EPIDEMIOLOGY STUDY PROTOCOL

EFFECTIVENESS OF MINIMISATION MEASURES OF RISK MANAGEMENT PLAN (RMP): EDUCATIONAL MATERIALS

TITLE: Behaviour and knowledge survey regarding the educational materials provided to the Healthcare Professional population prescribing Aubagio® (cross-sectional survey)

Study type:	Knowledge survey
Company:	Sanofi
Version Number/Status:	1.1
Study number:	Using the ClubNet numbering system

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

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Date: 8 May 2017 Total number of pages 25

PASS information:

Title:	Behaviour and knowledge survey regarding the educational materials provided to the Healthcare Professional population prescribing Aubagio® (cross-sectional survey)
Protocol version identifier	1.1
Date of last version of protocol	February 27, 2017.
EU PAS register number (if applicable)	n.a.
Active substance	Teriflunomide
Medicinal product	Aubagio®
Product reference	EU/1/13/838/001-005
Procedure number	EMEA/H/C/002514/
Marketing authorization holder(s)	Sanofi-Aventis Group, Paris, France
Joint PASS	No
Research questions and objective(s):	The objective of the survey is to assess descriptively knowledge and behaviour of healthcare professionals who prescribe Aubagio about the items of the educational materials ('Healthcare Professional Education/Discussion Guide') and thus the effectiveness of these materials to promote safe and adequate use of Aubagio. Research questions: • What is the knowledge of healthcare professionals about the healthcare professionals Education/Discussion guide? • What are reasons for not using this guide, or suggestions for changes of this guide? • What is the knowledge of healthcare professionals about the key points of content: - Hepatic effects - Pregnancy and lactation - Hematologic effects - Infections? • Are the patient cards delivered to patients? • What is the behaviour of healthcare professionals relating to liver enzyme monitoring and discussion of risks with patients?
Country(-ies) of study	The survey will be conducted in two waves at 18 months and at 3 years after launch of Aubagio in at least 5 countries, including at least 2 of the most populated 5 EU countries, with adequate translations in local languages.
Author	Tbd

MARKETING AUTHORIZATION HOLDER(S)

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1 LIST OF ABBREVIATIONS

AE	Adverse Event
EMA	European Medicines Agency
EU	European Union
HCP	Healthcare Professional
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 involved in the preparation of the protocol and its amendments and will develop the survey and analyse the results.

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

The survey is sponsored by the global medical affairs department of Sanofi Genzyme.

3 SYNOPSIS

Title

Behaviour and Knowledge Survey regarding the educational materials provided to the HCP population prescribing Aubagio (cross-sectional survey).

Rationale and background

The efficacy of Aubagio was demonstrated in two placebo controlled phase III studies, the TEMSO and the TOWER study, that evaluated once daily doses of teriflunomide 7mg and 14mg in patients with multiple sclerosis (MS). To date, only the 14mg dose has been approved by European Medicines Agency (EMA). However, serious adverse events (SAEs) relating to liver function, susceptibility to infection and potential teratogenicity mean that implementation of Risk Management Plan (RMP) educational materials has been agreed between Marketing Authorization Holder (MAH) and EMA. The healthcare professional (HCP) educational pack consists of the Summary of Product Characteristics (SmPC) and "Healthcare Professional Education/Discussion Guide". The core elements of the HCP educational materials is the "Healthcare Professional Education/Discussion Guide". 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 and behaviour of HCPs prescribing Aubagio will provide assessment of the effectiveness of the RMP educational materials in HCPs. Very little published research exists relating to the evaluation of RMP educational materials, 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 knowledge and behaviour of HCPs who prescribe Aubagio about the key items of the educational materials and thus the effectiveness of these materials to promote the safe and adequate use of Aubagio. 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 "Healthcare Professional Education/Discussion Guide" and knowledge of risk minimisation activities to be undertaken.

Study design

The survey will be conducted in two waves at 18 months and at 3 years after launch of Aubagio in at least 5 countries, including at least 2 of the most populated 5 European Union (EU) countries. The surveys will be conducted online, using a structured questionnaire. Results will be analysed and reported to the EMA.

Population

The population for this study will be a sample of HCPs involved in the treatment of MS using Aubagio. To have wide coverage of HCPs across the EU, the survey will be conducted in at least 5 countries of the EU. Based on an estimation of Aubagio prescribers across Europe, the survey will be administered to approximately 200 HCPs.

Variables

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

1. Knowledge of the HCP Education/Discussion guide

2. Use of HCP Education/Discussion guide, and suggestions for change of the guide

3. Knowledge of the key points of the content:

    a. Hepatic effects and associated assessment of liver enzymes

    b. Pregnancy and lactation. It includes pregnancy check, contraception information and implementation, and knowledge on the accelerated elimination procedure of teriflunomide from the blood, and existence of the Pregnancy Registry.

    c. Hematological effects

    d. Infections

4. Behaviour relating to liver enzyme monitoring and discussion of risks with patients (including delivery of Patient Card (PC) to patients).

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 a questionnaire.

Study size

The survey will be administered to 200 HCPs.

Data analysis

Descriptive analyses only will be performed. Sub-populations will be analyzed to identify patient groups that may require further education efforts. A threshold of 70% will be defined as ‘adequate’ knowledge. There is no pre-defined threshold for behavior.

Milestones

The survey will be conducted in 2 waves at 18 months and at 3 years after launch of Aubagio in at least 5 countries, including launch in at least 2 of the most populated 5 EU countries.

4 AMENDMENTS AND UPDATES

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

5 MILESTONES

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

6 RATIONALE AND BACKGROUND

BACKGROUND

Safety hazards

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

Safety profile

For the safety profile of Aubagio, please refer to the SmPC.

Description of Aubagio Risk Management Plan

The Aubagio RMP includes risk minimisation measures to support the safe use of the product. Educational materials form the core element of risk minimisation.

The primary objectives of the educational materials are to:

- Ensure early detection of symptoms indicative of AEs
- Communicate risks of symptoms, and the importance of periodic monitoring, to patients and prescribers
- Inform about benefit-risk decisions before each treatment course.

HCPs will receive relevant educational materials in hard copy for their own use. The HCP educational pack consists of the “Healthcare Professional Education/Discussion Guide” and the “Summary of Product Characteristics (SmPC)”.

Additionally, the educational materials will be available on a MS One to One website to provide electronic access to HCPs who prescribe the product.

Relevant published research

This study will assess the knowledge and behaviour of HCPs who prescribe Aubagio about the items of the educational materials and thus the effectiveness of these materials to promote the safe and adequate use of Aubagio.

Alongside two other surveys (“A Tracking Survey Assessing the Distribution of Hard Copy and Online Risk Minimisation Materials relating to Aubagio” and “A Cross-Sectional Survey assessing the Effectiveness of minimisation measures of a Risk Management Plan (RMP): Behaviour and Knowledge Survey in patients treated with Aubagio”) this is the first study to assess the effectiveness of the Aubagio RMP educational materials. Historically, there have been few published studies reporting the effectiveness of risk management interventions[1]. This still remains the case, which may be due to the relative recent enforcement of assessing effectiveness of RMP measures.

RATIONALE

This RMP assessment of effectiveness survey will provide information relating to HCPs' understanding of the risk messages that are discussed in the "Healthcare Professional Education/Discussion Guide" for Aubagio prescribed for MS. It will evaluate both the knowledge and behaviour of HCPs that are prescribing Aubagio. 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 literature as well as providing the first data regarding knowledge and behaviour relating to risk minimisation with Aubagio specifically.

7 RESEARCH QUESTION AND OBJECTIVES

Research questions:

1. What is the knowledge of HCPs about the HCP Education/Discussion Guide?

2. Do HCPs use the HCP Education/Discussion Guide and are there suggestions for change of the guide?

3. What is the knowledge of HCPs of the key points of the content

    a. Hepatic effects and associated assessment of liver enzymes
    b. Pregnancy and lactation. It includes pregnancy check, contraception information and implementation, and knowledge on the accelerated elimination procedure of Aubagio from the blood, and existence of the Pregnancy Registry
    c. Hematological effects
    d. Infections.

4. What is the behaviour of HCPs relating to liver enzyme monitoring and discussion of risks with patients (including delivery of PC to patients)?

7.1 PRIMARY OBJECTIVE

The objective of the study is to assess descriptively knowledge and behaviour of HCPs who prescribe Aubagio about the items of the educational materials and thus the effectiveness of these materials to promote the safe and adequate use of Aubagio.

7.2 SECONDARY OBJECTIVES

Not applicable.

8 RESEARCH METHODS

8.1 STUDY DESIGN

In this international, cross-sectional study, information will be collected regarding the knowledge and behaviour relating to risk minimisation (as described in the HCP Education/Discussion Guide) of HCPs involved in the treatment of MS using Aubagio.

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

Data will be collected in two distinct waves (Wave 1 and Wave 2). The survey will be conducted online 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 survey is conducted in 2 waves at 18 months and at 3 years after launch of Aubagio in at least 5 countries, including launch in at least 2 of the most populated 5 EU countries. Collection of survey data will take place online.

8.2.1 Duration of the study

Start of data collection for Wave 1 is at 18 months after launch in 2 of the most populated EU countries (Feb. 2016).

End of data collection for Wave 2 is (September 2017).

8.2.2 Eligibility criteria

8.2.2.1 Inclusion criteria

- HCP is a neurologist/MS specialist
- HCP has already prescribed Aubagio at study entry
- HCP supplies informed consent by ticking a box on the survey website.

8.2.2.2 Exclusion criteria

- HCP has not prescribed Aubagio
- For Wave 2 only: 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 is conducted in at least 5 countries of the EU. HCPs involved in the treatment of MS patients receiving Aubagio 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.

8.2.4.2 Patient selection

Not applicable.

8.3 VARIABLES

Knowledge is defined as awareness and understanding of important risk minimisation information contained in the HCP Education/Discussion Guide. Important risk information measured:

- Awareness and use of the HCP Education/Discussion Guide
- Identification of symptoms indicating AEs associated with the liver, hematological effects, and infection
- Awareness of the accelerated elimination procedure of Aubagio from the blood
- Awareness of the need for contraception while taking Aubagio
- Awareness of the existence of the Pregnancy Registry.

Behaviour is defined as report of appropriate risk minimisation behaviour. Appropriate risk minimisation behaviour measured:

- Using the HCP Education/Discussion guide

- Undertaking liver function monitoring as per SmPC
- Discussion of risks with patients
- Delivery of PC to patients.

Both knowledge and behaviour will be measured via self-report using a questionnaire which HCPs will complete. To a high response rate a more personal approach may also be used (e.g. via mail or interview). The questionnaire will measure knowledge and behaviour using questions with single choice or multiple choice responses (as appropriate). The questionnaire has been user tested by HCPs (described below).

Potential confounding factors

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

8.4 DATA SOURCES

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

The online questionnaire has been developed by psychologists with experience of developing questionnaires (CAJ, SNM). It has been tested by HCPs who would be eligible to prescribe Aubagio.

User testing

Twelve HCPs (4 in the UK, 4 in Germany, 4 in Spain) participated in recorded interviews. During the interviews, the HCPs completed the questionnaire aloud 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.

8.5 STUDY SIZE

8.5.1 Determination of sample size

Based on an estimation of Aubagio prescribers across Europe, the survey will be administered to approximately 200 HCPs.

8.5.2. Sample size

It is planned to recruit 200 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 Aubagio 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 elements 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 Aubagio), 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 Appendix 1.

HCP population data

In order to provide information regarding the representativeness of the HCPs completing the questionnaires as regards to the overall population of physicians prescribing Aubagio, known MS population statistics for participating countries will be supplied by the MAH.

8.6.2 Data collected

Questionnaire

- For Wave 2 only: whether HCP took part in Wave 1
- Gender
- Country of practice

- Year of qualification (as a doctor, as a specialist neurologist)
- Work setting (public/private; university/community hospital)
- Prescribed at least one dose of Aubagio
- Behaviour and knowledge relating to Aubagio 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. There is no pre-defined threshold for the behavior.

8.7.2 Secondary analysis

1. The analysis will be descriptive. Knowledge and behavior are analysed in conjunction with each other. 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 patients HCPs treat with Aubagio
    - Length of time since last prescription
    - University/community, public/private hospital
    - General neurologist or MS specialist
    - Country

8.7.3 Interim analysis

No interim analysis is planned for this registry. 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 anonymised and stored on a password protected computer in a locked office. The data will be stored electronically in this way for 5 years (from completion of Wave 2) and then erased.

Analysis will be undertaken using the IBM statistical software package by qualified research personnel employed by Ipsos.

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

8.8.2 Data quality control at site level

Not applicable.

8.9 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

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 affiliate should locally ensure all necessary regulatory submissions (e.g.: IRB/IEC) are performed in accordance with local regulations including local data protection regulations.

9.2.3 Data protection

The participant'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.

The web services provided as educational material and alongside the educational material will be completely separate from any promotional activities. Personal information provided by HCPs as part of this survey will not be used for any promotional activities.

When archiving or processing personal data pertaining to the participants, 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

Ipsos shall arrange for the retention of study documentation until the end of the study. In addition, Ipsos will comply with specific local regulations/ recommendations with regards to patient record retention.

It is recommended that Ipsos retains the study documents at least five years (5) after the completion or discontinuation of the study.

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.

If appropriate, according to local regulations, Ethic Committee(s) (IRB/IEC) and Competent Authorities should be informed.

9.2.10 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 informed consent form 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 AND REPORTING OF 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 APPENDICES

Appendix 1 List of stand-alone documents

Documents listed in Appendix 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request.

Number	Document reference number	Date	Title
1	GZEMEA.AUBA.15.09.0544	21 January 2016	Aubagio RMP Materials Study
2	4_130408 EU HCP Education Guide final	8th April 2013	HCP education guide (as submitted to CHMP)