NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siponimod

Trial Indication(s)

Relapsing Remitting Multiple Sclerosis

Protocol Number

CBAF312A2201E1

Protocol Title

A dose blinded extension study to the CBAF312A2201 study to evaluate long-term safety, tolerability and efficacy of BAF312 given orally once daily in patients with relapsing-remitting multiple sclerosis

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase II

Study Start/End Dates

Study Start Date: August 2010 (Actual)
Primary Completion Date: October 2016 (Actual)
Study Completion Date: October 2016 (Actual)

Reason for Termination (If applicable)

The study was prematurely discontinued after approximately 5 years. The decision to discontinue the study was due to the change of the targeted multiple sclerosis population.

Study Design/Methodology

This was a Phase II, multicenter, multinational, Extension Study designed to provide data on the long-term safety, tolerability and efficacy of siponimod in patients with RRMS who had completed the Phase II Core Study (CBAF312A2201).

Originally designed as a 2-year, 5 arm, parallel group, dose-blinded study; it was subsequently prolonged by protocol amendment with the addition of a sequential Open-Label Phase (when all patients received the optimal siponimod 2mg dose selected on the basis of the analysis of the Core study) making the total study duration approximately 5 years.

An initial siponimod dose-titration was used at the start of the treatment or at the start of treatment re-initiation in this study.

The two parts of the study were:

Dose-blinded Phase (DB Phase): This parallel group phase was started, while the Core Study was still ongoing and the patients received 1 of 5 active doses of siponimod used in the Core Study (10 mg, 2 mg, 1.25 mg, 0.5 mg and 0.25 mg), in a blinded fashion. This Phase was required to be conducted in a blinded manner in order to avoid unblinding of the ongoing Core Study.

Open-label Phase (OL Phase): Based on the Core Study results, siponimod at a dose of 2 mg/day was selected as the optimal treatment dose. All patients in the Extension Study were shifted to Open-label treatment with the dose of 2 mg in this Phase.

Centers

48 centers in 12 countries: United States(8), Turkey(5), Russia(5), Poland(3), Norway(2), Italy(4), Hungary(4), Finland(3), Spain(3), Germany(4), Switzerland(3), Canada(4)

Objectives:

Primary objectives:

The primary objective was to evaluate long-term safety and tolerability of siponimod in relapsing-remitting multiple sclerosis (RRMS) patients, with specific emphasis on:

- effects on cardiac conduction during the titration of the study drug
- long-term blood pressure effects
- viral infections
- incidence of macular edema
- dermatologic alterations

Secondary objectives:

The secondary objectives were to evaluate long-term efficacy on clinical grounds (relapse rate and disability progression) and paraclinical grounds.

Test Product (s), Dose(s), and Mode(s) of Administration

Oral tablets of siponimod, daily doses of 0.25mg, 0.5mg, 1.25mg, 2mg and 10mg.

Statistical Methods

Statistical analyses were, as planned, descriptive rather than inferential.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
- Patients completed the core study BAF312A2201
- Written informed consent provided before any assessment of the extension study
- Female patients at risk of becoming pregnant must have a negative pregnancy test and use simultaneously two forms of effective contraception

Exclusion Criteria:
- Newly diagnosed systemic disease other than MS (which may require immunosuppressive treatment)
- Malignancies, diabetes, significant cardiovascular and pulmonary diseases and conditions
- Active infections

Participant Flow Table

Overall Study

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Started	33	29	43	29	50
Patients with washout	33	29	39	29	33
Patients without washout	0	0	4	0	17
Patients on placebo in Core	8	7	9	8	2
Completed	26	20	33	23	26
Not Completed	7	9	10	6	24
Abnormal laboratory value(s)	1	2	1	0	0
Protocol Violation	0	0	0	1	1
Abnormal test procedure result	0	0	0	0	1
Death	0	1	0	0	0
Condition no longer	0	0	0	0	1

required study drug					
Adverse Event	2	3	1	2	5
Lack of Efficacy	0	0	3	0	9
Withdrawal by Subject	3	2	2	1	3
Lost to Follow-up	1	1	2	1	2
Administrative problems	0	0	1	1	2

Baseline Characteristics

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg	Total
Number of Participants [units: participants]	33	29	43	29	50	184
Gender, Male/Female (units: Participants)						
Female	21	18	32	18	41	130
Male	12	11	11	11	9	54
Age Continuous (units: years) Mean ± Standard Deviation	36.8±9.09	35.1±9.16	34.0±7.57	35.2±9.10	37.2±8.42	35.7±8.59

Expanded disability status scale (EDSS)[1] (units: Combined scores) Mean ± Standard Deviation	2.03±0.960	2.19±1.278	1.95±1.096	1.88±1.374	2.22±1.258	2.07±1.190

[1] Disability progression was assessed based on the EDSS scores ranging from 0 (normal) to 10 (death due to MS)

Primary Result(s)

Total number of adverse events during evaluation of long term safety and tolerability of BAF312A in Extension study.

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Number of Participants Analyzed [units: participants]	33	29	43	29	50
Total number of adverse events during evaluation of long term safety and tolerability of BAF312A in Extension study. (units: events)					
Serious adverse events	4	7	6	6	8
Other adverse events	30	26	42	29	42

Number of participants with cardiac conduction abnormalities during the titration phase of the study

BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg

Number of Participants Analyzed [units: participants]	33	29	39	29	33
Number of participants with cardiac conduction abnormalities during the titration phase of the study (units: participants)					
With WO (33,29,39,29,33) Conduction-Prolonged QTc	5	2	5	2	4
With washout (33,29,39,29,33) Conduction - IVCD	3	8	1	3	0
With WO (33,29,39,29,33) Conduction - AV Mobitz I	1	0	0	0	0
With WO (33,29,39,29,33) Con:1st degree AV block	0	1	1	1	1
With washout (33,29,39,29,33) Conduction - WPW	0	0	0	1	0
Without washout (0,0,4,0,17) Conduction - IVCD	0	0	0	0	4

Number of participants with changes in blood pressure for overall extension study. (Extension analysis set)

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Number of Participants Analyzed [units: participants]	33	29	43	29	50
Number of participants with changes in blood pressure for overall extension study. (Extension analysis set) (units: participants)					

SBP Low: ≤ 90	1	3	2	1	1
SBP ≥ 20 decrease from baseline	8	10	4	6	10
SBP High: ≥ 160	1	1	1	3	3
SBP ≥ 20 increase from baseline	9	8	12	13	18
DBP Low: ≤ 50	1	0	1	0	1
DBP ≥ 15 decrease from baseline	14	8	10	10	10
DBP High: ≥ 100	4	7	4	4	4
DBP ≥ 15 increase from baseline	9	13	13	11	17

Number of participants with viral infections of interest greater or equal to 5% in any dose group (Extension Set)

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Number of Participants Analyzed [units: participants]	33	29	43	29	50
Number of participants with viral infections of interest greater or equal to 5% in any dose group (Extension Set) (units: participants)					
Oral herpes	5	0	4	2	4
Herpes zoster	5	0	3	2	0
Influenza	3	4	3	6	6

Number of participants with dermatologic alterations - basal cell carcinoma (Extension Set)

BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg

Number of Participants Analyzed [units: participants]	33	29	43	29	50
Number of participants with dermatologic alterations - basal cell carcinoma (Extension Set) (units: participants)	1	0	1	0	1

Secondary Outcome Result(s)

Number of relapses in one year - annualized relapse rates for overall extension study (ARR) (Extension Set)

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Number of Participants Analyzed [units: participants]	33	29	43	29	50
Number of relapses in one year - annualized relapse rates for overall extension study (ARR) (Extension Set) (units: Group level ARR) Mean (95% Confidence Interval)	0.18 (0.11 to 0.31)	0.15 (0.08 to 0.26)	0.16 (0.10 to 0.26)	0.19 (0.11 to 0.33)	0.22 (0.14 to 0.35)

Percentage of participants free of Magnetic Resonance Imaging (MRI) identified disease activity at any scan during Extension Study (Extension Set)

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Number of Participants Analyzed [units: participants]	31	26	43	29	47

Percentage of participants free of Magnetic Resonance Imaging (MRI) identified disease activity at any scan during Extension Study (Extension Set)
(units: percentage of participants)

Free of Gd-enhanced T1 lesions at any scan	58.1	57.7	58.1	44.8	66.0
Free of new/enlarging T2 lesions at any scan	32.3	42.3	46.5	20.7	40.4
Free of Gd-enhanced T1 and new enlarged T2 lesions	32.3	42.3	44.2	20.7	40.4

Percentage of participants free of confirmed disability progression in Extension Study (Extension Set)

	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Number of Participants Analyzed [units: participants]	33	29	43	29	50
Percentage of participants free of confirmed disability progression in Extension Study (Extension Set) (units: percentage of participants) Number (95% Confidence Interval)	72.3 (56.0 to 88.7)	82.4 (66.6 to 98.3)	84.8 (73.5 to 96.0)	81.4 (66.6 to 96.1)	78.6 (65.4 to 91.9)

Summary of Safety

Safety Results

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.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment

	BAF312 10/2 mg N = 33	BAF312 2/2 mg N = 29	BAF312 1.25/2 mg N = 43	BAF312 0.5/2 mg N = 29	BAF312 0.25/2 mg N = 50	All patients N = 184

Total participants affected	4 (12.12%)	7 (24.14%)	6 (13.95%)	6 (20.69%)	8 (16.00%)	31 (16.85%)
Blood and lymphatic system disorders						
Splenic cyst	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Ear and labyrinth disorders						
Otosclerosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Eye disorders						
Glaucoma	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Gastrointestinal disorders						
Abdominal discomfort	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Gastritis	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Pancreatitis acute	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
General disorders and administration site conditions						
Submandibular mass	1 (3.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Hepatobiliary disorders						
Biliary dyskinesia	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Immune system disorders						
Anaphylactic reaction	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Infections and infestations						

Oral herpes	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Pyelonephritis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Pyelonephritis acute	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Injury, poisoning and procedural complications						
Ankle fracture	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Craniocerebral injury	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Femur fracture	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Tendon rupture	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Investigations						
Smear cervix abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Metabolism and nutrition disorders						
Decreased appetite	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						
Basal cell carcinoma	1 (3.03%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Breast cancer	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	1 (2.00%)	2 (1.09%)
Colon cancer metastatic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)
Nervous system disorders						

Dysaesthesia	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Generalised tonic-clonic seizure	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Multiple sclerosis relapse	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	2 (4.00%)	3 (1.63%)
Sciatica	1 (3.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Seizure	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Pregnancy, puerperium and perinatal conditions						
Abortion	0 (0.00%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Psychiatric disorders						
Depression	1 (3.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Drug abuse	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Mental disorder	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Renal and urinary disorders						
Stress urinary incontinence	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Reproductive system and breast disorders						
Benign prostatic hyperplasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	1 (0.54%)
Metrorrhagia	1 (3.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (0.54%)
Uterine cervical metaplasia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	1 (0.54%)

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.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	3.999%

	BAF312 10/2 mg N = 33	BAF312 2/2 mg N = 29	BAF312 1.25/2 mg N = 43	BAF312 0.5/2 mg N = 29	BAF312 0.25/2 mg N = 50	All patients N = 184
Total participants affected	30 (90.91%)	26 (89.66%)	42 (97.67%)	29 (100.00%)	42 (84.00%)	169 (91.85%)
Blood and lymphatic system disorders						
Leukopenia	0 (0.00%)	1 (3.45%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	3 (1.63%)
Lymphadenitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	2 (1.09%)
Lymphopenia	6 (18.18%)	5 (17.24%)	4 (9.30%)	6 (20.69%)	3 (6.00%)	24 (13.04%)
Cardiac disorders						
Palpitations	0 (0.00%)	2 (6.90%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	3 (1.63%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	2 (4.00%)	3 (1.63%)
Ear and labyrinth disorders						
Ear pain	0 (0.00%)	1 (3.45%)	2 (4.65%)	0 (0.00%)	1 (2.00%)	4 (2.17%)
Tinnitus	1 (3.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	3 (1.63%)

Vertigo	4 (12.12%)	1 (3.45%)	3 (6.98%)	2 (6.90%)	6 (12.00%)	16 (8.70%)
Vertigo positional	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	1 (2.00%)	3 (1.63%)
Eye disorders						
Conjunctivitis	1 (3.03%)	0 (0.00%)	2 (4.65%)	1 (3.45%)	1 (2.00%)	5 (2.72%)
Eye pain	2 (6.06%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	3 (1.63%)
Iridocyclitis	0 (0.00%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Vision blurred	2 (6.06%)	0 (0.00%)	3 (6.98%)	0 (0.00%)	0 (0.00%)	5 (2.72%)
Gastrointestinal disorders						
Abdominal pain	0 (0.00%)	1 (3.45%)	2 (4.65%)	1 (3.45%)	3 (6.00%)	7 (3.80%)
Abdominal pain upper	0 (0.00%)	1 (3.45%)	3 (6.98%)	5 (17.24%)	3 (6.00%)	12 (6.52%)
Aphthous ulcer	0 (0.00%)	0 (0.00%)	1 (2.33%)	2 (6.90%)	0 (0.00%)	3 (1.63%)
Constipation	1 (3.03%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	4 (2.17%)
Diarrhoea	1 (3.03%)	2 (6.90%)	7 (16.28%)	3 (10.34%)	6 (12.00%)	19 (10.33%)
Dyspepsia	1 (3.03%)	1 (3.45%)	1 (2.33%)	0 (0.00%)	2 (4.00%)	5 (2.72%)
Enteritis	0 (0.00%)	2 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Gastritis	0 (0.00%)	2 (6.90%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	3 (1.63%)
Gastrooesophageal reflux disease	1 (3.03%)	0 (0.00%)	1 (2.33%)	3 (10.34%)	1 (2.00%)	6 (3.26%)
Irritable bowel syndrome	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	2 (1.09%)
Nausea	1 (3.03%)	0 (0.00%)	0 (0.00%)	3 (10.34%)	4 (8.00%)	8 (4.35%)
Toothache	0 (0.00%)	2 (6.90%)	4 (9.30%)	1 (3.45%)	4 (8.00%)	11 (5.98%)
Vomiting	1 (3.03%)	3 (10.34%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	7 (3.80%)
General disorders and administration site conditions						
Asthenia	0 (0.00%)	1 (3.45%)	2 (4.65%)	0 (0.00%)	1 (2.00%)	4 (2.17%)

Fatigue	1 (3.03%)	4 (13.79%)	5 (11.63%)	2 (6.90%)	6 (12.00%)	18 (9.78%)
Gait disturbance	3 (9.09%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	4 (2.17%)
Influenza like illness	1 (3.03%)	0 (0.00%)	2 (4.65%)	1 (3.45%)	1 (2.00%)	5 (2.72%)
Non-cardiac chest pain	3 (9.09%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	2 (4.00%)	6 (3.26%)
Oedema peripheral	0 (0.00%)	2 (6.90%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	3 (1.63%)
Pyrexia	2 (6.06%)	1 (3.45%)	4 (9.30%)	3 (10.34%)	5 (10.00%)	15 (8.15%)
Infections and infestations						
Acute sinusitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	3 (1.63%)
Bronchitis	0 (0.00%)	2 (6.90%)	5 (11.63%)	3 (10.34%)	6 (12.00%)	16 (8.70%)
Conjunctivitis	2 (6.06%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	3 (1.63%)
Cystitis	3 (9.09%)	1 (3.45%)	2 (4.65%)	1 (3.45%)	1 (2.00%)	8 (4.35%)
Fungal infection	3 (9.09%)	1 (3.45%)	0 (0.00%)	1 (3.45%)	1 (2.00%)	6 (3.26%)
Fungal skin infection	2 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Gastroenteritis	0 (0.00%)	2 (6.90%)	1 (2.33%)	3 (10.34%)	4 (8.00%)	10 (5.43%)
Gastroenteritis viral	0 (0.00%)	0 (0.00%)	3 (6.98%)	0 (0.00%)	2 (4.00%)	5 (2.72%)
Herpes zoster	5 (15.15%)	0 (0.00%)	3 (6.98%)	2 (6.90%)	0 (0.00%)	10 (5.43%)
Influenza	4 (12.12%)	4 (13.79%)	5 (11.63%)	7 (24.14%)	7 (14.00%)	27 (14.67%)
Nasopharyngitis	10 (30.30%)	8 (27.59%)	17 (39.53%)	11 (37.93%)	18 (36.00%)	64 (34.78%)
Onychomycosis	1 (3.03%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	5 (2.72%)
Oral herpes	5 (15.15%)	0 (0.00%)	4 (9.30%)	2 (6.90%)	4 (8.00%)	15 (8.15%)
Otitis media	1 (3.03%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	5 (2.72%)
Pharyngitis	1 (3.03%)	4 (13.79%)	3 (6.98%)	6 (20.69%)	3 (6.00%)	17 (9.24%)
Pneumonia	1 (3.03%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	4 (2.17%)
Respiratory tract infection	0 (0.00%)	1 (3.45%)	1 (2.33%)	1 (3.45%)	2 (4.00%)	5 (2.72%)
Rhinitis	3 (9.09%)	2 (6.90%)	1 (2.33%)	0 (0.00%)	1 (2.00%)	7 (3.80%)

Sinusitis	3 (9.09%)	2 (6.90%)	3 (6.98%)	5 (17.24%)	5 (10.00%)	18 (9.78%)
Subcutaneous abscess	0 (0.00%)	2 (6.90%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Tinea versicolour	0 (0.00%)	2 (6.90%)	2 (4.65%)	0 (0.00%)	1 (2.00%)	5 (2.72%)
Tonsillitis	1 (3.03%)	1 (3.45%)	5 (11.63%)	2 (6.90%)	1 (2.00%)	10 (5.43%)
Tooth infection	1 (3.03%)	2 (6.90%)	1 (2.33%)	1 (3.45%)	0 (0.00%)	5 (2.72%)
Upper respiratory tract infection	4 (12.12%)	6 (20.69%)	4 (9.30%)	7 (24.14%)	9 (18.00%)	30 (16.30%)
Urinary tract infection	6 (18.18%)	4 (13.79%)	2 (4.65%)	4 (13.79%)	4 (8.00%)	20 (10.87%)
Vaginal infection	0 (0.00%)	0 (0.00%)	1 (2.33%)	2 (6.90%)	2 (4.00%)	5 (2.72%)
Vulvovaginal candidiasis	0 (0.00%)	0 (0.00%)	1 (2.33%)	1 (3.45%)	2 (4.00%)	4 (2.17%)
Injury, poisoning and procedural complications						
Contusion	2 (6.06%)	2 (6.90%)	0 (0.00%)	3 (10.34%)	1 (2.00%)	8 (4.35%)
Fall	3 (9.09%)	3 (10.34%)	0 (0.00%)	2 (6.90%)	1 (2.00%)	9 (4.89%)
Joint injury	1 (3.03%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	3 (1.63%)
Ligament sprain	2 (6.06%)	0 (0.00%)	2 (4.65%)	2 (6.90%)	1 (2.00%)	7 (3.80%)
Limb injury	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (4.00%)	3 (1.63%)
Investigations						
Alanine aminotransferase increased	3 (9.09%)	5 (17.24%)	3 (6.98%)	2 (6.90%)	2 (4.00%)	15 (8.15%)
Blood bilirubin increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	2 (1.09%)
Blood cholesterol increased	0 (0.00%)	0 (0.00%)	1 (2.33%)	2 (6.90%)	1 (2.00%)	4 (2.17%)
C-reactive protein increased	1 (3.03%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	3 (6.00%)	5 (2.72%)

Gamma-glutamyltransferase increased	3 (9.09%)	3 (10.34%)	2 (4.65%)	3 (10.34%)	2 (4.00%)	13 (7.07%)
Hepatic enzyme increased	2 (6.06%)	1 (3.45%)	1 (2.33%)	0 (0.00%)	1 (2.00%)	5 (2.72%)
Lymphocyte count decreased	4 (12.12%)	2 (6.90%)	4 (9.30%)	2 (6.90%)	3 (6.00%)	15 (8.15%)
Metabolism and nutrition disorders						
Hypercholesterolaemia	2 (6.06%)	4 (13.79%)	2 (4.65%)	1 (3.45%)	3 (6.00%)	12 (6.52%)
Hypoglycaemia	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	2 (1.09%)
Musculoskeletal and connective tissue disorders						
Arthralgia	4 (12.12%)	3 (10.34%)	2 (4.65%)	2 (6.90%)	3 (6.00%)	14 (7.61%)
Back pain	6 (18.18%)	2 (6.90%)	5 (11.63%)	3 (10.34%)	3 (6.00%)	19 (10.33%)
Intervertebral disc degeneration	0 (0.00%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Joint swelling	2 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (2.00%)	3 (1.63%)
Muscle spasms	1 (3.03%)	0 (0.00%)	2 (4.65%)	1 (3.45%)	1 (2.00%)	5 (2.72%)
Muscular weakness	2 (6.06%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	4 (2.17%)
Musculoskeletal pain	1 (3.03%)	2 (6.90%)	4 (9.30%)	0 (0.00%)	2 (4.00%)	9 (4.89%)
Myalgia	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	3 (6.00%)	4 (2.17%)
Neck pain	1 (3.03%)	2 (6.90%)	1 (2.33%)	0 (0.00%)	2 (4.00%)	6 (3.26%)
Pain in extremity	2 (6.06%)	1 (3.45%)	0 (0.00%)	4 (13.79%)	5 (10.00%)	12 (6.52%)
Tendonitis	0 (0.00%)	2 (6.90%)	0 (0.00%)	2 (6.90%)	2 (4.00%)	6 (3.26%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)						

Fibrous histiocytoma	0 (0.00%)	1 (3.45%)	3 (6.98%)	1 (3.45%)	0 (0.00%)	5 (2.72%)
Melanocytic naevus	2 (6.06%)	1 (3.45%)	6 (13.95%)	2 (6.90%)	7 (14.00%)	18 (9.78%)
Seborrhoeic keratosis	2 (6.06%)	1 (3.45%)	0 (0.00%)	0 (0.00%)	4 (8.00%)	7 (3.80%)
Skin papilloma	2 (6.06%)	3 (10.34%)	1 (2.33%)	2 (6.90%)	2 (4.00%)	10 (5.43%)
Uterine leiomyoma	2 (6.06%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	3 (1.63%)
Nervous system disorders						
Burning sensation	0 (0.00%)	0 (0.00%)	1 (2.33%)	0 (0.00%)	2 (4.00%)	3 (1.63%)
Dizziness	1 (3.03%)	1 (3.45%)	1 (2.33%)	1 (3.45%)	4 (8.00%)	8 (4.35%)
Headache	9 (27.27%)	4 (13.79%)	9 (20.93%)	4 (13.79%)	10 (20.00%)	36 (19.57%)
Hypoaesthesia	1 (3.03%)	0 (0.00%)	0 (0.00%)	1 (3.45%)	2 (4.00%)	4 (2.17%)
Migraine	2 (6.06%)	0 (0.00%)	3 (6.98%)	1 (3.45%)	0 (0.00%)	6 (3.26%)
Muscle spasticity	0 (0.00%)	2 (6.90%)	0 (0.00%)	3 (10.34%)	0 (0.00%)	5 (2.72%)
Neuralgia	1 (3.03%)	0 (0.00%)	4 (9.30%)	0 (0.00%)	0 (0.00%)	5 (2.72%)
Paraesthesia	4 (12.12%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	3 (6.00%)	9 (4.89%)
Psychiatric disorders						
Anxiety	3 (9.09%)	1 (3.45%)	1 (2.33%)	0 (0.00%)	4 (8.00%)	9 (4.89%)
Depression	1 (3.03%)	1 (3.45%)	6 (13.95%)	3 (10.34%)	7 (14.00%)	18 (9.78%)
Insomnia	1 (3.03%)	2 (6.90%)	8 (18.60%)	3 (10.34%)	6 (12.00%)	20 (10.87%)
Sleep disorder	0 (0.00%)	1 (3.45%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	3 (1.63%)
Renal and urinary disorders						
Bladder dysfunction	0 (0.00%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Micturition urgency	2 (6.06%)	1 (3.45%)	1 (2.33%)	0 (0.00%)	1 (2.00%)	5 (2.72%)
Nephrolithiasis	2 (6.06%)	2 (6.90%)	0 (0.00%)	1 (3.45%)	0 (0.00%)	5 (2.72%)
Urinary retention	1 (3.03%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	3 (1.63%)

Respiratory, thoracic and mediastinal disorders						
Catarrh	1 (3.03%)	0 (0.00%)	1 (2.33%)	2 (6.90%)	0 (0.00%)	4 (2.17%)
Cough	3 (9.09%)	3 (10.34%)	3 (6.98%)	4 (13.79%)	2 (4.00%)	15 (8.15%)
Dyspnoea	0 (0.00%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	1 (2.00%)	3 (1.63%)
Epistaxis	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	2 (1.09%)
Oropharyngeal pain	3 (9.09%)	1 (3.45%)	3 (6.98%)	0 (0.00%)	3 (6.00%)	10 (5.43%)
Rhinitis allergic	0 (0.00%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	2 (4.00%)	4 (2.17%)
Wheezing	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	2 (1.09%)
Skin and subcutaneous tissue disorders						
Actinic keratosis	0 (0.00%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Alopecia	2 (6.06%)	0 (0.00%)	2 (4.65%)	0 (0.00%)	1 (2.00%)	5 (2.72%)
Dermal cyst	1 (3.03%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	3 (1.63%)
Dermatitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (4.00%)	2 (1.09%)
Dermatitis allergic	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	2 (4.00%)	4 (2.17%)
Dermatitis contact	1 (3.03%)	0 (0.00%)	0 (0.00%)	2 (6.90%)	0 (0.00%)	3 (1.63%)
Eczema	3 (9.09%)	2 (6.90%)	2 (4.65%)	0 (0.00%)	1 (2.00%)	8 (4.35%)
Hyperkeratosis	2 (6.06%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (1.09%)
Pigmentation disorder	2 (6.06%)	2 (6.90%)	1 (2.33%)	0 (0.00%)	0 (0.00%)	5 (2.72%)
Pruritus	1 (3.03%)	0 (0.00%)	2 (4.65%)	1 (3.45%)	3 (6.00%)	7 (3.80%)
Urticaria	0 (0.00%)	0 (0.00%)	3 (6.98%)	1 (3.45%)	1 (2.00%)	5 (2.72%)
Vascular disorders						
Hypertension	1 (3.03%)	1 (3.45%)	3 (6.98%)	3 (10.34%)	8 (16.00%)	16 (8.70%)

Other Relevant Findings

None

Conclusion:

Siponimod treatment was generally well tolerated and safe in patients with relapsing-remitting multiple sclerosis for up to approximately 5 years. Almost all patients (94.6%) reported at least one AE. Considering the long duration of this study, the number of patients with SAEs (16.8%) and AEs leading to discontinuation (9.2%) was low.

Specific areas of safety interest included effects on cardiac conduction during the dose titration phase of the study and long-term blood pressure effects. Post-dose ECG abnormalities were similar across all dose groups including limited number of ectopic disorders (IVCD); minor conduction (first degree AV block) and rhythm disorders being the most common abnormalities; none were of clinical relevance. There were no reports of significant QTc prolongation in the dose-blinded titration period. During the dose-blinded titration period, dose titration may effectively mitigate the effects of siponimod on AV conduction.

Any clinically significant abnormality (change from Extension baseline) in any of the above safety events were captured as an adverse event or serious adverse event.

The extension study also evaluated the occurrence of viral infections, macular edema and dermatological alterations as part of the long term safety and tolerability assessment of siponimod. The incidence of viral infections was similar across the dose groups. None of the patients reported macular edema in the overall Extension Study. Basal cell carcinoma was reported in 3 patients, none of the cases were suspected to be study drug related by the investigator.

Overall, both the relapse rate and the MRI lesion activity were low throughout the approximately 5-year duration of this study. The Extension Study data suggested that the efficacy of siponimod on reducing inflammatory disease activity seen in the Core study was maintained with long-term treatment in patients with relapsing-remitting multiple sclerosis. Lack of a

placebo control in this study, and the inherent selection bias of longitudinal long-term studies should be considered when interpreting the results.

Date of Clinical Trial Report

05 October 2017