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Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siponimod (BAF312)

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 4

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Study Start/End Dates

Study Start Date: December 20, 2012 (Actual)
Primary Completion Date: April 29, 2016 (Actual)
Study Completion Date: March 31, 2023 (Actual)

Study Design/Methodology

This study had two parts, a Core Part and an Extension Part.

The Core Part of the study was a randomized, multicenter, double-blind, placebo-controlled parallel-group study in patients with secondary progressive multiple sclerosis (SPMS). Eligible patients were randomized (2:1) to receive either siponimod or placebo. The duration of the Core Part of the study was variable for each patient, given that this was an event-driven study and terminated when a pre-defined number of confirmed disability progression (CDP) events had occurred irrespective of duration of individual patient participation.

Patients who were eligible to enter the Extension Part received open label siponimod.

Centers

294 centers in 31 countries: Turkey(7), Netherlands(6), Hungary(11), Canada(10), Austria(3), United States(52), Sweden(3), Slovakia (Slovak Republic)(8), Russia(9), Romania(7), Portugal(5), Poland(8), Latvia(3), Lithuania(3), Italy(10), Israel(2), Ireland(2), Greece(3), United Kingdom(10), France(11), Estonia(2), Spain(15), Germany(45), Czech Republic(5), Switzerland(7), Bulgaria(5), Belgium(8), Australia(5), Argentina(6), Japan(14), China(9)

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Objectives:

Primary Objective

Core Part

The primary objective was to demonstrate the efficacy of BAF312 relative to placebo in delaying the time to 3-month confirmed disability progression in patients with SPMS as measured by Expanded Disability Status Scale (EDSS).

Key Secondary objectives

Core Part

- The first key secondary objective was to demonstrate the efficacy of BAF312 relative to placebo in delaying the time to 3-month confirmed worsening of at least 20% from Baseline in the timed 25-foot walk test (T25W)
- The second key secondary objective was to demonstrate the efficacy of BAF312 relative to placebo in reducing the increase in T2 lesion volume from Baseline

Additional Secondary objectives

Core Part

- To evaluate the efficacy of BAF312 relative to placebo in delaying the time to 6-month confirmed disability progression as measured by EDSS
- To evaluate the efficacy of BAF312 relative to placebo in reducing the frequency of confirmed relapses as evaluated by the annualized relapse rate (ARR), and to evaluate time to first relapse and proportion of relapse-free patients
- To evaluate the effect of BAF312 compared to placebo on the patient reported outcome Multiple Sclerosis Walking Scale (MSWS-12)

- To evaluate the efficacy of BAF312 compared to placebo with respect to inflammatory disease activity and burden of disease, as measured by conventional magnetic resonance imaging (MRI) (T1 Gd-enhancing lesions, new or enlarging T2 lesions, brain volume)
- To evaluate the efficacy of BAF312 relative to placebo on 3-month confirmed disability progression as measured by EDSS in the following subgroups:
  - SPMS patients with or without superimposed relapses
  - rapidly evolving patients, defined as 1.5 point or greater EDSS change in the 2 years prior to study start, and in those not meeting this criteria
  - patients with moderate and severe disease course, as defined by Multiple Sclerosis Severity Score (MSSS) of 4 or more at baseline, and in those not meeting this criteria
- To evaluate the safety and tolerability of BAF312 vs. placebo

Extension Part

- To evaluate the long-term safety and tolerability of BAF312

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

The study drugs are siponimod (BAF312) and dose-matched placebo (control). Both were administered orally once daily as film-coated tablets.

Following randomization in the Core Part (CP), patients underwent 6-day titration to the target maintenance dose of blinded study drug (2 mg siponimod or placebo). The titration schedule is 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 confirmed disability progression (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.

Eligible patients who entered the Extension Part (EP) received open label siponimod. For the EP, treatment for patients who had completed the CP on either double-blind treatment or on the abbreviated schedule, initiated with the 6-day dose titration pack. Patients who had been on 2 mg with double-blind treatment were titrated to the 2 mg dose while patients who were taking 1 mg were titrated to the 1 mg dose. Patients who had been on open-label siponimod in the CP initiated treatment on their current dose of siponimod.

Statistical Methods

Efficacy

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.

For the primary endpoint, the criteria to reach the 3-month disability progression included confirmation of progression at least 3 months (i.e., ≥76 days) after onset showed progression and every EDSS score (scheduled or unscheduled) obtained between the onset and confirmation visits also met the progression criterion.

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.

The first key secondary efficacy variable was time to 3-month confirmed worsening of at least 20% from baseline in T25W defined as an increase from baseline sustained for at least 3 months. The hypothesis was tested using a Cox proportional hazards model.

The second key secondary variable was change from baseline in T2 lesion volume. Statistical inference was performed using a mixed model for repeated measures (MMRM) with visit as a categorical factor and an unstructured covariance matrix. The response variable was the change from baseline at Month 12 and Month 24 and Month 36. Parameters were estimated using restricted maximum likelihood (REML) methodology, whereby all available assessments contributed to parameter estimation. The null hypothesis was that the difference between siponimod and placebo, averaged over Month 12 and Month 24, was zero. This model did not make assumptions on the linearity of the mean trajectory of T2 lesion volume over time.

A hierarchical testing procedure was implemented for the primary and key secondary endpoints, which were tested in the following order:

1. Time to 3-month CDP based on EDSS

2. Time to 3-month confirmed worsening of at least 20% from baseline in T25W
3. Change from baseline in T2 lesion volume

The first hypothesis was performed at a two-sided significance level adjusted according to the O'Brien-Fleming alpha level correction which was calculated to be 0.0434. The second and third hypothesis tests were performed at a two-sided significance level of 0.05.

The primary efficacy variable was analyzed in the following subgroups: SPMS patients with/without superimposed relapses (baseline definition), rapidly and not rapidly evolving patients, patients with and without moderate/severe disease course (as defined by global Multiple Sclerosis Severity Score (MSSS)).

Respective models included subgroup as a covariate and a treatment-by-subgroup interaction term. The treatment effect within a subgroup was estimated by the appropriate contrast of this interaction model.

Additional secondary end points were evaluated at a nominal significance level of 0.05 without correction for multiplicity, or hierarchical testing.

Other disability progression variable based on EDSS included time to 6-month CDP. The Hazard ratio was estimated.

Relapses: Time to first confirmed relapse was analyzed using Cox proportional hazards model. Annualized relapse rate (ARR) for confirmed relapses and all relapses (confirmed and unconfirmed) was analyzed using a negative binomial regression model.

Other MRI variables: The number of new or enlarging T2 lesions at each yearly scan (compared to previous scan) and cumulative number of T1 Gd-enhancing lesions (from all post-baseline scan) were analyzed by repeated measures regression analysis, assuming a negative binomial distribution for the counts. The log of the time relative to previous scan was used as an offset in the negative binomial regression model of number of new or enlarging T2 lesions. The log of number of scans in the analysis period was used as an offset in the negative binomial regression model of number of cumulative number of T1 Gd-enhancing lesions: the unit was lesions/patient/scan. The percentage brain volume change

(PBVC) relative to baseline was analyzed using a repeated measures model with visit as a categorical factor and an unstructured covariance matrix.

MSWS-12 was analyzed using mixed model for repeated measures (MMRM).

Safety

Summaries were presented by treatment group using the safety population.

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

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Participant Flow Table

Core Part

	Siponimod (BAF312)	Placebo	Placebo-BAF312	Total
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.	Participants who received placebo in the Core Part and switched to siponimod in the Extension Part.	
Started	1105	546	0	1651
Safety set	1099	546	0	1645
Full analysis set	1099	546	0	1645
Completed	903	424	0	1327
Not Completed	202	122	0	324
Withdrawal by Subject	96	77	0	173
Adverse Event	45	18	0	63
Lack of Efficacy	16	11	0	27
Lost to Follow-up	9	8	0	17
Physician Decision	13	1	0	14
Progressive disease	8	4	0	12
Non-compliance with study treatment	5	0	0	5
Death	3	1	0	4
Protocol deviation	3	1	0	4
New therapy for study indication	2	1	0	3
Technical problems	2	0	0	2

Extension Part

	Siponimod (BAF312)	Placebo	Placebo-BAF312	Total
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.	Participants who received placebo in the Core Part and switched to siponimod in the Extension Part.	
Started	821	0	399	1220
Completed	326	0	159	485
Not Completed	495	0	240	735
Patient/guardian decision	180	0	98	278
Adverse Event	104	0	59	163
Study terminated by sponsor	42	0	19	61
Progressive disease	36	0	14	50
Lack of Efficacy	37	0	12	49
Physician Decision	29	0	13	42
Technical problems	20	0	8	28
Death	20	0	4	24
Missing	12	0	6	18
Lost to Follow-up	9	0	5	14
New therapy for study indication	3	0	2	5
Protocol deviation	3	0	0	3

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Baseline Characteristics

	Siponimod (BAF312)	Placebo	Total
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.	
Number of Participants [units: participants]	1105	546	1651
Baseline Analysis Population Description			
Age Continuous (units: Years) Analysis Population Type: Mean ± Standard Deviation			
	48.0±7.84	48.1±7.94	48.0±7.87
Sex: Female, Male (units: Participants) Analysis Population Type: Participants Count of Participants (Not Applicable)			
Female	669	323	992
Male	436	223	659
Race (NIH/OMB) (units: Participants) Analysis Population Type: 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 Disability Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS)

Description	The EDSS uses an ordinal scale to assess neurologic impairment in MS based on a neurological examination. Scores in each of 7 functional systems (Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral) and an ambulation score were combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS). 3-month confirmed disability progression is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5 sustained for at least 3 months.
Time Frame	Baseline, every 3 month up to the maximum of approximately 3 years
Analysis Population Description	The Full analysis set (FAS), which comprised all randomized patients with assigned treatments who took at least one dose of study medication, was considered for the analysis. Only participants from the FAS with non-missing covariates were analyzed for this outcome.

	Siponimod (BAF312)	**Placebo**
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1096	545
Percentage of participants with 3-month Confirmed Disability 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
Type of Statistical Test	Superiority
P Value	0.0134
Method	Other Cox proportional hazards model
Hazard Ratio (HR)	0.79
95 % Confidence Interval 2-Sided	0.65 to 0.95

Secondary Outcome Result(s)

Percentage of participants with 3-month confirmed worsening in T25W of at least 20% from baseline

Description	The Timed 25-Foot Walk Test (T25W) measured the time, in seconds, to walk 25 feet (7.62 meters). A 3-month confirmed worsening of at least 20% from baseline in the T25W was defined as an increase from baseline sustained for at least 3 months. This outcome measure was analyzed using a Cox proportional hazards model.
Time Frame	Baseline, every 3 months up to the maximum of approximately 3 years
Analysis Population Description	Participants from the FAS with non-missing covariates for the model.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.

	After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	
Number of Participants Analyzed [units: participants]	1087	543
Percentage of participants with 3-month confirmed worsening in T25W of at least 20% from baseline (units: Percentage of participants)		
	39.7	41.4

Statistical Analysis

Groups	Siponimod (BAF312), Placebo
Type of Statistical Test	Superiority
P Value	0.4398
Method	Other Cox proportional hazards model
Hazard Ratio (HR)	0.94
95 % Confidence Interval 2-Sided	0.80 to 1.10

Change from baseline in T2 lesion volume

Description	Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the total volume of T2 lesions. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center. The change from baseline in T2 lesion volume was analyzed using a mixed model for repeated measures (MMRM) with visit as a categorical factor and an unstructured covariance matrix and with adjustment for baseline covariates.
Time Frame	Baseline, Month 12 and Month 24
Analysis Population Description	Participants from the FAS with at least one post-baseline MRI scan and non-missing covariates for the model.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	995	495
Change from baseline in T2 lesion volume (units: mm^3)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Month 12	204.9 ± 67.47	818.0 ± 87.29
Month 24	162.9 ± 73.90	940.4 ± 97.20
Average over Month 12 and Month 24	183.9 ± 66.33	879.2 ± 85.43

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 12
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Mixed model for repeated measures	
Mean Difference (Final Values)	-613.1	
Standard Error of the mean	95.39	
95 % Confidence Interval 2-Sided	-800.2 to -426.0	

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Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 24
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Mixed model for repeated measures	
Mean Difference (Final Values)	-777.5	
Standard Error of the mean	108.62	
95 % Confidence Interval 2-Sided	-990.6 to -564.4	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Average over Month 12 and Month 24
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Mixed model for repeated measures	
Mean Difference (Final Values)	-695.3	
Standard Error of the mean	92.79	
95 % Confidence Interval 2-Sided	-877.3 to -513.3	

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Percentage of participants with 6-month Confirmed Disability Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS)

Description	The EDSS uses an ordinal scale to assess neurologic impairment in multiple sclerosis (MS) based on a neurological examination. Scores in each of 7 functional systems (Visual, Brain Stem, Pyramidal, Cerebellar, Sensory, Bowel & Bladder, and Cerebral) and an ambulation score were combined to determine the EDSS steps, ranging from 0 (normal) to 10 (death due to MS). 6-month confirmed disability progression is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5 sustained for at least 6 months. This outcome measure was analyzed using a Cox proportional hazards model.
Time Frame	Baseline, every 3 months up to the maximum of approximately 3 years
Analysis Population Description	Participants from the FAS with non-missing covariates for the model.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1096	545
Percentage of participants with 6-month Confirmed Disability Progression (CDP) events as measured by the Expanded Disability Status Scale (EDSS) (units: Percentage of participants)		
	19.9	25.5

Statistical Analysis

Groups	Siponimod (BAF312), Placebo
Type of Statistical Test	Superiority
P Value	0.0058

Method	Other Cox proportional hazards model
Hazard Ratio (HR)	0.74
95 % Confidence Interval 2-Sided	0.60 to 0.92

Annualized relapse rate (ARR) for confirmed relapses

Description	Multiple sclerosis (MS) relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality had to be present for at least 24 hours and occur in the absence of fever (<37.5°C) or known infection. A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS, as defined in the study protocol, performed by the Independent EDSS Rater. ARR was defined as the average number of confirmed relapses per year. ARR was analyzed using a negative binomial regression model.
Time Frame	Up to maximum approximately 3 years
Analysis Population Description	All participants in the FAS

	Siponimod (BAF312)	**Placebo**
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1099	546
Annualized relapse rate (ARR) for confirmed relapses (units: Number of relapses)	**Mean** **(95% Confidence Interval)**	**Mean** **(95% Confidence Interval)**
	0.071 (0.055 to 0.092)	0.160 (0.123 to 0.207)

Statistical Analysis

Groups	Siponimod (BAF312), Placebo
Type of Statistical Test	Superiority
P Value	<0.0001
Method	Other Negative binomial regression model
Other ARR ratio	0.445
95 % Confidence Interval 2-Sided	0.337 to 0.587

Percentage of participants with first relapse events as measured by time to first confirmed relapse

Description	Multiple sclerosis (MS) relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality had to be present for at least 24 hours and occur in the absence of fever (<37.5°C) or known infection. A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS, as defined in the study protocol, performed by the Independent EDSS Rater. Time to first relapse was defined as the time from Day 1 until the start of relapse symptoms. Patients without relapse were censored at the latest known date to be at risk. This outcome measure was analyzed using a Cox proportional hazards model.
Time Frame	Up to maximum approximately 3 years
Analysis Population Description	Participants from the FAS with non-missing covariates for the model.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.

Number of Participants Analyzed [units: participants]	1061	528
Percentage of participants with first relapse events as measured by time to first confirmed relapse (units: Percentage of participants)		
	10.7	18.9

Statistical Analysis

Groups	Siponimod (BAF312), Placebo
Type of Statistical Test	Superiority
P Value	<0.0001
Method	Other Cox proportional hazards model
Hazard Ratio (HR)	0.54
95 % Confidence Interval 2-Sided	0.41 to 0.70

Percentage of patients with relapse (confirmed relapse and any relapse)

Description	Multiple sclerosis (MS) relapse was defined as appearance of a new neurological abnormality or worsening of previously stable or improving pre-existing neurological abnormality, separated by at least 30 days from onset of a preceding clinical demyelinating event. Additionally, the abnormality had to be present for at least 24 hours and occur in the absence of fever (<37.5°C) or known infection. A confirmed MS relapse was defined as accompanied by a clinically-relevant change in the EDSS, as defined in the study protocol, performed by the Independent EDSS Rater.
Time Frame	Up to maximum approximately 3 years
Analysis Population Description	All participants in the FAS

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1099	546
Percentage of patients with relapse (confirmed relapse and any relapse) (units: Percentage of participants)		
Any relapse (confirmed or unconfirmed)	16.7	26.0
Confirmed relapse	10.3	18.7

Change from baseline in MSWS-12 converted score

Description	The Multiple Sclerosis Walking Scale (MSWS-12) version 2 is a patient-rated measure of walking consisting of 12 items. Walking limitations were reported by the patients using categories, generating a total transformed score ranging from 0-100. Higher scores reflected greater impairment. The change from baseline in MSWS-12 converted score was analyzed using a repeated measures model.
Time Frame	Baseline, Month 12 and Month 24
Analysis Population Description	Participants from the FAS with an available value for the MSWS-12 converted score at baseline and at least one post-baseline.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1022	516
Change from baseline in MSWS-12 converted score (units: score on a scale)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**

Month 12	1.53 ± 0.678	3.36 ± 0.908
Month 24	4.16 ± 0.848	5.38 ± 1.167

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 12
Type of Statistical Test	Superiority	
P Value	0.0764	
Method	Other Repeated measures model	
Mean Difference (Final Values)	-1.83	
Standard Error of the mean	1.030	
95 % Confidence Interval 2-Sided	-3.85 to 0.19	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 24
Type of Statistical Test	Superiority	
P Value	0.3671	
Method	Other Repeated measures model	
Mean Difference (Final Values)	-1.23	
Standard Error of the mean	1.359	

95 % Confidence Interval 2-Sided	-3.89 to 1.44

Number of T1 Gd-enhancing lesions per patient per scan

Description	Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the number of T1 gadolinium (Gd)-enhancing lesions. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center. The number of T1 Gd-enhancing lesions per patient per scan was analyzed using a negative binomial regression model.
Time Frame	Baseline, Month 12 and Month 24
Analysis Population Description	Participants from the FAS with at least one post-baseline MRI scan and non-missing values for the covariates included in the model.

	Siponimod (BAF312)	**Placebo**
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	996	496
Number of T1 Gd-enhancing lesions per patient per scan (units: Number of T1 Gd-enhancing lesions)	**Least Squares Mean** **(95% Confidence Interval)**	**Least Squares Mean** **(95% Confidence Interval)**
Month 12	0.080 (0.058 to 0.111)	0.640 (0.488 to 0.839)
Month 24	0.074 (0.040 to 0.138)	0.418 (0.288 to 0.607)

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 12

Type of Statistical Test	Superiority
P Value	<0.0001
Method	Other Negative binomial regression model
Other Rate ratio	0.126
95 % Confidence Interval 2-Sided	0.083 to 0.191

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 24
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Negative binomial regression model	
Other Rate ratio	0.178	
95 % Confidence Interval 2-Sided	0.087 to 0.362	

Number of new or enlarging T2 lesions per patient per year

Description	Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the number of new or enlarging T2 lesions. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center. The number of new or enlarging T2 lesions compared to previous scan was analyzed using a repeated measures negative binomial regression model.
Time Frame	Baseline, Month 12 and Month 24
Analysis Population Description	Participants from the FAS with at least one post-baseline MRI scan and non-missing values for the covariates included in the model.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	997	496
Number of new or enlarging T2 lesions per patient per year (units: Number of T2 lesions)	**Least Squares Mean (95% Confidence Interval)**	**Least Squares Mean (95% Confidence Interval)**
Month 12	1.003 (0.858 to 1.172)	3.776 (3.148 to 4.528)
Month 24	0.489 (0.371 to 0.644)	3.437 (2.800 to 4.220)

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 12
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Regression model	Repeated measures negative binomial regression model
Other Rate ratio	0.266	
95 % Confidence Interval 2-Sided	0.215 to 0.328	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 24
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Regression model	Repeated measures negative binomial regression model
Other Rate ratio	0.142	
95 % Confidence Interval 2-Sided	0.103 to 0.196	

Percent brain volume change (PBVC) relative to baseline

Description	Magnetic resonance imaging (MRI) scans of the brain were performed every 12 months. MRI evaluation during the Core Part included the percentage change in brain volume. Each MRI scan was reviewed by a local neurologist and by a central blinded MRI reading center. PBVC relative to baseline was analyzed using a repeated measures model (for normally distributed data) with visit as a categorical factor.
Time Frame	Baseline, Month 12 and Month 24
Analysis Population Description	Participants from the FAS with at least one post-baseline MRI scan and non-missing values for the covariates included in the model.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	894	436

Percent brain volume change (PBVC) relative to baseline (units: % change from baseline in brain volume)	**Least Squares Mean ± Standard Error**	**Least Squares Mean ± Standard Error**
Month 12	-0.283 ± 0.0264	-0.458 ± 0.0341
Month 24	-0.711 ± 0.0356	-0.839 ± 0.0476

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 12
Type of Statistical Test	Superiority	
P Value	<0.0001	
Method	Other Repeated measures model	
Mean Difference (Final Values)	0.175	
Standard Error of the mean	0.0367	
95 % Confidence Interval 2-Sided	0.103 to 0.247	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Month 24
Type of Statistical Test	Superiority	
P Value	0.0196	
Method	Other Repeated measures model	
Mean Difference (Final Values)	0.128	

Standard Error of the mean	0.0549
95 % Confidence Interval 2-Sided	0.021 to 0.236

Number of participants with 3-month CDP events as measured by EDSS in the subgroup of SPMS patients with/without superimposed relapses

Description	The Expanded Disability Status Scale (EDSS) assesses neurologic impairment in multiple sclerosis (MS). EDSS scale ranges from 0 (normal) to 10 (death due to MS). Confirmed disability is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5. The definition of 3-month confirmed disability progression (CDP) was an increase from baseline in EDSS as defined before sustained for at least 3 months. The following secondary progressive multiple sclerosis (SPMS) groups were defined for the analysis of this endpoint: • Without superimposed relapses in the 2 years prior to study start (baseline definition) • With superimposed relapses in the 2 years prior to study start (baseline definition) • Without superimposed relapses during the Core Part of study (post-treatment) • With superimposed relapses during the Core Part of study (post-treatment) Data was analyzed using a Cox proportional hazard model.
Time Frame	Baseline, every 3 months up to the maximum of approximately 3 years
Analysis Population Description	Participants from the FAS in each subgroup with an available value for the outcome measure.

	Siponimod (BAF312)	**Placebo**
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1099	546
Number of participants with 3-month CDP events as measured by EDSS in the subgroup of SPMS patients with/without superimposed relapses (units: Participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
Without superimposed relapses at baseline (n=708, 343)	190 (26.84%)	101 (29.45%)

With superimposed relapses at baseline (n=388, 202)	98 (25.26%)	72 (35.64%)
Without superimposed relapses post-treatment (n=986, 444)	237 (24.04%)	122 (27.48%)
With superimposed relapses post-treatment (n=113, 102)	51 (45.13%)	51 (50%)

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Without superimposed relapses at baseline
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.87	
95 % Confidence Interval 2-Sided	0.68 to 1.11	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	With superimposed relapses at baseline
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.67	
95 % Confidence Interval 2-Sided	0.49 to 0.91	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Without superimposed relapses post-treatment
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.85	
95 % Confidence Interval 2-Sided	0.69 to 1.06	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	With superimposed relapses post-treatment
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.80	
95 % Confidence Interval 2-Sided	0.53 to 1.19	

Number of participants with 3-month CDP events as measured by EDSS in the subgroup of rapidly and not rapidly evolving patients

Description: The Expanded Disability Status Scale (EDSS) assesses neurologic impairment in multiple sclerosis (MS). EDSS scale ranges from 0 (normal) to 10 (death due to MS). Confirmed disability is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5. The definition of 3-month confirmed disability progression (CDP) was an increase from baseline in EDSS as defined before sustained for at least 3 months. Rapidly evolving patients are defined as subjects with 1.5 or greater EDSS change in the 2 years prior to or at study start and disability progression in the 2 years prior to study start was not adjudicated. Data was analyzed using a Cox proportional hazard model.

Time Frame	Baseline, every 3 months up to the maximum of approximately 3 years
Analysis Population Description	Participants from the FAS in each subgroup with an available value for the outcome measure.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days. After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.
Number of Participants Analyzed [units: participants]	1099	546
Number of participants with 3-month CDP events as measured by EDSS in the subgroup of rapidly and not rapidly evolving patients (units: Participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
Rapidly evolving patients (n=264, 145)	82 (31.06%)	60 (41.38%)
Not rapidly evolving patients (n=835, 401)	206 (24.67%)	113 (28.18%)

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Rapidly evolving patients
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.65	

95 % Confidence Interval 2-Sided	0.46 to 0.91

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Not rapidly evolving patients
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.86	
95 % Confidence Interval 2-Sided	0.69 to 1.09	

Number of participants with 3-month CDP events as measured by EDSS in the subgroup of patients with and without moderate/severe disease course

Description	The Expanded Disability Status Scale (EDSS) assesses neurologic impairment in multiple sclerosis (MS). EDSS scale ranges from 0 (normal) to 10 (death due to MS). Confirmed disability is defined as an increase of score of 1 point in patients with baseline score of 3.0 to 5.0 and 0.5 point increase with baseline score of 5.5 to 6.5. The definition of 3-month confirmed disability progression (CDP) was an increase from baseline in EDSS as defined before sustained for at least 3 months. Moderate or severe course of disease is defined as global Multiple Sclerosis Severity Score (MSSS) of 4 or more at baseline. Data was analyzed using a Cox proportional hazard model.
Time Frame	Baseline, every 3 months up to the maximum of approximately 3 years
Analysis Population Description	Participants from the FAS in each subgroup with an available value for the outcome measure.

	Siponimod (BAF312)	Placebo
Arm/Group Description	Participants started on Day 1 and were uptitrated from 0.25 mg to 2 mg of BAF312 orally over a period of 6 days.	Matching placebo to BAF312 was administered orally during the Core Part of the trial.

	After Day 7, participants continued on 2 mg BAF312 daily for a variable duration.	
Number of Participants Analyzed [units: participants]	1099	546
Number of participants with 3-month CDP events as measured by EDSS in the subgroup of patients with and without moderate/severe disease course (units: Participants)	**Count of Participants (Percentage)**	**Count of Participants (Percentage)**
With moderate or severe course of disease (n=904, 459)	232 (25.66%)	141 (30.72%)
Without moderate or severe course of disease (n=195, 87)	56 (28.72%)	32 (36.78%)

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	With moderate or severe course of disease
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	
Hazard Ratio (HR)	0.80	
95 % Confidence Interval 2-Sided	0.65 to 0.99	

Statistical Analysis

Groups	Siponimod (BAF312), Placebo	Without moderate or severe course of disease
Type of Statistical Test	Superiority	
Method	Other Cox proportional hazard model	

Hazard Ratio (HR)	0.73
95 % Confidence Interval 2-Sided	0.47 to 1.13

Safety Results

Time Frame	Core Part: from first dose of double-blind study treatment until end of Core Part (up to approximately 3 years). Core and Extension: from first dose of siponimod until end of study (up to approximately 10 years).
Additional Description	Safety is assessed in the Safety Set, including all patients who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

All-Cause Mortality

	Core-BAF312 N = 1099	**Core-Placebo N = 546**	**All BAF312 N = 1517**
Arm/Group Description	Participants who were randomized to siponimod (BAF312) during the Core Part	Participants who were randomized to placebo during the Core Part	All participants who received at least one dose of siponimod (BAF312) during the Core Part and/or the Extension Part
Total Number Affected	4	4	33
Total Number At Risk	1099	546	1517

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Serious Adverse Events

Time Frame	Core Part: from first dose of double-blind study treatment until end of Core Part (up to approximately 3 years). Core and Extension: from first dose of siponimod until end of study (up to approximately 10 years).
Additional Description	Safety is assessed in the Safety Set, including all patients who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

	Core-BAF312 N = 1099	**Core-Placebo N = 546**	**All BAF312 N = 1517**
Arm/Group Description	Participants who were randomized to siponimod (BAF312) during the Core Part	Participants who were randomized to placebo during the Core Part	All participants who received at least one dose of siponimod (BAF312) during the Core Part and/or the Extension Part
Total # Affected by any Serious Adverse Event	196	83	610
Total # at Risk by any Serious Adverse Event	1099	546	1517
Blood and lymphatic system disorders			
Anaemia	0 (0.00%)	2 (0.37%)	4 (0.26%)
Hypochromic anaemia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Leukopenia	1 (0.09%)	0 (0.00%)	1 (0.07%)
Lymphocytic infiltration	0 (0.00%)	0 (0.00%)	1 (0.07%)

Lymphopenia	0 (0.00%)	0 (0.00%)	4 (0.26%)
Pancytopenia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Thrombocytopenia	1 (0.09%)	0 (0.00%)	2 (0.13%)
Cardiac disorders			
Acute coronary syndrome	1 (0.09%)	0 (0.00%)	1 (0.07%)
Acute myocardial infarction	1 (0.09%)	1 (0.18%)	3 (0.20%)
Angina pectoris	1 (0.09%)	1 (0.18%)	3 (0.20%)
Arrhythmia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Atrial fibrillation	1 (0.09%)	0 (0.00%)	1 (0.07%)
Atrioventricular block second degree	2 (0.18%)	0 (0.00%)	2 (0.13%)
Bradycardia	3 (0.27%)	0 (0.00%)	4 (0.26%)
Cardiac arrest	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cardiac failure	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cardiac failure acute	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cardio-respiratory arrest	0 (0.00%)	0 (0.00%)	1 (0.07%)
Coronary artery disease	1 (0.09%)	1 (0.18%)	2 (0.13%)
Myocardial infarction	0 (0.00%)	0 (0.00%)	2 (0.13%)
Myocardial ischaemia	1 (0.09%)	0 (0.00%)	1 (0.07%)
Myocarditis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Palpitations	0 (0.00%)	0 (0.00%)	1 (0.07%)
Supraventricular extrasystoles	0 (0.00%)	0 (0.00%)	1 (0.07%)
Supraventricular tachycardia	0 (0.00%)	1 (0.18%)	1 (0.07%)
Tachyarrhythmia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Tachycardia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Ventricular tachycardia	0 (0.00%)	0 (0.00%)	2 (0.13%)

Congenital, familial and genetic disorders			
Brugada syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)
Corneal dystrophy	0 (0.00%)	0 (0.00%)	1 (0.07%)
Malformation venous	0 (0.00%)	0 (0.00%)	1 (0.07%)
Ear and labyrinth disorders			
Deafness transitory	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hypoacusis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Vertigo	0 (0.00%)	1 (0.18%)	0 (0.00%)
Endocrine disorders			
Goitre	0 (0.00%)	0 (0.00%)	1 (0.07%)
Graves' disease	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hyperthyroidism	0 (0.00%)	0 (0.00%)	1 (0.07%)
Eye disorders			
Blindness	1 (0.09%)	0 (0.00%)	2 (0.13%)
Cataract	0 (0.00%)	1 (0.18%)	2 (0.13%)
Diplopia	0 (0.00%)	1 (0.18%)	0 (0.00%)
Eye haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Macular hole	0 (0.00%)	0 (0.00%)	1 (0.07%)
Macular oedema	3 (0.27%)	0 (0.00%)	6 (0.40%)
Photophobia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Retinal detachment	0 (0.00%)	1 (0.18%)	1 (0.07%)
Retinoschisis	0 (0.00%)	1 (0.18%)	0 (0.00%)
Gastrointestinal disorders			

Abdominal pain	0 (0.00%)	0 (0.00%)	2 (0.13%)
Abdominal pain upper	0 (0.00%)	1 (0.18%)	0 (0.00%)
Acquired oesophageal web	0 (0.00%)	0 (0.00%)	1 (0.07%)
Anal fissure	0 (0.00%)	1 (0.18%)	0 (0.00%)
Anal haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Constipation	2 (0.18%)	1 (0.18%)	6 (0.40%)
Diarrhoea	1 (0.09%)	1 (0.18%)	2 (0.13%)
Duodenal ulcer	0 (0.00%)	1 (0.18%)	0 (0.00%)
Dysphagia	0 (0.00%)	0 (0.00%)	3 (0.20%)
Faecaloma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Gastric haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Gastric perforation	0 (0.00%)	0 (0.00%)	1 (0.07%)
Gastric ulcer perforation	0 (0.00%)	1 (0.18%)	0 (0.00%)
Gastritis	0 (0.00%)	0 (0.00%)	2 (0.13%)
Gastritis erosive	1 (0.09%)	0 (0.00%)	1 (0.07%)
Gastrointestinal inflammation	0 (0.00%)	0 (0.00%)	1 (0.07%)
Gastrooesophageal reflux disease	0 (0.00%)	0 (0.00%)	1 (0.07%)
Haematemesis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Haemorrhoids	0 (0.00%)	0 (0.00%)	1 (0.07%)
Ileus	0 (0.00%)	0 (0.00%)	2 (0.13%)
Ileus paralytic	0 (0.00%)	0 (0.00%)	1 (0.07%)
Impaired gastric emptying	0 (0.00%)	0 (0.00%)	1 (0.07%)
Incarcerated inguinal hernia	1 (0.09%)	0 (0.00%)	1 (0.07%)
Inguinal hernia	1 (0.09%)	0 (0.00%)	7 (0.46%)
Intestinal obstruction	1 (0.09%)	1 (0.18%)	2 (0.13%)
Nausea	1 (0.09%)	0 (0.00%)	1 (0.07%)

Oesophagitis	0 (0.00%)	1 (0.18%)	0 (0.00%)
Pancreatitis	0 (0.00%)	0 (0.00%)	2 (0.13%)
Pancreatitis acute	0 (0.00%)	1 (0.18%)	0 (0.00%)
Peritoneal adhesions	0 (0.00%)	0 (0.00%)	1 (0.07%)
Rectal haemorrhage	0 (0.00%)	0 (0.00%)	2 (0.13%)
Rectal polyp	0 (0.00%)	0 (0.00%)	1 (0.07%)
Rectal prolapse	0 (0.00%)	0 (0.00%)	1 (0.07%)
Small intestinal obstruction	0 (0.00%)	1 (0.18%)	1 (0.07%)
Subileus	0 (0.00%)	0 (0.00%)	1 (0.07%)
Toothache	0 (0.00%)	0 (0.00%)	1 (0.07%)
Umbilical hernia, obstructive	1 (0.09%)	0 (0.00%)	1 (0.07%)
Volvulus	0 (0.00%)	0 (0.00%)	1 (0.07%)
Vomiting	1 (0.09%)	0 (0.00%)	1 (0.07%)
General disorders and administration site conditions			
Accidental death	0 (0.00%)	0 (0.00%)	1 (0.07%)
Asthenia	2 (0.18%)	0 (0.00%)	4 (0.26%)
Chills	0 (0.00%)	0 (0.00%)	1 (0.07%)
Disease progression	0 (0.00%)	0 (0.00%)	2 (0.13%)
Fatigue	1 (0.09%)	0 (0.00%)	3 (0.20%)
Gait disturbance	1 (0.09%)	3 (0.55%)	3 (0.20%)
General physical health deterioration	0 (0.00%)	0 (0.00%)	2 (0.13%)
Granuloma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hyperpyrexia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Impaired healing	0 (0.00%)	0 (0.00%)	1 (0.07%)
Influenza like illness	0 (0.00%)	0 (0.00%)	1 (0.07%)

Malaise	0 (0.00%)	0 (0.00%)	2 (0.13%)
Multiple organ dysfunction syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	1 (0.07%)
Oedema peripheral	0 (0.00%)	1 (0.18%)	1 (0.07%)
Pain	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pyrexia	2 (0.18%)	0 (0.00%)	11 (0.73%)
Sudden cardiac death	0 (0.00%)	0 (0.00%)	1 (0.07%)
Sudden death	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hepatobiliary disorders			
Bile duct stone	0 (0.00%)	0 (0.00%)	1 (0.07%)
Biliary colic	1 (0.09%)	0 (0.00%)	1 (0.07%)
Cholecystitis	1 (0.09%)	0 (0.00%)	4 (0.26%)
Cholecystitis acute	1 (0.09%)	0 (0.00%)	3 (0.20%)
Cholelithiasis	1 (0.09%)	0 (0.00%)	5 (0.33%)
Hepatic failure	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hepatic function abnormal	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hepatic steatosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hepatitis acute	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hepatotoxicity	1 (0.09%)	0 (0.00%)	1 (0.07%)
Liver disorder	0 (0.00%)	0 (0.00%)	1 (0.07%)
Non-alcoholic steatohepatitis	0 (0.00%)	1 (0.18%)	0 (0.00%)
Immune system disorders			
Hypersensitivity	1 (0.09%)	0 (0.00%)	1 (0.07%)
Immune reconstitution inflammatory syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)

Infections and infestations

Abscess soft tissue	0 (0.00%)	0 (0.00%)	1 (0.07%)
Acute sinusitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Appendiceal abscess	1 (0.09%)	0 (0.00%)	1 (0.07%)
Appendicitis	3 (0.27%)	0 (0.00%)	3 (0.20%)
Appendicitis perforated	0 (0.00%)	0 (0.00%)	2 (0.13%)
Bacteraemia	1 (0.09%)	0 (0.00%)	2 (0.13%)
Bacterial infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Bronchitis	0 (0.00%)	0 (0.00%)	3 (0.20%)
Burn infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Campylobacter gastroenteritis	0 (0.00%)	1 (0.18%)	0 (0.00%)
Cellulitis	2 (0.18%)	0 (0.00%)	3 (0.20%)
Central nervous system infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Chorioretinitis	1 (0.09%)	0 (0.00%)	2 (0.13%)
Chronic sinusitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Complicated appendicitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
COVID-19	0 (0.00%)	0 (0.00%)	14 (0.92%)
COVID-19 pneumonia	0 (0.00%)	0 (0.00%)	6 (0.40%)
Cystitis	0 (0.00%)	0 (0.00%)	4 (0.26%)
Diarrhoea infectious	0 (0.00%)	0 (0.00%)	1 (0.07%)
Diverticulitis	1 (0.09%)	0 (0.00%)	3 (0.20%)
Encephalitis viral	0 (0.00%)	0 (0.00%)	1 (0.07%)
Enterovirus infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Escherichia urinary tract infection	1 (0.09%)	0 (0.00%)	2 (0.13%)
Gastroenteritis	2 (0.18%)	1 (0.18%)	7 (0.46%)

Gastroenteritis proteus	0 (0.00%)	1 (0.18%)	0 (0.00%)
Gastrointestinal infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Groin abscess	0 (0.00%)	0 (0.00%)	2 (0.13%)
Hepatitis E	1 (0.09%)	0 (0.00%)	1 (0.07%)
Herpes zoster	1 (0.09%)	0 (0.00%)	5 (0.33%)
Herpes zoster meningitis	1 (0.09%)	0 (0.00%)	1 (0.07%)
Influenza	1 (0.09%)	1 (0.18%)	6 (0.40%)
Labyrinthitis	1 (0.09%)	0 (0.00%)	1 (0.07%)
Lower respiratory tract infection	0 (0.00%)	0 (0.00%)	4 (0.26%)
Meningitis cryptococcal	0 (0.00%)	0 (0.00%)	2 (0.13%)
Nasal abscess	1 (0.09%)	0 (0.00%)	1 (0.07%)
Ophthalmic herpes zoster	0 (0.00%)	0 (0.00%)	2 (0.13%)
Oral viral infection	1 (0.09%)	0 (0.00%)	1 (0.07%)
Orchitis	0 (0.00%)	0 (0.00%)	2 (0.13%)
Otosalpingitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Parainfluenzae virus infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Peritonitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pneumonia	1 (0.09%)	2 (0.37%)	28 (1.85%)
Pneumonia aspiration	1 (0.09%)	0 (0.00%)	4 (0.26%)
Pneumonia bacterial	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pneumonia influenzal	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pneumonia legionella	0 (0.00%)	0 (0.00%)	1 (0.07%)
Postoperative wound infection	1 (0.09%)	1 (0.18%)	1 (0.07%)
Progressive multifocal leukoencephalopathy	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pulmonary tuberculosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pyelonephritis	0 (0.00%)	1 (0.18%)	9 (0.59%)

Pyelonephritis chronic	1 (0.09%)	0 (0.00%)	1 (0.07%)
Respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Rhinovirus infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Sepsis	1 (0.09%)	0 (0.00%)	15 (0.99%)
Septic encephalopathy	0 (0.00%)	0 (0.00%)	1 (0.07%)
Septic shock	2 (0.18%)	0 (0.00%)	7 (0.46%)
Subcutaneous abscess	0 (0.00%)	0 (0.00%)	1 (0.07%)
Tooth abscess	0 (0.00%)	0 (0.00%)	1 (0.07%)
Upper respiratory tract infection	3 (0.27%)	0 (0.00%)	4 (0.26%)
Urinary tract infection	15 (1.36%)	7 (1.28%)	67 (4.42%)
Urinary tract infection bacterial	0 (0.00%)	0 (0.00%)	3 (0.20%)
Urosepsis	5 (0.45%)	1 (0.18%)	13 (0.86%)
Vestibular neuronitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Viral infection	0 (0.00%)	0 (0.00%)	2 (0.13%)
Viral upper respiratory tract infection	0 (0.00%)	0 (0.00%)	1 (0.07%)
Wound infection	0 (0.00%)	1 (0.18%)	0 (0.00%)
Injury, poisoning and procedural complications			
Accidental overdose	0 (0.00%)	0 (0.00%)	1 (0.07%)
Ankle fracture	2 (0.18%)	0 (0.00%)	8 (0.53%)
Bone contusion	0 (0.00%)	0 (0.00%)	2 (0.13%)
Brain contusion	0 (0.00%)	0 (0.00%)	1 (0.07%)
Burns third degree	0 (0.00%)	0 (0.00%)	1 (0.07%)
Bursa injury	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cervical vertebral fracture	1 (0.09%)	0 (0.00%)	1 (0.07%)
Clavicle fracture	2 (0.18%)	0 (0.00%)	2 (0.13%)

Concussion	5 (0.45%)	0 (0.00%)	8 (0.53%)
Contusion	1 (0.09%)	0 (0.00%)	3 (0.20%)
Craniocerebral injury	0 (0.00%)	0 (0.00%)	2 (0.13%)
Eye contusion	1 (0.09%)	0 (0.00%)	1 (0.07%)
Fall	2 (0.18%)	0 (0.00%)	11 (0.73%)
Femoral neck fracture	3 (0.27%)	1 (0.18%)	13 (0.86%)
Femur fracture	0 (0.00%)	0 (0.00%)	3 (0.20%)
Fibula fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)
Foot fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)
Fracture displacement	1 (0.09%)	0 (0.00%)	2 (0.13%)
Head injury	0 (0.00%)	1 (0.18%)	2 (0.13%)
Hip fracture	0 (0.00%)	2 (0.37%)	5 (0.33%)
Humerus fracture	0 (0.00%)	0 (0.00%)	4 (0.26%)
Injection related reaction	0 (0.00%)	0 (0.00%)	1 (0.07%)
Injury corneal	1 (0.09%)	0 (0.00%)	1 (0.07%)
Intentional overdose	0 (0.00%)	0 (0.00%)	1 (0.07%)
Joint dislocation	0 (0.00%)	0 (0.00%)	3 (0.20%)
Ligament injury	0 (0.00%)	0 (0.00%)	1 (0.07%)
Lower limb fracture	0 (0.00%)	1 (0.18%)	2 (0.13%)
Lumbar vertebral fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)
Maisonneuve fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)
Meniscus injury	0 (0.00%)	1 (0.18%)	2 (0.13%)
Nerve root injury cervical	0 (0.00%)	0 (0.00%)	1 (0.07%)
Post procedural haematoma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Post procedural haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Post-traumatic pain	0 (0.00%)	0 (0.00%)	1 (0.07%)

Procedural pain	0 (0.00%)	0 (0.00%)	2 (0.13%)
Radius fracture	1 (0.09%)	0 (0.00%)	3 (0.20%)
Reactive gastropathy	0 (0.00%)	0 (0.00%)	1 (0.07%)
Rib fracture	1 (0.09%)	0 (0.00%)	4 (0.26%)
Road traffic accident	0 (0.00%)	0 (0.00%)	1 (0.07%)
Shoulder fracture	0 (0.00%)	0 (0.00%)	2 (0.13%)
Skin abrasion	0 (0.00%)	0 (0.00%)	1 (0.07%)
Skin laceration	4 (0.36%)	0 (0.00%)	8 (0.53%)
Spinal compression fracture	1 (0.09%)	0 (0.00%)	2 (0.13%)
Splenic injury	0 (0.00%)	0 (0.00%)	1 (0.07%)
Splenic rupture	1 (0.09%)	0 (0.00%)	2 (0.13%)
Sternal fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)
Stress fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)
Subarachnoid haematoma	1 (0.09%)	0 (0.00%)	1 (0.07%)
Subdural haematoma	1 (0.09%)	0 (0.00%)	6 (0.40%)
Tendon rupture	0 (0.00%)	1 (0.18%)	0 (0.00%)
Thermal burn	1 (0.09%)	0 (0.00%)	2 (0.13%)
Tibia fracture	0 (0.00%)	1 (0.18%)	3 (0.20%)
Toxicity to various agents	0 (0.00%)	0 (0.00%)	1 (0.07%)
Traumatic fracture	1 (0.09%)	0 (0.00%)	1 (0.07%)
Traumatic haemorrhage	1 (0.09%)	0 (0.00%)	1 (0.07%)
Traumatic haemothorax	1 (0.09%)	0 (0.00%)	1 (0.07%)
Traumatic liver injury	1 (0.09%)	0 (0.00%)	2 (0.13%)
Upper limb fracture	0 (0.00%)	0 (0.00%)	2 (0.13%)
Wound	0 (0.00%)	0 (0.00%)	1 (0.07%)
Wrist fracture	0 (0.00%)	0 (0.00%)	1 (0.07%)

Investigations			
Alanine aminotransferase increased	10 (0.91%)	2 (0.37%)	19 (1.25%)
Aspartate aminotransferase increased	5 (0.45%)	1 (0.18%)	9 (0.59%)
Blood bilirubin increased	2 (0.18%)	0 (0.00%)	3 (0.20%)
Blood glucose increased	1 (0.09%)	0 (0.00%)	1 (0.07%)
Blood pressure decreased	0 (0.00%)	0 (0.00%)	1 (0.07%)
CD4 lymphocytes decreased	0 (0.00%)	0 (0.00%)	1 (0.07%)
CD8 lymphocytes decreased	0 (0.00%)	0 (0.00%)	1 (0.07%)
Columbia suicide severity rating scale abnormal	2 (0.18%)	0 (0.00%)	2 (0.13%)
Heart rate decreased	1 (0.09%)	0 (0.00%)	1 (0.07%)
Hepatic enzyme abnormal	1 (0.09%)	0 (0.00%)	1 (0.07%)
Hepatic enzyme increased	1 (0.09%)	0 (0.00%)	4 (0.26%)
Liver function test abnormal	0 (0.00%)	1 (0.18%)	1 (0.07%)
Liver function test increased	0 (0.00%)	0 (0.00%)	2 (0.13%)
Lung diffusion test decreased	1 (0.09%)	0 (0.00%)	2 (0.13%)
Magnetic resonance imaging abnormal	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pulmonary function test decreased	1 (0.09%)	0 (0.00%)	2 (0.13%)
Troponin increased	0 (0.00%)	0 (0.00%)	1 (0.07%)
Walking distance test abnormal	1 (0.09%)	0 (0.00%)	1 (0.07%)
Weight decreased	1 (0.09%)	0 (0.00%)	1 (0.07%)
Metabolism and nutrition disorders			
Dehydration	2 (0.18%)	0 (0.00%)	4 (0.26%)
Haemochromatosis	1 (0.09%)	0 (0.00%)	1 (0.07%)
Hyperglycaemic crisis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hyperkalaemia	0 (0.00%)	0 (0.00%)	1 (0.07%)

Hypokalaemia	0 (0.00%)	0 (0.00%)	2 (0.13%)
Hyponatraemia	0 (0.00%)	0 (0.00%)	2 (0.13%)
Iron deficiency	0 (0.00%)	0 (0.00%)	1 (0.07%)
Lactic acidosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Shock hypoglycaemic	0 (0.00%)	1 (0.18%)	0 (0.00%)
Musculoskeletal and connective tissue disorders			
Arthralgia	1 (0.09%)	0 (0.00%)	3 (0.20%)
Arthritis	1 (0.09%)	0 (0.00%)	0 (0.00%)
Back pain	1 (0.09%)	0 (0.00%)	4 (0.26%)
Bursitis	1 (0.09%)	0 (0.00%)	3 (0.20%)
Femoroacetabular impingement	0 (0.00%)	0 (0.00%)	1 (0.07%)
Foot deformity	1 (0.09%)	0 (0.00%)	2 (0.13%)
Intervertebral disc protrusion	1 (0.09%)	1 (0.18%)	2 (0.13%)
Ligament disorder	0 (0.00%)	0 (0.00%)	1 (0.07%)
Lumbar spinal stenosis	1 (0.09%)	0 (0.00%)	2 (0.13%)
Muscle spasms	0 (0.00%)	0 (0.00%)	1 (0.07%)
Muscular weakness	3 (0.27%)	0 (0.00%)	7 (0.46%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	2 (0.13%)
Musculoskeletal pain	1 (0.09%)	0 (0.00%)	1 (0.07%)
Musculoskeletal stiffness	0 (0.00%)	1 (0.18%)	0 (0.00%)
Neck pain	0 (0.00%)	0 (0.00%)	1 (0.07%)
Osteoarthritis	1 (0.09%)	0 (0.00%)	9 (0.59%)
Patellofemoral pain syndrome	0 (0.00%)	1 (0.18%)	0 (0.00%)
Rotator cuff syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)
Spinal deformity	1 (0.09%)	0 (0.00%)	1 (0.07%)

Spinal stenosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Spondylolisthesis	0 (0.00%)	0 (0.00%)	4 (0.26%)
Synovial cyst	1 (0.09%)	0 (0.00%)	1 (0.07%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Astrocytoma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Basal cell carcinoma	11 (1.00%)	7 (1.28%)	68 (4.48%)
Benign neoplasm of thyroid gland	1 (0.09%)	0 (0.00%)	2 (0.13%)
Benign renal neoplasm	0 (0.00%)	0 (0.00%)	1 (0.07%)
Bladder cancer	0 (0.00%)	1 (0.18%)	0 (0.00%)
Bowen's disease	1 (0.09%)	1 (0.18%)	18 (1.19%)
Brain neoplasm malignant	0 (0.00%)	0 (0.00%)	1 (0.07%)
Breast cancer	1 (0.09%)	1 (0.18%)	7 (0.46%)
Central nervous system lymphoma	0 (0.00%)	1 (0.18%)	1 (0.07%)
Cervix carcinoma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Colon cancer	0 (0.00%)	0 (0.00%)	1 (0.07%)
Colon cancer metastatic	0 (0.00%)	0 (0.00%)	1 (0.07%)
Colon cancer stage IV	1 (0.09%)	0 (0.00%)	1 (0.07%)
Colorectal cancer	0 (0.00%)	0 (0.00%)	1 (0.07%)
Diffuse large B-cell lymphoma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Dysplastic naevus	0 (0.00%)	0 (0.00%)	1 (0.07%)
Endometrial cancer	1 (0.09%)	0 (0.00%)	1 (0.07%)
Gastric cancer	0 (0.00%)	1 (0.18%)	0 (0.00%)
Gastrointestinal melanoma	1 (0.09%)	0 (0.00%)	1 (0.07%)
Glioma	0 (0.00%)	1 (0.18%)	1 (0.07%)
Intraductal proliferative breast lesion	0 (0.00%)	0 (0.00%)	3 (0.20%)

Invasive ductal breast carcinoma	0 (0.00%)	0 (0.00%)	4 (0.26%)
Keratoacanthoma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Lip squamous cell carcinoma	1 (0.09%)	0 (0.00%)	1 (0.07%)
Lung adenocarcinoma	1 (0.09%)	1 (0.18%)	1 (0.07%)
Lung neoplasm	0 (0.00%)	0 (0.00%)	1 (0.07%)
Malignant melanoma	0 (0.00%)	0 (0.00%)	6 (0.40%)
Malignant melanoma in situ	2 (0.18%)	0 (0.00%)	2 (0.13%)
Melanocytic naevus	1 (0.09%)	0 (0.00%)	4 (0.26%)
Meningioma	0 (0.00%)	0 (0.00%)	2 (0.13%)
Neurofibroma	1 (0.09%)	0 (0.00%)	1 (0.07%)
Non-small cell lung cancer metastatic	0 (0.00%)	0 (0.00%)	1 (0.07%)
Prostate cancer	0 (0.00%)	2 (0.37%)	3 (0.20%)
Renal oncocytoma	0 (0.00%)	1 (0.18%)	0 (0.00%)
Seminoma	2 (0.18%)	0 (0.00%)	2 (0.13%)
Skin cancer	0 (0.00%)	0 (0.00%)	2 (0.13%)
Small cell lung cancer metastatic	0 (0.00%)	0 (0.00%)	1 (0.07%)
Squamous cell carcinoma	1 (0.09%)	0 (0.00%)	8 (0.53%)
Squamous cell carcinoma of skin	0 (0.00%)	0 (0.00%)	10 (0.66%)
Squamous cell carcinoma of the vagina	0 (0.00%)	0 (0.00%)	1 (0.07%)
Superficial spreading melanoma stage unspecified	0 (0.00%)	0 (0.00%)	1 (0.07%)
Testis cancer	0 (0.00%)	0 (0.00%)	1 (0.07%)
Uterine leiomyoma	1 (0.09%)	1 (0.18%)	6 (0.40%)
Vulval cancer stage 0	0 (0.00%)	0 (0.00%)	1 (0.07%)
Nervous system disorders			
Allodynia	0 (0.00%)	1 (0.18%)	0 (0.00%)

Amnestic disorder	0 (0.00%)	1 (0.18%)	0 (0.00%)
Amyotrophic lateral sclerosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Aphasia	1 (0.09%)	0 (0.00%)	2 (0.13%)
Ataxia	1 (0.09%)	0 (0.00%)	2 (0.13%)
Autoimmune demyelinating disease	0 (0.00%)	0 (0.00%)	1 (0.07%)
Brain injury	1 (0.09%)	0 (0.00%)	1 (0.07%)
Brain stem infarction	1 (0.09%)	0 (0.00%)	1 (0.07%)
Central nervous system lesion	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cerebral haematoma	0 (0.00%)	0 (0.00%)	2 (0.13%)
Cerebral haemorrhage	0 (0.00%)	0 (0.00%)	2 (0.13%)
Cerebral infarction	0 (0.00%)	0 (0.00%)	3 (0.20%)
Cerebral venous sinus thrombosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cerebrovascular accident	2 (0.18%)	1 (0.18%)	7 (0.46%)
Clonic convulsion	0 (0.00%)	0 (0.00%)	1 (0.07%)
Cognitive disorder	0 (0.00%)	0 (0.00%)	1 (0.07%)
Disturbance in attention	1 (0.09%)	0 (0.00%)	1 (0.07%)
Dizziness	1 (0.09%)	0 (0.00%)	1 (0.07%)
Dysaesthesia	0 (0.00%)	1 (0.18%)	0 (0.00%)
Dysarthria	0 (0.00%)	0 (0.00%)	3 (0.20%)
Epilepsy	5 (0.45%)	0 (0.00%)	22 (1.45%)
Facial paresis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Febrile infection-related epilepsy syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)
Generalised tonic-clonic seizure	1 (0.09%)	0 (0.00%)	3 (0.20%)
Haemorrhagic stroke	0 (0.00%)	1 (0.18%)	0 (0.00%)
Head titubation	1 (0.09%)	0 (0.00%)	1 (0.07%)
Hemiparesis	3 (0.27%)	0 (0.00%)	4 (0.26%)

Hypoaesthesia	0 (0.00%)	1 (0.18%)	0 (0.00%)
Hypokinesia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Intention tremor	1 (0.09%)	0 (0.00%)	1 (0.07%)
Intracranial aneurysm	1 (0.09%)	0 (0.00%)	1 (0.07%)
Ischaemic stroke	1 (0.09%)	0 (0.00%)	4 (0.26%)
Lacunar infarction	0 (0.00%)	0 (0.00%)	1 (0.07%)
Lacunar stroke	0 (0.00%)	0 (0.00%)	1 (0.07%)
Loss of consciousness	0 (0.00%)	0 (0.00%)	1 (0.07%)
Meralgia paraesthetica	0 (0.00%)	1 (0.18%)	0 (0.00%)
Migraine	0 (0.00%)	0 (0.00%)	2 (0.13%)
Migraine with aura	0 (0.00%)	0 (0.00%)	1 (0.07%)
Motor dysfunction	0 (0.00%)	0 (0.00%)	1 (0.07%)
Multiple sclerosis	2 (0.18%)	0 (0.00%)	17 (1.12%)
Multiple sclerosis pseudo relapse	0 (0.00%)	0 (0.00%)	3 (0.20%)
Multiple sclerosis relapse	2 (0.18%)	7 (1.28%)	7 (0.46%)
Muscle spasticity	2 (0.18%)	1 (0.18%)	9 (0.59%)
Optic neuritis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Paraparesis	0 (0.00%)	3 (0.55%)	2 (0.13%)
Parkinson's disease	0 (0.00%)	0 (0.00%)	1 (0.07%)
Partial seizures	2 (0.18%)	0 (0.00%)	6 (0.40%)
Polyneuropathy	1 (0.09%)	0 (0.00%)	2 (0.13%)
Post herpetic neuralgia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Postictal paralysis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Presyncope	0 (0.00%)	0 (0.00%)	2 (0.13%)
Progressive multiple sclerosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pseudobulbar palsy	0 (0.00%)	0 (0.00%)	1 (0.07%)

Putamen haemorrhage	0 (0.00%)	1 (0.18%)	0 (0.00%)
Quadriparesis	0 (0.00%)	0 (0.00%)	2 (0.13%)
Quadriplegia	0 (0.00%)	0 (0.00%)	1 (0.07%)
Radiculopathy	1 (0.09%)	0 (0.00%)	1 (0.07%)
Secondary progressive multiple sclerosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Seizure	4 (0.36%)	0 (0.00%)	7 (0.46%)
Status epilepticus	0 (0.00%)	0 (0.00%)	4 (0.26%)
Status migrainosus	1 (0.09%)	0 (0.00%)	1 (0.07%)
Subarachnoid haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Subdural hygroma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Syncope	4 (0.36%)	1 (0.18%)	6 (0.40%)
Transient ischaemic attack	1 (0.09%)	1 (0.18%)	6 (0.40%)
Tremor	0 (0.00%)	1 (0.18%)	0 (0.00%)
Trigeminal neuralgia	3 (0.27%)	0 (0.00%)	12 (0.79%)
Uhthoff's phenomenon	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pregnancy, puerperium and perinatal conditions			
Abortion spontaneous	1 (0.09%)	0 (0.00%)	2 (0.13%)
Product issues			
Device breakage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Psychiatric disorders			
Acute psychosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Adjustment disorder	0 (0.00%)	0 (0.00%)	1 (0.07%)
Anxiety	1 (0.09%)	0 (0.00%)	2 (0.13%)
Anxiety disorder due to a general medical condition	1 (0.09%)	0 (0.00%)	1 (0.07%)

Completed suicide	1 (0.09%)	0 (0.00%)	1 (0.07%)
Confusional state	0 (0.00%)	0 (0.00%)	4 (0.26%)
Depressed mood	1 (0.09%)	0 (0.00%)	0 (0.00%)
Depression	3 (0.27%)	2 (0.37%)	3 (0.20%)
Depression suicidal	1 (0.09%)	0 (0.00%)	1 (0.07%)
Depressive symptom	1 (0.09%)	0 (0.00%)	1 (0.07%)
Disorientation	0 (0.00%)	0 (0.00%)	3 (0.20%)
Drug abuse	0 (0.00%)	0 (0.00%)	1 (0.07%)
Euphoric mood	1 (0.09%)	0 (0.00%)	1 (0.07%)
Hallucination	1 (0.09%)	0 (0.00%)	1 (0.07%)
Insomnia	0 (0.00%)	0 (0.00%)	2 (0.13%)
Major depression	0 (0.00%)	0 (0.00%)	1 (0.07%)
Mania	1 (0.09%)	0 (0.00%)	1 (0.07%)
Mental status changes	1 (0.09%)	0 (0.00%)	1 (0.07%)
Mixed anxiety and depressive disorder	2 (0.18%)	0 (0.00%)	2 (0.13%)
Panic attack	1 (0.09%)	1 (0.18%)	1 (0.07%)
Psychotic disorder	1 (0.09%)	0 (0.00%)	2 (0.13%)
Suicidal behaviour	3 (0.27%)	0 (0.00%)	4 (0.26%)
Suicidal ideation	3 (0.27%)	1 (0.18%)	8 (0.53%)
Suicide attempt	4 (0.36%)	3 (0.55%)	8 (0.53%)
Renal and urinary disorders			
Acute kidney injury	1 (0.09%)	0 (0.00%)	5 (0.33%)
Bladder dysfunction	2 (0.18%)	0 (0.00%)	3 (0.20%)
Bladder hypertrophy	0 (0.00%)	0 (0.00%)	2 (0.13%)
Bladder leukoplakia	0 (0.00%)	0 (0.00%)	1 (0.07%)

Calculus bladder	1 (0.09%)	0 (0.00%)	2 (0.13%)
Calculus urinary	0 (0.00%)	0 (0.00%)	2 (0.13%)
Cystitis noninfective	0 (0.00%)	0 (0.00%)	1 (0.07%)
Dysuria	0 (0.00%)	0 (0.00%)	1 (0.07%)
Haematuria	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hydronephrosis	2 (0.18%)	1 (0.18%)	2 (0.13%)
Nephritis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Nephrolithiasis	1 (0.09%)	1 (0.18%)	4 (0.26%)
Nephrotic syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)
Neurogenic bladder	1 (0.09%)	0 (0.00%)	2 (0.13%)
Obstructive nephropathy	0 (0.00%)	0 (0.00%)	1 (0.07%)
Renal colic	0 (0.00%)	0 (0.00%)	1 (0.07%)
Renal cyst	0 (0.00%)	0 (0.00%)	1 (0.07%)
Single functional kidney	1 (0.09%)	0 (0.00%)	1 (0.07%)
Ureterolithiasis	1 (0.09%)	0 (0.00%)	3 (0.20%)
Urethral stenosis	1 (0.09%)	0 (0.00%)	1 (0.07%)
Urge incontinence	1 (0.09%)	0 (0.00%)	1 (0.07%)
Urinary incontinence	2 (0.18%)	0 (0.00%)	3 (0.20%)
Urinary retention	3 (0.27%)	2 (0.37%)	9 (0.59%)
Urinary tract obstruction	0 (0.00%)	0 (0.00%)	1 (0.07%)
Reproductive system and breast disorders			
Benign prostatic hyperplasia	0 (0.00%)	0 (0.00%)	2 (0.13%)
Cervical dysplasia	0 (0.00%)	1 (0.18%)	0 (0.00%)
Cervical polyp	0 (0.00%)	0 (0.00%)	1 (0.07%)
Endometrial hyperplasia	0 (0.00%)	0 (0.00%)	2 (0.13%)

Heavy menstrual bleeding	2 (0.18%)	0 (0.00%)	3 (0.20%)
Intermenstrual bleeding	2 (0.18%)	1 (0.18%)	2 (0.13%)
Ovarian cyst	0 (0.00%)	0 (0.00%)	1 (0.07%)
Ovarian disorder	1 (0.09%)	0 (0.00%)	1 (0.07%)
Prostatitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Testicular atrophy	0 (0.00%)	1 (0.18%)	0 (0.00%)
Vaginal haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Respiratory, thoracic and mediastinal disorders			
Acute respiratory failure	0 (0.00%)	0 (0.00%)	3 (0.20%)
Asthma	0 (0.00%)	0 (0.00%)	1 (0.07%)
Chronic obstructive pulmonary disease	0 (0.00%)	0 (0.00%)	3 (0.20%)
Dyspnoea	0 (0.00%)	0 (0.00%)	2 (0.13%)
Hyperventilation	0 (0.00%)	0 (0.00%)	1 (0.07%)
Laryngeal stenosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Nasal polyps	0 (0.00%)	0 (0.00%)	1 (0.07%)
Pneumothorax	0 (0.00%)	0 (0.00%)	2 (0.13%)
Pulmonary embolism	1 (0.09%)	1 (0.18%)	8 (0.53%)
Pulmonary hypertension	1 (0.09%)	0 (0.00%)	1 (0.07%)
Pulmonary mass	0 (0.00%)	0 (0.00%)	1 (0.07%)
Respiratory depression	1 (0.09%)	0 (0.00%)	1 (0.07%)
Respiratory disorder	1 (0.09%)	0 (0.00%)	1 (0.07%)
Respiratory failure	0 (0.00%)	0 (0.00%)	5 (0.33%)
Respiratory paralysis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Sleep apnoea syndrome	0 (0.00%)	0 (0.00%)	1 (0.07%)
Skin and subcutaneous tissue disorders			

Actinic elastosis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Actinic keratosis	0 (0.00%)	1 (0.18%)	1 (0.07%)
Decubitus ulcer	1 (0.09%)	1 (0.18%)	4 (0.26%)
Dermal cyst	0 (0.00%)	0 (0.00%)	1 (0.07%)
Eczema	0 (0.00%)	0 (0.00%)	1 (0.07%)
Rash	1 (0.09%)	0 (0.00%)	1 (0.07%)
Rash papular	1 (0.09%)	0 (0.00%)	1 (0.07%)
Social circumstances			
Immobile	1 (0.09%)	0 (0.00%)	1 (0.07%)
Walking disability	0 (0.00%)	1 (0.18%)	0 (0.00%)
Vascular disorders			
Circulatory collapse	0 (0.00%)	1 (0.18%)	2 (0.13%)
Deep vein thrombosis	1 (0.09%)	0 (0.00%)	5 (0.33%)
Essential hypertension	0 (0.00%)	0 (0.00%)	1 (0.07%)
Haematoma	1 (0.09%)	0 (0.00%)	1 (0.07%)
Hypertension	1 (0.09%)	0 (0.00%)	2 (0.13%)
Hypertensive emergency	0 (0.00%)	0 (0.00%)	1 (0.07%)
Hypotension	0 (0.00%)	0 (0.00%)	1 (0.07%)
Internal haemorrhage	0 (0.00%)	0 (0.00%)	1 (0.07%)
Orthostatic hypotension	1 (0.09%)	0 (0.00%)	1 (0.07%)
Peripheral artery occlusion	0 (0.00%)	0 (0.00%)	1 (0.07%)
Vasculitis	0 (0.00%)	0 (0.00%)	1 (0.07%)
Venous thrombosis limb	1 (0.09%)	0 (0.00%)	1 (0.07%)

NOVARTIS

Other (Not Including Serious) Adverse Events

Time Frame	Core Part: from first dose of double-blind study treatment until end of Core Part (up to approximately 3 years). Core and Extension: from first dose of siponimod until end of study (up to approximately 10 years).
Additional Description	Safety is assessed in the Safety Set, including all patients who received at least one dose of study medication.
Source Vocabulary for Table Default	MedDRA (26.0)
Collection Approach for Table Default	Systematic Assessment

Frequent Event Reporting Threshold 5%

	Core-BAF312 N = 1099	**Core-Placebo N = 546**	**All BAF312 N = 1517**
Arm/Group Description	Participants who were randomized to siponimod (BAF312) during the Core Part	Participants who were randomized to placebo during the Core Part	All participants who received at least one dose of siponimod (BAF312) during the Core Part and/or the Extension Part
Total # Affected by any Other Adverse Event	778	348	1267
Total # at Risk by any Other Adverse Event	1099	546	1517
Blood and lymphatic system disorders			
Lymphopenia	9 (0.82%)	0 (0.00%)	137 (9.03%)
Gastrointestinal disorders			

Constipation	39 (3.55%)	21 (3.85%)	103 (6.79%)
Diarrhoea	69 (6.28%)	22 (4.03%)	119 (7.84%)
Nausea	73 (6.64%)	19 (3.48%)	119 (7.84%)
General disorders and administration site conditions			
Fatigue	100 (9.10%)	51 (9.34%)	171 (11.27%)
Oedema peripheral	50 (4.55%)	13 (2.38%)	107 (7.05%)
Infections and infestations			
Bronchitis	36 (3.28%)	16 (2.93%)	94 (6.20%)
COVID-19	0 (0.00%)	0 (0.00%)	189 (12.46%)
Cystitis	28 (2.55%)	13 (2.38%)	79 (5.21%)
Herpes zoster	24 (2.18%)	4 (0.73%)	92 (6.06%)
Influenza	72 (6.55%)	40 (7.33%)	152 (10.02%)
Nasopharyngitis	149 (13.56%)	79 (14.47%)	325 (21.42%)
Upper respiratory tract infection	89 (8.10%)	41 (7.51%)	165 (10.88%)
Urinary tract infection	128 (11.65%)	75 (13.74%)	369 (24.32%)
Injury, poisoning and procedural complications			
Contusion	34 (3.09%)	15 (2.75%)	96 (6.33%)
Fall	126 (11.46%)	59 (10.81%)	295 (19.45%)
Investigations			
Alanine aminotransferase increased	58 (5.28%)	8 (1.47%)	108 (7.12%)
Gamma-glutamyltransferase increased	43 (3.91%)	6 (1.10%)	120 (7.91%)
Lymphocyte count decreased	4 (0.36%)	0 (0.00%)	84 (5.54%)
Metabolism and nutrition disorders			

Hypercholesterolaemia	28 (2.55%)	11 (2.01%)	99 (6.53%)
Musculoskeletal and connective tissue disorders			
Arthralgia	69 (6.28%)	42 (7.69%)	184 (12.13%)
Back pain	65 (5.91%)	43 (7.88%)	186 (12.26%)
Pain in extremity	60 (5.46%)	21 (3.85%)	113 (7.45%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Melanocytic naevus	45 (4.09%)	15 (2.75%)	130 (8.57%)
Nervous system disorders			
Dizziness	74 (6.73%)	26 (4.76%)	145 (9.56%)
Headache	158 (14.38%)	71 (13.00%)	249 (16.41%)
Muscle spasticity	41 (3.73%)	23 (4.21%)	89 (5.87%)
Psychiatric disorders			
Depression	43 (3.91%)	28 (5.13%)	134 (8.83%)
Insomnia	37 (3.37%)	19 (3.48%)	84 (5.54%)
Respiratory, thoracic and mediastinal disorders			
Cough	35 (3.18%)	18 (3.30%)	90 (5.93%)
Skin and subcutaneous tissue disorders			
Actinic keratosis	15 (1.36%)	6 (1.10%)	80 (5.27%)
Vascular disorders			
Hypertension	114 (10.37%)	41 (7.51%)	294 (19.38%)

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.
- The safety data on long-term exposure, corresponding to an overall exposure of 7731.4 patient-years was overall consistent with the safety data previously reported for the placebo-controlled Core Part of the study. No new safety signals unexpected for an S1P modulator were observed with long-term treatment with siponimod for up to 10 years.
- 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

21-Feb-2018 (Interim CSR) and 13-Mar-2024 (Final CSR).