NOVARTIS

Clinical Trial Results Website

Sponsor

Novartis Pharmaceuticals

Generic Drug Name

Siponimod

Trial Indication(s)

Polymyositis

Protocol Number

CBAF312X2205

Protocol Title

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

Clinical Trial Phase

Phase 2

Phase of Drug Development

Phase III

Study Start/End Dates

Study Start Date: April 2013 (Actual)
Primary Completion Date: August 2016 (Actual)
Study Completion Date: August 2016 (Actual)

Reason for Termination (If applicable)

The study was prematurely terminated in May 2016 because a strategic decision was made to terminate siponimod development in polymyositis (PM) and dermatomyositis (DM) given the very slow recruitment and the moderate efficacy signals in this indication observed.

Study Design/Methodology

For the 12 week Period 1, the study initially had 2 treatment arms (BAF312 2 mg and placebo) and approximately 9 patients had been randomized to 2 mg and placebo in a 2:1 ratio before a BAF312 10 mg treatment arm was added to the protocol. The overall target was a randomization ratio of 1:1:1 among the 2 mg, 10 mg and matching placebo arm thereafter.
In Period 2, all patients who completed Period 1 opted to enter an open-label extension period of an additional 12 weeks (Period 1 treatment remained blinded). Patients on active treatment in Period 1 continued to receive BAF312 of the same dose. Patients randomized to placebo in Period 1 were randomized to receive either 2 mg or 10 mg of BAF312 treatment at a 1:1 ratio for Period 2. Therefore, patients could also be viewed as being randomized to 1 of the 4 treatment sequences: 2 mg/2 mg, 10 mg/10 mg, placebo/2 mg, and placebo/10 mg at study entry.

Centers

20 centers in 8 countries: United States(8), Poland(3), Hungary(2), Czech Republic(1), Canada(2), Taiwan(2), Belgium(1), Switzerland(1)

Objectives:

The primary objective 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.
Secondary objectives were:

- To assess the safety and tolerability of BAF312 in patients with PM.
- To characterize the steady state pharmacokinetics (PK) of BAF312 in patients with PM.
- To assess the effect of BAF312 on muscle function-dependent physical performance using the 6 minutes walking distance test (6MWD).

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

Oral tablets of BAF312 0.25 mg, 0.5 mg, 1mg, 2 mg and matching placebo

Statistical Methods

Primary variables: the efficacy of BAF312 2 mg and 10 mg once daily treatment over placebo at Week 12 was evaluated using both MMT24 and CK as a combined endpoint. The analyses were based on predefined criteria for statistical significance and clinical relevance of efficacy over placebo via a Bayesian approach.

Secondary variables: included the improvements of the 6MWD test results, safety and tolerability, and plasma BAF312 concentrations. These data were summarized by treatment, properly visualized where applicable and listed by patient.

Two unplanned interim analyses were conducted to when 6 and 8 patients had completed 12 weeks treatment respectively for internal decision purposes. No other interim analyses were conducted by the time the study was decided to terminate prematurely. Safety data were listed and summarized by treatment.

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:
-"definite" or “probable” for polymyositis at least three months before Baseline
- active disease as defined by elevated CK levels, or other enzymes, or MRI/biopsy if enzymes are normal, and persisting muscle weakness

- stable dose of corticosteroid for at least 2 weeks prior to Baseline and should not have received a medium or high dose in the last 8 weeks prior to study entry.
- patients treated with methotrexate must have been on a stable dose for at least 6 weeks prior to Baseline.

Exclusion Criteria:
- Patients with overlap polymyositis, late-stage polymyositis, or other types of myositis.
- Preexisting severe cardiac or pulmonary involvement, 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

Period 1 - Randomized

	BAF312 2mg/BAF312 2mg	BAF312 10 mg/BAF312 10 mg	Placebo/BAF312 2 mg	Placebo/BAF312 10 mg
Started	7	2	4	1
Completed	6	2	3	1
Not Completed	1	0	1	0
Adverse Event	1	0	1	0

Extension - All Active

	BAF312 2mg/BAF312 2mg	BAF312 10 mg/BAF312 10 mg	Placebo/BAF312 2 mg	Placebo/BAF312 10 mg
Started	6	0	3	0
Completed	6	0	3	0
Not Completed	0	0	0	0

Baseline Characteristics

	BAF312 2mg/BAF312 2mg	BAF312 10 mg/BAF312 10 mg	Placebo/BAF312 2 mg	Placebo/BAF312 10 mg	Total
Number of Participants [units: participants]	7	2	4	1	14
Age Continuous (units: years) Mean ± Standard Deviation	50.3±14.78	47.0±21.21	48.0±8.83	53.0±0.0	49.4±12.51
Gender, Male/Female (units: participants)					
Female	5	2	2	1	10
Male	2	0	2	0	4
Race/Ethnicity, Customized (units: participants)					
Caucasian	7	1	3	0	11
Black	0	0	0	1	1
Asian	0	1	1	0	2
Disease duration (units: years) Mean ± Standard Deviation	5.6±4.46	5.4±2.74	2.7±1.67	16.9±0	5.6±4.77
Baseline MMT24 Score[1] (units: score) Mean ± Standard	202.6±41.74	184.0±19.80	189.5±45.65	166.0±0	193.6±37.90

Deviation					
Taking DMARD at baseline[2] (units: participants)	7	2	4	1	14

[1] Manual muscle testing in 26 muscle groups (MMT24, max value 260
[2] Taking a disease-modifying antirheumatic drugs

Summary of Efficacy

- Numerically BAF312 10 mg group met the pre-defined efficacy criteria for MMT24 and CK at Week 12 when compared with placebo and BAF312 2 mg group did not. However due to study premature termination, the sample sizes are too small: 5 patients in placebo group, 7 patients in BAF312 2 mg and 2 in BAF312 10 mg. These results are therefore considered inconclusive. All other efficacy and PD data were also inconclusive due to small sample sizes.
- In Period 1, BAF312 steady state plasma concentrations were observed on Day 28 and thereafter following daily administration of 2 mg. Arithmetic mean BAF312 trough plasma levels confirmed adequate BAF312 exposure in the 2 mg and 10 mg groups.

Primary Outcome Result(s)

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

	BAF312 2mg	BAF312 10 mg	Placebo
Number of Participants Analyzed [units: participants]	7	2	5
Change from baseline at week 12 for BAF312 2 mg, 10 mg or placebo	11.2 (3.5 to 19.2)	39.0 (10.7 to 67.2)	9.1 (-1.6 to 20.0)

(once daily) for combined efficacy endpoint: Manual Muscle Testing (MMT24)
(units: scores)
Mean (90% Confidence Interval)

Statistical Analysis

Groups	BAF312 2mg, Placebo	It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: ≥ 90% posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: ≥ 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
Non-Inferiority/Equivalence Test	No	

Method	
Other Bayesian	0.586

Statistical Analysis

Groups	BAF312 2mg, Placebo	It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: ≥ 90% posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: ≥ 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
Non-Inferiority/Equivalence Test	No	

Method	
Other Bayesian	0.022

Statistical Analysis

Groups	BAF312 10 mg, Placebo	It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: ≥ 90% posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: ≥ 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
Non-Inferiority/Equivalence Test	No	

Method	
Other Bayesian	0.963

Statistical Analysis

Groups	BAF312 10 mg, Placebo	It was a Bayesian analysis with non-informative prior for co-primary endpoints, MMT-24 and CK, with dual criteria for statistical significance: ≥ 90% posterior probability (PP) of achieving an increase from baseline in MMT24 and decrease in CK and clinical relevance: ≥ 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

Non-Inferiority/Equivalence Test	No
Method	
Other Bayesian	0.837

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

	BAF312 2mg	BAF312 10 mg	Placebo
Number of Participants Analyzed [units: participants]	7	2	5
Percent change from baseline at week 12 for BAF312 2 mg, 10 mg or placebo (once daily) serum creatine kinase (CK) levels (units: U/L) Mean (90% Confidence Interval)	-19.7 (-32.3 to -4.7)	-55.6 (-77.1 to -13.5)	-0.5 (-21.8 to 25.9)

Secondary Outcome Result(s)

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

	BAF312 2mg	BAF312 10 mg	Placebo
Number of Participants Analyzed [units: participants]	7	2	4
Six-minute walking distance (6MWD) at week 12 (units: meters) Mean ± Standard Deviation			
Period 1, Baseline	341.99 ± 110.880	280.00 ± 127.279	319.60 ± 104.610
Period 1, Week 12 (6,1,4)	362.47 ± 52.02	393.00 ± 0.0	303.10 ± 112.480
Distance walked,change from BL at Wk 12 (6,1,4)	46.82 ± 65.64	23.00 ± 0.0	-6.40 ± 21.981

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

	BAF312 2mg	Placebo/BAF312 2 mg

Number of Participants Analyzed [units: participants]	6	3
Six-minute walking distance (6MWD) at week 24 (units: meters) Mean ± Standard Deviation		
Period 2, Week 24	364.60 ± 73.803	329.33 ± 186.551
Distance walked,change from baseline at Wk 24	48.95 ± 91.922	4.33 ± 51.637

BAF312 trough plasma concentrations

	BAF312 2mg	BAF312 10 mg
Number of Participants Analyzed [units: participants]	6	2
BAF312 trough plasma concentrations (units: ng/mL) Mean ± Standard Deviation		
Day - 7 (6,2)	0 ± 0	0 ± 0
Day 28 (6,1)	25.3 ± 11.2	182 ± 0
Day 56 (5,1)	25.1 ± 12.6	270 ± 0
Day 84 (6,1)	21.4 ± 10.1	240 ± 0

Summary of Safety

- There were no deaths reported during the study or the 30-day follow-up period.
- There were 3 SAEs in the entire study, all reported in 1 patient of the BAF312 2 mg/2 mg treatment sequence during Period 1. The SAEs were suspected to be related to study treatment, while other factors including medical history and concomitant medication could also contributed. The patient permanently discontinued from study treatment due to the SAEs. Another patient in the placebo group permanently discontinued from study treatment due to a moderate AE that was suspected to be related to study treatment.
- There were no apparent difference between treatments in the incidence of AEs during Period 1 and Period 2.
- Majority of the AEs were mild to moderate in severity.
- Treatment-related decreases in ALC and increases in GGT were observed in patients receiving BAF312 2 mg throughout the study and also in patients who switched from placebo to BAF312 2 mg. One patient in the placebo/ 2 mg treatment sequence experienced a mild AE of GGT increased during Period 2 after being switched to BAF312 2 mg that was suspected to be related study treatment.

Safety Results

Serious Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment

	Period 1 BAF312 2mg N = 7	Period 1 BAF312 10mg N = 2	Period 1 Placebo N = 5	Period 2 BAF312 2mg/ BAF312 2mg N = 6	Period 2 Placebo/ BAF312 2mg N = 3
Total participants affected	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Blood and lymphatic system disorders					
Haemolytic anaemia	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Haemolytic uraemic syndrome	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Renal and urinary disorders					
Acute kidney injury	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)

Other Adverse Events by System Organ Class

Time Frame	Adverse Events (AEs) are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All AEs reported in this record are from date of First Patient First Treatment until Last Patient Last Visit.
Source Vocabulary for Table Default	MedDRA (19.0)
Assessment Type for Table Default	Systematic Assessment
Frequent Event Reporting Threshold	0%

Period 1 BAF312 2mg	Period 1 BAF312 10mg	Period 1 Placebo N = 5	Period 2 BAF312 2mg/	Period 2 Placebo/ BAF312

	N = 7	N = 2		BAF312 2mg N = 6	2mg N = 3
Total participants affected	6 (85.71%)	2 (100.00%)	4 (80.00%)	4 (66.67%)	2 (66.67%)
Cardiac disorders					
Palpitations	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Eye disorders					
Cataract	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Eye pain	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Ocular hyperaemia	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Vitreous detachment	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Gastrointestinal disorders					
Abdominal pain upper	1 (14.29%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Diarrhoea	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Nausea	1 (14.29%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Vomiting	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
General disorders and administration site conditions					
Asthenia	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Chest discomfort	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Fatigue	0 (0.00%)	0 (0.00%)	1 (20.00%)	1 (16.67%)	0 (0.00%)
Feeling cold	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pyrexia	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Hepatobiliary disorders					

Cholelithiasis	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Infections and infestations					
Nasopharyngitis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Upper respiratory tract infection	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	1 (33.33%)
Urinary tract infection	0 (0.00%)	1 (50.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Injury, poisoning and procedural complications					
Epicondylitis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Investigations					
Carbon monoxide diffusing capacity decreased	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Cardiac murmur	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Gamma-glutamyltransferase increased	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Musculoskeletal and connective tissue disorders					
Back pain	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Musculoskeletal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Myalgia	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Pain in extremity	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Polymyositis	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (33.33%)
Spinal pain	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)
Nervous system disorders					

Cerebral artery stenosis	0 (0.00%)	0 (0.00%)	1 (20.00%)	0 (0.00%)	0 (0.00%)
Dizziness	0 (0.00%)	1 (50.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)
Headache	2 (28.57%)	0 (0.00%)	2 (40.00%)	0 (0.00%)	0 (0.00%)
Psychiatric disorders					
Depression	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Reproductive system and breast disorders					
Benign prostatic hyperplasia	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Respiratory, thoracic and mediastinal disorders					
Rhinorrhoea	1 (14.29%)	0 (0.00%)	0 (0.00%)	0 (0.00%)	0 (0.00%)
Skin and subcutaneous tissue disorders					
Papule	0 (0.00%)	0 (0.00%)	0 (0.00%)	1 (16.67%)	0 (0.00%)

Other Relevant Findings

Not applicable

Conclusion:

This study was prematurely terminated and the efficacy results are inconclusive due to small sample sizes. Safety signals of the study may indicate a potential risk for kidney injury and an isolated increase of GGT without any other hints for liver damage and a potential risk for abnormal macula findings in the eye. Besides the expected ALC decreases, no other

hematologic findings were noted. There was no discernable risk for any cardiac or pulmonary injury in this small study. A potential effect on signs and symptoms of polymyositis cannot be claimed with acceptable certainty from this study.

Date of Clinical Trial Report

04-May-2017