



Clinical trial results:

A multi-centre, double-blind, placebo controlled, proof of concept study to evaluate the efficacy and tolerability of BAF312 in patients with polymyositis

Summary

EudraCT number	2012-002859-42
Trial protocol	HU CZ PL BE
Global end of trial date	04 August 2016

Results information

Result version number	v1 (current)
This version publication date	16 August 2017
First version publication date	06 February 2019

Trial information

Trial identification

Sponsor protocol code	CBAF312X2205
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01801917
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
Sponsor organisation name	Novartis Pharma AG
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Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

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	04 August 2016
Is this the analysis of the primary completion data?	Yes
Primary completion date	04 August 2016
Global end of trial reached?	Yes
Global end of trial date	04 August 2016
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Main objective of the trial was to assess the clinical effect of 2 mg and 10 mg BAF312 once daily in patients with polymyositis (PM) over 12 weeks using both manual muscle testing (MMT)-24 and serum creatine kinase (CK) as a combined endpoint

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	23 April 2013
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	Czech Republic: 1
Country: Number of subjects enrolled	Hungary: 6
Country: Number of subjects enrolled	Poland: 1
Country: Number of subjects enrolled	Taiwan: 2
Country: Number of subjects enrolled	United States: 4
Worldwide total number of subjects	14
EEA total number of subjects	8

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)	13
From 65 to 84 years	1
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

The study initially had 2 treatment arms and 9 patients had been randomized to BAF312 2 mg and placebo in a 2:1 ratio until protocol amendment which added BAF312 10 mg treatment arm. The overall targeted randomization ratio after amendment was 1:1:1 among BAF312 10 mg: 2 mg: placebo but study was terminated after 14 patients were randomized

Period 1

Period 1 title	Period 1 - Randomized
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer

Arms

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

Arm description:

Patients in Period 1 continue on same 2 mg dose of BAF312 in Period 2

Arm type	Experimental
Investigational medicinal product name	BAF312 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg once daily + 4 placebo for BAF312 and 5 - 2 mg tablets for BAF312 for 10 mg arm

Arm title	BAF312 10 mg/BAF312 10 mg
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Arm description:

Patients in Period 1 continue on same 10 mg dose of BAF312 in Period 2

Arm type	Experimental
Investigational medicinal product name	BAF312 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg once daily + 4 placebo for BAF312 and 5 - 2 mg tablets for BAF312 for 10 mg arm

Arm title	Placebo/BAF312 2 mg
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Arm description:

Patients on placebo in Period 1 switch to active 2 mg BAF312 in Period 2

Arm type	Experimental
Investigational medicinal product name	BAF312 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg once daily + 4 placebo for BAF312 2 mg

Arm title	Placebo/BAF312 10 mg
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Arm description:

Patients on placebo in Period 1 switch to active 10 mg BAF312 in Period 2

Arm type	Experimental
Investigational medicinal product name	matching placebo for BAF312 2 mg arm
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

10 mg once daily

Investigational medicinal product name	BAF312 2 mg
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

2 mg once daily + 4 placebo for BAF312 and 5 - 2 mg tablets for BAF312 for 10 mg arm

Number of subjects in period 1	BAF312 2mg/BAF312 2mg	BAF312 10 mg/BAF312 10 mg	Placebo/BAF312 2 mg
Started	7	2	4
Completed	6	2	3
Not completed	1	0	1
Adverse event, non-fatal	1	-	1

Number of subjects in period 1	Placebo/BAF312 10 mg
Started	1
Completed	1
Not completed	0
Adverse event, non-fatal	-

Period 2

Period 2 title	Extension - All Active
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms

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

Patients in Period 1 continue on same 2 mg dose of BAF312 in Period 2

Arm type	Experimental
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Investigational medicinal product name	BAF312 2mg
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

2 mg tablet daily

Arm title	Placebo/BAF312 2 mg
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Arm description:

Patients on placebo in Period 1 switch to active 2 mg BAF312 in Period 2

Arm type	Experimental
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Investigational medicinal product name	BAF312 2 mg
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Investigational medicinal product code	
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Other name	
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Pharmaceutical forms	Tablet
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Routes of administration	Oral use
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Dosage and administration details:

2 mg once daily + 4 placebo for BAF312

Number of subjects in period 2 ^[1]	BAF312 2mg/BAF312 2mg	Placebo/BAF312 2 mg
Started	6	3
Completed	6	3

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.

Justification: Patient and investigator determined if patient would enter extension period. Patients with disease worsening had to be approved by Central Unblinded Investigator.

Baseline characteristics

Reporting groups

Reporting group title	BAF312 2mg/BAF312 2mg
Reporting group description:	
Patients in Period 1 continue on same 2 mg dose of BAF312 in Period 2	
Reporting group title	BAF312 10 mg/BAF312 10 mg
Reporting group description:	
Patients in Period 1 continue on same 10 mg dose of BAF312 in Period 2	
Reporting group title	Placebo/BAF312 2 mg
Reporting group description:	
Patients on placebo in Period 1 switch to active 2 mg BAF312 in Period 2	
Reporting group title	Placebo/BAF312 10 mg
Reporting group description:	
Patients on placebo in Period 1 switch to active 10 mg BAF312 in Period 2	

Reporting group values	BAF312 2mg/BAF312 2mg	BAF312 10 mg/BAF312 10 mg	Placebo/BAF312 2 mg
Number of subjects	7	2	4
Age categorical			
Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	6	2	4
From 65-84 years	1	0	0
85 years and over	0	0	0
Age Continuous			
Units: years			
arithmetic mean	50.3	47	48
standard deviation	± 14.78	± 21.21	± 8.83
Gender, Male/Female			
Units: Subjects			
Female	5	2	2
Male	2	0	2
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	7	1	3
Black	0	0	0
Asian	0	1	1
Taking DMARD at baseline			
Taking a disease-modifying antirheumatic drugs			
Units: Subjects			
DMRD at baseline	7	2	4

Study Specific Characteristic Disease duration			
Units: years			
arithmetic mean	5.6	5.4	2.7
standard deviation	± 4.46	± 2.74	± 1.67
Study Specific Characteristic Baseline MMT24 Score			
Manual muscle testing in 26 muscle groups (MMT24, max value 260)			
Units: score			
arithmetic mean	202.6	184	189.5
standard deviation	± 41.74	± 19.8	± 45.65

Reporting group values	Placebo/BAF312 10 mg	Total	
Number of subjects	1	14	
Age categorical			
Units: Subjects			
In utero	0	0	
Preterm newborn infants (gestational age < 37 wks)	0	0	
Newborns (0-27 days)	0	0	
Infants and toddlers (28 days-23 months)	0	0	
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	1	13	
From 65-84 years	0	1	
85 years and over	0	0	
Age Continuous			
Units: years			
arithmetic mean	53	-	
standard deviation	± 0		
Gender, Male/Female			
Units: Subjects			
Female	1	10	
Male	0	4	
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	0	11	
Black	1	1	
Asian	0	2	
Taking DMARD at baseline			
Taking a disease-modifying antirheumatic drugs			
Units: Subjects			
DMRD at baseline	1	14	
Study Specific Characteristic Disease duration			
Units: years			
arithmetic mean	16.9	-	
standard deviation	± 0		
Study Specific Characteristic Baseline MMT24 Score			
Manual muscle testing in 26 muscle groups (MMT24, max value 260)			
Units: score			

arithmetic mean	166		
standard deviation	± 0	-	

End points

End points reporting groups

Reporting group title	BAF312 2mg/BAF312 2mg
Reporting group description:	
Patients in Period 1 continue on same 2 mg dose of BAF312 in Period 2	
Reporting group title	BAF312 10 mg/BAF312 10 mg
Reporting group description:	
Patients in Period 1 continue on same 10 mg dose of BAF312 in Period 2	
Reporting group title	Placebo/BAF312 2 mg
Reporting group description:	
Patients on placebo in Period 1 switch to active 2 mg BAF312 in Period 2	
Reporting group title	Placebo/BAF312 10 mg
Reporting group description:	
Patients on placebo in Period 1 switch to active 10 mg BAF312 in Period 2	
Reporting group title	BAF312 2mg/BAF312 2mg
Reporting group description:	
Patients in Period 1 continue on same 2 mg dose of BAF312 in Period 2	
Reporting group title	Placebo/BAF312 2 mg
Reporting group description:	
Patients on placebo in Period 1 switch to active 2 mg BAF312 in Period 2	
Subject analysis set title	BAF312 2mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
1 tablet of BAF312 2 mg + 4 tablets of Placebo daily during Period 1	
Subject analysis set title	BAF312 10 mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
5 tablets of BAF312 2 mg daily during Period 1	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
matching placebo	
Subject analysis set title	Placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
matching placebo	
Subject analysis set title	BAF312 2mg
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
1 tablet of BAF312 2 mg + 4 tablets of Placebo daily during Period 1	

Primary: Change from baseline at week 12 for BAF312 2 mg, 10 mg or placebo (once daily) for combined efficacy endpoint: Manual Muscle Testing (MMT24)

End point title	Change from baseline at week 12 for BAF312 2 mg, 10 mg or placebo (once daily) for combined efficacy endpoint: Manual Muscle Testing (MMT24)
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End point description:

Manual Muscle Testing Scoring Sheet: Neck flexors, neck extensors and other designated muscles bilaterally (Biceps brachii, Deltoid middle, Quadriceps, Gluteus maximus, Gluteus medius, Trapezius, Iliopsoas, Hamstrings, Wrist extensors, Wrist Flexors, Ankle plantar flexors and Ankle dorsiflexors) were tested on a 0-10 scale by the Investigator. Note that due to system limitations in choices for intervals,

Posterior credibility interval from Bayesian analysis is displayed as confidence interval in table. Also, all 4 statistical analysis results for posterior probability are entered in the P value data field (could not be entered into Parameter estimate because Confidence Interval was required and is not calculated with posterior probability).

End point type	Primary
End point timeframe:	
Baseline, at 12 weeks	

End point values	BAF312 2mg	BAF312 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	2	5	
Units: scores				
arithmetic mean (confidence interval 90%)	11.2 (3.5 to 19.2)	39 (10.7 to 67.2)	9.1 (-1.6 to 20)	

Statistical analyses

Statistical analysis title	Increase in MMT24 and decrease in CK - 2mg group
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Statistical analysis description:

It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: $\geq 90\%$ posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: $\geq 50\%$ PP achieving an increase of 15 points in MMT24 and a decrease of 30% in CK vs. placebo. For this table the value is the posterior probability of achieving an increase in MMT24 and a decrease in CK in 2mg group vs. placebo

Comparison groups	BAF312 2mg v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.586 ^[1]
Method	Bayesian

Notes:

[1] - Value displayed is posterior probability from Bayesian analysis, it is NOT a P value. Eudract system required a confidence interval (not calculated for posterior probability) for Parameter estimate module and error prevented upload to the system.

Statistical analysis title	INCR of 15 pts in MMT24 and DCR of 30% in CK-2mg
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Statistical analysis description:

It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: $\geq 90\%$ posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: $\geq 50\%$ PP achieving an increase of 15 points in MMT24 and a decrease of 30% in CK vs. placebo. For this table the value is the PP of achieving an increase of 15 points in MMT24 and a decrease of 30% in CK in 2mg group vs. placebo

Comparison groups	BAF312 2mg v Placebo
Number of subjects included in analysis	12
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.022 ^[2]
Method	Bayesian

Notes:

[2] - Value displayed is posterior probability from Bayesian analysis, it is NOT a P value. Eudract system required a confidence interval (not calculated for posterior probability) for Parameter estimate module and error prevented upload to the system.

Statistical analysis title	Increase in MMT24 and decrease in CK - 10mg group
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Statistical analysis description:

It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: $\geq 90\%$ posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: $\geq 50\%$ PP achieving an increase of 15 points in MMT24 and a decrease of 30% in CK vs. placebo. For this table the value is the posterior probability of achieving an increase in MMT24 and a decrease in CK in 10mg group vs. placebo

Comparison groups	BAF312 10 mg v Placebo
Number of subjects included in analysis	7
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.963 ^[3]
Method	Bayesian

Notes:

[3] - Value displayed is posterior probability from Bayesian analysis, it is NOT a P value. Eudract system required a confidence interval (not calculated for posterior probability) for Parameter estimate module and error prevented upload to the system.

Statistical analysis title	INCR of 15 pts in MMT24 and DCR of 30% in CK-10mg
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Statistical analysis description:

It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: $\geq 90\%$ posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: $\geq 50\%$ PP achieving an increase of 15 points in MMT24 and a decrease of 30% in CK vs. placebo. . For this table the value is the PP of achieving an increase of 15 points in MMT24 and a decrease of 30% in CK in 10mg group vs. placebo

Comparison groups	BAF312 10 mg v Placebo
Number of subjects included in analysis	7
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.837 ^[4]
Method	Bayesian

Notes:

[4] - Value displayed is posterior probability from Bayesian analysis, it is NOT a P value. Eudract system required a confidence interval (not calculated for posterior probability) for Parameter estimate module and error prevented upload to the system.

Primary: Percent change from baseline at week 12 for BAF312 2 mg, 10 mg or placebo (once daily) serum creatine kinase (CK) levels.

End point title	Percent change from baseline at week 12 for BAF312 2 mg, 10 mg or placebo (once daily) serum creatine kinase (CK) levels. ^[5]
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End point description:

Serum creatine kinase (CK) were analyzed as part of the blood chemistry panel. The variable CK was log-transformed for statistical analysis and after estimation was converted to percent change from baseline divided by the mean baseline

End point type	Primary
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End point timeframe:

Baseline, at 12 weeks

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: The statistical analysis presented in primary outcome measurement 1 analyzes the data from primary outcome measurement 1 and 2

End point values	BAF312 2mg	BAF312 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	2	5	
Units: U/L				
arithmetic mean (confidence interval 90%)	-19.7 (-32.3 to -4.7)	-55.6 (-77.1 to -13.5)	-0.5 (-21.8 to 25.9)	

Statistical analyses

No statistical analyses for this end point

Secondary: Six-minute walking distance (6MWD) at week 12

End point title	Six-minute walking distance (6MWD) at week 12
End point description:	This test assessed the distance a patient could walk in 6 minutes (Rutkove et al 2002). If the patient was not able to walk for 6 minutes then a 2 minute walking test was conducted
End point type	Secondary
End point timeframe:	Baseline, 12 weeks

End point values	BAF312 2mg	BAF312 10 mg	Placebo	
Subject group type	Subject analysis set	Subject analysis set	Subject analysis set	
Number of subjects analysed	7	2	4	
Units: meters				
arithmetic mean (standard deviation)				
Period 1, Baseline	341.99 (± 110.88)	280 (± 127.279)	319.6 (± 104.61)	
Period 1, Week 12 (6,1,4)	362.47 (± 52.02)	393 (± 0)	303.1 (± 112.48)	
Distance walked, change from BL at Wk 12 (6,1,4)	46.82 (± 65.64)	23 (± 0)	-6.4 (± 21.981)	

Statistical analyses

No statistical analyses for this end point

Secondary: Six-minute walking distance (6MWD) at week 24

End point title	Six-minute walking distance (6MWD) at week 24
End point description:	This test assessed the distance a patient could walk in 6 minutes (Rutkove et al 2002). If the patient was not able to walk for 6 minutes then a 2 minute walking test was conducted
End point type	Secondary
End point timeframe:	Baseline, 24 weeks

End point values	BAF312 2mg/BAF312 2mg	Placebo/BAF31 2 2 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	6	3		
Units: meters				
arithmetic mean (standard deviation)				
Period 2, Week 24	364.6 (± 73.803)	329.33 (± 186.551)		
Distance walked, change from baseline at Wk 24	48.95 (± 91.922)	4.33 (± 51.637)		

Statistical analyses

No statistical analyses for this end point

Secondary: BAF312 trough plasma concentrations

End point title	BAF312 trough plasma concentrations
End point description:	
All blood samples were taken by either direct venipuncture or an indwelling cannula inserted in a forearm vein. For each sample, approximately 2 mL of blood was drawn. BAF312 was determined in ethylenediaminetetraacetic acid (EDTA) plasma using a validated liquid chromatography–tandem mass spectrometry (LC-MS/MS) bioanalytical method for the quantification. The anticipated lower limit of quantification (LLOQ) was 0.02 ng/mL using 0.1 mL of plasma	
End point type	Secondary
End point timeframe:	
-7 Baseline, day 28, 56, 84	

End point values	BAF312 10 mg	BAF312 2mg		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	2	6		
Units: ng/mL				
arithmetic mean (standard deviation)				
Day - 7 (6,2)	0 (± 0)	0 (± 0)		
Day 28 (6,1)	182 (± 0)	25.3 (± 11.2)		
Day 56 (5,1)	270 (± 0)	25.1 (± 12.6)		
Day 84 (6,1)	240 (± 0)	21.4 (± 10.1)		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse Events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All Adverse events are reported in this record from First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	19.0
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Reporting groups

Reporting group title	Period 1 BAF312 2mg
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Reporting group description:

Period 1 BAF312 2mg

Reporting group title	Period 1 BAF312 10mg
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Reporting group description:

Period 1 BAF312 10mg

Reporting group title	Period 1 Placebo
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Reporting group description:

Period 1 Placebo

Reporting group title	Period 2 BAF312 2mg/ BAF312 2mg
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Reporting group description:

Period 2 BAF312 2mg/ BAF312 2mg

Reporting group title	Period 2 Placebo/ BAF312 2mg
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Reporting group description:

Period 2 Placebo/ BAF312 2mg

Serious adverse events	Period 1 BAF312 2mg	Period 1 BAF312 10mg	Period 1 Placebo
Total subjects affected by serious adverse events			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 5 (0.00%)
number of deaths (all causes)	0	0	0
number of deaths resulting from adverse events	0	0	0
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemolytic uraemic syndrome			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			

Acute kidney injury			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Period 2 BAF312 2mg/ BAF312 2mg	Period 2 Placebo/ BAF312 2mg	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Blood and lymphatic system disorders			
Haemolytic anaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haemolytic uraemic syndrome			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences causally related to treatment / all	0 / 0	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Period 1 BAF312 2mg	Period 1 BAF312 10mg	Period 1 Placebo
Total subjects affected by non-serious adverse events			
subjects affected / exposed	6 / 7 (85.71%)	2 / 2 (100.00%)	4 / 5 (80.00%)
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 7 (14.29%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	1	0	0
Chest discomfort			

subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 2 (50.00%) 1	0 / 5 (0.00%) 0
Fatigue subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1
Feeling cold subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Pyrexia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Reproductive system and breast disorders Benign prostatic hyperplasia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Respiratory, thoracic and mediastinal disorders Rhinorrhoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Investigations Carbon monoxide diffusing capacity decreased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1
Cardiac murmur subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Injury, poisoning and procedural complications			

Epicondylitis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1
Nervous system disorders Cerebral artery stenosis subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0 0 / 7 (0.00%) 0 2 / 7 (28.57%) 2	0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 0 / 2 (0.00%) 0	1 / 5 (20.00%) 1 2 / 5 (40.00%) 2 2 / 5 (40.00%) 2
Eye disorders Cataract subjects affected / exposed occurrences (all) Eye pain subjects affected / exposed occurrences (all) Ocular hyperaemia subjects affected / exposed occurrences (all) Vitreous detachment subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 0 / 7 (0.00%) 0 1 / 7 (14.29%) 1 0 / 7 (0.00%) 0	0 / 2 (0.00%) 0 1 / 2 (50.00%) 1 0 / 2 (0.00%) 0 0 / 2 (0.00%) 0	0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0 0 / 5 (0.00%) 0
Gastrointestinal disorders Abdominal pain upper subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1 1 / 7 (14.29%) 1	0 / 2 (0.00%) 0 0 / 2 (0.00%) 0	1 / 5 (20.00%) 1 0 / 5 (0.00%) 0

Nausea subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	1 / 5 (20.00%) 1
Vomiting subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	1 / 2 (50.00%) 1	0 / 5 (0.00%) 0
Hepatobiliary disorders Cholelithiasis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Skin and subcutaneous tissue disorders Papule subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Musculoskeletal and connective tissue disorders Back pain subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Musculoskeletal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Myalgia subjects affected / exposed occurrences (all)	1 / 7 (14.29%) 1	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Pain in extremity subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Polymyositis subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Spinal pain subjects affected / exposed occurrences (all)	0 / 7 (0.00%) 0	0 / 2 (0.00%) 0	0 / 5 (0.00%) 0
Infections and infestations Nasopharyngitis			

subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	1 / 5 (20.00%)
occurrences (all)	0	0	1
Upper respiratory tract infection			
subjects affected / exposed	0 / 7 (0.00%)	0 / 2 (0.00%)	0 / 5 (0.00%)
occurrences (all)	0	0	0
Urinary tract infection			
subjects affected / exposed	0 / 7 (0.00%)	1 / 2 (50.00%)	0 / 5 (0.00%)
occurrences (all)	0	1	0

Non-serious adverse events	Period 2 BAF312 2mg/ BAF312 2mg	Period 2 Placebo/ BAF312 2mg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	4 / 6 (66.67%)	2 / 3 (66.67%)	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Chest discomfort			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Fatigue			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Feeling cold			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Pyrexia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Respiratory, thoracic and mediastinal disorders			
Rhinorrhoea			

subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	
Psychiatric disorders Depression subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	
Investigations Carbon monoxide diffusing capacity decreased subjects affected / exposed occurrences (all) Cardiac murmur subjects affected / exposed occurrences (all) Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 1 / 3 (33.33%) 1	
Injury, poisoning and procedural complications Epicondylitis subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0	0 / 3 (0.00%) 0	
Nervous system disorders Cerebral artery stenosis subjects affected / exposed occurrences (all) Dizziness subjects affected / exposed occurrences (all) Headache subjects affected / exposed occurrences (all)	0 / 6 (0.00%) 0 0 / 6 (0.00%) 0 0 / 6 (0.00%) 0	0 / 3 (0.00%) 0 0 / 3 (0.00%) 0 0 / 3 (0.00%) 0	
Eye disorders			

Cataract			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Eye pain			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Ocular hyperaemia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vitreous detachment			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Diarrhoea			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Vomiting			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Skin and subcutaneous tissue disorders			
Papule			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal and connective tissue disorders			
Back pain			

subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Musculoskeletal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Myalgia			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Pain in extremity			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	2	0	
Polymyositis			
subjects affected / exposed	0 / 6 (0.00%)	1 / 3 (33.33%)	
occurrences (all)	0	1	
Spinal pain			
subjects affected / exposed	1 / 6 (16.67%)	0 / 3 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	
Upper respiratory tract infection			
subjects affected / exposed	1 / 6 (16.67%)	1 / 3 (33.33%)	
occurrences (all)	1	1	
Urinary tract infection			
subjects affected / exposed	0 / 6 (0.00%)	0 / 3 (0.00%)	
occurrences (all)	0	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 August 2012	Added safety measures imposed by health authorities in the Phase III program studying BAF312 in secondary progressive multiple sclerosis. The safety measures also included new exclusion criteria that reflected updates to the label for Gilenya®, which belongs to the same pharmacological class
01 January 2014	The planned expansion of the study to more countries, in some of which the MCT system was not available. The cardiac monitoring was performed with a Holter ECG instead of the MCT used in the other participating countries. New clinical information had become available (study CBAF312A2116) that justified the concomitant use of beta blockers with study drug; corresponding changes were made to the eligibility criteria to allow the use of beta blockers. Azathioprine was added as permitted background medication (methotrexate or azathioprine) since it was a frequently used steroid-sparing agent in this patient population. The ivIg therapy washout window was decreased to 3 months to allow more patients in to the study. Changes were made to update safety and tolerability information on BAF312, and to align and make consistent eligibility criteria with another similar study of BAF312 in dermatomyositis patients.
01 April 2014	The addition of recent findings in a mouse carcinogenicity study. A section of efficacy data in PM/DM was updated with final data of a completed proof-of-concept that had become available. The study stopping rules were modified to allow for a full safety review prior to discontinuation of all subjects in case of 2 patients experiencing a study drug related AE, as specified in the stopping rules
01 June 2015	The requirement for vital signs to be within defined ranges at screening and baseline was deleted (systolic blood pressure 90 - 140 mm Hg; diastolic blood pressure 50 -90 mm Hg; pulse rate, 50- 90 bpm). The requirement for elevated levels of blood creatine kinase at baseline ($\geq 1.3 \times \text{ULN}$) was changed to allow for alternative indicators of active muscle inflammation, i.e. other muscle enzymes, MRI imaging, or recent biopsy. The inclusion requirement for muscle weakness based on an MMT8 score of no more than 135/150 was changed to be based on the MMT24 scoring system, i.e. patients had an MMT24 score of no more than 245/260. The assessment of 6-minutes-walking distance (6MWD) was moved from exploratory to secondary objective. The requirement for previous treatment failure or toxicities to previous treatment was removed. The washout times for immunosuppressive regimens were adapted based on current knowledge about the duration of physiological effects of individual drugs and clinical practice for switching therapeutic regimens. If a patient had interrupted the intake of study drug, the permitted duration of treatment pause was changed from "48 hours" to less than four missed doses. In patients with specific genetic variants of CYP2C9 (CYP2C9*1*3 and *2*3), new restrictions applied for the use of CYP3A4 inhibitors. Potent CYP2C9 inhibitors as well as potent CYP2C9 and/or CYP3A4 inducers were not permitted during the study. The screening and baseline windows were expanded for logistical reasons. An additional dose arm of 10 mg BAF312 was added. The titration period was increased for all dosing arms. A new set of randomization numbers were generated to modify the ratio of subjects assigned to the placebo, 2 mg and 10 mg. The total number of subjects to be enrolled was increased from 30 to up to 45.
01 April 2016	To ensure that the maximum exposure reported at maximum tolerated dose (MTD) (20 mg q.d.) in the multiple ascending dose (MAD) study 2105 won't be exceeded, especially in the 10 mg dose group, specific exclusions criteria in terms of 2C9/3A4 inhibitors were defined for CYP2C9 *1/*3, *2/*2 and *2/*3 carriers. Further to the CYP2C9*3 genotyping at screening, this amendment additionally described the need for CYP2C9*2 genotyping

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.

Study terminated due to slow recruitment and lack of efficacy in parallel study in dermatomyositis (similar pathophysiology). The overall results for this study for all outcome measurements are inconclusive due to small sample size

Notes: