Sponsor

Novartis

Generic Drug Name

BYM338

Therapeutic Area of Trial

Sporadic Inclusion Body Myositis

Approved Indication

Investigational

Protocol Number

CBYM338X2205

Title

A double-blind, placebo-controlled study to evaluate the safety, tolerability, pharmacokinetics, pharmacodynamics and preliminary efficacy of BYM338 in patients with sporadic Inclusion Body Myositis

Study Phase

Phase II

Study Start/End Dates

09 Aug 2011 to 08 Nov 2012

Study Design/Methodology

A double-blind, placebo-controlled preliminary efficacy assessment of single dose i.v. BYM338 in patients with sporadic inclusion body myositis (sIBM) followed by 24 weeks follow-up period. This was an exploratory proof-of-concept study to demonstrate the safety and pharmacodynamics effect of BYM338 in patients with sIBM

Centers

3 centers in 1 country: USA

Publication

None

Test Product, Doses, and Mode of Administration

BYM338 30mg/kg administered i.v.

Statistical Methods

Efficacy: T-tests of % TMV change from baseline to week 8, week 16, and week 24 were conducted at final analysis. The TMV data were log transformed and analyzed by analysis of covariance including baseline TMV as a covariate. The contrast between placebo and BYM338 was estimated and reported on the original scale. The same analysis was done at interim and final analysis.

As additional analysis, the change in thigh muscle volume from baseline at week 8 was also evaluated in terms of the ratio of follow-up to baseline values (denoted here as E_{max}). The analysis consisted in calculating posterior probabilities as follows:

- Probability{log(E_{max}BYM338) – log(Emax Placebo) > log(1.05) | data} > 50%
- Probability{log(E_{max} BYM338) – log(Emax Placebo) > log(1) | data} > 95%,

The minimum significant difference of 5% chance from baseline (1.05 on the ratio scale) drives the first criterion; while the second criterion is based on targeting a non-null difference between treatments.

Timed up and go test results were summarized by treatment and listed by subject. Change from baseline was summarized and graphically displayed. A similar analysis of covariance for TUG together with least squared estimates of the treatment effect was conducted.

Change from baseline in LBM (as assessed by DXA) was evaluated in the PD population. The change was expressed as % change from baseline in the active and placebo treatment groups. The same t-tests used for the primary endpoint were carried out also for the LBM change.

Change from baseline in IMAT (intra-muscular) and SC (sub-cutaneous) adipose tissue volume was evaluated in the PD analysis set. The change was expressed as % change from the baseline in the active and placebo treatment groups.

All physical functioning endpoints (isometric quantitative and manual muscle testing, hand-grip, pinch-grip, 6-minute walking distance) were summarized by treatment and listed by subject. Questionnaire data were reported by treatment and listed by subject.

Safety: For adverse events (any AEs and SAEs) a graph presenting the incidence of AEs (SOC and PT) by treatment groups, and the odds ratios and 95% confidence interval (when >1 in favor of placebo) were provided.

Pharmacokinetics: The following pharmacokinetic parameters was determined for all cohorts, if data allowed: Cmax, Tmax, AUClast, AUCinf and T1/2

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion Criteria:

- Male and female patients age 40 to 80 years of age (inclusive), diagnosed with definite sIBM by the European Neuromuscular Center (ENMC) diagnostic criteria.

Exclusion Criteria:

- Unable to walk at least 3 meters without assistance from another person. Assistance in rising from a chair was acceptable, and so was use of assistive devices, such as canes or walkers.
- Swallowing difficulty or other reason that precluded adequate intake of energy and protein, defined as at least 20 kcal/kg/day and 0.6 g protein/kg/day as determined by a registered dietician.

- Use of oral beta agonists, oral corticosteroids, androgens or androgen inhibitors (including LHRH agonists), or intravenous gamma globulin (IVIG) within the previous 6 months. Short-term corticosteroids for unrelated indications, defined as < 20 mg/d for < 30 days and ending at least 60 days prior to screening, were acceptable.
- Patients with known claustrophobia, presence of pacemaker and/or ferromagnetic material in their body that would preclude MRI assessments.

Participant Flow

	Total (BYM338) N=14 n (%)
Patients	
Completed	14 (100.0)
Discontinued core study	0 (0.0)
Discontinued follow-up period	2 (14.3.)
Main cause of discontinuation	
Did not take part in follow-up	2 (14.3)

N= Total number of patients; n= no. of patients

Baseline Characteristics

		30 mg/kg BYM338 N=11	**Placebo N=3**	**Total N=14**
Age (years)	Mean (SD)	67.4 (9.04)	68.0 (14.00)	67.5 (9.65)
	Median	68.0	74.0	69.0
	Range	45 - 77	52 - 78	45 - 78
Gender - n(%)	Male	7 (64%)	1 (33%)	8 (57%)
	Female	4 (36%)	2 (67%)	6 (43%)
Predominant race - n(%)	Caucasian	10 (91%)	3 (100%)	13 (93%)
	Other	1 (9%)		1 (7%)
Ethnicity - n(%)	Other	10 (91%)	3 (100%)	13 (93%)
	Mixed Ethnicity	1 (9%)		1 (7%)
Height (cm)	Mean (SD)	169 (13.2)	174 (13.1)	170 (12.8)
	Median	172	180	172
	Range	150 - 192	159 - 183	150 - 192
Weight (kg)	Mean (SD)	79.0 (19.5)	95.1 (10.2)	82.4 (18.9)
	Median	82.6	98.4	83.9
	Range	47.4 - 115	83.6 - 103	47.4 - 115
BMI (kg/m2)	Mean (SD)	27.4 (5.77)	31.4 (1.49)	28.3 (5.37)
	Median	26.2	30.8	28.8
	Range	18.8 - 36.3	30.3 - 33.1	18.8 - 36.3

Outcome measures

Primary Outcome Measures:

- To evaluate the preliminary efficacy of BYM338 on thigh muscle volume by MRI in terms of change from baseline.
- To evaluate the safety and tolerability of BYM338 when administered as single or multiple intravenous (i.v.) infusion(s) to patients with sporadic inclusion body myositis (sIBM)

Secondary Outcome Measures:

- To assess the effect of BYM338 on muscle function by "timed up and go" test in terms of change from baseline.
- To evaluate the effect of BYM338 on total lean body mass by DXA in patients with sIBM in terms of change from baseline.

Primary Outcome Results

Safety and Tolerability:

See the safety results section

Efficacy on thigh muscle volume:

Total thigh muscle volume – % change from baseline (Right leg)

		% change from Baseline (cm^3) W8	% change from Baseline (cm^3) W16	% change from Baseline (cm^3) W24
30 mg/kg BYM338	N	11	9	9
	Mean (SD)	6.67 (3.87)	2.70 (4.42)	-1.46 (3.23)
	Median	5.75	3.52	-2.32
	(min/max)	2.04 - 13.5	-5.63 - 8.30	-5.38 - 4.02
Placebo	N	3	1	1
	Mean (SD)	0.326 (3.98)	-6.40	-9.20
	Median	0.165	-6.40	-9.20
	(min/max)	-3.57 - 4.39	-6.40 - -6.40	-9.20 - -9.20

Total thigh muscle volume – % change from baseline (Left leg)

		% change from Baseline (cm^3) W8	% change from Baseline (cm^3) W16	% change from Baseline (cm^3) W24
30 mg/kg BYM338	N	11	1	1
	Mean (SD)	5.20 (2.47)	1.68	1.27
	Median	5.64	1.68	1.27
	(min/max)	1.26 - 9.35	1.68 - 1.68	1.27 - 1.27

		% change from Baseline (cm^3) W8	% change from Baseline (cm^3) W16	% change from Baseline (cm^3) W24
Placebo	N	3	1	1
	Mean (SD)	-2.10 (6.54)	-3.49	-3.33
	Median	-4.19	-3.49	-3.33
	(min/max)	-7.34 - 5.23	-3.49 - -3.49	-3.33 - -3.33

Secondary Outcome Results

Timed up and go:

Percent change from baseline in timed up and go

Treatment	Statistic	Week 4 (sec)	Week 6 (sec)	Week 8 (sec)	Week 12 (sec)	Week 16 (sec)	Week 24 (sec)
30 mg/kg BYM338	N	10	10	10	6	9	9
	Mean (SD)	-0.13 (6.827)	-5.00 (6.839)	-7.75 (7.081)	-12.98 (7.166)	-12.80 (9.655)	-9.37 (9.598)
	Median	0.7	-6.6	-6.6	-10.7	-12.6	-12.1
	Min-Max	-9.8 - 10.6	-11.9 - 8.9	-18.9 - 2.0	-24.9 - -6.7	-33.3 - 0.6	-25.4 - 4.3
Placebo	N	3	3	3	0	2	2
	Mean (SD)	-10.18 (12.924)	-17.76 (6.927)	-9.83 (6.342)		-9.63 (11.138)	-7.24 (13.965)
	Median	-13.7	-15.7	-9.3		-9.6	-7.2
	Min-Max	-21.0 - 4.1	-25.5 - -12.1	-16.4 - -3.8		-17.5 - -1.8	-17.1 - 2.6

Change in lean body mass:

Percent change from baseline in LBM as assessed by DXA

Treatment	Statistic	Week 8 (%)	Week 12 (%)	Week 16 (%)	Week 24 (%)
30 mg/kg BYM338	n	11	7	10	10
	Mean (SD)	4.74 (3.305)	4.89 (4.709)	2.96 (3.557)	1.47 (1.873)
	Median	5	5.5	3.1	1.8
	(min/max)	0.2-10.8	-3.1 - 12.4	-2.9 - 7.1	-2.4 - 4.8
Placebo	n	3	0	2	2
	Mean (SD)	-1.60 (3.834)		-1.73 (4.330)	1.03 (3.806)
	Median	-1.4		-1.7	1
	(min/max)	-5.5 - 2.1		-4.8 - 1.3	-1.7 - 3.7

Safety Results

Adverse events by system organ classes - n (%) of subjects (all patients)

Body system	Preferred Term	30 mg/kg BYM338 N=11 n (%)	Placebo N=3 n (%)	Total N=14 n (%)
Any Body System		10 (90.9%)	3 (100.0%)	13 (92.9%)
Eye disorders	TOTAL	1 (9.1%)		1 (7.1%)
	Vision blurred	1 (9.1%)		1 (7.1%)
Gastrointestinal disorders	TOTAL	4 (36.4%)	2 (66.7%)	6 (42.9%)
	Aphthous stomatitis		1 (33.3%)	1 (7.1%)
	Diarrhoea	3 (27.3%)		3 (21.4%)
	Dry mouth	1 (9.1%)		1 (7.1%)
	Nausea	1 (9.1%)	1 (33.3%)	2 (14.3%)
General disorders and administration site conditions	TOTAL	1 (9.1%)		1 (7.1%)
	Influenza like illness	1 (9.1%)		1 (7.1%)
Infections and infestations	TOTAL	5 (45.5%)		5 (35.7%)
	Gastroenteritis	1 (9.1%)		1 (7.1%)
	Herpes zoster	1 (9.1%)		1 (7.1%)
	Pharyngitis streptococcal	1 (9.1%)		1 (7.1%)
	Subcutaneous abscess	1 (9.1%)		1 (7.1%)
	Urinary tract infection	2 (18.2%)		2 (14.3%)
Injury, poisoning and procedural complications	TOTAL		1 (33.3%)	1 (7.1%)
	Fall		1 (33.3%)	1 (7.1%)
Musculoskeletal and connective tissue disorders	TOTAL	7 (63.6%)		7 (50.0%)
	Arthralgia	2 (18.2%)		2 (14.3%)
	Muscle spasms	6 (54.5%)		6 (42.9%)
	Muscular weakness	1 (9.1%)		1 (7.1%)
	Myalgia	1 (9.1%)		1 (7.1%)
Nervous system disorders	TOTAL	1 (9.1%)		1 (7.1%)
	Dysgeusia	1 (9.1%)		1 (7.1%)
Skin and subcutaneous tissue disorders	TOTAL	3 (27.3%)		3 (21.4%)
	Acne	3 (27.3%)		3 (21.4%)

Incidence of AEs by preferred term (all patients)

	30 mg/kg BYM338 N=11 n (%)	Placebo N=3 n (%)	Total N=14 n (%)
Subjects with AE(s)	10 (90.9%)	3 (100.0%)	13 (92.9%)
Muscle spasms	6 (54.5%)	0	6 (42.9%)
Diarrhoea	3 (27.3%)	0	3 (21.4%)
Acne	3 (27.3%)	0	3 (21.4%)
Urinary tract infection	2 (18.2%)	0	2 (14.3%)
Nausea	1 (9.1%)	1 (33.3%)	2 (14.3%)
Arthralgia	2 (18.2%)	0	2 (14.3%)
Vision blurred	1 (9.1%)	0	1 (7.1%)
Subcutaneous abscess	1 (9.1%)	0	1 (7.1%)
Pharyngitis streptococcal	1 (9.1%)	0	1 (7.1%)
Myalgia	1 (9.1%)	0	1 (7.1%)
Muscular weakness	1 (9.1%)	0	1 (7.1%)
Influenza like illness	1 (9.1%)	0	1 (7.1%)
Herpes zoster	1 (9.1%)	0	1 (7.1%)
Gastroenteritis	1 (9.1%)	0	1 (7.1%)
Fall	0	1 (33.3%)	1 (7.1%)
Dysgeusia	1 (9.1%)	0	1 (7.1%)
Dry mouth	1 (9.1%)	0	1 (7.1%)
Aphthous stomatitis	0	1 (33.3%)	1 (7.1%)

Other Relevant Findings

None

Date of Clinical Trial Report

23 Oct 2013

Date Inclusion on Novartis Clinical Trial Results Database

7 November 2013

Date of Latest Update