PROTOCOL

PRODUCT OBSERVATIONAL STUDY

COMPOUND: Aubagio® (Teriflunomide)

A prospective, observational, UK study to describe patient reported quality of life in relapsing remitting multiple sclerosis patients treated with Aubagio® (teriflunomide) 14 mg in a routine clinical practice.

STUDY NUMBER: TERIFL08182

STUDY NAME: TERI-QoL

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1 SYNOPSIS

COMPOUND: Aubagio® (Teriflunomide) STUDY No: TERIFL08182	
TITLE	A prospective, observational, UK study to describe patient reported quality of life in relapsing remitting multiple sclerosis patients treated with Aubagio® (teriflunomide) 14 mg in routine clinical practice.
LOCATION	United Kingdom
STUDY OBJECTIVES	<u>Primary objectives:</u> To describe the change in health related quality of life (HRQoL) at 2 years, in patients commencing treatment with Aubagio® in routine clinical practice for relapsing remitting multiple sclerosis (RRMS). <u>Secondary objectives</u> To describe the change in the following patient reported outcomes (PROs) at 2 years, in patients commencing on treatment with Aubagio® in routine clinical practice for RRMS: • Fatigue • Anxiety and depression • Cognition • Sexual dysfunction • Disease progression • Treatment satisfaction • Treatment adherence To describe the number of relapses during the two year study period in patients commencing on treatment with Aubagio® in routine clinical practice for RRMS. To describe health economic outcomes in patients with RRMS treated with Aubagio® assessed by the number of scheduled and unscheduled healthcare provider (HCP) encounters and emergency visits, as well as productivity loss. <u>Exploratory objective</u> Additional exploratory objective will be to evaluate primary and secondary objectives in at least 4 specific subgroups: treatment naïve patients, patients previously treated with a MS disease modifying therapy (DMT) within the past 2 years, injectable switch patients and oral switch patients.
STUDY DESIGN & DURATION	Multi-centre, prospective non-interventional study. This is a 2 year prospective, observational UK study to describe HRQoL, PROs in RRMS patients treated with Aubagio® (teriflunomide) 14 mg in a routine clinical practice. The decision to treat with Aubagio® must be made prior to and independently from the proposal to enrol the patient on this study. All patients must be prescribed Aubagio® in accordance with the UK

	summary of product characteristics (SmPC). Visits will be scheduled by the treating HCP according to patient specific needs and local clinical practice. For purposes of this study, 6 visits are expected: study baseline (Visit 1), with follow-up visits at months 3 (if part of routine clinical setting), 6, 12, 18 (if part of routine clinical practice) and 24.
STUDY POPULATION	<u>Inclusion Criteria</u> 1. Adult patients (>18 years old) with RRMS according to a neurologist's diagnosis, where the physician and patient have decided to start treatment with Aubagio® according to the SmPC. 2. Initiated Aubagio® treatment for the first time within 4 weeks of study entry 3. Patient having signed written informed consent 4. Patients who are willing and able to fill out the questionnaires for the full duration of the study. Note: If a designated caregiver is available to assist the patient, they may physically complete the questionnaire for the patient. A nurse or other health care professional may assist with instructing the patient on how to complete a questionnaire. Exclusion criteria: 1. Patients with contraindications to Aubagio® according to SmPC 2. Patients who are currently participating in an investigational interventional study if, in the judgment of the Investigator, such participation would interfere with the current study. 3. Patients who are unwilling or unable to complete any questionnaire to be used in the study 4. Women of child bearing age who are not willing to use an effective form of contraception
RECRUITMENT MODALITIES	Selection of Investigator Investigators who are experienced in the treatment of patients with RRMS will undergo a feasibility assessment performed by Sponsor representatives. Selection of patients Consecutive recruitment after decision to begin Aubagio® therapy, and determination of patient eligibility and willingness to participate. The decision to treat with Aubagio® must be made before considering a patient's entry into the study.

ENDPOINTS	Primary Endpoint Mean change in Multiple Sclerosis Impact Scale (MSIS-29) scores from baseline to month 24. Secondary endpoints Clinical outcomes: • Number of relapses (since baseline) at each visit and at month 24 Patient reported outcomes: • Disability accumulation: change in Patient Determined Disease Steps (PDDS) over time at each visit (except visit 2) and at month 24 compared with baseline • Fatigue: change in Fatigue score, assessed using the MFIS-5, at each visit (except visit 2) and at month 24 compared with baseline • Anxiety and Depression: Change in anxiety and depression at each visit (except visit 2) and at month 24 compared with baseline, as measured by the Hospital Anxiety and Depression Scale (HADS) • Cognition: Change in cognition at each visit and at month 24 compared with baseline, as measured by the Symbol Digit Modalities Test (SDMT). • Sexual Function: Change in intimacy and sexual health at each visit and at month 24 compared with baseline as measured by MSISQ-19. • Treatment satisfaction: change in Treatment Satisfaction Questionnaire for Medication version 1.4 (TSQM v1.4) score over time, from baseline to each visit (except visit 2) and month 24. • In patients switching from another disease modifying treatment (DMT): change in TSQM from baseline to month 6 and to month 24 • For naïve patients: change in TSQM from month 6 to month 24. • Treatment adherence: number of missed doses of Aubagio® Health economics outcomes: • Number of scheduled and unscheduled HCP encounters • Number of emergency visits • Change in work capacity reported using the Health Related Productivity Question-MS (HRPQ-MS) at months 12 and 24 compared with baseline. Safety endpoint Adverse events (AEs), serious adverse events (SAEs), and AEs of special interest (AESIs) recorded at each visit according to standard clinical practice. Patients will be followed with laboratory monitoring in a regular healthcare setting in line with local approved label requirements and the risk management plan (RMP) for Aubagio®.
MAIN DATA COLLECTED	The decision for treatment with Aubagio® must be made prior to and independently from the proposal to enrol the patient into this study

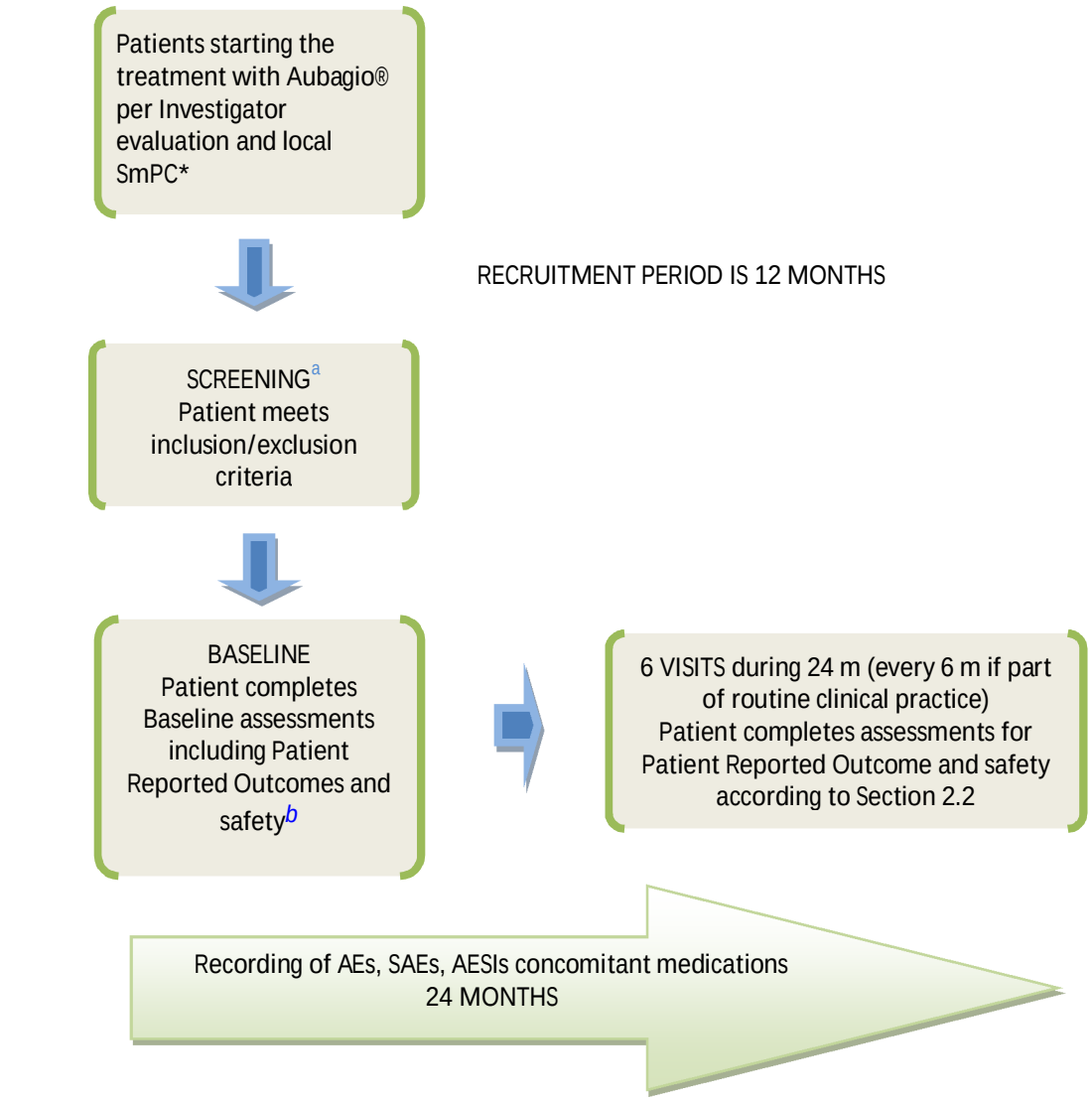
	and in line with the approved SmPC. Administration of Aubagio® and monitoring of patients according to the SmPC and safety reporting will be the sole responsibility of the treating neurologist. <u>Visit 1 (Baseline)</u> • Eligibility (according to the approved SmPC) • Informed consent • Patient demographics (gender, year of birth, smoking history) • MS disease history (including date of first symptoms, date of diagnosis, number of relapses in the 2 years prior to enrolment, time since last relapse, disability progression (current Expanded Disability Status Scale [EDSS]) • If applicable, previous DMTs, current DMT, treatment start and stop dates, reason for starting/changing treatment • Prior and concomitant medications • Medical/surgical history and co-morbidities • MSIS-29 • MFIS-5 • HADS • SDMT • MSISQ-19 • TSQM v1.4 • PDDS • Number of scheduled and unscheduled HCP encounters in the past 12 months. • Number of emergency visits, if any in the past 12 months • HRPQ-MS Safety (AEs/SAEs/AESIs) since first dose of Aubagio will be retrospectively collected upon signature of the Informed Consent Form. <u>Visit 2 (Month 3)</u> – only performed if part of routine clinical care. • Prior and concomitant medications • Number of relapses since last visit • Treatment adherence – number of missed doses since last visit • Number of scheduled and unscheduled HCP encounters since last visit • Number of emergency visits since last visit • Safety information (AEs/AESIs/SAEs). <u>V3, V4, V5* V6/EOS</u> • Prior and concomitant medications • Number of relapses since last visit • MSIS-29 • MFIS-5 • HADS • SDMT

	• MSISQ-19 • TSQM v1.4 • PDDS • Treatment adherence - Number of missed doses since last visit • Number of scheduled and unscheduled HCP encounters since last visit • Number of emergency visits since last visit • HRPQ-MS (months 12 and 24/EOS only) • Safety information (AEs/AESIs/SAEs) * Visit 5 only performed if part of routine clinical practice <u>Safety</u> • AEs/AESIs/SAEs since first dose of Aubagio® will be retrospectively collected upon signing Informed Consent Form. • AEs/AESIs/SAEs will be recorded at each visit according to standard clinical practice • Up to 3 Monthly telephone calls may be performed as and when needed in order to follow up on potential AEs/AESIs/SAEs. • Patients will be followed with laboratory monitoring in a regular healthcare setting in line with local approved label requirements and the RMP for Aubagio®.
STATISTICAL METHODOLOGY	The following represents an overview of planned analyses. Further elaboration of statistical issues will be specified in the Statistical Analysis Plan (SAP). Sample size determination The sample size has been calculated in order to assess the primary objective, describe changes in MSIS-29 scores from baseline to month 24. Mean MSIS-29 score on baseline, 24 months and changes during the follow-up (baseline to 24 months) will be calculated with the 95% confidence interval (CI). Taking into account a standard deviation of 20 points in MSIS-29 (Glenn, 2016), a sample size of 100 allows to estimate the MSIS-29 scores with a precision (distance from the mean to the limits of the 95% CI) of about 4 points with a significance level of 0.05. The sample size of 100 patients has been also determined based on the average number of patients at each site within the recruitment period of 2 years. Analysis populations The analysis population will include all enrolled patients who received at least one dose of study medication. All study analysis, including safety analysis, will be performed in this population. Statistical analysis All recorded clinical observations will be analysed using descriptive statistics. <u>Primary analysis:</u> The primary endpoint of change from baseline to month 24 in the MSIS-

	29 will be analysed descriptively providing the mean change with 95% CI and also using an analysis of covariance (ANCOVA), adjusting for baseline covariates, including the baseline MSIS-29 value. A p-value below 0.05 will be considered statistically significant. Additional exploratory pre-specified analysis of the primary endpoint will be performed in at least 4 specific subgroups: treatment naïve patients, patients previously treated with a MS DMT within the past 2 years, injectable switch patients and oral switch patients. <u>Secondary analyses:</u> The changes from baseline to month 24, and to each follow-up visit before 24 months visit, in TSQM v1.4, PDDS, MFIS-5, HRPQ-MS v2, MSISQ-19, SDMT and HADS will be tested using the t-distribution. The mean changes between study visits with the corresponding 95% (CI) will be given. If required, an ANCOVA, adjusting for baseline covariates will be performed. A p-value below 0.05 will be considered statistically significant. The evolution of PRO scores during the follow-up period will be also represented graphically. In addition to PRO scores, the same statistical methods will be used to analyse number of missed doses of Aubagio® (adherence), number of relapses, number of HCP encounters and number of emergency room visits. Additional exploratory pre-specified analysis of the secondary endpoints will be performed in at least 4 specific subgroups: treatment naïve patients, patients previously treated with a MS DMT within the past 2 years, injectable switch patients and oral switch patients. Safety analysis All patients will be evaluated for safety based on incidence, duration, intensity, and seriousness of AEs, SAEs, and AESIs. Interim Analysis Final study analysis will be performed after all patients have completed the core study (24 months±1 month), or discontinuation of the study before the 24 months duration. One interim analysis is planned to be performed at 18 months post first patient in. The results of the interim analysis will be used in publications at medical congresses and presentations, providing an update on the study.
ESTIMATED DURATION OF THE STUDY	Estimated enrolment duration: 12 months with competitive enrolment. Estimated date for First Patient In (FPI): Q2 2018 Estimated study duration per patient: 2 years (24 months).

2 FLOW CHARTS

2.1 GRAPHICAL DESIGN OF EVENTS LEADING TO, AND PARTICIPATION IN, THE STUDY



* Before the consideration to enrol the patient to the study

a Baseline visit completed within 4 weeks of first dose of Aubagio®
b Patient-reported outcomes completed within 4 weeks of first dose of Aubagio®

AE = adverse event, SAE= Serious Adverse Event or AESI= Adverse Event of Special Interest; m = months; SmPC = Summary of Product Characteristics

2.2 STUDY FLOW CHART

		Core Study				
Visits (V)	V1	*V2 (if part of clinical practice)*	V3	V4	*V5 (if part of clinical practice)*	V6/EOS
Months	Baseline[a]	M3 ±1 month	M6 ±1 month	M12 ±1 month	M18 ±1 month	M24 ±1 month
Eligibility (according to SmPC)	X					
Patient Information / Informed Consent	X					
Demographics (gender, year of birth, smoking history[b])	X					
MS disease history (date of first symptoms, date of diagnosis, number of relapses in the past 2 years, time since last relapse, disability progression / current EDSS)	X					
Previous DMTs (previous drugs), current drug, time since treatment)[c]	X					
Reason to start/change DMT	X					
Prior and concomitant medications	X	X	X	X	X	X
Number of relapses since last visit		X	X	X	X	X
MSIS-29	X[d]		X[i]	X[i]	X[i]	X[i]
MFIS-5	X[d]		X[i]	X[i]	X[i]	X[i]
HADS	X[d]		X[i]	X[i]	X[i]	X[i]
SDMT	X[d]		X	X	X	X
MSISQ-19	X[d]		X[i]	X[i]	X[i]	X[i]
TSQM v1.4	X[c,d]		X[i]	X[i]	X[i]	X[i]
PDDS	X[d]		X[i]	X[i]	X[i]	X[i]
Treatment adherence to Aubagio (number of missed doses since last visit)		X	X	X	X	X
Number of unscheduled and scheduled HCP encounters[f]	X	X	X	X	X	X
Number of emergency visits[f]	X	X	X	X	X	X
HRPQ-MS	X[d]			X[i]		X[i]
AEs, AESIs, SAEs[e]	X	X	X	X	X	X

a Baseline visit completed within 4 weeks of first dose of Aubagio®.

b Smoking history includes current/former smoker, average consumption, pack years exposure, and time since cessation of smoking (if applicable).

c Patients with previous DMT.

d Within 4 weeks of first dose of Aubagio®.

e AEs (including SAEs & AESIs) within 4 weeks after first dose of Aubagio® will be retrospectively collected upon signing of the informed consent and on an ongoing basis including scheduled visits (eg., patients should report all AEs, SAEs and AESIs during the study period)..

f For baseline this is over the past 12 months

g Performed in accordance with the local approved SmPC and the Aubagio® RMP

h In addition to study visits there may be up to 3 monthly telephone calls in order to follow up on potential AEs/AESIs/SAEs

i As per patient convenience, questionnaires can be completed within one week prior to the visit. Each questionnaire can be completed on a different day. However, a patient must complete an individual questionnaire once it has been started. Note: if a designated caregiver is available to assist the patient, they may physically complete the questionnaire for the patient. A nurse or other health care professional may assist with instructing the patient on how to complete a questionnaire.

AE = adverse event; AESI = adverse event of special interest; DMT = disease-modifying therapy; EDSS = Expanded Disability Status Scale; EOS = end of study; MFIS-5 = Modified Fatigue Impact Scale; HCP = health care professional; HRPQ: Health related productivity questionnaire HRPQ-MS = Health Related

Productivity Questionnaire V2 (MS); MS = multiple sclerosis; MSIS-29 = Multiple Sclerosis Impact Scale; PDDS = Patient Determined Disease Steps;
SAE = serious adverse event; TSQM v1.4 = Treatment Satisfaction Questionnaire for Medications; MSIS-19 = MS Intimacy & Sexuality Questionnaire

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4 LIST OF ABBREVIATIONS

AE:	Adverse Event
AEP:	Accelerated Elimination Procedure
AESI:	Adverse Event of Special Interest
DBP:	Diastolic Blood Pressure
DMT:	Disease Modifying Therapy
eCRF:	Electronic Case Report Form
EDC:	Electronic Data Capture
EDSS:	Expanded Disability Status Scale
EMA:	European Medicines Agency
FDA:	Food and Drug Administration
HADS	Hospital Anxiety and Depression Scale
HCP:	Healthcare Provider
HRPQ-MS v2:	Health Related Productivity Questionnaire Forms Version 2
HRQL	Health Related Quality of Life
ILD:	Interstitial Lung Disease
IRB/IEC	Institutional Review Board/Independent Ethics Committee
MFIS-5	Modified Fatigue Impact Scale – 5
MRI:	Magnetic Resonance Imaging
MS:	Multiple Sclerosis
MSIS-19	Multiple Sclerosis Intimacy & Sexuality Questionnaire – 19
MSIS-29:	Multiple Sclerosis Impact Scale
PDDS:	Patient Determined Disease Steps
PRO:	Patient Reported Outcome
RMP:	Risk Management Plan
RRMS:	Relapsing Remitting Multiple Sclerosis
SAE:	Serious Adverse Event
SAP:	Statistical Analysis Plan
SBP:	Systolic Blood Pressure
SGPT	Serum Glutamate-Pyruvate Transferase
SDMT	Symbol Digit Modalities Test
SmPC:	Summary of Product Characteristics
TSQM v1.4:	Treatment Satisfaction Questionnaire for Medication Version 1.4
ULN:	Upper Limit of Normal

5 INTRODUCTION AND RATIONALE

5.1 BACKGROUND

Multiple Sclerosis (MS) is a demyelinating disease of the central nervous system that affects as many as 2.3 million people worldwide [1]. Its clinical course is typically characterized by initial episodes of transient neurological compromise (relapses) with a recovery period, followed by a phase of cumulative deficits that may increase with each new episode. This is known as Relapsing Remitting Multiple Sclerosis (RRMS). Although patients typically experience some degree of recovery in RRMS, even a single relapse can lead to permanent disability in a substantial number of patients, with a sizeable majority being left with disability after 2 events.

RRMS is a chronic disease that affects people differently, and symptoms which may be physical or non-physical, can range from mild to severe, and may be present, absent or may progress with time [2]. As a neuropsychiatric disease, MS threatens personal autonomy, independence, dignity, and future plans [3].

There is now increasing recognition that there are psychological, social, and psychiatric issues resulting from vital segments of health-related quality of life (HRQoL), which are distinct from disease-related physical disabilities [4-6]. The main neuropsychiatric features include anxiety, depression, cognitive impairment, irritability, and anger [7].

HRQoL measurements are being considered increasingly important with regard to evaluating treatments, anticipating disease progression, and providing comprehensive care to MS patients [4, 5]. Health authorities (FDA and EMA) encourage the use of HRQoL assessments in patients with chronic illnesses [8, 9], and several groups have published detailed recommendations for HRQoL assessments [10, 11].

Despite the acknowledged need to consider HRQoL issues, HRQoL assessment remains under-utilized in routine clinical practice [12]. Recognising this gap and considering the main neuropsychiatric features of MS, the objective of this observational study will be to assess patient reported outcomes (PROs) in patients with RRMS who have initiated treatment with Aubagio® according to the approved Summary of Product Characteristics (SmPC).

5.2 RATIONALE

Aubagio® (teriflunomide; A771726, ATC code L04AA31) is a once-daily, oral disease-modifying therapy (DMT) indicated for the treatment of patients with relapsing remitting MS (RRMS). Aubagio® has shown significant efficacy across a number of key measures for MS disease, including relapse rate reduction, slowing the progression of physical disability and reducing the number of brain lesions as detected by magnetic resonance imaging (MRI) [13-15]. The cumulative exposure to Aubagio® in the clinical program exceeds 6800 patient-years, and in long-term studies individual exposure exceeds 12 years [16]. Aubagio® once-daily 14 mg oral tablets were approved in June 2014 for the treatment of adult patients with RRMS to reduce the frequency of clinical relapses and to delay the progression of physical disability.

The functional consequences of MS disease progression, such as increased fatigue, changes in cognition, increased disability and reduced ability to work are important from the patients' perspective as well as the clinician's and impact overall quality of life [17-20].

Over the past several years, the development of evaluations for PROs has provided the tools to assess patient outcomes in clinical practice and real world settings. Various instruments to collect patient reported outcomes have been developed and validated in MS and provide a means by which patients can document important information on their disease state and the impact of MS treatment on their overall quality of life.

Health authorities (e.g. EMA) encourage the use of quality of life assessment in patients with chronic illness [9], and several groups have published detailed recommendations for HRQoL assessments in the evaluation and approval for medicinal products [10, 11].

Despite the acknowledged need to consider HRQoL, in routine clinical practice these assessments remain underutilized [12]. Recognising this gap and considering the main neuropsychiatric features of MS, the objective of this observational study is to provide real world patient reported outcomes in MS patients treated with Aubagio®. This study will assess PROs measuring HRQoL, treatment adherence and satisfaction, and health economics outcomes in real-life medical practice in patients with RRMS.

Safety will also be assessed by collecting adverse events (AEs), adverse events of special interest (AESIs), and serious AEs (SAEs).

6 STUDY OBJECTIVES

6.1 PRIMARY

The primary objective of this study is to describe the change in HRQoL at 2 years in patients commencing treatment with Aubagio® in routine clinical practice for RMMS.

6.2 SECONDARY

To describe the change in the following PROs at 2 years, in patients commencing on treatment with Aubagio® in routine clinical practice for RRMS:

- Fatigue
- Anxiety and depression
- Cognition
- Sexual dysfunction
- Disease progression
- Treatment satisfaction
- Treatment adherence

To describe the number of relapses during the two year study period in patients commencing on treatment with Aubagio® in routine clinical practice for RRMS

To describe health economic outcomes in patients with RRMS treated with Aubagio® assessed by the number of scheduled and unscheduled healthcare provider (HCP) encounters and emergency visits as well as productivity loss.

6.3 EXPLORATORY OBJECTIVE

An additional exploratory objective will be to evaluate primary and secondary objectives in at least 4 specific subgroups: treatment naïve patients, patients previously treated with a MS DMT within the past 2 years, injectable switch patients and oral switch patients.

7 STUDY DESIGN

7.1 DESCRIPTION OF THE STUDY DESIGN

This is a 2 year prospective, multicentre observational UK Study to describe HRQoL and other PROs in RRMS patients treated with Aubagio® (teriflunomide) 14 mg in a routine clinical practice. The study will be conducted at approximately 20 sites in the UK and will collect data on the current status, characteristics, and management of patients who are starting treatment with Aubagio® as part of their routine medical care.

The decision to treat with Aubagio® must be made prior to and independently from the proposal to enrol the patient on this study. All patients must be prescribed Aubagio® in accordance with the UK SmPC.

This is an observational study with no experimental intervention. Enrolled patients will receive treatment and evaluations for their MS as determined by their treating physicians in accordance with the local standard of care. Visits will be scheduled by the treating HCP according to patient-specific needs and local clinical practice. Administration of Aubagio® and monitoring of patients according to the SmPC and safety reporting will be the sole responsibility of the treating neurologist. Patients will be followed with laboratory monitoring in a regular healthcare setting in line with locally approved label requirements and the Risk Management Plan (RMP) for Aubagio®.

For purposes of this study, 6 visits are expected: study baseline (Visit 1), with follow up visits at months 3 (if part of clinical setting), 6, 12, 18 and 24. Patients will be expected to complete up to 7 questionnaires (see section 2.2) at different time points. Completing all of the questionnaires takes approximately 45 minutes. Questionnaires will be completed by the patient at the site during study visits or within 7 days before study visits (for visits V3-V6). Each questionnaire can be completed on a different day. However, a patient must complete an individual questionnaire in the same session once it has been started. Note: if a designated caregiver is available to assist the patient, they may physically complete the questionnaire for the patient. A nurse or other health care professional may assist with instructing the patient on how to complete a questionnaire.

Patient-reported outcomes, clinical outcomes and safety findings during routine clinical practice will be recorded for the entire cohort as well as for defined subgroups (i.e., patients who are treatment naïve, patients who switched from other DMT's). No control group will be included.

7.2 DURATION OF STUDY PARTICIPATION FOR EACH PATIENT

The duration of the study for each patient will be 2 years (24±1 months). There will be a maximum of 6 study visits for participating patients. Data collection will be at baseline (Visit 1) and at month 3* (Visit 2), month 6 (visit 3), month 12 (visit 4), month 18* (visit 5), and month 24/End of study (EOS).

The baseline visit should occur within 4 weeks of the first dose of Aubagio®. All other visits should occur within a time window of ±1 month.

Note that not all study sites will have a month 3 and / or month 18 office visit, according to local practice, but if a month 3 and/ or month 18 visit is performed, data will be collected). Additional visits may occur according to the local clinical practice.

Eligible patients who meet the inclusion and exclusion criteria and sign the informed consent will be enrolled into the study.

7.3 STUDY VARIABLES

7.3.1 Baseline Visit

The following patient characteristics will be recorded at the baseline visit (completed within 4 weeks of first dose of Aubagio®):

- Patient demographics (gender, year of birth, smoking history)
- MS disease history
  - Date of first symptoms: month and year
  - Date of diagnosis: month and year
  - Number of relapses in the 2 years prior to enrolment
  - Time since last relapse
  - Disability progression/Expanded Disability Status Scale (EDSS) score
- Previous/current treatment with DMTs, if applicable
  - Treatment start and stop dates
  - Reason for starting/changing treatment
- Prior and concomitant medications
- Medical/surgical history and co-morbidities
- PROs (collected within 4 weeks of first dose of Aubagio®):
  - Multiple Sclerosis Impact Scale (MSIS-29) questionnaire
  - Modified Fatigue Impact Scale (MFIS-5) questionnaire
  - Hospital Anxiety and Depression (HADS) questionnaire
  - Symbol Digit Modalities Test
  - Multiple Sclerosis Intimacy and Sexuality (MSISQ-19) Questionnaire
  - Treatment Satisfaction Questionnaire for Medication version 1.4 (TSQM v1.4) questionnaire
  - Patient Determined Disease Steps (PDDS) questionnaire
- Number of scheduled and unscheduled HCP encounters within the past 12 months
- Number of emergency visits in past 12 months
- Health Related Productivity Question-MS (HRPQ-MS) questionnaire
- AEs/SAEs/AESIs since first dose of Aubagio® will be retrospectively collected upon signature of Informed Consent Form

7.3.2 Visit 2 (Month 3)

The following data will be recorded at visit 2 (month 3), this visit will only occur if part of routine clinical practice:

- Prior and concomitant medications
- Number of relapses since last visit
- Treatment adherence – number of missed doses since last visit
- Number of unscheduled and scheduled HCP encounters since last visit
- Number of emergency visits since last visit
- Safety information (AEs/AESIs/SAEs)

7.3.3 Visits 3, 4, 5 and 6/EOS

The following data will be recorded after initiation of Aubagio® (V3, V4, V5, V6/EOS). Visit 5 will only occur if part of routine clinical practice:

- Prior and concomitant medications
- Number of relapses since last visit
- PROs:
  - MSIS-29 questionnaire
  - MFIS-5 questionnaire
  - HADS questionnaire
  - SDMT
  - MSISQ-19 questionnaire
  - TSQM v1.4 questionnaire
  - PDDS questionnaire
- Treatment adherence – number of missed doses since last visit
- Number of unscheduled and scheduled HCP encounters since last visit
- Number of emergency visits since last visit
- Safety information (AEs/AESIs/SAEs)

In addition to the study visits there may be up to 3 monthly telephone calls between the study visits from the sites to the patients as and when needed in order to follow up on potential AEs/AESIs/SAEs. The results of these calls will also be documented in the study CRF.

Patients will be followed with laboratory monitoring in a regular healthcare setting in line with local approved label requirements and the Risk Management Plan (RMP) for Aubagio®.

7.4 STUDY ENDPOINTS

7.4.1 Primary Endpoint

The primary study endpoint is the change in HRQL at month 24 compared with baseline, as measured by the MSIS-29.

7.4.2 Secondary Endpoints

The secondary variables are clinical outcomes, PROs, and health economics outcomes.

Clinical Outcomes:

- Number of relapses (at baseline), at each visit and at month 24

Patient reported outcomes:

- Fatigue: change in Fatigue score, assessed using the MFIS-5, at each visit (except visit 2) and at month 24 (MFIS-5) compared with baseline

- Anxiety/Depression: Change in anxiety/depression at each visit (except visit 2) and at month 24 compared with baseline, as measured by the HADS
- Cognition: Change in cognition at each visit and at month 24 compared with baseline, as measured by the SDMT.
- Sexual Function: Change in intimacy and sexual health at each visit and at month 24 compared with baseline as measured by MSISQ-19
    - Treatment satisfaction: change in TSQM v1.4 score over time, from baseline to each visit (except visit 2) and month 24.
- In patients switching from another DMT: change in TSQM from baseline to month 6 and to month 24
- For naïve patients: change in TSQM from month 6 to month 24
- Disability accumulation: change in PDDS over time at each visit (except visit 2) and at month 24 compared with baseline
- Treatment adherence: number of missed doses of Aubagio®

Health economics outcomes:

- Number of scheduled and unscheduled HCP encounters
- Number of emergency visits
- Change in work capacity reported using the HRPQ-MS at months 12 and 24 compared with baseline.

7.4.3 Safety Measurements and Variables

AEs, SAEs, and AESIs recorded at each visit according to standard clinical practice. Patients will be followed with laboratory monitoring in a regular healthcare setting in line with local approved label requirements and RMP for Aubagio®.

In addition the sites may telephone the patient every 3 months during the study in order to follow up on potential AEs/AESIs/SAEs. The results of these calls will be documented in the study CRF.

7.4.4 Appropriateness of Measurements and Variables

The selected variables and measurements focusing on PROs of HRQoL, disease progression, treatment satisfaction, and clinical effectiveness represent an appropriate approach and setting for this post market authorization observational study in routine medical care collecting real-life outcomes in patients with RRMS who are being treated with Aubagio®. Completing all the questionnaires takes approximately 45 minutes, but as per patient convenience, questionnaires can be completed within one week prior to the date of the scheduled visit; each questionnaire can be completed on a different day.

7.4.4.1 Expanded Disability Status Scale

Patient disability is evaluated using the EDSS, which has long been considered the standard for assessing disability in patients with MS [21]. The EDSS must be performed by a qualified practitioner.

The EDSS is an ordinal clinical rating scale which ranges from 0 (normal neurologic examination) to 10 (death due to MS) in half-point increments. Briefly, the assessing neurologist rates 7 functional systems (pyramidal, cerebellar, brainstem, sensory, bowel and bladder, visual ratings in conjunction with observations and information concerning the patient's mobility, gait, and use of assistive devices to assign an EDSS score.

EDSS steps 1.0 to 4.5 refer to people with MS who are fully ambulant, while EDSS steps 5.0 to 9.5 are defined by the impairment to ambulation.

7.4.4.2 Multiple Sclerosis Impact Scale (MSIS-29)

The MSIS-29 is a scale that measures the physical (20 items) and psychological (9 items) impact of MS that was developed and validated by members of the Multiple Sclerosis Society of Great Britain and Northern Ireland [22, 23]. Two summary scores (i.e., the physical scale and the psychological scale) are calculated by summing up individual items in each scale and transforming the scores into a 0-100 scale. High scores indicate a higher impact of MS on the patient's physical and/or psychological health. It takes approximately 5 to 10 minutes to complete.

7.4.4.3 Modified Fatigue Impact Scale – 5 (MFIS-5)

The MFIS-5 consists of a subset of 5 questions from the 21 item MFIS instrument that focus on physical and mental fatigue. Patient answers are scored from 0 (never) to 4 (almost always). Administration time is 2-3 minutes for the abbreviated version [24].

7.4.4.4 Hospital Anxiety and Depression Scale (HADS)

The HADS is a 14-item self-report scale that was designed to screen for mood disorders in general (non-psychiatric) medical outpatients [25, 26]. It focuses on subjective disturbances of mood rather than physical signs and aims at distinguishing between depression and anxiety. The scale consists of depression and anxiety subscales, each with 7 items. Each subscale has a score ranging from 0-21. Items are rated from 0-3, generating a scale range of 0 to 42 points, with higher scores representing greater symptom severity. Subscales scores of 0-7 indicate normal levels of anxiety and depression; 8-10 indicate borderline abnormal anxiety and depression levels and 11-21 suggest abnormal levels of anxiety and depression. It takes approximately 2 to 5 minutes to administer.

7.4.4.5 Symbol Digit Modality Test (SDMT)

The SDMT has been designed to detect cognitive impairment. Brief and easy to administer, the SDMT has demonstrated remarkable sensitivity in detecting not only the presence of brain damage, but also changes in cognitive functioning over time and in response to treatment.

The SDMT involves a simple substitution task that normal children and adults can easily perform. Using a reference key, the examinee has 90 seconds to pair specific numbers with given geometric figures. Responses can be written, oral, and for either response mode, administration time is approximately 5 minutes.

7.4.4.6 Multiple Sclerosis Intimacy and Sexuality Questionnaire (MSISQ-19)

The MSISQ -19 is composed of 19 self-report items measuring the influence of MS symptoms on sexual activity and satisfaction and how they have interfered with the patient's sexual life over the preceding six months. The instrument is divided into three subscales: SD1, for primary sexual dysfunction (items 12, 16, 17, 18, and 19); SD2,

secondary (items 1, 2, 3, 4, 5, 6, 8, 10, and 11), and SD3, tertiary (items 7, 9, 13,14, and 15). Each item is rated from 1–5 based on the Likert scale (1 = never; 2 = seldom; 3 = sometimes; 4 = often, and 5 = always); a final score is generated by the summation of the scores across items. The higher the score, the greater the impact of SD on patients' lives.

7.4.4.7 Treatment Satisfaction for Medication Version 1.4 (TSQM v1.4)

The TSQM v1.4 is a global satisfaction scale which is used to assess the overall level of patient satisfaction or dissatisfaction with the medication that the patients are receiving. The TSQM v1.4 includes 14 questions in 4 domains: Effectiveness (Q1 to Q3); Side Effects (Q4 to Q8); Convenience (Q9 to Q11) and Global Satisfaction (Q12 to Q14) [27].

7.4.4.8 Patient Determined Disease Steps (PDDS)

The PDDS is a PRO of disability in MS and was developed by researchers associated with the Patient Registry of the North American Research Committee on MS. This instrument shows a strong correlation with EDSS scores [28]. The PDDS has 9 ordinal levels ranging between 0 (normal) and 8 (bedridden), and PDDS scores can be converted into EDSS scores as well as classifications of mild, moderate, or severe disability.

Administration time will vary depending upon the ability of the patient. Total administration time should be approximately 1 to 5 minutes.

7.4.4.9 Health Related Productivity Questionnaire-MS Version 2 (HRPQ-MS) v2

The HRPQ-MS v2 is a comprehensive instrument that measures several aspects of health-related lost productivity, such as absenteeism and attendance for paid and unpaid work, and long-term loss of workforce participation. It was designed for patients who have a particular disease and/or are being treated for the disease. The HRPQ-MS v2 consists of 9 questions that can be divided into 4 sections:

- Patient's employment status (full-time, part-time, not currently employed)
- Number of hours missed due to the disease/treatment, and percent of impact of the disease/treatment on work output (patients employed full- or part-time)
- Impact of the disease/treatment on productivity related to household chores (patients not currently employed)
- Disease history, including whether the disease/treatment forced the patient to change working situation (e.g., go from full-time to part-time, quit working, etc.).

The HRPQ-MS v2 asks patients to report lost productivity in the past week to minimize recall bias. Administration time is approximately 5 minutes at baseline collection and 3 to 4 minutes at follow-up.

8 SELECTION OF PATIENTS

8.1 SAMPLE SIZE

It is planned to recruit up to 100 eligible patients at approximately 20 sites in the UK. See sample size calculation provided in section 14.1.

8.2 INCLUSION CRITERIA

I 01. Adult patients (≥18 years old) with RRMS according to a neurologist's diagnosis, where the physician together with the patient have decided to start treatment with Aubagio® according to the approved SmPC.

I 02. Initiated Aubagio® treatment for the first time within 4 weeks of study entry

I 03. Patients who have signed written informed consent

I 04. Patients who are willing and able to complete the questionnaires for the full duration of the study

Note: (if a designated caregiver is available to assist the patient, they may physically complete the questionnaire for the patient)

8.3 EXCLUSION CRITERIA

E 01. Patients with contraindications to Aubagio® treatment according to the SmPC

E 02. Patients who are currently participating in an investigational interventional study if, in the judgment of investigator, such participation would interfere with the current study

E 03. Patients who are unwilling or unable to complete any questionnaire to be used in the study

E 04. Women of child bearing age who are not willing to use and effective form of contraception

8.4 MODALITIES OF RECRUITMENT

Investigators at participating sites will identify patients with relapsing remitting forms of MS who are eligible for Aubagio® treatment according to the approved SmPC. Upon the decision to start treatment with Aubagio®, there will be consecutive recruitment of all eligible patients who are willing to participate. Recruitment of patients into the study must never be an incentive to start treatment with Aubagio®. Investigators will be asked to track the sequence of events, making sure the decision to start treatment with Aubagio® occurs before patients are informed about potential study participation. The study visit schedule will be performed according to the site specific clinical practice.

8.5 WITHDRAWALS AND DROPOUTS

Patients may withdraw from treatment with Aubagio ® if they decide to do so, at any time and irrespective of the reason, or this may be the Investigator's decision. All efforts should be made to document the reasons for treatment discontinuation, and this should be documented in the eCRF.

If a patient discontinues Aubagio® treatment before month 24, the V6 (month 24/EOS visit) evaluations should be performed as soon as possible.

Patients who have withdrawn from the study cannot be re-included (treated) in the study. Their inclusion numbers must not be reused.

Patients who prematurely discontinue participation in the study will not be replaced. The Investigator may continue to enrol patients in the study for the duration of the recruitment phase.

The Statistical Analysis Plan (SAP) will specify how patients who are lost to follow-up for their primary endpoints will be considered.

9 SELECTION OF INVESTIGATORS

Investigators who are experienced in the treatment of patients with RRMS will undergo a feasibility assessment performed by Sponsor representatives. Study sites will be selected in facilities where qualified physicians diagnose, treat, and manage healthcare for patients with MS, including treatment with Aubagio® and other DMT as their routine practice. Upon qualification and confirmation to comply with the protocol-defined requirements, Investigators will be selected and the contract will be signed. Thereafter operational activities to start and conduct this study will be performed.

10 TREATMENTS

The prescription of therapies is under the responsibility of the Investigator only; the Sponsor will not provide Aubagio® for this study. Administration of Aubagio® and monitoring of patients according to the label will be the sole responsibility of the treating Investigator.

The patients who will be enrolled in the study will be selected among the patients for whom the Investigator has decided to prescribe Aubagio® prior to, and independently from, study entry.

The Investigator should refer to the SmPC for any information on treatment prescribed.

This agreement also implies that all labelled restrictions such as contraindications, special warnings and precautions for use, interaction with other medicinal products, and other forms of interactions and instructions for pregnancy and lactation will be followed. Concomitant therapy may be administered according to the approved SmPC and at the discretion of the Investigator. Any other concomitant MS DMTs are prohibited, except that symptomatic MS therapies or corticosteroids for treatment of relapse are allowed.

11 DATA COLLECTION

Data to be collected, and the corresponding schedule of recordings, are presented in Section 2.2.

11.1 DATA COLLECTION SCHEDULE

Data collection should occur as close to the visit schedule outlined in Section 2.2 as possible, with all data collected as outlined for the applicable visit. In the case of premature termination of study participation, data collection for month 24 (V6/EOS visit) should occur as soon as possible.

11.2 DEFINITION OF SOURCE DATA

Source data includes any hospital records and original (electronic or paper) questionnaires completed by any healthcare professionals or patients. It also includes PRO data collected at scheduled visits.

11.3 DATA COLLECTED

11.3.1 Patient Data

Patients will complete all PRO questionnaires in paper format. Physicians will handle the questionnaires to the patients to be completed. For baseline visit, patients will be asked to complete the questionnaires at the physicians' office/ waiting room, and give them back to the study nurse or physician.

During visit 1 the study nurse or physician will give the questionnaires for visit 3 to the patients to be completed at home within one week before visit 3. The same will be done at visits 3, 4, and 5. If visits 2 or 5 are not part of the site's routine clinical practice the patient will be given their questionnaires for their next planned study visit (visits 3 and 6).

If a designated caregiver is available to assist the patient, they may physically complete the questionnaire for the patient. A nurse or other health care professional may assist with instructing the patient on how to complete a questionnaire, in case they prefer to do it in the health care centre.

The completed questionnaires will be sent to the data management company to be entered into the study database.

11.3.2 Patient/Subject Tracking Logs

All consecutive patients who have started on Aubagio® in the past 4 weeks will be approached to enter the study. The patient's visit sequence will be documented in a patient tracking log for all enrolled and non-enrolled patients, with the reason for non-inclusion (not eligible or no consent). Data collected for patients who end up not enrolling are fully anonymous (gender, age).

The patient identification log for enrolled patients shall be kept by the Investigator to comply with the data privacy requirement. This log is not part of the eCRF and will not be entered into the clinical database.

11.4 PROCEDURE AND CONSEQUENCE FOR PATIENT WITHDRAWAL FROM STUDY

The participating Investigator should make every effort to re-contact the patient to determine his/her health status, including at least his/her vital status.

12 MANAGEMENT OF DATA

12.1 DATA COLLECTION, VALIDATION AND DATA QUALITY CONTROL

An eCRF will be provided by the Sponsor or a designated representative to record all clinical data.

Access to, and user roles in, the Electronic Data Capture (EDC) system and the corresponding domains will be managed and granted by the Sponsor or a designated representative. The confidentiality of all data collected using this EDC system is fully secured.

The computerized handling of the data by the Sponsor or a designated representative may generate additional requests, to which the participating Investigator is obliged to respond by confirming or modifying the data questioned (eQuery process).

Data collection and validation procedures will be detailed in appropriate operational documents (e.g., data validation plan) provided by the Sponsor or a designated representative and approved by the Sponsor.

12.2 MONITORING AND DATA QUALITY CONTROL AT SITE LEVEL

The EDC System will include integrated central data monitoring, quality check programs, and data management procedures (electronic query management) in order to supervise data recordings and to ensure completeness and high quality of all collected clinical data.

Data quality control (site monitoring) will be performed at site level by qualified monitors, according to the Study Manual.

Upon request, written informed consent forms, completed questionnaires, notes and copies of laboratory and medical records should be available at all times for monitoring or audits by the Sponsor's clinical professionals, and for inspections by authorities.

The Sponsor's representative, auditor, or inspector may review written informed consents and recordings in the eCRFs as deemed necessary and appropriate, and the accuracy of the data will be verified by reviewing the above referenced documents.

13 MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

All AEs, regardless of seriousness or relationship to Aubagio®, spanning from the first Aubagio intake after the signature of the informed consent form until the end of the study as defined by the protocol for each patient are to be collected by the Investigator and reported to the Sponsor within an expedited time frame.

13.1 SAFETY INSTRUCTIONS

All events will be managed and reported in compliance with all applicable regulations.

13.1.1 Definitions of Adverse Event (AE) and Serious Adverse Event (SAE)

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation patient administered a pharmaceutical product and which does not necessarily have to have a causal relationship with a treatment.

A Serious Adverse Event is any untoward medical occurrence that at any dose:

- Results in death or;
- Is life-threatening or;
- Note: The term "life-threatening" in the definition of "serious" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.
- Requires inpatient hospitalization or prolongation of existing hospitalization or;
- Results in persistent or significant disability/incapacity or;

- Is a congenital anomaly/birth defect;
- Is a medically important event:
  - Suspected transmission of infectious agent is any suspected transmission of an infectious agent via a medicinal product (e.g., product contamination)

Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above.

Adverse Event of Special Interest (AESI)
See section 13.3 for definition and list of AESIs

13.1.2 Collection of overdose and pregnancy

Overdose:
In cases of an overdose (accidental or intentional) with Aubagio® is an event suspected by the Investigator or spontaneously notified by the patient (not based on systematic pills count) and defined as at least twice the intended dose within the intended therapeutic interval.
The circumstances (i.e., accidental or intentional) should be clearly specified in the verbatim and symptoms, if any, entered on separate AE forms. In case of symptomatic overdose, even if not fulfilling a seriousness criterion, is to be reported to the representative of Sanofi within 24 hours of awareness and recorded accordingly on the corresponding pages of the eCRF as explained below. Overdose in the absence of an AE (asymptomatic), is to be reported to the representative of Sanofi within 30 days of awareness. Overdose will be qualified as a SAE only if it fulfils one of the seriousness criteria.

In case of overdose the patient should remain under observation for as long as it is considered appropriate by the Investigator. Appropriate symptomatic measures should be taken.

Pregnancy:
The effect of Aubagio® on human foetal development is not known, and may be potentially harmful based on results from animal studies. Therefore, all patients must be fully informed as to this risk. If during the study, a female patient becomes pregnant or decides to attempt to become pregnant, then she must stop Aubagio® and undergo the accelerated elimination procedure (AEP) (or according to local labeling) [29].

Pregnancy occurring in the patient or the female partner of a male patient included in the study will be reported as an AESI to the representative of Sanofi and recorded within 24 hours of awareness on the corresponding page(s) of the eCRF as explained below.

A pregnancy data collection form will be provided to the Investigator to ensure collection of additional information regarding the outcome of the pregnancy. If the exposed female refuses to provide any information regarding the pregnancy and its outcome, this information will be captured on the Sanofi Pregnancy/Drug Exposure via pregnancy data collection form.

13.1.3 Obligations of the Investigator regarding safety reporting

Adverse Event collection
All AEs, regardless of relationship to Aubagio® spanning from the first dose of Aubagio® after signature of the informed consent until the end of the study as defined by the protocol for each patient, are to be recorded

immediately (within 24 hours of awareness) for serious AE and AESI and within 30 days of awareness for non-serious AEs on the corresponding page(s) of the eCRF as explained below. Assessment of causality of the AE to the study drug should be recorded (i.e., related, not related) as well as information about assessment of intensity and outcome of the AEs.

Laboratory and vital signs abnormalities are to be recorded as AEs only if they are medically relevant: symptomatic, requiring corrective treatment, leading to treatment modification (delay, reduction, or discontinuation) and/or fulfilling a seriousness/adverse event of special interest criterion.

Adverse Event reporting to Sanofi

Serious Adverse Events and Adverse Events of Special Interest
In the case of an SAE or AESI the Investigator must immediately:

- Enter the information related to the SAE or AESI in the appropriate screens of the eCRF and SEND (within 24 hours of awareness, preferably by email or fax) the signed and dated corresponding page(s) in the Case Report Form to the Sponsor:

E-mail: be-cru-safety@sanofi.com
International Toll Free Fax: 0080027105511
Back up Fax 1: 0032 (0) 2/710 54 49
Back up Fax 2: 0032 (0) 2/710 56 99

- ATTACH the photocopy of all examinations carried out and the dates on which these examinations were performed. Care should be taken to ensure that the patient's identity is protected and the patient's identifiers in the study are properly mentioned on any copy of source document provided to for laboratory results, include the laboratory normal ranges;

All further documentation should be sent to the Sponsor within 24 hours of knowledge. In addition, any effort should be made to further document each SAE that is fatal or life threatening within the week (7 days) following initial notification.

A back-up plan is used (using paper forms) in case the eCRF system does not work.

Non-Serious Adverse Events
In the case of an AE that does not meet the criteria for serious, the Investigator must:

- ENTER (within 30 days of awareness) the information related to the AE in the appropriate screens of the eCRF; and send (within 30 days of awareness) the signed and dated corresponding pages in the eCRF preferably by fax or email to the sponsor:

E-mail: be-cru-safety@sanofi.com
International Toll Free Fax: 0080027105511
Back up Fax 1: 0032 (0) 2/710 54 49
Back up Fax 2: 0032 (0) 2/710 56 99

A back-up plan is used (using paper forms) in case the eCRF system does not work.

Safety observations

- The Investigator should take all appropriate measures to ensure the safety of the patients as per normal practice.
- The patient must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until progression has been stabilized. This may imply that follow-up will continue after the patient has left the study.
- In case of any SAE brought to the attention of the Investigator at any time after cessation of Aubagio®, and considered by him/her to be caused by Aubagio® with a reasonable possibility, this should be reported to the Sponsor.

13.2 ADVERSE EVENTS OF SPECIAL INTEREST (AESI)

An AESI (serious or non-serious) is one of scientific and medical concern specific to the product, for which ongoing monitoring and rapid communication by the Investigator to the Sponsor or a designated representative is required. Such AEs normally require thorough documentation and investigation to characterize them.

AESIs may be added or removed during a study by protocol amendment.

For AESIs the sponsor will be informed immediately (i.e., within 24 hours), as per the SAE/AESI notification instructions described in Section 13.1.3, even if the AESI does not fulfil a seriousness criterion, using the corresponding screens in the eCRF and reporting the corresponding CRF pages by fax or email.

AESIs

The following events must be systematically reported by the Investigator as AESIs with immediate notification:

- Pregnancy
- Symptomatic overdose with Aubagio®
- Liver disorder with increases in transaminases and bilirubin
  - ALT ≥3ULN (if baseline ALT <ULN); or ALT ≥2 x ALT baseline (if baseline ≥ ULN)
  - Any occurrence of ALT >8 x ULN. This should be reported as SAE with the criteria of medical importance
  - Per the Aubagio® product information [29], discontinuation of Aubagio® therapy is to be considered if elevated liver enzymes (>3 x ULN) are confirmed
- Medically significant neutropenia (any occurrence of neutrophil count of less than 1000 cells/μL)
- Respiratory symptoms compatible with interstitial lung disease (ILD)
- Peripheral neuropathy
- Acute renal failure/ hyperkalaemia
- Medically significant increases in blood pressure (hypertension: SBP ≥160 mmHg AND/OR DBP ≥100 mmHg)
- Severe skin or allergic reaction
- Major depressive disorder and suicidal attempt (based on Investigator's clinical judgment)
- Intense treatment in an emergency room or at home for:
  - Allergic bronchospasm
  - Blood dyscrasias (i.e., agranulocytosis, aplastic anaemia, bone marrow aplasia, myelodysplasia, pancytopenia, etc)
  - Convulsions (Seizures, epilepsy, epileptic fit, absence, etc.)
- Development of drug dependency or drug abuse
- Suicide attempt or any event suggestive of suicidality
- Syncope, loss of consciousness (expect if documented as a consequence of blood sampling)
- Bullous cutaneous eruptions

- Cancers diagnosed during the study or aggravated during the study (only if judged unusual/significant by the investigators)
- Chronic neurodegenerative disease (newly diagnosed) or aggravated during the study (only if judged unusual/significant by the investigators in studies assessing specifically the effect of a study drug on these diseases).

13.3 OBLIGATIONS OF THE SPONSOR

During the course of the study, the Sponsor or the Sponsor's representative will report to the appropriate Health Authorities all cases that meet expedited reporting criteria in accordance with all local and global regulations.

The Sponsor will report all safety observations made during the conduct of the study in the study report.

14 STATISTICAL CONSIDERATIONS

14.1 DETERMINATION OF SAMPLE SIZE The sample size has been calculated in order to assess the primary objective, describe changes in MSIS-29 scores from baseline to month 24. Mean MSIS-29 score on baseline, 24 months and changes during the follow-up (baseline to 24 months) will be calculated with the 95% confidence interval (CI). Taking into account a standard deviation of 20 points in MSIS-29 (Glenn, 2016), a sample size of 100 allows to estimate the MSIS-29 scores with a precision (distance from the mean to the limits of the 95% CI) of about 4 points with a significance level of 0.05. The sample size of 100 patients has been also determined based on the average number of patients at each site within the recruitment period of 2 years.

14.2 ANALYSIS POPULATIONS

The analysis population will include all enrolled patients who received at least one dose of study medication. All study analysis, including safety analysis, will be performed in this population.

14.3 STATISTICAL METHODS

This section provides specifications for preparation of the final SAP, which will be issued prior to database lock. Any differences compared to this statistical section will be identified and documented in the final SAP.

14.3.1 Statistical Analysis

All recorded clinical observations will be analysed using descriptive statistics.

Data will be summarized into counts of non-missing data, mean, standard deviation, and minimum, maximum, median, Q1, and Q3 for quantitative variables and frequency and percent for categorical data. The 95% confidence interval will be provided when necessary.

Subgroup analysis may be conducted as deemed necessary.

14.3.1.1 Primary Analysis

The primary endpoint of change from baseline to month 24 in the MSIS-29 will be analysed descriptively providing the mean change with 95% confidence interval and also using an analysis of covariance (ANCOVA), adjusting for baseline covariates, including the baseline MSIS-29 value. A p-value below 0.05 will be considered statistically significant.

Additional exploratory pre-specified analysis of the primary endpoint will be performed in at least 4 specific subgroups: treatment naïve patients, patients previously treated with a MS DMT within the past 2 years, injectable switch patients and oral switch patients.

14.3.1.2 Secondary Analysis

The changes from baseline to month 24, and to each follow-up visit before 24 months visit, in TSQM v1.4, PDDS, MFIS-5, HRPQ-MS v2, MSISQ-19, SDMT and HADS will be tested using the t-distribution. The mean changes between study visits with the corresponding 95% confidence interval will be given. If required, an ANCOVA, adjusting for baseline covariates will be performed. A p-value below 0.05 will be considered statistically significant. The evolution of PRO scores during the follow-up period will be also represented graphically.

In addition to PRO scores, the same statistical methods will be used to analyse number of missed doses of Aubagio® (adherence), number of relapses, number of HCP encounters and number of emergency room visits.

Additional exploratory pre-specified analysis of the secondary endpoints will be performed in at least 4 specific subgroups: treatment naïve patients, patients previously treated with a MS DMT within the past 2 years, injectable switch patients and oral switch patients.

14.3.2 Safety Analysis

The frequency and percentage of patients experiencing AEs, SAEs, and AESIs will be reported. The number and proportion of not serious and serious adverse events will be calculated. All non-serious and serious adverse events and the related information will be presented in individual data listing tables as well.

14.3.3 Interim Analysis

Final study analysis will be performed after all patients have completed the core study (24 months±1 month), or discontinued study before the 24 months duration. One interim analysis is planned to be performed at 18 months from first patient in. The results of the interim analysis will be mainly used in publications at medical congresses and presentations, providing update on the study.

15 TASKS AND RESPONSIBILITIES

15.1 RESPONSIBILITIES OF STUDY COMMITTEES

The Sponsor will be responsible for scientific communications including writing publications.

15.2 RESPONSIBILITIES OF THE INVESTIGATOR(S)

The Investigator will perform the study in accordance with this protocol, applicable local regulations, and international guidelines.

It is the Investigator's responsibility to:

- obtain written informed consent from patients prior to inclusion in the study
- complete all eCRFs and record all data pertinent to the study. She/he will ensure that the information reported in the eCRF is precise and accurate.
- Provide study questionnaires to the patient for completion
- Enter confirmation in the eCRF that patient questionnaires have been completed

The Investigator or a person designated by the Investigator, and under the Investigator's responsibility, should fully inform the patient of all pertinent aspects of the study including the written information. All patients should be informed to the fullest extent possible about the study, in language and terms they are able to understand.

Prior to a patient's participation in the study, the written Informed Consent Form should be signed, name filled in and personally dated by the patient or the patient's legally acceptable representative, and by the person who conducted the informed consent discussion. A copy of the signed and dated written Informed Consent Form will be provided to the patient.

The Informed Consent Form and the Information Sheet used by the Investigator for obtaining the patient's informed consent must be reviewed and approved by the Sponsor's representative prior to submission to the appropriate IRB/REB for approval/favourable opinion.

15.3 RESPONSIBILITIES OF SPONSOR OR DESIGNEE

The Sponsor or a designated representative is responsible for taking all reasonable steps and providing adequate resources to ensure the proper conduct of the study.

The Sponsor or a designated representative is responsible for:

- local submission(s) complying with data protection rules
- any other local submission(s).

16 ETHICAL AND REGULATORY STANDARDS

16.1 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.

16.2 LAWS AND REGULATIONS

This study will be conducted in accordance with the guidelines for Good Epidemiology Practice (European [30]).

The participating country should locally ensure all necessary regulatory submissions (eg, IEC) are performed in accordance with local regulations including local data protection regulations.

17 ADMINISTRATIVE EXPECTATIONS

17.1 RECORD RETENTION IN STUDY SITES

The Investigator should retain the study documents at least 5 years after the completion or discontinuation of the study, unless otherwise specified in the Investigator Agreement in line with additional standards and/or local laws.

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

17.2 CONFIDENTIALITY

All material, information (oral or written) and unpublished documentation provided to the Investigator (or any action carried out by the Sponsor or a designated representative on their behalf), including the present protocol and the eCRF, are exclusive property of the Sponsor or their designated representative.

These materials or information (both global and partial) cannot be given or disclosed by the Investigators or by any person of her/his group to unauthorized persons without the prior formal written consent of the Sponsor or their designated representative.

The Investigator shall consider as confidential all the information received, acquired or deduced during the study and will take all necessary steps to ensure that there is no break of confidentiality, other than for information to be disclosed by law.

17.3 DATA PROTECTION

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

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

17.4 INSURANCE

The Sponsor will contract for insurance according to locally specific requirements.

17.5 AUDITS AND INSPECTIONS

The Investigator agrees to allow the Sponsor or designated representative auditors/competent authority 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.

The Investigator 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 the Investigator to the Sponsor or their designated representative.

The Investigator shall take appropriate measures required by the Sponsor or their designated representative to take corrective actions for all problems found during the audit or inspections.

17.6 PREMATURE DISCONTINUATION OF THE STUDY OR PREMATURE CLOSE-OUT OF A SITE

The Sponsor can decide at any time and for any reason to discontinue the study; the decision will be communicated in writing to the participating Investigators.

Similarly, should the Investigator decide to withdraw from the study, she/he will have to inform the Sponsor or designated representative in writing.

If appropriate, according to local regulations, IECs and competent authorities should be informed.

17.7 OWNERSHIP AND USE OF DATA AND STUDY RESULTS

No use of the data will be possible without the authorization of the Sponsor conducting the study.

The Sponsor will have full access to the final data allowing for appropriate academic analysis and reporting of the study results.

17.8 PUBLICATIONS

The Sponsor is responsible for presentations and/or publications. The study results must be submitted to the review of the Sponsor before publication.

All study Investigators give full authority to the Sponsor for primary presentation and/or primary publication of results. No other publication is allowed before the primary publication. Any subsequent presentation or publication by a study participant (including for sub studies) must be approved by the Sponsor and make reference to the study and the primary publication.

The final decision to publish any manuscript/abstract/ presentation will be made by the Sponsor.

All manuscripts/abstracts/presentations must be submitted to the internal review of the Sponsor at least 45 calendar days in advance of submission. The Sponsor may request that the Sponsor's name and/or names of one or several of its employees appear or do not appear in such publication.

The Sponsor can delay publication or communication for a limited time in order to protect the confidentiality or proprietary nature of any information contained therein.

18 STUDY PROTOCOL AMENDMENTS

Any change to the protocol will be recorded in a written amendment, which will be signed by the Investigator. Amendment to the protocol may require regulatory submissions (e.g., IEC) in accordance with local regulations.

In some cases, an amendment may require a change to the Informed Consent Form.

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