Sponsor

Novartis

Generic Drug Name

Siponimod (BAF312)

Therapeutic Area of Trial

Neuroinflammation – Relapsing-remitting multiple sclerosis (RRMS)

Approved Indication

Investigational

Study Number

CBAF312A2201

Title

A phase II, double-blind, randomized, multi-center, adaptive dose-ranging, placebo-controlled, parallel-group study evaluating safety, tolerability and efficacy on MRI lesion parameters and determining the dose response curve of BAF312 given orally once daily in patients with relapsing-remitting multiple sclerosis

Phase of Development

Phase II

Study Start/End Dates

30 Mar 2009 to 04 May 2011

Study Design/Methodology

This was a double-blind, randomized, multi-center, adaptive dose-ranging, placebo-controlled, parallel-group study in 297 patients with RRMS. Two patient groups were tested sequentially, separated by an interim analysis (IA). The first group of patients (Period 1) was randomized in a 1:1:1:1 fashion to treatment with three doses of BAF312 (10 mg, 2 mg and 0.5 mg given orally o.d) or placebo for a period 6 months. After IA, the second group of patients (Period 2) was randomized (4:4:1) to two additional doses of BAF312, 1.25 mg and 0.25mg, as defined on the basis of the IA results, and placebo. These patients were treated for 3 months.

Eligible patients who completed the double-blind treatment phase could enter an optional long-term extension study under a separate protocol (CBAF312A2201E1).

Centers

73 centers in 12 countries: 5 centers in Canada, 3 centers in Finland, 10 centers in Germany, 4 centers in Hungary, 6 centers in Italy, 3 centers in Norway, 3 centers in Poland, 9 centers in Russia, 5 centers in Spain, 4 centers in Switzerland, 5 centers in Turkey, and 16 centers in the United States of America.

Publication

BAF312, a selective sphingosine-1-phosphate receptor modulator improves MRI and clinical outcomes in relapsing-remitting multiple sclerosis (RRMS). Stüve, O., Selmaj, K., Li, D., Hartung, H.P., Hemmer, B., Kappos, L., Freedman, M., Rieckmann, P., Montalban, X., Zhang Auberson, L., Pohlmann, H., Mercier, F., Dahlke, F., Wallström, E.. AAN 2012, Abstract.

MRI findings of BOLD: A phase 2 dose-finding study using adaptive design and modeling methods for BAF312 in relapsing-remitting MS. Li, D., Selmaj, K., Zhao, G., Cheng, Y., Rochotte, E., Mercier, F., Wallström, E.. AAN 2012, Abstract.

Dose titration regimen attenuates bradyarrhythmic events with BAF312 during treatment initiation. DiMarco, J., Selmaj, K., Kappos, L., Jordaan, P., Mendzelevski, B., Goncalves, J., Zhang Auberson, L.. AAN 2011, Abstract.

BAF312, a selective sphingosine 1-phosphate receptor modulator, effectively suppresses MRI lesion activity in Relapsing-Remitting Multiple Sclerosis: findings of an adaptive dose-ranging Phase 2 study. Selmaj, K., Li, D., Stüve, O., Kappos, L., Hartung, H.P., Hemmer, B., Freedman, M.S., Rieckmann, P., Montalban, X., Zhang-Auberson, L., Pohlmann, H., Mercier, F., Dahlke, F., Wallström, E.. ECTRIMS 2011, Abstract (Late Breaker).

Objectives

Primary objective

- The primary objective of this study was to evaluate the dose response relationship among five doses of BAF312 and placebo during 3 months of treatment in patients with RRMS, as measured by the number of combined unique active [MRI] lesions (CUAL).

Secondary objectives

- To evaluate the safety and tolerability (including cardiac events and blood pressure effects) of BAF312 during 6 months and 3 months of treatment in MS patients
- To evaluate the dose response relationship of BAF312 and placebo during 6 months of treatment in patients with RRMS, as measured by CUAL
- To explore the effect of BAF312 on the number of relapses and thereof derived measures (e.g. annualized relapse rate (ARR), proportion of relapse-free patients)
- To explore the correlation of the course of the lymphocyte count with paraclinical (MRI activity) and clinical course
- To evaluate the effect of BAF312 at 6 and 3 months treatment on additional MRI parameters:
  1. Total number of monthly new [Gd]-enhanced lesions (T1 weighted lesions)
  2. Total number of all [Gd]-enhanced lesions (T1 weighted lesions)
  3. Total number of monthly new or enlarging T2-weighted lesions
  4. Proportion of subjects without any new MRI disease activity
  5. MRI response in subjects with high disease activity at baseline (≥ 2 [Gd]-enhanced lesions)
- To assess the steady state plasma concentrations of BAF312 in RRMS patients

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

BAF312 was administered as tablets (available at doses of 0.25 mg, 1 mg, and 5 mg) for oral administration at a once daily dose of 10mg, BAF312 2mg, BAF312 1.25mg, BAF312 0.5mg, or BAF312 0.25 mg.

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

Matching BAF312 placebo tablets for oral administration once daily.

Criteria for Evaluation

Primary variables

- Monthly number of combined unique active MRI lesions (CUAL) during 3 months of treatment: Combined unique active lesions were defined as new gadolinium [Gd]-enhanced lesions on T1-weighted MRI scans or new or enlarging lesions on T2-weighted MRI scans, without double-counting of lesions.

Secondary variables

MRI variables

- number of monthly new Gd-enhanced T1 lesions
- number of all monthly Gd-enhanced T1 lesions
- number of monthly new or enlarging T2 lesions
- proportion of patients without any new MRI disease activity
- number of monthly CUAL
- number of monthly new Gd-enhanced T1 lesions in patients with high baseline disease activity

Relapse variables

- Annualized Relapse Rate (ARR)
- Proportion of relapse-free patients

Expanded Disability Status Scale (EDSS) - Neurological Examination

The EDSS (including the functional system scores and EDSS score) was summarized by time point and change from baseline categories for each treatment group.

Safety and tolerability

Safety assessments consisted of collecting all AEs, SAEs, with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of laboratory values and assessments of vital signs, ECG, physical condition and body weight. Additional safety assessments as specified per protocol included dermatological examinations, ophthalmic examinations, chest x-ray/HRCT, and pulmonary function tests.

MS relapses were reported on the MS relapse CRF. If, in the judgment of the investigator, a MS relapse was unusually severe or unexpected and warranted specific notification, then a SAE form was completed and submitted in addition.

Special safety guidances were provided for elevated blood pressure (ambulatory blood pressure monitoring), 24-h ECG (Holter monitoring), elevated liver function tests, notable lym-

phopenia, symptoms of neurological deterioration inconsistent with MS course, infections, pulmonary function monitoring, and ophthalmic monitoring.

Other (Bioanalytics)

Blood samples for pharmacokinetic (PK) analysis were collected in all patients at Month 1, Month 3 and End of Treatment Visit.

Statistical Methods

Efficacy

An extension of the MCP-Mod methodology that was suitable for count data was used to address the primary objective. The null hypothesis of a flat dose-response relationship for the percentage reduction in the monthly number of CUAL as compared to placebo was tested at a one-sided significance level of 2.5% against the alternative hypothesis of a monotonic increase dose response relationship. Five candidate models were used to describe the potential dose-response curve (linear, emax, exponential and two hill-emax). For each candidate model, a t-statistic based on linear combination of the mean responses per individual doses and using optimal contrast coefficient corresponding to the candidate model was derived to test the null hypothesis of no dose-response versus the alternative of a dose-response in the shape of the candidate model. A critical value q for testing each individual candidate model contrast was evaluated under the null hypothesis and under the constraint that the family wise error rate was controlled at the desired one sided 2.5% level. If the maximum t-statistic exceeded the critical value q, the overall null hypothesis of a flat dose-response curve was rejected.

If the presence of a dose response relationship was evaluated in the previous step of the methodology, the next steps consisted of selecting the best family of dose-response model within those corresponding to significant test statistics (based on the AIC) and in fitting it to the data. Using this model, the doses of interest were estimated with a 95% confidence interval.

As a sensitivity analysis to the primary efficacy analysis, a Bayesian longitudinal Emax model with random effects and a Poisson observation level error structure was fitted to the data. Separate Emax dose response models were assumed for each month, with correlation accounted for by a patient level random effect. The dose-response curve at Month 3 was estimated from this model, as well the doses of interest with a 95% confidence interval.

All statistical testing for the secondary efficacy variables were performed at the two-sided 5% level of significance without adjusting for multiplicity. Secondary endpoints were analyzed using negative binomial (NB) generalized estimating equation (GEE) regression model, logistic regression and NB regression.

An interim analysis was performed when 181 patients from period1 had completed the 3-month visit (if they did not prematurely withdraw from the study). This was performed using an independent unblinded statistician and programmer and was reviewed by an external DMC to see if the sample-size should be adjusted and to select the two BAF312 doses to be investigated in period 2. The sample size was found to be appropriate and the BAF312 1.25mg and 0.25mg doses were selected for period 2.

Safety

Summary statistics were used for safety variables; summaries were presented by treatment group using the safety set.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

- Males or females aged 18 to 55 years inclusive.
- Provided written informed consent prior to participating in the study
- Diagnosis of MS as defined by revised McDonald criteria
- A relapsing-remitting course of disease with
  - At least 1 documented relapse during the previous year, or
  - 2 documented relapses during the previous 2 years, or
  - A positive Gd-enhanced MRI scan at screening (in case the first MRI scan obtained at screening was negative, a second scan could be obtained 1 month later)
- An Expanded Disability Status Scale (EDSS) score of 0-5.0 inclusive at randomization
- Neurologically stable with no evidence of relapse or corticosteroid treatment within 30 days prior to randomization

Exclusion criteria

- A manifestation of another type of MS than RRMS
- History or presence of malignancy (except for successfully-treated basal or squamous cell carcinoma of skin)
- Had been treated with immunomodulatory or immunosuppressive medications for varying prior time windows
- Patients with significant cardiovascular conditions
- Patients with significant pulmonary conditions
- Patients with significant hepatic conditions
- Unable to undergo MRI scans due to claustrophobia or metallic implants incompatible with MRI
- Unable to receive gadolinium-based MRI contrast agents due to a history of hypersensitivity to gadolinium-based contrast agents, or severe renal insufficiency
- Participation in any clinical research study evaluating another investigational drug or therapy within 3 months prior to randomization
- History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes
- Pregnant or nursing (lactating) women

Other protocol defined inclusion/exclusion criteria may apply.

Number of Subjects

Patient disposition, by treatment (Period 1; Randomized set)

Reason	BAF312 10 mg N=50		BAF312 2 mg N=49		BAF312 0.5 mg N=43		Placebo N=46		All Patients N=188	
	n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Study phase completion	35	(70.0)	44	(89.8)	36	(83.7)	42	(91.3)	157	(83.5)
On study drug	32	(64.0)	42	(85.7)	33	(76.7)	41	(89.1)	148	(78.7)
Off study drug	3	(6.0)	2	(4.1)	3	(7.0)	1	(2.2)	9	(4.8)
Discontinued from the study	15	(30.0)	5	(10.2)	7	(16.3)	3	(6.5)	30	(16.0)
Abnormal laboratory value(s)	3	(6.0)	0		0		1	(2.2)	4	(2.1)
Administrative problems	2	(4.0)	1	(2.0)	0		1	(2.2)	4	(2.1)
Adverse Event(s)	6	(12.0)	4	(8.2)	3	(7.0)	1	(2.2)	14	(7.4)
Protocol deviation	1	(2.0)	0		0		0		1	(0.5)
Subject withdrew consent	3	(6.0)	0		2	(4.7)	0		5	(2.7)
Unsatisfactory therapeutic effect	0		0		2	(4.7)	0		2	(1.1)
Discontinued study drug	18	(36.0)	7	(14.3)	10	(23.3)	4	(8.7)	39	(20.7)
Abnormal laboratory value(s)	1	(2.0)	0		0		0		1	(0.5)
Abnormal test procedure result(s)	1	(2.0)	0		0		0		1	(0.5)
Administrative problems	3	(6.0)	1	(2.0)	2	(4.7)	2	(4.3)	8	(4.3)
Adverse Event(s)	9	(18.0)	6	(12.2)	4	(9.3)	2	(4.3)	21	(11.2)
Protocol deviation	1	(2.0)	0		0		0		1	(0.5)
Subject withdrew consent	2	(4.0)	0		2	(4.7)	0		4	(2.1)
Unsatisfactory therapeutic effect	1	(2.0)	0		2	(4.7)	0		3	(1.6)

The study discontinuation reason is the primary reason from the Study Phase Completion page. The study drug discontinuation reason is the primary reason from the Study Drug Discontinuation page. Reasons are sorted alphabetically.
All percentages are calculated based on the number of randomized patients.
No study completion information available for patient 306/1 in the Placebo group, who was misrandomized and never received study medication.

Patient disposition, by treatment (Period 2; Randomized set)

Reason	BAF312 1.25 mg N=42		BAF312 0.25 mg N=51		Placebo N=16		All Patients N=109	
	n	(%)	n	(%)	n	(%)	n	(%)
Study phase completion	40	(95.2)	50	(98.0)	16	(100.0)	106	(97.2)
On study drug	40	(95.2)	49	(96.1)	15	(93.8)	104	(95.4)
Off study drug	0		1	(2.0)	1	(6.3)	2	(1.8)
Discontinued from the study	2	(4.8)	1	(2.0)	0		3	(2.8)
Adverse Event(s)	2	(4.8)	0		0		2	(1.8)
Subject withdrew consent	0		1	(2.0)	0		1	(0.9)
Discontinued study drug	2	(4.8)	2	(3.9)	1	(6.3)	5	(4.6)
Administrative problems	0		1	(2.0)	0		1	(0.9)
Adverse Event(s)	1	(2.4)	0		0		1	(0.9)
Lost to follow-up	1	(2.4)	0		0		1	(0.9)
Subject withdrew consent	0		1	(2.0)	1	(6.3)	2	(1.8)

The study discontinuation reason is the primary reason from the Study Phase Completion page. The study drug discontinuation reason is the primary reason from the Study Drug Discontinuation page. Reasons are sorted alphabetically.

All percentages are calculated based on the number of randomized patients.

Demographic and Background Characteristics

Demographics, by treatment (Period 1; Randomized set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 0.5 mg N=43	Period 1 Placebo N=46	All Placebo N=62	Period 1 All Patients N=188
Sex - n (%)						
Female	30 (60.0)	34 (69.4)	30 (69.8)	36 (78.3)	45 (72.6)	130 (69.1)
Male	20 (40.0)	15 (30.6)	13 (30.2)	10 (21.7)	17 (27.4)	58 (30.9)
Age groups (years) - n (%)						
18-20	1 (2.0)	2 (4.1)	0	1 (2.2)	1 (1.6)	4 (2.1)
21-30	12 (24.0)	10 (20.4)	10 (23.3)	14 (30.4)	19 (30.6)	46 (24.5)
31-40	23 (46.0)	21 (42.9)	21 (48.8)	18 (39.1)	24 (38.7)	83 (44.1)
41-50	10 (20.0)	12 (24.5)	9 (20.9)	8 (17.4)	12 (19.4)	39 (20.7)
>=51	4 (8.0)	4 (8.2)	3 (7.0)	4 (8.7)	5 (8.1)	15 (8.0)
Missing	0	0	0	1	1	1
Age (years)						
n	50	49	43	45	61	187
Mean	36.4	37.4	36.0	35.2	35.4	36.3
SD	8.43	8.94	8.79	8.75	8.56	8.69
Median	37.0	37.0	35.0	35.0	35.0	36.0
Minimum	20	19	21	19	19	19
Maximum	53	55	55	52	52	55
Predominant race - n (%)						
Black	0	1 (2.0)	0	1 (2.2)	1 (1.6)	2 (1.1)
Caucasian	48 (96.0)	47 (95.9)	42 (97.7)	45 (97.8)	60 (96.8)	182 (96.8)
Other	2 (4.0)	1 (2.0)	1 (2.3)	0	1 (1.6)	4 (2.1)
Ethnicity - n (%)						
Hispanic/Latino	1 (2.0)	1 (2.0)	1 (2.3)	0	1 (1.6)	3 (1.6)
Chinese	0	0	0	0	0	0
Indian (Indian subcontinent)	0	0	0	0	0	0
Japanese	0	0	0	0	0	0
Mixed Ethnicity	2 (4.0)	0	3 (7.0)	1 (2.2)	1 (1.6)	6 (3.2)
Other	47 (94.0)	48 (98.0)	39 (90.7)	45 (97.8)	60 (96.8)	179 (95.2)
Height (cm)						
n	50	49	43	45	61	187
Mean	171.798	169.105	169.144	168.913	169.226	169.788
SD	10.3381	9.1796	9.6370	8.5584	8.7309	9.4704
Median	170.000	167.640	168.000	169.000	169.000	168.000

Minimum	152.00	155.00	152.40	150.00	150.00	150.00
Maximum	190.00	192.00	192.00	187.00	188.00	192.00
Weight (kg)						
n	48	49	42	45	61	184
Mean	70.960	74.386	71.836	68.868	68.981	71.561
SD	12.3027	19.6126	19.3827	17.7003	16.9890	17.4155
Median	70.500	71.000	64.900	65.000	65.000	69.000
Minimum	50.90	47.00	42.00	43.00	43.00	42.00
Maximum	98.40	126.09	115.50	123.60	123.60	126.09
BMI (kg/m^2)						
n	48	49	42	45	61	184
Mean	23.9323	25.9032	24.9139	23.9726	23.9518	24.6911
SD	3.21811	6.01399	5.82491	5.07291	4.94293	5.15931
Median	23.8732	24.5390	23.7519	23.2912	23.1837	23.8639
Minimum	16.787	17.211	16.406	16.135	16.135	16.135
Maximum	30.863	40.859	46.561	39.216	39.216	46.561

Demographics, by treatment (Period 2 and overall; Randomized set)

	BAF312 1.25 mg N=42	BAF312 0.25 mg N=51	Period 2 Placebo N=16	All Placebo N=62	Period 2 All Patients N=109	All Patients N=297
Sex - n (%)						
Female	31 (73.8)	42 (82.4)	9 (56.3)	45 (72.6)	82 (75.2)	212 (71.4)
Male	11 (26.2)	9 (17.6)	7 (43.8)	17 (27.4)	27 (24.8)	85 (28.6)
Age groups (years) - n (%)						
18-20	2 (4.8)	0	0	1 (1.6)	2 (1.8)	6 (2.0)
21-30	10 (23.8)	10 (19.6)	5 (31.3)	19 (30.6)	25 (22.9)	71 (23.9)
31-40	16 (38.1)	21 (41.2)	6 (37.5)	24 (38.7)	43 (39.4)	126 (42.4)
41-50	12 (28.6)	15 (29.4)	4 (25.0)	12 (19.4)	31 (28.4)	70 (23.6)
>=51	2 (4.8)	5 (9.8)	1 (6.3)	5 (8.1)	8 (7.3)	23 (7.7)
Missing	0	0	0	1	0	1
Age (years)						
n	42	51	16	61	109	296
Mean	35.4	37.4	35.9	35.4	36.4	36.3
SD	8.87	8.39	8.24	8.56	8.53	8.62
Median	35.0	36.0	34.0	35.0	35.0	36.0
Minimum	19	23	25	19	19	19
Maximum	55	53	51	52	55	55
Predominant race - n (%)						
Black	1 (2.4)	1 (2.0)	0	1 (1.6)	2 (1.8)	4 (1.3)
Caucasian	41 (97.6)	50 (98.0)	15 (93.8)	60 (96.8)	106 (97.2)	288 (97.0)
Other	0	0	1 (6.3)	1 (1.6)	1 (0.9)	5 (1.7)
Ethnicity - n (%)						
Hispanic/Latino	1 (2.4)	1 (2.0)	1 (6.3)	1 (1.6)	3 (2.8)	6 (2.0)
Chinese	0	0	0	0	0	0
Indian (Indian subcontinent)	0	0	0	0	0	0
Japanese	0	0	0	0	0	0

Mixed Ethnicity	1 (2.4)	0	0	1 (1.6)	1 (0.9)	7 (2.4)
Other	40 (95.2)	50 (98.0)	15 (93.8)	60 (96.8)	105 (96.3)	284 (95.6)
Height (cm)						
n	40	50	16	61	106	293
Mean	169.012	165.786	170.106	169.226	167.655	169.016
SD	9.2256	9.0471	9.4308	8.7309	9.2626	9.4359
Median	169.650	165.000	170.000	169.000	167.500	168.000
Minimum	147.50	150.00	156.00	150.00	147.50	147.50
Maximum	192.00	191.00	188.00	188.00	192.00	192.00
Weight (kg)						
n	40	50	16	61	106	290
Mean	72.910	66.449	69.300	68.981	69.318	70.741
SD	17.2586	13.2238	15.3407	16.9890	15.3197	16.6881
Median	68.600	62.900	65.000	65.000	65.500	67.250
Minimum	50.00	50.00	52.00	43.00	50.00	42.00
Maximum	120.00	102.70	97.70	123.60	120.00	126.09
BMI (kg/m^2)						
n	40	50	16	61	106	290
Mean	25.7547	24.2701	23.8933	23.9518	24.7734	24.7212
SD	7.42705	5.15741	4.71570	4.94293	6.05669	5.49407
Median	23.8228	22.5371	22.6468	23.1837	23.0147	23.5475
Minimum	17.820	17.099	18.339	16.135	17.099	16.135
Maximum	52.445	40.166	36.772	39.216	52.445	52.445

MS baseline disease characteristics and MS history, by treatment (Period 1+2; Randomized set)

	BAF312 10 mg N=50	**BAF312 2 mg N=49**	**BAF312 1.25 mg N=42**	**BAF312 0.5 mg N=43**	**BAF312 0.25 mg N=51**	**Placebo N=62**
Disease duration since onset of symptoms (years)						
N	50	49	42	43	51	61
Mean (SD)	6.004 (6.0849)	7.248 (6.8415)	7.210 (6.6416)	8.657 (7.3472)	7.653 (5.7420)	8.039 (6.6327)
Median	4.678	5.057	5.552	7.198	5.703	7.551
Minimum-Maximum	0.35-33.80	0.34-34.97	0.26-25.14	0.39-27.85	0.41-25.23	0.20-28.20
Number of relapses in the last year						
N	50	49	42	43	51	61
Mean (SD)	1.4 (0.78)	1.3 (0.63)	1.3 (0.64)	1.5 (0.85)	1.4 (0.78)	1.3 (0.64)
Median	1.0	1.0	1.0	1.0	1.0	1.0
Minimum-Maximum	0-3	0-3	0-3	0-4	0-3	0-4
Number of relapses in the past 2 years						
N	50	49	42	43	51	61
Mean (SD)	2.0 (0.97)	2.1 (0.96)	1.8 (0.79)	1.8 (0.97)	2.0 (0.91)	1.8 (0.74)
Median	2.0	2.0	2.0	2.0	2.0	2.0
Minimum-Maximum	0-5	1-5	1-3	1-4	0-4	1-4

Number of relapses since first MS symptoms						
N	50	49	42	43	51	60
Mean (SD)	3.6 (1.70)	4.1 (2.24)	3.9 (3.22)	4.3 (2.71)	6.2 (10.25)	4.1 (5.16)
Median	3.0	3.0	3.0	4.0	4.0	3.0
Minimum-Maximum	1-9	1-11	1-16	1-11	1-72	1-40
Baseline EDSS						
N	50	49	41	43	51	60
Mean (SD)	2.26 (0.981)	2.41 (1.236)	1.95 (1.011)	2.23 (1.250)	2.33 (1.112)	2.29 (1.147)
Median	2.00	2.00	2.00	1.50	2.00	2.00
Minimum-Maximum	0.0-4.5	0.0-5.0	0.0-5.0	0.0-5.0	0.0-5.0	0.0-5.0

EDSS = Expanded Disability Status Scale

MRI baseline characteristics, by treatment (Period 1+2; Randomized set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 1.25 mg N=42	BAF312 0.5 mg N=43	BAF312 0.25 mg N=51	Placebo N=62
Number of patients with MRI scan *	50 (100.0)	48 (98.0)	42 (100.0)	43 (100.0)	51 (100.0)	61 (98.4)
Number of patients free of Gd-enhanced T1 lesions - n (%)	28 (56.0)	22 (45.8)	20 (47.6)	20 (46.5)	28 (54.9)	26 (42.6)
Number of Gd-enhanced T1 lesions per patient						
Mean (SD)	1.5 (3.85)	1.7 (3.40)	1.6 (2.42)	3.7 (8.14)	1.6 (3.36)	2.2 (3.41)
Median	0.0	1.0	1.0	1.0	0.0	1.0
Minimum-Maximum	0-25	0-20	0-9	0-38	0-17	0-15
Number of patients free of T1 non-enhancing hypointense lesions - n (%)	1 (2.0)	1 (2.1)	4 (9.5)	3 (7.0)	3 (5.9)	0
Number of T1 non-enhancing hypointense lesions per patient						
Mean (SD)	16.0 (17.41)	14.2 (14.54)	11.4 (11.53)	17.4 (13.61)	15.9 (14.69)	16.9 (16.41)
Median	8.5	9.0	6.5	15.0	11.0	11.0
Minimum-Maximum	0-77	0-63	0-40	0-46	0-57	1-64

* Number of patients with MRI scan at baseline is the denominator for percentage of patients free of Gd-enhanced T1 lesions and T1 non-enhancing hypointense lesions.

Primary Objective Result(s)

Testing significance of candidate dose response models at 3 months (Full Analysis Set)

Model	T statistic	p-value (one-sided)*
Linear	1.75	0.0696
Emax (with ED50=1mg)	3.93	0.0001
Hill Emax 1 (with ED50=2mg and h=2)	2.53	0.0115
Hill Emax 2 (with ED50=3mg and h=3)	1.65	0.0858
Exponential (with delta=3.633)	1.20	0.1817

* Models with a p-value <0.025 are significantly different from a flat dose-response (i.e. no dose-response) model.
With ED50 the dose that gives half of the asymptotic maximum change over placebo, E_{max} the asymptotic maximum change in effect over placebo, h the Hill coefficient, delta the rate of increase.

Estimation of doses of interest at 3 months (Full Analysis Set)

Selected Model	Doses of interest	Dose (mg)	95% CI
Emax	Dose achieving 50% reduction	0.38	(0.02, Inf)
	ED50	0.01	(0.01, 1.79)
	ED90	0.09	(0.09, 16.08)

ED50 is the dose that gives half of the asymptotic maximum change over placebo.
ED90 is the dose that gives 90% of the asymptotic maximum change over placebo.

Estimation of doses of interest at 3 months, based on mixed-effect model (Full Analysis Set)

Doses of interest	Dose (mg)	95% CI
Dose achieving 50% reduction	0.51	(0.19, 1.34)
ED50	0.83	(0.30, 2.27)
ED90	7.46	(2.72, 20.47)

ED50 is the dose that gives half of the asymptotic maximum change over placebo.
ED90 is the dose that gives 90% of the asymptotic maximum change over placebo.
Estimation of the dose response curve is based on a non-linear (Emax) mixed effect Poisson model allowing for over-dispersion and taking the within patient (time-dependent) correla tion structure into account.

Secondary Objective Result(s)

Analysis of annualized relapse rate for confirmed relapses up to 6 months (Period 1; Full Analysis Set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 0.5 mg N=43	Placebo N=45
Summary statistics				
- Number of confirmed relapses up to 6 months	9	5	13	13
- Time in study (days)	8557	8336	7408	8212
- Group level ARR (raw)	0.38	0.22	0.64	0.58
- Patient level ARR (mean/SD)	2.73/17.190*	0.36/1.488	0.85/1.732	0.57/0.993
Model based results**				
- Group level ARR	0.30	0.20	0.61	0.58
- 95% CI of ARR	(0.151, 0.613)	(0.081, 0.478)	(0.351, 1.062)	(0.337, 1.002)
- ARR-ratio to placebo	0.524	0.340	1.051	
- 95% CI for ARR-ratio	(0.219, 1.257)	(0.121, 0.956)	(0.486, 2.273)	
- p-value	0.148	0.041	0.899	
- % relative reduction	47.6	66.0	-5.1	

Annualized relapse rates (ARR) are defined as the number of relapses in one year.
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.
A cut-off is applied for inclusion in this analysis. This is the Month 6 visit or the last available visit prior to Month 6. For premature discontinuation before Month 6, days on study are defined as the end of study (or early discontinuation) visit - date of randomization + 1.
Pair wise comparison and p-values refer to ARR on active treatment compared to placebo. An ARR-ratio <1 favors active treatment. N.E. = Not estimable.
* Patient level ARR in the 10mg group of 2.73 is due to Patient A2201-0351-0002. He was randomized on 27OCT2009, had a relapse on 28OCt2009 and discontinued study drug and withdrew from study on 29OCT2009 because of this relapse. That patient individual ARR = (1 relapse / 3 days) * 365.25 = 121.75. All other patients in the study had an individual ARR of less than 10.
** Model estimates and pair wise treatment comparisons to placebo are based on a negative binomial regression model, adjusted for treatment group and baseline number of relapses in previous 2 years, with log(time on study in years) as the offset variable, using the log link.

Analysis of annualized relapse rate for confirmed relapses up to 6 months (Period 1; Per-protocol set)

	BAF312 10 mg N=37	BAF312 2 mg N=42	BAF312 0.5 mg N=40	Placebo N=42
Summary statistics				
- Number of confirmed relapses up to 6 months	6	3	11	13
- Time in study (days)	6518	7648	7100	7568
- Group level ARR (raw)	0.34	0.14	0.57	0.63
- Patient level ARR (mean/SD)	0.34/0.780	0.14/0.518	0.66/1.426	0.62/1.037
Model based results**				
- Algorithm did not converge or convergence is questionable.				

Annualized relapse rates (ARR) are defined as the number of relapses in one year.
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.
A cut-off is applied for inclusion in this analysis. This is the Month 6 visit or the last available visit prior to Month 6. For premature discontinuation before Month 6, days on study are defined as the end of study (or early discontinuation) visit - date of randomization + 1.
Pair wise comparison and p-values refer to ARR on active treatment compared to placebo. An ARR-ratio <1 favors active treatment. N.E. = Not estimable.
** Model estimates and pair wise treatment comparisons to placebo are based on a negative binomial regression model, adjusted for treatment group and baseline number of relapses in previous 2 years, with log(time on study in years) as the offset variable, using the log link.

Analysis of proportion of relapse-free patients (confirmed relapses only) up to month 3 and 6 (Full Analysis Set)

Treatment	n	Estimated proportion	Odds ratio	95% CI of the odds ratio	p-value
Month 3 (Period 1+2)					
BAF312 10 mg (N=50)	50	0.87	0.915	(0.288, 2.925)	0.879
BAF312 2 mg (N=49)	49	0.93	1.745	(0.484, 7.167)	0.399
BAF312 1.25 mg (N=42)	42	0.93	1.697	(0.438, 8.296)	0.454
BAF312 0.5 mg (N=43)	43	0.79	0.509	(0.166, 1.511)	0.223
BAF312 0.25 mg (N=51)	51	0.86	0.785	(0.253, 2.392)	0.668
Placebo (N=61)	61	0.88			
Month 6 (Period 1 only)					
BAF312 10 mg (N=50)	50	0.84	1.996	(0.731, 5.669)	0.178
BAF312 2 mg (N=49)	49	0.92	4.120	(1.328, 14.681)	0.014
BAF312 0.5 mg (N=43)	43	0.77	1.266	(0.468, 3.494)	0.642
Placebo (N=45)	45	0.72			

n = number of patients with non-missing number of relapses in the previous 2 years.

Pairwise comparison of treatments to placebo are based on odds ratios estimated from a logistic regression model adjusted for treatment group and using number of relapses in the previous 2 years as a covariate. Proportions are estimated from the logistic regression model.

An odds ratio of > 1 indicates an increased odds in favor of the active treatment. N.E. = Not estimable.

Analysis of monthly new Gd-enhanced T1 lesions at months 3 and 6 (Full Analysis Set)

Period Treatment	n	Estimated number of lesions	Lesion ratio	95% CI of lesion ratio	Relative reduction (%) in lesions compared to placebo	p-value *
Month 3 (Period 1+2)						

BAF312 10 mg (N=50)	44	0.18	0.138	(0.047, 0.408)	86.2	<0.001
BAF312 2 mg (N=49)	45	0.40	0.307	(0.123, 0.771)	69.3	0.012
BAF312 1.25 mg (N=42)	42	0.15	0.113	(0.036, 0.358)	88.7	<0.001
BAF312 0.5 mg (N=43)	43	0.48	0.375	(0.163, 0.860)	62.5	0.021
BAF312 0.25 mg (N=51)	51	0.62	0.478	(0.220, 1.037)	52.2	0.062
Placebo (N=61)	61	1.29				
Month 6 (Period 1 only)						
BAF312 10 mg (N=50)	44	0.25	0.154	(0.063, 0.376)	84.6	<0.001
BAF312 2 mg (N=49)	45	0.38	0.228	(0.081, 0.641)	77.2	0.005
BAF312 0.5 mg (N=43)	43	0.31	0.188	(0.070, 0.509)	81.2	<0.001
Placebo (N=45)	45	1.65				

* p-values correspond to pair wise comparisons of active treatment to placebo (i.e. to lesion ratios).
n = number of observations considered in the analysis (i.e. patients with at least one scan up to month 3 or month 6).
Month 3 and Month 6 results are based on two separate negative binomial GEE regression models accounting for repeated measures on each patient. Both models were adjusted for baseline number of Gd-enhanced T1 lesions and treatment group x month (the month number of each lesion count measurement) interaction, using the log link.
Lesion ratio (and corresponding 95% CI) is the ratio between the estimated number of lesions on active treatment compared to placebo. N.E. = Not estimable. Estimates are computed at Month 3 and Month 6 respectively.

Analysis of number of all monthly Gd-enhanced T1 lesions (Period 1+2; Full Analysis Set)

Period Treatment	n	Estimated number of lesions	Lesion ratio	95% CI of lesion ratio	Relative reduction (%) in lesions compared to placebo	p-value *
Month 3 (Period 1+2)						
BAF312 10 mg (N=50)	44	0.48	0.279	(0.124, 0.628)	72.1	0.002
BAF312 2 mg (N=49)	45	0.69	0.396	(0.182, 0.861)	60.4	0.019
BAF312 1.25 mg (N=42)	42	0.27	0.154	(0.059, 0.400)	84.6	<0.001
BAF312 0.5 mg (N=43)	43	0.79	0.454	(0.219, 0.945)	54.6	0.035
BAF312 0.25 mg (N=51)	51	0.96	0.555	(0.283, 1.090)	44.5	0.087
Placebo (N=61)	61	1.73				
Month 6 (Period 1 only)						
BAF312 10 mg (N=50)	44	0.28	0.095	(0.033, 0.273)	90.5	<0.001
BAF312 2 mg (N=49)	45	0.53	0.180	(0.069, 0.470)	82.0	<0.001
BAF312 0.5 mg (N=43)	43	0.51	0.173	(0.069, 0.434)	82.7	<0.001
Placebo (N=45)	45	2.94				

* p-values correspond to pair wise comparisons of active treatment to placebo (i.e. to lesion ratios).
n = number of observations considered in the analysis (i.e. patients with at least one scan up to month 3 or month 6).
Month 3 and Month 6 results are based on two separate negative binomial GEE regression models accounting for repeated measures on each patient. Both models were adjusted for treatment group x month (the month number of each lesion count measurement) interaction, using the log link.
Lesion ratio (and corresponding 95% CI) is the ratio between the estimated number of lesions on active treatment compared to placebo. N.E. = Not estimable. Estimates are computed at Month 3 and Month 6 respectively.

Analysis of number of monthly new/enlarging T2 lesions at months 3 and 6 (Full Analysis Set)

Period Treatment	n	Estimated number of lesions	Lesion ratio	95% CI of lesion ratio	Relative reduction (%) in lesions compared to placebo	p-value *

Month 3 (Period 1+2)						
BAF312 10 mg (N=50)	44	0.38	0.259	(0.100, 0.670)	74.1	0.005
BAF312 2 mg (N=49)	45	0.40	0.276	(0.112, 0.676)	72.4	0.005
BAF312 1.25 mg (N=42)	42	0.17	0.118	(0.034, 0.409)	88.2	<0.001
BAF312 0.5 mg (N=43)	43	1.00	0.683	(0.234, 1.991)	31.7	0.485
BAF312 0.25 mg (N=51)	51	0.87	0.591	(0.292, 1.193)	40.9	0.142
Placebo (N=61)	61	1.47				
Month 6 (Period 1 only)						
BAF312 10 mg (N=50)	44	0.34	0.161	(0.062, 0.421)	83.9	<0.001
BAF312 2 mg (N=49)	45	0.41	0.197	(0.074, 0.527)	80.3	0.001
BAF312 0.5 mg (N=43)	43	0.87	0.416	(0.130, 1.331)	58.4	0.139
Placebo (N=45)	45	2.09				

* p-values correspond to pair wise comparisons of active treatment to placebo (i.e. to lesion ratios).
n = number of observations considered in the analysis (i.e. patients with at least one scan up to month 3 or month 6).
Month 3 and Month 6 results are based on two separate negative binomial GEE regression models accounting for repeated measures on each patient. Both models were adjusted for treatment group x month (the month number of each lesion count measurement) interaction, using the log link.
Lesion ratio (and corresponding 95% CI) is the ratio between the estimated number of lesions on active treatment compared to placebo. N.E. = Not estimable. Estimates are computed at Month 3 and Month 6 respectively.

Analysis of proportion of patients without any new MRI disease activity (CUAL) up to months 3 and 6 (sensitivity with weight) (Full Analysis Set)

Period Treatment	N'	n	%	p-value*
Month 3 (Period 1+2)				
BAF312 10 mg (N=50)	44	15	34.1	0.227
BAF312 2 mg (N=49)	45	18	40.0	0.020
BAF312 1.25 mg (N=42)	42	20	47.6	0.001
BAF312 0.5 mg (N=43)	43	13	30.2	0.122
BAF312 0.25 mg (N=51)	51	20	39.2	0.034
Placebo (N=61)	61	11	18.0	
Month 6 (Period 1 only)				
BAF312 10 mg (N=50)	44	12	27.3	0.335
BAF312 2 mg (N=49)	45	16	35.6	0.022
BAF312 0.5 mg (N=43)	43	11	25.6	0.124
Placebo (N=45)	45	6	13.3	

Observed proportions are presented, along with p-values from the logistic regression. As proportions estimated from the logistic regression are estimated for patients at the overall group level mean number of baseline Gd-enhanced T1 lesions (i.e. 2.0) and therefore are not appropriate to represent the observed data.

Patients free of new MRI activity are defined as patients free of CUAL over the time period specified (i.e. without evidence of any new Gd-enhanced T1 lesions and without evidence of new or enlarged T2 lesions).

n = Number of patients free of new MRI activity. N' = Number of patients with at least one post-baseline MRI scan.
* p-value for treatment comparison of BAF312 versus placebo, calculated using a weighted logistic regression model adjusted for treatment group and baseline number of Gd-enhanced T1 lesions. The weight used is equal to 1 if all post-baseline scans up to month 3 are available and (k-x)/k if x scans out of k scans are missing.

Analysis of number of monthly new Gd-enhanced T1 lesions at months 3 and 6 in patients with high baseline disease activity (Period 1+2; Full Analysis Set)

Period Treatment	n	Estimated number of lesions	Lesion ratio	95% CI of lesion ratio	Relative reduction (%) in lesions compared to placebo	p-value*
Month 3 (Period 1+2)						
BAF312 10 mg (N=50)	12	0.37	0.129	(0.030, 0.561)	87.1	0.006
BAF312 2 mg (N=49)	14	0.46	0.159	(0.044, 0.578)	84.1	0.005
BAF312 1.25 mg (N=42)	14	0.15	0.052	(0.007, 0.405)	94.8	0.005
BAF312 0.5 mg (N=43)	18	0.79	0.271	(0.091, 0.807)	72.9	0.019
BAF312 0.25 mg (N=51)	13	1.46	0.504	(0.190, 1.337)	49.6	0.169
Placebo (N=45)	23	2.90				
Month 6 (Period 1+2)						
BAF312 10 mg (N=50)	12	0.49	0.214	(0.091, 0.499)	78.6	<0.001
BAF312 2 mg (N=49)	14	0.55	0.240	(0.074, 0.779)	76.0	0.018
BAF312 0.5 mg (N=43)	18	0.53	0.231	(0.081, 0.653)	76.9	0.006
Placebo (N=45)	18	2.28				

* p-value corresponds to the lesion ratio and 95% CI of lesion ratio for active treatment in comparison to placebo.
- n = number of observations considered in the analysis (i.e. patients with at least one scan up to month 6).
- Pairwise comparison of treatments are based on a negative binomial GEE regression model accounting for repeated measures on each patient, adjusted for baseline number of Gd-enhanced T1 lesions and treatment group x month (the month number of each lesion count measurement) interaction, using the log link.
- Lesion ratio (and corresponding 95% CI) is the ratio between the estimated number of lesions on active treatment compared to placebo. N.E. = Not estimable. Estimates are computed at Month 3 and Month 6, respectively.
- High baseline disease activity is defined as >=2 Gd-enhanced T1 lesions at baseline.

Number of CUAL at Month 6 by treatment (Full Analysis Set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 1.25 mg N=42	BAF312 0.5 mg N=43	BAF312 0.25 mg N=51	Placebo N=45
Month 6						
Number of patients with MRI scan – n (%)	39 (78.0)	43 (87.8.)	N/A	35 (81.4)	N/A	43 (95.6)
Number of CUAL						
Mean	0.4	0.4		0.9		2.0
SD	1.04	1.26		3.42		2.71

Combined unique active lesions (CUAL) are defined as new Gd-enhanced T1 lesions or new or enlarging T2 lesions, without double counting of lesions at any specific point in time.

New lesions at a specific visit are assessed relative to the previous scheduled visit scan.

Month 1 through Month 3 include patients from both Period 1 and Period 2. Month 4 through Month 6 only include patients from Period 1.

Number of CUAL at Month 6 by treatment (Per Protocol Set)

	BAF312 10 mg N=37	BAF312 2 mg N=42	BAF312 1.25 mg N=40	BAF312 0.5 mg N=40	BAF312 0.25 mg N=48	Placebo N=42
Month 6						
Number of patients with MRI scan – n (%)	22 (59.5)	22 (52.4)	N/A	15 (37.5)	N/A	27 (64.3)
Number of CUAL						
Mean	0.4	0.5		1.8		1.9
SD	0.58	0.96		5.14		3.11

Combined unique active lesions (CUAL) are defined as new Gd-enhanced T1 lesions or new or enlarging T2 lesions, without double counting of lesions at any specific point in time.

New lesions at a specific visit are assessed relative to the previous scheduled visit scan.

Month 1 through Month 3 include patients from both Period 1 and Period 2. Month 4 through Month 6 only include patients from Period 1.

Summary statistics for EDSS, by visit and treatment (Period 1+2) (Full Analysis Set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 1.25 mg N=42	BAF312 0.5 mg N=43	BAF312 0.25 mg N=51	Placebo N=61
EDSS Total Score						
Baseline						
N	50	49	41	43	51	60
Mean	2.26	2.41	1.95	2.23	2.33	2.29
SD	0.981	1.236	1.011	1.250	1.112	1.147
Month 3						
N	40	44	40	40	49	58
Mean	2.38	2.32	1.96	2.13	2.21	2.17
SD	1.142	1.172	1.002	1.275	1.132	1.333
Month 6						
N	39	43	N/A	36	N/A	44
Mean	2.12	2.52		2.08		2.35
SD	1.035	1.332		1.233		1.341
EDSS change from baseline categories						
Month 3						

Number of patients with EDSS score	40	44	39	40	49	57
Patients with disability improvement	3 (7.5)	5 (11.4)	3 (7.7)	6 (15.0)	6 (12.2)	6 (10.5)
Patients with stable disability	33 (82.5)	39 (88.6)	32 (82.1)	33 (82.5)	38 (77.6)	46 (80.7)
Patients with disability progression	4 (10.0)	0	4 (10.3)	1 (2.5)	5 (10.2)	5. (8.8)
Month 6						
Number of patients with EDSS score	39	43	N/A	36	N/A	43
Patients with disability improvement	5 (12.8)	5 (11.6)		5 (13.9)		5 (11.6)
Patients with stable disability	32 (82.1)	32 (74.4)		30 (83.3)		33 (76.7)
Patients with disability progression	2 (5.1)	6 (14.0)		1 (2.8)		5 (11.6)

Baseline is the last assessment taken prior to 1st dose of study medication in the study.

Percentages are based on number of patients with an EDSS score at each month.

Disability improvement is defined as a 1 point decrease from baseline on EDSS score if baseline EDSS was between 0 and 5.0 or a 0.5 point decrease if baseline EDSS was 5.5 or higher.

Disability progression is defined as a 1 point increase from baseline on EDSS score if baseline EDSS was between 0 and 5.0, or a 0.5 point increase if baseline EDSS was 5.5 or higher.

Patients are counted in the stable disability category if their change from baseline in EDSS score did not fulfill disability improvement or disability progression criterion.

N/A=Not applicable.

Correlation of the course of the lymphocyte count with MRI activity

A scatter plot of CUAL per patient by absolute lymphocytes at Month 3 (Period 1+2) was prepared. A detailed analysis of the correlation of lymphocyte counts with MRI activity and clinical course will be reported separately using a model-based approach.

Geometric mean (% geometric mean coefficient of variation) BAF312 plasma trough concentrations by treatment and visit (PK analysis set)

Visit	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 1.25 mg N=42	BAF312 0.5 mg N=43	BAF312 0.25 mg N=51
Month 1	114 (52)	22.6 (54)	12.8 (46)	6.05 (52)	2.68 (40)
Month 3	113 (51)	21.7 (48)	11.4 (49)	5.28 (60)	2.43 (57)
Month 6	52.7 (530)	23.7 (58)	N/A	5.17 (66)	N/A

Safety Results

Adverse Events by System Organ Class

Incidence of AEs by primary system organ class and treatment (Period 1+2; Safety set)

	BAF312 10 mg N=50 n (%)	BAF312 2 mg N=49 n (%)	BAF312 1.25 mg N=42 n (%)	BAF312 0.5 mg N=43 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Any primary system organ class	**48 (96.0)**	**48 (98.0)**	**29 (69.0)**	**37 (86.0)**	**38 (74.5)**	**49 (80.3)**
Nervous system disorders	32 (64.0)	24 (49.0)	9 (21.4)	15 (34.9)	9 (17.6)	13 (21.3)
Infections and infestations	20 (40.0)	16 (32.7)	17 (40.5)	27 (62.8)	17 (33.3)	32 (52.5)
Cardiac disorders	17 (34.0)	11 (22.4)	0	5 (11.6)	2 (3.9)	7 (11.5)
General disorders and administration site conditions	15 (30.0)	7 (14.3)	7 (16.7)	10 (23.3)	5 (9.8)	12 (19.7)
Gastrointestinal disorders	14 (28.0)	8 (16.3)	7 (16.7)	11 (25.6)	6 (11.8)	10 (16.4)
Eye disorders	11 (22.0)	5 (10.2)	1 (2.4)	4 (9.3)	0	4 (6.6)
Respiratory, thoracic and mediastinal disorders	9 (18.0)	13 (26.5)	3 (7.1)	6 (14.0)	9 (17.6)	4 (6.6)
Investigations	9 (18.0)	7 (14.3)	3 (7.1)	5 (11.6)	6 (11.8)	4 (6.6)
Skin and subcutaneous tissue disorders	8 (16.0)	9 (18.4)	6 (14.3)	7 (16.3)	5 (9.8)	7 (11.5)
Blood and lymphatic system disorders	6 (12.0)	2 (4.1)	0	1 (2.3)	0	0
Musculoskeletal and connective tissue disorders	6 (12.0)	4 (8.2)	7 (16.7)	11 (25.6)	6 (11.8)	7 (11.5)
Metabolism and nutrition disorders	4 (8.0)	1 (2.0)	1 (2.4)	0	0	1 (1.6)
Vascular disorders	4 (8.0)	2 (4.1)	0	1 (2.3)	2 (3.9)	5 (8.2)
Ear and labyrinth disorders	3 (6.0)	6 (12.2)	5 (11.9)	1 (2.3)	1 (2.0)	4 (6.6)
Injury, poisoning and procedural complications	3 (6.0)	3 (6.1)	3 (7.1)	5 (11.6)	1 (2.0)	6 (9.8)
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	3 (6.0)	4 (8.2)	1 (2.4)	3 (7.0)	0	3 (4.9)
Psychiatric disorders	1 (2.0)	2 (4.1)	2 (4.8)	3 (7.0)	4 (7.8)	5 (8.2)
Endocrine disorders	0	1 (2.0)	0	0	0	0
Hepatobiliary disorders	0	0	0	2 (4.7)	0	1 (1.6)
Immune system disorders	0	0	0	0	0	1 (1.6)
Psychiatric disorder	0	0	0	0	1 (2.0)	0
Renal and urinary disorders	0	1 (2.0)	1 (2.4)	2 (4.7)	0	0
Reproductive system and breast disorders	0	0	0	1 (2.3)	3 (5.9)	0

Primary system organ classes are presented alphabetically. A patient with multiple occurrences of an AE for a system organ class under one treatment is counted only once in each specific category for that treatment.
Period 1 patients took BAF312 10 mg, 2 mg, and 0.5 mg doses for up to 6 months, whereas Period 2 patients took BAF312 1.25 mg and 0.25 mg for up to 3 months. Placebo is pooled over both periods.
Only AEs up to and including 10 days post-treatment end are included.
Psychiatric disorder(s) SOC is presented twice here due to a spelling error in the SOC for one event.

Number of patients with adverse events (>=3% for any treatment group) adverse events, by preferred term and treatment (Period 1+2; Safety set)

Preferred term	BAF312 10 mg N=50 n (%)	BAF312 2 mg N=49 n (%)	BAF312 1.25 mg N=42 n (%)	BAF312 0.5 mg N=43 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Any preferred term	**48 (96.0)**	**48 (98.0)**	**29 (69.0)**	**37 (86.0)**	**38 (74.5)**	**49 (80.3)**
Headache	23 (46.0)	15 (30.6)	5 (11.9)	8 (18.6)	5 (9.8)	5 (8.2)
Bradycardia	14 (28.0)	3 (6.1)	0	2 (4.7)	2 (3.9)	2 (3.3)
Dizziness	13 (26.0)	5 (10.2)	1 (2.4)	5 (11.6)	0	6 (9.8)
Nasopharyngitis	9 (18.0)	6 (12.2)	8 (19.0)	11 (25.6)	7 (13.7)	8 (13.1)
Fatigue	8 (16.0)	4 (8.2)	4 (9.5)	1 (2.3)	0	5 (8.2)
Nausea	8 (16.0)	2 (4.1)	3 (7.1)	2 (4.7)	3 (5.9)	2 (3.3)
Lymphopenia	5 (10.0)	2 (4.1)	0	0	0	0
Cough	4 (8.0)	5 (10.2)	1 (2.4)	4 (9.3)	3 (5.9)	1 (1.6)
Sinusitis	4 (8.0)	2 (4.1)	3 (7.1)	1 (2.3)	0	1 (1.6)
Lymphocyte count decreased	4 (8.0)	0	1 (2.4)	0	0	0
Alanine aminotransferase increased	3 (6.0)	4 (8.2)	1 (2.4)	0	1 (2.0)	0
Back pain	3 (6.0)	2 (4.1)	2 (4.8)	3 (7.0)	1 (2.0)	3 (4.9)
Migraine	3 (6.0)	2 (4.1)	0	0	3 (5.9)	1 (1.6)
Atrioventricular block first degree	3 (6.0)	0	0	1 (2.3)	0	0
Chills	3 (6.0)	0	0	0	0	0
Vertigo	2 (4.0)	6 (12.2)	3 (7.1)	1 (2.3)	1 (2.0)	3 (4.9)
Upper respiratory tract infection	2 (4.0)	4 (8.2)	1 (2.4)	3 (7.0)	0	7 (11.5)
Influenza	2 (4.0)	4 (8.2)	1 (2.4)	1 (2.3)	2 (3.9)	4 (6.6)
Atrioventricular block second degree	2 (4.0)	3 (6.1)	0	0	0	2 (3.3)
Urinary tract infection	2 (4.0)	2 (4.1)	3 (7.1)	2 (4.7)	1 (2.0)	2 (3.3)
Melanocytic naevus	2 (4.0)	2 (4.1)	1 (2.4)	1 (2.3)	0	3 (4.9)
Oropharyngeal pain	2 (4.0)	2 (4.1)	0	2 (4.7)	2 (3.9)	1 (1.6)
Eye pain	2 (4.0)	2 (4.1)	0	0	0	2 (3.3)
Oral herpes	2 (4.0)	1 (2.0)	2 (4.8)	1 (2.3)	1 (2.0)	3 (4.9)
γ-glutamyltransferase increased	2 (4 0)	1 (2.0)	0	0	2 (3.9)	0
Consti ation	2 (4.0)	1 (2.0)	0	0	0	0
Hypercholesterolaemia	2 (4.0)	0	1 (2.4)	0	0	1 (1.6)
Paraesthesia	2 (4.0)	0	0	2 (4.7	0	
Oe ema peripheral	2 (4.0)	0	0	1 (2.3)	1 (2.0)	1 (1.6)
Hypotens on	2 (4.0)	0	0	1 (2.)	1 (2.0)	0
Dry mouth	2 (4.0)	0	0	1 (2.3)	0	1 (1.6)
Muscular weakness	2 (4.0)	0	0	0	0	1 (1.6)
Temperature intolerance	2 (4.0)	0	0	0	0	0
Somnolence	1 (2.0)	4 (8.2)	1 (2.4)	0	1 (2.0)	1 (1.6)
Diarrhoea	1 (2.0)	2 (4.1)	0	1 (2.3)	1 (2.0)	3 (4.9)
Palpitations	1 (2.0)	2 (4.1)	0	0	0	1 (1.6)
Sinus bradycardia	1 (2.0)	2 (4.1)	0	0	0	1 (1.6)
Dyspnoea	1 (2.0)	1 (2.0)	1 (2.4)	1 (2.3)	3 (5.9)	1 (1.6)
Pharyngitis	1 (2.0)	1 (2.0)	1 (2.4)	0	2 (3.9)	3 (4.9)

Ecchymosis	1 (2.0)	1 (2.0)	0	2 (4.7)	0	1 (1.6)
Cystitis	1 (2.0)	1 (2.0)	0	0	1 (2.0)	2 (3.3)
Pyrexia	1 (2.0)	0	1 (2.4)	7 (16.3)	1 (2.0)	4 (6.6)
Vomiting	1 (2.0)	0	1 (2.4)	3 (7.0)	0	2 (3.3)
Pain in extremity	1 (2.0)	0	1 (2.4)	2 (4.7)	2 (3.9)	0
Dry eye	1 (2.0)	0	1 (2.4)	2 (4.7)	0	0
Hypoaesthesia	1 (2.0)	0	1 (2.4)	0	0	2 (3.3)
Asthenia	1 (2.0)	0	0	2 (4.7)	0	3 (4.9)
Toothache	0	2 (4.1)	0	1 (2.3)	0	3 (4.9)
Aphthous stomatitis	0	2 (4.1)	0	0	0	0
Pruritus	0	1 (2.0)	3 (7.1)	1 (2.3)	0	1 (1.6)
Abdominal pain	0	1 (2.0)	2 (4.8)	0	0	1 (1.6)
C-reactive protein increased	0	1 (2.0)	0	2 (4.7)	1 (2.0)	0
Myalgia	0	1 (2.0)	0	2 (4.7)	1 (2.0)	0
Visual impairment	0	1 (2.0)	0	2 (4.7)	0	2 (3.3)
Erythema	0	1 (2.0)	0	2 (4.7)	0	0
Bronchitis	0	0	1 (2.4)	3 (7.0)	0	0
Arthralgia	0	0	1 (2.4)	2 (4.7)	0	2 (3.3)
Acne	0	0	1 (2.4)	1 (2.3)	1 (2.0)	2 (3.3)
Depression	0	0	1 (2.4)	0	2 (3.9)	2 (3.3)
Dyspepsia	0	0	0	2 (4.7)	1 (2.0)	0
Hyperthermia	0	0	0	2 (4.7)	1 (2.0)	0
Respiratory tract infection viral	0	0	0	2 (4.7)	1 (2.0)	0
Abdominal pain lower	0	0	0	2 (4.7)	0	0
Anxiety	0	0	0	1 (2.3)	1 (2.0)	2 (3.3)
Abdominal pain upper	0	0	0	1 (2.3)	0	2 (3.3)
Dry skin	0	0	0	0	2 (3.9)	0
Epicondylitis	0	0	0	0	0	2 (3.3)
Hot flush	0	0	0	0	0	2 (3.3)
Hypoaesthesia oral	0	0	0	0	0	2 (3.3)

Events are listed in descending frequency by dose.
A patient with multiple occurrences of an AE for total or a preferred term under one treatment is counted only once in each specific category for that treatment.
Period 1 patients took BAF312 10 mg, 2 mg, and 0.5 mg doses for up to 6 months, whereas Period 2 patients took BAF312 1.25 mg and 0.25 mg for up to 3 months. Placebo is pooled over both periods.
Only AEs up to and including 10 days post-treatment end are included.

Most Frequently Reported AEs Overall by Preferred Term n (%)

Adverse events with at least 5% higher incidence on any BAF312 group compared to placebo (Period 1+2), by preferred term and treatment (Safety set)

	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 1.25 mg N=42	BAF312 0.5 mg N=43	BAF312 0.25 mg N=51	Placebo N=61
Headache	23 (46.0)	15 (30.6)	5 (11.9)	8 (18.6)	5 (9.8)	5 (8.2)
Bradycardia	14 (28.0)	3 (6.1)	0	2 (4.7)	2 (3.9)	2 (3.3)
Dizziness	13 (26.0)	5 (10.2)	1 (2.4)	5 (11.6)	0	6 (9.8)
Nasopharyngitis	9 (18.0)	6 (12.2)	8 (19.9)	11 (25.6)	7 (13.7)	8 (13.1)
Nausea	8 (16.0)	2 (4.1)	3 (7.1)	2 (4.7)	3 (5.9)	2 (3.3)
Fatigue	8 (16.0)	4 (8.2)	4 (9.5)	1 (2.3)	0	5 (8.2)
Lymphopenia	5 (10.0)	2 (4.1)	0	0	0	0
Lymphocyte count de-creased	4 (8.0)	0	1 (2.4)	0	0	0
Sinusitis	4 (8.0)	2 (4.1)	3 (7.1)	1 (2.3)	0	1 (1.6)
Cough	4 (8.0)	5 (10.2)	1 (2.4)	4 (9.3)	3 (5.9)	1 (1.6)
AV block first degree	3 (6.0)	0	0	1 (2.3)	0	0
Chills	3 (6.0)	0	0	0	0	0
ALT increased	3 (6.0)	4 (8.2)	1 (2.4)	0	1 (2.0)	0
Vertigo	2 (4.0)	6 (12.2)	3 (7.1)	1 (2.3)	1 (2.0)	3 (4.9)
Pyrexia	1 (2.0)	0	1 (2.4)	7 (16.3)	1 (2.0)	4 (6.6)
Somnolence	1 (2.0)	4 (8.2)	1 (2.4)	0	1 (2.0)	1 (1.6))
Bronchitis	0	0	1 (2.4)	3 (7.0)	0	0
Pruritus	0	1 (2.0)	3 (7.1)	1 (2.3)	0	1 (1.6)

Preferred terms were sorted by highest frequency in the BAF312 10mg group.
A patient with multiple occurrences of an AE for a preferred term or system organ class under one treatment is counted only once in each specific category for that treatment.
Period 1 patients were followed up for 6 months and Period 2 patients were followed up for 3 months; however, only AEs up to and including 10 days post-treatment end are included.

Serious Adverse Events and Deaths

Number (%) of patients who died, had other serious or clinically significant AEs or discontinuation of study drug due to AE (Period 1+2; Safety population)

	BAF312 10 mg N=50 n (%)	BAF312 2 mg N=49 n (%)	BAF312 1.25 mg N=42 n (%)	BAF312 0.5 mg N=43 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Number of patients with serious or other signifi-cant events	12 (24.0)	6 (12.2)	2 (4.8)	8 (18.6)	1 (2.0)	2 (3.3)
Death	0	0	1 (2.4)	0	0	0
Serious adverse events	3 (6.0)	4 (8.2) *	2 (4.8)	8 (18.6)	0	0
AE(s) leading to study drug discontinuation	10 (20.0)	6 (12.2)	1 (2.4)	5 (11.6)	1 (2.0)	2 (3.3)

Period 1 patients took BAF312 10 mg, 2 mg, and 0.5 mg doses for up to 6 months, whereas Period 2 patients took BAF312 1.25 mg and 0.25 mg for up to 3 months. Placebo is pooled over both periods.
All reported deaths and SAEs are included, discontinuations due to adverse events up to and including 10 days post-treatment end are included.

* One additional patient was recorded with precancerous cells about five months after receiving the last dose of study medication. This event was not captured in the database.

One patient died 27 days after having discontinued treatment with BAF312 1.25mg.

Serious adverse events, by primary system organ class, preferred term and treatment (Period 1+2; Safety set)

	BAF312 10 mg N=50 n (%)	BAF312 2 mg N=49 n (%)	BAF312 1.25 mg N=42 n (%)	BAF312 0.5 mg N=43 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Any primary system organ class	3 (6.0)	4 (8.2) *	2 (4.8)	8 (18.6)	0	0
Cardiac disorders	2 (4.0)	3 (6.1)	0	1 (2.3)	0	0
Atrioventricular block second degree	1 (2.0)	3 (6.1)	0	0	0	0
Myocardial infarction	1 (2.0)	0	0	0	0	0
Bradycardia	0	0	0	1 (2.3)	0	0
General disorders & admin. site conditions	0	0	1 (2.4)	0	0	0
Death	0	0	1 (2.4)	0	0	0
Infections and infestations	0	0	1 (2.4)	1 (2.3)	0	0
Perineal abscess	0	0	1 (2.4)	0	0	0
Pyelonephritis acute	0	0	0	1 (2.3)	0	0
Injury, poisoning and procedural complications	0	1 (2.0)	0	0	0	0
Intentional overdose	0	1 (2.0)	0	0	0	0
Musculoskeletal & connective tissue disorders	0	0	0	1 (2.3)	0	0
Myopathy	0	0	0	1 (2.3)	0	0
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	0	0	0	2 (4.7)	0	0
Basal cell carcinoma	0	0	0	1 (2.3)	0	0
Uterine leiomyoma	0	0	0	1 (2.3)	0	0
Nervous system disorders	1 (2.0)	0	0	3 (7.0)	0	0
Benign intracranial hypertension	1 (2.0)	0	0	0	0	0
Headache	0	0	0	1 (2.3)	0	0
Multiple sclerosis relapse	0	0	0	1 (2.3)	0	0
Optic neuritis	0	0	0	1 (2.3)	0	0
Psychiatric disorders	0	0	0	1 (2.3)	0	0
Schizophreniform disorder	0	0	0	1 (2.3)	0	0

Primary system organ classes are presented alphabetically; preferred terms are sorted within primary system organ class in descending frequency by dose.

Period 1 patients took BAF312 10 mg, 2 mg, and 0.5 mg doses for up to 6 months, whereas Period 2 patients took BAF312 1.25 mg and 0.25 mg for up to 3 months. Placebo is pooled over both periods.
* One additional patient (A2201-0102-00002) was recorded with precancerous cells about five months after receiving the last dose of study medication. This event was not captured in the database.

Clinical laboratory evaluation

Incidence of notable on-treatment hematology abnormalities, by treatment (Period 1+2; Safety set) Patients with newly occurring or worsening hematological abnormalities (Safety set)

	BAF312 10 mg N=50 n (%)	BAF312 2 mg N=49 n (%)	BAF312 1.25 mg N=42 n (%)	BAF312 0.5 mg N=43 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Absolute Lymphocytes						
N'	47	47	42	43	50	61
Low: < 0.2 x 10E9/L	17 (36.2)	8 (17.0)	1 (2.4)	0	0	0
High: >= 8 x 10E9/L	0	0	0	0	0	0
Absolute Neutrophils (Seg. + Bands)						
N'	47	47	42	43	50	61
Low: <= 1 x 10E9/L	0	0	1 (2.4)	0	0	0
High: >= 12 x 10E9/L	0	0	0	1 (2.3)	1 (2.0)	2 (3.3)
Haemoglobin						
N'	47	47	42	43	50	61
Low: <= 100 g/L	1 (2.1)	0	0	0	1 (2.0)	0
Platelet count (direct)						
N'	47	46	42	43	50	61
Low: <= 100 x 10E9/L	0	0	0	0	0	0
High: >= 600 x 10E9/L	0	0	0	0	0	0
RBC						
N'	47	47	42	43	50	61
Low: < 3.30 x 10E12/L	0	0	0	0	0	0
High: > 6.80 x 10E12/L	0	0	1 (2.4)	0	0	0
WBC (total)						
N'	47	47	42	43	50	61
Low: <= 2.0 x 10E9/L	0	1 (2.1)	0	1 (2.3)	1 (2.0)	0
High: >= 15 x 10E9/L	0	0	0	0	1 (2.0)	2 (3.3)

A patient can be counted in both low and high categories.
The highest post-baseline value is used for high ranges. The lowest post-baseline value is used for low range.
Percentages are out of N' (the total number of patients with available post-baseline assessments for each treatment).
On treatment includes measurements up to and including 10 days post-treatment end.
Period 1 doses were observed for 6 months and Period 2 for 3 months only.

Incidence of notable on-treatment biochemistry abnormalities, by treatment (Period 1+2; Safety set)

	BAF312 10 mg N=50 n (%)	BAF312 2 mg N=49 n (%)	BAF312 1.25 mg N=42 n (%)	BAF312 0.5 mg N=43 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=61 n (%)
Bilirubin (total)						
N'	47	47	42	43	50	61
High: >= 34.2 umol/L	0	1 (2.1)	0	0	0	1 (1.6)
C-reactive protein						

N'	47	47	42	43	50	61
High: > 6 mg/L	11 (23.4)	9 (19.1)	10 (23.8)	10 (23.3)	11 (22.0)	10 (16.4)
Cholesterol (total)						
N'	47	47	42	43	50	61
High: >= 6.21 mmol/L	11 (23.4)	12 (25.5)	7 (16.7)	7 (16.3)	9 (18.0)	16 (26.2)
Gamma Glutamyltransferase						
N'	47	47	42	43	50	61
High: > 130 U/L	5 (10.6)	7 (14.9)	1 (2.4)	2 (4.7)	3 (6.0)	0
Glucose (fasting)						
N'	28	31	30	30	33	42
High: >= 7.8 mmol/L	1 (3.6)	0	0	0	1 (3.0)	0
SGOT (AST)						
N'	47	47	42	43	50	61
High: > 82 U/L	0	1 (2.1)	0	0	0	0
SGPT (ALT)						
N'	47	47	42	43	50	61
High: > 90 U/L	8 (17.0)	9 (19.1)	2 (4.8)	0	3 (6.0)	0
Triglycerides						
N'	47	47	42	43	50	61
High: >= 3.39 mmol/L	4 (8.5)	4 (8.5)	3 (7.1)	1 (2.3)	3 (6.0)	3 (4.9)

A patient can be counted in both low and high categories.
The highest post-baseline value is used for high ranges. The lowest post-baseline value is used for low range.
Percentages are out of N' (the total number of patients with available post-baseline assessments for each treatment).
This table includes liver function tests.
On treatment includes measurements up to and including 10 days post-treatment end.
Period 1 doses were observed for 6 months and Period 2 for 3 months only.

Incidence rate of notable abnormalities in vital signs over 3 and 6 months, by treatment (Safety Set)

Vital Sign	Notable Criteria	BAF312 10 mg N=50	BAF312 2 mg N=49	BAF312 1.25 mg N=42	BAF312 0.5 mg N=43	BAF312 0.25 mg N=51	Placebo N=61
Systolic BP (mmHg)							
Month 3	N'	49	47	42	43	51	61
(Periods 1+2)	Low: <=90	0	1 (2.1)	1 (2.4)	1 (2.3)	0	0
	>=20 decrease from baseline	6 (12.2)	5 (10.6)	3 (7.1)	4 (9.3)	5 (9.8)	5 (8.2)
	High: >=160	3 (6.1)	1 (2.1)	0	0	2 (3.9)	1 (1.6)
	>=20 increase from baseline	3 (6.1)	4 (8.5)	3 (7.1)	1 (2.3)	7 (13.7)	5 (8.2)
Month 6 (Period 1)	N'	49	47	N/A	43	N/A	45
	Low: <=90	0	1 (2.1)		1 (2.3)		1 (2.2)
	>=20 decrease from baseline	7 (14.3)	5 (10.6)		5 (11.6)		5 (11.1)
	High: >=160	3 (6.1)	1 (2.1)		1 (2.3)		0
	>=20 increase from baseline	3 (6.1)	8 (17.0)		3 (7.0)		6 (13.3)
Diastolic BP (mmHg)							
Month 3	N'	49	47	42	43	51	61

(Periods 1+2)	Low:	<=50	0	1 (2.1)	1 (2.4)	0	0	0
		>=15 decrease from baseline	4 (8.2)	5 (10.6)	3 (7.1)	7 (16.3)	8 (15.7)	6 (9.8)
	High:	>=100	2 (4.1)	1 (2.1)	1 (2.4)	1 (2.3)	3 (5.9)	1 (1.6)
		>=15 increase from baseline	3 (6.1)	1 (2.1)	3 (7.1)	4 (9.3)	3 (5.9)	11 (18.0)
Month 6 (Period 1)	N'		49	47	N/A	43	N/A	45
	Low:	<=50	0	1 (2.1)		0		0
		>=15 decrease from baseline	5 (10.2)	5 (10.6)		9 (20.9)		6 (13.3)
	High:	>=100	3 (6.1)	1 (2.1)		2 (4.7)		1 (2.2)
		>=15 increase from baseline	3 (6.1)	1 (2.1)		4 (9.3)		10 (22.2)
Pulse (bpm)								
Month 3	N'		49	47	42	43	51	61
(Periods 1+2)	Low:	<50	0	0	0	0	1 (2.0)	0
		>=15 decrease from baseline	2 (4.1)	7 (14.9)	7 (16.7)	8 (18.6)	7 (13.7)	7 (11.5)
	High:	>120	0	0	0	0	0	0
		>=15 increase from baseline	8 (16.3)	7 (14.9)	5 (11.9)	8 (18.6)	9 (17.6)	15 (24.6)
Month 6 (Period 1)	N'		49	47	N/A	43	N/A	45
	Low:	<50	0	0		0		0
		>=15 decrease from baseline	2 (4.1)	7 (14.9)		9 (20.9)		10 (22.2)
	High:	>120	0	0		0		0
		>=15 increase from baseline	11 (22.4)	12 (25.5)		11 (25.6)		17 (37.8)

A patient can be counted once in each criterion. The hourly dose monitoring vital signs for study drug starts / re-starts are not included. Percentages are out of N' (the total number of patients with available post-baseline assessments for each treatment). Period 1+2 assesses data up to Month 3, whereas Period 1 assesses data up to Month 6 for Period 1 only. On treatment includes measurements up to and including 10 days post-treatment end. Baseline is defined as the mean of the measurements at the last available visit before treatment start, with the pre-dose measurement being considered.

Other Relevant Findings

Holter findings, by visit and treatment (Safety Set) Period 2

Visit Finding	BAF312 1.25 mg N=42 n (%)	BAF312 0.25 mg N=51 n (%)	Placebo N=16 n (%)
Day 1			
N'	40	51	15
Normal sinus rhythm	40 (100.0)	51 (100.0)	15 (100.0)
Sinus tachycardia	39 (97.5)	49 (96.1)	15 (100.0)
Sinus bradycardia	38 (95.0)	47 (92.2)	13 (86.7)
APC	38 (95.0)	43 (84.3)	9 (60.0)

Other Arrhythmia	35 (87.5)	41 (80.4)	12 (80.0)
VPC	23 (57.5)	31 (60.8)	5 (33.3)
Other Conduction	4 (10.0)	3 (5.9)	0
Ventricular tachycardia	2 (5.0)	0	1 (6.7)
Supraventricular Tachycardia	1 (2.5)	6 (11.8)	1 (6.7)
First degree AV block	0	2 (3.9)	2 (13.3)
Ectopic atrial rhythm	0	1 (2.0)	0
Nonconducted PAC	0	1 (2.0)	0
AVB Mobitz I	0	0	2 (13.3)
Day 2 (6 hour) *			
N'	23	27	11
Normal sinus rhythm	23 (100.0)	27 (100.0)	11 (100.0)
Sinus tachycardia	21 (91.3)	20 (74.1)	10 (90.9)
Sinus bradycardia	18 (78.3)	18 (66.7)	8 (72.7)
APC	15 (65.2)	16 (59.3)	8 (72.7)
Other Arrhythmia	13 (56.5)	13 (48.1)	9 (81.8)
VPC	9 (39.1)	5 (18.5)	4 (36.4)
Other Conduction	1 (4.3)	1 (3.7)	0
First degree AV block	0	1 (3.7)	0
Supraventricular Tachycardia	0	1 (3.7)	0
Premature junctional contraction (PJC)	0	1 (3.7)	0
Ectopic atrial rhythm	0	0	1 (9.1)
Day 2 (24 hour) **			
N'	15	21	5
Normal sinus rhythm	15 (100.0)	21 (100.0)	5 (100.0)
Sinus tachycardia	15 (100.0)	20 (95.2)	5 (100.0)
Sinus bradycardia	15 (100.0)	19 (90.5)	3 (60.0)
APC	13 (86.7)	17 (81.0)	3 (60.0)
Other Arrhythmia	12 (80.0)	14 (66.7)	4 (80.0)
VPC	11 (73.3)	9 (42.9)	1 (20.0)
Other Conduction	1 (6.7)	0	0
Supraventricular Tachycardia	0	1 (4.8)	0
Day 7 (6 hour) *			
N'	24	27	11
Normal sinus rhythm	24 (100.0)	26 (96.3)	11 (100.0)
Sinus bradycardia	20 (83.3)	19 (70.4)	7 (63.6)
APC	17 (70.8)	14 (51.9)	7 (63.6)
Sinus tachycardia	11 (45.8)	20 (74.1)	10 (90.9)
VPC	7 (29.2)	12 (44.4)	3 (27.3)
Other Arrhythmia	4 (16.7)	9 (33.3)	9 (81.8)
Other Conduction	2 (8.3)	0	0
Supraventricular Tachycardia	1 (4.2)	1 (3.7)	0
Nonconducted PAC	0	1 (3.7)	0
First degree AV block	0	0	1 (9.1)
Day 7 (24 hour) **			
N'	17	21	4
Normal sinus rhythm	17 (100.0)	21 (100.0)	4 (100.0)

Sinus bradycardia	17 (100.0)	18 (85.7)	3 (75.0)
APC	17 (100.0)	17 (81.0)	3 (75.0)
Sinus tachycardia	15 (88.2)	19 (90.5)	4 (100.0)
Other Arrhythmia	10 (58.8)	10 (47.6)	3 (75.0)
VPC	5 (29.4)	10 (47.6)	1 (25.0)
Other Conduction	3 (17.6)	1 (4.8)	0
Supraventricular Tachycardia	2 (11.8)	1 (4.8)	0
First degree AV block	0	0	1 (25.0)
AVB Mobitz I	0	0	1 (25.0)

APC=Atrial Premature Complex, VPC=Ventricular Premature Complex, AVB=Atrioventricular Block, PAC=Premature Atrial Complex
Percentages are out of N' (the total number of patients with available assessment).
* Measurements recorded on Day 2 and Day 7 at sites where Mobile Cardiac Telemetry is possible.
** Measurements recorded at sites where Mobile Cardiac Telemetry is not feasible.

Date of Clinical Trial Report

03-May-2012

Date Inclusion on Novartis Clinical Trial Results Database

04-May-2012

Date of Latest Update