Full Novartis Clinical Trials Result

Sponsor

Novartis

Generic Drug Name

BYM338 (Bimagrumab)

Trial Indication(s)

Proof of concept study in sarcopenic adults with mobility limitations

Protocol Number

CBYM338X2201

Protocol Title

A randomized, double-blind, placebo-controlled multi-center study to assess the effects of BYM338 on skeletal muscle in sarcopenic adults with mobility limitations.

Clinical Trial Phase

Phase IIA

Phase of Drug Development

Phase II

Study Start/End Dates

Study initiation date: 31-Jan-2012

Study completion date: 10-Dec-2013

Reason for Termination (If applicable)

N/A

Study Design/Methodology

This was a randomized, double-blind, placebo-controlled, multi-center study to assess the effects of BYM338 on skeletal muscle in sarcopenic adults with mobility limitations.

Centers

USA (five centers)

Publication

None

Objectives:

Primary objectives:
-Characterize the pharmacodynamic (PD) effect of BYM338 administered as i.v. infusions on muscle volume of the thigh (assessed by MRI) in sarcopenic adults with mobility limitations as compared to placebo.
-Evaluate the effect of BYM338 on gait speed in these older patients.
Secondary objectives:
-Assess the safety and tolerability of BYM338 administered as i.v. infusions to older adults with sarcopenia.
-Determine the pharmacokinetic (PK) profile of infusions of BYM338 in the older population with low muscle mass.

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

30mg/kg i.v. infusion of 150mg Liquid in vial BYM338

Statistical Methods

The primary objective was to assess the preliminary efficacy of one or two i.v. doses of BYM338 to increase mid-thigh muscle volume and gait speed compared to placebo.
The primary endpoints were change in TMV by MRI from baseline in patients receiving BYM338 compared to placebo at 8 weeks (for the interim analysis) and gait speed at 16 weeks post-first dose in terms of ratio post-baseline to baseline. Primary endpoints were also assessed at 2 (only for muscle mass increase), 4 and 20 (only for gait speed) and 24 weeks, to document any decline in both outcomes beyond week 16. The choice of the 8 week time-point was driven by the assumption that a measurable post-dose effect of BYM338 on TMV was likely to be observed at that time, while 16 weeks were necessary to achieve a clinically significant effect on gait speed.
In order to compare the BYM338 group versus the Placebo group, an analysis of covariance model was performed on the log scale for the muscle mass assessed by MRI. Values were back transformed with exponential transformation to estimate the LS means of ratio to baseline. The analysis of covariance models included the treatment and the baseline (log transformed). P values were provided for the ratio to baseline at each time point and for the comparison between the BYM338 group and the placebo group. For each time point, values were considered independently. Least square means for each treatment group was calculated with the corresponding 90% confidence intervals, as well as differences vs. placebo.
For the gait speed, the same model was applied on the absolute change from baseline, with the treatment and the baseline as covariates. No back transformation was needed. The same results as with the model on the log scale for muscle mass assessed by MRI were provided. For gait speed, the same model was also applied on the values stratified by score at baseline: high value at baseline (>= 0.8 m/s) and low value at baseline (<0.8 m/s).
The same analysis of covariance used to describe the muscle volume by MRI was also performed on parameters assessed by DXA (lean body mass), grip strength, stair climbing, 1-RM leg press and physical activity monitoring (ActivPAL).
For the 6 minute walk test, the same model used for gait speed (on the absolute change from baseline) was performed. A stratified analysis was also performed according to the baseline value: High value (>=300 m) and Low value (<300m).
Descriptive statistics of PK parameters included mean, SD, and CV, min and max. When a geometric mean was presented it was stated as such. Since Tmax is generally evaluated by a nonparametric method, median values and ranges were given for this parameter.
No exploratory analyses to investigate the relationship between exposure and primary PD endpoints were carried out.

Study Population: Key Inclusion/Exclusion Criteria

Diagnosis and main criteria for inclusion

Key criteria to qualify for this study include:

1. Men and women aged 65 or older with difficulty standing up from a chair or walking for longer than 10 minutes on a flat surface or climbing a flight of stairs.
2. A gait speed over 4 meters of <1.0 m/s but ≥0.4 m/s.
3. Appendicular skeletal muscle index (skeletal muscle in kg/height in m2) by DXA of ≤ 7.25 kg/m2 for men and ≤ 5.67 kg/m2 for women.
4. Patients had to weigh between 40 and 120 kg and have a body mass index (BMI) within the range of 18-32 kg/m2.

Exclusion criteria:

1. Use of other investigational drugs at the time of enrollment, or within 30 days or 5 half-lives of enrollment, whichever was longer; or longer if required by local regulations, and for any other limitation of participation in an investigational trial based on local regulations.
2. History of hypersensitivity to antibody therapy.
3. A history of clinically significant ECG abnormalities, which, in the opinion of the investigator, might indicate active cardiac disease.
4. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there was evidence of local recurrence or metastases.
5. Diseases other than cancer known to cause cachexia or muscle atrophy, including but was not limited to congestive heart failure, COPD, chronic kidney disease (estimated GFR < 30 mL/min using the MDRD equation), rheumatoid arthritis, primary myopathy, stroke, HIV infection, tuberculosis or other chronic infection, uncontrolled diabetes mellitus, etc.
6. Diseases known to cause malabsorption of protein or energy, including inflammatory bowel disease, celiac disease, short bowel syndrome, pancreatic insufficiency, etc.
7. Liver disease or liver injury as indicated by abnormal liver function tests such as SGOT (AST), SGPT (ALT), γ-GT, alkaline phosphatase, or serum bilirubin (except Gilbert's Disease). The

Investigator was guided by the following criteria:

- Any single transaminase listed above was not to exceed 3x upper limit of normal (ULN).
- If the total bilirubin concentration was increased above 1.5 x ULN, total bilirubin was required to be differentiated into the direct and indirect reacting bilirubin. In any case, serum bilirubin was not to exceed the value of 1.6 mg/dL (27 µmol/L).

8. Use of any prescription drugs known to affect muscle mass, including androgen supplements, anti-androgens (such as LHRH agonists), recombinant human growth hormone (rhGH), insulin, oral beta agonists, megestrol acetate, dronabinol, etc.
9. Donation or loss of 400 ml or more of blood within eight weeks prior to initial dosing, or longer if required by local regulation.
10. Plasma donation (> 250 ml) within 14 days prior to first dosing.
11. Hemoglobin levels below 11.0 g/dL at screening.
12. Significant illness within two weeks prior to dosing.
13. Recent (within the last three years) and/or recurrent history of autonomic dysfunction (e.g., recurrent episodes of fainting, palpitations, etc.).
14. Patients with known claustrophobia, presence of pacemaker and/or ferromagnetic material in their body that would prohibit administration of MRI assessments
15. Patient smokes more than one cigarette, pipe or cigar a month

Participant Flow Table

Subject disposition – n (percent) of patients (All patients)

	30 mg/kg BYM338 N=19	Placebo N=21	Total N=40
Patients			
Completed	15 (78.9%)	17 (81.0%)	32 (80.0%)
Discontinued	3 (15.8%)	2 (9.5%)	5 (12.5%)
Withdrew due to Adverse Event(s)	1 (5.3%)		1 (2.5%)
Lost to follow-up	1 (5.3%)		1 (2.5%)
Subject withdrew consent	1 (5.3%)	2 (9.5%)	3 (7.5%)
Missing *EOS visit data	1 (5.3%)	2 (9.5%)	3 (7.5%)

* Three patients (BYM338: 1003/5104; Placebo: 1002/5141 and 1003/5109) are missing study completion data

Baseline Characteristics

Demographic summary (Safety analysis set)

		30 mg/kg BYM338 N=19	Placebo N=21	Total N=40
Age (years)	Mean (SD)	71.6 (6.34)	72.4 (4.62)	72.0 (5.45)
	Median	69.0	73.0	73.0
	Range	65 – 86	65 - 83	65 - 86
Gender - n(%)	Male	13 (68%)	8 (38%)	21 (53%)
	Female	6 (32%)	13 (62%)	19 (48%)
Predominant race - n(%)	Caucasian	18 (95%)	21 (100%)	39 (98%)
	Black	1 (5%)		1 (3%)
Ethnicity - n(%)	Hispanic/Latino	15 (79%)	13 (62%)	28 (70%)
	Other	4 (21%)	8 (38%)	12 (30%)
Height (cm)	Mean (SD)	166.5 (9.3)	165.2 (8.7)	165.8 (8.9)
	Median	167.6	163.0	164.5
	Range	144.0 - 182.0	152.0 - 185.0	144.0 - 185.0
Weight (kg)	Mean (SD)	69.0 (10.8)	71.4 (10.3)	70.3 (10.5)
	Median	70.9	68.2	69.6
	Range	47.7 - 91.4	55.1 - 100.0	47.7 - 100.0
BMI (kg/m^2)	Mean (SD)	24.9 (3.7)	26.2 (3.5)	25.6 (3.6)
	Median	25.2	25.8	25.7
	Range	18.0 - 30.9	19.1 - 32.0	18.0 - 32.0

Summary of Efficacy

Primary Outcome Result(s)

Total thigh muscle volume - Percentage change from baseline (PD analysis set)

Treatment	Statistic	% change from Baseline (%) W4D29	% change from Baseline (%) W8D57	% change from Baseline (%) W16D113	% change from Baseline (%) EOS
30 mg/kg BYM338	n	17	17	16	14
	Mean (SD)	6.1 (2.6)	8.0 (3.7)	7.7 (5.3)	4.8 (5.8)
	CV% mean	41.9	46.2	68.8	121.1
	Median	5.9	8.3	7.7	4.5
	Min-max	2.1 - 10.8	0.73 - 15.7	0.015 - 17.6	-3.9 - 15.0
Placebo	n	19	18	17	16
	Mean (SD)	0.16 (3.4)	0.35 (3.3)	0.42 (5.1)	-1.01 (4.4)
	CV% mean	2151.1	955.7	1224.4	-437.3
	Median	0.54	1.11	1.21	-0.05
	Min-max	-9.39 - 5.93	-10.2 - 5.9	-16.3 - 6.7	-15.9 - 2.8

CV% = coefficient of variation (%)=sd/mean*100;
Baseline is Day -1 value

ANCOVA results on gait speed abs change (m/s) from baseline - stratified by baseline score - Pharmacodynamic analysis set

Status at Baseline	Visit	Treatment/ contrast	Number of patients	P value	Estimate	90% CI	
						Lower	Upper
High Value at Baseline (>=0.8 m/s)	W2D15	30mg/kg BYM338	10		0.05	-0.04	0.13
		Placebo	12		-0.00	-0.07	0.07
		Difference 30mg/kg BYM338 vs Placebo		0.501	0.05	-0.07	0.16
	W4D29	30 mg/kg BYM338	9		0.06	0.01	0.12
		Placebo	12		0.03	-0.02	0.07
		Difference 30mg/kg BYM338 vs Placebo		0.442	0.03	-0.04	0.11
	W6D43	30 mg/kg BYM338	9		0.10	0.02	0.19
		Placebo	12		0.03	-0.04	0.10
		Difference 30mg/kg BYM338 vs Placebo		0.304	0.07	-0.05	0.19
	W8D57	30 mg/kg BYM338	9		0.13	0.05	0.20
		Placebo	12		0.06	-0.01	0.12
		Difference 30mg/kg BYM338 vs Placebo		0.232	0.07	-0.03	0.17
	W10D71	30 mg/kg BYM338	9		0.15	0.08	0.22
		Placebo	12		0.07	0.01	0.13
		Difference 30mg/kg BYM338 vs Placebo		0.194	0.08	-0.02	0.18
	W12D85	30 mg/kg BYM338	9		0.12	0.02	0.22
		Placebo	12		0.10	0.02	0.22
		Difference 30mg/kg BYM338 vs Placebo		0.851	0.02	-0.12	0.15
	W16D113	30 mg/kg BYM338	8		0.11	0.01	0.22
		Placebo	11		0.09	0.00	0.18
		Difference 30mg/kg BYM338 vs Placebo		0.786	0.02	-0.12	0.16

Status at Baseline	Visit	Treatment/ contrast	Number of patients	P value	Estimate	90% CI	
						Lower	Upper
	W20D141	30 mg/kg BYM338	9		0.19	0.11	0.27
		Placebo	11		0.14	0.07	0.22
		Difference 30mg/kg BYM338 vs Placebo		0.449	0.05	-0.06	0.17
	EOS	30 mg/kg BYM338	9		0.17	0.08	0.26
		Placebo	11		0.11	0.03	0.19
		Difference 30mg/kg BYM338 vs Placebo		0.401	0.06	-0.06	0.19
Low Value at Baseline (<0.8 m/s)	W2D15	30 mg/kg BYM338	8		0.23	0.10	0.35
		Placebo	8		0.28	0.15	0.41
		Difference 30mg/kg BYM338 vs Placebo		0.599	-0.05	-0.23	0.12
	W4D29	30 mg/kg BYM338	9		0.29	0.18	0.40
		Placebo	8		0.21	0.09	0.33
		Difference 30mg/kg BYM338 vs Placebo		0.389	0.08	-0.08	0.25
	W6D43	30 mg/kg BYM338	9		0.29	0.15	0.43
		Placebo	8		0.27	0.12	0.41
		Difference 30mg/kg BYM338 vs Placebo		0.853	0.02	-0.18	0.22
	W8D57	30 mg/kg BYM338	8		0.36	0.27	0.46
		Placebo	8		0.38	0.28	0.47
		Difference 30mg/kg BYM338 vs Placebo		0.824	-0.02	-0.15	0.12
	W10D71	30 mg/kg BYM338	8		0.43	0.35	0.51
		Placebo	7		0.36	0.28	0.45
		Difference 30mg/kg BYM338 vs Placebo		0.328	0.07	-0.05	0.19
	W12D85	30 mg/kg BYM338	8		0.34	0.24	0.43
		Placebo	7		0.30	0.20	0.41
		Difference 30mg/kg BYM338 vs		0.686	0.03	-0.11	0.18

Status at Baseline	Visit	Treatment/ contrast	Number of patients	P value	Estimate	90% CI	
						Lower	Upper
		Placebo					
	W16D113	30 mg/kg BYM338	8		0.50	0.44	0.56
		Placebo	7		0.35	0.28	0.41
		Difference 30mg/kg BYM338 vs Placebo		0.009	0.15	0.06	0.24
	W20D141	30 mg/kg BYM338	8		0.51	0.39	0.64
		Placebo	7		0.40	0.27	0.54
		Difference 30mg/kg BYM338 vs Placebo		0.310	0.11	-0.08	0.30
	EOS	30 mg/kg BYM338	7		0.42	0.30	0.55
		Placebo	7		0.37	0.25	0.49
		Difference 30mg/kg BYM338 vs Placebo		0.604	0.05	-0.12	0.23

CI: Confidence Interval
Model: Change from baseline=Treatment + Baseline
Baseline: Last value before first treatment dose (Screening or Day -1).

Secondary Outcome Result(s)

Summary statistics for PK parameters (Pharmacokinetic analysis set)

Dose	Statistic	Cmax (µg/mL)	Tmax (hr)	AUC0-56 (day*µg/mL)	AUClast (day*µg/mL)
1	n	19	19	16	7
	Mean (SD)	707 (118)		6060 (1100)	6550 (870)
	CV% mean	16.8		18.2	13.3
	Geo-mean	697		5970	6500
	CV% geo-mean	17.1		18.3	13.2
	Median	702	2.57	5970	6610
	(min/max)	530 - 903	1.83 - 6.28	3840 - 8940	5500 – 7820
2	n	9	9	9	9
	Mean (SD)	808 (162)		9130 (1770)	9690 (2110)
	CV% mean	20.0		19.4	21.8
	Geo-mean	794		8990	9500
	CV% geo-mean	20.3		19.0	20.8
	Median	812	2.15	9150	9590
	(min/max)	595 - 1060	2.08 - 2.32	6550 - 12900	6870 – 14400

CV% = coefficient of variation (%)=sd/mean*100;
CV% geo-mean=(sqrt (exp. (variance for log transformed data)-1))*100

Summary of Safety

Safety Results

Adverse events overall and frequently affected system organ classes - n (percent) of patients (Safety analysis set)

	30mg/kg BYM338 N=19 n (%)	Placebo N=21 n (%)	Total N=40 n (%)
Patients with AE(s)	**16 (84.2%)**	**12 (57.1%)**	**28 (70.0%)**
Musculoskeletal and connective tissue disorders	13 (68.4%)	8 (38.1%)	21 (52.5%)
Nervous system disorders	4 (21.1%)	4 (19.0%)	8 (20.0%)
Gastrointestinal disorders	6 (31.6%)	2 (9.5%)	8 (20.0%)
Infections and infestations	5 (26.3%)	2 (9.5%)	7 (17.5%)
Skin and subcutaneous tissue disorders	3 (15.8%)	2 (9.5%)	5 (12.5%)
Investigations	2 (10.5%)	2 (9.5%)	4 (10.0%)
Respiratory, thoracic and mediastinal disorders	1 (5.3%)	1 (4.8%)	2 (5.0%)
General disorders and administration site conditions	1 (5.3%)	1 (4.8%)	2 (5.0%)
Vascular disorders	1 (5.3%)	0	1 (2.5%)
Reproductive system and breast disorders	0	1 (4.8%)	1 (2.5%)
Injury, poisoning and procedural complications	0	1 (4.8%)	1 (2.5%)
Immune system disorders	1 (5.3%)	0	1 (2.5%)
Ear and labyrinth disorders	0	1 (4.8%)	1 (2.5%)
Cardiac disorders	1 (5.3%)	0	1 (2.5%)
Blood and lymphatic system disorders	1 (5.3%)	0	1 (2.5%)

Adverse events - n (percent) of patients (all patients) – Safety analysis set

	30 mg/kg BYM338 N=19 n (%)	Placebo N=21 n (%)	Total N=40 n (%)
Patients with AE(s)	**16 (84.2%)**	**12 (57.1%)**	**28 (70.0%)**
Muscle spasms	9 (47.4%)	4 (19.0%)	13 (32.5%)
Muscle twitching	3 (15.8%)	1 (4.8%)	4 (10.0%)
Limb discomfort	2 (10.5%)	2 (9.5%)	4 (10.0%)
Diarrhoea	4 (21.1%)	0	4 (10.0%)
Pain in extremity	1 (5.3%)	2 (9.5%)	3 (7.5%)
Vomiting	2 (10.5%)	0	2 (5.0%)
Skin exfoliation	0	2 (9.5%)	2 (5.0%)
Paraesthesia	1 (5.3%)	1 (4.8%)	2 (5.0%)
Myalgia	0	2 (9.5%)	2 (5.0%)
Muscle tightness	1 (5.3%)	1 (4.8%)	2 (5.0%)
Hypoaesthesia	1 (5.3%)	1 (4.8%)	2 (5.0%)
Headache	1 (5.3%)	1 (4.8%)	2 (5.0%)
Blood pressure increased	1 (5.3%)	1 (4.8%)	2 (5.0%)
Blood creatine phosphokinase increased	1 (5.3%)	1 (4.8%)	2 (5.0%)
Back pain	1 (5.3%)	1 (4.8%)	2 (5.0%)
Acne	2 (10.5%)	0	2 (5.0%)
Vertigo	0	1 (4.8%)	1 (2.5%)
Urinary tract infection	0	1 (4.8%)	1 (2.5%)
Upper respiratory tract infection	0	1 (4.8%)	1 (2.5%)
Tooth loss	1 (5.3%)	0	1 (2.5%)
Soft tissue injury	0	1 (4.8%)	1 (2.5%)
Soft tissue disorder	0	1 (4.8%)	1 (2.5%)
Skin fissures	0	1 (4.8%)	1 (2.5%)
Sinus arrhythmia	1 (5.3%)	0	1 (2.5%)
Rhinitis allergic	1 (5.3%)	0	1 (2.5%)
Respiratory tract infection	1 (5.3%)	0	1 (2.5%)
Rash pustular	1 (5.3%)	0	1 (2.5%)

	30 mg/kg BYM338 N=19 n (%)	Placebo N=21 n (%)	Total N=40 n (%)
Pruritus	0	1 (4.8%)	1 (2.5%)
Perineal abscess	1 (5.3%)	0	1 (2.5%)
Papule	1 (5.3%)	0	1 (2.5%)
Neck pain	1 (5.3%)	0	1 (2.5%)
Nausea	1 (5.3%)	0	1 (2.5%)
Nasal congestion	0	1 (4.8%)	1 (2.5%)
Musculoskeletal discomfort	0	1 (4.8%)	1 (2.5%)
Musculoskeletal chest pain	1 (5.3%)	0	1 (2.5%)
Muscular weakness	1 (5.3%)	0	1 (2.5%)
Muscle fatigue	0	1 (4.8%)	1 (2.5%)
Malaise	1 (5.3%)	0	1 (2.5%)
Intracranial venous sinus thrombosis	1 (5.3%)	0	1 (2.5%)
Infusion site reaction	0	1 (4.8%)	1 (2.5%)
Hypertension	1 (5.3%)	0	1 (2.5%)
Herpes zoster	1 (5.3%)	0	1 (2.5%)
Hair growth abnormal	1 (5.3%)	0	1 (2.5%)
Gingival inflammation	0	1 (4.8%)	1 (2.5%)
Gastro esophageal reflux disease	1 (5.3%)	0	1 (2.5%)
Fibrocystic breast disease	0	1 (4.8%)	1 (2.5%)
Fall	0	1 (4.8%)	1 (2.5%)
Erythema	0	1 (4.8%)	1 (2.5%)
Drug hypersensitivity	1 (5.3%)	0	1 (2.5%)
Dizziness	0	1 (4.8%)	1 (2.5%)
Bronchitis	1 (5.3%)	0	1 (2.5%)
Arthralgia	1 (5.3%)	0	1 (2.5%)
Anaemia	1 (5.3%)	0	1 (2.5%)
Abdominal pain upper	0	1 (4.8%)	1 (2.5%)
Abdominal pain	1 (5.3%)	0	1 (2.5%)

Arranged by frequency in the total column

Adverse events - n (percent) of patients (all patients) – Suspected treatment related (Safety analysis set)

	30mg/kg BYM338 N=19 n (%)	Placebo N=21 n (%)	Total N=40 n (%)
Patients with AE(s)	**13 (68.4%)**	**6 (28.6%)**	**19 (47.5%)**
Muscle spasms	9 (47.4%)	4 (19.0%)	13 (32.5%)
Muscle twitching	2 (10.5%)	1 (4.8%)	3 (7.5%)
Myalgia	0	2 (9.5%)	2 (5.0%)
Muscle tightness	1 (5.3%)	1 (4.8%)	2 (5.0%)
Hypoaesthesia	1 (5.3%)	1 (4.8%)	2 (5.0%)
Skin exfoliation	0	1 (4.8%)	1 (2.5%)
Rash pustular	1 (5.3%)	0	1 (2.5%)
Paraesthesia	1 (5.3%)	0	1 (2.5%)
Papule	1 (5.3%)	0	1 (2.5%)
Pain in extremity	0	1 (4.8%)	1 (2.5%)
Muscle fatigue	0	1 (4.8%)	1 (2.5%)
Malaise	1 (5.3%)	0	1 (2.5%)
Limb discomfort	0	1 (4.8%)	1 (2.5%)
Infusion site reaction	0	1 (4.8%)	1 (2.5%)
Hair growth abnormal	1 (5.3%)	0	1 (2.5%)
Erythema	0	1 (4.8%)	1 (2.5%)
Diarrhea	1 (5.3%)	0	1 (2.5%)
Acne	1 (5.3%)	0	1 (2.5%)
Abdominal pain	1 (5.3%)	0	1 (2.5%)

Arranged by frequency in the total column

Conclusion:

One or two doses of BYM338 over 16 weeks was efficacious at increasing muscle mass in older adults with sarcopenia and promoting clinically meaningful improvements in physical function in patients with greater mobility disability. In addition, treatment with BYM338 was safe and well tolerated and resulted in a pharmacokinetic profile suggesting target mediated drug disposition with no treatment related immunogenicity signal, both consistent with prior studies with BYM338. Data from this study support the further evaluation of BYM338 in the older adult population with lower skeletal muscle mass and impaired physical function to bring about clinically meaningful improvement in functional capacity and a reduction in health risk and cost.

Date of Clinical Trial Report

07-Oct-2014

Date of Initial Inclusion on Novartis Clinical Trial Results website

08-Dec-2014

Date of Latest Update

20-Jan-2015

Reason for Update

Administrative update