PROTOCOL

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

TITLE: Behaviour and knowledge survey of educational materials in patients treated with Aubagio (Teriflunomide)

COMPOUND: Teriflunomide

STUDY NAME: Aubagio EU-RMP Survey in patients

The Study is conducted by Sanofi and Atlantis Healthcare (2nd Floor, Building 5, Chiswick Park, 566 Chiswick High Road, London W4 5YA), hereinafter referred also as the "MAH/MAH REPRESENTATIVE".

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Protocol Agreement Form

Not applicable.

PASS Information

Title	Behaviour and knowledge survey of educational materials in patients treated with Aubagio (Teriflunomide)
Protocol version identifier	1.0
Date of last version of protocol	Not applicable
EU PAS register number	Not applicable
Active substance	Teriflunomide
Medicinal product	Aubagio®
Product reference	EU/1/13/838/001-005
Procedure number	EMEA/H/C/002514/
Marketing authorisation holder(s)	Sanofi-Aventis Group, Paris, France
Joint PASS	No
Research question and objectives	The objective of the survey is to assess descriptively knowledge and behavior of treated patients about the educational materials and thus the effectiveness of these materials and tools to ensure the safe use of Aubagio®. Research questions: 1. Has the patient received the Patient Card? 2. What is the knowledge of patients about the Patient Card (PC)? 3. What is the knowledge of patients about the risks associated with the use of Aubagio®? 4. Does patients' self-report indicate that they are undertaking risk minimization behaviour (contraception, compliance with blood monitoring)?
Countries 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.
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1 TABLE OF CONTENTS

PROTOCOL **1**

EFFECTIVENESS OF MINIMIZATION MEASURES OF RISK MANAGEMENT PLAN (RMP): EDUCATIONAL MATERIALS **1**

1 TABLE OF CONTENTS **6**

2 LIST OF ABBREVIATIONS **9**

3 RESPONSIBLE PARTIES **10**

4 ABSTRACT **11**

5 AMENDMENTS AND UPDATES **13**

6 MILESTONES **14**

7 RATIONALE AND BACKGROUND **15**

8 RESEARCH QUESTION AND OBJECTIVES **17**

8.1 PRIMARY OBJECTIVE 17

8.2 SECONDARY OBJECTIVES 17

9 RESEARCH METHODS **18**

9.1 STUDY DESIGN 18

9.2 SETTING 18

9.2.1 Duration of the study 18

9.2.2 Eligibility criteria 18

9.2.2.1 Inclusion criteria 18

9.2.2.2 Exclusion criteria 18

9.2.3 Modalities of recruitment 19

9.2.3.1 Physician selection 19

9.2.3.2 Patient selection 19

9.3 VARIABLES 19

9.4 DATA SOURCES 20

9.5 STUDY SIZE 20

9.5.1 Determination of sample size 20

9.5.2 Sample size 21

9.6 DATA MANAGEMENT 21

9.6.1 Data collection schedule 21
9.6.2 Data collected 22
9.6.3 Site / Physician questionnaire 22
9.6.4 Screening log (if applicable) 22
9.6.5 Patient data 22
9.6.6 Procedure for withdrawal of patients from study follow-up schedule 23
9.6.7 Logistic aspects 23
9.7 DATA ANALYSIS 23
9.7.1 Primary analysis 23
9.7.2 Secondary analysis 23
9.7.3 Interim analysis 24
9.8 QUALITY CONTROL 24
9.8.1 Data collection, validation and data quality control at MAH/MAH representative level 24
9.8.2 Data quality control at site level 24
9.9 LIMITATIONS OF THE RESEARCH METHODS 24
9.10 OTHER ASPECTS 24
10 PROTECTION OF HUMAN SUBJECTS 25
10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS 25
10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES 25
10.2.1 Ethical principles 25
10.2.2 Laws and regulations 25
10.2.3 Data protection 25
10.2.4 Insurance 26
10.2.5 Secrecy agreement 26
10.2.6 Record retention 26
10.2.7 Discontinuation of the study 26
10.2.8 MAH/MAH representative audits and inspections by competent authorities 26
11 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS 27
12 PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS 28
12.1 OWNERSHIP AND USE OF DATA AND STUDY RESULTS 28
12.2 PUBLICATIONS 28
13 REFERENCES 29

ANNEXES 30

ANNEX 1 LIST OF STAND-ALONE DOCUMENTS 30

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 and administer the survey and analyse the results.

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

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

4 ABSTRACT

Title

Behaviour and knowledge survey of educational materials in patients treated with 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 MS. However, serious adverse events relating to teratogenicity, liver function and susceptibility to infection mean that a Risk Management Plan (RMP) has been agreed between MAH and EMA. The Patient educational pack consists of the Patients Information Leaflet (PIL) and Patient Card (PC). 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 effectiveness of the RMP in patients prescribed Aubagio® for MS will be evaluated by assessing patients' knowledge of risk management and behavior.

Research question and objectives

The objective of the survey is to assess descriptively knowledge and behavior of treated patients about the key items of the educational materials and thus the effectiveness of these materials and tools to ensure the safe use of Aubagio®. Research questions relate to the extent of knowledge of the Patient Card (PC), knowledge of serious adverse events relating to Aubagio® and self-reported performance of risk minimization behaviour.

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 EU countries. Each wave will be conducted over a 6-week period. The surveys will be conducted online, using structured questionnaires. Results will be analysed and reported to the European Medicines Agency (EMA).

Population

The population for this study will be a randomly generated sample of patients treated for MS with Aubagio®. To have wide coverage of patients across the European Union (EU), the survey will be conducted in at least 5 countries of the EU. The registered patient population will be described in terms of age and basic disease history and compared in each participating country with the known MS population statistics.

Variables

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

1. Knowledge of the patient card
2. Knowledge of serious adverse effects of Aubagio:
    a. Hepatic risks or hematological risks and associated biology monitoring
    b. Pregnancy and lactation. It includes contraception information and implementation, and knowledge on the accelerated elimination procedure of teriflunomide from the blood, and existence of the Pregnancy registry
    c. Infection risk
3. Self-reported risk-minimisation behaviour: adherence to treatment, biology monitoring and contraception over the recent period, reading the Patient Information Leaflet and Patient Card and carrying the Patient Card.

Data Sources

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

Study size

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

Data analysis

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

Milestones

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

5 AMENDMENTS AND UPDATES

Write "None" or indicate any substantial amendment and update to the study protocol after the start of data collection in a table as indicated below.

Number	Date	Section of study protocol	Amendment or update	Reason
None				

6 MILESTONES

Milestone	Planned date
Start of data collection Wave 1	Feb. 2016
End of data collection Wave 1	Mar. 2016
Interim Report 1	May 2016
Start of data collection Wave 2	Apr. 2017
End of data collection Wave 2	May 2017
Final report of study results	Aug. 2017

7 RATIONALE AND BACKGROUND

BACKGROUND

Safety hazards

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

Safety profile

For the safety profile of teriflunomide, please refer to the SmPC / PIL.

Description of Aubagio® Risk Management Plan

The teriflunomide risk management plan (RMP) includes risk minimisation measures and tools to support the safe use of the product.

A patient information leaflet (PIL) and Patient card (PC) form the core element of risk minimization targeted at them.

The primary objectives of the educational materials are to:

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

Patients will receive the PC in hard copy, at the time the product is prescribed to them, from their HCP. The PIL is in the treatment box. Additionally, the educational materials will be available on a MS One to One website to provide electronic access to Health Care Professionals (HCPs) who prescribe the product, and to patients who have been prescribed the treatment.

Relevant published research

This study will assess the knowledge and behavior of treated patients about the items of the educational materials and thus the effectiveness of these materials and tools to ensure the safe 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 minimization measures of a Risk Management Plan (RMP): Behaviour and Knowledge Survey regarding the educational materials provided to the Healthcare Professional population prescribing Aubagio®") this is the first study to assess the effectiveness of

the Aubagio® RMP. Historically, there have been few published studies reporting the effectiveness of risk management interventions[1].

RATIONALE

This RMP assessment of effectiveness survey will provide information relating to patients' understanding of the risk messages that are discussed in the PC and PIL for Aubagio® prescribed for MS. It will evaluate both the knowledge and behavior of patients prescribed Aubagio®.
Research question and objectives

8 RESEARCH QUESTION AND OBJECTIVES

Research questions:

1. What is the knowledge of patients about the Patient Card (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 related to Aubagio®?
    c. Can patients identify serious adverse events that should prompt a visit to the doctor?
    d. Do patients understand the risks of pregnancy and procedures to be followed?
3. Does patients' self-report indicate that they are performing risk minimization behaviour (contraception, compliance with blood monitoring, reading PC and PIL, carrying PC)?

8.1 PRIMARY OBJECTIVE

The objective of the study is to assess descriptively knowledge and behavior of treated patients about the items of the educational materials and thus the effectiveness of these materials and tools to ensure the safe use of Aubagio®.

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 and behaviour relating to risk minimization (as described in the PIL and PC) of patients involved in the treatment of MS using Aubagio®.

It 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) conducted each time over a 6-week period. The surveys will be conducted using structured questionnaires, both online and on paper, comprising of questions where the response format is either the selection of 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 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.Web and telephone recruitment will be used. Collection of survey daya will take place online.

9.2.1 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 (May 2017).

9.2.2 Eligibility criteria

9.2.2.1 Inclusion criteria

- Patient is being treated with Aubagio® at study entry
- Patient supplies informed consent by ticking a box on the website (see Annex 1).

9.2.2.2 Exclusion criteria

- (Applies in Wave 2 only) Patient completed the survey in Wave 1
- Patients has not been prescribed Aubagio®

9.2.3 Modalities of recruitment

9.2.3.1 Physician selection

Not applicable.

9.2.3.2 Patient selection

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

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

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

9.3 VARIABLES

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

- Awareness of the patient card and purpose of the patient card
- Identification of symptoms indicating adverse events (infection risks, hepatic risks or hematological risks), and understanding of the need to contact the doctor
- Awareness of the accelerated elimination procedure of teriflunomide from the blood
- Awareness of the need for contraception while taking Aubagio®

Behavior is defined as report of appropriate risk minimization behavior. Appropriate risk minimization behaviour measured:

- Adherence to contraception (contraception questions will not be asked to male patients)
- Adherence to biological monitoring
- Carrying the patient card
- Having read the PIL and PC
- Adherence to medication

Both knowledge and behavior will be measured via self-report using an online questionnaire (see Annex 1). The questionnaire will measure knowledge and behaviour using questions with single and multiple choice responses (as appropriate). The questionnaire has been user tested by people with MS (described below).

Potential confounding factors

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

2. Childbearing potential: it is possible that men and women without childbearing potential would not retain knowledge regarding safety measures in the event of pregnancy in treated women since this would not apply to them. Self-reported childbearing potential will be included as a variable for sub-group analysis.

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

9.4 DATA SOURCES

Data regarding the known MS population statistics for participating countries will be supplied by EU SA/GZ marketing.

All other data will be collected via patient self-report in the online questionnaire.

The online questionnaire has been developed by psychologists with experience of developing questionnaires (CAJ, SNM). It was refined through a user testing exercise with people with MS.

User testing

Twelve people with MS who would meet the criteria for prescription of Aubagio® participated in recorded interviews (4 participants in the UK, 4 in Germany, 4 in Spain). During the interviews, participants 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 rewording of questionnaire items that were considered difficult to understand.

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.

9.5.2 Sample size

It is planned to recruit 200 patients in Wave 1 and 200 patients in Wave 2, from at least 5 countries including at least 2 highly populated EU countries.

9.6 DATA MANAGEMENT

9.6.1 Data collection schedule

Patient data

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

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

.

On following the link within the invitation email, the information sheet and survey consent page will be displayed. Patients will also be provided with an email address to make contact with the research team in the event of having questions prior to consent into the study.

Following receipt of consent, the patient will be able to move into the pages of the online questionnaire. In order to minimize missing data, it will be mandatory to answer all questions within the questionnaire.

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

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

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

MS population data

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

9.6.2 Data collected

Online questionnaire

- (Wave 2 only) Whether patient took part in Wave 1
- Age
- Country
- Treatment start date
- MS diagnosis date
- Gender
- Childbearing potential (for women)
- Behaviour and Knowledge relating to Aubagio® risk management

MS population data

- Age
- MS diagnosis date
- Gender
- Childbearing potential (for women)

9.6.3 Site / Physician questionnaire

Not applicable.

9.6.4 Screening log (if applicable)

Not applicable.

9.6.5 Patient data

Patient data

- Age: Self-reported
- Country: Self-reported
- Treatment start date: Self-reported

- MS diagnosis date: Self-reported
- Gender: self-reported
- Childbearing potential (for women): self-reported
- Behaviour and Knowledge relating to Aubagio® risk management: self-reported

MS population data

Age: from EU SA/GZ marketing

MS diagnosis date: from EU SA/GZ marketing

Gender: from EU SA/GZ marketing

Childbearing potential (for women): from EU SA/GZ marketing

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

Not applicable.

9.6.7 Logistic aspects

Not applicable.

9.7 DATA ANALYSIS

9.7.1 Primary analysis

The analysis will be descriptive. (e.g. frequency distributions for each item). The response on knowledge and behavior is considered satisfactory if participants provide >70% of correct answers.

9.7.2 Secondary analysis

The analysis will be descriptive.

1. Where knowledge or behaviour is found to be <100% a more detailed analysis will be conducted (e.g. to identify specific areas where knowledge is low).

2. Responses in sub-groups compared to the rest of the sample. Sub-groups to be analysed are: country, childbearing potential, having read the RMP materials, time since prescription with Aubagio®.

3. Comparison of age and time since diagnosis of the sample from each participating country with known MS population statistics in participating countries as a gauge of the representativeness of the sample.

9.7.3 Interim analysis

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

9.8 QUALITY CONTROL

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

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

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

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

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

9.8.2 Data quality control at site level

Not applicable.

9.9 LIMITATIONS OF THE RESEARCH METHODS

All data supplied will be self-report, and it will not be possible to objectively verify information (e.g. gender or age). Self-reported measures of behaviour have been found to be adequately correlated to other methods (e.g. electronic records of medication adherence)[3,4]. The study uses descriptive statistics only. Therefore it is not possible to determine whether findings are statistically significant or could be due to chance. However, given that the main objective is to measure knowledge and behavior, descriptive statistics are sufficient.

9.10 OTHER ASPECTS

Not applicable.

10 PROTECTION OF HUMAN SUBJECTS

10.1 RESPONSIBILITIES OF THE PHYSICIAN/HEALTH CARE PROVIDERS

Not applicable.

The Informed Consent Form and the Information Sheet used online for obtaining the Patient's Informed Consent must be reviewed and approved by the MAH/MAH representative prior to submission to the appropriate Ethics Committee (IRB/IEC) for approval / favorable opinion.

Responsibilities of MAH/MAH REPRESENTATIVE

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

The MAH/MAH REPRESENTATIVE is responsible for:

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

10.2 ETHICAL, REGULATORY AND ADMINISTRATIVE RULES

10.2.1 Ethical principles

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

10.2.2 Laws and regulations

Each participating country should locally ensure all necessary regulatory submissions (e.g: IRB/IEC) are 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

Atlantis Healthcare and IPSOS shall arrange for the retention of study documentation for at least five years. In addition Atlantis Healthcare 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.

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

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 an online 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.

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

3. Walsh JC, Mandalia S, Gazzard BG. Responses to a 1 month self-report on adherence to antiretroviral therapy are consistent with electronic data and virological treatment outcome. Aids 2002;16:269-77.

4. Cohen JL, Mann DM, Wisnivesky JP, et al. Assessing the validity of self-reported medication adherence among inner-city asthmatic adults: the Medication Adherence Report Scale for Asthma. Annals of allergy, asthma & immunology : official publication of the American College of Allergy, Asthma, & Immunology 2009;103:325-31.

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

Documents listed in Annex 1 can be maintained separately from the study protocol. They should be clearly identifiable and provided on request. Write “None” if there is no document or list documents in a table as indicated below.

Number	Document reference number	Date	Title
1	GZEMEA.AUBA.15.09.0544	21 January 2016	Aubagio® RMP Materials Study
2	Number	DD Month YYYY	Patient information leaflet
3	Number	DD Month YYYY	Patient card