61 (81%)**
	Patient Alert Card + special women's brochure	8 (11%)
	Patient Guide + special women's brochure	3 (4%)
	None of the above	3 (4%)
Q.14a Did you review any of the patient materials yourself, before you gave them to patients?	Yes	60 (80%)
	No	15 (20%)

HCP = Healthcare Provider; SmPC = Summary of Patient Characteristics

a Answered by respondents who have received and reviewed the HCP Guide

b Answered by respondents who have received and reviewed the HCP Checklist

c Answered by respondents who have received and reviewed the SmPC

✓ Correct answer

10.2.1.2 Knowledge of the key points of the content

First prescription of LEMTRADA

The majority of HCPs (85%) correctly indicated that they were aware of the need to discuss ITP, active infections, and pregnancy and contraception (if applicable) (Table 3). A total of 10 (13%) HCPs correctly indicated at least 2 of the 3 'correct' topics to be discussed, and 1 HCP selected only 1 of the 3 topics, suggesting that the large majority of HCPs had, from memory, an excellent knowledge about important potential risks to be discussed with patients at first prescription.

Table 3 - Knowledge about topics to be discussed at first prescription of LEMTRADA (N=75)

Questionnaire item	Response option	n (%)
Q.15 At first prescription of LEMTRADA, patients need to be informed on nephropathies (including anti-GBM disease) and thyroid disorders. Which potential risks need to be discussed as well?	ITP, active infections and depression	6 (8%)
	Pregnancy & contraception (if applicable) and depression	1 (1%)
	ITP, active infections and pregnancy & contraception (if applicable) ✓	**64 (85%)**
	Pregnancy & contraception (if applicable), active infections and gastro-intestinal issues	4 (5%)

GBM = Glomerular Basement Membrane; ITP = immune thrombocytopenic purpura
✓ Correct answer

Knowledge of contraindications (conditions)

The majority (85%) of HCPs correctly indicated they were aware that contraindications for LEMTRADA include human immunodeficiency virus (HIV) and hypersensitivity to the active substance or any of the excipients (Table 4). Nine (12%) HCPs selected an answer containing HIV but the wrong alternative answer, and 2 (3%) HCPs did not select either desired answer.

Table 4 - Knowledge about contraindications for LEMTRADA - comorbid conditions (N=75)

Questionnaire item	Response option	n (%)
Q.16 In which patients with the following condition(s) is LEMTRADA contraindicated?	Human immunodeficiency virus (HIV) and ischemic heart disease	7 (9%)
	Human immunodeficiency virus (HIV) and hypersensitivity to the active substance or any of the excipients ✓	**64 (85%)**
	Human immunodeficiency virus (HIV) and depression	2 (3%)
	Ischemic heart disease and depression	2 (3%)

✓ Correct answer

Contraindications – treatments

The majority of HCPs (71%) correctly indicated that LEMTRADA is contraindicated in patients prescribed immunosuppressive therapy and antineoplastic therapy (Table 5). The remainder of respondents selected only 1 of the 2 desired response options, incorrectly identifying SSRIs or antiviral therapies.

Table 5 - Knowledge about contraindications for LEMTRADA – treatments (N=75)

Questionnaire item	Response option	n (%)
Q.17 Which of the following treatment is to be used cautiously due to potential combined effects on the patient's immune system with LEMTRADA?	SSRIs and immunosuppressive therapy	9 (12%)
	SSRIs and antineoplastic therapy	5 (7%)
	Antineoplastic therapy and antiviral therapies	8 (11%)
	Immunosuppressive therapy and antineoplastic therapy ✓	**53 (71%)**

SSRI = selective serotonin reuptake inhibitor
✓ Correct answer

Tests to be conducted before prescribing LEMTRADA

Responses to questions about knowledge of tests to be conducted before first prescription of LEMTRADA are shown in Table 6. The majority of HCPs (59%) were aware of the need to perform urinalysis with microscopy and thyroid function blood tests such as TSH. The remainder of respondents selected only 1 of the 2 desired response options, incorrectly identifying urine protein creatinine test or cholesterol.

Table 6 - Knowledge of tests to be conducted before first prescription of LEMTRADA (N=75)

Questionnaire item	Response option	n (%)
Q.18 According to the HCP Guide and HCP Checklist, serum creatinine and complete blood count with differential should be conducted before first prescription of LEMTRADA; what other tests are required?	**Urinalysis with microscopy and thyroid function tests such as TSH ✓**	**44 (59%)**
	Urinalysis with microscopy and urine protein creatinine test	5 (7%)
	Urine protein creatinine test and thyroid function tests such as TSH	24 (32%)
	Thyroid function tests such as TSH and cholesterol	2 (3%)

HCP = Healthcare Provider; TSH = thyroid stimulating hormone
✓ Correct answer

Wait period after last vaccination

A combined total of 49 HCPs (65%) correctly indicated that at least a 6-week wait period following vaccination is necessary before administering LEMTRADA (Table 7). Twenty-six HCPs selected a shorter period of time (2 weeks [4 HCPs; 5%] and 4 weeks [22 HCPs; 29%]).

Table 7 - Knowledge about wait period after vaccination (N=75)

Questionnaire item	Response option	n (%)
Q.19 How long after the patient's last vaccination should you wait before administering LEMTRADA?	2 weeks	4 (5%)
	4 weeks	22 (29%)
	6 weeks ✓	**30 (40%)**
	6 months	19 (25%)

✓ Correct answer

When to check serum creatinine levels

The majority of HCPs (76%) correctly indicated that serum creatinine should be checked before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA (Table 8). Twenty-three percent answered incorrectly but did indicate that serum creatinine levels should be checked before the patient is prescribed LEMTRADA and then at regular intervals (every 3 months [15%]; every 8 weeks or as indicated by clinical signs and symptoms [8%]). One HCP indicated that these tests do not need to be carried out.

Table 8 - Knowledge about when to check serum creatinine levels (N=75)

Questionnaire item	Response option	n (%)
Q.20 When do you need to check serum creatinine? Select as many as apply	Before the patient is prescribed LEMTRADA and every 3 months until 48 months after last infusion of LEMTRADA	11 (15%)
	Before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA ✓	**57 (76%)**
	Before the patient is prescribed LEMTRADA and every 8 weeks until last infusion of LEMTRADA or as indicated by clinical signs and symptoms	6 (8%)
	These tests do not need to be carried out	1 (1%)

✓ Correct answer

When to check complete blood count with differential

The majority of HCPs (68%) correctly answered that a complete blood count (CBC) with differential should be checked before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA (Table 9). Twenty-nine percent answered incorrectly but did indicate that CBC with differential should be checked before the patient is prescribed LEMTRADA and then at regular intervals (every 3 months [21%]; every 8 weeks or as

indicated by clinical signs and symptoms [8%]). Two HCPs (3%) indicated that these tests do not need to be carried out.

Table 9 - Knowledge about when to check complete blood count with differential (N=75)

Questionnaire item	Response option	n (%)
Q.21 When do you need to check complete blood count with differential?	**Before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA ✓**	**51 (68%)**
	Before the patient is prescribed LEMTRADA and every 3 months until 48 months after the last infusion of LEMTRADA	16 (21%)
	Every 8 weeks until last infusion of LEMTRADA or as indicated by clinical signs and symptoms	6 (8%)
	These tests do not need to be carried out	2 (3%)

✓ Correct answer

When to conduct urinalysis with microscopy

Almost half of HCPs (49%) correctly answered that urinalysis with microscopy should be conducted before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA (Table 10). Thirty percent answered incorrectly but did indicate that urinalysis with microscopy should be conducted before the patient is prescribed LEMTRADA and then at regular intervals (every 3 months [19%]; every 8 weeks or as indicated by clinical signs and symptoms [11%]). One-fifth (21%) answered incorrectly that the test is not conducted prior to prescribing LEMTRADA but it should be conducted monthly.

Table 10 - Knowledge about when to conduct urinalysis with microscopy (N=75)

Questionnaire item	Response option	n (%)
Q.22 When do you need to conduct urinalysis with microscopy?	Monthly from the start of treatment until 48 months after the last infusion of LEMTRADA	16 (21%)
	Before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA ✓	**37 (49%)**
	Before the patient is prescribed LEMTRADA and every 3 months until 48 months after the last infusion of LEMTRADA	14 (19%)
	Before the patient is prescribed LEMTRADA and every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	8 (11%)

✓ Correct answer

When to conduct liver function tests

A small proportion of HCPs (28%) correctly answered that liver function tests do not need to be carried out in patients prescribed LEMTRADA without known liver disease or symptoms (Table 11). The remainder of HCPs (72%) indicated that liver function tests should be conducted before prescription with LEMTRADA and then at regular intervals (monthly [55%]; not before prescription but every 3 months [11%]; or not before prescription but every 8 weeks or as indicated by clinical signs and symptoms [7%]).

Table 11 - Knowledge about when to conduct liver function tests (N=75)

Questionnaire item	Response option	n (%)
Q.23 When do you need to conduct liver function tests in LEMTRADA treated patients without known liver disease or symptoms?	Before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA	41 (55%)
	Every 3 months until 48 months after last infusion of LEMTRADA	8 (11%)
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	5 (7%)
	These tests do not need to be carried out ✓	**21 (28%)**

✓ Correct answer

When to conduct thyroid function tests

Just over half (55%) of HCPs correctly answered that thyroid function blood tests should be conducted before the patient is prescribed LEMTRADA and every 3 months until 48 months after the last infusion of LEMTRADA (Table 12). Thirty-six percent answered incorrectly but did select one of the alternate answers which stated that these tests need to be done more frequently (every month instead of every 3 months until 48 months after the last infusion) (Table 12; also see footnote to Table 29). Combining the 2 responses demonstrates that 91% of HCPs understand

thyroid function tests should be conducted at least every 3 months. Seven percent answered incorrectly that the tests are not conducted prior to prescribing LEMTRADA but should be conducted every 8 weeks or as indicated by clinical signs and symptoms. Two HCPs (3%) incorrectly answered these tests do not need to be carried out.

Table 12 - Knowledge about when to conduct thyroid function tests (N=75)

Questionnaire item	Response option	n (%)
Q.24 When do you need to conduct thyroid function tests (such as TSH)? (N = 75)	Before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA	27 (36%)
	Before the patient is prescribed LEMTRADA and every 3 months until 48 months after last infusion of LEMTRADA ✓	**41 (55%)**
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	5 (7%)
	These tests do not need to be carried out	2 (3%)

✓ Correct answer

When to conduct urine protein creatinine ratio tests

A small proportion of HCPs (27%) correctly answered that urine protein creatinine ratio tests do not need to be carried out in patients initiating LEMTRADA (Table 13). Sixty percent gave incorrect but more conservative answers that urine protein creatinine ratio tests should be conducted at regular intervals (monthly [35%]; every 3 months [16%]; every 8 weeks or as indicated by clinical signs and symptoms [9%]). Thirteen percent answered incorrectly that they need to be done only prior to prescribing LEMTRADA, but without regular follow-up.

Table 13 - Knowledge about when to conduct urine protein creatinine ratio tests (N=75)

Questionnaire item	Response option	n (%)
Q.25 When do you need to conduct urine protein creatinine ratio tests?	Before the patient is prescribed LEMTRADA	10 (13%)
	Monthly until 48 months after last infusion of LEMTRADA	26 (35%)
	Every 3 months until 48 months after last infusion of LEMTRADA	12 (16%)
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	7 (9%)
	These tests do not need to be carried out ✓	**20 (27%)**

✓ Correct answer

Use of contraception in women of childbearing potential

Just over half (57%) of HCPs correctly answered that women of childbearing potential should use effective contraceptive measures during treatment and for at least 4 months following each treatment (Table 14). Incorrect responses included: during treatment and for at least 5 days

following each treatment (5%); during treatment and for at least 30 days following each treatment (16%); and during treatment and for at least 48 months following each treatment (21%). Given the risk related to pregnancy whilst exposed to a drug, the 21% who gave an answer of less than 4 months follow-up, which could lead to a woman or her child being exposed to high drug levels, may be of concern.

Table 14 - Knowledge about use of contraception in women of childbearing potential (N=75)

Questionnaire item	Response option	n (%)
Q.26 How long should women of childbearing potential use effective contraceptive measures?	During treatment and for at least 5 days following each treatment	4 (5%)
	During treatment and for at least 30 days following each treatment	12 (16%)
	During treatment and for at least 4 months following each treatment ✓	**43 (57%)**
	During treatment and for at least 48 months following each treatment	16 (21%)

✓ Correct answer

What to do if patient has suspected immune thrombocytopenic purpura (ITP)

The majority of HCPs (87%) correctly indicated the need to obtain a CBC immediately if they suspect that a patient has ITP and refer to a specialist immediately if thrombocytopenia is confirmed (Table 15). Ten HCPs (13%) indicated that they would obtain a CBC immediately and repeat thrombocyte counts only if thrombocytopenia is confirmed.

Table 15 - Knowledge about what to do if a patient has suspected ITP (N=75)

Questionnaire item	Response option	n (%)
Q.27 What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)?	**Obtain a complete blood count and if thrombocytopenia is confirmed, refer to a specialist (haematologist) immediately ✓**	**65 (87%)**
	Obtain a complete blood count and if thrombocytopenia is confirmed, repeat thrombocyte counts within 1 week	10 (13%)

✓ Correct answer

What to do if patient has suspected nephropathy

Overall, nearly all HCPs would refer the patient to a specialist upon suspicion of nephropathy (Table 16). Just over half (53%) of HCPs correctly indicated that they would refer the patient to a specialist immediately. Nearly half of HCPs (47%) indicated that they would ask the patient to come in as soon as possible, conduct urine tests, and then refer the patient to a nephrologist. Two HCPs (3%) indicated that they would wait until the patient's next scheduled appointment when any change in serum creatinine level from baseline could be confirmed.

Table 16 - Knowledge about what to do if a patient has suspected nephropathy (N=75)

Questionnaire item	Response option	n (%)
Q.28 What should you do if your monitoring results lead you to suspect nephropathy?	**Refer the patient to a specialist (nephrologist) immediately ✓**	**40 (53%)**
	Ask the patient to come in as soon as possible, conduct urine tests and if suspected nephropathy refer/send the patient to nephrologist immediately	35 (47%)
	Wait until the patient's next scheduled appointment when any change in serum creatinine level from baseline can be confirmed	2 (3%)

✓ Correct answer

Counseling for patients treated with LEMTRADA

The vast majority of HCPs (91%) were aware of the need to counsel patients on the importance of contraception and on the risks and importance of monthly monitoring appointments (Table 17). Seven percent selected only contraception and depression prevention as important discussion points, and 3% selected only the importance of monthly monitoring appointments, indicating some gaps in HCP understanding of key points to discuss with patients.

Table 17 - Knowledge about what counseling should be provided to patients treated with LEMTRADA (N=75)

Questionnaire item	Response option	n (%)
Q.29 What counseling should you provide patients treated with LEMTRADA?	Coping with MS, importance of contraception and depression prevention	5 (7%)
	Coping with MS, importance of contraception and risks and importance of monthly monitoring appointments ✓	**68 (91%)**
	Only the importance of monthly monitoring appointments	2 (3%)

✓ Correct answer

10.2.2 Secondary analyzes

Subgroup comparisons were descriptive/qualitative only and no statistical analyzes were conducted. The number of HCPs in a group often was small. For example, in the category "Number of MS patients seen in a typical year", no HCP saw 10 or fewer patients and only 4 (5%) HCPs saw 11-50 patients (Table 1). Conversely, nearly equivalent numbers of HCPs saw 51-99 patients (n=21 [28%]), 100-250 patients (n=29 [(39%]), and >250 patients (n=21 [28%]). In the discussions, HCPs who saw up to 10 patients and 11-50 patients are combined with those who saw 51-99 patients, and that group is designated "HCPs who saw <100 patients per year."

In the same way, only 2 HCPs reported themselves as a neurologist with a sub-specialism other than MS (Table 1). For discussion purposes, these 2 HCPs are combined with those who self-reported "General neurologist". Finally, 2 HCPs reported all of their time spent in an office-based

work setting rather than in a clinic; the discussions that follow do not take into account these HCPs who worked in an office exclusively although their data are shown in the tables.

10.2.2.1 Knowledge of the HCP guide, HCP checklist, and SmPC

The number of HCPs who had received and reviewed the HCP educational materials is shown in Table 18. Consistent with the primary analysis, the majority of HCPs reported that they had received and reviewed the HCP educational materials (Table 2). Generally, the percentages of HCPs who reported receiving and reviewing the educational materials was consistent regardless of subgroup. However, there were some differences within subgroups. HCPs in the UK consistently had among the lowest scores for all 3 materials (53%-60%), whereas HCPs in Belgium and the Netherlands were consistently among the highest scores (90%-100%). Overall, fewer HCPs identifying themselves as general neurologists (~66%) reported having received and reviewed the HCP educational materials than those identifying themselves as MS specialised neurologists (~85%). A higher percentage of HCPs who last initiated LEMTRADA more than 3 months ago (80%-100%) responded 'Yes' compared with HCPs who initiated LEMTRADA at other times (64%-86%).

Table 18 - Subgroup analysis: Knowledge about the HCP Educational Materials

Q.11 Have you received and reviewed the HCP educational materials?			Yes n (%)	No n (%)	Don't remember n (%)
Country	UK (N=15)	Guide	8 (53%)	2 (13%)	5 (33%)
		Checklist	9 (60%)	1 (7%)	5 (33%)
		SmPC	9 (60%)	2 (13%)	4 (27%)
	Germany (N=10)	Guide	7 (70%)	1 (10%)	2 (20%)
		Checklist	7 (70%)	--	3 (30%)
		SmPC	8 (80%)	--	2 (20%)
	Italy (N=10)	Guide	8 (80%)	--	2 (20%)
		Checklist	6 (60%)	--	4 (40%)
		SmPC	10 (100%)	--	--
	Spain (N=10)	Guide	8 (80%)	--	2 (20%)
		Checklist	7 (70%)	2 (20%)	1 (10%)
			6 (60%)	1 (10%)	3 (30%)
	Greece (N=10)	Guide	8 (80%)	1 (10%)	1 (10%)
		Checklist	9 (90%)	--	1 (10%)
		SmPC	8 (80%)	--	2 (20%)
	Belgium (N=10)	Guide	10 (100%)	--	--
		Checklist	9 (90%)	1 (10%)	--
		SmPC	9 (90%)	1 (10%)	--
	Netherlands (N=10)	Guide	10 (100%)	--	--
		Checklist	9 (90%)	--	1 (10%)
		SmPC	10 (100%)	--	--
Specialist role	General neurologist (N=28)	Guide	18 (64%)	4 (14%)	6 (21%)
		Checklist	18 (64%)	1 (4%)	9 (32%)
		SmPC	19 (68%)	1 (4%)	8 (29%)
	MS specialised neurologist (N=45)	Guide	39 (87%)	--	6 (13%)
		Checklist	36 (80%)	3 (7%)	6 (13%)
		SmPC	39 (87%)	3 (7%)	3 (7%)
	Neurologist with sub specialism other than MS (N=2)[a]	Guide	2 (100%)	--	--
		Checklist	2 (100%)	--	--
		SmPC	2 (100%)	--	--

Q.11 Have you received and reviewed the HCP educational materials?			Yes n (%)	No n (%)	Don't remember n (%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	Guide	14 (82%)	--	3 (18%)
		Checklist	13 (76%)	--	4 (24%)
		SmPC	15 (88%)	1 (6%)	1 (6%)
	MS clinic in a community hospital (N=17)	Guide	14 (82%)	--	3 (18%)
		Checklist	12 (71%)	2 (12%)	3 (18%)
		SmPC	12 (71%)	2 (12%)	3 (18%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	Guide	11 (65%)	1 (6%)	5 (29%)
		Checklist	12 (71%)	1 (6%)	4 (24%)
		SmPC	12 (71%)	1 (6%)	4 (24%)
	Neurology clinic (other than MS) in a community hospital (N=22)	Guide	19 (86%)	3 (14%)	--
		Checklist	18 (82%)	1 (5%)	3 (14%)
		SmPC	20 (91%)	--	2 (9%)
	Office-based setting (N=2)[b]	Guide	1 (50%)	--	1 (50%)
		Checklist	1 (50%)	--	1 (50%)
		SmPC	1 (50%)	--	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	Guide	9 (82%)	--	2 (18%)
		Checklist	7 (64%)	2 (18%)	2 (18%)
		SmPC	9 (82%)	1 (9%)	1 (9%)
	Within last month (N=29)	Guide	23 (79%)	1 (3%)	5 (17%)
		Checklist	25 (86%)	--	4 (14%)
		SmPC	24 (83%)	1 (3%)	4 (14%)
	Within last 3 months (N=25)	Guide	17 (68%)	3 (12%)	5 (20%)
		Checklist	16 (64%)	2 (8%)	7 (28%)
		SmPC	18 (72%)	2 (8%)	5 (20%)
	More than 3 months ago (N=10)	Guide	10 (100%)	--	--
		Checklist	8 (80%)	--	2 (20%)
		SmPC	9 (90%)	--	1 (10%)

Q.11 Have you received and reviewed the HCP educational materials?			Yes n (%)	No n (%)	Don't remember n (%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	Guide	4 (100%)	--	--
		Checklist	4 (100%)	--	--
		SmPC	4 (100%)	--	--
	51-99 patients (N=21)	Guide	12 (57%)	2 (10%)	7 (33%)
		Checklist	13 (62%)	--	8 (38%)
		SmPC	14 (67%)	--	7 (33%)
	100-250 patients (N=29)	Guide	25 (86%)	1 (3%)	3 (10%)
		Checklist	24 (83%)	--	5 (17%)
		SmPC	25 (86%)	--	4 (14%)
	>250 patients (N=21)	Guide	18 (86%)	1 (5%)	2 (10%)
		Checklist	15 (71%)	4 (19%)	2 (10%)
		SmPC	17 (81%)	4 (19%)	--

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes

10.2.2.2 Knowledge of Patient Educational Materials

Across all of the subgroups, HCP awareness of the Patient Educational Materials was highest among HCPs who had received and reviewed all the HCP educational materials (87%-94%) (Table 19). Generally the percentages of HCPs who knew about the existence of the Patient Guide and the Patient Alert Card were consistent regardless of subgroup.

Table 19 - Subgroup analysis: Knowledge about available Patient Educational Materials

Q.14 What Patient Educational Materials are available for patients prescribed LEMTRADA? ***Patient Guide+ Patient Alert Card***		Correct answer N=61 n (%)	Incorrect answer N=14 n (%)
Country	UK (N=15)	10 (67%)	5 (33%)
	Germany (N=10)	8 (80%)	2 (20%)
	Italy (N=10)	7 (70%)	3 (30%)
	Spain (N=10)	8 (80%)	2 (20%)
	Greece (N=10)	10 (100%)	--
	Belgium (N=10)	9 (90%)	1 (10%)
	Netherlands (N=10)	9 (90%)	1 (10%)

Q.14 What Patient Educational Materials are available for patients prescribed LEMTRADA? ***Patient Guide+ Patient Alert Card***		**Correct answer N=61** n (%)	**Incorrect answer N=14** n (%)
Specialist area	General neurologist (N=28)	22 (79%)	6 (21%)
	MS specialised neurologist (N=45)	37 (82%)	8 (18%)
	Neurologist with sub specialism other than MS (N=2)[a]	2 (100%)	2 (100%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	13 (76%)	4 (24%)
	MS clinic in a community hospital (N=17)	13 (76%)	4 (24%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	15 (88%)	2 (12%)
	Neurology clinic (other than MS) in a community hospital (N=22)	19 (86%)	3 (14%)
	Office based specialist (N=2)[b]	1 (50%)	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	11 (100%)	--
	Within last month (N=29)	22 (76%)	7 (24%)
	Within last 3 months (N=25)	20 (80%)	5 (20%)
	More than 3 months ago (N=10)	8 (80%)	2 (20%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	17 (81%)	4 (19%)
	100-250 patients (N=29)	22 (76%)	7 (24%)
	>250 patients (N=21)	18 (86%)	3 (14%)
Amount of HCP Guide read?[d]	All of it (N=33)	31 (94%)	2 (6%)
	More than half of it (N=16)	12 (75%)	4 (25%)
	About half of it (N=9)	7 (78%)	2 (22%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	49 (88%)	7 (12%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=15)	9 (60%)	6 (40%)
Received and reviewed SmPC?	Yes (N=60)	52 (87%)	8 (13%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	7 (64%)	4 (34%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.3 Knowledge of potential risks to be discussed at first prescription of LEMTRADA

Across all of the subgroups, HCPs' knowledge of the potential risks to be discussed at first prescription of LEMTRADA was 70% or better, with the exception of HCPs who had initiated LEMTRADA within the last week (64%) (Table 20).

Table 20 - Subgroup analysis: Potential risks to be discussed at first prescription

Q.15 What potential risks should be discussed at first prescription of LEMTRADA? ***ITP, active infections and pregnancy & contraception (if applicable)***		**Correct answer N=64** n (%)	**Incorrect answer N=11** n (%)
Country	UK (N=15)	13 (87%)	2 (13%)
	Germany (N=10)	9 (90%)	1 (10%)
	Italy (N=10)	7 (70%)	3 (30%)
	Spain (N=10)	7 (70%)	3 (30%)
	Greece (N=10)	9 (90%)	1 (10%)
	Belgium (N=10)	10 (100%)	--
	Netherlands (N=10)	10 (100%)	--
Specialist area	General neurologist (N=28)	25 (89%)	3 (11%)
	MS specialised neurologist (N=45)	38 (84%)	7 (16%)
	Neurologist with sub specialism other than MS (N=2)[a]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	14 (82%)	3 (18%)
	MS clinic in a community hospital (N=17)	13 (76%)	4 (24%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	15 (88%)	2 (12%)
	Neurology clinic (other than MS) in a community hospital (N=22)	21 (95%)	1 (5%)
	Office based specialist (N=2)[b]	1 (50%)	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	7 (64%)	4 (34%)
	Within last month (N=29)	24 (83%)	5 (17%)
	Within last 3 months (N=25)	25 (100%)	--
	More than 3 months ago (N=10)	8 (80%)	2 (20%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	20 (95%)	1 (5%)
	100-250 patients (N=29)	22 (76%)	7 (24%)
	>250 patients (N=21)	18 (86%)	3 (14%)

Q.15 What potential risks should be discussed at first prescription of LEMTRADA? ***ITP, active infections and pregnancy & contraception (if applicable)***		**Correct answer N=64** n (%)	**Incorrect answer N=11** n (%)
Amount of HCP Guide read?[d]	All of it (N=33)	29 (88%)	4 (12%)
	More than half of it (N=16)	15 (94%)	1 (6%)
	About half of it (N=9)	7 (78%)	2 (22%)
	Less than half of it (N=1)	--	1 (100%)
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	49 (88%)	7 (12%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=15)	12 (80%)	3 (20%)
Received and reviewed SmPC?	Yes (N=60)	54 (90%)	6 (10%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=11)	7 (64%)	4 (26%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes
d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.4 Knowledge of contraindications (conditions)

Subgroup comparisons of HCPs knowledge of conditions in which LEMTRADA is contraindicated are shown in Table 21. In general, the percentage of correct answers was high (>75%) for all subgroups, with the exception of HCPs who had initiated LEMTRADA within the last week (64%).

Table 21 - Subgroup analysis: Knowledge of contraindications (conditions)

Q.16 In which patients is LEMTRADA contraindicated? ***In patients with human immunodeficiency virus (HIV) and hypersensitivity to the active substance or any of the excipients***		**Correct answer N=64** n (%)	**Incorrect answer N=11** n (%)
Country	UK (N=15)	13 (87%)	2 (13%)
	Germany (N=10)	9 (90%)	1 (10%)
	Italy (N=10)	7 (70%)	3 (30%)
	Spain (N=10)	10 (100%)	--
	Greece (N=10)	7 (70%)	3 (30%)
	Belgium (N=10)	8 (80%)	2 (20%)
	Netherlands (N=10)	10 (100%)	--

Q.16 In which patients is LEMTRADA contraindicated? ***In patients with human immunodeficiency virus (HIV) and hypersensitivity to the active substance or any of the excipients***		**Correct answer N=64** n (%)	**Incorrect answer N=11** n (%)
Specialist area	General neurologist (N=28)	22 (79%)	6 (21%)
	MS specialised neurologist (N=45)	40 (89%)	5 (11%)
	Neurologist with sub specialism other than MS (N=2)[a]	2 (100%)	--
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	13 (76%)	4 (24%)
	MS clinic in a community hospital (N=17)	15 (88%)	2 (12%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	14 (82%)	3 (18%)
	Neurology clinic (other than MS) in a community hospital (N=22)	21 (95%)	1 (5%)
	Office based specialist (N=2)[b]	1 (50%)	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	7 (64%)	4 (34%)
	Within last month (N=29)	26 (90%)	3 (10%)
	Within last 3 months (N=25)	22 (88%)	3 (12%)
	More than 3 months ago (N=10)	9 (90%)	1 (10%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	17 (81%)	4 (19%)
	100-250 patients (N=29)	25 (86%)	4 (14%)
	>250 patients (N=21)	18 (86%)	3 (14%)
Amount of HCP Guide read?[d]	All of it (N=33)	26 (79%)	7 (21%)
	More than half of it (N=16)	15 (94%)	1 (6%)
	About half of it (N=9)	9 (100%)	--
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	48 (86%)	8 (14%)
	No (N=4)	4 (100%)	--
	Don't remember (N=15)	12 (80%)	3 (20%)
Received and reviewed SmPC?	Yes (N=60)	51 (85%)	9 (15%)
	No (N=4)	4 (100%)	--
	Don't remember (N=11)	9 (82%)	2 (18%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.5 Knowledge of contraindications (treatments)

Subgroup comparisons of HCPs' knowledge of treatment combinations with which LEMTRADA is contraindicated are shown in Table 22. Overall, the percentage of correct answers ranged between 55% and 82% (within the exception of Country and review of HCP educational materials) and was relatively consistent within subgroups. HCPs in the UK had the lowest percentage of correct answers regarding knowledge of the treatments in which LEMTRADA was contraindicated (53%), whereas HCPs in Belgium scored 100% correct. HCPs who initiated LEMTRADA a month or more ago scored better (70%-76%) than those who initiated LEMTRADA within the last week (55%). Correct answers were provided by more HCPs who typically treated 100 or more patients per year (76%) than those who treated fewer than 100 patients per year (68%). Scores among the HCP educational materials group were disparate, but generally HCPs who had received and reviewed all HCP educational materials had a higher percentage of correct answers those who indicated that they did not receive the materials or did not remember receiving them.

Table 22 - Subgroup analysis: Knowledge of contraindications (treatments)

Q.17a In which patients is LEMTRADA to be used cautiously due to potential combined effects on the patient's immune system? ***Immunosuppressive therapy and antineoplastic therapy***		**Correct answer N=53** n (%)	**Incorrect answer N=22** n (%)
Country	UK (N=15)	8 (53%)	7 (47%)
	Germany (N=10)	8 (80%)	2 (20%)
	Italy (N=10)	6 (60%)	4 (40%)
	Spain (N=10)	7 (70%)	3 (30%)
	Greece (N=10)	7 (70%)	3 (30%)
	Belgium (N=10)	10 (100%)	--
	Netherlands (N=10)	7 (70%)	3 (30%)
Specialist area	General neurologist (N=28)	19 (68%)	9 (32%)
	MS specialised neurologist (N=45)	34 (76%)	11 (24%)
	Neurologist with sub specialism other than MS (N=2)[a]	--	2 (100%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	14 (82%)	3 (18%)
	MS clinic in a community hospital (N=17)	12 (71%)	5 (29%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	13 (76%)	4 (24%)
	Neurology clinic (other than MS) in a community hospital (N=22)	18 (82%)	4 (18%)
	Office based specialist (N=2)[b]	1 (50%)	1 (50%)

Q.17a In which patients is LEMTRADA to be used cautiously due to potential combined effects on the patient's immune system? ***Immunosuppressive therapy and antineoplastic therapy***		**Correct answer N=53** n (%)	**Incorrect answer N=22** n (%)
Last initiation of LEMTRADA	Within last week (N=11)	6 (55%)	5 (45%)
	Within last month (N=29)	21 (72%)	8 (28%)
	Within last 3 months (N=25)	19 (76%)	6 (24%)
	More than 3 months ago (N=10)	7 (70%)	3 (30%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	13 (62%)	8 (38%)
	100-250 patients (N=29)	22 (76%)	7 (24%)
	>250 patients (N=21)	16 (76%)	5 (24%)
Amount of HCP Guide read?[d]	All of it (N=33)	27 (82%)	6 (18%)
	More than half of it (N=16)	10 (63%)	6 (37%)
	About half of it (N=9)	7 (78%)	2 (22%)
	Less than half of it (N=1)	--	1 (100%)
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	44 (79%)	12 (21%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=15)	6 (40%)	9 (60%)
Received and reviewed SmPC?	Yes (N=60)	46 (77%)	14 (23%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	5 (45%)	6 (55%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes
d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.6 Knowledge of tests to be conducted before first prescription of LEMTRADA

Subgroup comparisons of HCPs' knowledge of tests to be conducted before the first prescription of LEMTRADA are shown in Table 23. In general, the percentage of correct answers was low, consistent with the primary analysis where only 59% of respondents answered correctly (Table 6). Scores ranged between 36% and 73% (with the exception of Country and review of HCP educational materials). HCPs in Italy had the lowest percentage of correct answers (30%), followed by HCPs in Spain and Greece (50% each). However, while the correct answer was 'Urinalysis with microscopy and thyroid function tests such as TSH', one of the alternative answers, 'Urine protein creatinine test and thyroid function tests such as TSH', was selected by 60% of Italian HCPs, which was considerably higher than for HCPs in the other countries

(10%-50%) (also see footnote to Table 23). Regarding the other subgroups, there were not large differences for any subgroup including HCP educational materials.

Table 23 - Subgroup analysis: Knowledge of tests to be conducted before first prescription of LEMTRADA

Q.18 According to the HCP Guide and HCP Checklist, serum creatinine and complete blood count with differential should be conducted before first prescription of LEMTRADA; what other tests are required? ***Urinalysis with microscopy and thyroid function tests such as TSH***		**Correct answer N=44** n (%)	**Incorrect answer N=31** n (%)
Country	UK (N=15)	10 (67%)	5 (33%)
	Germany (N=10)	6 (60%)	4 (40%)
	Italy (N=10)	3 (30%)[a]	7 (70%)
	Spain (N=10)	5 (50%)	5 (50%)
	Greece (N=10)	5 (50%)	5 (50%)
	Belgium (N=10)	8 (80%)	2 (20%)
	Netherlands (N=10)	7 (70%)	3 (30%)
Specialist area	General neurologist (N=28)	18 (64%)	10 (36%)
	MS specialised neurologist (N=45)	25 (56%)	20 (44%)
	Neurologist with other sub specialism other than MS (N=2)[b]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	10 (59%)	7 (41%)
	MS clinic in a community hospital (N=17)	10 (59%)	7 (41%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	7 (41%)	10 (59%)
	Neurology clinic (other than MS) in a community hospital (N=22)	16 (73%)	6 (27%)
	Office based specialist (N=2)[c]	1 (50%)	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	4 (36%)	7 (64%)
	Within last month (N=29)	18 (62%)	11 (38%)
	Within last 3 months (N=25)	17 (68%)	8 (32%)
	More than 3 months ago (N=10)	5 (50%)	5 (50%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[d]	3 (75%)	1 (25%)
	51-99 patients (N=21)	10 (48%)	11 (52%)
	100-250 patients (N=29)	18 (62%)	11 (38%)
	>250 patients (N=21)	13 (62%)	8 (38%)

Q.18 According to the HCP Guide and HCP Checklist, serum creatinine and complete blood count with differential should be conducted before first prescription of LEMTRADA; what other tests are required? ***Urinalysis with microscopy and thyroid function tests such as TSH***		**Correct answer N=44** n (%)	**Incorrect answer N=31** n (%)
Amount of HCP Guide read?[e]	All of it (N=33)	21 (64%)	12 (36%)
	More than half of it (N=16)	8 (50%)	8 (50%)
	About half of it (N=9)	6 (67%)	3 (33%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	38 (68%)	18 (32%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=15)	5 (33%)	10 (67%)
Received and reviewed SmPC?	Yes (N=60)	35 (58%)	25 (42%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	7 (64%)	4 (34%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a An alternative answer 'Urine protein creatinine test and thyroid function tests such as TSH' was selected by 60% of Italian HCPs. This percentage was higher than for the other countries: UK, 13%; Germany, 30%; Spain, 40%; Greece, 50%; Belgium, 10%; the Netherlands, 30%.

b Combined with those who self-reported "General neurologist" discussion purposes

c Not included in discussion

d Combined with HCPs who saw 51-99 patients for discussion purposes

e Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.7 Wait period after vaccination before administering LEMTRADA

Subgroup comparisons of wait period after vaccination before administering LEMTRADA are shown in Table 24. In general, the percentage of correct answers was low, with few of the subgroups scoring more than 50% correct.

Table 24 - Subgroup analysis: Knowledge of wait period after last vaccination before administering LEMTRADA

Q.19 How long after the patient's last vaccination should you wait before administering LEMTRADA? ***6 weeks***		**Correct answer N=30** n (%)	**Incorrect answer N=45** n (%)
Country	UK (N=15)	8 (53%)	7 (47%)
	Germany (N=10)	4 (40%)	6 (60%)
	Italy (N=10)	2 (20%)	8 (80%)
	Spain (N=10)	3 (30%)	7 (70%)
	Greece (N=10)	5 (50%)	5 (50%)
	Belgium (N=10)	3 (30%)	7 (70%)
	Netherlands (N=10)	5 (50%)	5 (50%)
Specialist area	General neurologist (N=28)	10 (36%)	18 (64%)
	MS specialised neurologist (N=45)	19 (42%)	26 (58%)
	Neurologist with sub specialism other than MS (N=2)[a]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	8 (47%)	9 (53%)
	MS clinic in a community hospital (N=17)	5 (29%)	12 (71%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	5 (29%)	12 (71%)
	Neurology clinic (other than MS) in a community hospital (N=22)	12 (55%)	20 (45%)
	Office based specialist (N=2)[b]	--	2 (100%)
Last initiation of LEMTRADA	Within last week (N=11)	5 (45%)	6 (55%)
	Within last month (N=29)	12 (41%)	17 (59%)
	Within last 3 months (N=25)	10 (40%)	15 (60%)
	More than 3 months ago (N=10)	3 (30%)	7 (70%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	7 (33%)	14 (67%)
	100-250 patients (N=29)	9 (31%)	20 (69%)
	>250 patients (N=21)	10 (48%)	11 (52%)
Amount of HCP Guide read?[d]	All of it (N=33)	14 (42%)	19 (58%)
	More than half of it (N=16)	8 (50%)	8 (50%)
	About half of it (N=9)	2 (22%)	7 (78%)
	Less than half of it (N=1)	--	1 (100%)
	None of it (0)	--	--

Q.19 How long after the patient's last vaccination should you wait before administering LEMTRADA? ***6 weeks***		**Correct answer N=30** n (%)	**Incorrect answer N=45** n (%)
Received and reviewed HCP Checklist?	Yes (N=56)	26 (46%)	30 (54%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=15)	3 (20%)	12 (80%)
Received and reviewed SmPC?	Yes (N=60)	24 (40%)	36 (60%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	4 (36%)	7 (64%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes
d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.8 Knowledge of monitoring activities for the autoimmune events

Serum creatinine

Overall, the percentage of correct answers for knowledge of when to check serum creatinine ranged between 70% and 82% (within the exception of Country and review of HCP educational materials) and was fairly consistent within subgroups (Table 25). HCPs in the UK had a lower percentage of correct answers (53%) compared with HCPs in the other countries (70%-90%).

Table 25 - Subgroup analysis: When do you need to check serum creatinine?

Q.20 When do you need to check serum creatinine? ***Before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA***		**Correct answer N=57** n (%)	**Incorrect answer N=18** n (%)
Country	UK (N=15)	8 (53%)	7 (47%)
	Germany (N=10)	7 (70%)	3 (30%)
	Italy (N=10)	8 (80%)	2 (20%)
	Spain (N=10)	8 (80%)	2 (20%)
	Greece (N=10)	9 (90%)	1 (10%)
	Belgium (N=10)	9 (90%)	1 (10%)
	Netherlands (N=10)	8 (80%)	1 (20%)
Specialist area	General neurologist (N=28)	20 (71%)	8 (29%)
	MS specialised neurologist (N=45)	36 (80%)	9 (20%)
	Neurologist with sub specialism other than MS (N=2)[a]	1 (50%)	1 (50%)

Q.20 When do you need to check serum creatinine? ***Before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA***		**Correct answer N=57** n (%)	**Incorrect answer N=18** n (%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	13 (76%)	4 (24%)
	MS clinic in a community hospital (N=17)	13 (76%)	4 (24%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	13 (76%)	4 (24%)
	Neurology clinic (other than MS) in a community hospital (N=22)	18 (82%)	4 (18%)
	Office based specialist (N=2)[b]	--	2 (100%)
Last initiation of LEMTRADA	Within last week (N=11)	8 (73%)	3 (27%)
	Within last month (N=29)	22 (76%)	7 (24%)
	Within last 3 months (N=25)	20 (80%)	5 (20%)
	More than 3 months ago (N=10)	7 (70%)	3 (30%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	15 (71%)	6 (29%)
	100-250 patients (N=29)	21 (72%)	8 (28%)
	>250 patients (N=21)	17 (81%)	4 (19%)
Amount of HCP Guide read?[d]	All of it (N=33)	28 (85%)	5 (15%)
	More than half of it (N=16)	11 (69%)	5 (31%)
	About half of it (N=9)	8 (89%)	1 (11%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	45 (80%)	9 (20%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=15)	9 (60%)	6 (40%)
Received and reviewed SmPC?	Yes (N=60)	48 (80%)	12 (20%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	7 (64%)	4 (36%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

Complete blood count with differential

Overall, the percentage of correct answers for knowledge of when to conduct a CBC with differential ranged between 55% and 82% (within the exception of Country and review of HCP

educational materials) and was fairly consistent within subgroups (Table 26). HCPs in the UK had a lower percentage of correct answers (53%) compared with HCPs in the other countries (70%-90%).

Table 26 - Subgroup analysis: When do you need to check complete blood count with differential?

Q.21 When do you need to conduct complete blood count with differential? ***Before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA***		**Correct answer N=51** n (%)	**Incorrect answer N=24** n (%)
Country	UK (N=15)	8 (53%)	7 (47%)
	Germany (N=10)	7 (70%)	3 (30%)
	Italy (N=10)	7 (70%)	3 (30%)
	Spain (N=10)	6 (60%)	4 (40%)
	Greece (N=10)	6 (60%)	4 (40%)
	Belgium (N=10)	9 (90%)	1 (10%)
	Netherlands (N=10)	8 (80%)	2 (20%)
Specialist area	General neurologist (N=28)	19 (68%)	9 (32%)
	MS specialised neurologist (N=45)	31 (69%)	14 (31%)
	Neurologist with sub specialism other than MS (N=2)[a]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	11 (65%)	6 (35%)
	MS clinic in a community hospital (N=17)	11 (65%)	6 (35%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	11 (65%)	6 (35%)
	Neurology clinic (other than MS) in a community hospital (N=22)	18 (82%)	4 (18%)
	Office based specialist (N=2)[b]	--	2 (100%)
Last initiation of LEMTRADA	Within last week (N=11)	6 (55%)	5 (45%)
	Within last month (N=29)	18 (62%)	11 (38%)
	Within last 3 months (N=25)	20 (80%)	5 (20%)
	More than 3 months ago (N=10)	7 (70%)	3 (30%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	14 (67%)	7 (33%)
	100-250 patients (N=29)	19 (66%)	10 (34%)
	>250 patients (N=21)	14 (67%)	7 (33%)

Q.21 When do you need to conduct complete blood count with differential? ***Before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA***		**Correct answer N=51** n (%)	**Incorrect answer N=24** n (%)
Amount of HCP Guide read?[d]	All of it (N=33)	25 (76%)	8 (24%)
	More than half of it (N=16)	10 (63%)	6 (37%)
	About half of it (N=9)	6 (67%)	3 (33%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	40 (71%)	16 (29%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=15)	9 (60%)	6 (40%)
Received and reviewed SmPC?	Yes (N=60)	43 (72%)	17 (28%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=11)	7 (64%)	4 (36%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes
d Answered by respondents who have received and reviewed the HCP Guide (N=59)

Urinalysis with microscopy

Overall, half the HCPs responded with correct answers for when to conduct urinalysis with microscopy (Table 27), consistent with the primary analysis (Table 10). There were no remarkable differences within subgroups.

Table 27 - Subgroup analysis: When do you need to conduct urinalysis with microscopy?

Q.22 When do you need to conduct urinalysis with microscopy? ***Before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA***		**Correct answer N=37** n (%)	**Incorrect answer N=38** n (%)
Country	UK (N=15)	8 (53%)	7 (47%)
	Germany (N=10)	7 (70%)	3 (30%)
	Italy (N=10)	3 (30%)	7 (70%)
	Spain (N=10)	5 (50%)	5 (50%)
	Greece (N=10)	4 (40%)	6 (60%)
	Belgium (N=10)	5 (50%)	5 (50%)
	Netherlands (N=10)	5 (50%)	5 (50%)

Q.22 When do you need to conduct urinalysis with microscopy? ***Before the patient is prescribed LEMTRADA and monthly until 48 months after the last infusion of LEMTRADA***		**Correct answer N=37** n (%)	**Incorrect answer N=38** n (%)
Specialist area	General neurologist (N=28)	13 (46%)	15 (54%)
	MS specialised neurologist (N=45)	23 (51%)	22 (49%)
	Neurologist with sub specialism other than MS (N=2)[a]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	10 (59%)	7 (41%)
	MS clinic in a community hospital (N=17)	9 (53%)	8 (47%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	4 (24%)	13 (76%)
	Neurology clinic (other than MS) in a community hospital (N=22)	14 (64%)	4 (18%)
	Office based specialist (N=2)[b]	--	2 (100%)
Last initiation of LEMTRADA	Within last week (N=11)	5 (45%)	6 (55%)
	Within last month (N=29)	14 (48%)	15 (52%)
	Within last 3 months (N=25)	12 (48%)	13 (52%)
	More than 3 months ago (N=10)	6 (60%)	4 (40%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	3 (75%)	1 (25%)
	51-99 patients (N=21)	12 (57%)	9 (43%)
	100-250 patients (N=29)	12 (41%)	17 (59%)
	>250 patients (N=21)	10 (48%)	11 (52%)
Amount of HCP Guide read?[d]	All of it (N=33)	18 (55%)	15 (45%)
	More than half of it (N=16)	8 (50%)	8 (50%)
	About half of it (N=9)	4 (44%)	5 (56%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	31 (55%)	25 (45%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=15)	5 (33%)	10 (67%)
Received and reviewed SmPC?	Yes (N=60)	28 (47%)	32 (53%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=11)	6 (55%)	5 (45%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

Liver function tests

The percentage of correct answers for knowledge of when to conduct liver function tests was low (Table 28) and consistent with the primary analysis in which only 28% of respondents answered correctly (Table 11).

Table 28 - Subgroup analysis: When do you need to conduct liver function tests?

Q23 When do you need to conduct liver function tests? ***These tests do not need to be carried out***		**Correct answer N=21** n (%)	**Incorrect answer N=54** n (%)
Country	UK (N=15)	3 (20%)	12 (80%)
	Germany (N=10)	6 (60%)	4 (40%)
	Italy (N=10)	3 (30%)	7 (70%)
	Spain (N=10)	3 (30%)	7 (70%)
	Greece (N=10)	1 (10%)	9 (90%)
	Belgium (N=10)	2 (20%)	8 (80%)
	Netherlands (N=10)	3 (30%)	7 (70%)
Specialist area	General neurologist (N=28)	5 (18%)	13 (82%)
	MS specialised neurologist (N=45)	16 (36%)	29 (64%)
	Neurologist with sub specialism other than MS (N=2)[a]	--	2 (100%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	7 (41%)	10 (59%)
	MS clinic in a community hospital (N=17)	5 (29%)	12 (71%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	2 (12%)	15 (88%)
	Neurology clinic (other than MS) in a community hospital (N=22)	6 (27%)	16 (73%)
	Office based specialist (N=2)[b]	1 (50%)	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	1 (9%)	10 (91%)
	Within last month (N=29)	12 (41%)	17 (59%)
	Within last 3 months (N=25)	5 (20%)	20 (80%)
	More than 3 months ago (N=10)	3 (30%)	7 (70%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	3 (75%)	1 (25%)
	51-99 patients (N=21)	2 (10%)	19 (90%)
	100-250 patients (N=29)	8 (28%)	21 (72%)
	>250 patients (N=21)	8 (38%)	13 (62%)

Q23 When do you need to conduct liver function tests? ***These tests do not need to be carried out***		**Correct answer N=21** n (%)	**Incorrect answer N=54** n (%)
Amount of HCP Guide read?[d]	All of it (N=33)	10 (30%)	23 (70%)
	More than half of it (N=16)	5 (31%)	11 (69%)
	About half of it (N=9)	2 (22%)	7 (78%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	18 (32%)	38 (68%)
	No (N=4)	--	--
	Don't remember (N=15)	3 (20%)	12 (80%)
Received and reviewed SmPC?	Yes (N=60)	18 (30%)	42 (70%)
	No (N=4)	--	--
	Don't remember (N=11)	3 (27%)	8 (73%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

Thyroid function tests

In general, the percentage of correct answers for knowledge of when to conduct thyroid function tests was low (Table 29), consistent with the primary analysis in which 55% of respondents answered correctly (Table 12). HCPs in Italy had the lowest percentage of correct answers (20%), followed by HCPs in Spain and UK (40% and 47%, respectively). However, while the correct answer was 'Before the patient is prescribed LEMTRADA and every 3 months until 48 months after the last infusion of LEMTRADA', 36% of respondents selected an incorrect but more conservative answer which stated that these tests needed to be done more frequently (every month instead of every 3 months until 48 months after the last infusion) (Table 12; also see footnote to Table 29). Combining the 2 responses demonstrates that 91% of HCPs understand thyroid function tests should be conducted at least every 3 months. Regarding the other subgroups, there were no remarkable differences for any subgroup including HCP educational materials.

Table 29 - Subgroup analysis: When do you need to conduct thyroid function tests?

Q.24 When do you need to conduct thyroid function tests (such as TSH)? ***Before the patient is prescribed LEMTRADA and every 3 months until 48 months after the last infusion of LEMTRADA***		**Correct answer N=41** n (%)	**Incorrect answer N=34** n (%)
Country	UK (N=15)	7 (47%)	8 (53%)
	Germany (N=10)	8 (80%)	2 (20%)
	Italy (N=10)	2 (20%)[a]	8 (80%)
	Spain (N=10)	4 (40%)	6 (60%)
	Greece (N=10)	7 (70%)	3 (30%)
	Belgium (N=10)	5 (50%)	5 (50%)
	Netherlands (N=10)	8 (80%)	2 (20%)
Specialist area	General neurologist (N=28)	13 (46%)	15 (54%)
	MS specialised neurologist (N=45)	27 (60%)	18 (40%)
	Neurologist with sub specialism other than MS (N=2)[b]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	8 (47%)	9 (53%)
	MS clinic in a community hospital (N=17)	11 (65%)	6 (35%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	10 (59%)	7 (41%)
	Neurology clinic (other than MS) in a community hospital (N=22)	10 (45%)	12 (55%)
	Office based specialist (N=2)[c]	2 (100%)	--
Last initiation of LEMTRADA	Within last week (N=11)	7 (64%)	4 (36%)
	Within last month (N=29)	16 (55%)	13 (45%)
	Within last 3 months (N=25)	13 (52%)	12 (48%)
	More than 3 months ago (N=10)	5 (50%)	5 (50%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[d]	3 (75%)	1 (25%)
	51-99 patients (N=21)	12 (57%)	9 (43%)
	100-250 patients (N=29)	15 (52%)	14 (48%)
	>250 patients (N=21)	11 (52%)	10 (48%)
Amount of HCP Guide read?[e]	All of it (N=33)	13 (39%)	20 (61%)
	More than half of it (N=16)	10 (63%)	6 (37%)
	About half of it (N=9)	4 (44%)	5 (56%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--

Q.24 When do you need to conduct thyroid function tests (such as TSH)? ***Before the patient is prescribed LEMTRADA and every 3 months until 48 months after the last infusion of LEMTRADA***		**Correct answer N=41** n (%)	**Incorrect answer N=34** n (%)
Received and reviewed HCP Checklist?	Yes (N=56)	30 (54%)	26 (46%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=15)	9 (60%)	10 (67%)
Received and reviewed SmPC?	Yes (N=60)	29 (48%)	36 (60%)
	No (N=4)	4 (100%)	--
	Don't remember (N=11)	8 (73%)	3 (27%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a An alternative, more stringent answer 'Before the patient is prescribed LEMTRADA and monthly until 48 months after last infusion of LEMTRADA' was selected by 36% of HCPs from all countries: UK, 40%; Germany, 20%; Italy, 50%; Spain, 50%; Greece, 20%; Belgium, 50%; the Netherlands, 20%.

b Combined with those who self-reported "General neurologist" discussion purposes

c Not included in discussion

d Combined with HCPs who saw 51-99 patients for discussion purposes

e Answered by respondents who have received and reviewed the HCP Guide (N=59)

Urine protein creatinine ratio tests

The percentage of correct answers for knowledge of when to conduct urine protein creatinine ratio tests was overwhelmingly low (Table 30), consistent with the primary analysis in which only 27% of respondents answered correctly (Table 13).

Table 30 - Subgroup analysis: When do you need to conduct urine protein creatinine ratio tests?

Q.25 When do you need to conduct urine protein creatinine ratio tests? ***These tests do not need to be carried out***		**Correct answer N=20** n (%)	**Incorrect answer N=55** n (%)
Country	UK (N=15)	4 (27%)	11 (73%)
	Germany (N=10)	5 (50%)	5 (50%)
	Italy (N=10)	--	10 (100%)
	Spain (N=10)	2 (20%)	8 (80%)
	Greece (N=10)	2 (20%)	8 (80%)
	Belgium (N=10)	1 (10%)	9 (90%)
	Netherlands (N=10)	6 (60%)	4 (40%)

Q.25 When do you need to conduct urine protein creatinine ratio tests? ***These tests do not need to be carried out***		**Correct answer N=20** n (%)	**Incorrect answer N=55** n (%)
Specialist area	General neurologist (N=28)	4 (14%)	14 (86%)
	MS specialised neurologist (N=45)	16 (36%)	29 (64%)
	Neurologist with sub specialism other than MS (N=2)[a]	--	2 (100%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	4 (24%)	13 (76%)
	MS clinic in a community hospital (N=17)	4 (24%)	13 (76%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	3 (18%)	14 (82%)
	Neurology clinic (other than MS) in a community hospital (N=22)	9 (41%)	13 (59%)
	Office based specialist (N=2)[b]	--	2 (100%)
Last initiation of LEMTRADA	Within last week (N=11)	--	11 (100%)
	Within last month (N=29)	9 (31%)	20 (69%)
	Within last 3 months (N=25)	8 (32%)	17 (68%)
	More than 3 months ago (N=10)	3 (30%)	7 (70%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	1 (25%)	3 (75%)
	51-99 patients (N=21)	3 (14%)	18 (86%)
	100-250 patients (N=29)	8 (28%)	21 (72%)
	>250 patients (N=21)	8 (36%)	13 (64%)
Amount of HCP Guide read?[d]	All of it (N=33)	9 (27%)	24 (73%)
	More than half of it (N=16)	2 (13%)	14 (87%)
	About half of it (N=9)	3 (33%)	6 (67%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	16 (29%)	40 (71%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=15)	3 (20%)	12 (80%)
Received and reviewed SmPC?	Yes (N=60)	15 (25%)	45 (75%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	3 (27%)	8 (73%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.9 Knowledge of contraception in women of childbearing potential

Subgroup comparisons of HCPs' knowledge of contraception in women of childbearing potential are shown in Table 31. Overall, 57% of the HCPs responded with correct answers. Although by country, the percentage of correct answers was 50% to 70%, 21% of respondents selected a more stringent alternative answer which stated that contraception should be used for 48 months rather than 4 months after each treatment (Table 14; also see footnote to Table 31). Combining these 2 responses demonstrates that 78% of HCPs understand contraception should be used for at least 4 months after each treatment. There were no remarkable differences in any other subgroup including HCP educational materials.

Table 31 - Subgroup analysis: Knowledge of contraception in women of childbearing potential

Q.26 How long should women of childbearing potential use effective contraceptive measures? ***During treatment and for at least 4 months following each treatment***		**Correct answer N=43** n (%)	**Incorrect answer N=32** n (%)
Country[a]	UK (N=15)	8 (52%)	7 (48%)
	Germany (N=10)	7 (70%)	3 (30%)
	Italy (N=10)	7 (70%)	3 (30%)
	Spain (N=10)	5 (50%)	5 (50%)
	Greece (N=10)	5 (50%)	5 (50%)
	Belgium (N=10)	6 (60%)	4 (40%)
	Netherlands (N=10)	5 (50%)	5 (50%)
Specialist area	General neurologist (N=28)	12 (43%)	16 (57%)
	MS specialised neurologist (N=45)	30 (67%)	15 (33%)
	Neurologist with sub specialism other than MS (N=2)[b]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	11 (65%)	6 (35%)
	MS clinic in a community hospital (N=17)	10 (59%)	7 (41%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	10 (59%)	7 (41%)
	Neurology clinic (other than MS) in a community hospital (N=22)	12 (55%)	10 (45%)
	Office based specialist (N=2)[c]	--	2 (100%)

Q.26 How long should women of childbearing potential use effective contraceptive measures? ***During treatment and for at least 4 months following each treatment***		**Correct answer N=43** n (%)	**Incorrect answer N=32** n (%)
Last initiation of LEMTRADA	Within last week (N=11)	5 (45%)	6 (55%)
	Within last month (N=29)	18 (62%)	11 (38%)
	Within last 3 months (N=25)	16 (64%)	9 (36%)
	More than 3 months ago (N=10)	4 (40%)	6 (60%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[d]	2 (50%)	2 (50%)
	51-99 patients (N=21)	9 (43%)	12 (57%)
	100-250 patients (N=29)	17 (59%)	12 (41%)
	>250 patients (N=21)	15 (71%)	6 (29%)
Amount of HCP Guide read?[e]	All of it (N=33)	19 (58%)	14 (42%)
	More than half of it (N=16)	9 (56%)	7 (44%)
	About half of it (N=9)	7 (78%)	2 (22%)
	Less than half of it (N=1)	1 (100%)	
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	33 (59%)	22 (41%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=15)	8 (53%)	7 (47%)
Received and reviewed SmPC?	Yes (N=60)	36 (60%)	24 (40%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	5 (45%)	6 (55%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a An alternative, more stringent answer '…for at least 48 months after each treatment' was selected by 21% of HCPs from all countries: UK, 27%; Germany, 0%; Italy, 10%; Spain, 20%; Greece, 40%; Belgium, 20%; the Netherlands, 30%.

b Combined with those who self-reported "General neurologist" discussion purposes

c Not included in discussion

d Combined with HCPs who saw 51-99 patients for discussion purposes

e Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.10 Knowledge of what to do if adverse events are suspected

Immune thrombocytopenic purpura

Knowledge of what to do if the HCP suspects that a patient has ITP was high (≥70% for most subgroups) and similar within most subgroups (Table 32).

Table 32 - Subgroup analysis: What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)?

Q.27 What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)? ***Obtain a complete blood count and if thrombocytopenia is confirmed, refer to a specialist (haematologist) immediately***		**Correct answer N=65** n (%)	**Incorrect answer N=10** n (%)
Country	UK (N=15)	13 (87%)	2 (13%)
	Germany (N=10)	9 (90%)	1 (10%)
	Italy (N=10)	7 (70%)	3 (30%)
	Spain (N=10)	9 (90%)	1 (10%)
	Greece (N=10)	9 (90%)	1 (10%)
	Belgium (N=10)	9 (90%)	1 (10%)
	Netherlands (N=10)	9 (90%)	1 (10%)
Specialist area	General neurologist (N=28)	23 (82%)	5 (18%)
	MS specialised neurologist (N=45)	40 (89%)	4 (11%)
	Neurologist with sub specialism other than MS (N=2)[a]	2 (100%)	--
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	15 (88%)	2 (12%)
	MS clinic in a community hospital (N=17)	15 (88%)	2 (12%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	16 (94%)	1 (6%)
	Neurology clinic (other than MS) in a community hospital (N=22)	17 (77%)	5 (23%)
	Office based specialist (N=2)[b]	2 (100%)	--
Last initiation of LEMTRADA	Within last week (N=11)	10 (91%)	1 (9%)
	Within last month (N=29)	26 (90%)	3 (10%)
	Within last 3 months (N=25)	23 (92%)	2 (8%)
	More than 3 months ago (N=10)	6 (60%)	4 (40%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	17 (81%)	4 (19%)
	100-250 patients (N=29)	26 (90%)	9 (10%)
	>250 patients (N=21)	18 (86%)	2 (14%)
Amount of HCP Guide read?[d]	All of it (N=33)	29 (88%)	4 (12%)
	More than half of it (N=16)	14 (88%)	2 (12%)
	About half of it (N=9)	7 (78%)	2 (22%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--

Q.27 What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)? ***Obtain a complete blood count and if thrombocytopenia is confirmed, refer to a specialist (haematologist) immediately***		**Correct answer N=65** n (%)	**Incorrect answer N=10** n (%)
Received and reviewed HCP Checklist?	Yes (N=56)	52 (93%)	5 (7%)
	No (N=4)	3 (75%)	1 (25%)
	Don't remember (N=15)	10 (67%)	5 (33%)
Received and reviewed SmPC?	Yes (N=60)	53 (88%)	7 (12%)
	No (N=4)	2 (50%)	2 (50%)
	Don't remember (N=11)	10 (91%)	1 (8%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes
d Answered by respondents who have received and reviewed the HCP Guide (N=59)

Nephropathy

Knowledge of what to do if the HCP suspects that a patient has nephropathy was 53% (Table 16) and similar within most subgroups with the exception of Country (Table 33). The percentage of correct answers within the Country subgroup ranged from 10% to 100%, with no apparent trend or pattern. The percentages of correct answers among HCPs who had received and reviewed at least half of the HCP educational materials, while low, were higher than those who indicated that they did not receive the materials or did not remember receiving them.

Table 33 - Subgroup analysis: What should you do if your monitoring results lead you to suspect nephropathy?

Q.28 What should you do if your monitoring results lead you to suspect nephropathy? ***Refer the patient to a specialist (nephrologist) immediately***		**Correct answer N=40** n (%)	**Incorrect answer N=35** n (%)
Country	UK (N=15)	7 (47%)	8 (53%)
	Germany (N=10)	9 (90%)	1 (10%)
	Italy (N=10)	1 (10%)	9 (90%)
	Spain (N=10)	6 (60%)	4 (40%)
	Greece (N=10)	10 (100%)	--
	Belgium (N=10)	2 (20%)	8 (80%)
	Netherlands (N=10)	5 (50%)	5 (50%)
Specialist area	General neurologist (N=28)	14 (50%)	14 (50%)
	MS specialised neurologist (N=45)	24 (53%)	21 (47%)
	Neurologist with sub specialism other than MS (N=2)[a]	2 (100%)	--

Q.28 What should you do if your monitoring results lead you to suspect nephropathy? ***Refer the patient to a specialist (nephrologist) immediately***		**Correct answer N=40** n (%)	**Incorrect answer N=35** n (%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	5 (29%)	12 (71%)
	MS clinic in a community hospital (N=17)	11 (65%)	6 (35%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	10 (59%)	7 (41%)
	Neurology clinic (other than MS) in a community hospital (N=22)	13 (59%)	9 (41%)
	Office based specialist (N=2)[b]	1 (50%)	1 (50%)
Last initiation of LEMTRADA	Within last week (N=11)	3 (27%)	8 (73%)
	Within last month (N=29)	15 (52%)	14 (48%)
	Within last 3 months (N=25)	15 (60%)	10 (40%)
	More than 3 months ago (N=10)	7 (70%)	3 (30%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	2 (50%)	2 (50%)
	51-99 patients (N=21)	13 (62%)	8 (38%)
	100-250 patients (N=29)	15 (52%)	14 (48%)
	>250 patients (N=21)	10 (48%)	11 (52%)
Amount of HCP Guide read?[d]	All of it (N=33)	20 (61%)	13 (39%)
	More than half of it (N=16)	6 (38%)	10 (62%)
	About half of it (N=9)	4 (44%)	5 (56%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	33 (59%)	22 (41%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=15)	6 (40%)	9 (60%)
Received and reviewed SmPC?	Yes (N=60)	31 (52%)	29 (48%)
	No (N=4)	1 (25%)	3 (75%)
	Don't remember (N=11)	8 (73%)	3 (27%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics

a Combined with those who self-reported "General neurologist" discussion purposes

b Not included in discussion

c Combined with HCPs who saw 51-99 patients for discussion purposes

d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.2.2.11 Knowledge of the types of counselling that should be provided to patients treated with LEMTRADA

Knowledge of the types of counselling that should be provided to patients treated with LEMTRADA was high for all subgroups and similar within subgroups (Table 34), including HCP educational materials.

Table 34 - Subgroup analysis: What counseling should you provide patients treated with LEMTRADA?

Q.29 What counseling should you provide patients treated with LEMTRADA? ***Coping with MS, importance of contraception and risks and importance of monthly monitoring appointments***		**Correct answer N=68** n (%)	**Incorrect answer N=7** n (%)
Country	UK (N=15)	12 (80%)	3 (20%)
	Germany (N=10)	10 (100%)	--
	Italy (N=10)	10 (100%)	--
	Spain (N=10)	9 (90%)	1 (10%)
	Greece (N=10)	8 (80%)	2 (20%)
	Belgium (N=10)	10 (100%)	--
	Netherlands (N=10)	9 (90%)	1 (10%)
Specialist area	General neurologist (N=28)	26 (93%)	2 (7%)
	MS specialised neurologist (N=45)	41 (91%)	4 (9%)
	Neurologist with sub specialism other than MS (N=2)[a]	1 (50%)	1 (50%)
Time spent in each work setting (summary)	MS clinic in an university hospital/specialty clinic (N=17)	15 (88%)	2 (12%)
	MS clinic in a community hospital (N=17)	13 (76%)	4 (24%)
	Neurology clinic (other than MS) in an university hospital/specialty clinic (N=17)	17 (100%)	--
	Neurology clinic (other than MS) in a community hospital (N=22)	21 (95%)	1 (5%)
	Office based specialist (N=2)[b]	2 (100%)	--

Q.29 What counseling should you provide patients treated with LEMTRADA? ***Coping with MS, importance of contraception and risks and importance of monthly monitoring appointments***		**Correct answer N=68** n (%)	**Incorrect answer N=7** n (%)
Last initiation of LEMTRADA	Within last week (N=11)	10 (91%)	1 (9%)
	Within last month (N=29)	28 (97%)	1 (3%)
	Within last 3 months (N=25)	22 (88%)	3 (12%)
	More than 3 months ago (N=10)	8 (80%)	2 (20%)
Number of MS patients seen in a typical year	11-50 patients (N=4)[c]	4 (100%)	--
	51-99 patients (N=21)	19 (90%)	2 (10%)
	100-250 patients (N=29)	25 (86%)	4 (14%)
	>250 patients (N=21)	20 (95%)	1 (5%)
Amount of HCP Guide read?[d]	All of it (N=33)	29 (88%)	4 (12%)
	More than half of it (N=16)	15 (94%)	1 (6%)
	About half of it (N=9)	8 (89%)	1 (11%)
	Less than half of it (N=1)	1 (100%)	--
	None of it (0)	--	--
Received and reviewed HCP Checklist?	Yes (N=56)	50 (89%)	6 (11%)
	No (N=4)	4 (100%)	--
	Don't remember (N=15)	14 (93%)	1 (7%)
Received and reviewed SmPC?	Yes (N=60)	55 (92%)	5 (8%)
	No (N=4)	4 (100%)	--
	Don't remember (N=11)	9 (82%)	2 (18%)

HCP = Healthcare Provider; MS = Multiple Sclerosis; SmPC = Summary of Patient Characteristics
a Combined with those who self-reported "General neurologist" discussion purposes
b Not included in discussion
c Combined with HCPs who saw 51-99 patients for discussion purposes
d Answered by respondents who have received and reviewed the HCP Guide (N=59)

10.3 OTHER ANALYZES

No additional analyzes were performed.

10.4 ADVERSE EVENTS/ADVERSE REACTIONS

Not applicable.

11 DISCUSSION

The LEMTRADA RMP includes risk minimization measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimization. The objective of this LEMTRADA EU-RMP Survey in HCPs was to assess descriptively the knowledge of HCPs who prescribe LEMTRADA with regard to the items of the HCP educational materials (HCP guide, HCP checklist, and SmPC) and thus the effectiveness of these materials to ensure the safe use of LEMTRADA.

The survey was conducted with 75 HCPs from 7 countries (UK, Germany, Italy, Spain, Greece, Belgium, and the Netherlands). Forty-five (60%) HCPs were MS specialists. The majority of HCPs (n=50; 67%) treated at least 100 patients with MS in a typical year. Forty HCPs (64%) had initiated LEMTRADA treatment with at least 1 patient within the last month.

For all analyzes, a threshold of 70% was defined as 'adequate' knowledge.

11.1 PRIMARY ANALYSIS

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

HCPs received and read the HCP guide, HCP checklist, and the SmPC, and they were familiar with the Patient Guide and Patient Alert Card. A total of 79% of HCPs recalled receiving, reviewing, and using the educational materials. Among them, 83% reported reading more than half of the HCP guide, 83% reported they always or usually use the HCP checklist, and 63% reported they always or usually reviewed the SmPC. This demonstrates that these materials have a well established place in the HCPs' practice for risk minimization activities. In addition, 81% of HCPs were aware of the available patient materials, and 80% reported to have read them before handing them to patients.

The results of the survey indicated that HCPs had adequate knowledge (ie, ≥70% correct answers) for about one-third of the questions. Topics where HCP knowledge was higher included risks to be discussed at first prescription of LEMTRADA, contraindicated conditions and treatments, when to check serum creatinine levels, the appropriate medical intervention if the patient has suspected ITP, and the need to counsel patients on essential topics.

Areas in which HCP knowledge was lower than the 70% limit for acceptability were for the most part related to timing. The one exception was related to knowledge around the appropriate medical intervention for suspected nephropathy. The timing-related questions were: the required wait period following vaccination, timing for the use of contraception for women of childbearing potential, and the specific timing for checking CBC with differential as well as testing for thyroid function, urinalysis with microscopy, liver function, and urine protein creatinine ratio.

Regarding the lower scores about timing of clinical assessments, it is possible that the HCPs were influenced by the wording of the questions. Some examples are presented as follows:

Vaccinations: In many cases where responses were deemed 'incorrect' according to the survey, some HCPs were in fact answering cautiously and selecting a more stringent answer. For example, for Q19 (required wait period following vaccination), the correct answer was '6 weeks', however, one alternative answer selected by 25% of HCPs was '6 months'. Taking this more cautious response into account, a combined total of 65% of HCPs correctly indicated that at least a 6-week wait period following vaccination is necessary before administering LEMTRADA (Table 7). However, there is a risk in waiting unnecessarily long after vaccination when the patient could begin treatment with LEMTRADA sooner.

Nephropathy: Some of the alternative answers were very similar. For example, in Q28 (what to do if the HCP suspects that a patient has nephropathy), the correct answer was, 'Refer the patient to a specialist (nephrologist) immediately' and this option was selected by 53% of HCPs. An alternative answer contained the exact same phrase following the request to let patients come in as soon as possible, ie, 'Ask the patient to come in as soon as possible, conduct urine tests and if suspected nephropathy refer/send the patient to nephrologist immediately'. This option was selected by 47% of HCPs overall (Table 16). It may be that this option confused respondents as it holds the correct answer plus extra features that may be appealing or even standard practice for some HCPs, such as asking the patient to come in as soon as possible and conducting urine tests. In fact, many subgroups also scored high on this particular alternative answer, sometimes even higher than on the correct answer, which supports the speculation that presentation of answer may have been confusing. Moreover, only 3% of respondents choose the incorrect option, 'Wait until the patient's next scheduled appointment when any change in serum creatinine level from baseline can be confirmed', which is an encouraging result.

Contraception: Regarding the length of time that women of childbearing potential should use effective contraceptive measures (Q26): based on a half-life for LEMTRADA of an estimated 2 days with no drug detectable within 30 days, the MAH selected a cautious measure of 4 months post treatment (5 half-lives, assuming a 3-week half-life). Just over half (57%) of HCPs correctly selected this answer, and another 21% thought contraception should be used for at least 48 months following each treatment (Table 14). An additional 21% of respondents selected a shorter time frame of 30 days or less following each treatment (which does not meet the requirements of the MAH's very cautious and reasonable approach).

Clinical testing: Scores for the timing of clinical tests were generally well below the 70% criterion for adequate knowledge. There are several potential explanations for this result. In addition to the possibility of HCPs erring on the side of caution when responding to the questions, it may be that some HCPs have adapted their own monitoring schedules and conduct tests more often than what was considered as 'correct' in the survey. Indeed, the majority of HCPs provided answers that were correct OR more cautious (ie, more often testing). For example, an HCP who reports performing thyroid tests monthly (an 'incorrect' survey response) is responding in a more thorough manner than one who reports performing thyroid tests every 3 months (the 'correct' survey response). Therefore, although their behavior is clinically sound, the responses would be interpreted as 'incorrect'.

Other explanations for less than optimal responses in certain areas include the following: The HCP population was heterogeneous (eg, area of specialty, work setting, experience with LEMTRADA, etc.). Some of these HCPs – particularly the general neurologists – would be

responsible for a wide range of patients with many different diagnoses and medication risks; those HCPs may not be able to easily recall all potential risks to be discussed and time points of tests to be conducted without having to refer to the educational materials or other resources. Also, sometimes LEMTRADA treatment is given in expert centers far away from patients' homes. MS specialists and neurologists arrange with the patients' general practitioner or a local neurologist to perform the monitoring tests locally, and this may have influenced the routine knowledge of the prescribing HCPs and therefore their responses to the pertinent questions. Finally, infusion clinics often employ MS-nurse specialists and/or other support staff with specific responsibilities. In well-organized clinics the neurologist prescribes a LEMTRADA monitoring package but not the individual tests. The nurses and/or support staff are highly involved and in some places taking care of ordering the clinical tests, which in this particular case with LEMTRADA follow a pre-defined schedule.

Importantly, the HCPs were asked to answer the survey questions without referencing the educational materials, which may not reflect their clinical practice where these materials would be available to them to use during their clinical decision making and patient counseling. Even so, the scores of some topics were quite high, demonstrating that, overall, HCPs have a good understanding of the most important risks associated with the use of LEMTRADA and are aware of the monitoring needed. For some areas that scored lower, having the materials at hand to reference may have increased the percentage of correct answers. The fact that a large percentage of HCPs reported that they read and used the educational materials indicates that the materials are valuable in providing the kinds of information the HCPs need to treat their patients safely. While no changes to the RMP are considered warranted at this time, the MAH is still working on improving our reach to HCPs, eg, via digital initiatives.

11.2 SECONDARY ANALYZES BY SUBGROUP

Subgroup comparisons were consistent with the primary analysis results in demonstrating that review of all HCP educational materials leads to improved knowledge, further supporting the efficacy of the materials. Ensuring that all HCPs receive the materials and reinforcing the importance of the HCP educational materials may increase knowledge in all areas.

There were, however, a few differences of interest within subgroups.

Subgroup comparison by country showed that the UK physicians scored lower than the HCPs of other countries on, eg, awareness of the available materials, including the patient materials, and the frequency and duration of monitoring. This may be at least partly due to the active role MS nurses play in the UK clinics in patient treatment, preparation, and education. In larger centers, MS nurses may be tasked with patient counseling, and/or staff physicians may delegate this task to junior physicians.

Subgroup comparisons also indicated that MS specialised neurologists had more knowledge about the HCP educational materials than did general neurologists. However, in nearly all secondary comparisons, there were only minor or no differences between the 2 groups. Despite the fact that fewer general neurologists reported having received and reviewed the HCP educational materials,

it may be that those who did receive the materials consulted them more often, demonstrating that the materials do fulfill their purpose.

HCPs based in community hospitals were more knowledgeable than those based in university hospitals about conditions in which LEMTRADA is contraindicated, tests to be conducted before the first LEMTRADA prescription, wait period after vaccination, and monitoring activities for autoimmune events. The latter finding may be because doctors in university hospitals are more likely to refer patients back to community hospitals following LEMTRADA infusions.

11.3 STRENGTHS AND LIMITATIONS

The strength of this comprehensive survey include the potential reach of HCPs for recruitment (there was a total of 668 clicks on the survey website link) from 7 countries including 2 of the most populated countries in which LEMTRADA has been launched. The completion rate was high (95%): in total, only 4 HCPs who began the survey quit without completing.

Limitations of this survey include the use of a cross-sectional design which made it difficult to determine whether the HCP 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, motivation, or greater experience with the drug. All data were self-reported, and there was no opportunity to verify source data. A convenience sample (non-randomized) was used, rather than a random sample, which means that the findings may not be representative of the whole population of HCPs prescribing LEMTRADA, thereby limiting the generalizability of the results. However, it should be noted that a random sample was not possible given that there is not a database of names and addresses of LEMTRADA HCPs that could be accessed in order to randomly select HCPs. In addition, due to the (relatively) low number of HCPs who enrolled in the survey, formal statistical analyzes of subgroups would not be informative, and therefore the results are only descriptive. The survey only targeted the prescribing HCP and therefore in some cases may not reach the population directly involved in the patient treatment, preparation, and education who may be accessing the educational materials most often. For example, in larger treatment or medical centers, MS nurses or junior physicians may play a more dominant role in the actual treatment logistics, and therefore they would be the ones who are using the educational materials most often. Finally, the caveat of a relatively small number or physicians and the fact that the participants were asked to answer the questions without referring to the educational materials should be considered when interpreting the results of the study.

Ensuring that all HCPs receive the materials and reinforcing the importance of the HCP educational materials may increase knowledge in these areas in demonstrating that review of all HCP educational materials leads to improved knowledge, further supporting the efficacy of the materials.

12 OTHER INFORMATION

Not applicable.

13 CONCLUSION

The Wave 2 survey findings suggest that the HCPs prescribing LEMTRADA have an adequate knowledge of risk minimization activities. A total of 79% of HCPs recalled receiving, reviewing, and using the educational materials. Of these, 83% reported reading more than half of the HCP guide, 83% reported they always or usually use the HCP checklist, and 63% reported they always or usually reviewed the SmPC. This demonstrates that these materials have a well-established place in the HCPs' practice for risk minimization activities. In addition, 81% of HCPs were aware of the available patient materials, and 80% reported to have read them before handing them to patients. There appears to be a link between use of the materials and the knowledge on LEMTRADA and its risks. The overall results show adequate knowledge and behavior of the HCPs around contraindications, identification of potential serious adverse events, and behavior when symptoms occur, based on a 70% threshold for correct responses. This suggests that the materials are effective in ensuring the safe use of LEMTRADA.

However, there is room for improvement in some areas of knowledge. Therefore, the need remains to ensure not only that all HCPs who prescribe LEMTRADA receive the HCP educational materials, but that they understand the importance of them as well.

Overall, the MAH considers that the results of the Wave 2 HCP knowledge and understanding survey confirm that the educational materials are overall effective in supporting HCP knowledge relating to the safe use of LEMTRADA. While no changes to the RMP are considered warranted at this time, the MAH is still working on improving our reach to HCPs, eg, via digital initiatives.

14 REFERENCES

1. Ishihara L, Lewis A, Kolli S, Brickel N. European Survey of Prescriber Understanding of Risks Associated with Retigabine. Drugs Real World Outcomes. 2015;2(4):345-353.

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

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

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

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

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: 8 May 2017 Total number of pages 28

PASS information:

Title:	Knowledge survey to assess the effectiveness of educational materials among healthcare professionals who prescribe Lemtrada (alemtuzumab)
Protocol version identifier	1.8
Date of last version of protocol	February 2017
EU PAS register number (if applicable)	n.a.
Active substance	Alemtuzumab (L04AA34)
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 overall objective of the survey is to assess descriptively the knowledge level of healthcare professionals with regard to educational messages and thus the effectiveness of the educational materials to support the safe use of Lemtrada. Research questions: 1. What is the prescriber's understanding and awareness of the risks associated with use of Lemtrada? 2. What is the prescriber's knowledge of the key safety messages in the content of the HCP guide and HCP checklist? 3. What is the prescriber's knowledge and understanding of the risk minimisation activities to be undertaken in relation to Lemtrada?
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	tbd.

MARKETING AUTHORIZATION HOLDER(S)

Marketing authorization holder(s)	Genzyme Therapeutics, Ltd 4620 Kingsgate Cascade Way Oxford Business Park South Oxford OX4 2SU United Kingdom
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TABLE OF CONTENTS

1 LIST OF ABBREVIATIONS

List of main abbreviations used in the study protocol

AE	Adverse Event
Anti-GBM	Anti-Glomerular Basement Membrane
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare Professional
IPT	Immune Thrombocytopenic Purpura
MAH	Marketing Authorization Holder
MG	Medication Guide
MS	Multiple Sclerosis
PC	Patient Card
PIL	Patient Information Leaflet
RMP	Risk Management Plan
SAE	Serious Adverse Events
SmPC	Summary of Product Characteristics

2 RESPONSIBLE PARTIES

Ipsos, together with Sanofi Genzyme, will be responsible for the preparation of the protocol and its amendments and will develop the survey.

Ipsos will also be involved with the recruitment of healthcare professionals (HCPs), management of the questionnaire and analyse the results.

The survey is sponsored by Sanofi Genzyme.

3 SYNOPSIS

Title

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

Rationale and background

The Lemtrada risk management plan (RMP) includes additional risk minimisation measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimisation. The HCP educational pack consists of the Summary of Product Characteristics (SmPC), HCP materials and patient materials. The core elements of the HCP educational materials are an HCP guide and checklist. These are aimed at ensuring early detection of key symptoms indicative of adverse events (AEs), communication of risks of symptoms and the importance of periodic monitoring, and to inform about benefit-risk decisions before each treatment course. The risk management knowledge of HCPs prescribing Lemtrada will assess the effectiveness of the RMP in HCPs. Very little published research exists relating to the evaluation of RMPs, however, the methods of extant published literature have been used to guide proposals wherever possible.

Research question and objectives

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

Study design

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

Population

A randomly generated sample of HCPs involved in the treatment of multiple sclerosis (MS) patients with Lemtrada. The selected countries will include at least 2 of the highly populated EU countries (DE, FR, UK, IT, ES). It is important that HCPs have prescribed Lemtrada to at least one of their patients in the last 6 months.

Variables

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

1. The prescriber's understanding and awareness of the risks associated with use of Lemtrada

2. The prescriber's knowledge of the key points in the content of the HCP guide and HCP checklist

3. The prescriber's knowledge of the risk minimisation activities to be undertaken.

Data sources

Data regarding the known distribution of neurologists and MS sub-specialists for participating countries will be supplied by the Marketing Authorization Holder (MAH). All other data will be collected via HCP self-report in a questionnaire.

Study size

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

Data analysis

Descriptive analyses only will be performed. Additional sub analyses may be conducted to further investigate any findings. A threshold of 70% will be defined as 'adequate' knowledge.

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).

4 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

5 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

6 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 Lemtrada, please refer to the SmPC.

Description of Lemtrada Risk Management Plan

The Lemtrada RMP includes risk minimisation measures and tools to support the safe use of the product. Educational materials form one of the core elements of risk minimisation.

The primary objectives of the educational materials are to:

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

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

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

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

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

Autoimmune conditions, including:

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

Additional items that HCPs need to be aware of:

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

Relevant published research

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

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

RATIONALE

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

the understanding of the effectiveness of the RMP strategy and the safe prescription of Lemtrada.

7 RESEARCH QUESTION AND OBJECTIVES

Research questions

1. What is the prescriber's understanding and awareness of the risks associated with use of Lemtrada?

2. What is the prescriber's knowledge of the key safety messages in the content of the HCP guide and HCP checklist?

3. What is the prescriber's knowledge and understanding of the risk minimisation activities to be undertaken in relation to Lemtrada?

7.1 PRIMARY OBJECTIVE

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

7.2 SECONDARY OBJECTIVES

Not applicable.

8 RESEARCH METHODS

8.1 STUDY DESIGN

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

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

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

8.2 SETTING

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

8.2.1 Duration of the study

The duration of the study will be 96 weeks.

8.2.2 Eligibility criteria

8.2.2.1 Inclusion criteria

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

Exclusion criteria

- HCP has not prescribed Lemtrada within the past 6 months
- Participation in the questionnaire in Wave 1.

8.2.3 Analysis populations

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

8.2.4 Modalities of recruitment

8.2.4.1 Physician selection

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

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

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

The registered HCP population will be described in terms of date when qualified as a doctor and MS specialist, practice setting and patient caseload and compared in each participating country with the known distribution of neurologists and MS sub specialists to ensure representativeness.

HCPs will provide informed consent and data will be anonymous for the MAH.

60 - 70 Lemtrada prescribing HCPs (excluding those who completed the first round) will be invited to complete the second round questionnaire. At each time point a follow-up reminder email will be sent two weeks after initial invitation to try to ensure adequate recruitment.

8.3 VARIABLES

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

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

1. Physician characteristics including:
   a) Country
   b) Type of hospital
   c) Speciality
   d) Total number of MS patients under treatment
   e) Number of patients prescribed Lemtrada
   f) Time since last prescription of Lemtrada.

2. The prescriber’s knowledge of the existence of:
   a) the HCP guide
   b) the HCP checklist
   c) the SmPC

d) the Patient Guide
e) the Patient Alert Card
f) the Package Leaflet.

4. The prescriber's understanding and awareness of the risks associated with use of the product:
   a) ITP
   b) Nephropathies
   c) Thyroid disorders
   d) Thyroid disorders in pregnancy

5. Knowledge of the key points in the content of the HCP guide, and HCP checklist:
   a) Contraindications
   b) Lists of tests to be conducted for the initial screening of the patient
   c) Vaccination, pre-treatment courses
   d) Monitoring activities for the autoimmune events
   e) Special warnings on pregnancy, contraception, and breast feeding.

6. The prescriber's knowledge of the risk minimisation activities to be undertaken
   a) Type of monitoring required (blood and urine, self-monitoring)
   b) Required time period for monitoring
   c) If ITP, 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

Knowledge will be measured via self-report using an online questionnaire, which HCPs will complete. The questionnaire will measure knowledge using questions with single choice or multiple-choice responses (as appropriate). The response on knowledge will be considered satisfactory if participants provide >70% of correct answers.

Potential confounding factors

1. Some HCPs may only have small numbers of patients eligible to be prescribed Lemtrada. Approximate number of patients treated with Lemtrada will be recorded and included as a variable for sub-group analysis.
2. Length of time since last prescription of Lemtrada to a patient will be recorded and included as a variable for sub-group analysis.
3. HCPs will have to conduct the survey by heart as they will be asked a variety of questions to which they will have to provide the answer to by memory.

8.4 DATA SOURCES

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

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

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 360 Lemtrada prescribers in the countries where the study is planned to be conducted, and taking into account an expected response rate of approximately 15 - 20%, the survey will be administered in a random selection of 60 - 70 HCPs.

8.5.2 Sample size

It is planned to recruit 60 - 70 HCPs.

8.6 DATA MANAGEMENT

8.6.1 Data collection schedule

HCP data

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

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

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

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

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

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

MS population data

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

8.6.2 Data collected

Online questionnaire

- Whether HCP took part in Wave 1 (only applicable for Wave 2)
- Country of practice
- Work setting (public/private; university/community hospital)
- Prescribed at least one dose of Lemtrada within the past 6 months
- Knowledge relating to Lemtrada risk management

8.6.3 Site / Physician questionnaire

Not applicable.

8.6.4 Screening log (if applicable)

Not applicable.

8.6.5 Patient data

Not applicable.

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

Not applicable.

8.6.7 Logistic aspects

Not applicable.

8.7 DATA ANALYSIS

8.7.1 Primary analysis

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

The response on knowledge is considered satisfactory if participants provide >70% correct answers.

8.8.2 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:
    - Number of eligible patients HCPs treated with Lemtrada
    - Length of time since last prescription
    - University or community hospital
    - General neurologist or MS sub-specialist
    - Country

8.7.3 Interim analysis

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

8.8 QUALITY CONTROL

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

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

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

Analysis will be undertaken using the 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.

8.8.2 Data quality control at site level

Not applicable.

8.9 LIMITATIONS OF THE RESEACH METHODS

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

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

8.10 OTHER ASPECTS

Not applicable.

9 PROTECTION OF HUMAN SUBJECTS

9.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

Not applicable.

9.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

9.2.1 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.

9.2.2 Laws and regulations

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

9.2.3 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.

9.2.4 Insurance

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

9.2.5 Secrecy agreement

Not applicable

9.2.6 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.

9.2.7 Discontinuation of the study

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

9.2.8 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.

10 MANAGEMENT OF REPORTING ADVERSE EVENTS/ADVERSE REACTIONS

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

11 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

11.1 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.

11.2 PUBLICATIONS

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

12 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.

13 ANNEXES

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	V11	July 2013	HCP guide
4	V12	July 2013	HCP checklist
5	V12	July 2013	Patient Guide
6	V10	July 2013	Patient Alert Card

14 APPENDICES

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 [show to all other markets] (alemtuzumab) [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 healthcare professionals who prescribe LEMTRADA® (alemtuzumab)

COMPOUND: ALEMTUZUMAB

STUDY NUMBER: N/A

Short title: LEMTRADA EU-RMP Survey in HCPs

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

Version Number:	6.0		
Date:	09 November 2016	Total number of pages:	76

PASS Information

Title	Knowledge Survey to assess the effectiveness of educational materials among healthcare professionals who prescribe LEMTRADA (alemtuzumab)
Version identifier of the final study report	Version 4
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)	Genzyme Therapeutics Ltd
Joint PASS	No
Research question and objectives	The overall objective of the survey is to assess descriptively the knowledge level of HCPs with regard to educational messages and thus the effectiveness of the educational materials to support the safe use of LEMTRADA. Research questions: 1. What is the prescriber's understanding and awareness of the risks associated with use of LEMTRADA? 2. What is the prescriber's knowledge of the key safety messages in the content of the HCP guide and HCP checklist?

	What is the prescriber's knowledge and understanding of the risk minimization activities to be undertaken in relation to LEMTRADA?
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)

Marketing authorization holder(s)	Genzyme Therapeutics, Ltd 4620 Kingsgate Cascade Way Oxford Business Park South Oxford OX4 2SU United Kingdom
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TABLE OF CONTENTS

1 ABSTRACT

Title

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

Keywords

LEMTRADA, audit, risk minimisation materials, effectiveness

Rationale and background

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

The risk management knowledge survey assesses the effectiveness of the educational materials for HCPs as part of the RMP amongst HCPs who have prescribed LEMTRADA. Very little published research exists relating to the evaluation of RMPs, however, the methods of existent published literature were used to guide proposals wherever possible.

Research question and objectives Study

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

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 will be analysed and reported to the European Medicines Agency (EMA). This report describes Wave 1 of the survey. Wave 2 will be conducted starting May 2017, three years after the launch of LEMTRADA in Spain.

Setting

- Site and patient selection: A convenience (i.e. non-random) sample of HCPs involved in the treatment of multiple sclerosis (MS) patients with LEMTRADA.
- Overall participation status: Seventy-four HCPs from Germany (n=20, 27%), Italy (n=20, 27%), Spain (n=15, 20%), UK (n=15, 20%), Denmark (n=1, 1%) and Norway (n=3, 4%) completed the survey
- Data collection: Data regarding the known distribution of neurologists and MS sub-specialists for participating countries were supplied by the MAH. All other data were collected via HCP self-report in a questionnaire.

Patients and study size, including dropouts

There were 606 clicks on the website link to the survey, and 74 HCPs completed the survey. An additional 60 to 70 HCPs (excluding those who completed the first round) will be invited to complete the second wave questionnaire. To avoid confusion, the set of HCPs who filled out the survey in Wave 1 will not be invited to participate in Wave 2 of the survey.

Variables and data sources

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

    1. The prescriber's understanding and awareness of the risks associated with use of the product

    2. The prescriber's knowledge of the key points in the content of the HCP guide and HCP checklist

    3. The prescriber's knowledge of the risk minimisation activities to be undertaken

- Data analyses: Descriptive analyses were performed.

Results

Seventy-four HCPs were involved in the study. Most considered themselves a MS-specialist neurologist (58%) while the remaining 42% considered themselves a neurologist (i.e. not a MS specialist). The country distribution was as follows: Germany (27%), Italy (27%), Spain (20%), UK (20%), Norway (4%) and Denmark (1%). There is estimated to be 1 neurologist per 100,000 population in the UK, 2.4 per 100,000 in Germany, 2.5 per 100,000 in Spain, 3 per 100,000 in Denmark, and 5 per 100,000 in Norway[3]. The distribution of the sample in this study is reflective of the estimated number of neurologists per country calculated using 2015 population statistics[4]. Seventy-six percent of HCPs recalled receiving and reviewing the HCP Guide; seventy-six percent recalled receiving and reviewing the HCP checklist. Sixty-nine percent recalled receiving and reviewing both the HCP guide and checklist. Eighty-nine percent recalled receiving and reviewing the SmPC. Only one HCP (1%) did not recall receiving or reviewing the HCP guide, the HCP checklist, or the SmPC. The proportions of HCPs who had knowledge of the Patient Guide, Patient Alert Card and Package Leaflet were 84%, 77% and 77% respectively. Fifty-seven percent indicated that they were aware of all three patient materials. All HCPs were all of at least one of the

materials; however, 14 (18.9%) HCPs knew only one of three materials, and 18 (24.3%) knew only two.

HCP knowledge of the topics to be discussed at first prescription of LEMTRADA ranged from 82% for nephropathies including anti-GBM disease to 89% for active infections. Fifty-eight percent of HCPs selected all of the five topics to be discussed and 94% selected at least three of the five topics. Knowledge of contraindicated conditions (HIV and hypersensitivity to the active substance or any of the excipients) was 92% and 89%, respectively, with 85% selecting at least both of these. Knowledge of contraindicated treatments (immunosuppressive therapy and antineoplastic therapy) was 91% and 77% respectively, with 72% selecting both contraindicated treatments. HCPs' knowledge of the tests to be conducted before first prescription of LEMTRADA ranged from 65% (for urinalysis with microscopy) to 93% (complete blood count with differential and thyroid function tests). Fifty-nine percent of HCPs selected at least four correct responses and therefore answered the question completely. Seventy-two percent of HCPs were aware of the wait period of at least six weeks after the last vaccination before administering LEMTRADA.

Knowledge of appropriate intervention if the patient had suspected immune thrombocytopenic purpura (ITP) or suspected nephropathy was 91% and 80% respectively. Seventy percent of HCPs were aware of the need for women of childbearing potential to use contraception for at least four months following each infusion course (4%, 7% and 19% of HCPs reported that contraception should be used during treatment and for at least 5 days, 30 days, and 48 months following treatment, respectively). Eighty percent of HCPs indicated that they were aware of the need to counsel patients on at least the importance of contraception and the risks and importance of monthly monitoring appointments. Sixty-eight percent also reported the need to counsel patients on coping with MS. Knowledge of all time-points at which monitoring activities for autoimmune events should or should not be conducted was lower. The area where HCPs were least knowledgeable was liver function tests where only 22% correctly answered that liver function tests do not need to be routinely carried out. HCPs may err on the side of caution and proceed with these tests regularly; 61% reported that these tests should be carried out before prescription and 42% reported tests should be monthly for 48 months following final infusion. The area where HCPs were most knowledgeable was time-points for complete blood counts; here 61% scored all time points correctly, namely that these should be conducted before the patient is prescribed and monthly until 48 months following final infusion (26% reported tests should be every 3 months and 8% reported they should be every 2 months). For the remaining tests, the proportions of correct answers were: 28% for urine protein creatinine ratio tests (not needed); 46% for thyroid function tests; 47% for urinalysis with microscopy; and 54% for serum creatinine levels.

HCPs who had received and reviewed HCP materials had significantly greater knowledge of patient education materials available (65% correct versus 40% correct, $p = .038$), the potential risks to be discussed at first prescription of LEMTRADA (76% complete answers versus 24% complete answers, $p = .000$), tests to conduct at first prescription ($p = .032$), when to conduct monitoring tests (specifically, complete blood count with differential, urinalysis with microscopy), and the types of counseling that should be provided for patients receiving LEMTRADA (88% complete answers versus 64% complete answers, $p = . 016$).

Subgroup analyses also indicated that knowledge was greater among (self-reported) MS specialists compared to (self-reported) non MS specialist neurologists, in those who had more recently prescribed LEMTRADA, and in those who saw more MS patients each year. Specifically, self-

reported MS specialist neurologists were significantly more likely than non-MS specialist neurologists to score correctly for what to do if there is suspected nephropathy (88% correct versus 68% correct, $p = .029$) and when to conduct complete blood counts with differentials ($p = .024$).

Those who had prescribed LEMTRADA within the last month were significantly more likely than those who had prescribed it more than one month ago to answer completely the potential risks that should be discussed with patients (70% answering completely versus 39%, $p = .010$).

Those working in a university hospital were significantly less able to score correctly for when to check complete blood count with differential (46% correct versus 71% correct, $p = .013$). Those in a community hospital were significantly less able to score correctly for how long women of childbearing potential should use effective contraception measures (54% correct versus 78% correct, $p = .036$). Those working in a university hospital were also significantly less able to score correctly for when to check serum creatinine levels than those not working in a university hospital (41% correct versus 75% correct, $p = .004$).

Lastly, specialists who typically see less than 100 MS patients per year were significantly *more able* than those who see more than 100 per year to know that liver function tests do not need to be routinely carried out. This is surprising. However, those who see more than 100 patients per year were more able to score correctly for knowledge of tests to be conducted at first prescription of LEMTRADA.

Discussion

The findings show that a high proportion of HCPs do recall receiving and reading the educational materials (>76%). However, there is some room for improvement, especially given that reading the materials is associated with substantially better knowledge. Therefore, there may be a need to ensure that not only all HCPs who prescribe LEMTRADA receive the HCP educational materials, but that they understand the importance of them as well. The understanding of the educational materials by HCPs warrants further attention. In addition, the distribution of educational materials to all appropriate HCPs, including non-MS-specialist neurologists and those who work in both community and university hospitals, is something that may also warrant further attention based on the fact that not all HCPs recall having received all of the educational materials.

There were areas where knowledge was high (>70% scoring correctly/completely), for example knowledge of contraindicated conditions and treatments, required wait period following vaccination, medical interventions following suspected ITP or nephropathy, and important issues to counsel patients on during appointments. Specific areas where knowledge was low (<70% scoring correctly/completely) included knowledge of potential risks that need to be discussed at first prescription, tests to be conducted at/prior to first prescription, the importance of contraceptive use in women of childbearing potential, and knowledge of tests that do and do not need to be conducted and when. However, it should be noted that in some cases where responses were deemed ‘incorrect’ or ‘incomplete’ according to the survey, HCPs were in fact answering cautiously and reporting that they would test more frequently than was required for a correct or complete answer. Given that 42% were non-MS specialists who are likely treating many different neurological syndromes, these results can be interpreted as reassuring. Although our conclusions are limited by the use of a cross-sectional design and potentially misleading survey questions, the findings suggest that the HCP educational materials are effective in increasing HCP knowledge of risk minimisation activities.

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Study Personnel

The Coordinating Investigator's and Company responsible medical officer's signed approvals of the report are provided in Annex 2.

This report was prepared by:

Alice Lee (Atlantis Healthcare), Marianne Berrens (Genzyme Europe BV), Femke Sanders (Genzyme Europe BV) and Ludivine Douarin (Sanofi aventis).

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

AEs:	Adverse events
HCP:	Healthcare professional
MAH:	Marketing authorization holder
PASS:	Post-authorization safety studies
QPPV:	Qualified person in pharmacovigilance
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	Comments
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	10 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.

Description of LEMTRADA Risk Management Plan

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

The primary objectives of the educational materials are to:

- Ensure early detection of events to mitigate the severity and sequelae of 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 cycle of treatment

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

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

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

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

Autoimmune conditions, including:

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

Additional items that HCPs need to be aware of:

- The patients' risks of developing the aforementioned autoimmune conditions, and the necessary monitoring procedures (blood and urine testing, watching for signs and symptoms) that must take place. HCPs need to be aware of the blood and urine tests that should be conducted before treatment initiation and continued for 48 months after last infusion. They should be aware of the need to counsel the patient on the risks and the need of monitoring and how to detect any signs or symptoms. This should be part of a benefit-risk discussion prior to LEMTRADA treatment.

- In addition, HCPs must be aware of the increased risks of thyroid disorders due to LEMTRADA during pregnancy as well as consequences of untreated thyroid disorders for a foetus.

- HCPs should be aware of the patient educational materials and how to access them.

- HCP should follow the recommended patient's screening, vaccination and pretreatment programs.

Relevant published research

This study assesses the knowledge of HCPs who prescribe LEMTRADA about the items of the educational materials and thus the effectiveness of these materials to ensure the safe use of LEMTRADA.

This is the first study to assess the effectiveness of the LEMTRADA RMP educational materials. Historically, there have been few published studies reporting the effectiveness of risk management interventions. A recent study showed greater knowledge of the risks of treatment among HCPs who had received an educational plan than those who had not.[3] The methods of existing published literature were used to guide proposals wherever possible.[4]

6.2 RATIONALE

This RMP assessment of effectiveness survey of HCP educational materials provides the first information relating to HCPs' understanding of the risk messages that are discussed in the education guide and SmPC for LEMTRADA prescribed for MS. It evaluates the HCP prescribers' knowledge of RMP materials. The findings of this study may make an important contribution to the understanding of the effectiveness of the RMP strategy and the safe prescription of LEMTRADA.

7 RESEARCH QUESTION AND OBJECTIVES

7.1 RESEARCH QUESTIONS

1. What is the prescriber's understanding and awareness of the risks associated with use of LEMTRADA?

2. What is the prescriber's knowledge of the key safety messages in the content of the HCP guide and HCP checklist?

3. What is the prescriber's knowledge and understanding of the risk minimisation activities to be undertaken in relation to LEMTRADA?

7.2 OBJECTIVES

7.2.1 Primary objectives

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

7.2.2 Secondary objectives

Not applicable.

8 AMENDMENTS AND UPDATES

None.

9 RESEARCH METHODS

9.1 STUDY DESIGN

This is a cross-sectional survey to be conducted in two distinct waves (Wave 1 and Wave 2), 18 months apart. In the current survey (Wave 1), HCPs were recruited from six countries across the EU, over an 11-week period. Online questionnaires were used to collect information regarding knowledge relating to risk minimisation (as described in the HCP guide and checklist) of HCPs involved in the treatment of MS using LEMTRADA.

Structured questions were used, where the response format was either the selection of a single response or multiple-choice responses (as appropriate). Results were analysed and will be reported to the European Medicines Agency (EMA).

The survey was not an interventional study to evaluate the impact of a predefined therapy or procedure.

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

9.2 SETTING

The survey was conducted in Denmark, Germany, Italy, Norway, Spain, and UK. Web and snowballing recruitment were used and the collection of survey data was conducted online.

Duration of the study

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

9.3 PARTICIPANTS

Eligibility criteria

Inclusion criteria

- HCP is a neurologist/ MS specialist
- HCP has prescribed LEMTRADA to at least one patient within the past six months
- HCP supplies informed consent by ticking a box on the survey website

Exclusion criteria

- HCP has not prescribed LEMTRADA within the past 6 months

Analysis populations

All surveys returned with at least one response completed were analysed

Modalities of recruitment

Physician selection

HCPs involved in the treatment of multiple sclerosis (MS) patients receiving LEMTRADA were invited to take part.

Multiple approaches were used to recruit the HCPs:

- Recruitment via online panels – panels exist for HCPs and were used as the first recruitment approach;
- Snowballing – respondents were requested to suggest other potential respondents that may be interested in participating.

HCPs have provided informed consent and the data has been anonymised for the Marketing Authorization Holder (MAH).

The target sample size was 60-70 LEMTRADA prescribing HCPs. This sample size was based on an estimate of 360 LEMTRADA prescribing HCPs in the countries where the survey was planned to be conducted. According to average response rate statistics in market research studies, a response rate of approximately 15%-20% could be expected. A further 60-70 LEMTRADA prescribing HCPs will be invited to complete the second round questionnaire. HCPs who participated in Wave 1 will not be invited to participate in Wave 2.

9.4 VARIABLES

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

The following elements were collected and assessed:

1. Physician characteristics including:

    a) Country
    b) Type of hospital
    c) Specialty
    d) Total number of MS patients under treatment
    e) Number of patients prescribed LEMTRADA
    f) Time since last prescription of LEMTRADA

2. The HCP’s knowledge of the existence of:

a) the HCP guide

b) the HCP checklist

c) the SmPC

d) the Patient Guide

e) the Patient Alert Card

f) the Package Leaflet

3. The prescriber's understanding and awareness of the risks associated with use of the product:

   a) Immune Thrombocytopenic Purpura (ITP)
   b) Kidney Disorders
   c) Thyroid Disorders
   d) Thyroid Disorders in pregnancy

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

   a) Contraindications
   b) Lists of tests to be conducted for the initial screening of the patient
   c) Vaccination
   d) Monitoring activities for the autoimmune events
   e) Special warnings on contraception, pregnancy and breast feeding

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

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

   b) Required duration and frequency for monitoring

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

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

Potential confounding factors

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

9.5 DATA SOURCES AND MEASUREMENT

Data regarding the known distribution of neurologists and MS sub specialists for participating countries were supplied by the MAH. All other data will be collected via HCP 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 HCPs who treat patients with MS to ensure the questions were understood and adequate.

User testing

User testing of the effectiveness questionnaire was conducted with 10 HCPs, all from the UK. Participants completed a telephone interview where they completed the online questionnaire and gave feedback on its clarity/ acceptability. Transcribed interviews were subjected to a content analysis and the findings used to refine the questionnaire. Modifications included clarification of some terms and alterations to the response format of some items.

9.6 BIAS

All data were self-reported, and there was no opportunity to verify source data. A convenience sample (rather than a random 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. Our estimated sample size was based on an estimate of 360 LEMTRADA prescribers in the countries where the study was planned. We expected a 15-20% response rate, equivalent to 60-70 HCPs.

Sample size

606 HCPs clicked the link to the survey website, of them 74 (12%) completed the questionnaire.

9.8 DATA TRANSFORMATION

Data collection schedule

HCP data

Data were collected online 21 months after launch of LEMTRADA in two highly populated countries (Germany and Spain). The change from the planned start date 18 months after launch was due to delays in contracting, compliance and local approvals. Recruitment took place over an 11-week period, rather than the planned 6-week period due to the limited number of prescribers presenting a potential challenge to recruitment.

Physicians 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 were translated into the local languages of participating countries.

On following the link within the invitation email, the information sheet was displayed. HCPs 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. The information sheet and consent statement emphasised that answers were anonymous and confidential. Following receipt of consent, the HCP 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 HCP was ineligible (e.g. has not prescribed 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 HCP was taken to a page thanking them for their participation.

HCP population data

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

Data collected

Online questionnaire

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

Patient and HCP data

No identifiable data regarding patients or HCP's were collected.

9.9 STATISTICAL METHODS

9.9.1 Primary analysis

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

9.9.2 Secondary analysis

The analysis was descriptive only.

1. Responses in sub-groups were compared to the rest of the sample. Sub-groups analysed were:
    - Number of eligible patients HCPs treat with LEMTRADA
    - Length of time since last prescription
    - University or community hospital
    - General neurologist or MS sub specialist
    - Country

9.9.3 Interim analysis

No interim analysis was planned for this registry. A report per wave is planned and a final report will combine results from 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.

9.10 QUALITY CONTROL

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

Data were collected electronically directly from HCPs using a secure system.

Data were 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 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 PARTICIPANTS

Table 1 summarises key demographic characteristics of the sample. Questionnaires were completed by 74 HCPs across six countries: Denmark (n=1; 1%), Germany (n=20; 27%), Italy (n=20; 27%), Norway (n=3; 4%), Spain (n=15; 20%) and the UK (n=15; 20%). The number of neurologists across 106 countries is reported to be over 85,000, with over 45,000 in Europe[5]. There is estimated to be one neurologist per 100,000 population in the UK, 2.4 per 100,000 in Germany, 2.5 per 100,000 in Spain, 3 per 100,000 in Denmark, and 5 per 100,000 in Norway[1]. Therefore, the distribution of the sample in this study is reflective of the estimated number of neurologists per country calculated using 2015 population statistics[2]; Germany should have the highest representation, followed by Spain, the UK, Norway, and Denmark. Italy figures could not be calculated as these were not accessible through the WHO.

Forty-three (58%) were MS specialists and 31 (42%) were non MS specialist neurologists. The majority of participants (n=49; 66%) treated at least 100 patients with MS in a typical year. Forty-six participants (62%) had initiated LEMTRADA with a patient within the last month. Descriptive data

Table 1 - Demographic characteristics of the HCP sample (n=74)

		N (%)
Country	Denmark	1 (1%)
	Germany	20 (27%)
	Italy	20 (27%)
	Norway	3 (4%)
	Spain	15 (20%)
	UK	15 (20%)
Specialist role	Neurologist	31 (42%)
	MS specialist neurologist	43 (58%)
Healthcare system	Public healthcare only	61 (82%)
	Private healthcare only	5 (7%)
	Both public and private healthcare	8 (11%)

Work setting	University hospital	46 (62%)
	Community hospital	24 (32%)[1]
	Office based specialist	5 (7%)
Number of MS patients treated in a typical year	<100	25 (34%)
	100+	49 (66%)
Number of patients treated with LEMTRADA	Median (range)	8 (1-300)
Last initiation of LEMTRADA	Within the last month	46 (62%)
	More than a month ago	28 (38%)
Number of prescriptions each month	<5	52 (70%)
	5-10	17 (23%)
	11-20	3 (4%)
	>20	2 (3%)

10.2 MAIN RESULTS

10.2.1 Primary analysis

Knowledge about HCP and Patient Educational Materials

The majority of participants (76%) reported that they had received and reviewed the HCP Guide, 8% reported that they had not received and reviewed the guide and 16% did not remember (Table 2). The same proportion of HCPs (76%) reported that they had received and reviewed the HCP Checklist; 8% reported that they had not received and reviewed the checklist and 16% did not remember. Fifty-one participants (69%) reported that they had received and reviewed both the HCP Guide and HCP Checklist. A higher proportion of participants (89%) reported that they had received and reviewed the Summary of Product Characteristics (SmPC); two HCPs (3%) reported they had not received and reviewed the SmPC (they were both from Italy) and 8% did not remember. Only one HCP (1%) had not received or reviewed the HCP guide, the HCP checklist, or the SmPC.

[1] One HCP indicated that they worked both at a community hospital and were office based

With regard to patient educational materials, the majority of HCPs were aware of the availability of the Patient Guide (84%), Patient Alert Card (77%) and Package Leaflet (77%) (Table 2). Forty-two participants (57%) correctly identified the existence of all three patient materials. Remarkably, all HCPs were aware of at least one patient material. There were 14 (19%) that reported knowing one of three materials, and 18 (24%) that reported knowing two.

Table 2 - Knowledge about Health Care Professional (HCP) and Patient Educational Materials

Questionnaire item	Response option	n (%)
Q.11 Have you received and reviewed the HCP guide? (n=74)	Yes	56 (76%)
	No	6 (8%)
	Don't remember	12 (16%)
Q.12 Have you received and reviewed the HCP checklist?	Yes	56 (76%)
	No	6 (8%)
	Don't remember	12 (16%)
Received both HCP guide and HCP checklist	Yes	51 (69%)
Q. 13 Have you received and reviewed the SmPC?	Yes	66 (89%)
	No	2 (3%)
	Don't remember	6 (8%)
Q14. What patient educational materials are available for patients prescribed Lemtrada?	Patient Guide	62 (84%)
	Patient Alert Card	57 (77%)
	Patient Checklist	43 (58%)
	Package Leaflet	57 (77%)
Q14. Complete answer*	3/3 responses selected (Patient Guide + Patient Alert Card + Package Leaflet)	42 (57%)

* Completeness of answers is irrespective of additional responses (Patient Checklist) selected by participants

Knowledge of the key points of the content

First prescription of LEMTRADA

Table 3 shows HCP responses to the question of what needs to be discussed at first prescription of LEMTRADA. The majority of participants indicated that they were aware of the need to discuss nephropathies including anti-GBM disease (82%), thyroid disorders (88%), immune thrombocytopenic purpura (ITP) (86%), active infections (89%), and pregnancy and contraception (if applicable) (85%). Forty-three participants (58%) seemed to have a complete understanding of what needs to be discussed, correctly indicating all five issues to be discussed at first prescription of LEMTRADA. A total of 61 participants (82%) correctly indicated at least four of the five issues, and a total of 70 participants (94%) correctly indicated at least three of the five issues. Two participants selected only two issues; one selected only one issue to be discussed; and one HCP selected zero of the five 'correct' issues to be discussed, suggesting that the large majority of HCPs had, from memory, an excellent knowledge about important risks to be discussed with patients at first prescription.

Table 3 - Knowledge about topics to be discussed at first prescription of LEMTRADA

Questionnaire item	**Response option**	**n (%)**
Q.15 What potential risk needs to be discussed at first prescription of LEMTRADA with a patient? Select as many as apply.	**Nephropathies including anti-GBM disease**	**61 (82%)**
	Thyroid disorders	**65 (88%)**
	Immune thrombocytopenic purpura (ITP)	**64 (86%)**
	Active infections	**66 (89%)**
	Pregnancy and contraception (if applicable)	**63 (85%)**
	Depression	17 (23%)
	Gastro-intestinal issues	22 (30%)
Q.15 Complete answer*	5/5 responses selected (Nephropathies including anti-GBM disease + thyroid disorders + immune thrombocytopenic purpura [ITP] + active infections + pregnancy & lactation (if applicable)	43 (58%)
Q.15 Partially complete answer*	4/5 responses selected	18 (24%)
	3/5 responses selected	9 (12%)
Q.15 Incomplete answer*	2/5 responses selected	2 (3%)
	1/5 or 0/5 responses selected	2 (3%)

* Completeness of answers is irrespective of additional responses (Depression and Gastrointestinal Issues) selected by participants

Contraindications – comorbid conditions

The vast majority of prescribers indicated they were aware that contraindications for LEMTRADA include Human Immunodeficiency Virus (HIV) (92%) and hypersensitivity to the active substance or any of the excipients (89%) (Table 4). A total of 63 HCPs (85%) answered this question completely, meaning they selected *at least* the two desired response options. Eight HCPs (11%) selected one of two desired responses and three (4%) did not select either desired answer.

Table 4 - Knowledge about contraindications for LEMTRADA – comorbid conditions

Questionnaire item	Response option	n (%)
Q.16 LEMTRADA is contra-indicated in patients with which of the following conditions: select as many as apply.	**Human Immunodeficiency Virus (HIV)**	**68 (92%)**
	Ischemic heart disease	14 (19%)
	Depression	11 (15%)
	Hypersensitivity to the active substance or any of the excipients	**66 (89%)**
Q16 Complete answer*	2/2 responses selected (HIV and Hypersensitivity to the active substance or any of the excipients)	63 (85%)
Q16 Partially complete answer*	1/2 responses selected	8 (11%)
Q16 Incomplete answer*	0/2 responses selected	3 (4%)

* Completeness of answers is irrespective of additional responses (Ischemic Heart Disease and Depression) selected by participants

Contraindications – treatments

The majority of prescribers indicated that LEMTRADA is contraindicated in patients prescribed immunosuppressive therapy (91%) and antineoplastic therapy (77%) (Table 5). A total of 53 HCPs (72%) answered this question completely, meaning they selected *at least* the two desired response options. Eighteen (24%) participants selected one of two desired responses and three (4%) did not select either desired answer.

Table 5 - Knowledge about contraindications for LEMTRADA - treatments

Questionnaire item	Response option	n (%)
Q.17 LEMTRADA is contra-indicated in patients prescribed the following treatments: select as many as apply.	Selective serotonin reuptake inhibitors (SSRIs)	8 (11%)
	Immunosuppressive therapy	**67 (91%)**
	Antineoplastic therapy	**57 (77%)**
	Antiviral therapies	31 (42%)
Q.17 Complete answer*	2/2 responses selected (Immunosuppressive therapy + Antineoplastic therapy)	53 (72%)
Q17 Partially complete answer*	1/2 responses selected	18 (24%)
Q17 Incomplete answer*	0/2 responses selected	3 (4%)

* Completeness of answers is irrespective of additional responses (SSRIs and Antiviral therapies)) selected by participants

Tests to be conducted before prescribing LEMTRADA

Responses to questions about knowledge of tests to be conducted before first prescription of LEMTRADA are shown in Table 6. The vast majority of HCPs were aware of the need to check serum creatinine (92%), complete blood count with differential (93%), and thyroid function blood-tests such as TSH (93%), but fewer indicated that they were aware of the need to perform urinalysis with microscopy (65%). The majority of participants also selected liver function (76%) and urine protein creatinine tests (58%), though tests are not demanded to be done. A majority of 44 HCPs (59%) answered completely, meaning they selected *at least* the four desired response options. Twenty-one (28%) selected three of four; seven (9%) selected two of four, and two (3%) selected one or none.

Table 6 - Knowledge of tests to be conducted before first prescription of LEMTRADA

		All (n=74)
Questionnaire item	**Response option**	**n (%)**
Q.18 According to the HCP guide and checklist, what tests should be conducted before first prescription of LEMTRADA?	**Serum creatinine**	**68 (92%)**
	Complete blood count with differential	**69 (93%)**
	Urinalysis with microscopy	**48 (65%)**

	Liver function tests	56 (76%)
	Thyroid function tests such as TSH	**69 (93%)**
	Urine protein creatinine test	43 (58%)
Q18 Complete answer*	4/4 responses selected (Serum creatinine + Complete blood count with differential + Urinalysis with microscopy + Thyroid function tests)	44 (59%)
Q18 Partially complete answer*	3/4 responses selected	21 (28%)
	2/4 responses selected	7 (9%)
Q18 Incomplete answer*	1/4 or 0/4 responses selected	2 (3%)

* Completeness of answers is irrespective of additional responses (liver function tests, urine protein creatinine tests) selected by participants

Wait period after last vaccination

A combined total of 53 HCPs (72%) correctly indicated that at least a 6-week wait period following vaccination is necessary before administering LEMTRADA (Table 7). Twenty-one HCPs (28%) incorrectly indicated that the wait period is 4 weeks.

Table 7 - Knowledge about wait period after vaccination

Questionnaire item	**Response option**	**n (%)**
Q.19 How long after the patient's last vaccination should you wait before administering LEMTRADA? (Single response)	4 weeks	21 (28%)
	6 weeks	**37 (50%)**
	8 weeks	**16 (22%)**
Correct answer	6 weeks OR 8 weeks selected	53 (72%)

When to check serum creatinine levels

A large majority of HCPs correctly indicated that serum creatinine should be checked before the patient is prescribed LEMTRADA (77%) and monthly until 48 months after last infusion of LEMTRADA (70%) (Table 9). Twenty-three percent incorrectly indicated that serum creatinine levels should be checked every three months until 48 months after last infusion of LEMTRADA and 9% incorrectly indicated that serum creatinine levels should be checked every eight weeks until

last infusion of LEMTRADA. None of the HCPs indicated that these tests do not need to be carried out. Forty HCPs (54%) answered completely, meaning they selected response options one and two; 29 (39%) had partially complete responses and five (7%) had incomplete responses.

Table 8 - Knowledge about when to check serum creatinine levels

		All (n=74)
Questionnaire item	**Response option**	**n (%)**
Q.20 When do you need to check serum creatinine? Select as many as apply	**Before the patient is prescribed Lemtrada**	**57 (77%)**
	Monthly until 48 months after last infusion of Lemtrada	**52 (70%)**
	Every 3 months until 48 months after last infusion of Lemtrada	17 (23%)
	Every 8 weeks until last infusion of Lemtrada	7 (9%)
	These tests do not need to be carried out	0
Q. 20 Complete answer*	2/2 responses selected (Before the patient is prescribed LEMTRADA + monthly until 48 months after last infusion of Lemtrada)	40 (54%)
Q. 20 Partially complete answer*	1/2 responses selected	29 (39%)
Q. 20 Incomplete answer*	0/2 responses selected	5 (7%)

* Completeness of answers is irrespective of additional responses (Every 3 months, Every 8 weeks, These tests do not need to be carried out) selected by participants

When to check complete blood count with differential

A large majority of participants (81%) correctly indicated that complete blood count with differential should be checked before the patient is prescribed LEMTRADA and 72% correctly mentioned monthly until 48 months after last infusion of LEMTRADA (Table 9). Nineteen HCPs (26%) incorrectly indicated that complete blood count with differential is only required every three months and six HCPs (8%) indicated that it is only required every 8 weeks or as indicated by

clinical signs and symptoms. No HCPs indicated that these tests do not need to be carried out. Forty-five (61%) HCPs answered the question completely by selecting options one and two, while 23 (31%) answered partially completely and 6 (8%) answered incompletely (Table 9).

Table 9 - Knowledge about when to check complete blood count with differential

		All (n=74)
Questionnaire item	**Response option**	**n (%)**
Q.21 When do you need to check complete blood count with differential? Select as many as apply.	**Before the patient is prescribed Lemtrada**	**60 (81%)**
	Monthly until 48 months after last infusion of Lemtrada	**53 (72%)**
	Every 3 months until 48 months after last infusion of Lemtrada	19 (26%)
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	6 (8%)
	These tests do not need to be carried out	0
Q. 21 Complete answer*	2/2 correct responses	45 (61%)
Q. 21 Partially complete answer*	1/2 correct responses	23 (31%)
Q. 21 Incomplete answer*	0/2 correct responses	6 (8%)

* Completeness of answers is irrespective of additional responses (Every 3 months, Every 8 weeks, These tests do not need to be carried out) selected by participants

When to conduct urinalysis with microscopy

Seventy percent of HCPs correctly indicated that urinalysis with microscopy should be conducted before the patient is prescribed LEMTRADA and 58% knew monthly urinalysis until 48 months after last infusion of LEMTRADA is indicated (Table 10). Thirty percent of participants incorrectly indicated that urinalysis with microscopy should be conducted every three months and 9% indicated that urinalysis with microscopy should be conducted every eight weeks or as indicated by clinical signs and symptoms. Five percent of HCPs incorrectly indicated that these tests do not need to be

carried out – three of these HCPs were from Germany and one was from Italy. Forty-seven percent of HCPs answered the question completely, meaning that they selected response option one and two; 25 (34%) answered partially completely and 14 (19%) answered incompletely as they did not select either of the correct response options.

Table 10 - Knowledge about when to conduct urinalysis with microscopy

Questionnaire item	Response option	n (%)
Q.22 When do you need to conduct urinalysis with microscopy?	Before the patient is prescribed Lemtrada	52 (70%)
	Monthly until 48 months after last infusion of Lemtrada	43 (58%)
	Every 3 months until 48 months after last infusion of LEMTRADA	22 (30%)
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	7 (9%)
	These tests do not need to be carried out	4 (5%)
Q.22 Complete answer*	2/2 responses selected (Before the patient is prescribed LEMTRADA + monthly until 48 months after last infusion of Lemtrada)	35 (47%)
Q.22 Partially complete answer*	1/2 responses selected	25 (34%)
Q.22 Incomplete answer*	0/2 responses selected	14 (19%)

* Completeness of answers is irrespective of additional responses (Every 3 months, Every 8 weeks, These tests do not need to be carried out) selected by participants

When to conduct liver function tests

A small proportion of HCPs (n = 16, 22%) correctly indicated that liver function tests do not need to be carried out in patients prescribed LEMTRADA (Table 11). The remainder indicated that liver function tests should be conducted before prescription with LEMTRADA (n = 45, 61%), monthly until 48 months after last infusion (n = 32, 42%), every three months until 48 months after last infusion (n = 18, 24%), and every eight weeks until last infusion or as indicated by clinical signs and symptoms (n = 8, 11%).

Table 11 - Knowledge about when to conduct liver function tests

Questionnaire item	Response option	n (%)

Q.23 When do you need to conduct liver function tests? Select as many as apply.	Before the patient is prescribed LEMTRADA	45 (61%)
	Monthly until 48 months after last infusion of LEMTRADA	31 (42%)
	Every 3 months until 48 months after last infusion of LEMTRADA	18 (24%)
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	8 (11%)
	These tests do not need to be carried out	**16 (22%)**
Q.23 correct answer	These tests do not need to be carried out	16 (22%)

When to conduct thyroid function tests

The vast majority (85%) of HCPs correctly indicated that thyroid function blood-tests should be conducted before the patient is prescribed LEMTRADA and 54% correctly indicated that thyroid function tests should be conducted every three months until 48 months after last infusion of LEMTRADA (Table 12). Many thought thyroid function tests should be conducted more often than every three months – 30% selected monthly until 48 months after last infusion of LEMTRADA and 16% selected every eight weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms. No HCP indicated that these tests do not need to be carried out. Thirty-four HCPs (46%) answered the question completely by selecting response options one and three, and 35 (47%) answered partially completely. Five HCPs (7%) did not select either of the desired responses and therefore had incomplete answers.

Table 12 - Knowledge about when to conduct thyroid function tests

Questionnaire item	**Response option**	**n (%)**
Q.24 When do you need to conduct thyroid function tests [such as TSH]? Select as many as apply.	**Before the patient is prescribed LEMTRADA**	**63 (85%)**
	Monthly until 48 months after last infusion of Lemtrada	22 (30%)
	Every 3 months until 48 months after last infusion of LEMTRADA	**40 (54%)**
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	12 (16%)

	These tests do not need to be carried out	0
Q.24 Complete answer*	2/2 responses selected (Before the patient is prescribed LEMTRADA + every 3 months until 48 months after last infusion of LEMTRADA)	34 (46%)
Q24 Partially complete answer*	1/2 responses selected	35 (47%)
Q24 Incomplete answer*	0/2 responses selected	5 (7%)

* Completeness of answers is irrespective of additional responses (Every 3 months, Every 8 weeks, These tests do not need to be carried out) selected by participants

When to conduct urine protein creatinine ratio tests

Twenty-eight percent of participants correctly indicated that urine protein creatinine ratio tests do not need to be carried out in patients initiating LEMTRADA (Table 13). Incorrect responses were as follows: urine protein creatinine ratio tests should be conducted before the patient is prescribed LEMTRADA (57%); monthly until 48 months after last infusion of LEMTRADA (35%); every three months until 48 months after last infusion of LEMTRADA (30%) and every eight weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms (11%).

Table 13 - Knowledge about when to conduct urine protein creatinine ratio tests

Questionnaire item	**Response option**	**n (%)**
Q.25 When do you need to conduct urine protein creatinine ratio tests? Select as many as apply.	Before the patient is prescribed LEMTRADA	42 (57%)
	Monthly until 48 months after last infusion of LEMTRADA	26 (35%)
	Every 3 months until 48 months after last infusion of LEMTRADA	22 (30%)
	Every 8 weeks until the last infusion of LEMTRADA or as indicated by clinical signs and symptoms	8 (11%)
	These tests do not need to be carried out	**21 (28%)**
Q.25 Correct answer	These tests do not need to be carried out	21 (28%)

Use of contraception in women of childbearing potential

Seventy percent of HCPs correctly indicated that women of childbearing potential should use effective contraceptive measures during treatment and for at least four months following each treatment (Table 14). Incorrect responses included: during treatment and for at least five days following each treatment (4%); during treatment and for at least 30 days following each treatment (7%) and during treatment and for at least 48 months following each treatment (19%). Given the risk related to pregnancy whilst exposed to a drug, the 11% who gave an answer that could lead to a woman or her child being exposed to high drug level, is of concern.

Table 14 - Knowledge about use of contraception in women of childbearing potential

Questionnaire item	Response option	n (%)
Q.26 How long should women of childbearing potential use effective contraceptive measures? Single response.	During treatment and for at least 5 days following each treatment	3 (4%)
	During treatment and for at least 30 days following each treatment	5 (7%)
	During treatment and for at least 4 months following each treatment	**52 (70%)**
	During treatment and for at least 48 months following each treatment	14 (19%)
Q.26 Correct answer	During treatment and for at least 4 months following each treatment	52 (70%)

What to do if patient has suspected immune thrombocytopenic purpura (ITP).

The vast majority of HCPs (91%) correctly indicated the need to obtain a complete blood count immediately if they suspect that a patient has ITP and refer to a specialist immediately if onset is confirmed (Table 15). Seven HCPs (9%) indicated that they would obtain a complete blood count immediately and continue to treat the patient themselves if onset confirmed. This answer option may have been misunderstood as saying that the alternative to this answer would be for the MS treatment to be done by another specialist, which was not implied. No HCPs indicated that they would ask the patient to self-monitor their symptoms until their next scheduled appointment when a complete blood count would be obtained.

Table 15 - Knowledge about what to do if a patient has suspected immune thrombocytopenic purpura ITP

Questionnaire item	Response option	n (%)
Q.27 What should you do if you	**Obtain a complete blood count immediately**	**67 (91%)**

suspect a patient has immune thrombocytopenic purpura (ITP)	**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	7 (9%)
	Ask patient to self-monitor symptoms until their next scheduled appointment when a complete blood count will be obtained	0
Q.27 Correct answer	Obtain a complete blood count immediately and refer to a specialist immediately if onset is confirmed	67 (91%)

What to do if patient has suspected nephropathy

Eighty percent of HCPs correctly indicated that they would refer the patient to a specialist immediately if they suspect that a patient has nephropathy (Table 16). Fifteen HCPs (20%) indicated that they would ask the patient to come in as soon as possible, conduct urine tests and keep monitoring the patient themselves. This last remark may have been misunderstood as the alternative being not to be able to monitor your own patients. No HCPs indicated that they would wait until the patient's next scheduled appointment when any change in serum creatinine level from baseline can be confirmed. This is a good result.

Table 16 - Knowledge about what to do if a patient has suspected nephropathy

Questionnaire item	**Response option**	**n (%)**
Q.28 What should you do if you suspect a patient nephropathy	**Refer the patient to a specialist immediately**	**59 (80%)**
	Ask the patient to come in as soon as possible, conduct urine tests and keep monitoring the patient myself	15 (20%)
	Wait until the patient's next scheduled appointment when any change in serum creatinine level from baseline can be confirmed	0
Q.27 Correct answer	Refer to a specialist immediately	59 (80%)

Counseling for patients treated with LEMTRADA

The vast majority of HCPs were aware of the need to counsel patients on the risks and importance of monthly monitoring appointments (89%) and on the importance of contraception (88%) (Table 17). Sixty-eight percent also indicated the importance of counseling on coping with MS. Overall, 59 HCPs (80%) identified that both contraception and the importance of monthly monitoring appointments should be discussed. Thirteen (18%) HCPs selected only one of these as important discussion points, and two (3%) selected neither, indicating some gaps in HCP understanding of key things to discuss with patients.

Table 17 - Knowledge about what counseling should be provided to patients treated with LEMTRADA

Questionnaire item	Response option	n (%)
Q.29 What counseling should you provide patients treated with LEMTRADA?	Coping with MS	50 (68%)
	Importance of contraception	**65 (88%)**
	Risks and importance of monthly monitoring appointments	**66 (89%)**
	None	0
Q.29 Complete answer*	2/2 responses selected (Importance of contraception + risks and importance of monthly monitoring appointments)	59 (80%)
Q.29 Partially complete answer*	1/2 responses selected	13 (18%)
Q.29 Incomplete answer*	0/2 responses selected	2 (3%)

* Completeness of answers is irrespective of additional responses (Coping with MS) selected by participants

10.2.2 Secondary analyses

Knowledge of the HCP guide, HCP checklist and SmPC

Sixty-six percent of HCPs had received and reviewed the HCP guide, HCP checklist as well as the SmPC. The sample size in each country was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on work setting or number of MS patients seen (Table 18). There was a trend (non-significant) for those identifying themselves as MS specialist neurologists to be more likely to have received and reviewed the HCP educational materials than those identifying themselves as neurologists, and for those who had prescribed LEMTRADA within the last month to be more likely to have received and reviewed the HCP educational materials than those who had last prescribed LEMTRADA over a month ago.

Table 18 - Subgroup analysis: Knowledge about the HCP Educational Materials

Q11-Q13. Have you received and reviewed the HCP guide, HCP checklist and SmPC?		**Yes** **n=49**	**No/don't remember** **n=25**	**p-value**
		N (%)	N (%)	
Country	Germany	15 (75)	5 (25)	NA
	Italy	16 (80)	4 (20)	
	Norway	1 (33)	2 (67)	
	Spain	10 (67)	5 (33)	
	UK	6 (40)	9 (60)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	32 (74)	11 (26)	0.079
	Neurologist	17 (55)	14 (45)	
Work setting	University hospital	30 (65)	16 (35)	0.816
	Community hospital	16 (67)	8 (33)	
Number of MS patients seen	<100 patients per year	14 (56)	11 (44)	0.184

	≥100 patients per year	35 (71)	14 (29)	
Last initiation of LEMTRADA	Within the last month	34 (74)	12 (26)	0.073
	More than 1 month ago	***15 (54)***	***13 (46)***	

Knowledge of Patient Educational Materials.

There were no significant differences between subgroups in relation to their knowledge about the existence of the patient guide, patient alert card and package leaflet. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on work setting, number of MS patients seen or last prescription of LEMTRADA (Table 19). There was a trend (non-significant) for self-described MS specialist-neurologists to have more complete knowledge of the patient educational materials than self-described neurologists. HCPs who had received and reviewed all the HCP educational materials (p = .038) were significantly more likely to have complete knowledge of the patient educational materials available than those who had not read all.

Table 19 - Subgroup analysis: Knowledge about available Patient Educational Materials

Q14. What patient educational materials are available for patients prescribed LEMTRADA?		**Complete*** **n=42**	**Incomplete** **n=32**	**p-value**
		N (%)	N (%)	
Country	Germany	12 (60)	8 (40)	NA
	Italy	12 (60)	8 (45)	
	Norway	1 (33)	2 (67)	
	Spain	8 (53)	7 (47)	
	UK	8 (53)	7 (47)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	28 (65)	15 (35)	0.087
	Neurologist	14 (45)	17 (55)	
University hospital	Yes	26 (57)	20 (43)	0.958

	No	16 (57)	12 (43)	
Community hospital	Yes	12 (50)	12 (50)	0.416
	No	30 (60)	20 (40)	
Office based	Yes	4 (80)	1 (20)	NA
	No	38 (55)	31 (45)	
Number of MS patients seen	<100 patients per year	12 (48)	13 (52)	0.277
	≥100 patients per year	30 (61)	19 (40)	
Last initiation of Lemtrada	Within the last month	28 (61)	18 (39)	0.360
	More than 1 month ago	14 (50)	14 (50)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	32 (65)	17 (35)	**0.038**
	No	10 (40)	15 (60)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	39 (64)	22 (36)	**0.007**
	No	3 (23)	10 (77)	

* Complete answer – Patient Guide, Patient Alert Card and Package Leaflet (and any additional selections)

Knowledge of potential risks to be discussed at first prescription of LEMTRADA

Subgroup analyses of HCPs knowledge of the potential risks to be discussed at first prescription of LEMTRADA are shown in Table 20. The sample size was insufficient to conduct an analysis by country. HCPs who had prescribed LEMTRADA within the previous month were significantly more likely to have complete knowledge of risks to be discussed at first prescription than those who had last prescribed LEMTRADA more than a month ago (p = .010). HCPs who had received and reviewed all HCP educational materials were significantly more likely to be aware of what potential risks should be discussed at first prescription of LEMTRADA than those who had not (p = .000), providing support for the efficacy of the documents. There were no significant differences between subgroups depending on work setting or number of MS patients seen.

Table 20 - Subgroup analysis: Potential risks to be discussed at first prescription

Q15. What potential risks should be discussed at first prescription of LEMTRADA?		**Complete*** **n=43**	**Incomplete** **n=31**	**p-value**
		N (%)	N (%)	
Country	Germany	12 (60)	8 (40)	NA
	Italy	13 (65)	7 (35)	
	Norway	2 (67)	1 (33)	
	Spain	10 (67)	5 (33)	
	UK	5 (33)	10 (67)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	29 (67)	14 (33)	0.055
	Neurologist	14 (45)	17 (55)	
University hospital	Yes	28 (61)	18 (39)	0.537
	No	15 (54)	13 (46)	
Community hospital	Yes	13 (54)	11 (46)	0.634
	No	30 (60)	20 (40)	
Office-based	Yes	3 (60)	2 (40)	NA
	No	40 (58)	29 (42)	
Number of MS patients seen	<100 patients per year	13 (52)	12 (48)	0.447
	≥100 patients per year	30 (61)	19 (39)	
Last initiation of LEMTRADA	Within the last month	32 (70)	14 (30)	**0.010**
	More than 1 month ago	11 (39)	17 (61)	

Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	37 (76)	12 (24)	**0.000**
	No	6 (24)	19 (76)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	41 (67)	20 (33)	**0.001**
	No	2 (15)	11 (85)	

* Complete answer: nephropathies including anti-GBM disease, thyroid disorders, ITP, active infections, pregnancy and contraception (if applicable) (and any additional selections)

Knowledge of contraindications (conditions)

Subgroup analyses of HCPs knowledge of conditions in which LEMTRADA is contraindicated are shown in Table 21. The sample size was insufficient to conduct an analysis by country, whether or not the HCP was based at a university hospital and whether or not the HCP was office-based. There were no significant differences between subgroups depending on specialist role, the number of MS patients seen, last prescription of LEMTRADA, or having received and reviewed the HCP educational materials.

Table 21 - Subgroup analysis: Knowledge of contraindications (conditions)

Q16. LEMTRADA is contraindicated in patients with the following conditions*		**Complete*** **n=63**	**Incomplete** **n=11**	**p-value**
		N (%)	N (%)	
Country	Germany	20 (100)	0 (0)	NA
	Italy	16 (80)	4 (20)	
	Norway	3 (100)	0 (0)	
	Spain	14 (93)	1 (7)	
	UK	9 (60)	6 (40)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	37 (86)	6 (14)	0.403
	Neurologist	26 (84)	5 (16)	
University hospital	Yes	39 (85)	4 (15)	NA

	No	24 (86)	7 (14)	
Community hospital	Yes	20 (83)	4 (17)	0.275
	No	43 (86)	7 (14)	
Office-based	Yes	5 (100)	0 (0)	NA
	No	58 (84)	11 (16)	
Number of MS patients seen	<100 patients per year	20 (80)	5 (20)	0.446
	≥100 patients per year	43 (88)	6 (12)	
Last initiation of Lemtrada	Within the last month	39 (85)	7 (15)	NA
	More than 1 month ago	24 (86)	4 (14)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	45 (88)	6 (12)	0.466
	No	18 (78)	5 (22)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	54 (86)	7 (14)	0.204
	No	9 (69)	4 (31)	

*Complete answer: (HIV and Hypersensitivity to the active substance or any of the excipients)

Knowledge of contraindications (treatments)

Subgroup analyses of HCPs' knowledge of treatments with which LEMTRADA is contraindicated are shown in Table 22. HCPs who initiated LEMTRADA within the last month were significantly more likely to have good knowledge of the treatments in which LEMTRADA was contraindicated than those who initiated LEMTRAA more than a month ago (p = .030). There were no significant differences between subgroups depending on country, specialist role, number of MS patients seen, setting of work, or having received and reviewed the HCP educational materials.

Table 22 - Subgroup analysis: Knowledge of contraindications (treatments)

Q17. LEMTRADA is contraindicated in patients prescribed the following treatments *	**Complete***	**Incomplete**	**p-value**

		n=53	n=21	
		N (%)	N (%)	
Country	Germany	15 (75)	5 (25)	0.961
	Italy	13 (65)	7 (35)	
	Norway	2 (67)	1 (33)	
	Spain	11 (73)	4 (27)	
	UK	11 (73)	4 (27)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	31 (72)	12 (28)	0.559
	Neurologist	22 (71)	9 (29)	
University hospital	Yes	35 (76)	11 (24)	0.204
	No	18 (64)	10 (36)	
Community hospital	Yes	14 (58)	10 (42)	0.071
	No	39 (78)	11 (22)	
Office-based	Yes	5 (100)	0 (0)	0.178
	No	48 (70)	21 (30)	
Number of MS patients seen	<100 patients per year	18 (72)	7 (28)	0.592
	≥100 patients per year	35 (71)	14 (29)	
Last initiation of Lemtrada	Within the last month	37 (80)	9 (20)	**0.030**
	More than 1 month ago	16 (57)	12 (43)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	35 (68)	16 (32)	0.288
	No	18 (78)	5 (22)	

Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	44 (72)	17 (28)	0.538
	No	9 (69)	4 (31)	

* Complete answer: Immunosuppressive therapy and antineoplastic therapy

Knowledge of tests to be conducted before first prescription of LEMTRADA

Regarding knowledge of tests to be conducted before first prescription of LEMTRADA, there was a significant difference in reporting between HCPs who see more than 100 and less than 100 patients per year; those who see more than 100 patients were significantly more likely to have a complete answer (p = .015). There was also a significant difference for receiving versus not receiving either of the HCP materials; HCPs who received either the Guide or Checklist were more likely to have a complete answer than those who did not receive either (p = .023). There were no other significant differences between subgroups in relation to their knowledge about the tests to be conducted before first prescription of LEMTRADA, according to the HCP guide and checklist (Table 23).

Table 23 - Subgroup analysis: Knowledge of tests to be conducted before first prescription of LEMTRADA

Q18 According to the HCP guide and checklist what tests should be conducted before first prescription of LEMTRADA?*		**Complete*** **n=44**	**Incomplete** **n=30**	**p-value**
		N (%)	N (%)	
Country	Germany	12 (60)	8 (40)	0.836
	Italy	12 (60)	8 (40)	
	Norway	2 (67)	1 (33)	
	Spain	8 (53)	7 (47)	
	UK	10 (67)	5 (33)	
	Denmark	0 (0)	1 (100)	
Specialist role	MS specialist	27 (63)	16 (27)	0.327
	Neurologist	17 (55)	14 (45)	
University hospital	Yes	26 (57)	20 (43)	0.340
	No	18 (64)	10 (36)	

Community hospital	Yes	15 (63)	9 (37)	0.456
	No	29 (58)	21 (42)	
Office-based specialist	Yes	3 (60)	2 (40)	0.678
	No	41 (59)	28 (41)	
Number of MS patients seen	<100 patients per year	10 (40)	15 (60)	**0.015**
	≥100 patients per year	34 (69)	15 (31)	
Last initiation of Lemtrada	Within the last month	25 (54)	21 (46)	0.183
	More than 1 month ago	19 (68)	9 (32)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	34 (67)	17 (33)	0.053
	No	10 (43)	13 (57)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	40 (66)	21 (34)	**0.023**
	No	4 (31)	9 (69)	

* Complete answer: serum creatinine and complete blood count with differential and urinalysis with microscopy and thyroid function tests (and any additional selections)

Wait period after vaccination before administering LEMTRADA

Subgroup analyses of wait period after vaccination before administering LEMTRADA are shown in Table 24. The sample size was insufficient to conduct an analysis by country or whether or not the HCP was office-based. There were no significant differences between subgroups depending on specialist role, work setting, number of MS patients seen, last prescription of LEMTRADA, or having received and reviewed the HCP educational materials.

Table 24 - Subgroup analysis: Knowledge of wait period after last vaccination before administering LEMTRADA

Q19 How long after the patient's last vaccination should you wait before administering LEMTRADA?	**Correct***	**Incorrect**	**p-value**
	n=53	**n=21**	
	N (%)	N (%)	

Country	Germany	16 (80)	4 (20)	NA
	Italy	16 (80)	4 (20)	
	Norway	2 (67)	1 (33)	
	Spain	10 (67)	5 (33)	
	UK	8 (53)	7 (47)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	31 (72)	12 (28)	0.916
	Neurologist	22 (71)	9 (29)	
University hospital	Yes	34 (74)	12 (26)	0.575
	No	19 (68)	9 (32)	
Community hospital	Yes	17 (71)	7 (29)	0.917
	No	36 (72)	14 (28)	
Office-based specialist	Yes	3 (60)	2 (40)	NA
	No	50 (73)	19 (27)	
Number of MS patients seen	<100 patients per year	19 (76)	6 (24)	0.551
	≥100 patients per year	34 (69)	15 (31)	
Last initiation of Lemtrada	Within the last month	33 (72)	13 (28)	0.977
	More than 1 month ago	20 (71)	8 (29)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	35 (71)	14 (29)	0.959
	No	18 (72)	7 (28)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	44 (72)	17 (28)	0.538
	No	9 (69)	4 (31)	

* Correct answer: 6 weeks OR 8 weeks

Knowledge of monitoring activities for the autoimmune events

Subgroup analyses of HCPs knowledge of tests to be conducted before first prescription of LEMTRADA are shown in Table 25-27. Table 25 shows the subgroup analyses for serum creatinine testing. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, number of MS patients seen or last prescription of LEMTRADA. However, HCPs who were based at a university hospital were significantly less likely to know when to check serum creatinine than those who were not university-hospital based (i.e. based within a community hospital or office based) (p = .004). Those who were community hospital based were significantly more likely to know when to check serum creatinine than others (p = .038). Office-based specialists were also more likely to know when to check serum creatinine (p = .041). There was a trend (non-significant) for those who had received and reviewed the HCP guide, HCP checklist and SmPC, and those who had received either the guide or the checklist, to be more likely to answer this question correctly than those who had not received and reviewed these materials.

Table 25 - Subgroup analysis: When do you need to check serum creatinine?

Q20 When do you need to check serum creatinine?		**Complete***	**Incomplete**	**p-value**
		n=40	**n=34**	
		N (%)	N (%)	
Country	Germany	14 (70)	6 (30)	NA
	Italy	11 (55)	9 (45)	
	Norway	3 (100)	0 (0)	
	Spain	7 (47)	8 (53)	
	UK	5 (33)	10 (67)	
	Denmark	0 (0)	1 (100)	
Specialist role	MS specialist	24 (56)	19 (44)	0.451
	Neurologist	16 (52)	15 (48)	
University hospital	Yes	19 (41)	27 (59)	**0.004**
	No	21 (75)	7 (25)	

Community hospital	Yes	17 (71)	7 (29)	**0.038**
	No	23 (46)	27 (54)	
Office-based specialist	Yes	5 (100)	0 (0)	**0.041**
	No	35 (51)	34 (49)	
Number of MS patients seen	<100 patients per year	16 (64)	9 (36)	0.164
	≥100 patients per year	24 (49)	25 (51)	
Last initiation of Lemtrada	Within the last month	25 (54)	21 (46)	0.569
	More than 1 month ago	15 (54)	13 (46)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	31 (61)	20 (39)	0.070
	No	9 (39)	14 (61)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	36 (59)	25 (41)	0.061
	No	4 (31)	9 (69)	

*Complete answer – before the patient is prescribed LEMTRADA and Monthly until 48 months after last infusion of LEMTRADA (and any additional selections)

Table 26 shows the subgroup analyses for when to check complete blood count with differentials. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, number of MS patients seen or last prescription of LEMTRADA. However, HCPs who were based at a university hospital were significantly less likely to know when to perform a complete blood count with differentials than those who were based within a community hospital or who were office based (p = .013). There was a trend towards significance for those working in a community hospital being more likely to have a complete answer than other HCPs (p = .068). The same was the case for office based specialists being more likely to have a complete answer (p = .076). HCPs who had received and reviewed all HCP educational materials were significantly more likely to likely to answer this question correctly than those who had not received and reviewed these materials (p = .037).

Table 26 - Subgroup analysis: When do you need to check complete blood count with differential?

Q21 When do you need to check complete blood count		**Complete***	**Incomplete**	**p-value**

with differential?		**n=45**	**n=29**	
		N (%)	N (%)	
Country	Germany	15 (75)	5 (35)	NA
	Italy	11 (55)	9 (45)	
	Norway	1 (33)	2 (67)	
	Spain	7 (47)	8 (53)	
	UK	11 (73)	4 (27)	
	Denmark	0 (0)	1 (100)	
Specialist role	MS specialist	28 (65)	15 (35)	0.257
	Neurologist	17 (55)	14 (45)	
University hospital	Yes	23 (50)	23 (50)	**0.013**
	No	22 (79)	6 (21)	
Community hospital	Yes	18 (75)	6 (25)	0.068
	No	27 (54)	23 (46)	
Office-based specialist	Yes	5 (100)	0 (0)	0.076
	No	40 (58)	29 (42)	
Number of MS patients seen	<100 patients per year	15 (60)	10 (40)	0.557
	≥100 patients per year	30 (61)	19 (39)	
Last initiation of LEMTRADA	Within the last month	28 (61)	18 (39)	0.590
	More than 1 month ago	17 (61)	11 (39)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	35 (69)	16 (31)	**0.037**
	No	10 (43)	13 (67)	

Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	40 (66)	21 (34)	0.067
	No	5 (38)	8 (62)	

*Complete answer – before the patient is prescribed LEMTRADA and Monthly until 48 months after last infusion of LEMTRADA (and any additional selections)

Table 27 shows the subgroup analyses for when to conduct urinalysis with microscopy. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on the number of MS patients seen or last prescription of LEMTRADA. MS specialists were significantly more likely to answer the question correctly than neurologists (p = .024). There was also a trend for HCPs who were based at a university hospital to be less likely to answer this question correctly than those who were based within a community hospital or who were office based. HCPs who had received and reviewed all the HCP educational materials were significantly more likely answer the question correctly than those who had not read these materials (p = .003).

Table 27 - Subgroup analysis: When do you need to conduct urinalysis with microscopy?

Q22 When do you need to conduct urinalysis with microscopy?		**Complete*** **n=35**	**Incomplete** **n=39**	**p-value**
		N (%)	N (%)	
Country	Germany	11 (55)	9 (45)	NA
	Italy	12 (60)	8 (40)	
	Norway	2 (67)	1 (33)	
	Spain	6 (40)	9 (60)	
	UK	4 (27)	11 (73)	
	Denmark	0 (0)	1 (100)	
Specialist role	MS specialist	25 (58)	18 (42)	**0.024**
	Neurologist	10 (32)	21 (68)	
University hospital	Yes	18 (39)	28 (61)	0.059
	No	17 (61)	11 (39)	
Community hospital	Yes	14 (58)	10 (42)	0.143

	No	21 (42)	29 (58)	
Office-based	Yes	3 (60)	2 (40)	NA
	No	32 (46)	37 (54)	
Number of MS patients seen	<100 patients per year	11 (44)	14 (56)	0.437
	≥100 patients per year	24 (49)	25 (51)	
Last initiation of Lemtrada	Within the last month	21 (46)	25 (54)	0.451
	More than 1 month ago	14 (50)	14 (50)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	30 (59)	21 (41)	**0.003**
	No	5 (22)	18 (78)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	33 (54)	28 (46)	**0.011**
	No	2 (15)	11 (85)	

*Complete answer – before the patient is prescribed LEMTRADA and Monthly until 48 months after last infusion of LEMTRADA (and any additional selections)

Table 28 shows the subgroup analyses for knowledge that liver function tests do not need to be conducted. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, work setting, or last prescription of LEMTRADA. HCPs who treated fewer than 100 patients with MS per year were significantly more likely to answer this question correctly than those who saw 100 or more patients with MS per year (p = .032). There was no significant difference between HCPs who had received and reviewed the HCP educational materials and those who had not read these materials.

Table 28 - Subgroup analysis: Knowledge that liver function tests do not need to be carried out

Q23 When do you need to conduct liver function tests?		**Correct***	**Incorrect**	**p-value**
		n=16	**n=58**	
		N (%)	N (%)	
Country	Germany	2 (10)	18 (90)	NA

	Italy	8 (40)	12 (60)	
	Norway	0 (0)	3 (100)	
	Spain	2 (13)	13 (87)	
	UK	4 (27)	11 (73)	
	Denmark	0 (0)	1 (100)	
Specialist role	MS specialist	12 (28)	31 (72)	0.122
	Neurologist	4 (13)	27 (87)	
University hospital	Yes	12 (26)	34 (74)	0.232
	No	4 (14)	24 (86)	
Community hospital	Yes	4 (17)	20 (83)	0.473
	No	12 (24)	38 (76)	
Office-based	Yes	0 (0)	5 (100)	NA
	No	16 (23)	53 (77)	
Number of MS patients seen	<100 patients per year	9 (36)	16 (64)	**0.032**
	≥100 patients per year	7 (14)	42 (86)	
Last initiation of Lemtrada	Within the last month	9 (10)	37 (80)	0.582
	More than 1 month ago	7 (25)	21 (75)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	11 (22)	38 (78)	0.809
	No	5 (20)	20 (80)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	14 (23)	47 (77)	0.428
	No	2 (15)	11 (85)	

*Correct answer: These tests do not need to be carried out [exclusive]

Table 29 shows the subgroup analysis for the need to conduct thyroid tests. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, work setting, number of patients seen per year, or last prescription of LEMTRADA. There was a trend towards significance for those who had received and reviewed the HCP educational materials being more likely to have a complete answer for this question (p = .060).

Table 29 - Subgroup analysis: When do you need to conduct thyroid function tests?

Q24 When do you need to conduct thyroid function tests [such as TSH]?		**Complete*** **n=34**	**Incomplete** **n=40**	**p-value**
		N (%)	N (%)	
Country	Germany	7 (35)	13 (65)	NA
	Italy	10 (50)	10 (50)	
	Norway	2 (67)	1 (33)	
	Spain	8 (53)	7 (47)	
	UK	6 (40)	9 (60)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	21 (49)	22 (51)	0.363
	Neurologist	13 (42)	18 (58)	
University hospital	Yes	21 (46)	25 (54)	0.569
	No	13 (46)	15(54)	
Community hospital	Yes	11 (46)	13 (54)	0.594
	No	23 (46)	27 (54)	
Office-based	Yes	2 (40)	3 (60)	0.578
	No	32 (46)	37 (54)	
Number of MS patients seen	<100 patients per year	11 (44)	14 (56)	0.504
	≥100 patients per	23 (47)	26 (53)	

	year			
Last initiation of LEMTRADA	Within the last month	20 (43)	26 (57)	0.380
	More than 1 month ago	14 (50)	14 (50)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	27 (53)	24 (47)	0.060
	No	7 (30)	16 (70)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	30 (49)	31 (51)	0.184
	No	4 (31)	9 (69)	

*Correct answer – Before the patient is prescribed LEMTRADA and Every 3 months until 48 months after last infusion of LEMTRADA

Table 30 shows the subgroup analyses for knowledge that urine protein creatinine ratio tests are not necessary. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, work setting, number of patients seen per year, last prescription of LEMTRADA, or depending on whether or not the HCPs had received and reviewed the HCP educational materials.

Table 30 - Subgroup analysis: Knowledge that urine protein creatinine ratio tests do not need to be carried out

Q25 When do you need to conduct urine protein creatinine ratio tests?		**Correct***	**Incorrect**	**p-value**
		n=21	**n=53**	
		N (%)	N (%)	
Country	Germany	5 (25)	15 (75)	NA
	Italy	8 (40)	12 (60)	
	Norway	1 (33)	2 (67)	
	Spain	3 (20)	12 (80)	
	UK	4 (27)	11 (73)	
	Denmark	0 (0)	1 (100)	
Specialist role	MS specialist	13 (30)	30 (70)	0.677

	Neurologist	8 (26)	23 (74)	
University hospital	Yes	13 (28)	33 (72)	0.977
	No	8 (29)	20 (71)	
Community hospital	Yes	8 (33)	16 (67)	0.512
	No	13 (26)	37 (74)	
Office-based	Yes	1 (20)	4 (80)	NA
	No	20 (29)	49 (71)	
Number of MS patients seen	<100 patients per year	10 (40)	15 (60)	0.113
	≥100 patients per year	11 (22)	38 (78)	
Last initiation of LEMTRADA	Within the last month	13 (28)	33 (72)	0.977
	More than 1 month ago	8 (29)	20 (71)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	13 (27)	36 (73)	0.622
	No	8 (32)	17 (68)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	16 (26)	45 (74)	0.284
	No	5 (39)	8 (61)	

*Correct answer – these tests do not need to be carried out [exclusive]

Knowledge of contraception in women of childbearing potential

Subgroup analyses of HCPs knowledge of contraception in women of childbearing potential are shown in Table 31. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, number of MS patients seen, last prescription of LEMTRADA, or whether or not the HCP had received and reviewed the HCP educational materials. However, HCPs who were based in a community hospital were significantly less likely to answer this question correctly than those who worked in a university hospital or were office based (p = .036).

Table 31 - Subgroup analysis: Knowledge of contraception in women of childbearing potential

Q.26 How long should women of childbearing potential use effective contraceptive measures?		**Correct*** n= 52	**Incorrect** n= 22	**p-value**
		N (%)	N (%)	
Country	Germany	14 (70)	6 (30)	NA
	Italy	14 (70)	6 (30)	
	Norway	3 (100)	0 (0)	
	Spain	9 (60)	6 (40)	
	UK	11 (73)	4 (27)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	32 (74)	11 (26)	0.358
	Neurologist	20 (64)	11 (36)	
University hospital	Yes	36 (78)	10 (22)	0.054
	No	16 (57)	12 (43)	
Community hospital	Yes	13 (54)	11 (46)	**0.036**
	No	39 (78)	11 (22)	
Office-based	Yes	4 (80)	1 (20)	NA
	No	48 (70)	21 (30)	
Number of MS patients seen	<100 patients per year	20 (80)	5 (20)	0.191
	≥100 patients per year	32 (65)	17 (35)	
Last initiation of LEMTRADA	Within the last month	35 (76)	11 (24)	0.161
	More than 1 month ago	17 (61)	11 (39)	

Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	35 (71)	14 (29)	0.760
	No	17 (68)	8 (32)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	44 (72)	17 (28)	0.327
	No	8 (62)	5 (38)	

* Correct answer: During treatment and for at least 4 months following each treatment

Knowledge of what to do if adverse events are suspected

Subgroup analyses of HCPs' knowledge of what to do if they suspect that a patient has immune thrombocytopenic purpura (ITP) are shown in Table 32. The high ratio of correct to incorrect responses meant that it was not possible to determine whether there were significant differences between subgroups.

Table 32 - Subgroup analysis: What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)?

Q27 What should you do if you suspect a patient has immune thrombocytopenic purpura (ITP)?		**Correct*** **n=67**	**Incorrect** **n=7**	**p-value**
		N (%)	N (%)	
Country	Germany	20 (100)	0 (0)	NA
	Italy	19 (95)	1 (5)	
	Norway	2 (67)	1 (33)	
	Spain	13 (87)	2 (13)	
	UK	12 (80)	3 (20)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	40 (93)	3 (7)	NA
	Neurologist	27 (87)	4 (13)	
University hospital	Yes	40 (87)	6 (13)	NA
	No	27 (96)	1 (4)	

Community hospital	Yes	23 (96)	1 (4)	NA
	No	44 (88)	6 (12)	
Office-based	Yes	5 (100)	0 (0)	NA
	No	62 (90)	7 (10)	
Number of MS patients seen	<100 patients per year	22 (88)	3 (12)	NA
	≥100 patients per year	45 (92)	4 (8)	
Last initiation of LEMTRADA	Within the last month	40 (87)	6 (13)	NA
	More than 1 month ago	27 (96)	1 (4)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	45 (92)	4 (8)	NA
	No	22 (88)	3 (12)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	56 (92)	5 (8)	NA
	No	11 (85)	2 (15)	

*Correct answer: obtain a complete blood count immediately and refer to a specialist immediately if onset is confirmed

Subgroup analyses of HCPs' knowledge of what to do if they suspect a patient has nephropathy are shown in Table 33. Self-reported MS specialists were significantly more likely than self-reported neurologists to answer the question correctly (p = .029). There were no other significant differences between groups based on work setting, number of MS patients seen, last prescription of LEMTRADA or having received and reviewed the HCP educational materials.

Table 33 - Subgroup analysis: What should you do if your monitoring results lead you to suspect nephropathy?

Q28 What should you do if your monitoring results lead you to suspect nephropathy?		**Correct*** **n=59**	**Incorrect** **n=15**	**p-value**
		N (%)	N (%)	
Country	Germany	17 (85)	3 (15)	NA

	Italy	17 (85)	3 (15)	
	Norway	2 (67)	1 (33)	
	Spain	14 (93)	1 (7)	
	UK	8 (53)	7 (47)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	38 (88)	5 (12)	**0.029**
	Neurologist	21 (68)	10 (32)	
University hospital	Yes	34 (74)	12 (26)	0.111
	No	25 (89)	3 (11)	
Community hospital	Yes	21 (88)	3 (12)	0.202
	No	38 (76)	12 (24)	
Office-based	Yes	5 (100)	0 (0)	NA
	No	54 (78)	15 (22)	
Number of MS patients seen	<100 patients per year	21 (84)	4 (16)	0.514
	≥100 patients per year	38 (78)	11 (22)	
Last initiation of LEMTRADA	Within the last month	34 (74)	12 (26)	0.111
	More than 1 month ago	25 (89)	3 (11)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	41 (84)	8 (16)	0.237
	No	18 (72)	7 (28)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	49 (80)	12 (20)	0.520
	No	10 (77)	3 (23)	

*Correct answer – Refer the patient to a specialist immediately

Knowledge of the types of counselling that should be provided to patients treated with LEMTRADA

Subgroup analyses of HCPs knowledge of the types of counselling that should be provided to patients treated with LEMTRADA are shown in Table 34. The sample size was insufficient to conduct an analysis by country. There were no significant differences between subgroups depending on specialist role, or last prescription of LEMTRADA. There was a (non-significant) trend for those who were based in a community hospital to be more likely to answer the question correctly than those who were based in a university hospital or office. There was also a (non-significant) trend for HCPs who saw 100 or more patients with MS per year to be more likely to answer the question correctly than those who saw less than 100 patients per year. HCPs who had received and reviewed the HCP educational materials were significantly more likely to answer the question correctly than those who had not (p = .016) (Table 34).

Table 34 - Subgroup analysis: What counseling should you provide patients treated with LEMTRADA?

Q.29 What counseling should you provide patients treated with LEMTRADA?		**Complete***	**Incomplete**	**p-value**
		n= 59	**n= 15**	
		N (%)	N (%)	
Country	Germany	19 (95)	1 (5)	NA
	Italy	15 (75)	5 (25)	
	Norway	3 (100)	0 (0)	
	Spain	10 (67)	5 (33)	
	UK	11 (73)	4 (27)	
	Denmark	1 (100)	0 (0)	
Specialist role	MS specialist	34 (79)	9 (21)	0.868
	Neurologist	25 (81)	6 (19)	
University hospital	Yes	34 (74)	12 (26)	0.111
	No	25 (89)	3 (11)	
Community hospital	Yes	22 (92)	2 (8)	0.067
	No	37 (74)	13 (26)	

Office-based	Yes	4 (80)	1 (20)	NA
	No	55 (80	14 (20)	
Number of MS patients seen	<100 patients per year	17 (68)	8 (32)	0.073
	≥100 patients per year	42 (86)	7 (14)	
Last initiation of LEMTRADA	Within the last month	38 (83)	8 (17)	0.430
	More than 1 month ago	21 (75)	7 (25)	
Received and reviewed all materials (HCP Guide, HCP Checklist, SmPC)	Yes	43 (88)	6 (12)	**0.016**
	No	16 (64)	9 (36)	
Received and reviewed one material (HCP Guide OR HCP checklist)	Yes	51 (84)	10 (16)	0.083
	No	8 (62)	5 (38)	

* Complete answer: Importance of contraception, risks and importance of monthly monitoring appointments (and any additional selections)

10.3 OTHER ANALYSES

No additional analyses were performed.

11 DISCUSSION

The goal of the LEMTRADA risk management plan is to ensure that all HCPs who prescribe LEMTRADA receive and review the HCP educational materials. The findings of this survey indicate that almost all HCPs reported that they had received and reviewed at least one of these materials; 76% of LEMTRADA prescribers who took part in the survey reported that they had received and reviewed the HCP Guide (8% - not received; 16% - don't remember); 76% indicated that they had received and reviewed the HCP checklist (8% - not received; 16% - don't remember); and 89% indicated that they had reviewed the SmPC (3% - not received; 8% - don't remember). Sixty-nine percent indicated that they had received and reviewed *both* the HCP Guide and Checklist, and only one HCP (1%) had not received or reviewed the HCP guide, the HCP checklist, or the SmPC.

The subgroup analyses for receipt and review of HCP educational materials (questions 11 to 13) showed no significant differences (all $p > .05$) depending on specialist role, work setting, number of MS patients seen or proximity of the last initiation of LEMTRADA. Though findings were non-significant (and therefore may be due to chance) the results showed that there was a trend for self-reported MS specialist neurologists to be more likely to have received and reviewed the materials, suggesting either that the materials are more likely to reach MS specialist neurologists than general neurologists, or that MS specialist neurologists are more likely to have reviewed the materials. There was another trend for prescription of LEMTRADA: HCPs who had initiated LEMTRADA in a patient within the last month were more likely to have received and reviewed the materials than those who had not initiated LEMTRADA within the last month. This finding may reflect greater recollection of the materials among those who have accessed them more recently, meaning that those who selected 'no' or 'don't remember' to receiving and reviewing the materials may have received or reviewed them too long ago to properly recall. The other findings demonstrate both doctors in community-hospital and university-hospital settings, and doctors who see more or less than 100 MS patients per year all have the same access to and likelihood of reading the educational materials.

Statistical analyses (chi-square tests) for countries could not be performed due to small sample sizes in some countries (e.g. Norway n = 3, Denmark n = 1). The proportions of HCPs who had knowledge of the Patient Guide, Patient Alert Card and Package Leaflet were 84%, 77%, and 77% respectively. A smaller proportion (57%) of HCPs indicated that they were aware of the availability of all three patient educational materials. Fortunately, there were no HCPs that were unaware of all materials. Fourteen (19%) knew only one of three materials and 18 (24%) knew only two. Subgroup analyses showed that HCPs who had received and reviewed the HCP materials had greater knowledge of the patient educational materials, indicating that the HCP educational materials may be effective in increasing knowledge of what is available to patients. The subgroup analyses did not identify significant differences depending on work setting, specialist role, number of MS patients seen or proximity of the last initiation of LEMTRADA. Even though the majority of the HCPs (84%) had knowledge of the patient guide, the finding that 43% of HCPs were unaware of all the materials available to patients suggests that this is an area where knowledge could be improved through reminding HCPs about each of these materials and reinforcing their individual importance.

Given that the HCPs were asked to answer from memory, the scores of some topics can be considered quite high. Topics where HCP knowledge was highest included the following:

1) knowledge of contraindicated conditions (Q16; 85% scored completely by selecting both 'HIV' and 'Hypersensitivity to the active substance or any of the excipients') and contraindicated treatments (Q17; 72% scored completely by selecting both 'Immunosuppressive therapy' and 'Antineoplastic therapy');

2) the required wait period following vaccination (Q19; 72% scored correctly by selecting either '6 weeks' or '8 weeks');

3) the appropriate medical intervention if the patient had suspected immune thrombocytopenic purpura (ITP) (Q27; 91% were correct) or suspected nephropathy (Q28; 80% were correct), and;

4) the need to counsel patients on the importance of contraception and the risks and the importance of monthly monitoring appointments (Q29; 80% answered completely by selecting at least both of these topics).

Of note, HCP knowledge of contraindications was 72%; however, the SmPC does not clearly indicate the 'correct' responses for the treatments where LEMTRADA is contraindicated (i.e. 'Immunosuppressive therapy' and 'Antineoplastic therapy'). Therefore, the survey question may be assessing knowledge that HCPs would not be expected to have just from reading the materials.

Areas in which HCP knowledge was lower included the following:

1) knowledge of all the risks to be discussed at first prescription of LEMTRADA (58% selected all five desired topics - nephropathies, thyroid disorders, ITP, active infections, and pregnancy/contraception - and therefore answered completely – 82% selected at least four out of the five topics),

2) the tests to be conducted before first prescription of LEMTRADA (59% answered completely by selecting all four tests recommended in the materials – serum creatinine, complete blood count with differential, urinalysis with microscopy, and thyroid function tests – 87% selected at least three out of the four options),

3) the need for women of childbearing potential to use contraception for at least four months following each infusion course (70% were correct – while 70% was the cut-off this can be considered sub-optimal knowledge given the seriousness of the topic – an additional 19% of the HCPs chose 48 months which is a longer period than required and may reflect an HCP's scientific opinion to tell patients to wait until the "at risk" period of auto immune disease is over);

4) knowledge of time-points at which monitoring activities for autoimmune events should be conducted (proportion with complete answers ranged from 46% for thyroid function tests to 61% for complete blood count with differential – an additional 30% of the HCPs choose

a higher number of time-points for monitoring autoimmune events and would hence still conduct testing at least 3-monthly)

5) knowledge of tests included in the risk management plan (only 22% and 28% of the sample, respectively, recognized that liver function tests and urine protein creatinine ratio tests are actually not part of the batch of tests recommended for risk management – however, it should be noted that the majority of HCPs choose more tests than required, not less).

One explanation for the latter three findings is that some HCPs may be erring on the side of caution and conducting tests more often than what was seen as 'correct' in the survey, and therefore though their behavior is clinically sound their responses would be interpreted as 'incorrect'. For example, an HCP that reports performing thyroid tests monthly (an 'incorrect' survey response) is behaving more thoroughly than one who reports performing thyroid tests every three months (the 'correct' survey response). Another explanation may be that some LEMTRADA is often given in expert centers far away from patients' homes. MS specialists and neurologists may have arranged with the patients' general practitioner or 'local neurologists' to perform the tests, and this may have influenced the routine knowledge of the HCPs and therefore their responses to questions 20 to 25. It is also necessary to consider the HCPs involved in this survey – particularly those general neurologists – would be responsible for a wide range of patients with many different diagnoses and medication risks. Therefore, it is possible that HCPs may not be able to easily recall all potential risks to be discussed and time-points of tests to be conducted without having to refer to the educational materials or other resources. Subgroup analyses revealed that HCPs who had received and reviewed all HCP materials, in comparison to those who had not or did not recall to have received or reviewed the materials, had significantly greater knowledge regarding patient educational materials available, the potential risks to be discussed at first prescription of LEMTRADA, tests to be conducted prior to first prescription of LEMTRADA, when to conduct monitoring tests (specifically, complete blood count with differential, urinalysis with microscopy, and thyroid tests (*ns*)), and the types of counseling that should be provided for patients receiving LEMTRADA. This suggests that the HCP educational materials increase the HCPs knowledge and supports the safe use of the product as intended. Ensuring that all HCPs receive the materials and reinforcing the importance of the HCP educational materials may increase knowledge in these areas.

Subgroup analyses also indicated that knowledge in certain areas was greater among MS specialist neurologists than non-MS-specialist neurologists (for example, what to do if there is suspected nephropathy; when to check complete blood count with differentials), in those who had more recently prescribed LEMTRADA (for example, knowledge of potential risks to be discussed), and in specialists who typically see more than 100 patients with MS per year (for example, knowledge of tests to be conducted before prescription with LEMTRADA) which is expected. That some knowledge was higher in those who see *less than* 100 MS patients each year (for example, knowledge that liver function tests do not need to be conducted) is surprising.

There were also some significant differences in knowledge amongst doctors based in community versus university hospitals and office based neurologists, however these differences did not always favor the same group. Doctors based in university hospitals or offices had better knowledge of contraception in women of childbearing age and knowledge of contraindications

than doctors in community hospitals. On the other hand, those based in university hospitals were less knowledgeable about when to check serum creatinine and blood count with differentials than those not based in university hospitals, and they were less likely to know when to complete blood count with differentials. The latter finding may be because doctors in university hospitals are more likely to refer patients back to community hospitals following LEMTRADA infusions.

Lastly, while statistical analyses could not be performed in order to detect differences between countries, the descriptive analyses revealed surprising results. The results warrant mention here as use of LEMTRADA is highest in UK compared to other countries involved in the survey. HCPs from the UK had the poorest knowledge in the following topics: potential risks to be discussed at first prescription, where LEMTRADA is contraindicated, wait period after patient vaccination, when to check serum creatinine and when to conduct urinalysis with microscopy, and what to do if there is suspected nephropathy. Since UK HCPs did have the best knowledge in some areas too (for example, tests that should be conducted before first prescription and when to check complete blood count with differential and liver function tests) this finding is interesting. Given that in the UK MS nurses play a more dominant role in the treatment and treatment logistics of MS patients, this may be the reason for lesser knowledge of the neurologists in this area. For this reason we may want to consider if specifically for the UK , MS nurses should be a target for the next wave of the survey.

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The strength of this survey include the potential reach of HCPs for recruitment (There was a total of 606 clicks on the survey website link) from six countries including two of the most populated countries in which LEMTRADA has been launched. However, the completion rate was not high (in total 74 HCPs completed the survey, which is 12%). Low completion rate could be due to the small market-share of LEMTRADA; the drug is only prescribed in a subset of patients and therefore many HCPs who clicked the survey may not have been eligible to complete it due to lack of experience with the drug. Limitations include the wording of survey questions that may have misled HCPs to provide answers that were later deemed ‘incorrect’ or ‘incomplete’ (when the HCP may in reality have sound clinical knowledge), and the use of a cross-sectional design which made it difficult to determine whether the HCP educational materials increased knowledge or whether increased knowledge among those who had received and reviewed the HCP educational materials was the result of another factor, such as conscientiousness, motivation, or greater experience with the drug. A convenience sample (non-randomized) was used, rather than a random sample, which means that the findings may be subject to bias, thereby limiting the generalisability of the results. However, it should be noted that a random sample is not possible given that there is not a database of names and addresses of LEMTRADA prescribers that could be accessed in order to randomly select HCPs.

12 OTHER INFORMATION

N/A

13 CONCLUSION

At least 76% of the 74 HCPs involved in this study recall receiving and reviewing the HCP guide, the HCP checklist, and the SmPC. 99% of HCPs had received and reviewed at least one of these materials. The proportion receiving at least one material is high and it is important to note that 89% of the HCPs mention to have reviewed and read the SmPC, which contains most of the information. Better understanding is needed on why the percentages for the guide and checklist are lower. It will be important to ensure that all potential LEMTRADA prescribers are aware of the importance of reviewing all HCP educational materials.

HCP knowledge was optimal in certain areas and less optimal in others. These findings may be a result of the heterogeneity in HCP participants: HCPs were from six different countries, just over half were MS-specialist neurologists, and one-third of HCPs see less than 100 MS patients per year. Areas where knowledge on spontaneous recall was good included knowledge of contraindicated conditions and treatments, required wait period following vaccination, medical interventions following suspected ITP or nephropathy, and important issues to counsel patients on during appointments. Although score on importance of contraceptive use of women of childbearing age was good, the knowledge on the time needed to take contraceptives (4 months after Lemtrada) needs improvement (8 HCPs, 11%, reported contraceptives are needed for less than 4 months). Areas where knowledge was less optimal (<70% scoring correctly/completely) included knowledge of potential risks to be discussed at first prescription, tests to be conducted at/prior to first prescription, and knowledge of tests that do and do not need to be conducted and when. However, it should be noted that in many cases where responses were deemed ‘incorrect’ according to the survey, HCPs were in fact answering cautiously and reporting that they would test more frequently than was required for a correct answer.

Sub-group analyses revealed that reviewing all HCP education materials (HCP guide, HCP checklist, and Summary of Product Characteristics) leads to improved knowledge, which shows the efficacy of the materials. Further, being a MS-specialist neurologist (as opposed to a non-MS specialist neurologist), and prescribing LEMTRADA more recently may lead to improved knowledge, likely because these doctors used LEMTRADA more frequently and are therefore more familiar with procedures. These findings may indicate a need to ensure that non-MS specialist neurologists and those who prescribe less frequently are reminded of the materials and the need to review the risk information and conduct appropriate monitoring with their patients. Given that the results of the survey may have been influenced by the wording of the questions presented to the HCPs, it is important that these are reviewed prior to wave two of the study.

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	V11	July 2013	HCP guide
4	V12	July 2013	HCP checklist
5	V12	July 2013	Patient Guide
6	V10	July 2013	Patient Alert Card

Annex 2 Supportive Documents

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

COMPOUND: Alemtuzumab

STUDY NAME: Lemtrada® EU-RMP Survey in HCPs

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

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Other experts/consultants

Protocol Agreement Form

Not applicable.

PASS Information

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

2 LIST OF ABBREVIATIONS

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

3 RESPONSIBLE PARTIES

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

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

The survey is sponsored by Genzyme, a Sanofi company.

4 ABSTRACT

Title

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

Rationale and background

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

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

Research question and objectives

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

Study design

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

Population

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

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

Variables

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

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

Data Sources

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

Study size

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

Data analysis

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

Milestones

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

5 AMENDMENTS AND UPDATES

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

6 MILESTONES

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

7 RATIONALE AND BACKGROUND

BACKGROUND

Safety hazards

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

Safety profile

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

Description of Lemtrada® Risk Management Plan

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

The primary objectives of the educational materials are to:

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

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

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

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

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

Autoimmune conditions, including:

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

Additional items that HCPs need to be aware of:

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

Relevant published research

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

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

RATIONALE

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

8 RESEARCH QUESTION AND OBJECTIVES

Research questions

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

8.1 PRIMARY OBJECTIVE

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

8.2 SECONDARY OBJECTIVES

Not applicable.

9 RESEARCH METHODS

9.1 STUDY DESIGN

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

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

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

9.2 SETTING

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

9.2.1 Duration of the study

The duration of the study will be 96 weeks.

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

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

Exclusion criteria

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

9.2.3 Analysis populations

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

9.2.4 Modalities of recruitment

9.2.4.1 Physician selection

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

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

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

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

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

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

9.3 VARIABLES

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

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

1. Physician characteristics including:

    a) Country

b) Type of hospital

c) Speciality

d) Total number of MS patients under treatment

e) Number of patients prescribed Lemtrada®

f) Time since last prescription of Lemtrada®

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

a) the HCP guide

b) the HCP checklist

c) the SmPC

d) the Patient Guide

e) the Patient Alert Card

f) the Package Leaflet

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

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

a) Contraindications

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

c) Vaccination, pre-treatment courses

d) Monitoring activities for the autoimmune events

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

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

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

   b) Required time period for monitoring

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

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

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

Potential confounding factors

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

9.4 DATA SOURCES

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

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

9.5 STUDY SIZE

9.5.1 Determination of sample size

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

9.5.2 Sample size

It is planned to recruit 60 - 70 HCPs.

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

HCP data

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

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

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

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

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

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

MS population data

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

9.6.2 Data collected

Online questionnaire

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

9.6.3 Site / Physician questionnaire

Not applicable.

9.6.4 Screening log (if applicable)

Not applicable.

9.6.5 Patient data

Not applicable.

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

Not applicable.

9.6.7 Logistic aspects

Not applicable.

9.7 DATA ANALYSIS

9.7.1 Primary analysis

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

9.7.2 Secondary analysis

The analysis will be descriptive.

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

9.7.3 Interim analysis

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

9.8 QUALITY CONTROL

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

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

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

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

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

9.8.2 Data quality control at site level

Not applicable.

9.9 LIMITATIONS OF THE RESEARCH METHODS

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

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

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

Not applicable.

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.2.1 Ethical principles

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

10.2.2 Laws and regulations

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

10.2.3 Data protection

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

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

10.2.4 Insurance

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

10.2.5 Secrecy agreement

Not applicable

10.2.6 Record retention

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

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

10.2.7 Discontinuation of the study

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

10.2.8 MAH/MAH representative audits and inspections by competent authorities

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

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

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

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

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

11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

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

12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

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

12.2 PUBLICATIONS

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

13 REFERENCES

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

ANNEXES

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

Annex 1 List of stand-alone documents

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

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>