Sponsor

Novartis Pharma AG

Generic Drug Name

BAF312

Therapeutic Area of Trial

Autoimmune Disease

Approved Indication

Investigational

Protocol Number

CBAF312A2202

Title

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

Study Phase

Phase II

Study Start/End Dates

First patient first visit: 15-June-2010

Last patient last visit: 13-June-2012

Study Design/Methodology

This Proof of Concept (PoC) study employed a randomized, parallel, double-blind, placebo-controlled, multicenter design followed by an open label extension period. Approximately 40 patients with polymyositis or dermatomyositis were planned to be enrolled (expected number of completers = 32). It was anticipated that at least 10 patients of each subtype (polymyositis or dermatomyositis) were included and stratified into active and placebo groups.

Patients who completed Period 1 (the double-blind treatment phase), entered Period 2 (the open label extension phase). The Period 2 extension phase study allowed:

a. all placebo patients of Period 1 to switch to BAF312;

b. patients already receiving BAF312 in Period 1 to continue to receive active treatment, and

c. patients demonstrating clinical improvements to taper down the dose of corticosteroid.

Baseline for all patients, whether receiving BAF312 for the first time or not, was the Baseline visit (Visit 2) directly preceding Period 1. The blind of Period 1 remained unbroken during

Period 2 in order to evaluate the efficacy, safety and tolerability of BAF312 in PM/DM patients.
The study consisted of a 4 week screening period (Week -6 to -2, Visit 1), one baseline period (Week -1, Visit 2), one placebo controlled treatment period (Period 1, Week 1 to 12) and one non-placebo controlled, open label, extension period (Period 2, Week 13 to 24) followed by a study completion evaluation approximately 4 weeks after the last drug administration (Follow-up, Weeks 25 – 28). Patients who met the inclusion/exclusion criteria at screening (Visit 1) were admitted to baseline evaluations (Visit 2). All baseline safety evaluation results were available prior to dosing. Patients visited the study site within 1 week prior to first dosing for baseline evaluations. On Day 1, (Visit 3) randomization to one of the treatment arms was conducted for patients whose eligibility, as per the inclusion/exclusion criteria checklist, was confirmed at the baseline visit (Visit 2). The 10 mg therapeutic dose of BAF312 was reached by successive subtherapeutic dose increases over a 10-day period (dose-titration) in order to minimize the negative chronotropic effect at first intake of BAF312. Treatment began on Day 1 (Visit 3) with the first dose of 0.25 mg study drug or matching placebo given orally in the morning under the supervision at the clinical site for 6-hours post dose. After Day 1, the following daily doses of BAF312 or matching placebo were administered:

- 0.25 mg (Day 2),
- 0.5 mg (Day 3),
- 0.75 mg (Day 4),
- 1.25 mg (Day 5),
- 2 mg (Day 6),
- 3 mg (Day 7),
- 5 mg (Day 8),
- 8 mg (Day 9),
- 10 mg (Day 10),

Although no negative chronotropic effects were expected during the dose-titration period, dosing on Day 1 and Day 8 was scheduled at the study site with a 6-hour monitoring post dose to further ensure cardiac safety. From Day 10 onwards until the end of Period 1 (last day of Week 12), 10 mg of BAF312 or matching placebo was administered once daily.
In Period 2, patients who were on placebo in Period 1 received once a day dose of 10 mg BAF312 after successive subtherapeutic dose increases over a 10-day period as described above. Patients who were on 10 mg BAF312 in Period 1 continued to receive 10 mg BAF312. Period 2 consisted of 12 weeks, ending the treatment period on Week 24. The blinding of Period 1 remained unbroken in Period 2.
Safety, efficacy, pharmacokinetic, pharmacodynamic and pharmacogenetic assessments were conducted for up to 4 weeks (± 5 days) after last drug administration. After the follow-up end of study visit patients were discharged from the study.

Centers

5 centers in 4 countries: Czech Republic (1), Hungary (2), Sweden (1), USA (1),

Publication

Not applicable

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

The investigational drug, BAF312, 0.25 mg, 1 mg, 4 mg and 5 mg tablets for once daily oral administration were prepared by Novartis and supplied to the Investigator as patient specific packs.

Statistical Methods

The total number of responders and non-responders in each arm (BAF312 and Placebo) was computed.
Bayesian methods were used with uninformative priors for the proportion of responders in each treatment arm. Based on these priors and the observed number of responders in each treatment arm, the posterior probabilities of the proportion of responders on BAF312 being greater than on placebo was calculated.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Patients with disease at least 3 months before study
- Muscle weakness
- Received corticosteroids with or without disease modifying antirheumatic drugs at least 3 months before study however not responding to this therapy

Exclusion Criteria:

- Other idiopathic inflammatory myopathies
- Myopathy other than polymyositis and dermatomyositis
- Patients with late stages of disease Other protocol-defined inclusion/exclusion criteria may apply

Participant Flow

	BAF312/BAF312 N=8 n (%)	**Placebo/BAF312 N=10 n (%)**	**Total N=18 n (%)**
Patients			
Completed	7 (87.5)	5 (50.0)	12 (66.7)
Discontinued	1 (12.5)	5 (50.0)	6 (33.3)
Main cause of discontinuation			
Adverse Event(s)		2 (20.0)	2 (11.1)
Unsatisfactory therapeutic effect		1 (10.0)	1 (5.6)
Subject withdrew consent		2 (20.0)	2 (11.1)
Protocol deviation	1 (12.5)		1 (5.6)

Baseline Characteristics

		BAF312/BAF312 N=8	Placebo/BAF312 N=10	Total N=18
Age (years)	Mean (SD)	51.4 (6.48)	48.1 (15.57)	49.6 (12.18)
	Median	51.0	48.0	49.0
	Range	43, 60	21, 74	21, 74
Gender - (n%)	Male	4 (50.0 %)	3 (30.0 %)	7 (38.9 %)
	Female	4 (50.0 %)	7 (70.0 %)	11 (61.1 %)
Race - (n%)	Caucasian	8 (100.0 %)	10 (100.0 %)	18 (100.0 %)
Ethnicity - (n%)	Hispanic/Latino	1 (12.5 %)		1 (5.6 %)
	Other	7 (87.5 %)	10 (100.0 %)	17 (94.4 %)
Weight (kg)	Mean (SD)	79.00 (13.310)	74.75 (15.212)	76.64 (14.148)
	Median	77.50	71.00	74.50
	Range	59.0, 96.0	58.0, 97.8	58.0, 97.8
Height (cm)	Mean (SD)	173.6 (11.53)	169.0 (13.52)	171.1 (12.53)
	Median	171.0	165.5	168.0
	Range	160, 192	152, 200	152, 200
BMI (kg/m^2)	Mean (SD)	26.194 (3.8185)	26.234 (5.0309)	26.216 (4.4050)
	Median	25.651	25.125	25.254
	Range	21.67, 34.53	21.05, 37.27	21.05, 37.27
Baseline CK (U/L)	Mean (SD)	204.0 (237.37)	779.7 (1207.98)	508.8 (917.60)
	Median	110.0	164.0	121.0
	Range	34, 759	37, 3610	34, 3610

BMI = body mass index

Outcome Measures

Primary Outcome Measures:
Variables included those required to satisfy the IMACS criteria for a responder in PM/DM (IMACS core set measures). Patient's responder/non-responder status was derived using the criteria of IMACS Preliminary Definitions of Improvement. Patients who had no assessment due to lack of efficacy and patients who obtained rescue medication were counted as non-responders. Patients who had no efficacy assessment or discontinued the study due to unknown reason and therefore cannot be classified as responders or non-responders, were excluded from the analysis. The following criteria were used to establish Definition of Improvement and define disease worsening in this study, respectively:
Improvement:
Myositis disease (MD) global activity improved by greater than 30% and MMT (Manual Muscle Testing) improved by 1 – 15%,
OR
MMT improved by greater than 15% and MD global activity improved by greater than 10%, AND in either case no more than 2 worse by 25% or more.
Disease worsening:
≥ 30% reduction in any three or more of six variables of the IMACS core set measures.
Secondary Outcome Measures:

- To characterize the steady state pharmacokinetics of BAF312 in PM/DM patients.
- To assess the exposure-effect relationship of BAF312 on various safety and efficacy parameters.
- To assess the efficacy of BAF312 to modify Health-related Quality of Life (QoL) in
- PM/DM patients, as measured by Short Form (SF)-36.
- To assess biomarkers reflecting the efficacy of BAF312 to reduce systemic inflammatory
- components of the disease using serum markers such as C-reactive protein (CRP) and
- erythrocyte sedimentation rate (ESR).
- To assess the change in steroids use after BAF312 administration (Period 2 only) in
- PM/DM patients.

ESR data were not captured in the database, but the assessment was performed and reviewed by the clinical sites. CRP values and changes in steroid use during period 2 were inconclusive.

Primary Outcome Result(s)

Responder status at Week 12

	No. of responders / No. of evaluable patients (%)
BAF312	4 / 7 (57.1%)
Placebo	1/7 (14.3%)

Bayesian analysis of responder status at Week 12

Threshold	Probability that the difference (BAF312 - Placebo) is greater than the threshold	Observed difference (BAF312-Placebo)
0	0.960	0.429

Secondary Outcome Result(s)

Summary statistics of absolute lymphocyte counts (Mean ALC x 10^9/L) by treatment group and week (wk)

	Visits				
	Baseline	**wk2**	**wk4**	**wk8**	**wk12**
BAF312/BAF312	1.989 N=8	0.710 N=7	0.461 N=7	0.391 N=7	0.467 N=7
Placebo/BAF312	2.419 N=10	1.980 N=10	2.414 N=9	2.046 N=8	2.225 N=8
	wk14	**wk16**	**wk20**	**wk24**	**End of study**
BAF312/BAF312	0.457 N=7	0.399 N=7	0.286 N=7	0.316 N=7	1.819 N=8
Placebo/BAF312	0.751 N=7	0.456 N=5	0.514 N=5	0.474 N=5	1.475 N=10

Summary statistics of CRP levels (Mean, mg/L) by treatment group and week (wk)

	Visits				
	Baseline	**wk2**	**wk4**	**wk8**	**wk12**
BAF312/BAF312	4.00 N=8	7.44 N=8	7.21 N=7	3.14 N=7	4.14 N=7
Placebo/BAF312	2.94 N=9	2.55 N=10	2.56 N=9	4.19 N=8	6.38 N=8
	wk14	**wk16**	**wk20**	**wk24**	**End of study**
BAF312/BAF312	6.36 N=7	7.14 N=7	8.43 N=7	6.14 N=7	6.00 N=8
Placebo/BAF312	8.57 N=7	3.50 N=5	2.60 N=5	2.90 N=5	5.65 N=10

SF-36 scores

		Time of assessment (visits)			
		Baseline	**12 weeks**	**24 weeks**	**End of study**
BAF312/BAF312	Physical component score	35.050 (N=8)	36.469 (N=7)	34.611 (N=7)	32.194 (N=8)
	Mental component score	45.260 (N=8)	44.449 (N=7)	48.491 (N=7)	46.962 (N=8)
Placebo/BAF312	Physical component score	35.443 (N=8)	30.406 (N=7)	28.612 (N=4)	28.264 (N=7)
	Mental component score	52.674 (N=8)	49.063 (N=7)	42.027 (N=4)	48.940 (N=7)

Mean plasma concentrations per treatment, PK analysis set

	Time of assessment (days)				
	0	**8**	**28**	**56**	**84**
BAF312 (ng/ml)	0 (N=7)	29.6 (n=7)	121 (n=6)	160 (n=6)	163 (n=6)
	92	**112**	**140**	**168**	**196***
BAF312 (ng/ml)	80 (N=14)	120 (n=12)	129 (n=12)	125 (n=12)	27.9 (n=15)

*end of study visit

Change in steroid use in Period 2 (Number of patients)

	Steroid Reduction	**Steroid Increase**	**Steroids Stable**	**Comments**
BAF312/BAF312 (N=7 in period 2)	3	1	3	Increase in steroid dose for treatment of urticaria facititia
Placebo/BAF312 (N=8 in period 2)	2	2	4	One of the patients with increase in steroid dose received BAF312 on 1 day only

Safety Results

Adverse Events by System Organ Class

	BAF312 10 mg N=16 n (%)*	Placebo N=10 n (%)	Total N=18 n (%)
Patients with AE(s)	12 (75.0)	8 (80.0)	17 (94.4)
System organ class			
Nervous system disorders	8 (50.0)	2 (20.0)	10 (55.6)
Gastrointestinal disorders	6 (37.5)	4 (40.0)	9 (50.0)
Musculoskeletal and connective tissue disorders	6 (37.5)	2 (20.0)	7 (38.9)
Respiratory, thoracic and mediastinal disorders	2 (12.5)	4 (40.0)	6 (33.3)
Eye disorders	2 (12.5)	2 (20.0)	4 (22.2)
Infections and infestations	3 (18.8)	1 (10.0)	4 (22.2)
Skin and subcutaneous tissue disorders	3 (18.8)	1 (10.0)	4 (22.2)
General disorders and administration site conditions	3 (18.8)	0 (0.0)	3 (16.7)
Vascular disorders	2 (12.5)	1 (10.0)	3 (16.7)
Cardiac disorders	1 (6.3)	0 (0.0)	1 (5.6)
Hepatobiliary disorders	0 (0.0)	1 (10.0)	1 (5.6)
Injury, poisoning and procedural complications	1 (6.3)	1 (10.0)	1 (5.6)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1 (6.3)	0 (0.0)	1 (5.6)

arranged by descending frequency
*of 18 patients enrolled, 16 received BAF312 in either Period 1 and/or Period 2

Adverse Events by preferred term

	BAF312 10 mg N=16 n (%)*	Placebo N=10 n (%)	Total N=18 n (%)
Patients with AE(s)	12 (75.0)	8 (80.0)	17 (94.4)
Preferred term			
Headache	4 (25.0)	2 (20.0)	6 (33.3)
Oropharyngeal pain	0 (0.0)	4 (40.0)	4 (22.2)
Diarrhoea	2 (12.5)	1 (10.0)	3 (16.7)
Arthralgia	1 (6.3)	1 (10.0)	2 (11.1)
Hypertension	2 (12.5)	0 (0.0)	2 (11.1)
Myalgia	2 (12.5)	0 (0.0)	2 (11.1)
Nausea	1 (6.3)	1 (10.0)	2 (11.1)
Pyrexia	2 (12.5)	0 (0.0)	2 (11.1)
Tremor	2 (12.5)	0 (0.0)	2 (11.1)
Abdominal pain upper	1 (6.3)	0 (0.0)	1 (5.6)
Aphthous stomatitis	0 (0.0)	1 (10.0)	1 (5.6)
Back pain	0 (0.0)	1 (10.0)	1 (5.6)
Basal cell carcinoma	1 (6.3)	0 (0.0)	1 (5.6)
Bronchitis	1 (6.3)	0 (0.0)	1 (5.6)
Cataract	0 (0.0)	1 (10.0)	1 (5.6)

Cholelithiasis	0 (0.0)	1 (10.0)	1 (5.6)
Conjunctivitis	1 (6.3)	0 (0.0)	1 (5.6)
Cough	1 (6.3)	0 (0.0)	1 (5.6)
Dental caries	1 (6.3)	0 (0.0)	1 (5.6)
Dermatitis	0 (0.0)	1 (10.0)	1 (5.6)
Dizziness	1 (6.3)	0 (0.0)	1 (5.6)
Dysgeusia	1 (6.3)	0 (0.0)	1 (5.6)
Dysphagia	1 (6.3)	0 (0.0)	1 (5.6)
Frequent bowel movements	1 (6.3)	0 (0.0)	1 (5.6)
Gastrooesophageal reflux disease	1 (6.3)	0 (0.0)	1 (5.6)
Haematoma	0 (0.0)	1 (10.0)	1 (5.6)
Haemorrhoids	0 (0.0)	1 (10.0)	1 (5.6)
Intervertebral disc compression	1 (6.3)	0 (0.0)	1 (5.6)
Intervertebral disc protrusion	1 (6.3)	0 (0.0)	1 (5.6)
Macular oedema	0 (0.0)	1 (10.0)	1 (5.6)
Mechanical urticaria	1 (6.3)	0 (0.0)	1 (5.6)
Neck pain	1 (6.3)	0 (0.0)	1 (5.6)
Oedema peripheral	1 (6.3)	0 (0.0)	1 (5.6)
Oral herpes	1 (6.3)	0 (0.0)	1 (5.6)
Pain in extremity	1 (6.3)	0 (0.0)	1 (5.6)
Palpitations	1 (6.3)	0 (0.0)	1 (5.6)
Periorbital oedema	0 (0.0)	1 (10.0)	1 (5.6)
Peritonitis	0 (0.0)	1 (10.0)	1 (5.6)
Productive cough	1 (6.3)	0 (0.0)	1 (5.6)
Rash	1 (6.3)	0 (0.0)	1 (5.6)
Rhinorrhoea	1 (6.3)	0 (0.0)	1 (5.6)
Rosacea	1 (6.3)	0 (0.0)	1 (5.6)
Salivary hypersecretion	1 (6.3)	0 (0.0)	1 (5.6)
Sciatica	1 (6.3)	0 (0.0)	1 (5.6)
Skin mass	1 (6.3)	0 (0.0)	1 (5.6)
Spinal compression fracture	1 (6.3)	1 (10.0)	1 (5.6)
Tinea versicolour	1 (6.3)	0 (0.0)	1 (5.6)
Vision blurred	1 (6.3)	0 (0.0)	1 (5.6)
Visual acuity reduced	0 (0.0)	1 (10.0)	1 (5.6)

arranged by descending frequency
*of 18 patients enrolled, 16 received BAF312 in either Period 1 and/or Period 2

Serious Adverse Events and Deaths

		BAF312 10 mg N=16* n	Placebo N=10 n	Total N=18 n
Patients with SAE(s)		0	4	4
System organ class	**Prefered term**			
Hepatobiliary disorders	Cholelithiasis	0	1	1
Musculoskeletal and connective tissue disorders	Back pain	0	1	1
Injury, poisoning and procedural complications	Spinal compression fracture	0	1	1
Infections and infestations	Peritonitis	0	1	1

*of 18 patients enrolled, 16 received BAF312 in either Period 1 and/or Period 2

There were no deaths in the study.

Other Relevant Findings

Date of Clinical Trial Report

10-June 2013

Date Inclusion on Novartis Clinical Trial Results Database

13 June 2013

Date of Latest Update

Not Applicable