Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siponimod

Trial Indication(s)

Active dermatomyositis

Protocol Number

CBAF312X2206

Protocol Title

A double blind, randomized, placebo-controlled study to evaluate, safety, tolerability, efficacy and preliminary dose-response of BAF312 in patients with active dermatomyositis (DM)

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase 2

Study Start/End Dates

Study Start Date: November 2013 (Actual)
Study Completion Date: February 2016 (Actual)

Reason for Termination (If applicable)

The study was terminated prematurely after an interim analysis for futility. The study did not provide any evidence for efficacy of BAF312 in dermatomyositis. There were no safety concerns.

Study Design/Methodology

This was a non-confirmatory, 48-week, Phase II, multiple-arm, multi-center, double-blind, randomized, placebo-controlled exploratory dose-ranging study. The study comprised a screening period (Days -30 to -10), a baseline visit (Day -9 to -3) a drug up-titration phase (Days 1-10) and 24 weeks of treatment with BAF312 or placebo (Days 1-167), and an open-label extension period of 24 weeks (plus 4 weeks follow-up).

In Period 1, patients were randomized to a daily oral regimen of placebo, 0.5, 2 or 10 mg of BAF312. Patients randomized to receive active BAF312 were up-titrated over 10 days. The extension Period 2 employed a fixed-dose dose regimen of 2 mg/day, which was up-titrated as in Period 1, regardless of what treatment the patient was taking in Period 1.

During the treatment period the patients underwent clinical assessments for safety and efficacy after 10 days and 4 weeks of treatment, followed by assessments at 4 week intervals. Optionally, skin biopsies were collected at baseline, and 6 months of treatment, or at time of drug discontinuation in case of early dropout.

After the last administration of BAF312, a follow-up period of 4 weeks was used to monitor safety and disease activity.

Centers

24 centers in 8 countries: Hungary(2), United States(10), Czech Republic(1), Canada(1), Poland(2), Japan(5), Belgium(1), Taiwan(2)

Objectives:

Primary objective:

- To assess the efficacy of different doses of BAF312 after 6 months of treatment in active DM patients as assessed by manual muscle testing using the MMT-24 scoring system.

Secondary objectives:

- To assess the effects of different doses of BAF312 on safety, pharmacokinetics and peripheral blood lymphocyte counts in active DM patients

- To assess the efficacy of different doses of BAF312 after 3 months of treatment in active DM patients as assessed by manual muscle testing using the MMT-24 scoring system.
- To assess the efficacy of different doses of BAF312 after 6 month of treatment in active DM patients as assessed by the 6-MWD test

The study was prematurely terminated based on the results of the interim analyses where despite a clear PD effect, BAF312 did not demonstrate superior efficacy over placebo and a dose-response relationship was not observed.

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

The formulations used in this trial were as film-coated tablets. The tablets appeared as white to yellowish convex, round beveled edged film-coated tablets without engraving and were available in strengths of 0.25 mg, 0.5 mg, 1 mg and 2 mg of BAF312 per tablet. The investigational drug and matching placebo tablets were prepared by Novartis and supplied to the Investigator as individual subject packs.

Study drug and strength	Formulation control number Packing Control Number	Basis/Variant	Batch number
BAF312 0.25 mg	13-2578CH; 13-3982CH	6002636.010	X002 0113
BAF312 0.5 mg	13-2578CH; 13-2579CH; 13-3982CH	6003459.001	X004 0113
BAF312 1 mg	13-2578CH; 13-3982CH	6002630.010	X005 0113
BAF312 2 mg	13-3983CH;13-2579CH; 13-3982CH	6003077.003	X007 0113
Placebo	13-2578CH; 13-2579CH; 13-3982CH	6002679.004	X001 0113; X096 0312

Statistical Methods

Primary variable: the overall efficacy of BAF312 was assessed by comparing the improvements of MMT-24 with every dose of BAF312 to that of placebo based on predefined criteria for statistical significance and clinical relevance of efficacy over placebo via a Bayesian approach. Then the dose-response curve of MMT-24 was estimated with the aim to determine a target dose for the program via emax models; however the model failed to fit due to not observing expected dose response from this study.

Secondary variables: included the improvements of the 6-MWD test results, incidence of adverse events, plasma BAF312 concentrations and peripheral blood lymphocyte counts. In addition, the changes from baseline in MMT-24 at 3 months was be evaluated. The dose-response was assessed in the same way as for the 6-month data.

Study Population: Key Inclusion/Exclusion Criteria

Key Inclusion Criteria:
Written informed consent must be obtained before any assessment is performed.
• Patients who have been defined as "definite" or “probable” based on the criteria of Bohan and Peter (Bohan and Peter 1975) for dermatomyositis at least 3 months before screening
• Patients must have active disease as defined by muscle weakness
• Patients may be on a stable dose of corticosteroid (up/equal to 20 mg once daily prednisone equivalent)
• Patients currently treated with oral or subcutaneous MTX must have been a stable dose of no more/equal to than 25 mg per week
• Patients currently treated with Azathioprine must have been a stable maintenance dose of no more/equal to 3 mg/kg/day
• Negative cancer screening conducted in the 12 months prior to screening visit

Key Exclusion Criteria
• Dermatomyositis patients having overlap myositis or any other type of myositis including paraneoplastic myositis, drug-induced myopathy, necrotizing myositis
• Preexisting severe cardiac or pulmonary conditions, malignancy of any organ system or significant eye diseases.
• Uncontrolled diabetes mellitus or diabetes complicated with organ involvement.
• Pregnant or nursing (lactating) women

Participant Flow Table

Overall Study

	BAF312 0.5mg	BAF312 2mg	BAF312 10 mg	Placebo
Started	5	4	4	4
Completed	4	4	2	2
Not Completed	1	0	2	2
Adverse	1	0	2	2

Event

Baseline Characteristics

	BAF312 0.5mg	BAF312 2mg	BAF312 10 mg	Placebo	Total
Number of Participants [units: participants]	5	4	4	4	17
Age Continuous (units: Years) Mean ± Standard Deviation	51.8±16.72	44.0±6.98	51.8±4.79	48.0±10.61	49.1±10.74
Gender, Male/Female (units: Participants)					
Female	4	2	4	3	13
Male	1	2	0	1	4

Summary of Efficacy

Primary Outcome Result(s)

Change from baseline in Manual Muscle Testing - 24 muscles (MMT-24) score

BAF312 0.5mg	BAF312 2mg	BAF312 10 mg	Placebo

Number of Participants Analyzed [units: participants]	3	4	3	3
Change from baseline in Manual Muscle Testing - 24 muscles (MMT-24) score (units: score on a scale) Least Squares Mean ± Standard Error	28.286 ± 8.1539	12.367 ± 7.0967	14.026 ± 8.1541	27.735 ± 8.2175

Statistical Analysis

Groups	BAF312 0.5mg, Placebo
Non-Inferiority/Equivalence Test	No
P Value	0.9621
Method	Other Repeated measures analysis
Mean Difference (Net)	0.551
Standard Error of the mean	11.5519
95 % Confidence Interval 2-Sided	-22.447 to 23.549

Statistical Analysis

Groups	BAF312 2mg, Placebo
Non-Inferiority/Equivalence Test	No

P Value	0.1637
Method	Other Repeated measures analysis
Mean Difference (Net)	-15.368
Standard Error of the mean	10.9297
95 % Confidence Interval 2-Sided	-37.128 to 6.391

Statistical Analysis

Groups	BAF312 10 mg, Placebo
Non-Inferiority/Equivalence Test	No
P Value	0.2409
Method	Other Repeated measures
Mean Difference (Net)	-13.709
Standard Error of the mean	11.6016
95 % Confidence Interval 2-Sided	-36.806 to 9.388

Summary of Safety

Safety Results

Serious Adverse Events by System Organ Class

Time Frame	Timeframe for AE
Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (18.1)
Assessment Type for Table Default	Systematic Assessment

	Period 1 Placebo N = 5	Period 1 BAF312 0.5 mg/day N = 4	Period 1 BAF312 2 mg/day N = 4	Period 1 BAF312 10 mg/day N = 4	Period 2 Placebo /BAF312 2 mg/day N = 5	Period 2 BAF312 0.5 mg/day/BAF312 2 mg/day N = 4	Period 2 BAF312 2 mg/day/BAF312 2 mg/day N = 4	Period 2 BAF312 10 mg/day/BAF312 2 mg/day N = 4
Total participants	1 (20.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)

affected								
Infections and infestations								
Pneumonia	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications								
Laceration	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Procedural pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders								
Subarachnoid haemorrhage	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Respiratory, thoracic and mediastinal disorders								
Pulmonary embolism	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders								
Dermatomyositis	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame Timeframe for AE

Additional Description	AE additional description
Source Vocabulary for Table Default	MedDRA (18.1)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	5%

	Period 1 Placebo N = 5	Period 1 BAF312 0.5 mg/day N = 4	Period 1 BAF312 2 mg/day N = 4	Period 1 BAF312 10 mg/day N = 4	Period 2 Placebo /BAF312 2 mg/day N = 5	Period 2 BAF312 0.5 mg/day/BAF312 2 mg/day N = 4	Period 2 BAF312 2 mg/day/BAF312 2 mg/day N = 4	Period 2 BAF312 10 mg/day/BAF312 2 mg/day N = 4
Total participants affected	1 (20.00%)	1 (25.00%)	4 (100.00%)	4 (100.00%)	2 (40.00%)	1 (25.00%)	4 (100.00%)	2 (50.00%)
Cardiac disorders								
Palpitations	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Ear and labyrinth disorders								
Tinnitus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Vertigo	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye disorders								
Blepharospasm	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chorioretinal atrophy	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Conjunctival haemorrhage	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eye swelling	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Eyelid oedema	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Retinal vein occlusion	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitreous detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)

Vitreous floaters	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Gastrointestinal disorders								
Abdominal discomfort	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Abdominal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Abdominal pain upper	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Diarrhoea	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Gingival recession	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Nausea	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Vomiting	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions								
Asthenia	0 (0.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Non-cardiac chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oedema peripheral	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Peripheral swelling	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Infections and infestations								
Bronchitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Cellulitis orbital	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Dacryocystitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Gastroenteritis	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes simplex	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Herpes zoster	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Influenza	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)
Nasopharyngitis	0 (0.00%)	0 (0.00%)	3 (75.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Oral candidiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Pharyngitis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Skin infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)
Urinary tract infection	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications								
Contusion	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Post procedural inflammation	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Investigations								
Carbon monoxide diffusing capacity decreased	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Lymphocyte count decreased	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Pulmonary function test abnormal	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal and connective tissue disorders								
Arthralgia	0 (0.00%)	0 (0.00%)	1 (25.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscle spasms	0 (0.00%)	1 (25.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Muscular weakness	0 (0.00%)	0 (0.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal chest pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Osteonecrosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in extremity	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)								
Fibroadenoma of breast	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nervous system disorders								
Dizziness postural	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Exertional headache	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Headache	0 (0.00%)	0 (0.00%)	1 (25.00%)	2 (50.00%)	0 (0.00%)	0 (0.00%)	2 (50.00%)	1 (25.00%)
Migraine	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Somnolence	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Syncope	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Transient global amnesia	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Tremor	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders								
Confusional state	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders								
Allergic sinusitis	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Dyspnoea	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Nasal congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)

Productive cough	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pulmonary congestion	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Pulmonary hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders								
Dermatitis atopic	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ecchymosis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Eczema	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)
Generalised erythema	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Pruritus	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Pruritus generalised	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)
Rash	1 (20.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin fissures	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Urticaria	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Surgical and medical procedures								
Internal limiting membrane peeling	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)
Vascular disorders								
Hypertension	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (25.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Relevant Findings

Not applicable

Conclusion:

This study did not provide evidence of clinical activity of BAF312 in Dermatomyositis. None of the primary endpoints showed in a clinically relevant improvement neither after 24 nor after 12 weeks. Furthermore, there was a lack of any evidence for a dose-response relationship for efficacy. Therefore this study did not provide any evidence for efficacy of BAF312 in Dermatomyositis. Therefore the study was terminated prematurely after an interim analysis for futility.

BAF312 showed the expected effect on a decrease of peripheral lymphocyte count due to the sequestering of lymphocytes in lymphoid tissue. Considering the amount of peripheral ALC decrease as a PD measure, a close to optimal effect seems to be achievable with a dose of BAF312 2 mg/day. A further increase of the dose to 10 mg/day seems not to significantly strengthen the PD effect of BAF312. In addition, this dose group had clearly the highest AE incidence. Also, the only possibly related SAE with syncope and laceration did occur in a subject that had received BAF312 10 mg/day during the 1st Period. Therefore, for any treatment considerations, a daily dose of 2 mg may offer an optimal PD effect, whereas further dose increase may not optimize the PD effect but may increase AE incidence and severity.

Date of Clinical Trial Report

August 12, 2016