Study report Sponsor review form for Local Medical studies

Product Code:	Teriflunomide / Aubagio®
Study Code / Name:	TERIFL08913 / AUBADHE
Study Title:	A prospective, open-label, multicenter, single-arm observational registry to describe adherence in relapsing remitting multiple sclerosis patients being prescribed teriflunomide (Aubagio®) in Belgium in routine clinical practice.
Document Type: (Tick appropriate box)	☐ Clinical Study Report / ☐ Synopsis ☒ Product Observational Study Report / ☐ Synopsis ☐ Disease Observational Study Report / ☐ Synopsis ☐ Post Authorization Safety Study (PASS) Report / ☐ Synopsis
Name of Sponsor's responsible medical officer (i.e. individual responsible for medical oversight of the report):	Vanina Belis, Medical Lead Neurology and Immunology for Belgium, Luxembourg and The Netherlands

THE STUDY REPORT Final Draft dated 12-Jan-2022 has been reviewed by:

Role	Name	Date and signature
Global Safety Officer	Myriam Benamor	See attached e-mail documenting review on the 31st of January 2022
Medical Product Leader at local level	Vanina Belis	Vanina Belis Vanina Belis (Feb 2, 2022 09:54 GMT+1)
Medical Product Leader at regional level	Suzanne Frankfort	Suzanne Frankfort Suzanne Frankfort (Feb 3, 2022 13:00 GMT+1)
Medical Product Leader at Global level	Janneke van Wingerden	J van Wingerden J van Wingerden (Feb 2, 2022 1[illegible]2 GMT+1)
Local Study Manager	Annelies Mottart	Annelies Mottart
Country Regulatory Manager	Brigitte De Witte	Brigitte De Witte Brigitte De Witte (Feb 2, 2022 09:57 GMT+1)
Country SGZ Medical Head	Ann Matthys	Ann Matthys Ann Matthys (Feb 2, 2022 09:54 GMT+1)
Country Medical Lead	Patrick Dhont	Patrick Dhont

From:	Benamor, Myriam /FR
To:	Belis, Vanina /BE
Cc:	Mottart, Annelies /BE
Subject:	RE: Aubadhe/TERIFL08913: final clinical study report for approval
Date:	lundi 31 janvier 2022 11:03:34
Attachments:	image001.png image002.png

Dear Colleagues, please note that I am not an approver, I am one of the reviewers per QSD. The approvals are the following:

Approval
Medical
Country GBU Medical Head
Country Medical Lead

I reviewed the documents and have no further comments.
Thanks

Bien Cordialement/ Best Regards, Myriam

De : Belis, Vanina /BE <vanina.belis@sanofi.com>
Envoyé : lundi 31 janvier 2022 10:46
À : Benamor, Myriam /FR <Myriam.Benamor@sanofi.com>
Cc : Mottart, Annelies /BE <Annelies.Mottart@sanofi.com>
Objet : Aubadhe/TERIFL08913: final clinical study report for approval
Importance : Haute

Dear Myriam,

We have the pleasure to transmit to you for final sign-off the Clinical Study Report (CSR) of Aubadhe.
According to the QSD-010935 (reviewers for local medical studies), you are in the loop to sign it.

You will receive the electronic signature form via my administrative support Chantal Michiels today or tomorrow to document your approval.

Aubadhe is a local product registry with Aubagio entitled:
A prospective, open-label, multicenter, single-arm observational registry to describe adherence in relapsing remitting multiple sclerosis patients being prescribed teriflunomide (Aubagio®) in Belgium in routine clinical practice.

Please find attached:

- The clean version of the Clinical Study Report TERIFL08913_AUBADHE_SAN060_CSR_final_12JAN2022_clean
- The full version of the report with the tables and figures attached as well as other appendixes TERIFL08913_AUBADHE_SAN060_CSR_final_14JAN2022_and appendix (002)

Safety data are to be found:

- In the clean version of the CSR: section *9.5.5 Prior and/or concomitant medication* and

section 11.2 adverse events, **pages 55-56-57 (and 1 line on page 58)**

- In the TFLs, should you need to see the details:
    - Prior medication, concomitant medication and relevant medical history in tables 2.1.5.4, 2.1.5.5, 2.1.5.6 **pages 94-138** of the full report with appendix
    - Adverse events tables: Overview of adverse event profile, All AEs by primary SOC and PT, All SAEs by primary SOC and PT, All related to treatment discontinuation AEs by primary SOC and, All AESIs by primary SOC and PT, All AEs leading to death by primary SOC and PT in tables 2.1.8.1 until 2.1.8.7, **pages 151-164** of the full report
- We concluded that no new safety signal was shown during the study (page 67 of the clinical study report)

Note on the template used:
The vendor for the database, data management, statistics and medical writing was Linical. We decided together last year at the time of the database cleaning and closing to work with a full CSR, according to QSOP-004712 version 5.0., seeing the non-classical endpoints used in this study. We were made aware that the SOP has been updated in the course of the year 2021, however, the work of the medical writer was too advanced to go back to the succinct version as per new SOP for product registries. The full attached CSR contains all the required information as per current SOP and regulatory requirements as it is much more extensive than the current synopsis template proposed for product registries. Therefore we made the decision to move on with the report in this template, seeing budget and timelines impacts.

Let me know if you have comments. We aim to collect all final comments by the end of this week, if possible.

I summarized some of the main outcomes below my signature (primary endpoint, safety, main secondary endpoints) . As a reminder, Aubadhe aimed to study the behaviors of patients in terms of adherence, taking into account all aspects of adherence: initiation (to start the treatment), implementation (to take the treatment correctly) and persistence/continuation rate (treatment duration). Let me know if you prefer to have a short briefing on the data, I can guide you through the main safety data.

Thanking you in advance for your review and approval,

Kind regards,
Vanina (on behalf of the Aubadhe team – Annelies Mottart for the CSU and Vanina Belis for medical affairs)

Topline summary Aubadhe:
Primary endpoint (on 103 patients): The continuation rate proportion (95% CI) on the patients who remained on treatment at 12 and 18 months was 5/10 (50.00%) (18.71; 81.29) for the patients falling under protocol amendment with shorter follow-up period (12 months) and 55/85 (64.71%) (53.59; 74.77) for the patients followed-up 18 months, respectively

Secondary endpoints:

Initiation rate: A total of 103 (96.26%) patients in the FAS were on treatment from baseline to the 3 months visit (Table 2.1.7.1), meaning that 4 patients (3.74%) out of the 107 patients evaluated did never initiate (start) treatment.
Implementation: The adherence in terms of implementation calculated on the primary analysis population showed that 42 out of these 95 patients (51.85%) had good implementation on the total observation period, i.e. did not report implementation issue in the BAASIS questionnaire.

Safety

A total of 89 out of 105 patients (84.76%) had any adverse event. The SOCs with the highest incidence of AEs were nervous system disorders and gastrointestinal disorders, (44 [41.90%] patients with AEs each), skin and subcutaneous tissue disorders (22 [20.95%] patients), infections and infestations (21 [20.00%] patients with AEs), musculoskeletal and connective tissue disorders (18 [17.14%] patients with AEs) and general disorders and administration site conditions [17 [16.19%] patients with AEs).

The AE more frequently reported during the study was diarrhoea reported by 22 (20.95%) patients followed by alopecia (16 [15.24%] patients), headache (13 [12.38%] patients) and multiple sclerosis relapse (11 [10.48] patients). Other AEs reported in less than 10 patients were nausea and fatigue each reported by 9 (8.57%) patients, lymphopenia, dizziness and gastrointestinal disorders each reported by 6 (5.71%) patients, paraesthesia, hypertension, abdominal pain and pain in extremity each reported by 4 (3.81%) patients and nasopharyngitis, tooth abscess, anxiety, carpal tunnel syndrome, neuropathy peripheral, arthralgia, back pain, intervertebral disc protrusion and pregnancy each reported in 3 (2.86%) patients. Other events were reported in less than 2% of the safety population.

Interesting clinical findings on fatigue, depression and cognition:
When looking at the PRO's evaluating MS-related specific symptoms like depression (PHQ-9), fatigue (MSIF-5) and cognition (SDMT) at the end of the study, we can see that the same proportion of patients had cognitive improvement and impairment while a half of patients did not change their cognitive status compared to baseline, the depression status improved and there was a lower percentage of patients reporting depressive symptoms at the end of the study compared to baseline, and that the fatigue scores improved at the end of the study compared to baseline and that a lower percentage of patients reported fatigue symptoms at the end of the study compared to baseline.
Exploratory analysis was performed to describe the correlation between cognition (measured via SDMT) and treatment adherence parameters, considering the initiation, implementation and persistence as variables. From this analysis it was observed that initiation, implementation and persistence were not statistically related to the changes observed in the cognition status assessed by SDMT.

Vanina Belis
Medical Lead – Neurology and Immunology – BeNeLux
Tel: +32 2 710 56 36 – Mob.: +32 479 45 81 70

Follow us on: www.mysanofi.be

Airport Plaza - Montreal Building
Leonardo Da Vinci laan 19
1831 Diegem
Belgium

CLINICAL STUDY REPORT

COMPOUND: teriflunomide / Aubagio®

A prospective, open-label, multicenter, single-arm observational registry to describe adherence in relapsing remitting multiple sclerosis patients being prescribed teriflunomide (Aubagio®) in Belgium in routine clinical practice.

STUDY NUMBER: TERIFL08913

STUDY NAME: AUBADHE

Study Initiation Date (first subject/patient enrolled): 28 August 2018

Study Completion Date (last subject/patient completed): 29 March 2021

Primary Completion Date: 29 March 2021

Phase: Observational

Design: This is an 18-month prospective, open-label, multicenter, single-arm observational, non-interventional study to describe adherence in relapsing remitting multiple sclerosis patients being prescribed teriflunomide (Aubagio®) in Belgium n routine clinical practice in which patients were prescribed Aubagio® according to local label and reimbursement criteria.

Investigator: Prof Dr. Vincent van Pesch, Cliniques Universitaires Saint-Luc. Brussels and Prof Fabienne Dobbels, KU Leuven

Report Date: 12-Jan-2022

Previous Versions (date): not applicable

This study was performed in compliance with Good Clinical Practices, including the archiving of essential documents. This report has been prepared in accordance with the ICH Harmonized Tripartite Guideline on the Structure and Content of Clinical Study Reports, dated November 1995, using QSOP-004712 Version 5.0.

Date: 12-Jan-2022 Total number of pages: 76

REPORT HISTORY

1 TABLE OF CONTENTS

CLINICAL STUDY REPORT **1**

REPORT HISTORY **3**

1 TABLE OF CONTENTS **4**

1.1 LIST OF TABLES 8

1.2 LIST OF FIGURES 8

2 LIST OF CLINICAL STUDY REPORT CONTENT **9**

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS **10**

4 ETHICAL CONSIDERATIONS **11**

4.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD 11

4.2 ETHICAL CONDUCT OF THE STUDY 11

4.3 SUBJECT/PATIENT INFORMATION AND CONSENT 11

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE **12**

6 INTRODUCTION **13**

7 STUDY OBJECTIVES **16**

7.1 PRIMARY 16

7.2 SECONDARY 16

7.3 EXPLORATORY 16

8 INVESTIGATIONAL PLAN **17**

8.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN 17

8.2 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS 17

8.3 SELECTION OF STUDY POPULATION 17

8.3.1 Inclusion criteria 17

8.3.2 Exclusion criteria 18

8.3.3 Removal of patients from therapy or assessment 18

8.3.3.1 Temporary treatment discontinuation with IMP(s) 18

8.3.3.2 Permanent treatment discontinuation with IMP(s) 18

8.3.3.3 List of criteria for permanent treatment discontinuation 18

8.3.3.4 Handling of patients after permanent treatment discontinuation 19

8.4 TREATMENTS 19
8.4.1 Treatments administered 19
8.4.2 Identity of investigational medicinal products 19
8.4.3 Method of assigning subjects/patients to treatment groups 19
8.4.4 Selection of doses in the study 19
8.4.5 Selection and timing of dose for each patient 19
8.4.6 Blinding procedures 20
8.4.7 Prior and concomitant therapy 20
8.4.8 Treatment compliance 20
8.5 EFFICACY AND SAFETY ASSESSMENTS 20
8.5.1 Primary endpoint assessments 22
8.5.2 Secondary endpoint assessment assessment 23
8.5.2.1 Adverse events 24
8.5.2.2 Laboratory safety parameters 26
8.5.2.3 Other safety parameters 26
8.5.3 Pharmacokinetics assessments and timing 26
8.5.3.1 Pharmacokinetic measurements and timing 26
8.5.3.2 Pharmacokinetic variables 26
8.5.4 Other assessments 26
8.5.5 Appropriateness of measurements 26
8.6 DATA QUALITY ASSURANCE 27
8.7 STATISTICAL CONSIDERATIONS 27
8.7.1 Determination of sample size 27
8.7.2 Analysis populations 28
8.7.3 Statistical analyses 28
8.7.3.1 Demographics and baseline characteristics 29
8.7.3.2 Prior or concomitant medications 29
8.7.3.3 Extent of investigational medicinal product exposure and compliance 29
8.7.3.4 Analyses of efficacy/pharmacodynamic endpoints 29
8.7.3.5 Analyses of safety data 30
8.7.3.6 Analyses of pharmacokinetic data 31
8.7.3.7 Other analyses 32
8.7.4 Interim analyses 32
8.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES 32
8.8.1 Changes in the conduct of the study 32
8.8.2 Changes in the planned analyses 32
8.8.2.1 From the protocol to the statistical analysis plan 32
8.8.2.2 From the statistical analysis plan to database lock 32
8.8.2.3 After database lock 33

9 STUDY SUBJECTS/PATIENTS 34

9.1 DISPOSITION OF SUBJECTS/PATIENTS 34
9.1.1 Participating sites 35

9.2 PROTOCOL DEVIATIONS 35
9.2.1 Major or critical efficacy/pharmacodynamic deviations relating to the primary efficacy/pharmacodynamic endpoint(s) (title flexible) 36
9.2.2 Randomization and dosing irregularities 36
9.2.3 Other major or critical deviations 36

9.3 BREAKING OF THE BLIND 36

9.4 DATA SETS ANALYZED 36

9.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS 37
9.5.1 Demography 37
9.5.1.1 Demographics by subgroups 38
9.5.2 Medical history 43
9.5.3 Disease characteristics at baseline 43
9.5.4 Other baseline characteristics 44
9.5.5 Prior and/or concomitant medication 44

9.6 MEASUREMENT OF TREATMENT COMPLIANCE 44

10 PRIMARY ENDPOINT EVALUATION 45

10.1 PRIMARY ENDPOINT(S) 45
10.1.1 Primary analysis 45

10.2 PRIMARY ANALYSIS CONCLUSIONS 46

11 SECONDARY EVALUATION 47

11.1 EXTENT OF EXPOSURE 55

11.2 ADVERSE EVENTS 55
11.2.1 Brief summary of adverse events 55
11.2.2 Analysis of adverse events 56

11.3 DEATHS, SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS 56
11.3.1 Deaths 56
11.3.2 Serious adverse events 57
11.3.3 Adverse events leading to treatment discontinuation 57
11.3.4 Adverse events of special interest 57

11.3.5 Other significant adverse events....58
11.4 CLINICAL LABORATORY EVALUATIONS....58
11.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER SAFETY OBSERVATIONS....58
11.6 SAFETY CONCLUSIONS....58
12 PHARMACOKINETIC EVALUATION....62
13 DISCUSSION AND OVERALL CONCLUSIONS....63
14 REFERENCES....68
15 SUPPORTIVE INFORMATION....70
15.1 DEMOGRAPHIC DATA....70
15.2 EFFICACY/PHARMACODYNAMIC DATA....70
15.3 SAFETY DATA....70
15.3.1 Displays of adverse events....75
15.3.2 Listings of deaths, serious adverse events, and other significant adverse events....75
15.3.3 Narratives of deaths, serious adverse events, and other significant adverse events....75
15.3.3.1 Comprehensive list of all subjects/patients number/narratives....75
15.3.3.2 Subject/patient narratives – Deaths....75
15.3.3.3 Subject/patient narratives – Serious adverse events....75
15.3.3.4 Subject/patient narratives – Withdrawals due to adverse events....75
15.3.3.5 Subject/patient narratives – Other category to be specified....75
15.3.4 Abnormal laboratory value listing (each subject/patient)....75
15.3.5 Listing of other observations related to safety (each subjects/patients)....76
15.4 PHARMACOKINETIC DATA....76

1.1 LIST OF TABLES

Table 1 – Schedule of Assessment....21
Table 2 - Any critical or major deviation – Included....35
Table 3 - Analysis populations – Included....36
Table 4 – Baseline analysis - Demographics....37
Table 5 - Demographics for patients who started and did not started the treatment....39
Table 6 – Demographics for patients who had and did not have implementation issues....40
Table 7 – Demographics for patients who had and did not have discontinued treatment....42
Table 8 - Persistence – Safety population....45
Table 9 - Overview of adverse event profile – Safety population....55

1.2 LIST OF FIGURES

Figure 1 – Study Flow Chart....21
Figure 2 – Disposition of Subjects....34
Figure 3 - Kaplan Meier plot for Persistence – Safety population....46

2 LIST OF CLINICAL STUDY REPORT CONTENT

16.1.1	Protocol Amendment(s)
16.1.2	Sample case report form
16.1.3	List of Independent Ethics Committees or Institutional Review Boards, representative subject/patient information, and sample consent forms.
16.1.4	Investigators, key study personnel, and study report authors.
16.1.5	Signature of Principal Investigator/Sponsor's responsible medical officer
16.1.6	Listing of subject/patient receiving investigational medicinal product (s) from specified batch
16.1.7	Randomization scheme, subject/patient identification, treatment codes, and randomization specifications
16.1.8	Audit certificates
16.1.9	Documentation of statistical methods Final statistical analysis plan (last version) Data Monitoring Committee charters, minutes, and data reports of meetings that led to a change of the protocol Supporting statistical documentation
16.1.10	Documentation of interlaboratory standardization methods and quality assurance procedures if used
16.1.11	Publications based on the study
16.1.12	Important publications referenced in the report
16.2.1	Subject/patient disposition
16.2.2	Protocol deviations
16.2.3	Subject/patient, visits, or observations excluded from the efficacy/pharmacodynamic analyses
16.2.4	Demographic data, data at baseline, and medication details
16.2.5	Compliance and drug concentration data
16.2.6	Efficacy/pharmacodynamic response data
16.2.7	Adverse event data Other safety observations
16.2.8	Clinical laboratory data

3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

AE:	Adverse event
AESI:	Adverse Event of Special Interes
ALT:	Alanine transaminase
BAASIS:	Basel Assessment of Adherence to Inmunossupressive Medication Scale
CI:	Confidence Interval
DMT:	Disease modifying therapy
eCRFs:	electronic Case Report Form
EDC:	Electronic Data Capture
EDSS:	Expanded Disability Status Scale
FAS:	Full Analysis Set
GCP:	Good Clinical Practice
ILD:	Intersticial lung disease
IMAB:	Identifying Medication Adherence Barriers
IMBP:	Integrative Model of Behavioral Prediction
KM:	Kaplan-Meier
LS:	Least square
MedDRA:	Medical Dictionary for Regulatory Activities
MMRM:	Mixed-effects model for repeated measures
MRI:	Magnetic resonance imaging
MS:	Multiple Sclerosis
OR:	Odds ratio
PHQ-9:	Patient Healt Questionnaire 9 items
PRO:	Patient-reported outcome
PSP:	Patient Support Program
PT:	Preferred Term
QC:	Quality Control
RMS:	Relapsing forms of MS
RRMS:	Relapsing-remitting MS
SAE:	Serious Adverse Evemt
SD:	Standar deviation
SDMT:	Symbol Digit Modality Test, Symbol Digit Modalities Test
SE:	Standard error
SmPC:	Summary of Product Characteristics
SOC:	System Organ Class
ULN:	Upper limits of normal
WBC:	White blood cell count

4 ETHICAL CONSIDERATIONS

4.1 INDEPENDENT ETHICS COMMITTEE OR INSTITUTIONAL REVIEW BOARD

The protocol and its amendment (@@16-1-1-protocol) were submitted to independent Ethics Committees for review and written approval.

The list of all committees consulted, with the name of the committee chair, is provided in @@16-1-3-iec-irb.

4.2 ETHICAL CONDUCT OF THE STUDY

The study was conducted in accordance with consensus ethics principles derived from international ethics guidelines, including the Declaration of Helsinki, and the ICH guidelines for Good Clinical Practice (GCP), all applicable laws, rules, and regulations.

4.3 SUBJECT/PATIENT INFORMATION AND CONSENT

Informed consent was obtained prior to the conduct of any study-related procedures. The subject/patient informed consent form was modified according to local regulations and requirements. A sample of the informed consent form used and representative written subject/patient information are provided in @@16-1-3-icf.

5 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The lists of Investigators and other key study personnel, with their affiliations, a description of their role in the study, and their qualifications, are provided in @@16-1-4-invest-enrolled. Signed approval of the report from the Principal/Coordinating Investigator is provided in @@16-1-5-invest-sign-[last name]. This report has been electronically approved by the Sponsor.

A list of global and local service providers is provided in @@16-1-4-providers.

The study employed an Independent Data Monitoring Committee, a Scientific committee and a Publication committee (refer to the protocol for further details). The lists of committee members are provided in @@16-1-4-committees and the charters of each committee are provided in @@16-1-9-dmc and @@16-1-10-interlab-standard.

This report was prepared by:

- Vanina Belis (Study Medical Manager)
- Cristina Castillejo (Medical Writer)
- Rosa González (Statistician)
-

6 INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory demyelinating disease of the central nervous system, which is primarily diagnosed in young adults. It represents the second most common cause of permanent disability and early retirement in this population. The incidence of MS in Europe has been estimated at 5 cases per 100,000 inhabitants per year. The incidence in Belgium is 108 per 100,000 inhabitants with a total of approximately 12600 patients affected by MS in Belgium. Although the cause of the disease is unknown, it has been shown that autoimmune mechanisms are involved in the production of antibodies against proteins of the myelin layer that trigger an inflammatory process responsible for their destruction. The repeated result of this process leads to the formation of sclerotic plaques disseminated throughout the central nervous system. These plaques result in neurological impairment manifested by varying clinical signs depending on the affected sensory and/or motor nerve pathways, and whose accumulation eventually causes disability and handicap. Thus, MS not only impacts physical health and survival of affected individuals, but also may lead to problems related to work, social relations and family dependence, producing, therefore, a high impact on the patient's quality of life.

Teriflunomide is a once-daily oral immunomodulator approved for the treatment of relapsing forms of MS (RMS) or relapsing-remitting MS (RRMS) in 70 countries, including the United States and the European Union. As of 2019, more than 100,000 patients were being treated with teriflunomide, with a total real-world exposure of ap-proximately 285,800 patient-years. In patients with RMS, teriflunomide 14 mg showed consistent efficacy on relapse rate (1), magnetic resonance imaging (MRI) markers of disease activity (1) (2), and neurodegeneration (3) vs placebo across phase 3 clinical trials; teriflunomide 14 mg is also the only oral disease-modifying therapy (DMT) to show consistent efficacy in disability outcomes (1) (4) in two phase 3 trials. In addition, teriflunomide has been shown to be effective in patients with a first demyelinating episode suggestive of MS (5). Teriflunomide has also demonstrated a manageable safety and tolerability profile that is consistent across phase 2 and 3 clinical trials (1) (4) (6) (7), and their extensions (7) (8) (9).

Patients reported high treatment satisfaction with teriflunomide, with switchers also reporting improved treatment satisfaction vs baseline. High treatment satisfaction in patients with RMS may lead to improved adherence, and hence treatment outcomes (10).

Clinical trials of DMTs for MS generally focus on evaluating treatment effects on clinician-rated objective outcomes such as relapse rates, confirmed disability worsening, and MRI markers of disease activity. The phase 4 Teri-PRO study, conducted in real-world, routine clinical practice settings, provided data that were complementary to the results of the earlier phase 2 and 3 randomized clinical trials of teriflunomide. The use of patient-reported outcome(s) (PRO) provided unique insights on treatment from the patient perspective.

PRO measures can complement traditional outcome measures, enhance clinicians' understanding of the effects of disease and treatment on health-related quality of life, and provide insight on global satisfaction with therapy (11) (Haase et al., 2016). Indeed, patient perception of, and

satisfaction with their treatment may affect adherence and, therefore, outcomes (12) (Haase et al., 2016).

Adherence to treatment reported in the Teri-PRO study was high, with 98.2% of patients reporting ≥80% adherence. The median duration of treatment was 337 (330, 342) days. However, those numbers are not confirmed in real life setting, based on the scarce and topline data obtained so far. Currently, this data does provide neither exact numbers about adherence in real life, nor the level of insights necessary to understand the specific parameters playing a role on adherence with Aubagio®.

Few studies investigated the prevalence and risk factors of non-adherence to oral MS therapies, and their impact on clinical outcomes. Moreover, existing studies do not describe adherence according to the new taxonomy used for adherence: 1) initiation phase: to check if the patient initiated the prescribed treatment; 2) implementation: which checks if the patient delays, omits or takes extra doses; and 3) persistence: which measures the time until the patient discontinues the treatment (13).

According to this new taxonomy, adherence to medications is the process by which patients take their medications as prescribed, composed of initiation, implementation and discontinuation. Initiation occurs when the patient takes the first dose of a prescribed medication. Discontinuation occurs when the patient stops taking the prescribed medication, for whatever reason(s). Implementation is the extent to which a patient's actual dosing corresponds to the prescribed dosing regimen, from initiation until the last dose. Persistence is the length of time between initiation and the last dose, which immediately precedes discontinuation

Most studies focus on persistence, while it remains insufficiently clear how many patients do not initiate treatment or show implementation problems, in the format of missed doses, wrong dosing or irregular timing of intake. The majority of studies also investigate adherence to injection therapies, while evidence on adherence to oral therapy remains scarce. In addition, few studies attempted to investigate risk factors for poor adherence, which has been a missed opportunity, given that the information on risk profiles could help to develop timely adherence enhancing interventions. More specifically, an in-depth understanding of the current situation of therapy adherence in the setting of Aubagio intake is currently lacking. Indeed, only persistence data from the phase III and IV data are available, with no analysis of the different treatment phases (initiation, implementation, persistence and discontinuation).

This registry study has brought innovation by collecting adherence data in a prospective manner in RRMS patients taking an MS oral therapy (Aubagio) that could allow an in-depth comprehension of the concept of adherence in those patients, including its prevalence, risk factors and association with treatment outcomes.

The primary aim was to describe adherence in terms of persistence during the first 18 months maximum in patients who took Aubagio in a real-life setting. Secondary objectives comprised the description of adherence in view of initiation and implementation, assessing both objectively, using prescription renewal data, and subjectively, using a validated questionnaire used for immunosuppressive medication use after transplantation surgery, the Basel Assessment of Adherence to Immunosuppressive Medication Scale (BAASIS) questionnaire, (recall period

limited to the last 4 weeks) (14), adapted for use in MS. Potential risk factors for poor adherence to be investigated were derived from a theoretical model explaining health behavior (i.e. The Integrative Model of Behavioral Prediction [IMBP]) (15), and empirical evidence on risk factors known to be also potentially associated with adherence. These factors were assessed as a secondary aim by means of validated self-report questionnaires: according to the IMBP, intention and motivation, knowledge and skills, and barriers were the most important drivers of adherence.

Additional PROs that were relevant to explore in the context of adherence to MS treatment were fatigue and depression. Also, cognitive impairment which affects about 50% of the people with RRMS was measured as an exploratory factor.

The observational (single-arm, open-label) design allowed to observe adherence in a real-life setting, on the Belgian Aubagio population. According to protocol amendment 1, the 18-month period of observation was chosen as it is long enough to provide valuable results in terms of adherence and exceeded what was generally proposed in other studies. However, a part of the patients enrolled at a later stage were observed for 12 months maximum. This duration is usually accepted as scientifically grounded and sufficient to maintain qualitative results.

No interventions (such as pill counts or devices) were allowed as per non-interventional design. Therefore, adherence was assessed via interviews and questionnaires on one hand and objectivized via refill data on the other hand (timing of prescription renewal and documentation of the medication delivery on the delivery form).

There were a number of potential limitations associated with this study that should be highlighted. Firstly, this was a single-arm, open-label study, without a comparator group, which limits interpretation. As with any open-label study, a selection bias could exist, with physicians selecting patients for teriflunomide treatment based on indication, disease severity, and previous experience with other DMTs. To avoid this bias as much as possible, participation in the study was proposed to every eligible patient.

With this study, we hoped to provide more insight on the underlying mechanisms of patient adherence in an innovative manner by observing the use of Aubagio in real life, using the most up-to-date tools to evaluate adherence drivers and barriers.

7 STUDY OBJECTIVES

7.1 PRIMARY

To describe adherence in terms of persistence and continuation rate during maximum the first 18 months in patients who take Aubagio in a real-life setting.

7.2 SECONDARY

- To describe adherence in terms of initiation and implementation
- To describe the reasons for treatment discontinuation
- To describe the drivers of adherence
- To assess the evolution of fatigue, depression and cognition in patients taking Aubagio and their impact on adherence

7.3 EXPLORATORY

Description of adherence parameters in terms of SDMT.

8 INVESTIGATIONAL PLAN

8.1 DESCRIPTION OF OVERALL STUDY DESIGN AND PLAN

This was a prospective, open-label, multicenter, single-arm observational registry study.

This observational study included a cohort of adults treated with teriflunomide (Aubagio) under normal conditions of use. The registry observation period lasted until the termination of the treatment or maximum 18 months, whichever came first.

According to protocol amendment 1, patients included until 31st of October 2019 were followed-up for 18 months or treatment termination, whichever came first. Patients included as from the 1st of November 2019 were followed-up for 12 months or treatment termination, whichever came first.

There was no fixed study visit schedule. The visits were done according to the clinical practice. However, Investigators were asked to record data for study endpoint assessments 2 weeks after inclusion, 3, 6, 12 and, if applicable, 18 months after inclusion.

Data were recorded prospectively during the follow-up of the patients for maximum 18 months at 3, 6, 12 and, if applicable, at 18 months. A window of ± 1 month was allowed at these time points. An additional checkpoint for adherence was planned (phone call) 2 weeks (± 3 days) after inclusion. Patients continued medication intake as long as this treatment was considered appropriate for this patient, independently form the registry.

8.2 DISCUSSION OF STUDY DESIGN AND CHOICE OF CONTROL GROUPS

This was an observational study designed according to routine clinical practice. No control group was planned for this study.

8.3 SELECTION OF STUDY POPULATION

Screened patients were defined as any patients who signed the informed consent. Patients were included in the study according to the following criteria.

8.3.1 Inclusion criteria

- Aubagio was prescribed to the patient independently from the decision to include the patient in the registry
- Patient was prescribed Aubagio according to reimbursement criteria in Belgium:
    - Adult patients (>18 years old)
    - Patients suffering from RRMS diagnosed using the most recent version of the McDonald criteria

- Expanded Disability Status Scale (EDSS) score ≤ 6.5

- Patient understood and signed informed consent form
- Patient did not have the first intake of Aubagio at the time of inclusion visit yet

8.3.2 Exclusion criteria

- Patient presenting a contraindication according to the local label.
- Prior treatment with Aubagio
- Participation to an Aubagio Patient Support Program (PSP).

8.3.3 Removal of patients from therapy or assessment

All patients had the right to end their participation in the study at any time without having to give a reason and without this decision affecting the treatment provided by the healthcare professional.

The participation of a patient was stopped immediately whenever the patient expressed the wish to do so. However, the healthcare professional made every effort to perform the End of Study visit. The minimal data that collected to support the study objectives were end of treatment date and reason (if applicable) and reason for end of study.

At any time, if considered necessary, the healthcare professional could end the participation of a patient in the study. However, the healthcare professional made every effort to determine the reason and record it in the patient's file and the end-of-study form of the electronic case report forms (eCRF).

8.3.3.1 Temporary treatment discontinuation with IMP(s)

Not applicable

8.3.3.2 Permanent treatment discontinuation with IMP(s)

Not applicable

8.3.3.3 List of criteria for permanent treatment discontinuation

According to the summary of product characteristics (SmPC), treatment with Aubagio had to be discontinued in any of the following circumstances:

- pregnancy
- liver injury
- severe hematological reactions, including pancytopenia

- ulcerative stomatitis, skin and/or mucosal reactions which raise the suspicion of severe generalized skin reactions (Stevens-Johnson syndrome or toxic epidermal necrolysis [Lyell's syndrome])

According to SmPC of Aubagio, treatment interruption had to be considered in these cases:

- suspected liver disorder (liver enzymes more than 3 times the upper limit of normal)
- severe infection
- pulmonary symptoms, such as persistent cough and dyspnea, which may be indicative of diffuse interstitial lung disease
- confirmed peripheral neuropathy

8.3.3.4 Handling of patients after permanent treatment discontinuation

In the case of patients who did not return to the site, the healthcare professional participating in the study made every effort to contact them and determine their health status, including their vital status, procedure and consequence for patient withdrawal from study

8.4 TREATMENTS

8.4.1 Treatments administered

The prescription of therapies was under the only responsibility of the Investigator. This was an observational study that was carried out according to daily clinical practice.

8.4.2 Identity of investigational medicinal products

The Investigator referred to the SmPC for any information on the treatment prescribed

8.4.3 Method of assigning subjects/patients to treatment groups

8.4.4 Selection of doses in the study

Teriflunomide is a once-daily oral inmunomodulator already approved for the treatment of RMS. In this study, it was administered as a daily dose of 14 mg since it has demonstrated consistent efficacy on relapse rate, MRI markers of disease activity and neurodegeneration as well as a manageable safety and tolerability profile at that dose.

8.4.5 Selection and timing of dose for each patient

According to the SmPC, teriflunomide was administered as once-daily dose of 14 mg in all study patients.

8.4.6 Blinding procedures

Not applicable.

8.4.7 Prior and concomitant therapy

Concomitant therapy could be administered according to the SmPC and at the discretion of the physician.

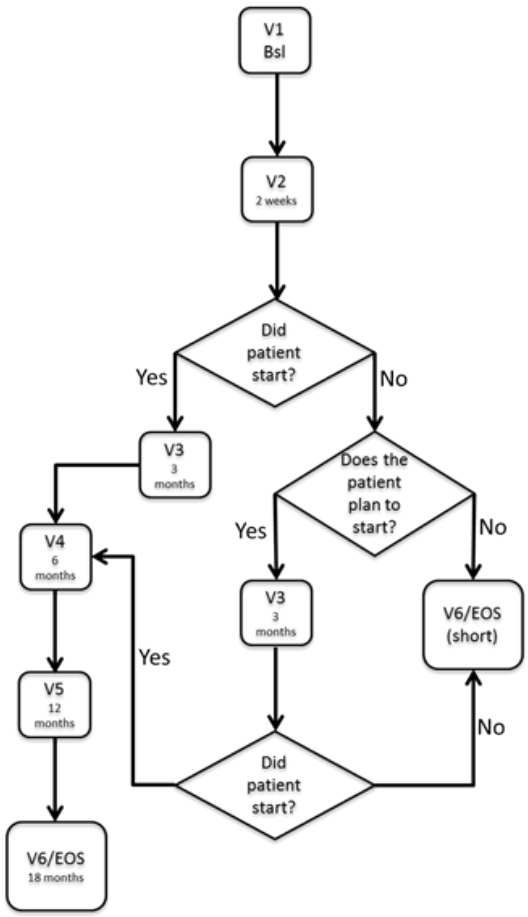
8.4.8 Treatment compliance

Treatment compliance was monitored by the treating physician according to standard clinical practice, besides the specific questionnaires used in the scope of this study, in relation with the study objectives and endpoints related to treatment adherence (administration of a specific questionnaire: the modified BAASIS questionnaire)

8.5 EFFICACY AND SAFETY ASSESSMENTS

The overall study flow and decision tree to move to the next visit was as follows:

Figure 1 – Study Flow Chart



1 - Visit 5 skipped in case patient is enrolled after November 1st, 2019 and replaced by V6 (anticipated at 12 months).
2 - Visit 6 planned at 18 months if patient is enrolled until 31st of October 2019 and anticipated at 12 months in case patient is enrolled as from November 1st, 2019.

Table 1 – Schedule of Assessment

		V1	V2	V3	V4	V5[a]	V6[b,c]
	Data collected per patient	**Baseline**	**Phone call**	**FU Visit**	**FU Visit**	**FU Visit**	**FU Visit/EOS**
			2 weeks	**3 months**	**6 months**	**12 months**	**12 or 18 months[c]**
Subject characteristics	Eligibility	x					
	Written Informed Consent	x					
	Patient demographics including socio-economic data	x					
	MS disease history	x					

	Prior/subsequent disease modifying treatments	x					x
	Relevant medical/surgical history	x					
	Disease status (relapses, EDSS, MRI)	x	x	x	x	x	x
	Concomitant medications	x	x	x	x	x	x
	Safety data	x	x	x	x	x	x
Treatment information	Start of treatment (effective intiation date)		x	x			
	Check for treatment discontinuation		x	x	x	x	x
	Prescription-related information	x		x	x	x	(x)[1]
	Medication delivery form check					x	(x)[1]
	Date and reason for ending study						x
	Questionnaires						
Adherence	BAASIS			x	x	x	(x)[1]
	Knowledge and skills	x		x		x	(x)[1]
	Intention and motivation	x		x		x	(x)[1]
	Health litteracy	x					
	IMAB			x		x	(x)[1]
PROs	PHQ-9 (assessment of depression)	x			x	x	x
	MFIS-5 (assessment of fatigue)	x			x	x	x
	SDMT (assessment of cognition)	x					x

1 - if applicable - see section 11 of the protocol "Data collection"

a - Visit 5 skipped in case patient is enrolled after November 1st, 2019 and replaced by V6 (anticipated at 12 months).
b - End of Study visit to be performed ad hoc if patient did not start or stops early the treatment with Aubagio®.
c - Visit 6 planned at 18 months if patient is enrolled until 31st of October 2019 and anticipated at 12 months in case patient is enrolled as from November 1st, 2019.

8.5.1 Primary endpoint assessments

The **main evaluation variables** of the study were the following:

- Persistence during the first 18 months maximum in patients who took Aubagio in a real-life setting. The persistence was defined as time to the first Aubagio discontinuation. Treatment discontinuation occurred when treatment end date was reported.
- Continuation rate in patients taking Aubagio at maximum 18 months was defined as the proportion of patients who remained on treatment at 12 and 18 months. Continuation rate was derived as:
    - Number of patients who remained on treatment at 12 and 18 months / number of patients who completed the study.

  Remaining on treatment at 12 and 18 months was defined as no end date reported in treatment information module and no answering “Yes” to question 3 of the modified BAASIS questionnaire.

8.5.2 Secondary endpoint assessment assessment

The **secondary evaluation variables** of the study were the following:

- To describe adherence in terms of initiation and implementation:
  - Initiation: Starting treatment from baseline to 3 months visit: Yes/No
  - Implementation: Patients who had a good implementation: Yes/No

  A good implementation was defined as answering "No" to questions 1 and 2 of modified BAASIS questionnaire in all visits while on treatment period. The number of patients taking Aubagio and the number of patients who had the opportunity to be compliant with the prescribed treatment in the duration of the treatment were also calculated.
- To describe the reasons for treatment discontinuation:
  - Proportion of patients discontinuing treatment for the following reasons: Health care professional decision / Patient decision / Joint decision / Other reason
  - Comparison on discontinued patients and non-discontinued patients, the following variables by visit: number of relapses, EDSS score and MRI result.
- To describe the drivers of adherence and their evolution at different time points:
  - Evaluation of intention and motivation via a 2-minute-long self-administered questionnaire by the patient (intention and motivation questionnaire) (see protocol section 7.3.3. and Appendix C).
  - Evaluation of barrier via 5-minute-long self-administered questionnaire to the patient (identifying medication adherence barriers [IMAB] scale) (see protocol section 7.3.3. and Appendix I).
  - Evaluation of knowledge and skills via a 4-minute-long interview of the patient (see protocol section 7.3.3. and Appendix B).
  - Health literacy evaluation at baseline score via a 2-minute-long self-administered questionnaire by the patient (see protocol section 7.3.3. and Appendix D).
- Impact of PROs
  - Fatigue via the MFIS-5 self-administered questionnaire by the patient (see protocol section 7.3.3. and Appendix G).
  - Depression via the Patient Health Questionnaire (PHQ-9) which was a self-administered questionnaire of 9 items (see protocol section 7.3.3. and Appendix F).
  - Symbol digit modality test (SDMT) which was a self-administered and brief test (see protocol section 7.3.3. and Appendix E).

Additionally, as part of the safety assessment, the following **tolerability variables** were also defined:

- Adverse event (AE)
- Serious adverse event (SAE)

- Related to treatment discontinuation adverse event
- Adverse Event of Special Interest (AESI)
- Adverse event leading to death

All adverse events were coded to a preferred term (PT), and associated system organ class (SOC) using the version of the Medical Dictionary for Regulatory Activities (MedDRA) currently in effect at Sanofi at the time of database lock

8.5.2.1 Adverse events

An **AE** 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 **SAE** 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.

All Adverse Events regardless of relationship to Aubagio, spanning from the signature of the informed consent form until the end of the study as defined by the protocol for each patient, were to be recorded immediately (within 24 hours of awareness) for serious AE and AESI, and within 30 days of awareness for non-serious AE on the corresponding page(s) of the paper Case Report Form or eCRF.

AESIs

An adverse event of special interest (serious or non-serious) is one of scientific and medical concern specific to the product or program, for which ongoing monitoring and rapid communication by the Investigator to Sanofi is required. Such adverse events normally require thorough documentation and investigation to characterize them.

In the event of an AESI, Sanofi was to be informed immediately (within 24 hours of awareness) even if it was not fulfilling a seriousness criterion, using the specific AESI form as appropriate.

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

- Pregnancy
  - Pregnancy of a female exposed to Aubagio (as well as pregnancy occurring in a female partner of a male exposed to Aubagio). It qualified as an SAE only if it fulfilled the SAE criteria.
  - In the event of pregnancy, Aubagio should have been discontinued, and it was recommended to undergo the accelerated elimination procedure.
  - Follow-up of the pregnancy was mandatory until the outcome had been determined.
- Symptomatic overdose with Aubagio (accidental or intentional): 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 have been clearly specified in the verbatim and symptoms, if any, entered on separate AE forms.
- Alanine transaminase (ALT) increase, i.e. ALT ≥ 3 upper limits of normal (ULN) (if baseline value for ALT < ULN) or ALT ≥ 2x ALT baseline value (if ALT baseline value ≥ ULN)
- Hepatic disorders (including liver enzymes)
- Gastrointestinal disorders (nausea and diarrhea)
- Pancreatic disorders (including pancreatic enzymes)
- Bone marrow disorders (mainly white blood cell count [WBC] and neutrophil count decreases)
- Infections and infestations
- Hypersensitivity and skin disorders
- Peripheral neuropathy
- Hypertension
- Malignancy
- Cardiac arrhythmia
- Lung disorders (interstitial lung disease [ILD])
- Thromboembolic events

- Hemorrhage
- Convulsions
- Alopecia

8.5.2.2 Laboratory safety parameters

Several lab parameters were assessed as part of the AESIs assessment. These parameters were ALT, liver enzymes, pancreatic enzymes and WBC and neutrophil count.

8.5.2.3 Other safety parameters

Not applicable

8.5.3 Pharmacokinetics assessments and timing

8.5.3.1 Pharmacokinetic measurements and timing

Not applicable

8.5.3.2 Pharmacokinetic variables

Not applicable

8.5.4 Other assessments

Describe the correlation of cognition with the adherence parameters measure by the Symbol Digit Modalities Test (SDMT) (see protocol section 7.3.3 and Appendix E). The adherence parameters in terms of SDMT Total Score were described

- Initiation: The patient started the treatment: Yes / No
- Implementation: Implementation issues: Yes / No.
  - Yes, if some of the question 1, 2 or 3 of BAASIS questionnaire are reported as “Yes”. No, otherwise.
- Persistence: The patient discontinued the treatment: Yes / No

Furthermore, the adherence in terms of persistence was also described.

8.5.5 Appropriateness of measurements

All questionnaires used during the study were validated questionnaires.

8.6 DATA QUALITY ASSURANCE

The electronic data capture (EDC) System included 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) was performed at site level by qualified monitors, according to the Study Manual.

Upon request, written informed consents, completed questionnaires, notes and copies of laboratory and medical records were 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 reviewed written informed consents and recordings in the electronic case report forms (eCRFs) as deemed necessary and appropriate, and the accuracy of the data was verified by reviewing the above referenced documents.

Regular site monitoring ensured the quality of trial conduct. On-site verification of 100% of signed informed consent forms was performed. Data quality control (QC) (site monitoring and/or phone QC) was performed at all active sites (which enrolled at least one patient). A data QC of minimum 10% of patient data was performed at each active site.

If specific issues were identified at a particular site, the percentage of QC in the concerned site was appropriately increased and corrective actions had to be taken. QC (site monitoring and/or phone QC) was performed by qualified designated personnel.

The methodology of QC (site monitoring and/or phone QC) and appropriate consecutive corrective actions was detailed in the study manual.

Sanofi conducted Investigator meetings and training sessions for clinical research associates as well as individual site initiation meetings to develop a common understanding of the clinical study protocol, case report form, and study procedures, in compliance with GCP.

No audits were conducted for this study.

8.7 STATISTICAL CONSIDERATIONS

8.7.1 Determination of sample size

The sample size calculation has been based on the primary objective.

A continuation rate with Aubagio of approximately 65% at 9 years has been observed in clinical trials. No precise data at 1 year were available from clinical trial data.

Treatment discontinuation rates extrapolated from real life data (based on commercial evaluations) were estimated to be between 15-20% at 1 year, meaning 80 to 85% persistence rate at 1 year. In reality, this number had to be smaller, probably ~70%. On that basis and also on the basis of feasibility of the study in Belgium, it was decided to include 120 patients, i.e. patients who signed informed consent. Since this was an observational setting, only descriptive analysis of any number realistically based on possible inclusion could be used.

Confidence interval for proportion using normal approximation (n large) Scenario	1	2	3	4	5
Confidence level, 1-α	0.950	0.950	0.950	0.950	0.950
1 or 2 sided interval?	2	2	2	2	2
Expected proportion, π	0.650	0.700	0.750	0.800	0.850
Distance from proportion to limit, ω	0.085	0.082	0.077	0.072	0.064
n	120	120	120	120	120

When the sample size was 120, a two-sided 95.0% confidence interval for a single proportion using the large sample normal approximation was extend to 8.2% and 7.7% from the observed proportion for an expected proportion of 70% and 75%, respectively.

8.7.2 Analysis populations

Identified populations for this study:

- Included patient population consisting of all patients included in the study (i.e. those who attended the inclusion visit, met all criteria and signed the informed consent).
- Full analysis set (FAS) population: patients part of the included patient populations for whom any follow-up evaluation is available. Any follow-up is defined as any data reported after the baseline visit.
- Primary Analysis Population: patients completing the study (visit at 18 months done or terminating the treatment in the study period).
- Safety population consisted of all patients who received at least one tablet of teriflunomide.

8.7.3 Statistical analyses

The continuous variables were summarized using the following statistics: Number of patients (Number), Mean, Standard deviation (SD), Median, Minimum (Min), Maximum (Max), Quartile 1 (Q1), Quartile 3 (Q3), Number of missing data (Missing).

The categorical variables were summarized using the following statistics: Number of patients (Number), Percentages for each category, Number of missing data (Missing), 95% confidence interval (CI) when specified in the analysis.

Categories were displayed in the same order as stated in this document.

Missing data or unknown responses were not counted in the percentages and were presented in tables as a separate category.

There was imputation for any missing data and the variables were analyzed as recorded in the Database unless otherwise specified in the PROs scoring methods (see statistical analysis plan Section 10.1) or missing data (see statistical analysis plan Section 11.4).

Statistical analyses were performed at the 5% significance level using 2-sided tests or 2-sided CI. Due to the exploratory nature of this study, p-values were provided for descriptive purpose only, and no adjustments for multiple comparisons were performed.

8.7.3.1 Demographics and baseline characteristics

Analysis of patient characteristics (eligibility screening, patient demographics, MS disease history and MS disease status, previous DMTs and relevant medical/surgical history) were summarized according to methods described above in the FAS.

The patient characteristics were also analyzed by the following subgroups and populations:

- Initiation: Yes/No (whether the patient started the treatment or not) in the FAS
- Implementation: Yes/No (whether there are some implementation issues or not) in the Safety population
- Persistence: Yes/No (whether the patient discontinued the treatment or not) in the Safety population

8.7.3.2 Prior or concomitant medications

Prior and concomitant medications were recorded and the number and percentage of patients for each medication by anatomic and therapeutic class were given for the FAS.

8.7.3.3 Extent of investigational medicinal product exposure and compliance

Treatment exposure was not reported for this study. No formal pill count was performed, as the study is observational and this was considered as intervention by Ethics Committees.

Treatment compliance was assessed as adherence in terms of persistence and continuation rate, refill data (prescription renewal documented in the source documents by the investigators and on the medication delivery form completed by pharmacist each renewal of the treatment prescription as well as by modified BAASIS questionnaire administered via 5 minutes interview) and in terms of initiation, implementation and persistence according to the prescription renewal dates and/or the modified BAASIS questionnaire. Drivers and barriers to adherence will be evaluated, as well as disease-related factors, such as fatigue, depression and cognition. More information about the methods used and test/questionnaires performed during the study have been described in Section 8.5.2.

8.7.3.4 Analyses of efficacy/pharmacodynamic endpoints

No efficacy/pharmacodynamic analysis was performed.

8.7.3.5 Analyses of safety data

Main evaluation variable(s)

- The persistence was analyzed as a time-to-event parameter using Kaplan-Meier (KM) survival analysis.

  Time to event was defined as time from the intake of Aubagio to the discontinuation of the treatment.

  A censored patient was a patient that did not reach the event or reached the event but the treatment end date was not reported, or reaching the event was unknown. The censoring time was defined as:

  - End of study date, if the event has not been reached.
  - Last Aubagio day intake (last Aubagio date was calculated as the last date available from all prescription dates, delivery dates and visit dates that the patient answered "No" to the third question of modified BAASIS) if the event was reached, was unknown or the event was reached but the end date was missing.

The KM incidence rates of event (+95% CI) at 3, 6, 12 and 18 months and the Q1, median and Q3 time of the event (+95%CI) were provided. The CIs were calculated using the log-log transformation.

Time to medication discontinuation analysis was performed on the Safety population

Additionally, a KM plot was displayed.

- The continuation rate proportion of the patients who remained on treatment at 12 and 18 months with 95% confidence limits (95% Clopper-Pearson's confidence interval) was obtained in the Primary Analysis Population.

Secondary evaluation variables

Analysis of secondary variables (defined in Section 8.5.2): Variables at all visits were summarized with their corresponding 95% CI. The population used in the analysis was:

- the adherence in terms of initiation was calculated in the FAS and in terms of implementation was calculated in Primary Analysis population.
- the proportion of patients discontinuing treatment was calculated in the FAS and the comparison of discontinued and non-discontinued patients was done in the Safety population.

For MFIS-5 and PHQ-9: mean changes from baseline to the end of study were summarized using least square (LS) Mean, 95% confidence intervals and p-values using a mixed model for repeated measures, which included a 6-month intermediate point from baseline to end of study visit (12/18 months).

For SDMT: mean changes from baseline to the end of study (12/18 month) were summarized using LS Mean, 95% confidence intervals and p-values using a mixed model for repeated measures.

Analyses were performed on the Primary Analysis population.

Tolerability evaluation variables

AEs incidence tables were presented by SOC and PT, sorted by the internationally agreed SOC order and decreasing frequency of PTs within each SOC, the number (n) and percentage (%) of patients experiencing an adverse event. The denominator for computation of percentages was the number of patients from the included population.

The following adverse event summaries were generated:

- Overview of adverse events, summarizing overall number (%) of patients with:
  - Any AE
  - Any SAE
  - Any AE leading to treatment discontinuation
  - Any AESI
  - Any AE leading to death
- All AEs by primary SOC and PT, showing number (%) of patients with at least 1 adverse event sorted by the SOC internationally agreed order and decreasing frequency of PTs within each SOC.
- All SAEs by primary SOC and PT, showing number (%) of patients with at least 1 serious adverse event sorted by the SOC internationally agreed order and decreasing frequency of PTs within each SOC.
- All related to treatment discontinuation AEs by primary SOC and PT, showing number (%) of patients with at least 1 related adverse event sorted by the SOC internationally agreed order and decreasing frequency of PTs within each SOC.
- All AESIs by primary SOC and PT, showing number (%) of patients with at least 1 related adverse event sorted by the SOC internationally agreed order and decreasing frequency of PTs within each SOC.
- All AEs leading to death by primary SOC and PT, showing number (%) of patients with at least 1 adverse event leading to death sorted by the SOC internationally agreed order and decreasing frequency of PTs within each SOC.
- Listing with all deaths.

8.7.3.6 Analyses of pharmacokinetic data

No pharmacokinetic analysis was performed

8.7.3.7 Other analyses

For the description of adherence parameters in terms of SDMT Total Score the correlation between Adherence parameters during study and baseline SDMT total score was studied.

The following adherence parameters were used as different dependent variables: initiation (whether the patient started the treatment or not), implementation (whether there are some implementation issues or not) and persistence (whether the patient discontinued the treatment or not).

A logistic regression model (Adherence parameter ~ baseline SDMT) was adjusted by the following factors/covariates: age, gender (Male / Female), EDSS, fatigue by MFIS-5 and depression by PHQ-9.

If these models did not converge due to small sample size, the univariate model was analyzed (without adjusting by any factor or covariate).

For the description of implementation in terms of persistence, number and percentages were calculated.

8.7.4 Interim analyses

Not applicable

8.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

8.8.1 Changes in the conduct of the study

The following changes were included in protocol amendment 1:

- No study sites were initiated in Luxembourg so this country was removed of the study.
- Primary objective was slightly adapted to allow shorter observation period during the first 18 months maximum in patients who took Aubagio in a real life setting in order to allow flexibility in the observation period for adherence, to allow timely data collection and study termination.

8.8.2 Changes in the planned analyses

8.8.2.1 From the protocol to the statistical analysis plan

No changes from the protocol to the statistical analysis plan were performed.

8.8.2.2 From the statistical analysis plan to database lock

No changes from the statistical analysis plan to database lock were performed.

8.8.2.3 After database lock

No changes have been performed after database lock.

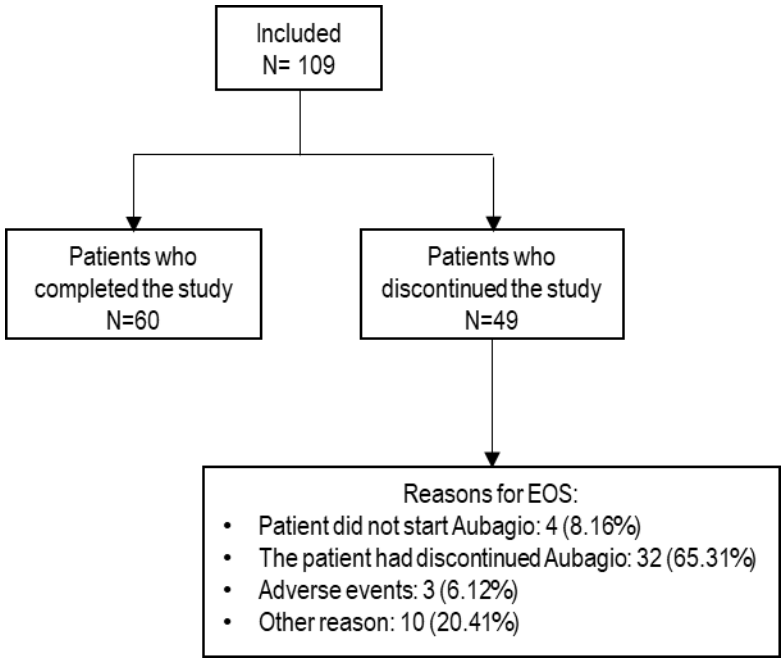
9 STUDY SUBJECTS/PATIENTS

9.1 DISPOSITION OF SUBJECTS/PATIENTS

A total of 109 patients were included in the study. In those patients, 95 (87.16%) completed the study, i.e. had their visit at month 18 done (month 12 for patients falling under protocol amendment) or terminated the treatment in the study period. However, only 60 (55.05%) patients completed the study follow-up period of 18 months (55 [91.67%] patients) or 12 months (5 [8.33%] patients) for patients falling into the protocol amendment). The reasons for ending the study were having discontinued Aubagio (32 [65.31%] patients), not having started Aubagio (4 [8.16%] patients), due to adverse events (3 [6.12%] patients) and due to other reasons (10 [20.41%] patients) (Figure 2).

Furthermore, after ending of study, It was planned that 68 (62.39%) patients continued on treatment with Aubagio (table 2.1.3.2).

Figure 2 – Disposition of Subjects



Tables 2.1.3.1 and 2.1.3.2 provide details of overall patient disposition.

9.1.1 Participating sites

More than a half of participating recruiting sites (8 [53.33%]) were non-university/regional hospitals. In a high percentage of sites (10 [66.67%]) the frequency of follow-up visits performed was every 6 months and in 3 sites (20.00%) this frequency was every 3 months. All participating sites had a team composed by neurologist MS experts, neurologist treating MS patients, rehabilitation physicians and physiotherapists. Furthermore, in 14 out of 15 sites (93.33%) the team was also composed by psychologists and social assistants, 13 sites had in their teams MS nurses, logopedists and ergotherapeuts and in 10 sites there were also dieticians (Table 2.1.1.1).

The mean (SD) average duration of a consultation for a new patient was of 52.33 (18.21) minutes and for a routine visit, this time decreased to 36.00 (11.98) minutes (Table 2.1.1.1).

The adherence (Table 2.1.1.2) was assessed on a routine basis in 14 out of the 15 participating sites (93.33%) although the adherence issue took part of the initial discussion at treatment initiation in the 100% of the participating sites. In all of them an explanation about the importance of adherence was given and in 11 (73.33%) sites, tips to integrate the treatment in patients' daily life were also given.

In routine follow-up visits, the adherence issue was part of the discussion in 14 out of 15 sites (93.33%) and in 12 (80.00%) sites it was discussed when disease breakthrough occurred. However, adherence interventions were offered to patients (for all MS treatments) in only 4 out of all participating sites (26.67%): 3 sites offered internal tools/interventions from the sites and 3 sites offered tools/intervention from pharma companies.

Depending on the MS treatment, adherence interventions were offered in only 2 sites (13.33%) to the patients starting Aubagio, in 13 (86.67%) sites additional contact was planned when a new treatment was started, and in less than a half of participating sites (6 [40.00%]) a specific action plan was followed when non-adherence was suspected.

9.2 PROTOCOL DEVIATIONS

All protocol deviations are presented in Table 2

Table 2 - Any critical or major deviation – Included

	Included (N=109)
Any critical or major protocol deviation	5 (4.59%)
Patients with no Modified BAASIS questionnaire reported	5 (4.59%)

	Included (N=109)

PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\pd_i_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\pd_i_t.rtf (06JUL21 - 20:03)
Source: table 2.1.4.1

9.2.1 Major or critical efficacy/pharmacodynamic deviations relating to the primary efficacy/pharmacodynamic endpoint(s) (title flexible)

Not applicable

9.2.2 Randomization and dosing irregularities

Not applicable.

9.2.3 Other major or critical deviations

Not applicable

9.3 BREAKING OF THE BLIND

Not applicable

9.4 DATA SETS ANALYZED

The 100% of patients enrolled in the study were included in the FAS population, 95 (87.16%) were included in the primary analysis population and 105 (96.33%) patients in the safety population (Table 3).

Table 3 - Analysis populations – Included

	Included (N=109)
Included population	109 (100.00%)
FAS	109 (100.00%)
Primary Analysis Population	95 (87.16%)
Safety population	105 (96.33%)

	Included (N=109)

Included patient consists of all patients included in the study (i.e. those attending the inclusion visit, met all criteria and signed the informed consent).
FAS consists of included patients for whom any follow-up evaluation is available. Any follow-up is defined as any data reported after baseline visit.
Primary Analysis Population consists of patients completing the study (Visit at 18 months done or terminating the treatment in the study period).
Safety population consists of all patients who received at least one tablet of Aubagio
According to protocol amendment 1, patients included until 31 October 2019 will be followed-up for 18 months or treatment termination, whichever comes first. Patients included as from the 1st of November 2019 will be followed-up for 12 months or treatment termination, whichever comes first
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dispo_i_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dispo_i_t.rtf (06JUL21 - 20:03)
Source: table 2.1.3.1

9.5 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

9.5.1 Demography

All demographic characteristics of study population are presented in Table 4. The mean (SD) age of the study population in the FAS was 46.86 (12.21) years. A higher proportion of the patients were women (73.39%). Most patients had upper secondary school completed (30.28%) or higher education (43.12%) but only 43.12% of the study population were employed.

Table 4 – Baseline analysis - Demographics

	FAS (N=109)
Age (years)	
Number	109
Mean (SD)	46.86 (12.21)
Median	47.00
Min ; Max	19 ; 69
Q1 ; Q3	39 ; 56
Missing	0
Gender	
Number	109
Male	29 (26.61%)
Female	80 (73.39%)
Missing	0
Marital status	
Number	109
Married/Legally cohabitant with partner	64 (58.72%)
Unmarried	28 (25.69%)
Divorced	15 (13.76%)
Widow(er)	2 (1.83%)
Missing	0

	FAS (N=109)
Education level	
Number	109
Primary school not completed	0 (0.00%)
Primary school completed	8 (7.34%)
Lower secondary school completed	21 (19.27%)
Upper secondary school completed	33 (30.28%)
Higher Education	47 (43.12%)
Vocational training completed*	11 (23.40%)
Bachelor completed*	25 (53.19%)
Master (and up) completed*	11 (23.40%)
Missing	0
Employment status	
Number	109
Employed	47 (43.12%)
Unemployed	12 (11.01%)
Retired	10 (9.17%)
Housewife/houseman	4 (3.67%)
Student	5 (4.59%)
Disability benefits	20 (18.35%)
Temporary disability	11 (10.09%)
Missing	0

*Percentages calculated over the number of patients that have higher education
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_f_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_f_t.rtf (06JUL21 - 20:03)
Source: table 2.1.5.1

9.5.1.1 Demographics by subgroups

Patients who started the treatment

A total of 105 patients started treatment. The mean (SD) age of these patients was 47.01 (12.39) years (Median [Q1; Q3] was 48.00 [39; 57] years). Almost 3 quarter of the patients were women (77 [73.33%]). More than a half of patients were married/legally cohabitant with partner (61 [58.10%]), 46 (43.81%) patients had higher education and 47 (44.76%) patients were employed (Table 5).

Patients who did not start the treatment

Only 4 patients did not start treatment. The mean (SD) age of those patients was 43.00 (4.24) years (Median [Q1; Q3] was 43.50 [40; 47] years). 3 out of 4 patients were women (75.00%), the same percentage of patients were married/legally cohabitant with partner, regarding the education level, only 1 patient (25%) had higher education (bachelor completed), 1 patient (25%) had upper secondary school completed and 2 patients (50%) had lower secondary school completed. Finally, all 4 patients were receiving disability benefits (Table 5).

Table 5 - Demographics for patients who started and did not started the treatment

	Patients who started treatment FAS (N=105)	Patients who did not started treatment FAS (N=4)
Age (years)		
Number	105	4
Mean (SD)	47.01 (12.39)	43.00 (4.24)
Median	48.00	43.50
Min ; Max	19 ; 69	38 ; 47
Q1 ; Q3	39 ; 57	40 ; 47
Missing	0	0
Gender		
Number	105	4
Male	28 (26.67%)	1 (25.00%)
Female	77 (73.33%)	3 (75.00%)
Missing	0	0
Marital status		
Number	105	4
Married/Legally cohabitant with partner	61 (58.10%)	3 (75.00%)
Unmarried	27 (25.71%)	1 (25.00%)
Divorced	15 (14.29%)	0 (0.00%)
Widow(er)	2 (1.90%)	0 (0.00%)
Missing	0	0
Education level		
Number	105	4
Primary school not completed	0 (0.00%)	0 (0.00%)
Primary school completed	8 (7.62%)	0 (0.00%)
Lower secondary school completed	19 (18.10%)	2 (50.00%)
Upper secondary school completed	32 (30.48%)	1 (25.00%)
Higher Education	46 (43.81%)	1 (25.00%)
Vocational training completed*	11 (23.91%)	0 (0.00%)
Bachelor completed*	24 (52.17%)	1 (100.00%)
Master (and up) completed*	11 (23.91%)	0 (0.00%)
Missing	0	0
Employment status		
Number	105	4
Employed	47 (44.76%)	0 (0.00%)
Unemployed	12 (11.43%)	0 (0.00%)
Retired	10 (9.52%)	0 (0.00%)
Housewife/houseman	4 (3.81%)	0 (0.00%)
Student	5 (4.76%)	0 (0.00%)
Disability benefits	16 (15.24%)	4 (100.00%)
Temporary disability	11 (10.48%)	0 (0.00%)
Missing	0	0

	Patients who started treatment FAS (N=105)	Patients who did not started treatment FAS (N=4)

*Percentages calculated over the number of patients that have higher education
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_ini_y_f_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_ini_y_f_t.rtf (06JUL21 - 20:03)
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_ini_n_f_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_ini_n_f_t.rtf (06JUL21 - 20:03)
Source: tables 2.2.1.1 and 2.2.1.2

Patients who had implementation issues

There were 50 patients who reported implementation issues. The mean (SD) age of these patients was 42.52 (11.57) (Median [Q1; Q3] was 44.50 [35; 51]) years. In this subgroup, there were 31 (62.00%) women, 25 (50%) patients were married/legally cohabitant with partner, 24 (48.00%) patients had higher education, 17 (34.00%) had upper secondary school completed and more than a half of the patients (28 [56%]) were employed (Table 6).

Patients who did not have implementation issues

Overall, 49 patients did not report implementation issues with a mean (SD) age of 50.80 (12.24) years (Median [Q1; Q3] age was 51 [41; 61] years), a total of 40 (81.63%) patients were women, 33 (67.35%) patients were married/legally cohabitant with partner, 20 (40.82%) patients had higher education while an equal percentage of patients had lower and upper secondary school completed (12 [24.49%] patients each), 17 (34.69%) patients were employed and 9 (18.37%) had disability benefits (Table 6).

Table 6 – Demographics for patients who had and did not have implementation issues

	Patients who had implementation issues	Patients who did not have implementation issues
	Safety (N=50)	Safety (N=49)
Age (years)		
Number	50	49
Mean (SD)	42.52 (11.57)	50.80 (12.24)
Median	44.50	51.00
Min ; Max	19 ; 62	26 ; 69
Q1 ; Q3	35 ; 51	41 ; 61
Missing	0	0
Gender		
Number	50	49
Male	19 (38.00%)	9 (18.37%)
Female	31 (62.00%)	40 (81.63%)
Missing	0	0
Marital status		

	Patients who had implementation issues	Patients who did not have implementation issues
	Safety (N=50)	Safety (N=49)
Number	50	49
Married/Legally cohabitant with partner	25 (50.00%)	33 (67.35%)
Unmarried	19 (38.00%)	6 (12.24%)
Divorced	5 (10.00%)	9 (18.37%)
Widow(er)	1 (2.00%)	1 (2.04%)
Missing	0	0
Education level		
Number	50	49
Primary school not completed	0 (0.00%)	0 (0.00%)
Primary school completed	3 (6.00%)	5 (10.20%)
Lower secondary school completed	6 (12.00%)	12 (24.49%)
Upper secondary school completed	17 (34.00%)	12 (24.49%)
Higher Education	24 (48.00%)	20 (40.82%)
Vocational training completed*	4 (16.67%)	6 (30.00%)
Bachelor completed*	15 (62.50%)	8 (40.00%)
Master (and up) completed*	5 (20.83%)	6 (30.00%)
Missing	0	0
Employment status		
Number	50	49
Employed	28 (56.00%)	17 (34.69%)
Unemployed	5 (10.00%)	7 (14.29%)
Retired	2 (4.00%)	8 (16.33%)
Housewife/houseman	2 (4.00%)	2 (4.08%)
Student	5 (10.00%)	0 (0.00%)
Disability benefits	4 (8.00%)	9 (18.37%)
Temporary disability	4 (8.00%)	6 (12.24%)
Missing	0	0

*Percentages calculated over the number of patients that have higher education
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_imp_y_s_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_imp_y_s_t.rtf (06JUL21 - 20:47)
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_imp_n_s_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_imp_n_s_t.rtf (06JUL21 - 20:03)
Source: tables 2.2.1.3 and 2.2.1.4

Patients who discontinued treatment

There were 35 patients who discontinued treatment with a mean (SD) age of 45.29 (12.79) (Median [Q1; Q3] of 43.00 [35; 57]) years; 26 (74.29%) patients were women, a high percentage were married/legally cohabitant with partner (25 [71.43%]), 18 (51.43%) and 12 (34.29%) had higher education and upper secondary school completed respectively, and finally, almost half of the patients (16 [45.71%]) were employed while an equal percentage of patients had disability benefits or were temporary disability (7 [20.00%] each) (Table 7).

Patients who did not have discontinued treatment

The number of patients who did not discontinue treatment was 70. The mean (SD) age of these patients was 47.87 (12.19) years (Median [Q1; Q3] age was 48.50 [40; 57] years); 51 (72.86%)

patients were women; more than a half of patients were married/legally cohabitant with partner (36 [51.43%]); there were 28 (40.00%) patients who had higher education, 20 (28.57%) had upper secondary school completed and 15 (21.43%) had lower education school completed. Finally, in this subgroup of patients, less than a half of patients were employed (31 [44.29%]) and 9 (12.86%) had disability benefits (Table 7).

Table 7 – Demographics for patients who had and did not have discontinued treatment

	Patients who had discontinued treatment Safety (N=35)	Patients who did not have discontinued treatment Safety (N=70)
Age (years)		
Number	35	70
Mean (SD)	45.29 (12.79)	47.87 (12.19)
Median	43.00	48.50
Min ; Max	24 ; 69	19 ; 69
Q1 ; Q3	35 ; 57	40 ; 57
Missing	0	0
Gender		
Number	35	70
Male	9 (25.71%)	19 (27.14%)
Female	26 (74.29%)	51 (72.86%)
Missing	0	0
Marital status		
Number	35	70
Married/Legally cohabitant with partner	25 (71.43%)	36 (51.43%)
Unmarried	6 (17.14%)	21 (30.00%)
Divorced	3 (8.57%)	12 (17.14%)
Widow(er)	1 (2.86%)	1 (1.43%)
Missing	0	0
Education level		
Number	35	70
Primary school not completed	0 (0.00%)	0 (0.00%)
Primary school completed	1 (2.86%)	7 (10.00%)
Lower secondary school completed	4 (11.43%)	15 (21.43%)
Upper secondary school completed	12 (34.29%)	20 (28.57%)
Higher Education	18 (51.43%)	28 (40.00%)
Vocational training completed*	2 (11.11%)	9 (32.14%)
Bachelor completed*	12 (66.67%)	12 (42.86%)
Master (and up) completed*	4 (22.22%)	7 (25.00%)
Missing	0	0
Employment status		
Number	35	70
Employed	16 (45.71%)	31 (44.29%)
Unemployed	2 (5.71%)	10 (14.29%)

	Patients who had discontinued treatment Safety (N=35)	Patients who did not have discontinued treatment Safety (N=70)
Retired	3 (8.57%)	7 (10.00%)
Housewife/houseman	0 (0.00%)	4 (5.71%)
Student	0 (0.00%)	5 (7.14%)
Disability benefits	7 (20.00%)	9 (12.86%)
Temporary disability	7 (20.00%)	4 (5.71%)
Missing	0	0

*Percentages calculated over the number of patients that have higher education
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_per_y_s_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_per_y_s_t.rtf (06JUL21 - 20:03)
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\dem_dem_per_n_s_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\dem_dem_per_n_s_t.rtf (06JUL21 - 20:03)
Source: tables 2.2.1.5 and 2.2.1.6

9.5.2 Medical history

The information reported about patients' medical history (Table 2.1.5.4) showed that 16 (14.68%) patients in the FAS presented history of depression, hypertension was reported in 15 (13.76%) patients, hypercholesterolaemia in 10 (9.17%) patients, hypothyroidism and insomnia were each presented in 8 (7.34%) patients, fatigue in 7 (6.42%), migraine in 5 (4.59%) patients and vitamin D deficiency, depressed mood, anxiety, visual impairment, asthma and appendicectomy were each reported in 4 (3.57%) patients. Other disorders were reported in medical history in less than 3% of patients.

9.5.3 Disease characteristics at baseline

The study population in the FAS had a mean (SD) number of relapses in the 2 years prior to enrolment of 0.79 (0.87) (Median [Min;Max] of 1.00 [0;5]). The mean (SD) EDSS score was 2.22 (1.32), with MRI results showing disease activity in more than a half of the patients (49 [58.33%] patients). The patients with disease activity presented a mean (SD) of 5.21 (5.74) new T2 lesions. It was registered that a mean (SD) of 10.09 (10.64) years passed since first symptoms while the time since first diagnosis was a mean (SD) of 7.94 (9.34) years before the study. In the past 2 years, 63 (57.80%) patients were treated with a DMT while 46 (42.20%) patients were DMT naïve. Finally, in 63 (63.00%) patients, the last relapse was registered at least 3 months ago and 38 (60.32%) patients switched from DMT at least once in the past 2 years due to safety reasons (Table 2.1.5.2).

A total of 70 (64.22%) patients had been on a previous DMT and the treatments most reported were Avonex (29 [26.61%] patients), Copaxone (27 [24.77%] patients), Tecdifera (19 [17.43%] patients), Rebif (14 [12.84%] patients) Betaferon (7 [6.42%] patients) and Plegridy (6 [5.50%] patients). Other previous DMT was reported by less than 5% of patients (Table 2.1.5.3).

9.5.4 Other baseline characteristics

Not applicable.

9.5.5 Prior and/or concomitant medication

Overall, 84 (77.06%) patients in the FAS reported prior medication. It is interesting to highlight that, 20 (18.35%) patients were previously treated with benzodiazepine derivatives and 16 (14.68%) were previously treated with other antidepressants. By therapeutic class, there were 30 (27.52%) patients previously treated with colecalciferol, 11 (10.09%) patients with pantoprazole sodium sesquihydrate, 9 (8.26%) with pregabalin, 8 (7.34%) patients with levothyroxine, 7 (6.42%) patients with paracetamol, 6 (5.50%) patients with acetylsalicylic acid, 5 (4.59%) with escitalopram oxalate and 4 (3.67%) patients each with alprazolam, clonazepam, lorazepam, mirtazapine, trazodone, rosuvastatin calcium, bisoprolol, metformin hydrochloride, baclofen and folic acid. Other treatments were reported in less than 3% of the study population (Table 2.1.5.5).

Furthermore, 94 (86.24%) patients reported any concomitant medication, specifically, 20 (20.18%) patients were concomitantly treated with benzodiazepine derivates and 19 (17.43%) were concomitantly treated with other antidepressants. By therapeutic class, it was reported that colecalciferol was concomitantly administered in 44 (40.37% patients), pantoprazole sodium sesquihydrate and paracetamol each in 17 (15.60%) patients, pregabalin in 13 (11.93%) patients, levothyroxine, methylprednisolone sodium succinate and acetylsalicylic acid each in 8 (7.34%) patients, bisoprolol and folic acid each in 7 (6.42%) patients, clonazepam, escitalopram oxalate and carbamazepine each in 6 (5.50%) patients, gabapentin, mirtazapine, trazodone, escitalopram, rosuvastatin calcium, tramadol, metformin hydrochloride, ibuprofen, solifenacin succinate, baclofen, amoxicillin trihydrate/clavulanate potassium and amitriptyline hydrochloride each in 5 (4.59%) patients and alprazolam, lorazepam, trazadone hydrochloride, venlafaxine, sertraline and zolpidem each in 4 (3.67%) patients. Other concomitant medications were administered in less than 3% of the study population (Table 2.1.5.6).

9.6 MEASUREMENT OF TREATMENT COMPLIANCE

Treatment compliance was not measured for this study by pill count since it was considered by the Ethics Committee as an intervention that was not allowed in this observational and non-interventional study.

However, this study aimed to evaluate all aspects of adherence to treatment: initiation, implementation, persistence and continuation rate. The modified BAASIS questionnaire provided most of the data and was complemented by refill data according to the prescription renewal dates. The results of all these analyses are presented and discussed in Section 11.

10 PRIMARY ENDPOINT EVALUATION

10.1 PRIMARY ENDPOINT(S)

10.1.1 Primary analysis

Assessment of adherence in terms of persistence and continuation rate

It was reported a total of 35 events (discontinuation of the treatment) and 68 censored (where the event was not observed) patients. The median (95% CI) time from the intake of Aubagio to the event (to the discontinuation of the treatment) was NR (not reached) (19.15;NR) since there were not enough events reported to reach the median value for "time to event" neither the Q3. The cumulative incidence (95% CI) at 12 and 18 months were 0.28 (0.21; 0.38) and 0.34 (0.26; 0.44), respectively (Table 8, Figure 3).

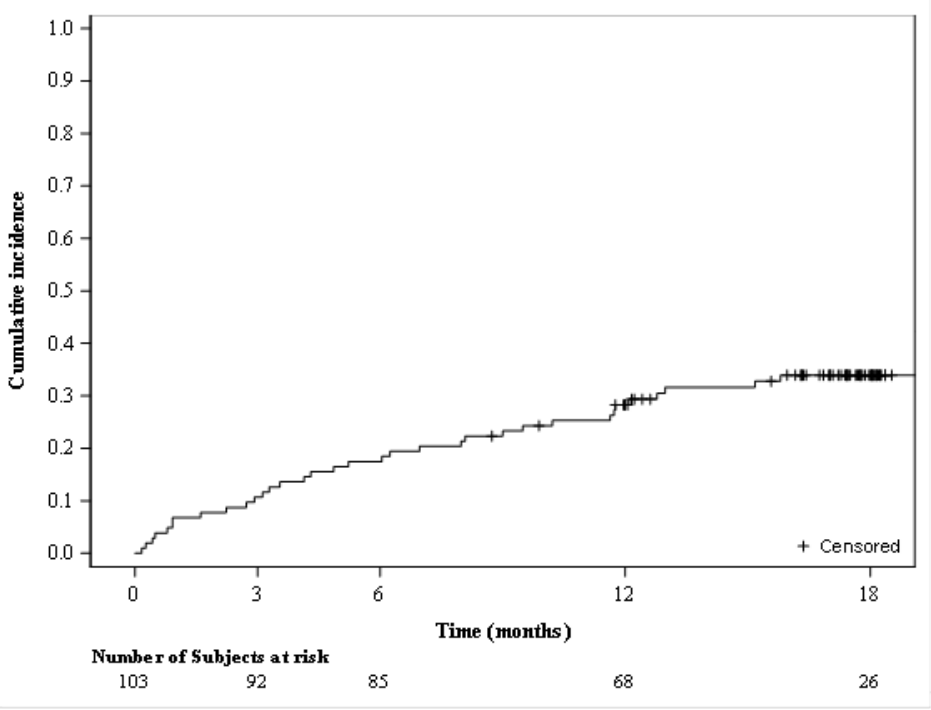
The continuation rate proportion (95% CI) on the patients who remained on treatment at 12 and 18 months was 5/10 (50.00%) (18.71; 81.29) for the patients falling under protocol amendment with shorter follow-up period and 55/85 (64.71%) (53.59; 74.77) for the patients followed-up 18 months, respectively (Table 2.1.6.3).

Table 8 - Persistence – Safety population

	Safety (N=105)
Persistence (time from the intake of Aubagio to the discontinuation of the treatment)	
Number of patients assessed	103
Number of events	35
Number of censored	68
Time to event in months[a]	
Q1 (95% CI)	10.22 (4.86; 15.80)
Median (95% CI)	NR (19.15; NR)
Q3 (95% CI)	NR (NR; NR)
Cumulative incidence (95% CI)at 3 months (95%CI)[a]	0.11 (0.06; 0.18)
Cumulative incidence (95% CI)at 6 months (95%CI)[a]	0.17 (0.11; 0.26)
Cumulative incidence (95% CI)at 12 months (95%CI)[a]	0.28 (0.21; 0.38)
Cumulative incidence (95% CI)at 18 months (95%CI)[a]	0.34 (0.26; 0.44)

[a] Kaplan-Meier method
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\prim_per_f_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\prim_per_f_t.rtf (06JUL21 - 20:03)
Source: table 2.1.6.1

Figure 3 - Kaplan Meier plot for Persistence – Safety population



PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\prim_km_f_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\prim_km_f_t.rtf (06JUL21 - 20:03)
Source: figure 2.1.6.2

10.2 PRIMARY ANALYSIS CONCLUSIONS

In the analysis of treatment adherence in terms of persistence, the median of the time from the intake of Aubagio to the discontinuation of the treatment was not reached since an insufficient number of events were reported to get this value. However, the cumulative incidences (95% CI) at 12 and 18 months were 0.28 (0.21; 0.38) and 0.34 (0.26; 0.44), respectively. The continuation rate proportion among the patients who remained on treatment at 12 for the patients falling under protocol amendment with shorter follow-up period and 18 months for the patients who could benefit from a complete follow-up was 50.00% and 64.71%, respectively.

11 SECONDARY EVALUATION

Secondary evaluation variable

Assessment of adherence in terms of initiation and implementation

A total of 103 (96.26%) patients in the FAS were on treatment from baseline to the 3 months visit (Table 2.1.7.1), meaning that 4 patients (3.74%) out of the 107 patients evaluated did never initiate (start) treatment.

The adherence in terms of implementation calculated on the primary analysis population showed that 42 out of these 95 patients (51.85%) had good implementation on the total observation period, i.e. did not report implementation issue in the BAASIS questionnaire. Furthermore, there were 34 (35.79%) patients of this population for whom enough supply in medication were reported as prescribed or delivered in the source documents and in the CRF. Those patients had the opportunity to be compliant with the prescribed treatment in the duration of the treatment according to available documentation (Table 2.1.7.2).

Description of reasons for treatment discontinuation

In the FAS (n=109), 35 patients discontinued treatment. Of these 35 patients, 16 (45.71%) discontinued treatment due to health care professional decision, 13 (37.14%) due to patient decision, 5 (14.29%) patients discontinued due to joint decision and 1 (2.86%) patient discontinued due to other unspecified reasons. (Table 2.1.7.3).

Description of drivers of adherence related to efficacy parameters and MS-related condition

At baseline, the mean (SD) EDSS score among those discontinued patients was 2.04 (1.36) which was very similar to the result obtained among those non-discontinued patients (2.29 [1.35]). However, this difference among both groups decreased in the EDSS scores obtained at Visit 6 (2.66 [1.46] among those discontinued patients and 2.64 [1.55] among those non-discontinued patients). A higher difference between both patient groups was seen in the MRI results obtained at baseline, where 15/28 (53.57%) discontinued patients had disease activity while in the group of non-discontinued patients 32/53 (60.38%) showed disease activity. However, these percentages changed in the MRI result obtained at Visit 6, where 6 out of 11 (54.55%) discontinued patients had disease activity compared to 7 out of 30 (23.33%) non-discontinued patients who presented disease activity. Finally, the percentage of patients who experimented a relapse was noticeably higher in the group of discontinued patients compared to the non-discontinued patients throughout the study visits (Table 2.1.7.4).

The drivers of adherence described by mean of the MFIS-5 score using a mixed-effects model for repeated measures (MMRM) showed that in this questionnaire, the mean (SD) score obtained among the primary analysis population was 9.81 (4.64) (Median [Q1;Q3] of 10.00 [7;13]) and the

least square (LS) mean (standard error [SE]) change in the MFSI-5 score at the end of study visit was -1.43 (0.43) (Table 2.1.7.5).

Likewise, the driver of adherence described by the PHQ-9 using MMRM in patients in the primary analysis population showed a mean (SD) score of 8.35 (5.66) (Median [Q1;Q3 of 8.00 [4;12]) and the LS mean (SE) change at the end of study visit was -1.95 (0.46) (Table 2.1.7.6).

Finally, the driver of adherence described by SDMT using MMRM in patients in the primary analysis population showed a mean (SD) score in this questionnaire of 47.11 (14.96) (Median [Q1;Q3 of 48.00 [40;56]) and the LS mean (SE) change at the end of study visit was 0.50 (0.99) (Table 2.1.7.7).

Questionnaires used to evaluate risk factors impacting treatment adherence

- Knowledge and skills evaluation

At baseline, the mean (SD) knowledge and skills evaluation score was 4.80 (0.54) and 103 out of 109 patients of the FAS population (97.17%) had good knowledge. The mean (SD) change from baseline to visit 6 was 0.14 (0.53) (Table 2.1.10.1).

The knowledge and skills evaluation at baseline of those patients who started treatment showed a mean (SD) score of 4.81 (0.54) and of 4.50 (0.58) among those patients who did not start treatment. This was translated into 97.06% and 100.00% of patients with a good knowledge at baseline according to this questionnaire. At visit 6, the mean (SD) score obtained in this questionnaire slightly increased compared to baseline (0.14 [0.53]) and the percentage of patients with good knowledge was also higher (98.88%). There were not results at visit 6 in the group of patients who did not start treatment (Tables 2.2.10.1.1 and 2.2.10.1.2).

In the group of patients with implementation issues, the mean (SD) score obtained at baseline in this questionnaire was 4.69 (0.71) and 93.88% of patients reported having a good knowledge which was very similar to the results obtained in the group of patients without implementation issues (4.92 [0.28] and 100.00% of patients with good knowledge according to this questionnaire). At visit 6, the mean (SD) score obtained on those patients with implementation issues, slightly increased by 0.20 [0.65] points as did the percentage of patients who reported having good knowledge (97.87%). The results at visit 6 in the group of patients without implementation issues did not change compared to baseline (Tables 2.2.10.1.3 and 2.2.10.1.4).

Finally, the knowledge and skills evaluation regarding the treatment discontinuation showed that the mean (SD) score obtained at baseline among those patients who discontinued treatment was 4.91 (0.29) and 100.00% of patients had good knowledge according to this questionnaire. The results obtained among those patients who did not discontinue treatment were quite similar (mean [SD] score was 4.77 [0.62]) and 66 out of 70 patients [95.65%] had good knowledge). At visit 6, in both groups, the mean (SD) score was very similar to baseline, and so was the percentage of patients with good knowledge (Tables 2.2.10.1.5 and 2.2.10.1.6).

- Intention and motivation evaluation

Regarding the intention and motivation evaluation, the mean (SD) score at baseline was 6.85 (0.37) and all the patients reported to be “more motivated”. It was observed that at visit 6, the mean score obtained was very similar to baseline (mean [SD] change from baseline to visit 6 was -0.09 [1.00]) (Table 2.1.10.2).

The results of this questionnaire at baseline in the group of patients who started the treatment showed a mean (SD) score of 6.85 (0.38) and all the patients were more motivated. The results were very similar among those patients who did not start treatment showing a mean (SD) score at baseline of 6.83 (0.33) and the percentage of patients who were more motivated was also a 100.00%. At visit 6, the results obtained among those patients who started treatment were very similar to the results at baseline which means that these patients did not change their intention and motivation in taking their medication during the study. At visit 6, there were no results in the group of patients who did not start treatment (Tables 2.2.10.2.1 and 2.2.10.2.2).

Regarding the implementation issues, the mean (SD) score obtained at baseline in the intention and motivation questionnaire in the group of patients who had implementation issues was 6.78 (0.46) and 100.00% of patients (n=50) were more motivated according to this questionnaire. In the group of patients without implementation issues, these results were quite similar (mean [SD] was 6.91 [0.27] and all patients were more motivated). At visit 6, the mean (SD) scores were quite similar to baseline in both groups, meaning that, regardless of implementation issues, the intention and motivation did not change at visit 6 (Tables 2.2.10.2.3 and 2.2.10.2.4).

Finally, the mean (SD) score obtained at baseline in the subgroup of patients who discontinued and did not discontinue treatment was 6.92 (0.22) and 6.82 (0.43), respectively and 100.00% of patients were more motivated in both groups. At visit 6, the mean (SD) score decreased 0.57 (1.81) points among those patients who discontinued treatment and the percentage of patients who were more motivated decreased to 90.48%, while the score was quite similar, even slightly higher (0.06 [0.46]), in the group of patients who did not discontinue treatment. In this case, it was seen that the score in the intention and motivation questionnaire worsened for patients who discontinued treatment at visit 6 (Tables 2.2.10.2.5 and 2.2.10.2.6).

- Health literacy evaluation

The mean (SD) health literacy evaluation score at baseline was 4.09 (0.95) and only 8 patients from the FAS population (7.41%) were inadequately health literate (Table 2.1.10.3).

The mean (SD) score obtained at baseline in the patients who started treatment was 4.12 (0.95) and almost all patients (93.27%) were health literate according to this questionnaire. The mean (SD) score obtained among the patients who did not start treatment was lower (3.50 [1.00]) so the percentage of patients considered to be health literate was lower (75.00%) (Tables 2.2.10.3.1 and 2.2.10.3.2).

Patients who reported implementation problems had a mean (SD) score at baseline of 4.28 (0.86) and a high percentage of patients were considered health literate (98.00%) according to this questionnaire. The mean (SD) score obtained at baseline among those patients without implementation issues was 3.96 (1.00) and 89.80% of these patients were considered health literate (Tables 2.2.10.3.3 and 2.2.10.3.4).

Finally, patients who discontinued treatment had a mean (SD) score at baseline of 4.26 (0.71) and 97.06% patients were health literate according to this questionnaire, and a similar result was obtained among patients who did not discontinue treatment (mean [SD] score of 4.04 [1.04] and 91.43% considered health literate) (Tables 2.2.10.3.5 and 2.2.10.3.6).

- SDMT

The mean (SD) SDMT score in the FAS at baseline was 47.44 (15.21) and at visit 6, this mean (SD) score increased only by a mean (SD) of 0.59 (9.26) points, with a similar percentage of patients who had cognitive improvement (20 [24.39%]) and cognitive impairment (17 [20.73%]) at this visit, while more than a half of patients (45 [54.88%]) had no changes in the SDMT score from baseline (Table 2.1.10.4).

The mean (SD) SDMT score obtained at baseline in the subgroup of patients who started treatment was 47.38 (15.38) and at visit 6 it was 48.93 (13.77). Cognitive improvement was observed in 25.00% of patients, no change in 55.00% and cognitive impairment in 20.00%. In the case of patients who did not start treatment, no cognitive improvement was seen at visit 6 compared to baseline while 50.00% of patients showed cognitive impairment (mean [SD] score at baseline was 48.75 [11.32] and 47.50 [19.09] at visit 6). However, this is based on data from 2 patients only. (Tables 2.2.10.4.1 and 2.2.10.4.2).

In the subgroup of patients who had implementation issues, the mean (SD) SDMT score was 50.54 (15.44) at baseline and 53.45 (11.67) at visit 6. This change at visit 6 compared to baseline was translated into a cognitive improvement in 27.50% of patients, no change in 57.50% while 15.00% of patients had a cognitive impairment. It is noticeable that, among the group of patients who did not have implementation issues, the mean (SD) SDMT score did not show such a change at visit 6 compared to baseline (44.65 [15.01] at baseline versus 44.10 [14.41] at visit 6) and that the percentage of patients with cognitive impairment was higher than in the group of patients who had implementation problems (23.08% of patients with cognitive improvement, 51.28% without changes and 25.64% had cognitive impairment) (Tables 2.2.10.4.3 and 2.2.10.4.4).

The mean (SD) score obtained at baseline among patients who discontinued treatment was 49.35 (13.20) which increased to 52.65 (10.51) at visit 6. Cognitive improvement was seen in 30.00% of patients, no change in 45.00% and 25.00% had cognitive impairment. Among those patients who did not discontinue treatment, the mean (SD) SDMT score did not change so much from baseline to visit 6 (46.43 [16.34] and 47.68 [14.56]) and a lower percentage presented cognitive improvement (23.33%), while 58.33% of patients had no change and 18.33% had cognitive impairment (Tables 2.2.10.4.5 and 2.2.10.4.6).

- PHQ-9

The PHQ-9 mean (SD) score at baseline obtained from 108 patients out of 109 of the FAS population was 8.90 (6.12) and 71 (65.74%) patients had a moderate to severe depression. At visit 6, the mean (SD) score decreased by 1.88 (5.11) points compared to the score obtained at baseline and 54.44% patients had moderate to severe depression (Table 2.1.10.5).

Mean (SD) score at baseline in the subgroup of patients who started treatment was 8.62 (5.88) and 67 out of 104 patients (64.42%) had moderate to severe depression. At visit 6, the mean (SD) score decreased to 6.69 (5.11) and the percentage of patients with moderate to severe depression decreased by more than 10 percent up to 53.93% (48 out of 89 patients). Comparing these results with those obtained in the group of patients who did not start treatment is difficult as in this group there were results from only one patient at visit 6 (Tables 2.2.10.5.1 and 2.2.10.5.2).

Among those patients who had implementation issues, the mean (SD) PHQ-9 score at baseline was 8.86 (5.60) and 33 out of 50 patients (66.00%) had moderate to severe depression. At visit 6, the mean (SD) score decreased to 6.91 (5.68) and the percentage of patients with moderate to severe depression also decreased to 50.00% (22 out of 44 patients). Among those patients who did not report implementation issues, the mean (SD) score at baseline was 8.59 (6.16) and 32 out of 49 patients (65.31%) had moderate to severe depression. And in this group of patients, the differences at visit 6 in the mean score was similar to that observed in the group of patients with implementation issues (mean [SD] score obtained at visit 6 was 6.55 [4.55]) while the percentage of patients with moderate to severe depression was higher (59.09%) (Tables 2.2.10.5.3 and 2.2.10.5.4).

And finally, the mean (SD) score in the PHQ-9 at baseline in patients who discontinued treatment was 8.50 (5.73) and 23 out of 34 patients (67.65%) had moderate to severe depression; at visit 6, the mean (SD) score decreased to 7.48 (5.21) as did the percentage of patients with moderate to severe depression (13 out of 23 patients [56.52%]). Compared to that, patients who did not discontinue treatment had a similar mean (SD) score at baseline at (8.67 [5.99]). The score obtained at visit 6 in this group was lower (6.41 [5.08]), while the percentage of patients with moderate and severe depression at baseline and at visit 6 was similar to that in patients who discontinued treatment (62.86% and 53.03%) (Tables 2.2.10.5.5 and 2.2.10.5.6).

- MFIS-5

The assessment of the MFIS-5 showed a mean (SD) score at baseline of 9.88 (4.76) and at this time point, 88 patients of the FAS population (81.48%) had feelings of fatigue according to this questionnaire. However, the mean (SD) score, decreased by 1.32 (4.23) points at visit 6 and 62 out of 91 patients (68.13%) had feelings of fatigue (Table 2.1.10.6).

In the subgroup of patients who started treatment, the mean (SD) score obtained at baseline was 9.47 (4.71) and a higher percentage of patients, 80.77% (84 out of 104) had fatigue according to this questionnaire; at visit 6, the mean (SD) score decreased to 8.26 (4.92) and the percentage of patients with fatigue decreased up to 67.78% (61 out of 90 patients). In comparison, the subgroup

of patients who did not start treatment, the mean (SD) score at baseline was much higher (13.50 [5.07]) with 100.00% of patients (n=4) reporting fatigue. As only one patient had results at visit 6 it is difficult to interpret the results from that visit (Tables 2.2.10.6.1 and 2.2.10.6.2).

The mean (SD) score obtained in the subgroup of patients who reported implementation issues was 9.64 (4.26) and 41 out of 50 patients (82.00%) had fatigue. At visit 6, this main (SD) score decreased to 8.33 (5.35) and the percentage of patients who had fatigue was 60.00% (27 out of 45 patients). Among patients who did not report implementation issues, the mean (SD) score at baseline was higher (10.00 [5.29]) and 39 out of 49 patients had fatigue (79.59%). Both scores decreased at visit 6, where a mean (SD) score of 8.18 (4.57) and fatigue in 33 out of 44 patients (75.00%) was observed (Tables 2.2.10.6.3 and 2.2.10.6.4).

Finally, the patients who reported treatment discontinuation had a mean (SD) score at baseline of 10.00 (4.44) and 29 out of 34 patients (85.29%) had fatigue; at visit 6, no changes were seen in this questionnaire since the results were very similar to those obtained at baseline. However, among those patients who did not discontinue treatment, a decrease in the score obtained from baseline to visit 6 was seen (mean [SD] score at baseline was 9.61 (4.86) and 7.62 (4.91) at visit 6). The percentage of patients who reported fatigue also decreased from 78.57% (55 out of 70) to 62.12% (41 out of 66) (Tables 2.2.10.6.5 and 2.2.10.6.6).

- IMAB

The mean (SD) IMAB score obtained at visit 3 and evaluated in 87 patients of the FAS population was 29.03 (6.02) and at this time point, 100.00% of patients reported the presence of at least one barrier when managing their Aubagio medication. Both data were the same at visit 6 so no changes were observed regarding the difficulties experienced by the patients when managing their Aubagio medication in daily life (Table 2.1.10.7).

The mean (SD) score obtained at visit 3 in the subgroup of patients who started treatment was 29.03 (6.02); at visit 6, no changes were seen in the results of this questionnaire. None of the patients in the subgroup of patients who did not start treatment completed this questionnaire (Tables 2.2.10.7.1 and 2.2.10.7.2).

In the subgroup of patients who reported having implementation problems, the mean (SD) score obtained at visit 3 was 30.53 (7.14) and 100.00% of patients reported the presence of at least one barrier when managing their Aubagio medication. No changes were seen in the results of this questionnaire at visit 6 (mean [SD] score was 30.49 [5.77] and 100.00% of patients reported the presence of at least one barrier). In the subgroup of patients without implementation issues, the mean (SD) score at visit 3 was 27.28 (3.73) and again 100.00% of these patients had at least one barrier when managing their Aubagio medication. No change was seen at visit 6 (mean [SD] 27.55 (4.18) and 100.00% of patients reported the presence of at least one barrier) (Tables 2.2.10.7.3 and 2.2.10.7.4).

Finally, in the subgroup of patients who reported treatment discontinuation, the mean (SD) score obtained at visit 3 was 30.52 (8.38) and all patients reported at least one barrier when managing

their Aubagio medication. At visit 6, the mean (SD) score obtained was quite similar (30.19 [5.91] but the percentage of patients reporting presence of at least one barrier was still 100.00%. In the subgroup of patients who did not discontinue treatment, the mean (SD) score obtained at baseline was 28.56 (5.04) and again, all patients reported the presence of at least one barrier. The same results were seen at visit 6 (mean [SD] score was 28.71 (5.02) and 100.00% of patients reported the presence of at least one barrier) (Tables 2.2.10.7.5 and 2.2.10.7.6).

- Modified BAASIS

Finally, the modified BAASIS questionnaire performed at visit 3 (Table 2.1.10.8), 4 (Table 2.1.10.9) 5 (Table 2.1.10.10) and 6 (Table 2.1.10.11) showed the following results: 30 (34.09%), 21 (27.63%), 23 (38.33%) and 21 (23.33%) patients respectively remembered missing a dose of their medication Aubagio in the last 4 weeks; only 1 (1.14%), 2 (2.63%), 3 (5.00%) and 3 (3.33%) respectively altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their doctors' indication; 2 (2.27%), 0 (0.00%), 0 (0.00%) and 3 (3.33%) respectively, stopped taking their medication Aubagio completely within the last year, without their doctors' indication; and finally, 30 (34.09%), 21 (27.63%), 24 (40.00%) and 23 (25.56%) respectively, reported having problems with the implementation.

This questionnaire performed at visit 3 (Table 2.2.10.8.1), 4 (Table 2.2.10.9.1) 5 (Table 2.2.10.10.1) and 6 (Table 2.2.10.11.1) in the subgroup of patients who started treatment showed the following results: 30/88 (34.09%), 21/76 (27.63%), 23/60 (38.33%) and 21/90 (23.33%) patients respectively remembered missing a dose of their medication Aubagio in the last 4 weeks; only 1/88 (1.14%), 2/76 (2.63%), 3/60 (5.00%) and 3/90 (3.33%) patients respectively altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their doctors' indication; 2/88 (2.27%), 0/76 (0.00%), 0/60 (0.00%) and 3/90 (3.33%) patients respectively stopped taking their medication Aubagio completely within the last year, without their doctors' indication; and finally, 30/88 (34.09%), 21/76 (27.63%), 24/60 (40.00%) and 23/90 (25.56%) respectively, reported having problems with the implementation.

For the subgroup of patients who did not start treatment, this questionnaire was not performed or the results were not reported at any visit (Tables 2.2.10.8.2, 2.2.10.9.2, 2.2.10.10.2 and 2.2.10.11.2).

This questionnaire performed at visit 3 (Table 2.2.10.8.3), 4 (Table 2.2.10.9.3) 5 (Table 2.2.10.10.3) and 6 (Table 2.2.10.11.3) in the subgroup of patients who reported having implementation issues showed the following results: 30/47 (63.83%), 21/39 (53.85%), 23/34 (67.65%) and 21/48 (43.75%) patients respectively remembered missing a dose of their medication Aubagio in the last 4 weeks; only 1/47 (2.13%), 2/39 (5.13%), 3/34 (8.82%) and 3/48 (6.25%) patients respectively altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their

doctors' indication; 2/47 (4.26%), 0/39 (0.00%), 0/34 (0.00%) and 3/48 (6.25%) patients respectively stopped taking their medication Aubagio completely within the last year, without their doctors' indication; and finally, 30/47 (63.83%), 21/39 (53.85%), 24/34 (70.59%) and 23/48 (47.92%) respectively, reported having problems with the implementation.

This questionnaire performed at visit 3 (Table 2.2.10.8.4), 4 (Table 2.2.10.9.4) 5 (Table 2.2.10.10.4) and 6 (Table 2.2.10.11.4) in the subgroup of patients who did not report implementation issues showed that there were no patients who remembered missing a dose of their medication Aubagio in the last 4 weeks, no patients who altered the prescribed amount of their medication Aubagio in the last four weeks without their doctors' indication, no patients who stopped taking their medication Aubagio completely within the last year without their doctors' indication and no patients who reported having problems with the implementation.

This questionnaire performed at visit 3 (Table 2.2.10.8.5), 4 (Table 2.2.10.9.5) 5 (Table 2.2.10.10.5) and 6 (Table 2.2.10.11.5) in the subgroup of patients who discontinued treatment showed the following results: 8/21 (38.10%), 5/13 (38.46%), 2/5 (40.00%) and 6/24 (25.00%) patients respectively remembered missing a dose of their medication Aubagio in the last 4 weeks; only 1/21 (4.76%), 1/13 (7.69%), 0/5 (0.00%) and 2/24 (8.33%) patients respectively altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their doctors' indication; 2/21 (9.52%), 0/13 (0.00%), 0/5 (0.00%) and 3/24 (12.50%) patients respectively stopped taking their medication Aubagio completely within the last year, without their doctors' indication; and finally, 8/21 (38.10%), 5/13 (38.46%), 2/5 (40.00%) and 7/24 (29.17%) respectively, reported having problems with the implementation.

Finally, this questionnaire performed at visit 3 (Table 2.2.10.8.6), 4 (Table 2.2.10.9.6) 5 (Table 2.2.10.10.6) and 6 (Table 2.2.10.11.6) in the subgroup of patients who did not discontinue treatment showed the following results: 22/67 (32.84%), 16/63 (25.40%), 21/55 (38.18%) and 15/66 (22.73%) patients respectively remembered missing a dose of their medication Aubagio in the last 4 weeks; 0/67 (0.00%), 1/63 (1.59%), 3/55 (5.45%) and 1/66 (1.52%) patients respectively altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their doctors' indication; 0/67 (0.00%), 0/63 (0.00%), 0/55 (0.00%) and 0/66 (0.00%) patients respectively stopped taking their medication Aubagio completely within the last year, without their doctors' indication; and finally, 22/67 (32.84%), 16/63 (25.40%), 22/55 (40.00%) and 16/66 (24.24%) respectively, reported having problems with the implementation.

Exploratory analyses

Description of adherence parameters in terms of SDMT

The logistic model using the initiation as a dependent variable showed an adjusted odds ratio(OR) (CI 95%) of 0.98 (0.86; 1.11) in patients who initiated the treatment and had a difference of only 1 point during the study compared to the SDMT score at baseline. This adjusted OR (CI 95%) was

0.89 (0.47; 1.68) and 0.79 (0.22; 2.82) for patients having a difference of 5 and 10 points respectively in the SDMT score obtained during the study compared to the result obtained at baseline. However, correlation between the initiation parameter and the baseline SDMT score was not significant (p = 0.710) on an exploratory level (Table 2.1.9.1).

The same analysis was done using the implementation as a dependent variable. Among patients who reported implementation issues, the adjusted OR (CI 95%) obtained for patients with a difference of 1 point during the study compared to baseline was 1.04 (0.99; 1.10), for patients with a difference of 5 points it was 1.22 (0.94; 1.59) and for patients with a difference of 10 points it was 1.49 (0.89; 2.52). However, the correlation between the implementation adherence parameter and the baseline SDMT score was not statistically significant (p = 0.131) on an exploratory level (Table 2.1.9.2).

Likewise, the same analysis was performed using the persistence as a dependent variable. In this case, the adjusted OR (CI 95%) for patients who persisted on treatment was 1.00 (0.96; 1.05) among those patients who reported a difference of only 1 point during the study compared to baseline, 1.02 (0.82; 1.27) for those patients with a difference of 5 points and 1.04 (0.68; 1.60) when the difference was of 10 points. The correlation between the persistence parameter and the baseline SDMT score was not statistically significant (p = 0.858) on an exploratory level (Table 2.1.9.3).

It was also reported that among the 50 (47.62%) patients of the safety population who had implementation issues, 36 (72.00%) did not discontinue the treatment. And among the patients who did not have implementation issues (49 [46.67%] patients) 34 (69.39%) did not discontinue treatment (Table 2.1.9.4).

11.1 EXTENT OF EXPOSURE

Not applicable

11.2 ADVERSE EVENTS

11.2.1 Brief summary of adverse events

The number and percentage of patients with AEs, SAEs, adverse events leading to treatment discontinuation, AESIs and adverse events leading to death is shown in Table 9.

Table 9 - Overview of adverse event profile – Safety population

n (%)	Safety (N=105)
Patients with any adverse event	89 (84.76%)
Patients with any serious adverse event (SAE)	10 (9.52%)

n (%)	Safety (N=105)
Patients with any related to treatment discontinuation adverse event	29 (27.62%)
Patients with any Adverse Event of Special Interest (AESI)	66 (62.86%)
Patients with any adverse event leading to death	0 (0.00%)

MedDRA dictionary version: MedDRA 23.1
PGM=\\linical-fs1\O\Projects\SAN60\9-BST\Programs\TFLs\Programs\ae_overview_s_t.sas OUT=\\linical-fs1\O\Projects\SAN60\9-BST\TFLs\Final TFLs\ae_overview_s_t.rtf (06JUL21 - 20:03)
Source: table 2.1.8.1

11.2.2 Analysis of adverse events

A total of 89 out of 105 patients (84.76%) had any adverse event. The SOCs with the highest incidence of AEs were nervous system disorders and gastrointestinal disorders, (44 [41.90%] patients with AEs each), skin and subcutaneous tissue disorders (22 [20.95%] patients), infections and infestations (21 [20.00%] patients with AEs), musculoskeletal and connective tissue disorders (18 [17.14%] patients with AEs) and general disorders and administration site conditions [17 [16.19%] patients with AEs).

The AE more frequently reported during the study was diarrhoea reported by 22 (20.95%) patients followed by alopecia (16 [15.24%] patients), headache (13 [12.38%] patients) and multiple sclerosis relapse (11 [10.48] patients). Other AEs reported in less than 10 patients were nausea and fatigue each reported by 9 (8.57%) patients, lymphopenia, dizziness and gastrointestinal disorders each reported by 6 (5.71%) patients, paraesthesia, hypertension, abdominal pain and pain in extremity each reported by 4 (3.81%) patients and nasopharyngitis, tooth abscess, anxiety, carpal tunnel syndrome, neuropathy peripheral, arthralgia, back pain, intervertebral disc protrusion and pregnancy each reported in 3 (2.86%) patients. Other events were reported in less than 2% of the safety population.

All AEs, described both by the preferred term and the original term used by the Investigator, are provided for each patient in @@16-2-7-ae-data.

11.3 DEATHS, SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Narratives have not been planned for this study.

11.3.1 Deaths

No deaths were reported during the study.

11.3.2 Serious adverse events

There were 10 out of 105 (9.52%) patients who reported any SAE. The SOCs with the highest incidence of SAEs were infections and infestations (4 [3.81%] patients with SAEs) and nervous system disorders (3 [2.86%] patients with SAEs). In other SOCs, SAEs were reported but only by 1 patient.

No preferred term (PT) was reported as a SAE more than once. The reported SAEs were: appendicitis, erysipelas, pneumonia, tooth abscess, suicidal ideation, headache, multiple sclerosis relapse, optic neuritis, asthma, cholecystitis, intervertebral disc protrusion and prostatitis (Table 2.1.8.3).

11.3.3 Adverse events leading to treatment discontinuation

During the study, 29 patients (27.62%) from the safety population reported any AE that led to treatment discontinuation. The SOCs with the highest incidence of AEs leading to treatment discontinuation were nervous system disorders (12 [11.43%] patients) and gastrointestinal disorders (11 [10.48%] patients). Events in other SOCs were reported in less than 3% of the safety population (Table 2.1.8.4).

The most frequently reported AEs by PT were diarrhoea that led to treatment discontinuation in 7 patients (6.67%); multiple sclerosis relapse and pregnancy were the reasons to discontinue treatment in 3 (2.86%) patients each, lymphopenia, headache, gastrointestinal disorder and alopecia led to treatment discontinuation in 2 (1.89%) patients each. Finally, the following AEs led to treatment discontinuation in one patient each: herpes zoster, affective disorder, insomnia, dizziness, migraine, optic neuritis, paraesthesia, peripheral sensory neuropathy, polyneuropathy, sciatica, speech disorder, visual impairment, palpitations, hot flush, abdominal discomfort, abdominal pain, abdominal pain upper, rheumatoid arthritis, premature separation of placenta, dysmenorrhea, asthenia and gait disturbance (Table 2.1.8.4).

11.3.4 Adverse events of special interest

A total of 66 patients from the safety population (62.86%) experienced any AESI during the study. The SOCs with the highest incidence of AESIs were gastrointestinal disorders, reported by 36 (34.29%) patients, skin and subcutaneous tissue disorders, reported by 19 (18.10%) patients, infections and infestations, reported by 16 (15.24%) patients, nervous system disorders, reported by 12 (11.43%) patients and blood and lymphatic disorders, reported by 6 (5.71%) patients. By PT, the most frequently reported AESI was diarrhoea, reported by 21 (20.00%) patients, followed by alopecia (16 [15.24%] patients), nausea (9 [8.57%] patients), gastrointestinal disorder and lymphopenia (each reported by 6 [5.71%] patients), hypertension (4 [3.81%] patients) and neuropathy peripheral, paraesthesia, abdominal pain and pregnancy (each reported by 3 [2.86%] patients). Other AESIs were reported by less than 2% of the safety population (Table 2.1.8.5).

11.3.5 Other significant adverse events

No other significant adverse events were defined in this study.

11.4 CLINICAL LABORATORY EVALUATIONS

No lab tests results were recorded during the study apart from lab parameters used to define ASEIs.

11.5 VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER SAFETY OBSERVATIONS

Not applicable

11.6 SAFETY CONCLUSIONS

The assessment of treatment adherence in terms of initiation showed that 4 patients (3.74%) out of the 107 patients evaluated did never initiate treatment. The assessment of treatment adherence in terms of implementation, showed that more than half of the primary analysis population had a good treatment implementation. According to data reported in the database regarding prescribed medication, only 34 patients of this population had the opportunity to be compliant with the treatment prescribed, but those data might be biased (see section 13 discussion). Among the reasons for treatment discontinuation, almost a half of the FAS (45.71%) discontinued treatment following health care professional decision and in more than one third of this population, (37.14%) discontinuation was the patient's decision.

The mean (SD) EDSS score obtained at baseline among those patients who discontinued and among those patients who did not discontinue treatment was not very different (2.04 [1.36] vs (2.29 [1.35]) but at visit 6, this difference was even lower. While a higher difference between both groups were seen in the MRI results: 53.57% of discontinued patients had disease activity compared to 60.38% of non-discontinued treatment. And at visit 6, this difference was higher: 54.55% of discontinued patients vs 23.33% of non-discontinued patients had disease activity at visit 6. Finally, the percentage of patients who experimented a relapse was noticeably higher in the group of discontinued patients compared to the non-discontinued patients throughout the study visits.

The drivers of adherence described by mean of the MFIS-5 score using a MMRM in the primary analysis population showed a mean (SD) MFIS-5 score at baseline of 9.81 (4.64) decreasing by 1.43 (0.43) points in the mean (SD) at the end of study.; same analysis done on PHQ-9 showed a mean (SD) PHQ-9 score at baseline of 8.35 (5.66) decreasing by 1.95 (0.46) at the end of study; and this analysis applied to SDMT showed a mean (SD) SDMT score at baseline of 47.11 (14.96) with a mean (SD) change of 0.50 (0.99) points at the end of study.

The other PROs assessment showed the following conclusions:

- Knowledge and skills evaluation: the mean (SD) score obtained at baseline was 4.8 (0.54), 97.17% of patients had good knowledge and at visit 6, the score increased a mean (SD) of 0.14 (0.53 points). The score obtained at baseline depending on if the patient started treatment or not, if there were implementation issues or not and if treatment was discontinued or not, was very similar. At visit 6, no great differences were seen in any of the subgroups compared to baseline.
- Intention and motivation evaluation: the mean (SD) score at baseline was 6.85 (0.37) and all the patients reported to be "more motivated". It was observed that at visit 6, the results obtained were very similar to baseline. The score of this questionnaire did not show modifications at visit 6 regardless treatment initiation and regardless implementation issues. However, the score worsened at visit 6 compared to baseline in the group of patients who discontinued treatment while was similar among those patients who did not discontinue treatment.
- Health literacy evaluation: the mean (SD) health literacy evaluation score at baseline was 4.09 (0.95) and only 7.41% patients from the FAS population were inadequately health literate. The score was lower in the group of patients who did not start treatment compared to those patients who started treatment and in the group of patients who did not report implementation issues compared to those patients who reported implementation issues. However, no differences were seen regardless of treatment discontinuation or continuation.
- SDMT: the mean (SD) score at baseline was 47.44 (15.21) and at visit 6, this score increased only by a mean (SD) of 0.59 (9.26) points, with a similar percentage of patients with cognitive improvement (24.39%) and cognitive impairment (20.73%). More patients had cognitive improvement at visit 6 in the group of patients who started treatment compared to those patients who did not start treatment although the low number of patients, makes these results not meaningful. It is noticeable that the percentage of patients with cognitive improvement at visit 6 was higher in the group of patients with implementation issues compared to those patients without these problems. Furthermore, a higher percentage of patients had cognitive improvement at visit 6 among those patients who discontinued treatment compared to non-discontinued patients.
- PHQ-9: the mean (SD) score at baseline was 8.90 (6.12) and 71 (65.74%) patients had a moderate to severe depression. At visit 6, the score had decreased by a mean (SD) of 1.88 (5.11) points and 54.44% patients reported moderate to severe depression. At visit 6, the percentage of patients with moderate to severe depression decreased more than 10% among those patients who initiated treatment, from 66% to 50% among those patients with implementation issues while a lower decreased was observed among those patients who did not reported implementation issues (from 65.31% to 59.09%); the percentage of patients with moderate to severe depression had a similar decrease among those patients who did and did not discontinue treatment.

- MFIS-5: the mean (SD) score at baseline was 9.88 (4.76), 81.48% patients had feelings of fatigue and at visit 6, the score decreased a mean (SD) of 1.32 (4.23) and 68.13% of patients had fatigue. It was seen an improvement among those patients who started treatment since the percentage of patients with fatigue decreased from 80.77% at baseline to 67.78% at visit 6. Due to the small number of patients who did not start treatment, the results obtained were not meaningful. It was also obtained a higher decrease in the percentage of patients with fatigue in the group of patients who reported compared to those who did not report implementation issues (from 82.00% at baseline to 60.00% at visit 6 and from 75.59% at baseline to 75.00% at visit 6). Finally, no improvement was seen among those patients who discontinued treatment however, a decreased from 78.57% of patients with fatigue at baseline to 62.12% at visit 6 was seen in the non-discontinued patients.
- IMAB: the mean (SD) score at visit 3 was 29.3 (6.02), 100% of patients reported the presence of at least one barrier when managing their Aubagio medication. However, no change (neither improvement nor worsen) was seen at visit 6. Therefore, no differences were seen in the patient subgroups regardless treatment initiation, implementation issues and treatment discontinuation.
- Modified BAASIS: the results from visit 3 to visit 6 showed a decreased in the percentage of patients who remembered missing a dose of their medication Aubagio in the last 4 weeks from 34.09% to 23.33% patients; an increase of patients who altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their doctors' indication from 1.14% to 3.33% respectively; it was also seen in increase of patients who stopped taking their medication Aubagio completely within the last year, without their doctors' indication from 2.27% to 3.33% and a decrease of patients who reported having problems with the implementation from 34.09% to 25.56%. The same results were obtained in the group of patients who started treatment and the questionnaire was not performed in those patients who did not start treatment. The same trend was seen among those patients with implementation issues: the percentage of patients who remembered missing a dose of their medication Aubagio in the last 4 weeks from 63.83% to 43.75% patients; the percentage of patients who altered the prescribed amount increased from 2.13% to 6.25%; the patients who stopped taking their Aubagio medication completely within the last year, without their doctors' indication increased from 4.26% to 6.25% and a the percentage of patients who reported having problems with the implementation decreased from 63.83% to 47.92%. In the group of patients who did not report implementation issues, obviously, none of them remembered missing a dose of their medication Aubagio in the last 4 weeks, or altered the prescribed amount of their medication Aubagio in the last four weeks without their doctors' indication, or stopped taking their medication Aubagio completely within the last year without their doctors' indication or reported having problems with the implementation. A

similar trend was seen regardless treatment discontinuation: percentage of patients decreased at visit 6 compared to visit 3 in the percentage of patients who remembered missing a dose of their medication Aubagio in the last 4 weeks and who stopped taking their medication Aubagio completely within the last year, without their doctors' indication, and an increase of patients who altered the prescribed amount (for example taken more or fewer pills or changed the dose) of their medication Aubagio in the last four weeks, without their doctors' indication. Obviously, there weren't non-discontinued patients who stopped taking their medication Aubagio completely within the last year, without their doctors' indication.

Regarding the exploratory analysis about the correlation between adherence and cognition (SDMT), the logistic model using the initiation as a dependent variable showed an adjusted OR (CI 95%) of 0.98 (0.86; 1.11), 0.89 (0.47; 1.68) and 0.79 (0.22; 2.82) in patients who initiated the treatment showing a difference of only 1, 5 and 10 points respectively during the study compared to the score obtained at baseline in the SDMT. When the implementation was used as a dependent variable, the adjusted OR (CI 95%) in the patients with implementation issues having a difference of 1, 5 and 10 points was 1.04 (0.99; 1.10), 1.22 (0.94; 1.59) and 1.49 (0.89; 2.52), respectively. And using the persistence as dependent variable, the adjusted OR (CI 95%) obtained in those patients who persisted on treatment having a difference of 1, 5 and 10 points was 1.00 (0.96; 1.05), 1.02 (0.82; 1.27) and 1.04 (0.68; 1.60), respectively.

Finally, the analysis of the implementation in terms of persistence showed that 72.00% patients among those who reported implementation issues did not discontinue treatment.

Along the study, the AE reporting was as follows: 84.76% reported any AE (mainly, diarrhoea, alopecia, headache and multiple sclerosis relapse); 9.52% of patients who reported any SAE that were: appendicitis, erysipelas, pneumonia, tooth abscess, suicidal ideation, headache, multiple sclerosis relapse, optic neuritis, asthma, cholecystitis, intervertebral disc protrusion and prostatitis (all this SAEs were presented only in 1 patient each one); 27.62% of patients reported any AE leading to treatment discontinuation (mainly diarrhoea, multiple sclerosis relapse and pregnancy); and 62.86% of patients reported any AESI being these events mainly diarrhoea, alopecia, nausea, gastrointestinal disorders and lymphopenia.

No deaths were reported during the study.

12 PHARMACOKINETIC EVALUATION

Not applicable

13 DISCUSSION AND OVERALL CONCLUSIONS

This was a prospective, open-label, multicenter, single-arm observational registry study in which a cohort of adults treated with teriflunomide (Aubagio) was included with an observation period of maximun 18 months. The study did not include fixed study visits because it was performed according to routine clinical practice. The patients included were adult patients suffering from RRMS with an EDSS score of maximum 6.5, prescribed with Aubagio, who did not present any contraindication to the study treatment and who would have not been previously treated with Aubagio.

There were 8 participant sites that were non-university/regional hospitals and 7 that were university hospitals with in general a follow-up visits frequency every 6 months. The teams were composed by neurologists MS experts, neurologists treating MS patients, rehabilitation physicians and physiotherapists. Visits for new patients took almost one hour which decreased up to 36 minutes in routine visits. In general, in the study participating sites, the adherence topic was present in the discussion between the physician and the MS patients, the importance of treatment adherence was highlighted and tips to integrate the treatment in patients' daily life were given at treatment initiation. Furthermore, when breakthrough occurred, it was also discussed in most of the sites. However, adherence interventions were offered only in 1 out of 4 participating sites.

During the study, only 5 patients had a critical or major deviation (patients with no Modified BAASIS questionnaire reported).

A total of 109 patients were included in the study, from which 87.16% completed the study (had their visit at month 18 done [month 12 for patients falling under protocol amendment] or terminated the treatment in the study period). However, only 55.05% patients completed the study follow-up period of 18 months (or 12 months for patients falling into the protocol amendment).

The FAS population was composed by 100% of patients included, 96.33% were included in the safety population and 87.16% in the primary analysis population.

In the FAS (n=109), 35 patients discontinued treatment, and, 45.71% out of them discontinued treatment due to health care professional decision, 37.14% due to patient decision, 14.29% due to joint decision and 2.86% due to other unspecified reasons.

The patients included in the study were around 47 years old, mainly women – in line with multiple sclerosis epidemiology – with upper secondary education or higher education level completed. Furthermore, almost half of the population were employed but approximately 20% had disability benefits. The demographic characteristics by subgroups showed overall similar results regardless treatment initiation, implementation issues and treatment discontinuation. However, the highest percentage of patients with disability benefits or temporary disability was among those patients with implementation issues and patients with treatment discontinuation.

The main disorders reported in the medical history were depression, hypertension and hypercholesterolaemia. The included patients presented less than 1 relapse in the previous 2 years. The EDSS mean score was 2.22 and the MRI assessments showed disease activity in more than a half of patients with more than 5 new T2 lesions and the last relapse was registered 3 months before the study. In the past 2 years, more than a half of patients were treated by another prior DMT and 60% switched from DMT at least once due to safety before study entry. The most reported previous DMTs were Avonex, Copaxone and Tecdifera. The most reported prior medications were colecalciferol, pantoprazole sodium sesquihydrate and pregabalin, and the concomitant treatments most prescribed were also colecalciferol and pantoprazole sodium sesquihydrate, and paracetamol.

The median of time from the intake of Aubagio to the discontinuation of the Aubagio treatment was not reached since an insufficient number of events were reported. However, it was observed a cumulative incidence at 12 and 18 months that was very low (0.28 and 0.34 events, respectively). And it was also observed that the differences in the cumulative incidence obtained at month 3, 6, 12 and 18 decreased along the study.

The protocol planned to collect adherence data from two different type of sources: patient reported outcomes (using the modified BAASIS questionnaire for adherence) and prescription and/or pharmacy delivery data. It appeared that collecting the prescription and delivery data based on source documentation was challenging. According to the data that could be collected (and were documented properly), only 36 % of the patient got the opportunity to be compliant, meaning that the other patients would not have received enough treatment boxes prescribed to cover their treatment intake. It is possible that some patients did not need as much treatment boxes as planned due to poor implementation or due to the pandemic conditions, but it is probably more the documentation of these data that has been problematic for the investigating sites, with a heterogeneous quality in the documentation: indeed, it is not standard to document the exact number of boxes prescribed per visit in the files of patient not enrolled in randomized clinical trials. It is probable that this way to collect data on adherence turns out to be not efficient and probably the data are not usable as such.

Based on modified-BAASIS questionnaire, the adherence assessment, in terms of implementation, showed that approximately a half of the primary analysis population had a good implementation. The main reasons for treatment discontinuation were due to health care professional decision and due to patient decision.

When looking at implementation of the Aubagio medication at the end of the study compared to baseline, the modified BASSIS, less patients missed a dose of their Aubagio medication within the last 4 weeks and less patients reported implementation problems; however, the percentage of patients who altered their prescription and who completely stopped their medication without doctor’s indication, increased. Factors known to impact treatment adherence and other factors potentially influencing adherence were analyzed: efficacy parameters, risk factors like health literacy and intention and motivation, the presence of barriers to take the medication and finally

MS-related conditions like depression, fatigue and cognition. An exploratory correlation analysis was performed on cognition.

The analysis of the efficacy parameters as drivers of treatment adherence showed that EDSS score at visit 6 did not change regardless treatment discontinuation, however, a higher percentage of patients who discontinued treatment had disease activity and relapse compared to those non-discontinued patients, which is in line with treatment guidelines and expectations.

The results given by the questionnaires evaluating risk factors showed that, in the overall population, almost all patients were health literate at baseline and that this important and well-known factor impacting adherence did not show an impact on the different aspects of treatment adherence in this patient population and in this study. Likewise, after being on treatment with Aubagio, the evaluation performed at visit 6 showed that the patients' knowledge of their Aubagio medication did not change much in the course of the study and was very similar between groups. Regarding patients' motivation and intention in taking the Aubagio medication, it did not change much in the course of the study but when comparing patient who continued on medication and patient who discontinued, it appeared that the score in the intention and motivation questionnaire worsened for patients who discontinued treatment at visit 6.

Throughout the study, 100% of patients reported having find at least one barrier when managing their Aubagio medication (this result was the same than at baseline, as well as the total mean score). The analysis was based on the finding of at least one barrier to detect an impact. As 100% of the patients reported at least one barrier and no in-depth analysis was performed on the number and type of barriers, it was not possible to draw conclusions from this analysis. This would require examining in detail the type of barriers reported and the burden assessed by patients for each of them by the 5-points Likert scale.

When looking at the PRO's evaluating MS-related specific symptoms like depression (PHQ-9), fatigue (MSIF-5) and cognition (SDMT) at the end of the study, we can see that the same proportion of patients had cognitive improvement and impairment while a half of patients did not change their cognitive status compared to baseline, the depression status improved and there was a lower percentage of patients reporting depressive symptoms at the end of the study compared to baseline, and that the fatigue scores improved at the end of the study compared to baseline and that a lower percentage of patients reported fatigue symptoms at the end of the study compared to baseline.

Exploratory analysis was performed to describe the correlation between cognition (measured via SDMT) and treatment adherence parameters, considering the initiation, implementation and persistence as variables. From this analysis it was observed that initiation, implementation and persistence were not statistically related to the changes observed in the cognition status assessed by SDMT.

Other analysis detailed the characteristics of the groups presenting different behaviors: patients who started treatment compared with patients who did not, patients having implementation issues

compared to patients without implementation issues and patients who continued treatment compared to patients who discontinued treatment.

In the group of patients who started treatment, it was observed that after having been on treatment with Aubagio, the knowledge evaluation improved, the intention and motivation in taking their medication did not change, no change in the cognitive status was observed in more than a half of these patients while cognitive improvement was seen in 1 out of 4 patients and both depression and fatigue improved; however, patients continued having barriers in the treatment management. Finally, when the adherence was assessed, it was observed that, at visit 6, more patients had altered or totally stopped their medication without doctor's indication compared to visit 3, although the implementation problems improved and there were less patients who missed doses of their Aubagio medication.

On the other side, there were only 4 patients who did not start treatment and most of the planned tests and questionnaires were not performed in those patients. However, it was observed that there were less patients evaluated as health literate compared to the patients who started treatment. Although the number of patients was very low, no cognitive improvement was seen but cognitive impairment was observed in a half of the patients. The low number of patients in this group does not allow to draw firm conclusions.

At week 6, patients with implementation issues improved their knowledge evaluation, slightly decrease their motivation in taking Aubagio and improved their cognitive status and their depression and fatigue status (in both latter cases, the improvement was even slightly higher compared to those patients without implementation issues). However, both, patients with and without implementation issues had barriers when managing their Aubagio medication at visit 6.

The percentage of patients with implementation issues who reported via modified BAASIS, having missed any dose, skipped two or more doses, altered the prescribed amount of medication or stopped taking their medication was higher at visit 6 compared to visit 3.

When the treatment discontinuation factor was considered, patients who discontinued treatment decreased their motivation in taking Aubagio at visit 6 compared to baseline while almost all of these discontinued patients were health literate at baseline. The mean SDMT score increased at visit 6 and up to 30% improved their cognitive status. The PHQ-9 also decreased from baseline to week 6 as well as the percentage of patients with moderate to severe depression although more patients had fatigue at visit 6 compared to baseline.

Regardless treatment discontinuation, all patients reported having barriers when managing their Aubagio medication at baseline and at visit 6.

Finally, the adherence assessed via the modified BAASIS questionnaire, showed a tangible difference in the percentage of patients who altered the prescription or totally stopped their medication, without doctor's indication: it was observed higher among those patients who discontinued treatment at visit 3 and at visit 6. However, a similar percentage of patients reported having missed any dose and having implementation issues in both groups at visit 6. The

implementation of this simple interview in the routine practice might support the MS teams in the hospitals in detecting early treatment adherence issues and take appropriate actions to help the patient in optimizing the treatment.

Regarding AE profile the most important were multiple sclerosis relapse, reported as SAE and AE related to treatment discontinuation and diarrhoea, reported during the study as AE related to treatment discontinuation. No new safety signal has been identified in this study.

CONCLUSION

The AUBADHE study showed that a half of the MS patients on treatment with Aubagio in a real-life setting had a good adherence in terms of implementation. However, regardless of the implementation issues encountered, 65% of the patients remained on treatment until the last follow-up visit (for the patients followed 18 months). 3.74 % of the patients never started the treatment.

Throughout the course of the study, there were less patients who missed any dose or who reported implementation problems although more patients reported altering their prescription and stopping their medication without doctor's indication. It was also observed that the differences in the cumulative incidence for treatment discontinuation obtained at month 3, 6, 12 and 18 decreased along the study.

.

When looking at the PRO's evaluating MS-related specific symptoms like depression (PHQ-9), fatigue (MSIF-5) and cognition (SDMT) at the end of the study, we can see that the same proportion of patients had cognitive improvement and impairment while a half of patients did not change their cognitive status compared to baseline, the depression status improved and there was a lower percentage of patients reporting depressive symptoms at the end of the study compared to baseline, and that the fatigue scores improved at the end of the study compared to baseline and that a lower percentage of patients reported fatigue symptoms at the end of the study compared to baseline.

Exploratory analysis was performed to describe the correlation between cognition (measured via SDMT) and treatment adherence parameters, considering the initiation, implementation and persistence as variables. From this analysis it was observed that initiation, implementation and persistence were not statistically related to the changes observed in the cognition status assessed by SDMT.

Furthermore, no new safety signal was shown during the study.

14 REFERENCES

1. O'Connor et al., Randomized trial of oral teriflunomide for relapsing multiple sclerosis N Engl J Med. 2011 Oct 6;365(14):1293-303

2. Wolinsky et al., Magnetic resonance imaging outcomes from a phase III trial of teriflunomide Mult Scler. 2013 Sep;19(10):1310-9

3. Radue et al., Teriflunomide slows BVL in relapsing MS 2017 Neurol Neuroimmunol Neuroinflamm; 4(5)

4. Confavreux et al., Oral teriflunomide for patients with relapsing multiple sclerosis (TOWER): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014 Mar;13(3):247-56

5. Miller et al., Oral teriflunomide for patients with a first clinical episode suggestive of multiple sclerosis (TOPIC): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet Neurol. 2014 Oct;13(10):977-86

6. Comi et al., Pooled safety and tolerability data from four placebo-controlled teriflunomide studies and extensions Mult Scler Relat Disord. 2016 Jan;5:97-104

7. O'Connor et al., Long-term safety and efficacy of teriflunomide: Nine-year follow-up of the randomized TEMSO study Neurology. 2016 Mar 8;86(10):920-30

8. Confavreux et al., Long-term follow-up of a phase 2 study of oral teriflunomide in relapsing multiple sclerosis: safety and efficacy results up to 8.5 years Mult Scler. 2012 Sep;18(9):1278-89

9. Freedman et al., Comparing outcomes from clinical studies of oral disease-modifying therapies (dimethyl fumarate, fingolimod, and teriflunomide) in relapsing MS: Assessing absolute differences using a number needed to treat analysis Mult Scler Relat Disord. 2016

10. Coyle PK et al., Patient-reported outcomes in relapsing forms of MS: Real-world, global treatment experience with teriflunomide from the Teri-PRO study Mult Scler Relat Disord. 2017 Oct;17:107-115

11. Chua et al., Patient-reported outcomes in multiple sclerosis: Relationships among existing scales and the development of a brief measure Mult Scler Relat Disord. 2015 Nov;4(6):598-606

12. Barbosa et al., A literature review to explore the link between treatment satisfaction and adherence, compliance, and persistence Patient Prefer Adherence. 2012;6:39-48

13. Vrijens, & et al. Br J Clin Pharmacol, 2012 - 73, 691-705.

14. Dobbels, F et al. The psychometric properties and practicability of self-report instruments to identify medication nonadherence in adult transplant patients: a systematic review. Transplantation, 2010, 90(2), 205-219.

15. Fishbeinet al. Communication theory, 2003 - 16, 164-183.

15 SUPPORTIVE INFORMATION

Table 2.1.1.1 Data related to site/hospital organization
Table 2.1.1.2 Data related to adherence interventions
Table 2.1.2.1 Screen log patients
Table 2.1.3.1 Analysis populations – Included
Table 2.1.3.2 End of Study – Included
Table 2.1.4.1 Any critical or major deviation – Included

15.1 DEMOGRAPHIC DATA

Table 2.1.5.1 Demographics
Table 2.1.5.2 Multiple Sclerosis: history and disease status
Table 2.1.5.3 Previous disease-modifying treatment
Table 2.1.5.4 Relevant medical/surgical history
Table 2.1.5.5 Previous medication
Table 2.1.5.6 Concomitant medication
Table 2.2.1.1 Demographics for patients that start the treatment
Table 2.2.1.2 Demographics for patients that do not start the treatment
Table 2.2.1.3 Demographics for patients that have implementation issues
Table 2.2.1.4 Demographics for patients that do not have implementation issues
Table 2.2.1.5 Demographics for patients that have discontinued the treatment
Table 2.2.1.6 Demographics for patients that do not have discontinued the treatment

15.2 EFFICACY/PHARMACODYNAMIC DATA

Not applicable

15.3 SAFETY DATA

Table 2.1.6.1 Persistence – Safety population
Figure 2.1.6.2 Kaplan Meier plot for Persistence – Safety population
Table 2.1.6.3 Continuation rate – Primary Analysis Population
Table 2.1.7.1 Adherence in terms of initiation – FAS
Table 2.1.7.2 Adherence in terms of implementation – Primary Analysis Population

Table 2.1.7.3 Reasons for treatment discontinuation – FAS
Table 2.1.7.4 Comparison of discontinued and non-discontinued patients – Safety population
Table 2.1.7.5 Drivers of Adherence: MFIS-5 score change from baseline to end of study visit using MMRM – Primary Analysis Population
Table 2.1.7.6 Drivers of Adherence: PHQ-9 score change from baseline to end of study visit using MMRM – Primary Analysis Population
Table 2.17.7 Drivers of Adherence: SDMT score change from baseline to end of study visit using MMRM – Primary Analysis Population
Table 2.1.9.1 Logistic Model using as a dependent variable the initiation – FAS
Table 2.1.9.2 Logistic Model using as a dependent variable the implementation – Safety population
Table 2.1.9.3 Logistic Model using as a dependent variable the persistence – Safety population
Table 2.1.9.4 Implementation in terms of persistence – Safety population
Table 2.1.10.1 Knowledge and skills evaluation score – FAS
Table 2.1.10.2 Intention and motivation evaluation score – FAS
Table 2.1.10.3 Health literacy evaluation score – FAS
Table 2.1.10.4 SDMT score – FAS
Table 2.1.10.5 PHQ-9 Score – FAS
Table 2.1.10.6 MFIS-5 Score – FAS
Table 2.1.10.7 IMAB Score – FAS
Table 2.1.10.8 Modified BAASIS questionnaire at visit 3 – FAS
Table 2.1.10.9 Modified BAASIS questionnaire at visit 4 – FAS
Table 2.1.10.10 Modified BAASIS questionnaire at visit 5 – FAS
Table 2.1.10.11 Modified BAASIS questionnaire at visit 6 – FAS
Table 2.2.10.1.1 Knowledge and skills evaluation score for patients that start the treatment – FAS
Table 2.2.10.1.2 Knowledge and skills evaluation score for patients that do not start the treatment – FAS
Table 2.2.10.1.3 Knowledge and skills evaluation score for patients that have implementation issues – Safety population
Table 2.2.10.1.4 Knowledge and skills evaluation score for patients that do not have implementation issues – Safety population
Table 2.2.10.1.5 Knowledge and skills evaluation score for patients that have discontinued the treatment – Safety population

Table 2.2.10.1.6 Knowledge and skills evaluation score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.2.1 Intention and motivation evaluation score for patients that start the treatment – FAS
Table 2.2.10.2.2 Intention and motivation evaluation score for patients that do not start the treatment – FAS
Table 2.2.10.2.3 Intention and motivation evaluation score for patients that have implementation issues – Safety population
Table 2.2.10.2.4 Intention and motivation evaluation score for patients that do not have implementation issues – Safety population
Table 2.2.10.2.5 Intention and motivation evaluation score for patients that have discontinued the treatment – Safety population
Table 2.2.10.2.6 Intention and motivation evaluation score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.3.1 Health literacy evaluation score for patients that start the treatment – FAS
Table 2.2.10.3.2 Health literacy evaluation score for patients that do not start the treatment – FAS
Table 2.2.10.3.3 Health literacy evaluation score for patients that have implementation issues – Safety population
Table 2.2.10.3.4 Health literacy evaluation score for patients that do not have implementation issues – Safety population
Table 2.2.10.3.5 Health literacy evaluation score for patients that have discontinued the treatment – Safety population
Table 2.2.10.3.6 Health literacy evaluation score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.4.1 SDMT score for patients that start the treatment – FAS
Table 2.2.10.4.2 SDMT score for patients that do not start the treatment – FAS
Table 2.2.10.4.3 SDMT score for patients that have implementation issues – Safety population
Table 2.2.10.4.4 SDMT score for patients that do not have implementation issues – Safety population
Table 2.2.10.4.5 SDMT score for patients that have discontinued the treatment – Safety population
Table 2.2.10.4.6 SDMT score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.5.1 PHQ-9 Score for patients that start the treatment – FAS

Table 2.2.10.5.2 PHQ-9 Score for patients that do not start the treatment – FAS
Table 2.2.10.5.3 PHQ-9 Score for patients that have implementation issues – Safety population
Table 2.2.10.5.4 PHQ-9 Score for patients that do not have implementation issues – Safety population
Table 2.2.10.5.5 PHQ-9 Score for patients that have discontinued the treatment – Safety population
Table 2.2.10.5.6 PHQ-9 Score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.6.1 MFIS-5 Score for patients that start the treatment – FAS
Table 2.2.10.6.2 MFIS-5 Score for patients that do not start the treatment – FAS
Table 2.2.10.6.3 MFIS-5 Score for patients that have implementation issues – Safety population
Table 2.2.10.6.4 MFIS-5 Score for patients that do not have implementation issues – Safety population
Table 2.2.10.6.5 MFIS-5 Score for patients that have discontinued the treatment – Safety population
Table 2.2.10.6.6 MFIS-5 Score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.7.1 IMAB Score for patients that start the treatment – FAS
Table 2.2.10.7.2 IMAB Score for patients that do not start the treatment – FAS
Table 2.2.10.7.3 IMAB Score for patients that have implementation issues – Safety population
Table 2.2.10.7.4 IMAB Score for patients that do not have implementation issues – Safety population
Table 2.2.10.7.5 IMAB Score for patients that have discontinued the treatment – Safety population
Table 2.2.10.7.6 IMAB Score for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.8.1 Modified BAASIS questionnaire at visit 3 for patients that start the treatment – FAS
Table 2.2.10.8.2 Modified BAASIS questionnaire at visit 3 for patients that do not start the treatment – FAS
Table 2.2.10.8.3 Modified BAASIS questionnaire at visit 3 for patients that have implementation issues – Safety population
Table 2.2.10.8.4 Modified BAASIS questionnaire at visit 3 for patients that do not have implementation issues – Safety population

Table 2.2.10.8.5 Modified BAASIS questionnaire at visit 3 for patients that have discontinued the treatment – Safety population
Table 2.2.10.8.6 Modified BAASIS questionnaire at visit 3 for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.9.1 Modified BAASIS questionnaire at visit 4 for patients that start the treatment – FAS
Table 2.2.10.9.2 Modified BAASIS questionnaire at visit 4 for patients that do not start the treatment – FAS
Table 2.2.10.9.3 Modified BAASIS questionnaire at visit 4 for patients that have implementation issues – Safety population
Table 2.2.10.9.4 Modified BAASIS questionnaire at visit 4 for patients that do not have implementation issues – Safety population
Table 2.2.10.9.5 Modified BAASIS questionnaire at visit 4 for patients that have discontinued the treatment – Safety population
Table 2.2.10.9.6 Modified BAASIS questionnaire at visit 4 for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.10.1 Modified BAASIS questionnaire at visit 5 for patients that start the treatment – FAS
Table 2.2.10.10.2 Modified BAASIS questionnaire at visit 5 for patients that do not start the treatment – FAS
Table 2.2.10.10.3 Modified BAASIS questionnaire at visit 5 for patients that have implementation issues – Safety population
Table 2.2.10.10.4 Modified BAASIS questionnaire at visit 5 for patients that do not have implementation issues – Safety population
Table 2.2.10.10.5 Modified BAASIS questionnaire at visit 5 for patients that have discontinued the treatment – Safety population
Table 2.2.10.10.6 Modified BAASIS questionnaire at visit 5 for patients that do not have discontinued the treatment – Safety population
Table 2.2.10.11.1 Modified BAASIS questionnaire at visit 6 for patients that start the treatment – FAS
Table 2.2.10.11.2 Modified BAASIS questionnaire at visit 6 for patients that do not start the treatment – FAS
Table 2.2.10.11.3 Modified BAASIS questionnaire at visit 6 for patients that have implementation issues – Safety population
Table 2.2.10.11.4 Modified BAASIS questionnaire at visit 6 for patients that do not have implementation issues – Safety population
Table 2.2.10.11.5 Modified BAASIS questionnaire at visit 6 for patients that have discontinued the treatment – Safety population

Table 2.2.10.11.6 Modified BAASIS questionnaire at visit 6 for patients that do not have discontinued the treatment – Safety population

15.3.1 Displays of adverse events

Table 2.1.8.1 Overview of adverse event profile – Safety population

Table 2.1.8.2 All AEs by primary SOC and PT – Safety population

Table 2.1.8.3 All SAEs by primary SOC and PT – Safety population

Table 2.1.8.4 All related to treatment discontinuation AEs by primary SOC and PT – Safety population

Table 2.1.8.5 All AESIs by primary SOC and PT – Safety population

Table 2.1.8.6 All AEs leading to death by primary SOC and PT – Safety population

15.3.2 Listings of deaths, serious adverse events, and other significant adverse events

Table 2.1.8.7 Listing with all death – Safety population

15.3.3 Narratives of deaths, serious adverse events, and other significant adverse events

Not applicable

15.3.3.1 Comprehensive list of all subjects/patients number/narratives

15.3.3.2 Subject/patient narratives – Deaths

Not applicable

15.3.3.3 Subject/patient narratives – Serious adverse events

Not applicable

15.3.3.4 Subject/patient narratives – Withdrawals due to adverse events

Not applicable

15.3.3.5 Subject/patient narratives – Other category to be specified

Not applicable

15.3.4 Abnormal laboratory value listing (each subject/patient)

Not applicable

15.3.5 Listing of other observations related to safety (each subjects/patients)

Not applicable

15.4 PHARMACOKINETIC DATA

Not applicable