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Novartis Clinical Trial Results

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siponimod

Trial Indication(s)

Secondary progressive multiple sclerosis

Protocol Number

CBAF312A2304

Protocol Title

A multicenter, randomized, double-blind, parallel-group, placebo-controlled variable treatment duration study evaluating the efficacy and safety of Siponimod (BAF312) in patients with secondary progressive multiple sclerosis followed by extended treatment with open-label BAF312.

Clinical Trial Phase

Phase 3

Phase of Drug Development

Phase 3

Study Start/End Dates

Study Start Date: December 2012 (Actual)
Primary Completion Date: April 2016 (Actual)
Study Completion Date: July 2023 (Anticipated)

Reason for Termination

Not applicable

Study Design/Methodology

This study has two parts, a Core Part and an Extension Part: the Core Part (presented in this clinical trial result) was a multicenter, randomized, double-blind, parallel-group, placebo-controlled, variable treatment duration study comparing the efficacy and safety of BAF312 in patients with SPMS relative to placebo.

The Screening Epoch was followed by the Treatment Epoch (double-blind treatment, which had a variable treatment duration) and was followed by the Post-Treatment Follow-up Epoch.

Patients were randomized to receive siponimod 2 mg or placebo (2:1 ratio).

Patients started treatment in the Core Part with a titration pack of siponimod or matched placebo to be administered for 6 days. The titration regimens are provided below. Patients with lymphocyte counts (at 2 consecutive visits) of $<0.2 \times 10^9$/L were to reduce the dose to 1 mg/day in a blinded fashion.

Titration and re-titration regimens

Target dose (siponimod or matched placebo)	Day 1	Day 2	Day 3	Day 4	Day 5	Day 6
2 mg	0.25 mg	0.25 mg	0.5 mg	0.75 mg	1.25 mg	2 mg
1 mg	0.25 mg	0.25 mg	0.5 mg	0.75 mg	1 mg	1 mg

Patients who had 6-month CDP during the Treatment Epoch were provided with options that included starting treatment with open-label siponimod as rescue medication. Patients who prematurely discontinued double-blind study drug during the Treatment Epoch were asked to remain in the study and follow an abbreviated visit schedule.

The CP is being followed by an Extension Part (EP), currently ongoing, during which eligible patients receive open-label siponimod. Patients will receive in the open-label Extension Part siponimod for up to approximately 7 years.

Centers

355 centers in 31 countries: Turkey(7), Netherlands(7), Hungary(12), Canada(11), Austria(3), United States(89), Sweden(3), Slovakia (Slovak Republic)(8), Russia(13), Romania(10), Portugal(5), Poland(8), Latvia(3), Lithuania(3), Italy(10), Israel(3), Ireland(3), Greece(4), United Kingdom(10), France(11), Estonia(2), Spain(16), Germany(46), Czech Republic(5), Switzerland(7), Bulgaria(5), Belgium(8), Australia(6), Argentina(6), Japan(20), China(11)

Objectives:

The primary objective was to demonstrate the efficacy of siponimod relative to placebo in delaying the time to 3-month confirmed disability progression (CDP) in patients with SPMS as measured by the Expanded Disability Status Scale (EDSS).

Statistical Methods

The primary analysis was based on the Full Analysis Set (FAS). The primary variable was time to 3-month CDP based on EDSS.

Disability progression was defined as an increase from baseline of: 1 point in patients with a Baseline EDSS score of 3.0 to 5.0, or 0.5 point in patients with a Baseline EDSS score of 5.5 to 6.5. Sustained disability progression for 3-month CDP (primary efficacy variable) was determined by confirming that the criteria were also met at visits 3 months later, with any intervening EDSS values also meeting the criteria for change.

The null hypothesis tested that there was no difference in the time to 3-month CDP between the siponimod and placebo group versus the alternative hypothesis that there was a difference between the groups. The null hypothesis was to be rejected if the observed p-value for the between-group comparison was less than a significance level (two sided) adjusted according to the O'Brien-Fleming alpha level correction which was calculated to be 0.0434. Derivation of the adjusted significance level was dependent on the number of 3-month CDP at interim and final analysis.

The hypothesis was tested using a Cox proportional hazards model with treatment, country, baseline EDSS and SPMS group (baseline definition) as covariate. The estimated hazard ratio (siponimod/placebo hazard rates) with 95% Wald confidence interval was obtained. Log-rank test was also performed; Kaplan-Meier curves and estimates were presented.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-Prior history of relapsing remitting MS
- SPMS defined as progressive increase of disability over at least 6 months
-EDSS score of 3.0 to 6.5
- No relapse of corticosteroid treatment within 3 months
Exclusion Criteria:
-Women of child bearing potential must use reliable forms of contraception.
- Diagnosis of Macular edema during screening period
- Any medically unstable condition determined by investigator.
-Unable to undergo MRI scans
- Hypersensitivity to any study drugs or drugs of similar class
Other protocol defined inclusion/exclusion may apply.

Participant Flow Table

Overall Study

	Siponimod (BAF312)	Placebo

Started	1105	546
Safety set	1099	546
Full analysis set	1099	546
Completed	903	424
Not Completed	202	122
New therapy for study indication	2	1
Technical problems	2	0
Death	3	1
Protocol deviation	3	1
Non-compliance w/study treatment	5	0
Progressive disease	8	4
Lost to Follow-up	9	8
Physician Decision	13	1
Lack of Efficacy	16	11
Adverse Event	45	18
Withdrawal by Subject	96	77

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Baseline Characteristics

	Siponimod (BAF312)	Placebo	Total
Number of Participants [units: participants]	1105	546	1651
Age Continuous (units: Years) Mean ± Standard Deviation			
	48.0±7.84	48.1±7.94	48.0±7.87
Sex: Female, Male (units: Participants) Count of Participants (Not Applicable)			
Female	669	323	992
Male	436	223	659
Race (NIH/OMB) (units: Participants) Count of Participants (Not Applicable)			
American Indian or Alaska Native	0	0	0
Asian	31	18	49
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	7	3	10
White	1050	513	1563
More than one race	0	0	0
Unknown or Not Reported	17	12	29

Primary Outcome Result(s)

Percentage of participants with 3-month Confirmed Disibility Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS)

	Siponimod (BAF312)	Placebo
Number of Participants Analyzed [units: participants]	1096	545
Percentage of participants with 3-month Confirmed Disibility Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS) (units: Percentage of participants)		
	26.3	31.7

Statistical Analysis

Groups	Siponimod (BAF312), Placebo
P Value	0.0134
Method	Other Cox proportional hazards model
Cox Proportional Hazard	0.79
95 % Confidence Interval 2-Sided	0.65 to 0.95

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Safety Results

All-Cause Mortality

	Siponimod (BAF312) N = 1099	Placebo N = 546
Total participants affected	4 (0.36%)	4 (0.73%)

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 3.5 years.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment

	Siponimod (BAF312) N = 1099	Placebo N = 546
Total participants affected	197 (17.93%)	83 (15.20%)
BLOOD AND LYMPHATIC SYSTEM DISORDERS		
ANAEMIA*	0 (0.00%)	2 (0.37%)
LEUKOPENIA*	1 (0.09%)	0 (0.00%)
THROMBOCYTOPENIA*	1 (0.09%)	0 (0.00%)
CARDIAC DISORDERS		
ACUTE CORONARY SYNDROME*	1 (0.09%)	0 (0.00%)

ACUTE MYOCARDIAL INFARCTION*	1 (0.09%)	1 (0.18%)
ANGINA PECTORIS*	1 (0.09%)	1 (0.18%)
ATRIAL FIBRILLATION*	1 (0.09%)	0 (0.00%)
ATRIOVENTRICULAR BLOCK SECOND DEGREE*	2 (0.18%)	0 (0.00%)
BRADYCARDIA*	3 (0.27%)	0 (0.00%)
BUNDLE BRANCH BLOCK LEFT*	1 (0.09%)	0 (0.00%)
CORONARY ARTERY DISEASE*	1 (0.09%)	1 (0.18%)
MYOCARDIAL ISCHAEMIA*	1 (0.09%)	0 (0.00%)
PALPITATIONS*	1 (0.09%)	0 (0.00%)
SINUS TACHYCARDIA*	1 (0.09%)	0 (0.00%)
SUPRAVENTRICULAR TACHYCARDIA*	0 (0.00%)	1 (0.18%)
EAR AND LABYRINTH DISORDERS		
VERTIGO*	0 (0.00%)	1 (0.18%)
EYE DISORDERS		
BLINDNESS*	1 (0.09%)	0 (0.00%)
CATARACT*	0 (0.00%)	1 (0.18%)
DIPLOPIA*	0 (0.00%)	1 (0.18%)
MACULAR OEDEMA*	3 (0.27%)	0 (0.00%)
RETINAL DETACHMENT*	0 (0.00%)	1 (0.18%)
RETINOSCHISIS*	0 (0.00%)	1 (0.18%)
GASTROINTESTINAL DISORDERS		
ABDOMINAL PAIN UPPER*	0 (0.00%)	1 (0.18%)

ANAL FISSURE*	0 (0.00%)	1 (0.18%)
CONSTIPATION*	2 (0.18%)	1 (0.18%)
DIARRHOEA*	1 (0.09%)	1 (0.18%)
DUODENAL ULCER*	0 (0.00%)	1 (0.18%)
GASTRIC ULCER PERFORATION*	0 (0.00%)	1 (0.18%)
GASTRITIS EROSIVE*	1 (0.09%)	0 (0.00%)
INCARCERATED INGUINAL HERNIA*	1 (0.09%)	0 (0.00%)
INGUINAL HERNIA*	1 (0.09%)	0 (0.00%)
INTESTINAL OBSTRUCTION*	1 (0.09%)	1 (0.18%)
NAUSEA*	1 (0.09%)	0 (0.00%)
OESOPHAGITIS*	0 (0.00%)	1 (0.18%)
PANCREATITIS ACUTE*	0 (0.00%)	1 (0.18%)
SMALL INTESTINAL OBSTRUCTION*	0 (0.00%)	1 (0.18%)
UMBILICAL HERNIA, OBSTRUCTIVE*	1 (0.09%)	0 (0.00%)
VOMITING*	1 (0.09%)	0 (0.00%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
ASTHENIA*	2 (0.18%)	0 (0.00%)
FATIGUE*	1 (0.09%)	0 (0.00%)
GAIT DISTURBANCE*	1 (0.09%)	3 (0.55%)
OEDEMA PERIPHERAL*	0 (0.00%)	1 (0.18%)
PYREXIA*	2 (0.18%)	0 (0.00%)
HEPATOBILIARY DISORDERS		
BILIARY COLIC*	1 (0.09%)	0 (0.00%)
CHOLECYSTITIS*	1 (0.09%)	0 (0.00%)

CHOLECYSTITIS ACUTE*	1 (0.09%)	0 (0.00%)
CHOLELITHIASIS*	1 (0.09%)	0 (0.00%)
HEPATOTOXICITY*	1 (0.09%)	0 (0.00%)
NON-ALCOHOLIC STEATOHEPATITIS*	0 (0.00%)	1 (0.18%)
IMMUNE SYSTEM DISORDERS		
HYPERSENSITIVITY*	1 (0.09%)	0 (0.00%)
INFECTIONS AND INFESTATIONS		
APPENDICEAL ABSCESS*	1 (0.09%)	0 (0.00%)
APPENDICITIS*	3 (0.27%)	0 (0.00%)
BACTERAEMIA*	1 (0.09%)	0 (0.00%)
CAMPYLOBACTER GASTROENTERITIS*	0 (0.00%)	1 (0.18%)
CELLULITIS*	2 (0.18%)	0 (0.00%)
CHORIORETINITIS*	1 (0.09%)	0 (0.00%)
DIVERTICULITIS*	1 (0.09%)	0 (0.00%)
ESCHERICHIA URINARY TRACT INFECTION*	1 (0.09%)	0 (0.00%)
GASTROENTERITIS*	2 (0.18%)	1 (0.18%)
GASTROENTERITIS PROTEUS*	0 (0.00%)	1 (0.18%)
HEPATITIS E*	1 (0.09%)	0 (0.00%)
HERPES ZOSTER*	1 (0.09%)	0 (0.00%)
HERPES ZOSTER MENINGITIS*	1 (0.09%)	0 (0.00%)
INFLUENZA*	1 (0.09%)	1 (0.18%)
LABYRINTHITIS*	1 (0.09%)	0 (0.00%)
NASAL ABSCESS*	1 (0.09%)	0 (0.00%)

ORAL VIRAL INFECTION*	1 (0.09%)	0 (0.00%)
PNEUMONIA*	1 (0.09%)	2 (0.37%)
POSTOPERATIVE WOUND INFECTION*	1 (0.09%)	1 (0.18%)
PYELONEPHRITIS*	0 (0.00%)	1 (0.18%)
PYELONEPHRITIS CHRONIC*	1 (0.09%)	0 (0.00%)
SEPSIS*	1 (0.09%)	0 (0.00%)
SEPTIC SHOCK*	2 (0.18%)	0 (0.00%)
UPPER RESPIRATORY TRACT INFECTION*	3 (0.27%)	0 (0.00%)
URINARY TRACT INFECTION*	15 (1.36%)	7 (1.28%)
UROSEPSIS*	5 (0.45%)	1 (0.18%)
WOUND INFECTION*	0 (0.00%)	1 (0.18%)
INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
ANKLE FRACTURE*	2 (0.18%)	0 (0.00%)
CERVICAL VERTEBRAL FRACTURE*	1 (0.09%)	0 (0.00%)
CLAVICLE FRACTURE*	2 (0.18%)	0 (0.00%)
CONCUSSION*	5 (0.45%)	0 (0.00%)
CONTUSION*	1 (0.09%)	0 (0.00%)
EYE CONTUSION*	1 (0.09%)	0 (0.00%)
FALL*	2 (0.18%)	0 (0.00%)
FEMORAL NECK FRACTURE*	3 (0.27%)	1 (0.18%)
FRACTURE DISPLACEMENT*	1 (0.09%)	0 (0.00%)
HEAD INJURY*	0 (0.00%)	1 (0.18%)
HIP FRACTURE*	0 (0.00%)	2 (0.37%)

INJURY CORNEAL*	1 (0.09%)	0 (0.00%)
LACERATION*	4 (0.36%)	0 (0.00%)
LOWER LIMB FRACTURE*	0 (0.00%)	1 (0.18%)
MENISCUS INJURY*	0 (0.00%)	1 (0.18%)
RADIUS FRACTURE*	1 (0.09%)	0 (0.00%)
RIB FRACTURE*	1 (0.09%)	0 (0.00%)
SPINAL COMPRESSION FRACTURE*	1 (0.09%)	0 (0.00%)
SPLENIC RUPTURE*	1 (0.09%)	0 (0.00%)
SUBDURAL HAEMATOMA*	1 (0.09%)	0 (0.00%)
TENDON RUPTURE*	0 (0.00%)	1 (0.18%)
THERMAL BURN*	1 (0.09%)	0 (0.00%)
TIBIA FRACTURE*	0 (0.00%)	1 (0.18%)
TRAUMATIC FRACTURE*	1 (0.09%)	0 (0.00%)
TRAUMATIC HAEMORRHAGE*	1 (0.09%)	0 (0.00%)
TRAUMATIC HAEMOTHORAX*	1 (0.09%)	0 (0.00%)
TRAUMATIC LIVER INJURY*	1 (0.09%)	0 (0.00%)
INVESTIGATIONS		
ALANINE AMINOTRANSFERASE INCREASED*	10 (0.91%)	2 (0.37%)
ASPARTATE AMINOTRANSFERASE INCREASED*	5 (0.45%)	1 (0.18%)
BLOOD BILIRUBIN INCREASED*	2 (0.18%)	0 (0.00%)

BLOOD GLUCOSE INCREASED*	1 (0.09%)	0 (0.00%)
CARBON MONOXIDE DIFFUSING CAPACITY DECREASED*	1 (0.09%)	0 (0.00%)
COLUMBIA SUICIDE SEVERITY RATING SCALE ABNORMAL*	2 (0.18%)	0 (0.00%)
HEART RATE DECREASED*	1 (0.09%)	0 (0.00%)
HEPATIC ENZYME ABNORMAL*	1 (0.09%)	0 (0.00%)
HEPATIC ENZYME INCREASED*	1 (0.09%)	0 (0.00%)
LIVER FUNCTION TEST ABNORMAL*	0 (0.00%)	1 (0.18%)
PULMONARY FUNCTION TEST DECREASED*	1 (0.09%)	0 (0.00%)
WALKING DISTANCE TEST ABNORMAL*	1 (0.09%)	0 (0.00%)
WEIGHT DECREASED*	1 (0.09%)	0 (0.00%)
METABOLISM AND NUTRITION DISORDERS		
DEHYDRATION*	2 (0.18%)	0 (0.00%)
HAEMOCHROMATOSIS*	1 (0.09%)	0 (0.00%)
SHOCK HYPOGLYCAEMIC*	0 (0.00%)	1 (0.18%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA*	1 (0.09%)	0 (0.00%)
ARTHRITIS*	1 (0.09%)	0 (0.00%)
BACK PAIN*	1 (0.09%)	0 (0.00%)
BURSITIS*	1 (0.09%)	0 (0.00%)

FOOT DEFORMITY*	1 (0.09%)	0 (0.00%)
INTERVERTEBRAL DISC PROTRUSION*	1 (0.09%)	1 (0.18%)
LUMBAR SPINAL STENOSIS*	1 (0.09%)	0 (0.00%)
MUSCULAR WEAKNESS*	3 (0.27%)	0 (0.00%)
MUSCULOSKELETAL PAIN*	1 (0.09%)	0 (0.00%)
MUSCULOSKELETAL STIFFNESS*	0 (0.00%)	1 (0.18%)
OSTEOARTHRITIS*	1 (0.09%)	0 (0.00%)
PATELLOFEMORAL PAIN SYNDROME*	0 (0.00%)	1 (0.18%)
SPINAL DEFORMITY*	1 (0.09%)	0 (0.00%)
SYNOVIAL CYST*	1 (0.09%)	0 (0.00%)
NEOPLASMS BENIGN, MALIGNANT AND UNSPECIFIED (INCL CYSTS AND POLYPS)		
BASAL CELL CARCINOMA*	11 (1.00%)	7 (1.28%)
BENIGN NEOPLASM OF THYROID GLAND*	1 (0.09%)	0 (0.00%)
BLADDER CANCER*	0 (0.00%)	1 (0.18%)
BOWEN'S DISEASE*	1 (0.09%)	1 (0.18%)
BREAST CANCER*	1 (0.09%)	1 (0.18%)
CENTRAL NERVOUS SYSTEM LYMPHOMA*	0 (0.00%)	1 (0.18%)
COLON CANCER STAGE IV*	1 (0.09%)	0 (0.00%)
ENDOMETRIAL CANCER*	1 (0.09%)	0 (0.00%)
GASTRIC CANCER*	0 (0.00%)	1 (0.18%)

GASTROINTESTINAL MELANOMA*	1 (0.09%)	0 (0.00%)
GLIOMA*	0 (0.00%)	1 (0.18%)
LIP SQUAMOUS CELL CARCINOMA*	1 (0.09%)	0 (0.00%)
LUNG ADENOCARCINOMA*	0 (0.00%)	1 (0.18%)
LUNG ADENOCARCINOMA METASTATIC*	1 (0.09%)	0 (0.00%)
MALIGNANT MELANOMA IN SITU*	2 (0.18%)	0 (0.00%)
MELANOCYTIC NAEVUS*	1 (0.09%)	0 (0.00%)
NEUROFIBROMA*	1 (0.09%)	0 (0.00%)
PROSTATE CANCER*	0 (0.00%)	2 (0.37%)
RENAL ONCOCYTOMA*	0 (0.00%)	1 (0.18%)
SEMINOMA*	2 (0.18%)	0 (0.00%)
SQUAMOUS CELL CARCINOMA*	1 (0.09%)	0 (0.00%)
UTERINE LEIOMYOMA*	1 (0.09%)	1 (0.18%)
NERVOUS SYSTEM DISORDERS		
ALLODYNIA*	0 (0.00%)	1 (0.18%)
AMNESTIC DISORDER*	0 (0.00%)	1 (0.18%)
APHASIA*	1 (0.09%)	0 (0.00%)
ATAXIA*	1 (0.09%)	0 (0.00%)
BRAIN INJURY*	1 (0.09%)	0 (0.00%)
BRAIN STEM INFARCTION*	1 (0.09%)	0 (0.00%)
CEREBROVASCULAR ACCIDENT*	2 (0.18%)	1 (0.18%)

DISTURBANCE IN ATTENTION*	1 (0.09%)	0 (0.00%)
DIZZINESS*	1 (0.09%)	0 (0.00%)
DYSAESTHESIA*	0 (0.00%)	1 (0.18%)
EPILEPSY*	5 (0.45%)	0 (0.00%)
GENERALISED TONIC-CLONIC SEIZURE*	1 (0.09%)	0 (0.00%)
HAEMORRHAGIC STROKE*	0 (0.00%)	1 (0.18%)
HEAD TITUBATION*	1 (0.09%)	0 (0.00%)
HEMIPARESIS*	3 (0.27%)	0 (0.00%)
HYPOAESTHESIA*	0 (0.00%)	1 (0.18%)
INTENTION TREMOR*	1 (0.09%)	0 (0.00%)
INTRACRANIAL ANEURYSM*	1 (0.09%)	0 (0.00%)
ISCHAEMIC STROKE*	1 (0.09%)	0 (0.00%)
MERALGIA PARAESTHETICA*	0 (0.00%)	1 (0.18%)
MULTIPLE SCLEROSIS*	2 (0.18%)	0 (0.00%)
MULTIPLE SCLEROSIS RELAPSE*	2 (0.18%)	7 (1.28%)
MUSCLE SPASTICITY*	2 (0.18%)	1 (0.18%)
PARAPARESIS*	0 (0.00%)	3 (0.55%)
PARTIAL SEIZURES*	2 (0.18%)	0 (0.00%)
POLYNEUROPATHY*	1 (0.09%)	0 (0.00%)
PUTAMEN HAEMORRHAGE*	0 (0.00%)	1 (0.18%)
RADICULOPATHY*	1 (0.09%)	0 (0.00%)
SEIZURE*	4 (0.36%)	0 (0.00%)
STATUS MIGRAINOSUS*	1 (0.09%)	0 (0.00%)

SUBARACHNOID HAEMATOMA*	1 (0.09%)	0 (0.00%)
SYNCOPE*	4 (0.36%)	1 (0.18%)
TRANSIENT ISCHAEMIC ATTACK*	1 (0.09%)	1 (0.18%)
TREMOR*	0 (0.00%)	1 (0.18%)
TRIGEMINAL NEURALGIA*	3 (0.27%)	0 (0.00%)
PREGNANCY, PUERPERIUM AND PERINATAL CONDITIONS		
ABORTION SPONTANEOUS*	1 (0.09%)	0 (0.00%)
PSYCHIATRIC DISORDERS		
ANXIETY*	1 (0.09%)	0 (0.00%)
ANXIETY DISORDER DUE TO A GENERAL MEDICAL CONDITION*	1 (0.09%)	0 (0.00%)
COMPLETED SUICIDE*	1 (0.09%)	0 (0.00%)
DEPRESSED MOOD*	1 (0.09%)	0 (0.00%)
DEPRESSION*	5 (0.45%)	2 (0.37%)
DEPRESSION SUICIDAL*	1 (0.09%)	0 (0.00%)
DEPRESSIVE SYMPTOM*	1 (0.09%)	0 (0.00%)
EUPHORIC MOOD*	1 (0.09%)	0 (0.00%)
HALLUCINATION*	1 (0.09%)	0 (0.00%)
MANIA*	1 (0.09%)	0 (0.00%)
MENTAL STATUS CHANGES*	1 (0.09%)	0 (0.00%)
PANIC ATTACK*	1 (0.09%)	1 (0.18%)
PSYCHOTIC DISORDER*	1 (0.09%)	0 (0.00%)

SUICIDAL BEHAVIOUR*	3 (0.27%)	0 (0.00%)
SUICIDAL IDEATION*	3 (0.27%)	1 (0.18%)
SUICIDE ATTEMPT*	4 (0.36%)	3 (0.55%)
RENAL AND URINARY DISORDERS		
ACUTE KIDNEY INJURY*	1 (0.09%)	0 (0.00%)
BLADDER DYSFUNCTION*	2 (0.18%)	0 (0.00%)
CALCULUS BLADDER*	1 (0.09%)	0 (0.00%)
HYDRONEPHROSIS*	2 (0.18%)	1 (0.18%)
NEPHROLITHIASIS*	1 (0.09%)	1 (0.18%)
NEUROGENIC BLADDER*	1 (0.09%)	0 (0.00%)
SINGLE FUNCTIONAL KIDNEY*	1 (0.09%)	0 (0.00%)
URETEROLITHIASIS*	1 (0.09%)	0 (0.00%)
URETHRAL STENOSIS*	1 (0.09%)	0 (0.00%)
URGE INCONTINENCE*	1 (0.09%)	0 (0.00%)
URINARY INCONTINENCE*	2 (0.18%)	0 (0.00%)
URINARY RETENTION*	3 (0.27%)	2 (0.37%)
REPRODUCTIVE SYSTEM AND BREAST DISORDERS		
CERVICAL DYSPLASIA*	0 (0.00%)	1 (0.18%)
MENORRHAGIA*	2 (0.18%)	0 (0.00%)
METRORRHAGIA*	2 (0.18%)	1 (0.18%)
OVARIAN DISORDER*	1 (0.09%)	0 (0.00%)
TESTICULAR ATROPHY*	0 (0.00%)	1 (0.18%)
RESPIRATORY, THORACIC AND		

MEDIASTINAL DISORDERS		
PNEUMONIA ASPIRATION*	1 (0.09%)	0 (0.00%)
PULMONARY EMBOLISM*	1 (0.09%)	1 (0.18%)
PULMONARY HYPERTENSION*	1 (0.09%)	0 (0.00%)
RESPIRATORY DEPRESSION*	1 (0.09%)	0 (0.00%)
RESPIRATORY DISORDER*	1 (0.09%)	0 (0.00%)
SKIN AND SUBCUTANEOUS TISSUE DISORDERS		
ACTINIC KERATOSIS*	0 (0.00%)	1 (0.18%)
DECUBITUS ULCER*	1 (0.09%)	1 (0.18%)
RASH*	1 (0.09%)	0 (0.00%)
RASH PAPULAR*	1 (0.09%)	0 (0.00%)
SOCIAL CIRCUMSTANCES		
IMMOBILE*	1 (0.09%)	0 (0.00%)
WALKING DISABILITY*	0 (0.00%)	1 (0.18%)
VASCULAR DISORDERS		
CIRCULATORY COLLAPSE*	0 (0.00%)	1 (0.18%)
DEEP VEIN THROMBOSIS*	1 (0.09%)	0 (0.00%)
HAEMATOMA*	1 (0.09%)	0 (0.00%)
HYPERTENSION*	1 (0.09%)	0 (0.00%)
ORTHOSTATIC HYPOTENSION*	1 (0.09%)	0 (0.00%)
VENOUS THROMBOSIS LIMB*	1 (0.09%)	0 (0.00%)

* Non-systematic Assessment

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit) up to approximately 3.5 years.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Siponimod (BAF312) N = 1099	**Placebo N = 546**
Total participants affected	698 (63.51%)	311 (56.96%)
GASTROINTESTINAL DISORDERS		
DIARRHOEA*	69 (6.28%)	22 (4.03%)
NAUSEA*	73 (6.64%)	19 (3.48%)
GENERAL DISORDERS AND ADMINISTRATION SITE CONDITIONS		
FATIGUE*	100 (9.10%)	51 (9.34%)
INFECTIONS AND INFESTATIONS		
INFLUENZA*	72 (6.55%)	40 (7.33%)
NASOPHARYNGITIS*	149 (13.56%)	79 (14.47%)
UPPER RESPIRATORY TRACT INFECTION*	89 (8.10%)	41 (7.51%)
URINARY TRACT INFECTION*	128 (11.65%)	75 (13.74%)

INJURY, POISONING AND PROCEDURAL COMPLICATIONS		
FALL*	126 (11.46%)	59 (10.81%)
INVESTIGATIONS		
ALANINE AMINOTRANSFERASE INCREASED*	58 (5.28%)	8 (1.47%)
MUSCULOSKELETAL AND CONNECTIVE TISSUE DISORDERS		
ARTHRALGIA*	49 (4.46%)	35 (6.41%)
BACK PAIN*	66 (6.01%)	43 (7.88%)
PAIN IN EXTREMITY*	60 (5.46%)	21 (3.85%)
NERVOUS SYSTEM DISORDERS		
DIZZINESS*	74 (6.73%)	26 (4.76%)
HEADACHE*	159 (14.47%)	71 (13.00%)
PSYCHIATRIC DISORDERS		
DEPRESSION*	44 (4.00%)	28 (5.13%)
VASCULAR DISORDERS		
HYPERTENSION*	114 (10.37%)	41 (7.51%)

* Non-systematic Assessment

Conclusion:

- SPMS patients treated with siponimod in this study showed a statistically significant and clinically meaningful delay in the time to 3-month CDP (primary endpoint) compared to patients who received placebo (21.2% risk reduction) compared to placebo and this was also the case for the more stringent secondary endpoint of time to 6-month CDP.

- Treatment with siponimod was generally safe and well tolerated, specifically regarding bradyarrhythmic effects at treatment initiation after introduction of a titration regimen. The safety profile observed in this study was generally consistent with the predefined risks associated with S1P receptor modulators.
- Dose titration during treatment initiation has proven successful in mitigating the cardiovascular effects of siponimod on heart rate and atrio-ventricular conduction; most events were asymptomatic and transient; the few individual reported symptomatic events were benign in nature. The proposed pre-defined criteria for assignment of patients to two groups can be used to further differentiate patients with potential cardiovascular risk during siponimod treatment initiation.

Date of Clinical Trial Report (Interim – Core Part)

March 1, 2018

Swiss Authorization date and authorization number

Swissmedic Approval Number: 67230

Swissmedic Approval Date: 22-Oct-2020

Novartis Study Code

CBAF312A2304

EudraCT Number

2012-003056-36

Planned and Actual Number of Patients

Planned: 1530 subjects

Enrolled: 1651 subjects

Batch Numbers

Study drug and strength	Formulation control number	Batch Number
Siponimod 1 mg	6002630.010	1010004143 X005 0113
Siponimod 2 mg	6003077.003	1010004147 X005 0212 X007 0113 X008 0113 X276 1111
Siponimod 2 mg Open-Label	6003077.003	1010004147 1010004149 X005 0212 X008 0113
Siponimod titration pack 2 mg	6002636.010	X002 0113 X274 1111
	6003077.003	1010004145 X007 0113
Siponimod titration pack 2 mg Open-Label	6002636.010	X002 0113
	6003077.003	1010004145 X008 0113

Information on comparators drug dosage, route of administration, batch numbers

Study drug and strength	Formulation control number	Batch Number
Placebo	6002679.004	X007 0112 X096 0312
Placebo titration pack	6002679.004	1010004139 X001 0113 X007 0112 X096 0312

Publication(s)

Not applicable.

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