Clinical trial results:
An 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

Summary

EudraCT number	2009-014392-51
Trial protocol	ES HU DE PL IT FI
Global end of trial date	10 October 2016

Results information

Result version number	v1 (current)
This version publication date	26 October 2017
First version publication date	26 October 2017

Trial information

Trial identification

Sponsor protocol code	CBAF312A2201E1

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01185821
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 October 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 October 2016
Global end of trial reached?	Yes
Global end of trial date	10 October 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

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, macular edema, dermatologic alterations

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	30 August 2010
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Canada: 11
Country: Number of subjects enrolled	Finland: 8
Country: Number of subjects enrolled	Germany: 27
Country: Number of subjects enrolled	Hungary: 21
Country: Number of subjects enrolled	Italy: 34
Country: Number of subjects enrolled	Norway: 5
Country: Number of subjects enrolled	Poland: 16
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 13
Country: Number of subjects enrolled	Switzerland: 8
Country: Number of subjects enrolled	Turkey: 5
Country: Number of subjects enrolled	United States: 21
Worldwide total number of subjects	184
EEA total number of subjects	124

Notes:

Subjects enrolled per age group	
In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	184
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

All patients enrolled in the Extension study had completed the Core study. All patients underwent a 10 day titration at the start of the dose blinded phase of the study

Pre-assignment

Screening details:

During the double blind phase of the extension study patients received the same dose from the Core study. Placebo patients from Core Period 1 were randomized to 0.5, 2 or 10mg, those from Period 2 were randomized to 0.25 or 1.25 mg. All patients received 2mg in Open Label phase (.5 and .25mg were titrated up to 2mg)

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BAF312 10 mg/2 mg

Arm description:

10 mg dose in Double Blind Phase and 2 mg in Open Label Phase

Arm type	Experimental
Investigational medicinal product name	siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

Arm title	BAF312 2 mg/2 mg

Arm description:

2 mg dose in Double Blind Phase and 2 mg in Open Label Phase

Arm type	Experimental
Investigational medicinal product name	siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

Arm title	BAF312 1.25 mg/2 mg

Arm description:

1.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase

Arm type	Experimental

Investigational medicinal product name	siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

1.25 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

Arm title	BAF312 .5 mg/2 mg

Arm description:

.5 mg dose in Double Blind Phase and 2 mg in Open Label Phase

Arm type	Experimental
Investigational medicinal product name	siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

.5 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

Arm title	BAF312 .25 mg/2 mg

Arm description:

.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase

Arm type	Experimental
Investigational medicinal product name	siponimod
Investigational medicinal product code	BAF312
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

.25 mg dose in Double Blind and 2 mg dose in Open Label dosed once a day

Number of subjects in period 1	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg
Started	33	29	43
Patients with washout	33	29	39
Patients without washout	0 [1]	0 [2]	4 [3]
Patients on placebo in Core	8 [4]	7 [5]	9 [6]
Completed	26	20	33
Not completed	7	9	10
Abnormal laboratory value(s)	1	2	1
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	3	2	2
Adverse event, non-fatal	2	3	1
Administrative problems	-	-	1
Lost to follow-up	1	1	2

Condition no longer required study drug	-	-	-
Abnormal test procedure result	-	-	-
Lack of efficacy	-	-	3
Protocol deviation	-	-	-

Number of subjects in period 1	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg
Started	29	50
Patients with washout	29	33
Patients without washout	0 [7]	17 [8]
Patients on placebo in Core	8 [9]	2 [10]
Completed	23	26
Not completed	6	24
Abnormal laboratory value(s)	-	-
Adverse event, serious fatal	-	-
Consent withdrawn by subject	1	3
Adverse event, non-fatal	2	5
Administrative problems	1	2
Lost to follow-up	1	2
Condition no longer required study drug	-	1
Abnormal test procedure result	-	1
Lack of efficacy	-	9
Protocol deviation	1	1

Notes:

[1] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[2] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[3] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[4] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[5] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[6] - The number of subjects at this milestone seems inconsistent with the number of subjects in the

arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[7] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[8] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[9] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.
[10] - The number of subjects at this milestone seems inconsistent with the number of subjects in the arm. It is expected that the number of subjects will be greater than, or equal to the number that completed, minus those who left.
Justification: Milestone added to provide additional information for patients entering the Extension study from the Core study.

Baseline characteristics

Reporting groups	
Reporting group title	BAF312 10 mg/2 mg
Reporting group description:	
10 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 2 mg/2 mg
Reporting group description:	
2 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 1.25 mg/2 mg
Reporting group description:	
1.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 .5 mg/2 mg
Reporting group description:	
.5 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 .25 mg/2 mg
Reporting group description:	
.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase	

Reporting group values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg
Number of subjects	33	29	43
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: years			
arithmetic mean	36.8	35.1	34.0
standard deviation	± 9.09	± 9.16	± 7.57
Gender, Male/Female Units: Subjects			
Female	21	18	32
Male	12	11	11
Study Specific Characteristic | Expanded disability status scale (EDSS)			
Disability progression was assessed based on the EDSS scores ranging from 0 (normal) to 10 (death due to MS)			
Units: Combined scores			
arithmetic mean	2.03	2.19	1.95
standard deviation	± 0.960	± 1.278	± 1.096

Reporting group values	BAF312 .5 mg/2 mg	BAF312 .25 mg/2 mg	Total
Number of subjects	29	50	184
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age Continuous Units: years			
arithmetic mean	35.2	37.2	
standard deviation	± 9.10	± 8.42	-
Gender, Male/Female Units: Subjects			
Female	18	41	130
Male	11	9	54
Study Specific Characteristic | Expanded disability status scale (EDSS)			
Disability progression was assessed based on the EDSS scores ranging from 0 (normal) to 10 (death due to MS)			
Units: Combined scores			
arithmetic mean	1.88	2.22	
standard deviation	± 1.374	± 1.258	-

End points

End points reporting groups

Reporting group title	BAF312 10 mg/2 mg
Reporting group description:	
10 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 2 mg/2 mg
Reporting group description:	
2 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 1.25 mg/2 mg
Reporting group description:	
1.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 .5 mg/2 mg
Reporting group description:	
.5 mg dose in Double Blind Phase and 2 mg in Open Label Phase	
Reporting group title	BAF312 .25 mg/2 mg
Reporting group description:	
.25 mg dose in Double Blind Phase and 2 mg in Open Label Phase	

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

End point title	Total number of adverse events during evaluation of long term safety and tolerability of BAF312A in Extension study.[1]
End point description:	
Refer to adverse events for complete listing of serious adverse events and other adverse events. Adverse events of interest were presented in separate tables. There were no reports of macular edema.	
End point type	Primary
End point timeframe:	
Baseline up to approximately 5 years	

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	43	29
Units: events				
Serious adverse events	4	7	6	6
Other adverse events	30	26	42	29

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: events				
Serious adverse events	8			

Other adverse events	42			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with cardiac conduction abnormalities during the titration phase of the study[2]

End point description:

Number of patients with abnormal ECG conduction findings during dose-blinded titration at any visit post-dose, by type of abnormality and treatment (Extension Set). Number analyzed represent participants who had ECG results. Washout was defined as not being on treatment drug between Core and Extension for >7 days. Abbreviations: washout = WO, Con=conduction

End point type	Primary

End point timeframe:

Baseline Extension up to day 10

Notes:

[2] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	39	29
Units: participants				
With WO (33,29,39,29,33) Conduction-Prolonged QTc	5	2	5	2
With washout (33,29,39,29,33) Conduction - IVCD	3	8	1	3
With WO (33,29,39,29,33) Conduction - AV Mobitz I	1	0	0	0
With WO (33,29,39,29,33) Con:1st degree AV block	0	1	1	1
With washout (33,29,39,29,33) Conduction - WPW	0	0	0	1
Without washout (0,0,4,0,17) Conduction - IVCD	0	0	0	0

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: participants				
With WO (33,29,39,29,33) Conduction-Prolonged QTc	4			

With washout (33,29,39,29,33) Conduction - IVCD	0			
With WO (33,29,39,29,33) Conduction - AV Mobitz I	0			
With WO (33,29,39,29,33) Con:1st degree AV block	1			
With washout (33,29,39,29,33) Conduction - WPW	0			
Without washout (0,0,4,0,17) Conduction - IVCD	4			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with changes in blood pressure for overall extension study. (Extension analysis set)[3]

End point description:

Sitting blood pressure was measured in triplicate. The categories of notably low and high values and changes are presented for systolic (SBP) and diastolic (DBP). Multiple occurrences for a patient are counted as one occurrence in this table.

End point type	Primary

End point timeframe:

Baseline Extension up to approximately 5 years

Notes:

[3] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	43	29
Units: participants				
SBP Low: ≤ 90	1	3	2	1
SBP ≥ 20 decrease from baseline	8	10	4	6
SBP High: ≥ 160	1	1	1	3
SBP ≥ 20 increase from baseline	9	8	12	13
DBP Low: ≤ 50	1	0	1	0
DBP ≥ 15 decrease from baseline	14	8	10	10
DBP High: ≥ 100	4	7	4	4
DBP ≥ 15 increase from baseline	9	13	13	11

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants				

SBP Low: ≤ 90	1			
SBP ≥ 20 decrease from baseline	10			
SBP High: ≥ 160	3			
SBP ≥ 20 increase from baseline	18			
DBP Low: ≤ 50	1			
DBP ≥ 15 decrease from baseline	10			
DBP High: ≥ 100	4			
DBP ≥ 15 increase from baseline	17			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with viral infections of interest greater or equal to 5% in any dose group (Extension Set)[4]

End point description:

Most infections were clinical diagnoses and were not confirmed by microbiology / virologic investigations. A patient with multiple occurrences of an infection for a preferred term is counted only once in each specific category. Events identified as infections by the Investigator and defined as an AE with onset on or after the first dose of Extension Study drug up to and including 30 days after the date of the last dose

End point type	Primary

End point timeframe:

Baseline Extension up to approximately 5 years

Notes:

[4] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	43	29
Units: participants				
Oral herpes	5	0	4	2
Herpes zoster	5	0	3	2
Influenza	3	4	3	6

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants				
Oral herpes	4			
Herpes zoster	0			
Influenza	6			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of participants with dermatologic alterations - basal cell carcinoma (Extension Set)[5]

End point description:

End point type	Primary

End point timeframe:

Baseline Extension up to approximately 5 years

Notes:

[5] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.
Justification: No statistical analyses for this end point

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	43	29
Units: participants	1	0	1	0

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: participants	1			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Group level ARR (raw) is calculated as the total number of relapses for all the patients in the treatment group divided by the total number of days on study for all patients in the group and multiplied by 365.25 to obtain the annual rate. Model estimates are based on a negative binomial regression model, adjusted for treatment group, age, baseline EDSS, baseline number of Gd-enhanced T1 lesions and

number of relapses in previous 2 years as covariates, with log(time on study in years) as the offset variable, using the log link.

End point type	Secondary

End point timeframe:

Baseline extension up to approximately 5 years

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	43	29
Units: Group level ARR				
arithmetic mean (confidence interval 95%)	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)

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: Group level ARR				
arithmetic mean (confidence interval 95%)	0.22 (0.14 to 0.35)			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Free of MRI disease activity is defined as free of Gadolinium enhanced T1 lesions at any scan; free of new or enlarging T2 lesions at any scan: free of both gadolinium enhanced T1 lesions and new or enlarging T2 lesions at any sca, N = Number of patients with at least one MRI scan during the specified time period. New lesions at a specific visit are assessed relative to the previous scheduled visit scan. No imputation of missing scans is performed. As a result missing scans can lead to an overestimation of the proportion of patients free of a specific MRI activity.

End point type	Secondary

End point timeframe:

Baseline Extension up to approximately 5 years

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	31	26	43	29
Units: percentage of participants				
number (not applicable)				
Free of Gd-enhanced T1 lesions at any scan	58.1	57.7	58.1	44.8
Free of new/enlarging T2 lesions at any scan	32.3	42.3	46.5	20.7
Free of Gd-enhanced T1 and new enlarged T2 lesions	32.3	42.3	44.2	20.7

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	47			
Units: percentage of participants				
number (not applicable)				
Free of Gd-enhanced T1 lesions at any scan	66.0			
Free of new/enlarging T2 lesions at any scan	40.4			
Free of Gd-enhanced T1 and new enlarged T2 lesions	40.4			

Statistical analyses

No statistical analyses for this end point

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

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

End point description:

Six-month disability progression was defined relative to extension baseline EDSS score: 1.5 point increase in patients with baseline EDSS score of 0, 1.0 increase in patients with baseline EDSS score of between 0.5 to 5.0, inclusive and 0.5 increase in patients with baseline EDSS score of ≥ 5.5. The criteria for 6-month disability progression included detection of onset of progression and confirmation of progression for a period of at least 6 months.

End point type	Secondary

End point timeframe:

Baseline Extension up to approximately 5 years

End point values	BAF312 10 mg/2 mg	BAF312 2 mg/2 mg	BAF312 1.25 mg/2 mg	BAF312 .5 mg/2 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	33	29	43	29
Units: percentage of participants				
number (confidence interval 95%)	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)

End point values	BAF312 .25 mg/2 mg			
Subject group type	Reporting group			
Number of subjects analysed	50			
Units: percentage of participants				
number (confidence interval 95%)	78.6 (65.4 to 91.9)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
Timeframe for AE	
Adverse event reporting additional description:	
AE additional description	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	19.0

Reporting groups	
Reporting group title	BAF312 10/2 mg
Reporting group description:	
BAF312 10/2 mg	
Reporting group title	BAF312 2/2 mg
Reporting group description:	
BAF312 2/2 mg	
Reporting group title	BAF312 1.25/2 mg
Reporting group description:	
BAF312 1.25/2 mg	
Reporting group title	BAF312 0.5/2 mg
Reporting group description:	
BAF312 0.5/2 mg	
Reporting group title	BAF312 0.25/2 mg
Reporting group description:	
BAF312 0.25/2 mg	
Reporting group title	All patients
Reporting group description:	
All patients	

Serious adverse events	BAF312 10/2 mg	BAF312 2/2 mg	BAF312 1.25/2 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	4 / 33 (12.12%)	7 / 29 (24.14%)	6 / 43 (13.95%)
number of deaths (all causes)	0	1	0
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Submandibular mass			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Anaphylactic reaction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cervical metaplasia			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Smear cervix abnormal			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Femur fracture			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Tendon rupture			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Multiple sclerosis relapse			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenic cyst			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Ear and labyrinth disorders			
Otosclerosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary dyskinesia			

subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Stress urinary incontinence			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis acute			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			

Decreased appetite			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	BAF312 0.5/2 mg	BAF312 0.25/2 mg	All patients
Total subjects affected by serious adverse events			
subjects affected / exposed	6 / 29 (20.69%)	8 / 50 (16.00%)	31 / 184 (16.85%)
number of deaths (all causes)	0	0	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Basal cell carcinoma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Breast cancer			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	2 / 184 (1.09%)
occurrences causally related to treatment / all	0 / 0	1 / 1	2 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colon cancer metastatic			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pregnancy, puerperium and perinatal conditions			
Abortion			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Submandibular mass			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			

Anaphylactic reaction			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metrorrhagia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Uterine cervical metaplasia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Drug abuse			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mental disorder			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Smear cervix abnormal			

subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Ankle fracture			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Craniocerebral injury			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Femur fracture			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tendon rupture			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dysaesthesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Generalised tonic-clonic seizure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Headache			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Multiple sclerosis relapse			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	3 / 184 (1.63%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sciatica			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Splenic cyst			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ear and labyrinth disorders			
Otosclerosis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Glaucoma			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal discomfort			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastritis			

subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nausea			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pancreatitis acute			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	1 / 1	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vomiting			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Biliary dyskinesia			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Stress urinary incontinence			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Oral herpes			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	1 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pyelonephritis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyelonephritis acute			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper respiratory tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 0	1 / 2	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	1 / 184 (0.54%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Frequency threshold for reporting non-serious adverse events: 4 %

Non-serious adverse events	BAF312 10/2 mg	BAF312 2/2 mg	BAF312 1.25/2 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 33 (90.91%)	26 / 29 (89.66%)	42 / 43 (97.67%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Fibrous histiocytoma			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	3 / 43 (6.98%)
occurrences (all)	0	1	3
Melanocytic naevus			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	6 / 43 (13.95%)
occurrences (all)	2	1	8
Seborrhoeic keratosis			

subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	2	1	0
Skin papilloma			
subjects affected / exposed	2 / 33 (6.06%)	3 / 29 (10.34%)	1 / 43 (2.33%)
occurrences (all)	2	3	1
Uterine leiomyoma			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	3 / 43 (6.98%)
occurrences (all)	2	1	3
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	2 / 43 (4.65%)
occurrences (all)	0	1	2
Fatigue			
subjects affected / exposed	1 / 33 (3.03%)	4 / 29 (13.79%)	5 / 43 (11.63%)
occurrences (all)	1	6	5
Gait disturbance			
subjects affected / exposed	3 / 33 (9.09%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	3	0	0
Influenza like illness			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	2
Non-cardiac chest pain			
subjects affected / exposed	3 / 33 (9.09%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	3	0	1
Oedema peripheral			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Pyrexia			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	4 / 43 (9.30%)
occurrences (all)	3	1	5
Respiratory, thoracic and mediastinal disorders			

Catarrh			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	2
Cough			
subjects affected / exposed	3 / 33 (9.09%)	3 / 29 (10.34%)	3 / 43 (6.98%)
occurrences (all)	3	6	3
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Epistaxis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Oropharyngeal pain			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	3 / 43 (6.98%)
occurrences (all)	3	1	3
Rhinitis allergic			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	4
Wheezing			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Psychiatric disorders			
Anxiety			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	1 / 43 (2.33%)
occurrences (all)	3	2	1
Depression			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	6 / 43 (13.95%)
occurrences (all)	1	1	6
Insomnia			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	8 / 43 (18.60%)
occurrences (all)	2	2	8
Sleep disorder			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Investigations			

Alanine aminotransferase increased			
subjects affected / exposed	3 / 33 (9.09%)	5 / 29 (17.24%)	3 / 43 (6.98%)
occurrences (all)	5	6	3
Blood bilirubin increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Blood cholesterol increased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
C-reactive protein increased			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 33 (9.09%)	3 / 29 (10.34%)	2 / 43 (4.65%)
occurrences (all)	4	4	2
Hepatic enzyme increased			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	1 / 43 (2.33%)
occurrences (all)	2	1	1
Lymphocyte count decreased			
subjects affected / exposed	4 / 33 (12.12%)	2 / 29 (6.90%)	4 / 43 (9.30%)
occurrences (all)	4	2	11
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	2 / 33 (6.06%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	5	3	0
Fall			
subjects affected / exposed	3 / 33 (9.09%)	3 / 29 (10.34%)	0 / 43 (0.00%)
occurrences (all)	3	4	0
Joint injury			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	2
Ligament sprain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	2	0	2
Limb injury			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Tachycardia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Dizziness			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	1 / 43 (2.33%)
occurrences (all)	1	1	1
Headache			
subjects affected / exposed	9 / 33 (27.27%)	4 / 29 (13.79%)	9 / 43 (20.93%)
occurrences (all)	14	7	9
Hypoaesthesia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	3	0	0
Migraine			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	3 / 43 (6.98%)
occurrences (all)	2	0	3
Muscle spasticity			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Neuralgia			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	4 / 43 (9.30%)
occurrences (all)	1	0	6
Paraesthesia			
subjects affected / exposed	4 / 33 (12.12%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	5	0	0
Blood and lymphatic system disorders			

Leukopenia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	0	1	0
Lymphadenitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Lymphopenia			
subjects affected / exposed	6 / 33 (18.18%)	5 / 29 (17.24%)	4 / 43 (9.30%)
occurrences (all)	9	7	4
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	2 / 43 (4.65%)
occurrences (all)	0	1	2
Tinnitus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Vertigo			
subjects affected / exposed	4 / 33 (12.12%)	1 / 29 (3.45%)	3 / 43 (6.98%)
occurrences (all)	4	1	4
Vertigo positional			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	3
Eye pain			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Iridocyclitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	5
Vision blurred			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	3 / 43 (6.98%)
occurrences (all)	2	0	3
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	2 / 43 (4.65%)
occurrences (all)	0	1	2
Abdominal pain upper			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	3 / 43 (6.98%)
occurrences (all)	0	1	3
Aphthous ulcer			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Constipation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Diarrhoea			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	7 / 43 (16.28%)
occurrences (all)	1	2	9
Dyspepsia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	1 / 43 (2.33%)
occurrences (all)	1	1	1
Enteritis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Gastritis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	3	0
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	1	0	2
Irritable bowel syndrome			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Toothache			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	4 / 43 (9.30%)
occurrences (all)	0	6	5

Vomiting			
subjects affected / exposed	1 / 33 (3.03%)	3 / 29 (10.34%)	0 / 43 (0.00%)
occurrences (all)	2	3	0
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	2	0	2
Dermal cyst			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Dermatitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dermatitis allergic			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Dermatitis contact			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Eczema			
subjects affected / exposed	3 / 33 (9.09%)	2 / 29 (6.90%)	2 / 43 (4.65%)
occurrences (all)	3	3	2
Hyperkeratosis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Pigmentation disorder			
subjects affected / exposed	2 / 33 (6.06%)	2 / 29 (6.90%)	1 / 43 (2.33%)
occurrences (all)	2	2	1
Pruritus			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	2
Urticaria			

subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Micturition urgency			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	1 / 43 (2.33%)
occurrences (all)	3	1	1
Nephrolithiasis			
subjects affected / exposed	2 / 33 (6.06%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	2	2	0
Urinary retention			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	1	0	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	4 / 33 (12.12%)	3 / 29 (10.34%)	2 / 43 (4.65%)
occurrences (all)	5	3	2
Back pain			
subjects affected / exposed	6 / 33 (18.18%)	2 / 29 (6.90%)	5 / 43 (11.63%)
occurrences (all)	7	2	7
Intervertebral disc degeneration			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	0	0	2
Joint swelling			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	2	0	0
Muscle spasms			
subjects affected / exposed	1 / 33 (3.03%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	1	0	2
Muscular weakness			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	2 / 43 (4.65%)
occurrences (all)	2	0	2
Musculoskeletal pain			

subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	4 / 43 (9.30%)
occurrences (all)	1	3	4
Myalgia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Neck pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	1 / 43 (2.33%)
occurrences (all)	1	4	1
Pain in extremity			
subjects affected / exposed	2 / 33 (6.06%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	2	1	0
Tendonitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0
Bronchitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	5 / 43 (11.63%)
occurrences (all)	0	4	9
Conjunctivitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	2	0	1
Cystitis			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	2 / 43 (4.65%)
occurrences (all)	13	1	2
Fungal infection			
subjects affected / exposed	3 / 33 (9.09%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	3	1	0
Fungal skin infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	3	0	0
Gastroenteritis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	1 / 43 (2.33%)
occurrences (all)	0	2	2

Gastroenteritis viral			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	3 / 43 (6.98%)
occurrences (all)	0	0	3
Herpes zoster			
subjects affected / exposed	5 / 33 (15.15%)	0 / 29 (0.00%)	3 / 43 (6.98%)
occurrences (all)	5	0	3
Influenza			
subjects affected / exposed	4 / 33 (12.12%)	4 / 29 (13.79%)	5 / 43 (11.63%)
occurrences (all)	4	4	8
Nasopharyngitis			
subjects affected / exposed	10 / 33 (30.30%)	8 / 29 (27.59%)	17 / 43 (39.53%)
occurrences (all)	27	13	29
Onychomycosis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Oral herpes			
subjects affected / exposed	5 / 33 (15.15%)	0 / 29 (0.00%)	4 / 43 (9.30%)
occurrences (all)	9	0	6
Otitis media			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Pharyngitis			
subjects affected / exposed	1 / 33 (3.03%)	4 / 29 (13.79%)	3 / 43 (6.98%)
occurrences (all)	1	4	4
Pneumonia			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	0 / 43 (0.00%)
occurrences (all)	1	1	0
Respiratory tract infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 29 (3.45%)	1 / 43 (2.33%)
occurrences (all)	0	1	1
Rhinitis			
subjects affected / exposed	3 / 33 (9.09%)	2 / 29 (6.90%)	1 / 43 (2.33%)
occurrences (all)	3	2	1
Sinusitis			
subjects affected / exposed	3 / 33 (9.09%)	2 / 29 (6.90%)	3 / 43 (6.98%)
occurrences (all)	4	2	5

Subcutaneous abscess			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	0 / 43 (0.00%)
occurrences (all)	0	2	0
Tinea versicolour			
subjects affected / exposed	0 / 33 (0.00%)	2 / 29 (6.90%)	2 / 43 (4.65%)
occurrences (all)	0	2	2
Tonsillitis			
subjects affected / exposed	1 / 33 (3.03%)	1 / 29 (3.45%)	5 / 43 (11.63%)
occurrences (all)	1	1	5
Tooth infection			
subjects affected / exposed	1 / 33 (3.03%)	2 / 29 (6.90%)	1 / 43 (2.33%)
occurrences (all)	1	4	1
Upper respiratory tract infection			
subjects affected / exposed	4 / 33 (12.12%)	6 / 29 (20.69%)	4 / 43 (9.30%)
occurrences (all)	11	10	7
Urinary tract infection			
subjects affected / exposed	6 / 33 (18.18%)	4 / 29 (13.79%)	2 / 43 (4.65%)
occurrences (all)	9	5	2
Vaginal infection			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	1
Vulvovaginal candidiasis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	1 / 43 (2.33%)
occurrences (all)	0	0	3
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	2 / 33 (6.06%)	4 / 29 (13.79%)	2 / 43 (4.65%)
occurrences (all)	2	4	3
Hypoglycaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 29 (0.00%)	0 / 43 (0.00%)
occurrences (all)	0	0	0

Non-serious adverse events	BAF312 0.5/2 mg	BAF312 0.25/2 mg	All patients
Total subjects affected by non-serious adverse events			
subjects affected / exposed	29 / 29 (100.00%)	42 / 50 (84.00%)	169 / 184 (91.85%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			

Fibrous histiocytoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	1	0	5
Melanocytic naevus			
subjects affected / exposed	2 / 29 (6.90%)	7 / 50 (14.00%)	18 / 184 (9.78%)
occurrences (all)	3	8	22
Seborrhoeic keratosis			
subjects affected / exposed	0 / 29 (0.00%)	4 / 50 (8.00%)	7 / 184 (3.80%)
occurrences (all)	0	4	7
Skin papilloma			
subjects affected / exposed	2 / 29 (6.90%)	2 / 50 (4.00%)	10 / 184 (5.43%)
occurrences (all)	2	4	12
Uterine leiomyoma			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	1	0	3
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 29 (10.34%)	8 / 50 (16.00%)	16 / 184 (8.70%)
occurrences (all)	3	8	17
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	4 / 184 (2.17%)
occurrences (all)	0	2	5
Fatigue			
subjects affected / exposed	2 / 29 (6.90%)	6 / 50 (12.00%)	18 / 184 (9.78%)
occurrences (all)	2	6	20
Gait disturbance			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	4 / 184 (2.17%)
occurrences (all)	1	0	4
Influenza like illness			
subjects affected / exposed	1 / 29 (3.45%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	2	1	6
Non-cardiac chest pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	6 / 184 (3.26%)
occurrences (all)	0	3	7
Oedema peripheral			

subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	1	0	3
Pyrexia			
subjects affected / exposed	3 / 29 (10.34%)	5 / 50 (10.00%)	15 / 184 (8.15%)
occurrences (all)	5	6	20
Respiratory, thoracic and mediastinal disorders			
Catarrh			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	4 / 184 (2.17%)
occurrences (all)	5	0	8
Cough			
subjects affected / exposed	4 / 29 (13.79%)	2 / 50 (4.00%)	15 / 184 (8.15%)
occurrences (all)	9	2	23
Dyspnoea			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	3 / 184 (1.63%)
occurrences (all)	0	1	3
Epistaxis			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	2	0	2
Oropharyngeal pain			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	10 / 184 (5.43%)
occurrences (all)	0	4	11
Rhinitis allergic			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	4 / 184 (2.17%)
occurrences (all)	0	2	6
Wheezing			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	2 / 184 (1.09%)
occurrences (all)	0	2	2
Psychiatric disorders			
Anxiety			
subjects affected / exposed	0 / 29 (0.00%)	4 / 50 (8.00%)	9 / 184 (4.89%)
occurrences (all)	0	4	10
Depression			
subjects affected / exposed	3 / 29 (10.34%)	7 / 50 (14.00%)	18 / 184 (9.78%)
occurrences (all)	3	11	22
Insomnia			

subjects affected / exposed	3 / 29 (10.34%)	6 / 50 (12.00%)	20 / 184 (10.87%)
occurrences (all)	3	8	23
Sleep disorder			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	4	0	5
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	2 / 29 (6.90%)	2 / 50 (4.00%)	15 / 184 (8.15%)
occurrences (all)	3	2	19
Blood bilirubin increased			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	2 / 184 (1.09%)
occurrences (all)	0	3	3
Blood cholesterol increased			
subjects affected / exposed	2 / 29 (6.90%)	1 / 50 (2.00%)	4 / 184 (2.17%)
occurrences (all)	2	2	5
C-reactive protein increased			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	5 / 184 (2.72%)
occurrences (all)	0	4	6
Gamma-glutamyltransferase increased			
subjects affected / exposed	3 / 29 (10.34%)	2 / 50 (4.00%)	13 / 184 (7.07%)
occurrences (all)	3	2	15
Hepatic enzyme increased			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	0	1	5
Lymphocyte count decreased			
subjects affected / exposed	2 / 29 (6.90%)	3 / 50 (6.00%)	15 / 184 (8.15%)
occurrences (all)	3	6	26
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 29 (10.34%)	1 / 50 (2.00%)	8 / 184 (4.35%)
occurrences (all)	5	1	14
Fall			
subjects affected / exposed	2 / 29 (6.90%)	1 / 50 (2.00%)	9 / 184 (4.89%)
occurrences (all)	3	8	18
Joint injury			

subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	0	0	3
Ligament sprain			
subjects affected / exposed	2 / 29 (6.90%)	1 / 50 (2.00%)	7 / 184 (3.80%)
occurrences (all)	2	1	7
Limb injury			
subjects affected / exposed	1 / 29 (3.45%)	2 / 50 (4.00%)	3 / 184 (1.63%)
occurrences (all)	1	2	3
Cardiac disorders			
Palpitations			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	3 / 184 (1.63%)
occurrences (all)	0	1	3
Tachycardia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	3 / 184 (1.63%)
occurrences (all)	0	3	4
Nervous system disorders			
Burning sensation			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	3 / 184 (1.63%)
occurrences (all)	0	2	3
Dizziness			
subjects affected / exposed	1 / 29 (3.45%)	4 / 50 (8.00%)	8 / 184 (4.35%)
occurrences (all)	1	4	8
Headache			
subjects affected / exposed	4 / 29 (13.79%)	10 / 50 (20.00%)	36 / 184 (19.57%)
occurrences (all)	12	14	56
Hypoaesthesia			
subjects affected / exposed	1 / 29 (3.45%)	2 / 50 (4.00%)	4 / 184 (2.17%)
occurrences (all)	2	2	7
Migraine			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	6 / 184 (3.26%)
occurrences (all)	1	0	6
Muscle spasticity			
subjects affected / exposed	3 / 29 (10.34%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	3	0	5
Neuralgia			

subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	0	0	7
Paraesthesia			
subjects affected / exposed	2 / 29 (6.90%)	3 / 50 (6.00%)	9 / 184 (4.89%)
occurrences (all)	3	3	11
Blood and lymphatic system disorders			
Leukopenia			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	2	0	3
Lymphadenitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	2 / 184 (1.09%)
occurrences (all)	0	2	2
Lymphopenia			
subjects affected / exposed	6 / 29 (20.69%)	3 / 50 (6.00%)	24 / 184 (13.04%)
occurrences (all)	9	3	32
Ear and labyrinth disorders			
Ear pain			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	4 / 184 (2.17%)
occurrences (all)	0	1	4
Tinnitus			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	3 / 184 (1.63%)
occurrences (all)	0	2	3
Vertigo			
subjects affected / exposed	2 / 29 (6.90%)	6 / 50 (12.00%)	16 / 184 (8.70%)
occurrences (all)	2	6	17
Vertigo positional			
subjects affected / exposed	2 / 29 (6.90%)	1 / 50 (2.00%)	3 / 184 (1.63%)
occurrences (all)	2	1	3
Eye disorders			
Conjunctivitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	1	1	6
Eye pain			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	1	0	3
Iridocyclitis			

subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	5
Vision blurred			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	0	0	5
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 29 (3.45%)	3 / 50 (6.00%)	7 / 184 (3.80%)
occurrences (all)	2	3	8
Abdominal pain upper			
subjects affected / exposed	5 / 29 (17.24%)	3 / 50 (6.00%)	12 / 184 (6.52%)
occurrences (all)	5	3	12
Aphthous ulcer			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	3	0	4
Constipation			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	4 / 184 (2.17%)
occurrences (all)	0	3	4
Diarrhoea			
subjects affected / exposed	3 / 29 (10.34%)	6 / 50 (12.00%)	19 / 184 (10.33%)
occurrences (all)	3	7	22
Dyspepsia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	5 / 184 (2.72%)
occurrences (all)	0	2	5
Enteritis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	3
Gastritis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	2	0	5
Gastrooesophageal reflux disease			
subjects affected / exposed	3 / 29 (10.34%)	1 / 50 (2.00%)	6 / 184 (3.26%)
occurrences (all)	3	1	7
Irritable bowel syndrome			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	2	0	2

Nausea			
subjects affected / exposed	3 / 29 (10.34%)	4 / 50 (8.00%)	8 / 184 (4.35%)
occurrences (all)	5	6	13
Toothache			
subjects affected / exposed	1 / 29 (3.45%)	4 / 50 (8.00%)	11 / 184 (5.98%)
occurrences (all)	1	6	18
Vomiting			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	7 / 184 (3.80%)
occurrences (all)	0	3	8
Skin and subcutaneous tissue disorders			
Actinic keratosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	2
Alopecia			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	0	1	5
Dermal cyst			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	2	0	3
Dermatitis			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	2 / 184 (1.09%)
occurrences (all)	0	2	2
Dermatitis allergic			
subjects affected / exposed	2 / 29 (6.90%)	2 / 50 (4.00%)	4 / 184 (2.17%)
occurrences (all)	2	2	4
Dermatitis contact			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	2	0	3
Eczema			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	8 / 184 (4.35%)
occurrences (all)	0	1	9
Hyperkeratosis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	2
Pigmentation disorder			

subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	0	0	5
Pruritus			
subjects affected / exposed	1 / 29 (3.45%)	3 / 50 (6.00%)	7 / 184 (3.80%)
occurrences (all)	1	4	8
Urticaria			
subjects affected / exposed	1 / 29 (3.45%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	1	1	5
Renal and urinary disorders			
Bladder dysfunction			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	2
Micturition urgency			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	0	1	6
Nephrolithiasis			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	1	0	5
Urinary retention			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	3	0	4
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 29 (6.90%)	3 / 50 (6.00%)	14 / 184 (7.61%)
occurrences (all)	2	3	15
Back pain			
subjects affected / exposed	3 / 29 (10.34%)	3 / 50 (6.00%)	19 / 184 (10.33%)
occurrences (all)	3	3	22
Intervertebral disc degeneration			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	2
Joint swelling			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	3 / 184 (1.63%)
occurrences (all)	0	1	3
Muscle spasms			

subjects affected / exposed	1 / 29 (3.45%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	1	1	5
Muscular weakness			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	4 / 184 (2.17%)
occurrences (all)	0	0	4
Musculoskeletal pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	9 / 184 (4.89%)
occurrences (all)	0	2	10
Myalgia			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	4 / 184 (2.17%)
occurrences (all)	0	4	5
Neck pain			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	6 / 184 (3.26%)
occurrences (all)	0	2	8
Pain in extremity			
subjects affected / exposed	4 / 29 (13.79%)	5 / 50 (10.00%)	12 / 184 (6.52%)
occurrences (all)	4	9	16
Tendonitis			
subjects affected / exposed	2 / 29 (6.90%)	2 / 50 (4.00%)	6 / 184 (3.26%)
occurrences (all)	2	2	6
Infections and infestations			
Acute sinusitis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	3 / 184 (1.63%)
occurrences (all)	0	3	3
Bronchitis			
subjects affected / exposed	3 / 29 (10.34%)	6 / 50 (12.00%)	16 / 184 (8.70%)
occurrences (all)	3	7	23
Conjunctivitis			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	3 / 184 (1.63%)
occurrences (all)	0	0	3
Cystitis			
subjects affected / exposed	1 / 29 (3.45%)	1 / 50 (2.00%)	8 / 184 (4.35%)
occurrences (all)	1	4	21
Fungal infection			
subjects affected / exposed	1 / 29 (3.45%)	1 / 50 (2.00%)	6 / 184 (3.26%)
occurrences (all)	1	3	8

Fungal skin infection			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	3
Gastroenteritis			
subjects affected / exposed	3 / 29 (10.34%)	4 / 50 (8.00%)	10 / 184 (5.43%)
occurrences (all)	4	5	13
Gastroenteritis viral			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	5 / 184 (2.72%)
occurrences (all)	0	2	5
Herpes zoster			
subjects affected / exposed	2 / 29 (6.90%)	0 / 50 (0.00%)	10 / 184 (5.43%)
occurrences (all)	2	0	10
Influenza			
subjects affected / exposed	7 / 29 (24.14%)	7 / 50 (14.00%)	27 / 184 (14.67%)
occurrences (all)	9	11	36
Nasopharyngitis			
subjects affected / exposed	11 / 29 (37.93%)	18 / 50 (36.00%)	64 / 184 (34.78%)
occurrences (all)	27	49	145
Onychomycosis			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	5 / 184 (2.72%)
occurrences (all)	0	3	5
Oral herpes			
subjects affected / exposed	2 / 29 (6.90%)	4 / 50 (8.00%)	15 / 184 (8.15%)
occurrences (all)	19	11	45
Otitis media			
subjects affected / exposed	0 / 29 (0.00%)	3 / 50 (6.00%)	5 / 184 (2.72%)
occurrences (all)	0	3	5
Pharyngitis			
subjects affected / exposed	6 / 29 (20.69%)	3 / 50 (6.00%)	17 / 184 (9.24%)
occurrences (all)	6	3	18
Pneumonia			
subjects affected / exposed	0 / 29 (0.00%)	2 / 50 (4.00%)	4 / 184 (2.17%)
occurrences (all)	0	2	4
Respiratory tract infection			
subjects affected / exposed	1 / 29 (3.45%)	2 / 50 (4.00%)	5 / 184 (2.72%)
occurrences (all)	1	4	7

Rhinitis			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	7 / 184 (3.80%)
occurrences (all)	0	6	12
Sinusitis			
subjects affected / exposed	5 / 29 (17.24%)	5 / 50 (10.00%)	18 / 184 (9.78%)
occurrences (all)	8	6	25
Subcutaneous abscess			
subjects affected / exposed	0 / 29 (0.00%)	0 / 50 (0.00%)	2 / 184 (1.09%)
occurrences (all)	0	0	2
Tinea versicolour			
subjects affected / exposed	0 / 29 (0.00%)	1 / 50 (2.00%)	5 / 184 (2.72%)
occurrences (all)	0	1	5
Tonsillitis			
subjects affected / exposed	2 / 29 (6.90%)	1 / 50 (2.00%)	10 / 184 (5.43%)
occurrences (all)	2	1	10
Tooth infection			
subjects affected / exposed	1 / 29 (3.45%)	0 / 50 (0.00%)	5 / 184 (2.72%)
occurrences (all)	2	0	8
Upper respiratory tract infection			
subjects affected / exposed	7 / 29 (24.14%)	9 / 50 (18.00%)	30 / 184 (16.30%)
occurrences (all)	14	11	53
Urinary tract infection			
subjects affected / exposed	4 / 29 (13.79%)	4 / 50 (8.00%)	20 / 184 (10.87%)
occurrences (all)	7	12	35
Vaginal infection			
subjects affected / exposed	2 / 29 (6.90%)	2 / 50 (4.00%)	5 / 184 (2.72%)
occurrences (all)	2	2	5
Vulvovaginal candidiasis			
subjects affected / exposed	1 / 29 (3.45%)	2 / 50 (4.00%)	4 / 184 (2.17%)
occurrences (all)	1	2	6
Metabolism and nutrition disorders			
Hypercholesterolaemia			
subjects affected / exposed	1 / 29 (3.45%)	3 / 50 (6.00%)	12 / 184 (6.52%)
occurrences (all)	1	10	20
Hypoglycaemia			

subjects affected / exposed occurrences (all)	0 / 29 (0.00%) 0	2 / 50 (4.00%) 2	2 / 184 (1.09%) 2

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
07 May 2010	The amendment was to introduce measures to mitigate observed bradyarrhythmic effects by means of dose titration and an enhanced monitoring to identify and to manage patients at risk. Further, the amendment introduced the need for re-screening of patients who had study drug interruptions of more than 4 weeks between completing the Core Study and starting the participation in the Extension Study. Corresponding changes were made to the study design and dose titration content as well as in-house monitoring and cardiac exclusion criteria.
05 November 2010	Introduced an interim analysis to evaluate the safety of the dose-titration scheme used during the first 10 days of the study. Data of interest included heart rate, ECG parameters, and AEs.
13 June 2012	Incorporated the OL Phase into the study design and changed siponimod dosing from 5 separate fixed-dose groups to a 2 mg/day fixed dose. Study was extended from 2 years up to 5 years
19 March 2014	Key changes were adding an abbreviated visit schedule option for patients who stopped taking study medication and continued in the study, allowed concomitant treatment with beta blockers, provided updated details on potent inhibitors/inducers of CYP2C9 and further extended the study duration (beyond 5 years)

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

This study was prematurely discontinued after approximately 5 years. The decision to prematurely discontinue the study was not taken due to safety-related concerns, but a decision to focus the development of siponimod in MS on a different population

Notes: