POST AUTHORIZATION SAFETY STUDY (PASS) REPORT

FINAL REPORT WAVE 1 AND WAVE 2

TITLE: Behavior and knowledge survey to assess the effectiveness of educational materials in patients treated with AUBAGIO® (teriflunomide) (cross-sectional survey)

COMPOUND: Teriflunomide

STUDY NAME: AUBAGIO® EU-RMP Survey in Patients

Wave 1 of the Study was conducted by Sanofi Genzyme, Atlantis Healthcare, and Ipsos. Wave 2 of the Study was conducted by Sanofi Genzyme, and Ipsos, hereinafter referred also as the "MAH/MAH REPRESENTATIVE".

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PASS Information

Title	Behavior and knowledge survey to assess the effectiveness of educational materials in patients treated with AUBAGIO® (teriflunomide)
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	Teriflunomide
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Procedure number	EMEA/H/C/002514/
Marketing authorization holder(s)	sanofi-aventis Groupe, Paris, France
Joint PASS	No
Research question and objectives	The objective of the study is to assess descriptively knowledge and behavior of treated patients about the items of the educational materials (Package Leaflet [Patient Information Leaflet; [PIL]/Patient Card [PC}') and thus the effectiveness of these materials and tools to ensure the safe use of AUBAGIO. Research questions: 1. What is the knowledge of patients about the PC? a. Have patients received the PC? b. Do patients understand the purpose of the PC? 2. What is the knowledge of patients about serious adverse events (SAEs) related to AUBAGIO? a. Can patients identify serious adverse events (SAEs) that should prompt a visit to the doctor? b. Do patients understand the risks of pregnancy and procedures to be followed? 3. Does patients' self-report indicate that they are performing risk minimization behavior (contraception, compliance with blood monitoring, reading PC and PIL, carrying PC)?
Countries of study	The first wave of the survey was conducted in the United Kingdom (UK), France, Germany, Italy, Spain, and Denmark. The second wave of the survey was conducted in the UK, France, Germany, Italy, Spain, Greece, Belgium and the Netherlands.

Marketing authorization holder(s)

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The Company Internal Staff

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

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

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Not applicable.

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Atlantis Healthcare has been involved in the preparation of the protocol and its amendments and has developed the survey and analyzed the results for Wave 1. Ipsos, together with Sanofi Genzyme, was involved in the preparation of the Wave 2 protocol and has analyzed the Wave 2 results.

Ipsos was involved with the recruitment of healthcare professionals (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	February 2016	March 2016	--
End of data collection Wave 1	March 2016	November 2016	--
Interim Report 1 (Wave 1 results)	May 2016	November 2016[a]	176 patients in Wave 1
Interim Report 2 (Wave 1 results)	--	February 2017	Wave 1 completed
Start of data collection Wave 2	April 2017	September 2017	--
End of data collection Wave 2	May 2017	February 2018	--
Results Wave 2	August 2017	April 2018	--
Final report Wave 1 and 2 results	August 2017	March 2019	--

a The planned sample size of 200 could not be reached at the cut-off date. Therefore, this report represents the first interim report for Wave 1.

4 LIST OF ABBREVIATIONS

AE:	adverse event
EMA:	European Medicines Agency
EU:	European
HCP:	healthcare professional
MAH:	Marketing Authorization Holder
MS:	multiple sclerosis
PASS:	Post Authorization Safety Study
PBRER:	Periodic Benefit Risk Evaluation Report
PC:	Patient Card
PIL:	Patient Information Leaflet
RMP:	risk management plan

5 INTRODUCTION

This report presents a concise overview of the combined results of Wave 1 and Wave 2 of the Behavior and knowledge survey of educational materials in patients treated with AUBAGIO® (teriflunomide).

The AUBAGIO 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 Package Leaflet (Patient Information Leaflet [PIL]) and Patient Card (PC). These patient educational materials are intended to ensure early detection of key symptoms indicative of adverse events (AEs), communicate risks of symptoms and the importance of periodic monitoring to patients and prescribers, and inform about benefit-risk decisions before treatment.

Apart from the PIL, which is included in the treatment box, patients should have received the PC from their prescriber in hard copy at the time they were confirmed to receive AUBAGIO. Additionally, the patient educational materials are available on a Multiple Sclerosis (MS) One to One program website to provide electronic access to patients who have been prescribed treatment.

5.1 METHODOLOGY

To define the familiarity of patients with the educational materials, the sponsor has performed an international, cross-sectional survey, recruiting from a total of 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, respectively, after the launch of AUBAGIO in at least 5 countries, including launch in at least 2 highly populated EU countries (Germany, France, the UK, Italy, and Spain). The objective of the survey was to assess the knowledge and behavior of patients treated with AUBAGIO with regard to the topics covered in the AUBAGIO educational materials (PC, PIL), and thus the effectiveness of these materials to ensure the safe use of AUBAGIO.

Research questions were related to the extent of patients' understanding and awareness of the purpose of the PC as well as their understanding of the risks associated with the use of the product, the key safety messages in the content of the PC and PIL, and knowledge of risk minimization activities to be undertaken (contraception, compliance with blood monitoring, reading the PC and PIL, carrying the PC). A convenience (ie, non-random) sample of MS patients treated with AUBAGIO was selected, and data was collected via patient self-report in an online questionnaire. Per protocol, the response on knowledge and behavior was considered 'satisfactory' if participants provided >70% of correct answers

The first wave of the survey (Wave 1) was conducted with 202 patients recruited from Italy (n=54 [27%]), Germany (n=51 [25%]), Spain (n=47 [23%]), the UK (n=26 [13%]), France (n=21 [10%]) and Denmark (n=3 [1%]). Results were analyzed and were reported to the European Medicines Agency (EMA) within submission of Periodic Benefit Risk Evaluation Report (PBRER) covering the period from 13 September 2016 to 12 September 2017 (procedure

EMEA/H/C/PSUSA/00010135/201709). The second wave of the survey (Wave 2) was conducted in the same manner as for Wave 1 with 200 patients recruited from Germany (n=45 [23%]), Italy (n=44 [22%]), Spain (n=32 [16%]), France (n=30 [15%]), Greece (n=15 [8%]), the UK (n=13 [7%]), the Netherlands (n=11 [6%]) and Belgium (n=10 [5%]). 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 patient characteristics, including:

- Patient's country, age, gender, year of first AUBAGIO prescription, year of MS diagnosis (Wave 2 only), childbearing potential and contraceptive use
- Patient's receipt and understanding of the purpose of the PC
- Patient's knowledge of symptoms indicating AEs (hepatic risks, infection risks), and understanding of the need to contact the doctor
- Patient's understand the risks of pregnancy and procedures to be followed
- Patient's knowledge of the risk minimization behavior (adherence to treatment, blood monitoring, contraception, reading the PIL and PC, and carrying the PC)

No personally identifiable information was collected from patients who participated in the surveys.

5.3 DIFFERENCES IN QUESTIONNAIRES AND SCORING

The protocol was amended once between Wave 1 and Wave 2 (Protocol version identifier 1.1, 08 May 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 risk management questions only 1 answer had to be chosen, instead of selecting a combination of correct responses in order to score the answer as 'completely correct'..
- A limited number of questions were added in Wave 2 to elicit additional information about existing or related questions in Wave 1. These questions included the number of years since MS diagnosis, how long ago patients had read the PIL, the contraception method used by female patients with childbearing potential, and the reason female patients were not using contraception if they indicated they could become pregnant.
- Per protocol, for knowledge and behavior analyses, a threshold of 70% was defined as 'satisfactory' knowledge.

6 RESULTS

6.1 DEMOGRAPHIC RESULTS

Over the 2 waves, the survey was conducted in a total of 402 (202 Wave 1, 200 Wave 2) patients from Germany, Italy, Spain, France, Greece, Denmark, Belgium, the UK, and the Netherlands. The population surveyed was generally consistent between Wave 1 and Wave 2 (ie, common demographics questions on both surveys). The majority (57% Wave 1, 71% Wave 2) were female patients, which is consistent with the MS population as a whole (1). Most participants (80% Wave 1, 62% Wave 2) were age 45 years or younger and began taking AUBAGIO in 2015 or later (73% Wave 1, 85% Wave 2). In Wave 2, 47% of patients had been diagnosed with MS less than 5 years ago.

6.1.1 Knowledge of the Patient Card

The majority of patients in Wave 1 (83%) but not Wave 2 (47%) recalled receiving the PC (Table 1). The lower proportion of patients who recalled receiving the PC in Wave 2 may reflect the longer length of time since these patients began treatment with AUBAGIO/receiving their PC and taking the survey. For example, 75% of Wave 1 patients initiated AUBAGIO in 2015 or later, and end of data collection for Wave 1 was the beginning of 2017 (Section 3). However, 85% of Wave 2 patients initiated AUBAGIO in 2015 but end of data collection for Wave 2 was 2018, which was a full year later than for Wave 1. Many patients with MS suffer cognitive impairments, including memory loss, that may increase their difficulty in recalling specific details and events, including whether they have ever received a PC.

Among patients who recalled receiving the PC, similarly low proportions of patients in both waves correctly identified both purposes of the PC (35% Wave 1, 38% Wave 2). Of note, 54% of patients in Wave 1 and 33% of patients in Wave 2 correctly indicated at least 1 of the 2 correct items (to provide important safety information).Therefore, more than two-thirds of patients in each wave who reported receiving the PC knew that it contained important safety information, which is an important response. The majority of all participants (93% Wave 1, 82% Wave 2) correctly answered the behavioral question about whether a patient on holiday who gets an infection should show a local doctor their PC during their doctor's visit, indicating that knowledge of required behavior with regard to the PC was satisfactory (≥70% correct).

Table 1 - Knowledge about the Patient Card

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.8 Have you ever received a PC for AUBAGIO?	Yes	168 (83%)	93 (47%)
	No	34 (17%)	94 (47%)
	Don't know	0	13 (6%)
Q.9 What is the purpose of the PC?[a]	To show a doctor or HCP involved in your medical care that you have been treated with AUBAGIO	136 (81%)	27 (29%)
	To give you important safety information you need to be aware of when receiving treatment with AUBAGIO	90 (54%)	31 (33%)
	Both of the above ✓	58 (35%)	35 (38%)
Q.21 Danny has gone on holiday for 2 weeks. Unfortunately, while he's on holiday he gets an infection & needs to visit the local doctor. Should he show the local doctor his PC?	Yes ✓	187 (93%)	164 (82%)
	No	15 (7%)	36 (18%)

HCP = Healthcare Professional; PC = Patient Card
a All respondents who have ever received a PC for AUBAGIO
✓ Correct answer

6.1.2 Knowledge of symptoms of adverse events and the need to contact a doctor

Patients' knowledge of signs and symptoms indicative of serious AEs of AUBAGIO (hepatic risks, infection risks) that should prompt a visit to the doctor was assessed in Wave 1 and Wave 2. The percentages of respondents who correctly identified signs and symptoms of liver problems and the need to contact a doctor are summarized in Table 2.

Of note, in Wave 1, for most questions a list of possible responses was provided and patients had to choose all of the correct responses to score a 'complete answer'. This resulted in the fact that questions could be answered partially, as explained in the Comments column. In Wave 2, several potential responses were offered but only 1 was correct.

Responses for the questions on signs and symptoms of liver problems and infection were below the adequacy level of 70% in both waves, although patients in Wave 2 had slightly higher scores than patients in Wave 1 (Q14: 35% Wave 1, 53% Wave 2; Q15: 9% Wave 1, 41% Wave 2). This may be because the questions in Wave 2 contained part of the correct answer, and patients then had to choose from only a few options to complete the answer instead of choosing multiple options to score a 'complete' answer, as mentioned above.

Responses for patient knowledge of the need to contact a doctor when a patient is 'feeling sick and is vomiting' (Q20) were below the adequacy level of 70% in both waves (64% Wave 1, 53% Wave 2), although correct responses were higher when patients were provided with fewer choices for correct responses in Wave 1 (Table 2). In addition, nearly one-third of patients in both waves

(34% Wave 1, 32% Wave 2) identified 'monitor symptoms for a few days' (an incorrect answer) as a valid option following the appearance of these symptoms.

Patients' knowledge of the need to contact a doctor when a patient 'got the influenza' (Q19) was satisfactory in Wave 1 (80%) but not in Wave 2 (45%). However, in Wave 2, a potential–and logical– response was 'No, he should simply follow general flu advice', and 67 (34%) patients chose that response. If the question had been structured with only 'Yes' or 'No' response options as was done in Wave 1, it may be that those 67 patients in Wave 2 would have selected the correct 'Yes' (i.e., call your doctor) option.

Table 2 - Knowledge of symptoms of adverse events and the need to contact a doctor

	Correct answers		
Question (abbreviated)	**Wave 1 n (%)**	**Wave 2 n (%)**	**Comments**
Q.14 Signs of a liver problem	71 (35%)	106 (53%)	In Wave 1, 4 signs had to be selected to answer completely (35% of patients); 29% selected 3/4 signs, 36% selected 2/4, and 0% selected 1/4 or 0/4 signs.
Q.20 Clare has been feeling sick and is vomiting. She has got an appointment with her doctor in one month's time. What should she do?	129 (64%)	105 (53%)	One-third (34% Wave 1, 32% Wave 2) selected '…monitor her symptoms for a few days before making a decision about what to do.'
Q.15 Signs of infection	18 (9%)	82 (41%)	In Wave 1, 5 signs had to be selected to answer completely (9% of patients); 13% selected 4/5 signs, 26% selected 3/5; and 52% selected 2/5 or 1/5 signs.
Q.19 John got influenza (flu). Should he tell his doctor?	161 (80%)	90 (45%)	In Wave 1, patients were provided simply 'Yes' and 'No' response choices. In Wave 2, the response option was, 'No, he should simply follow general flu advice', and 34% chose that option.

6.1.3 Risks of pregnancy and procedures to be followed

As shown in Table 3, knowledge of pregnancy risk and the procedures to be followed if a woman becomes pregnant while taking AUBAGIO was similar and near or above satisfactory in both waves (73% Wave 1, 66% Wave 2). In Wave 1, where the elimination procedure was included in the question and patients were given a choice between 'True' or 'False' responses, 73% of female patients correctly selected 'True'. In Wave 2, the 2-part correct response 'Tell her to stop taking AUBAGIO immediately and prescribe medicine to help remove AUBAGIO from her body' was selected by 66% of patients. An additional 17 (12%) patients selected 'Prescribe medicine to help remove AUBAGIO from her body' indicating their awareness of the AUBABIO elimination procedure.

In response to a behavioral question regarding the appropriate course of action when a pregnancy is suspected while taking AUBAGIO, 73% of female respondents in Wave 2 correctly answered that the patient should 'contact the doctor immediately'. In Wave 1, a 'complete answer' could include 'Contact a doctor immediately' and 'Consider enrolment in the Pregnancy Registry'. In Wave 1, most (64%) patients correctly responded that 'She should contact the doctor immediately' while an additional 3% selected the complete 2-part correct response 'Contact the doctor immediately AND Consider enrolment in the Pregnancy Registry'. This was just under the satisfactory response threshold of 70% set for behavioral questions in Wave 2.

Table 3 - Knowledge of pregnancy and procedures to be followed (female respondents only)

	Correct answers		
Question (abbreviated)	Wave 1 n (%)	Wave 2 n (%)	Comments
Q.16 If a woman taking AUBAGIO finds out that she is pregnant, her doctor should…	84 (73%)	93 (66%)	In Wave 2, 12% selected 'Prescribe medicine to help remove AUBAGIO from her body'.
Q.18a Rachel suspects that she may be pregnant. What should she do?	78 (67%)	103 (73%)	In Wave 1, 3% also selected 'Contact the doctor immediately AND Consider enrolment in the Pregnancy Registry'.

6.1.4 Risk minimization procedures

6.1.4.1 Taking AUBAGIO as prescribed

Patient medication compliance was highly satisfactory in both waves (96% Wave 1, 86% Wave 2) (Table 4). However, the question was posed differently in the 2 waves. In Wave 1, respondents were given a choice of 'Yes or 'No' in response to the question: 'Over the last week have you taken your AUBAGIO tablets as prescribed?', and there is no way of knowing how the patient was actually taking the medication. In Wave 2, respondents must have chosen the correct response 'Once daily' to the question: 'How often should AUBAGIO tablets be taken?', and it was clear that 14% of patient were taking it incorrectly.

Table 4 - Taking AUBAGIO as prescribed

	Correct answers		
Question	Wave 1 n (%)	Wave 2 n (%)	Comments
Q.6 How often should AUBAGIO tablets be taken?	194 (96%)	172 (86%)	Wave 1 Q.6 was, 'Over the last week have you taken your AUBAGIO tablets as prescribed?'

6.1.4.2 Blood monitoring compliance

The AUBAGIO SmPC states that blood monitoring should occur "…every 2 weeks during the first 6 months of treatment, and every 8 weeks thereafter" while the AUBAGIO PC instructs patients to "Please ensure you perform any follow up blood tests and blood pressure check-ups, as arranged by your doctor." In both Wave 1 and Wave 2 compliance with blood monitoring was satisfactory (82% and 83% respectively) (Table 5).

In Wave 2, the survey question and responses related to blood monitoring were modified to more accurately assess the time since the last blood test compared to Wave 1. In Wave 1, compliance with blood monitoring was more theoretical; that is, it was calculated indirectly by using the recommended frequency of the blood testing and the reported treatment start date (for more information, see the Wave 1 report in Annex 1). In Wave 2, the question asked, "When was your last blood test for AUBAGIO?", and patients could select from 5 possible responses (<2 weeks ago, between 2-4 weeks ago, between 1-3 months ago, >3 months ago, >6 months ago, don't know). Considering that the majority of patients had started treatment more than 6 months prior to the survey, an answer including 1 to 3 months ago or more recently was considered to indicate satisfactory compliance with AUBAGIO blood testing.

Table 5 - Blood monitoring compliance

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.7 When was your last blood test for AUBAGIO?	Compliance[a]	165 (82%)	164 (83%)
	Noncompliance	37 (18%)	35 (18%)

a. In Wave 1, compliance was defined as persistent blood monitoring for >6 months after start of AUBAGIO treatment. In Wave 2, compliance was defined as having the last blood test for AUBAGIO at least as frequent as '1-3 months ago'.

6.1.4.3 Use of the Patient Card and Patient Information Leaflet

The proportions of patients who recalled receiving the PC (see Section 6.1.1) was notably higher in Wave 1 (83%) than in Wave 2 (47%). Of those patients who recalled receiving the PC, 78% in Wave 1 and 81% in Wave 2 reported reading more than half or all of it, and the proportion of patients who reported always or usually carrying the PC with them increased from Wave 1 (42%) to Wave 2 (74%) (Table 6). The latter change can be attributed, at least in part, to the decline from Wave 1 (54%) to Wave 2 (10%) in the proportion of patients who reported keeping their PC in a safe place rather than carrying it with them.

Among patients who recalled receiving the PC but reported not carrying it with them, the most frequent reasons cited for not carrying the PC were 'I know all the information on the PC' in Wave 1 (29%), and 'I am not sure why it's important to carry the PC around' in Wave 2 (58%; although the number of Wave 2 patients responding was small [n=7]).

As an additional exploratory question in Wave 2, patients were asked if they had suggestions for improving the PG (Table 6; question was not asked in Wave 1). The most popular suggestion was

to add more detail in general (35%) followed by adding more pictures and covering topics other than side effects, such as quality of life (27% each).

All patients receive the PIL with each AUBAGIO package. The majority of patients in both waves (79% Wave 1, 67% Wave 2) reported reading more than half or all of the PIL. In Wave 2, patients who recalled having read the PIL were asked the additional question (Q13b) 'How long ago did you read the AUBAGIO materials?'. The majority (63%) of Wave 2 patients who had read the PIL responded that they had last read the PIL 'more than 3 months ago'.

Table 6 - Use of the Patient Card and Patient Information Leaflet

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.10 People differ in the amount of information they read about their medicines. How much of the PC have you read?[a]	All of it	83 (49%)	51 (55%)
	More than half of it	49 (29%)	24 (26%)
	About half of it	28 (17%)	11 (12%)
	Less than half of it	6 (4%)	5 (5%)
	None of it	2 (1%)	2 (2%)
Q.13 How much of the PIL, which is included in the AUBAGIO carton, have you read?	All of it	103 (51%)	99 (50%)
	More than half of it	56 (28%)	33 (17%)
	About half of it	24 (12%)	30 (15%)
	Less than half of it	12 (6%)	13 (7%)
	None of it	7 (3%)	25 (13%)
Q.13b How long ago did you read the AUBAGIO materials?[b]	Less than a week ago	NA	8 (5%)
	Between 1-2 weeks ago	NA	17 (10%)
	Between 2-4 weeks ago	NA	25 (14%)
	Between 1-3 months ago	NA	14 (8%)
	More than 3 months ago	NA	111 (63%)
Q.11 Where do you keep your PC?[a]	I always carry the PC with me	70 (42%)	45 (48%)
	I usually carry the PC with me	NA	24 (26%)
	I only carry the PC with me when I need it	NA	12 (13%)
	I never carry the PC with me (I keep it in a secure place)	91 (54%)	9 (10%)
	I no longer have a PC (eg, lost it or threw it away)	3 (2%)	2 (2%)
	Other	4 (2%)	1 (1%)
Q.12 If you don't carry the PC with you, please tell us why[c]	I was not given a PC	14 (14%)	NA
	I lost my PC	14 (14%)	1 (8%)
	The PC is not easy to carry around	25 (26%)	1 (8%)

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
	I know all the information on the PC	28 (29%)	3 (25%)
	I do not like having a reminder of my MS	15 (15%)	2 (17%)
	I am not sure why it's important to carry the PC around	19 (19%)	7 (58%)
	Other	4 (4%)	NA
Q.12a Do you have any suggestions to improve the PC?[a]	More detailed information in general	NA	33 (35%)
	Less detailed information in general	NA	16 (17%)
	More pictures	NA	25 (27%)
	Less pictures	NA	5 (5%)
	Covering topics other than side effects, such as quality of life	NA	25 (27%)
	More practical	NA	15 (16%)
	Other	NA	7 (8%)

NA = not included in the questionnaire; PC = Patient Card; PIL = Patient Information Leaflet
a All respondents who have ever received a PC for AUBAGIO
b All respondents who read the PIL for AUBAGIO in Wave 2
c All respondents who do not carry a PC for AUBAGIO. Patients in Wave 1 could have chosen more than 1 response.

6.1.4.4 Use of Contraception

Table 7 summarizes female patients' knowledge of the need for contraception while taking AUBAGIO. Childbearing potential was defined as those women who reported they do use a contraceptive method (Q17), and those women who reported they do not use a contraceptive method but could still get pregnant (Q18).

In Wave 1, the sample consisted of 115 female patients, and 68 women were considered to have childbearing potential. Of these, 8 (12%) women were not using contraception. However, it should be noted that some of these 8 women were not at high risk of pregnancy due to being over the age of 46. In Wave 2, 141 female patients were included in the study, and 66 were considered women of childbearing potential. Of these, 16 (24%) women were not using a contraceptive method. In Wave 2, to further explore female patients' knowledge of the risks of becoming pregnant while taking AUBAGIO, an additional question was included, asking women why they were not using a contraceptive method (Q18aa). Among the 16 women who said they could become pregnant but did not use contraception, 12 patients said they 'did not want to become pregnant but think they have a very small chance to get pregnant'; 3 patients actually wanted to become pregnant, and 1 patient from Germany responded that they 'want to become pregnant and my doctor does not think AUBAGIO is harmful for pregnant women or for women who wish to become pregnant'. The latter result may reflect evolving beliefs among some HCPs and their patients about the safety of disease-modifying therapies (DMTs) in women who wish to become pregnant (2, 3).

Table 7 - Use of contraception (female respondents only)

Questionnaire item	Response option	Wave 1 n (%)	Wave 2 n (%)
Q.17 Do you use a contraceptive method?	Yes	60 (52%)	50 (35%)
	No	40 (35%)	84 (60%)
	Don't want to answer	15 (13%)	7 (5%)
Q.17b Which contraceptive method do you use in general?[a]	Contraceptive pill	NA	22 (44%)
	Condom	NA	10 (20%)
	I am sterilized	NA	3 (6%)
	Coil	NA	8 (16%)
	Other	NA	5 (10%)
	Do not wish to answer	NA	2 (4%)
Q18 Please tell us why you don't use a contraceptive method.[b]	I do not have sexual intercourse	15 (38%)	25 (30%)
	I have sexual intercourse but it is not possible for me to become pregnant (eg, reached the menopause, partner has had a vasectomy or partner is a woman)	17 (43%)	32 (38%)
	I have sexual intercourse and it is possible for me to become pregnant but I do not use a contraceptive method	8 (20%)	16 (19%)
	Do not wish to answer	NA	11 (13%)
Q.18aa Please tell us why you don't use a contraceptive method[c]	I want to become pregnant	NA	3 (19%)
	I want to become pregnant and my doctor does not think AUBAGIO is harmful for pregnant women or for women who wish to become pregnant	NA	1 (6%)
	I do not want to become pregnant but I think I have a very small chance to get pregnant	NA	12 (75%)

NA = not included in the questionnaire;
a Female respondents in Wave 2 who are currently using contraception.
b Female respondents who are not currently using a contraceptive method.
c Female respondents in Wave 2 who are not currently using a contraceptive method but have sexual intercourse and can become pregnant.

6.2 SUMMARY OF SECONDARY ANALYSES

Note that in Wave 1, Denmark was included among the countries surveyed and included in the second interim report (see Annex 1). However, as only 3 of the 202 participants (1%) were from Denmark, that country is not included in the discussion of secondary analyses in this Wave 1/Wave 2 combined report.

Although there were some differences, the results of the subgroup analyses were generally consistent with the results obtained for the primary analysis in both Wave 1 and Wave 2. The results from subgroups with fewer than 15 patients are difficult to interpret and those from

subgroups with fewer than 12 patients are not detailed.

In both waves, patients who had read the PC and those who had read the PIL responded correctly in similar proportions and at similar or slightly higher rates than all patients in the primary analysis, with 2 exceptions. In Wave 2, more patients who recalled receiving the PC (79%) and reading the PIL (71%) correctly identified the AUBAGIO elimination procedures for a pregnant woman compared to all patients (66%) in the primary analysis. In Wave 2, when asked what a patient who suspects she might be pregnant should do (Q18a), 67% of patients who recalled receiving the PC compared to 73% of all patients in the primary analysis correctly responded that she 'Should contact her doctor immediately'.

The results of the secondary analyses by country were generally consistent with the primary analysis in Wave 1 except for the question about blood monitoring (Q7). In Germany, 67% of patients were compliant with blood monitoring compared to all patients (70%) in the primary analysis. These results may be related to varying requirements for biological monitoring across regions.

In Wave 2, the low proportion of patients in Italy who recalled receiving the PC (9%) or reading about half or more of the PIL (48%) may have contributed to a lower frequency of correct responses from patients in Italy on many survey questions. However, the responses from Italian patients were less than satisfactory on 2 questions compared to satisfactory responses from all patients in the primary analysis. In the primary analysis, 82% of all patients compared with 32% of patients in Italy correctly answered the behavioral question (Q21) about whether a patient who gets sick on holiday should show his PC to a local doctor. When asked what a patient who suspects she might be pregnant should do (Q18a), 73% of all patients in the primary analysis compared to 48% of patients in Italy correctly responded that she 'Should contact her doctor immediately'. With regard to taking AUBAGIO as prescribed, patients in Greece (67%) had a slightly lower proportion of correct responses compared to all patients (70%) in the primary analysis.

Although there was some variability observed by prescribing year, the results were not notably different from those observed in the primary analysis with 2 exceptions, both in the earliest prescribing year (2014) and both in Wave 2. When asked what a patient who suspects she might be pregnant should do (Q18a), 43% of patients who first received AUBAGIO in 2014 compared to 73% of all patients in the primary analysis correctly responded that she 'Should contact her doctor immediately'. In Wave 2, 66% of patients who were first prescribed AUBAGIO in 2014 reported having a blood test within the last 3 months (Q7) compared with 82% of all patients in the primary analysis.

The proportion of women who were determined to have childbearing potential was higher in Wave 1 (68%, n=100) than Wave 2 (54%, n=123) and a greater proportion of these women were using contraception in Wave 1 (88%) compared to Wave 2 (76%).

6.3 ANALYSIS BY COUNTRY

As noted above, because only 3 of the 202 participants (1%) in Wave 1 were from Denmark, that country is not included in the discussion of secondary analyses in this Wave 1/Wave 2 combined report or in Table 8.

Wave 2 was conducted in 5 of the Wave 1 countries but also in Greece, Belgium, and the Netherlands. Because of the additional countries included in Wave 2, this section presents by-country compilation of correct responses to secondary analysis questions in order to directly compare results for those countries included in both waves (Table 8) (shading indicates those countries only included in Wave 2). This discussion considers the 5 countries that both waves had in common.

As shown in Table 8, Percentages of correct answers were generally similar between countries in Wave 1 and Wave 2 with the following exceptions. More patients in Wave 2 appeared to have knowledge about symptoms of liver problems and signs of infection than those in Wave 1, although no country reached 70% correct answers. For the behavioral questions about contacting a doctor in case of infection or liver problems, the percentages of correct answers were mixed, with some countries performing better in Wave 1 and some better in Wave 2. More patients in Wave 1 answered correctly about contacting the doctor in case of flu, but that may be because of the way responses were posed, as discussed in Section 6.1.2 above. The percentages of correct answers regarding contraception and pregnancy and medication and blood testing compliance while taking AUBAGIO were generally high overall.

In Wave 2, Italy had among the lowest percentages of correct answers across the Questionnaire. Four (9%) Italian patients recalled receiving a PC for AUBAGIO, and of those, only 2 patients read more than half of it. Scores for Italian patients were the lowest or near lowest of all countries for question about safety risks and pregnancy. However, the percentages of correct answers about compliance with medication and blood testing were well above 70%. Disregarding the Italian results reveals that in each country about the half the questions reached the desired 70% correct response rate. And if one considers scores just below 70% but higher than 60%, the results remain about the same.

Table 8 - Subgroup analysis: Results by country only – percentage of correct answers (Wave 1 vs Wave 2)

			UK (N=13)	France (N=30)	Germany (N=45)	Italy (N=44)	Spain (N=32)	Greece (N=15)	Belgium (N=10)	The Netherlands (N=11)
Q.8 Have you ever received a PC for AUBAGIO?		Wave 1			NC					
		Wave 2	69%	47%	60%	9%	50%	53%	70%	73%
Q.9 What is the purpose of the PC?		Wave 1	38%	31%	41%	30%	24%			
		Wave 2	44%	36%	30%	0	25%	75%	29%	75%
Q.10 How much of the PC have you read? ***At least half***		Wave 1			NC					
		Wave 2	88%	78%	100%	50%	94%	100%	86%	50%
Q.21 Show local doctor the PC in case of infection?		Wave 1	88%	89%	96%	93%	93%			
		Wave 2	100%	93%	96%	32%	100%	93%	90%	100%
Q.14 Knowledge of symptoms of liver problems		Wave 1[a]	28%	26%	26%	39%	49%			
		Wave 2	46%	57%	64%	34%	69%	33%	50%	64%
Q.20 Knowledge of need to contact a doctor in case of liver problems		Wave 1	64%	63%	57%	76%	53%			
		Wave 2	38%	70%	62%	30%	63%	53%	50%	45%
Q.15 Knowledge of signs of infection		Wave 1[b]	12%	11%	15%	5%	4%			
		Wave 2	38%	40%	47%	30%	59%	27%	30%	45%
Q.19 Knowledge of need to contact a doctor in case of flu		Wave 1	96%	74%	78%	85%	71%			
		Wave 2	38%	57%	64%	16%	56%	67%	30%	9%
Q.16 If a woman taking AUBAGIO finds out that she is pregnancy, her doctor should …		Wave 1	87%	63%	81%	69%	64%			
		Wave 2	71%	71%	72%	24%	83%	86%	33%	90%
Q.17 Do you use a contraceptive method?		Wave 1			NC					
		Wave 2	29%	57%	36%	28%	24%	29%	50%	40%
Q.18a Knowledge of what to do in suspicion of pregnancy		Wave 1	60%	75%	54%	62%	82%			
		Wave 2	71%	90%	64%	48%	97%	71%	67%	70%
Q.6 Knowledge about how often AUBAGIO should be taken		Wave 1	88%	100%	98%	98%	98%			
		Wave 2	77%	93%	80%	89%	97%	67%	80%	91%
Q.7 Last blood test for AUBAGIO [c]	Compliant	Wave 1	84%	79%	72%	88%	96%			
		Wave 2	93%	93%	95%	98%	100%	93%	100%	99%
	Non-compliant	Wave 1	16%	21%	28%	12%	4%			
		Wave 2	8%	6%	4%	2%	0	7%	0	0

Info = information; mos = months; NC = not presented by country; wks = weeks

a In Wave 1, this was a multiple choice question, and 4 of 6 topics had to be selected for the answer to be 'completely correct'.

b In Wave 1, this was a multiple choice question, and 5 of 5 topics had to be selected for the answer to be 'completely correct'.

c Compliant means patient persisted in having blood tests for AUBAGIO for at least 6 months after treatment. Non-compliant means patient has not had a blood test for AUBAGIO within 6 months after treatment.

7 DISCUSSION

7.1 KEY RESULTS

The proportion of patients who recalled receiving the PC was notably higher in Wave 1 (83%) than in Wave 2 (47%), possibly reflecting the longer length of time since some patients in Wave 2 began treatment with AUBAGIO and received their PC. Every single patient receives a new PC at the beginning of their treatment, and many patients have been taking AUBAGIO for several years. In Wave 1, 75% of patients initiated AUBAGIO in 2015 or later, and end of data collection for Wave 1 was the beginning of 2017 (Section 3). However, 85% of Wave 2 patients initiated AUBAGIO in 2015 but end of data collection for Wave 2 was 2018, which was a full year later. Many patients with MS suffer cognitive impairments, including memory loss, which may increase the difficulty in recalling specific details and events, including whether they have ever received a PC. Of those patients who recalled receiving the PC, >70% of patients in both waves reported reading more than half or all of it, and the proportion of patients who reported always or usually carrying the PC with them increased from Wave 1 (42%) to Wave 2 (74%), possibly because 54% of patients in Wave 1 compared with only 10% of patients in Wave 2 reported keeping their PC in a safe place rather than carrying it with them. More than 80% of participants in both waves also demonstrated behavioral knowledge of showing the PC to a local doctor while on holiday.

Regarding knowledge of the purpose of the PC, when taking into account the percentage of patients who correctly indicated at least 1 of the 2 correct items (to provide important safety information), more than two-thirds of patients in each wave who reported receiving the PC knew that it contained important safety information.

All patients receive the PIL with the AUBAGIO package. In both waves, the majority (79% Wave 1, 67% Wave 2) of patients reported reading more than half or all of the PIL. In both waves, when patients who read the PC and those who read the PIL were analyzed as subgroups, patients in these subgroups responded correctly in similar proportions and at similar or slightly higher rates than all patients in the primary analysis. Thus, it may be that some patients who did not recall receiving the PC in Wave 2 obtained comparable levels of knowledge by reading the PIL.

Patients' understanding of the signs of liver problems was not satisfactory (35% Wave 1, 53% Wave 2), although the percentage of correct responses did increase in Wave 2 after a single correct response was provided for the question in Wave 2. Reasons for these results may include the need to choose multiple symptoms to obtain a complete correct answer in Wave 1 as well as the choice of symptoms used to identify liver problems in Wave 2. The PC does not identify symptoms of 'vomiting and your skin or the whites of your eyes turning yellow' as signs of liver problems per se; rather, they are included as symptoms that should prompt a patient to contact their HCP. Similarly, patients' knowledge of the need to contact a doctor when a patient is 'feeling sick and is vomiting' was not satisfactory (64% Wave 1, 53% Wave 2), although correct responses were higher when patients were provided with fewer choices for correct responses in Wave 1. In both waves, approximately one-third of patients responded that 'Clare should monitor

her symptoms for a few days before making a decision about what to do'. This finding is not unexpected, given that the PC mentions the drug 'may affect your liver function' but does not specifically list signs to look out for that signal liver problems. Rather, it lists the symptoms generally and mentions that patients should contact their HCP in case of such symptoms, but it does not link them to specifically to liver problems. The finding also may reflect the declining concern among HCPs about the liver-related risks of AUBAGIO treatment.

The risk of hepatotoxicity with AUBAGIO treatment is well known among HCPs as it has been widely communicated as a primary safety concern since the launch of AUBAGIO in 2013. As the clinical experience with AUBAGIO has grown, so has the practical experience of HCPs in conducting rigorous early monitoring for liver toxicity and a tendency for HCPs to stop treatment when a patient experiences increase in liver function tests before the occurrence of symptoms, resulting in fewer patients with hepatotoxic AEs. Possibly, a better knowledge of both patients and HCPs of liver disorders potentially related to AUBAGIO and how to manage them across the treatment course may make both patients and HCPs more confident. It should be noted that Sanofi Genzyme is aware that some neurologists consider that it is sufficient to monitor liver function less frequently than indicated in the SmPC, and that there are even national or local hospital treatment guidelines that advise on different monitoring schedules.

Patients' knowledge about signs of infection was also limited in Wave 1 (9%) but did improve in Wave 2 (41%) after a single correct response was possible for the question. As with signs of liver problems, a potential reason for these results could be the fact that the PC does not specify which symptoms are considered signs of infection, although the PIL does include this information. On the related behavioral question about whether John should tell his doctor that he has influenza, patients' knowledge was satisfactory in Wave 1 (80%) but not in Wave 2 (45%). However, in Wave 2, an additional 34% of patients chose the response 'No, he should simply follow general flu advice'. It is likely that many or most of these patients would have chosen the correct response if the limited 'Yes' or 'No' response options were provided in Wave 2 as they were in Wave 1, resulting in a similarly satisfactory level of knowledge in Wave 2. It is not possible to provide patients with an extensive list of all possible symptoms of infection, and this is especially not possible to include in the PC which is to be used as a wallet card. Although the PIL does include this information, neither the PC nor the PIL mentions that a patient should contact their physician immediately in case of influenza.

Knowledge of pregnancy risk and the procedures to be followed if a woman becomes pregnant while taking AUBAGIO was similar and near or above satisfactory in both waves (73% Wave 1, 66% Wave 2) as was behavioral knowledge of what a women should do if she suspects she may be pregnant (68% Wave 1, 73% Wave 2). The majority of female patients who indicated they could become pregnant were using contraception in both waves (88% Wave 1, 76% Wave 2). The small but notable proportion of women with childbearing potential who reported they were not using contraception suggests that not all patients may be fully aware of the potential impact of disease-modifying therapies (DMTs) on pregnancy outcomes, consistent with recent published data about risk behavior specific to MS patients and evolving beliefs among some HCPs about the safety of DMTs in women who wish to become pregnant (**2**, 3).

Large majorities (>85%) of patients in both waves indicated they were taking AUBAGIO as prescribed and had undergone recent blood monitoring (>80% in both waves).

7.2 SUBGROUP ANALYSES

Although there were some differences, the results of the subgroup analyses were generally consistent with the results obtained for the primary analysis in both Wave 1 and Wave 2.

The results of the secondary analyses by country were generally consistent with the primary analysis in Wave 1 for the question about blood monitoring (Q7). In Germany, 67% of patients were compliant with blood monitoring compared to 70% of all patients in the primary analysis. This result may be related to varying requirements for biological monitoring across regions and the recent trend in some countries toward less frequent monitoring.

In both waves, patients who had read the PC and those who had read the PIL responded correctly in similar proportions and at similar or slightly higher rates than all patients in the primary analysis.

Although there was some variability observed by prescribing year, the results were not notably different from those observed in the primary analysis.

There were 2 factors related to the distribution of participants by country in Wave 2 that may have contributed to some differences in the results observed across waves. In Wave 1, 202 participants were relatively equally distributed across 6 countries, with the exception of Denmark (n=3), such that no countries besides Denmark had fewer than 20 (10%) participants. In Wave 2, 200 participants were less evenly distributed across 8 countries, with 4 countries represented by fewer than 20 (10%) participants. Overall, the 4 countries with the largest participation in Wave 2 (France, Germany, Italy, and Spain) contributed 75% of participant responses compared to the 4 countries with the smallest participation (the UK, Greece, Belgium, and the Netherlands) that contributed only 25% of responses. The skewed distribution of participants across countries in Wave 2 limited the weight of responses from 4 countries overall and significantly limited the interpretive value of comparisons of results by country and across countries.

The unequal distribution of participants by country in Wave 2 also impacted the weight of results from countries with larger numbers of participants. In Wave 2, Italian patients (n=44) representing 22% of respondents overall, were consistently among the subgroups who provided the lowest frequency of correct answers. Only 4 (9%) patients in Italy recalled that they had received the PC. This result likely contributed to lower frequencies of satisfactory responses for Italian patients as well as in the survey overall, with patients from Italy constituting 37% of participants from all countries who did not recall receiving the PC. No patients in Italy correctly identified the purpose of the PC and patients from Italy contributed 83% of all incorrect responses to the related case study question about the PC. By contrast, more than 90% of patients from all other countries responded correctly to the case study question about the PC.

When taken together, these results suggest that the uneven distribution of participants across countries in Wave 2 may have contributed to the lower overall results observed in Wave 2 compared to Wave 1.

7.3 STRENGTHS AND LIMITATIONS

The strengths of these comprehensive surveys are the number of patients included (N=402) recruited from 9 different countries including 2 of the most populated countries in which AUBAGIO has been launched, and the wide range of questions presented to participants, which describe the most important aspects of AUBAGIO prescription. The majority of patients (57% Wave 1, 71% Wave 2) were female, which closely mirrors the sex distribution for the disease (2/3 female, 1/3 male) (1).

Limitations of this survey include the use of a cross-sectional design which made it difficult to determine whether receiving and reading the patient educational materials actually increased knowledge or patients who had received and reviewed the materials increased their knowledge as the result of another factor, such as conscientiousness or motivation. All data were self-reported by patients filling in the questionnaire online. Participating countries were generally in Western Europe, and therefore may not be reflective of all EU member states. Convenience samples (non-randomized) were used, rather than random sample, which means that the findings may not be representative of the whole population of patients taking AUBAGIO, thereby further limiting the generalizability of the results. Some of the subgroup analyses numbers were also small and comparisons were limited to descriptive observations.

Another likely limitation is that questions were to be answered without having the educational materials at hand. This is not reflective of real-word practice where patients are likely to check their PC for additional information in the event of questions or the emergence of new or worrisome symptoms. Moreover, MS is a disease in which many patients suffer from cognitive impairments, including memory loss, which may have increased the difficulty of many patients to recall salient details from memory. This would suggest that some patients may have forgotten receiving the materials and/or the content of the materials, especially in Wave 2. In practice, patients should be encouraged to have the educational materials on hand or be reminded how to access these materials through the MS One to One site, and should be encouraged to reference the materials as needed.

8 CONCLUSION

The survey findings indicated that 83% of patients in Wave 1 and 47% of patients in Wave 2 acknowledged the receipt of the PC. Among patients who recalled receiving the PC, >75% reported reading at least half of it, and the percentage of patients who reported always or usually carrying the PC with them increased from Wave 1 to Wave 2. The majority of participants in both waves also demonstrated behavioral knowledge of the PC.

All patients receive the PIL with the AUBAGIO package. In both waves, the majority (≥80%) of patients reported reading at least half of the PIL. In both waves, when patients who read the PC and those who read the PIL were analyzed as subgroups, patients in these subgroups responded correctly in similar proportions and at similar or slightly higher rates than all patients in the primary analysis. These results indicate that some patients who did not recall receiving the PC in Wave 2 may have obtained comparable levels of knowledge by reading the PIL.

Patients' overall scores were below satisfactory for knowledge of recognizing specific signs or symptoms indicating potential hepatic or infection risks and identifying occasions that should prompt a visit to the doctor, based on a 70% threshold for correct responses. A possible confounding factor may have been that patients are not provided with an extensive list of potential symptoms of hepatic or infection risks. While they are provided with information on main symptoms to look out for, they are not required to know if these are related infection or hepatic problems. The way the knowledge questions were asked assumed some level of medical knowledge about symptoms and causes, which not all patients may have. This could have played a role in the low rate of correct responses related to knowledge of symptoms of adverse events. This judgment should be made by the HCP, and the patient only needs to know to contact the HCP. With regard to signs of liver problems however, patient responses may also reflect the declining concern among HCPs about liver-related risks with AUBAGIO treatment. It should be noted that Sanofi Genzyme is aware that some neurologists consider that it is sufficient to monitor liver function less frequently than indicated in the SmPC, and that there are even national or local hospital treatment guidelines that advise on different monitoring schedules

Knowledge of pregnancy risk and the procedures to be followed if a woman becomes pregnant while taking AUBAGIO was similar and near or above satisfactory in both waves as was behavioral knowledge of what a women should do if she suspects she may be pregnant. The majority of female patients who indicated they could become pregnant were using contraception in both waves.

Large majorities (>85%) of patients in both waves indicated they were taking AUBAGIO as prescribed and had undergone recent blood monitoring (>80% in both waves).

The survey results also may be influenced by the design of the study, in that patients were not shown the educational materials nor allowed to reference them during the survey. This is not consistent with most patient settings wherein patients can reference the educational materials as needed. Thus, the survey results emphasize the importance of distributing the patient educational materials as well as the need for patients to access, reference, and read the materials as often as

necessary and discuss them with their HCP. Patients also should be reminded that the educational materials (PC and PIL) are available digitally at the MS One to One web site. To further strengthen the AUBAGIO risk minimization approach, the MAH continues its efforts to ensure that all patients are reached and commits to stressing the importance of these materials to HCPs in contact with the patients, including focusing on the key safety messages.

Overall, the results of the patient knowledge and understanding survey often did not reach an acceptable level of correct responses. These results however were influenced by the design of the study and assumption of a certain level of medical knowledge as well as the low Wave 2 scores from patients enrolled in Italy. The MAH is further investigating the Wave 2 results from Italian patients. While no changes to the RMP are considered warranted while this investigation is ongoing, the MAH continues to optimize outreach to HCPs to ensure they provide patients with the PC and PIL.

9 REFERENCES

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ANNEXES

Annex 1 List of stand-alone documents

Number	Document reference number	Date	Title
1	Post Authorization Safety Study (PASS) Interim Report (Wave 1)	15 February 2017	Behaviour and Knowledge Survey of educational materials in patients treated with AUBAGIO® (cross-sectional survey); (Interim Report 2)
2	Post Authorization Safety Study (PASS) Report (Wave 2)	XX March 2019	Behaviour and Knowledge Survey of educational materials in patients treated with AUBAGIO® (cross-sectional survey)