



Clinical trial results:

A randomized, double blind, placebo controlled, multi-center study to assess the pharmacodynamics, pharmacokinetics, safety and tolerability of BYM338 in chronic obstructive pulmonary disease patients with cachexia

Due to the EudraCT – Results system being out of service between 31 July 2015 and 12 January 2016, these results have been published in compliance with revised timelines.

Summary

EudraCT number	2011-000461-12
Trial protocol	GB NL
Global end of trial date	13 December 2014

Results information

Result version number	v1 (current)
This version publication date	26 May 2016
First version publication date	26 May 2016

Trial information

Trial identification

Sponsor protocol code	CBYM338X2204
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01669174
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111,

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	03 December 2014
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	13 December 2014
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

Assess the effect of BYM338 on muscle volume of the thigh (assessed by Magnetic Resonance Imaging (MRI)) at 4, 8, 16 and 24 weeks, compared to placebo, in chronic obstructive pulmonary disease (COPD) patients with pulmonary cachexia.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	07 June 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 24
Country: Number of subjects enrolled	Netherlands: 6
Country: Number of subjects enrolled	United States: 37
Worldwide total number of subjects	67
EEA total number of subjects	30

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	37

From 65 to 84 years	30
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Sixty-seven (33 in BYM338 and 34 in placebo groups) patients with COPD GOLD stage II to IV with associated cachexia were randomized into the study, with the aim of a minimum of 50 patients completing all study visits. Seven patients were added to the original 60 planned for enrollment due to unexpected attrition

Period 1

Period 1 title	Overall Study (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Carer, Subject, Assessor

Arms

Are arms mutually exclusive?	Yes
Arm title	BYM338

Arm description:

30 mg/kg

Arm type	Experimental
Investigational medicinal product name	Bimagrumab
Investigational medicinal product code	BYM338
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

lyophilized powder

Arm title	Placebo
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Arm description:

Placebo to BYM338 30mg/kg

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder and solution for solution for injection
Routes of administration	Intravenous use

Dosage and administration details:

lyophilized powder

Number of subjects in period 1	BYM338	Placebo
Started	33	34
Completed	27	28
Not completed	6	6
Subject withdrew consent	2	2
Adverse event, non-fatal	2	2
Administrative problems	1	2
Lost to follow-up	1	-

Baseline characteristics

Reporting groups

Reporting group title	BYM338
Reporting group description: 30 mg/kg	
Reporting group title	Placebo
Reporting group description: Placebo to BYM338 30mg/kg	

Reporting group values	BYM338	Placebo	Total
Number of subjects	33	34	67
Age categorical Units: Subjects			
In utero	0	0	0
Preterm newborn infants (gestational age < 37 wks)	0	0	0
Newborns (0-27 days)	0	0	0
Infants and toddlers (28 days-23 months)	0	0	0
Children (2-11 years)	0	0	0
Adolescents (12-17 years)	0	0	0
Adults (18-64 years)	17	20	37
From 65-84 years	16	14	30
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	64.5	63.1	
standard deviation	± 5.93	± 7.51	-
Gender, Male/Female Units: Participants			
Female	16	18	34
Male	17	16	33

End points

End points reporting groups

Reporting group title	BYM338
Reporting group description:	30 mg/kg
Reporting group title	Placebo
Reporting group description:	Placebo to BYM338 30mg/kg

Primary: Percentage Change from Baseline of Thigh Muscle Volume (TMV) by MRI Scan at week 4, 8, 16, and 24

End point title	Percentage Change from Baseline of Thigh Muscle Volume (TMV) by MRI Scan at week 4, 8, 16, and 24
End point description:	Thigh Muscle Volume (TMV) change was evaluated by a responder analysis. Patients whose loss of muscle TMV by MRI was no more than or equal to 2% at Week 4,8,16 and 24 was considered responders.
End point type	Primary
End point timeframe:	Baseline, Weeks 4, 8, 16, 24

End point values	BYM338	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: Percentage Change of TMV arithmetic mean (standard deviation)				
Week 4 Day 29 (n=30,31)	5.87 (± 3.413)	0.02 (± 3.261)		
Week 8 Day 57 (n=27,27)	7.01 (± 3.707)	-0.65 (± 2.752)		
Week 16 Day 113 (27,28)	7.84 (± 5.052)	-0.88 (± 4.471)		
End of Study, week 24 (n=27,28)	5.04 (± 4.872)	-1.31 (± 4.282)		

Statistical analyses

Statistical analysis title	Thigh Muscle Volume
Statistical analysis description:	Week 4
Comparison groups	BYM338 v Placebo

Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Mean difference (net)
Point estimate	106.1
Confidence interval	
level	90 %
sides	2-sided
lower limit	104.64
upper limit	107.58

Statistical analysis title	Thigh Muscle Volume
Statistical analysis description:	
Week 8	
Comparison groups	BYM338 v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	107.75
Confidence interval	
level	90 %
sides	2-sided
lower limit	106.18
upper limit	109.35

Statistical analysis title	Thigh Muscle Volume
Statistical analysis description:	
Week 16	
Comparison groups	BYM338 v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	108.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	106.31
upper limit	111

Statistical analysis title	Thigh Muscle Volume
Statistical analysis description:	
Week 24	
Comparison groups	BYM338 v Placebo
Number of subjects included in analysis	67
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	ANCOVA
Parameter estimate	Median difference (net)
Point estimate	106.63
Confidence interval	
level	90 %
sides	2-sided
lower limit	104.39
upper limit	108.93

Secondary: Change in 6 minute walk distance compared to placebo

End point title	Change in 6 minute walk distance compared to placebo
End point description:	
Practical simple test that requires a 100-ft hallway but no exercise equipment or advanced training for technicians. Walking is an activity performed daily by all but the most severely impaired patients. This test measures the distance that a patient can quickly walk on a flat, hard surface in a period of 6 minutes (the 6MWD)	
End point type	Secondary
End point timeframe:	
Baseline, Weeks 4, 8, 16, 24	

End point values	BYM338	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	34		
Units: meter				
arithmetic mean (standard deviation)				
Week 4 Day 29 (n=30,32)	364.6 (± 85.45)	388.5 (± 100.22)		
Week 8 Day 57 (n=27,29)	373.9 (± 101.42)	387.4 (± 99.73)		
Week 12 Day 85 (n=27,28)	383 (± 84.63)	385.6 (± 107.62)		
Week 16 Day 113 (n=25,28)	379.7 (± 83.78)	352.9 (± 104.01)		
End of Study week 24 (n=27, 28)	374.9 (± 98.29)	378.8 (± 81.5)		

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration (Cmax)

End point title | Maximum Observed Serum Concentration (Cmax)^[1]

End point description:

The observed maximum plasma concentration following drug administration

End point type | Secondary

End point timeframe:

0 hour, 2 hour, Day 8, 15, 29, 57, 71, 85, 99, 113, 127, 168 post dose

Notes:

[1] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this secondary outcome

End point values	BYM338			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: ug/mL				
arithmetic mean (standard deviation)				
Cmax dose 1 (n=31)	614 (± 143)			
Cmax dose 2 (n=26)	580 (± 121)			

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Concentration After Drug Administration (Tmax)

End point title | Time to Reach the Maximum Concentration After Drug Administration (Tmax)^[2]

End point description:

The time to reach the maximum concentration after drug administration

End point type | Secondary

End point timeframe:

24 weeks

Notes:

[2] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.

Justification: No statistical analysis for this secondary outcome

End point values	BYM338			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: hr				
median (full range (min-max))				
Tmax dose 1 (n=31)	2.22 (2.02 to 3.17)			
Tmax dose 2 (n=26)	2.23 (1.97 to 3.2)			

Statistical analyses

No statistical analyses for this end point

Secondary: AUC0-56 and AUClast

End point title	AUC0-56 and AUClast ^[3]
End point description:	AUC0-56, the area under the serum concentration-time curve from the time zero to the end of the dosing interval, day 56. AUC0-56 was analyzed for dose 1 and 2. AUClast is from time zero to the last quantifiable concentration. AUClast was analyzed for dose 2 only.
End point type	Secondary
End point timeframe:	0 hour, 2 hour, Day 8, 15, 29, 57, 71, 85, 99, 113, 127, 168 post dose

Notes:

[3] - The end point is not reporting statistics for all the arms in the baseline period. It is expected all the baseline period arms will be reported on when providing values for an end point on the baseline period.
Justification: No statistical analysis for this secondary outcome

End point values	BYM338			
Subject group type	Reporting group			
Number of subjects analysed	33			
Units: day*ug/mL				
arithmetic mean (standard deviation)				
AUC0-56 dose 1 (n=26)	4540 (± 897)			
AUC0-56 dose 2 (n=25)	5790 (± 1300)			
AUClast dose 2 (n=25)	7480 (± 2080)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV). All adverse events reported in this record are from date of First Patient First Treatment until Last Patient Last Visit

Assessment type	Systematic
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Dictionary used

Dictionary name	MedDRA
Dictionary version	17.1

Reporting groups

Reporting group title	Placebo
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Reporting group description:

Placebo

Reporting group title	BYM338 30mg/kg
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Reporting group description:

BYM338 30mg/kg

Serious adverse events	Placebo	BYM338 30mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 34 (8.82%)	4 / 33 (12.12%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Lung neoplasm malignant			
subjects affected / exposed	1 / 34 (2.94%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Throat cancer			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Injury, poisoning and procedural complications			
Cervical vertebral fracture			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hip fracture			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Road traffic accident			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Haemorrhage intracranial			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Inguinal hernia			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 34 (2.94%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumothorax			
subjects affected / exposed	1 / 34 (2.94%)	0 / 33 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Haematuria			

subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 34 (2.94%)	2 / 33 (6.06%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
Postoperative wound infection			
subjects affected / exposed	0 / 34 (0.00%)	1 / 33 (3.03%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 5 %

Non-serious adverse events	Placebo	BYM338 30mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	30 / 34 (88.24%)	31 / 33 (93.94%)	
Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 34 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 34 (0.00%)	3 / 33 (9.09%)	
occurrences (all)	0	3	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Blood creatine phosphokinase increased			
subjects affected / exposed	2 / 34 (5.88%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Blood glucose increased			
subjects affected / exposed	1 / 34 (2.94%)	2 / 33 (6.06%)	
occurrences (all)	1	3	

Gamma-glutamyltransferase increased subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	3 / 33 (9.09%) 3	
Haemoglobin urine present subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3	2 / 33 (6.06%) 2	
Urine leukocyte esterase positive subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 33 (6.06%) 4	
Injury, poisoning and procedural complications			
Contusion subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	2 / 33 (6.06%) 3	
Fall subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 33 (0.00%) 0	
Skin abrasion subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3	1 / 33 (3.03%) 1	
Vascular disorders			
Haematoma subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 2	2 / 33 (6.06%) 2	
Cardiac disorders			
Atrial fibrillation subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 33 (0.00%) 0	
Nervous system disorders			
Dizziness subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	3 / 33 (9.09%) 3	
Headache subjects affected / exposed occurrences (all)	8 / 34 (23.53%) 15	3 / 33 (9.09%) 6	
Paraesthesia			

subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	3 / 33 (9.09%) 4	
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	3 / 34 (8.82%)	2 / 33 (6.06%)	
occurrences (all)	5	2	
Feeling abnormal			
subjects affected / exposed	3 / 34 (8.82%)	4 / 33 (12.12%)	
occurrences (all)	4	4	
Feeling cold			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Influenza like illness			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Oedema peripheral			
subjects affected / exposed	2 / 34 (5.88%)	0 / 33 (0.00%)	
occurrences (all)	3	0	
Pain			
subjects affected / exposed	2 / 34 (5.88%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Diarrhoea			
subjects affected / exposed	3 / 34 (8.82%)	7 / 33 (21.21%)	
occurrences (all)	4	9	
Dyspepsia			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Nausea			
subjects affected / exposed	1 / 34 (2.94%)	2 / 33 (6.06%)	
occurrences (all)	1	3	
Respiratory, thoracic and mediastinal disorders			

Chronic obstructive pulmonary disease			
subjects affected / exposed	12 / 34 (35.29%)	16 / 33 (48.48%)	
occurrences (all)	20	25	
Cough			
subjects affected / exposed	5 / 34 (14.71%)	4 / 33 (12.12%)	
occurrences (all)	9	4	
Dyspnoea			
subjects affected / exposed	5 / 34 (14.71%)	5 / 33 (15.15%)	
occurrences (all)	6	6	
Dyspnoea exertional			
subjects affected / exposed	2 / 34 (5.88%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Rhinorrhoea			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Skin and subcutaneous tissue disorders			
Acne			
subjects affected / exposed	1 / 34 (2.94%)	3 / 33 (9.09%)	
occurrences (all)	1	3	
Blister			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	2	
Dermatitis			
subjects affected / exposed	2 / 34 (5.88%)	0 / 33 (0.00%)	
occurrences (all)	2	0	
Ecchymosis			
subjects affected / exposed	2 / 34 (5.88%)	2 / 33 (6.06%)	
occurrences (all)	2	2	
Erythema			
subjects affected / exposed	4 / 34 (11.76%)	4 / 33 (12.12%)	
occurrences (all)	4	8	
Papule			
subjects affected / exposed	0 / 34 (0.00%)	2 / 33 (6.06%)	
occurrences (all)	0	3	
Petechiae			

subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 33 (0.00%) 0	
Pruritus subjects affected / exposed occurrences (all)	7 / 34 (20.59%) 26	5 / 33 (15.15%) 7	
Skin exfoliation subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	0 / 33 (0.00%) 0	
Rash subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 3	0 / 33 (0.00%) 0	
Psychiatric disorders Anxiety subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 33 (0.00%) 0	
Depression subjects affected / exposed occurrences (all)	3 / 34 (8.82%) 3	1 / 33 (3.03%) 1	
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 2	2 / 33 (6.06%) 2	
Back pain subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 7	4 / 33 (12.12%) 4	
Muscle spasms subjects affected / exposed occurrences (all)	16 / 34 (47.06%) 120	26 / 33 (78.79%) 370	
Joint lock subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	2 / 33 (6.06%) 14	
Muscle tightness subjects affected / exposed occurrences (all)	5 / 34 (14.71%) 31	18 / 33 (54.55%) 122	
Muscle twitching			

subjects affected / exposed occurrences (all)	9 / 34 (26.47%) 65	15 / 33 (45.45%) 48	
Musculoskeletal chest pain subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	3 / 33 (9.09%) 7	
Myalgia subjects affected / exposed occurrences (all)	6 / 34 (17.65%) 7	7 / 33 (21.21%) 15	
Musculoskeletal stiffness subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	3 / 33 (9.09%) 3	
Neck pain subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	0 / 33 (0.00%) 0	
Pain in extremity subjects affected / exposed occurrences (all)	7 / 34 (20.59%) 15	8 / 33 (24.24%) 11	
Infections and infestations			
Gastroenteritis subjects affected / exposed occurrences (all)	1 / 34 (2.94%) 1	2 / 33 (6.06%) 2	
Nasopharyngitis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	4 / 33 (12.12%) 4	
Pneumonia subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	1 / 33 (3.03%) 1	
Rash pustular subjects affected / exposed occurrences (all)	2 / 34 (5.88%) 2	3 / 33 (9.09%) 5	
Sinusitis subjects affected / exposed occurrences (all)	0 / 34 (0.00%) 0	3 / 33 (9.09%) 3	
Upper respiratory tract infection subjects affected / exposed occurrences (all)	4 / 34 (11.76%) 4	2 / 33 (6.06%) 2	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
11 April 2012	The primary purpose of this amendment was to eliminate unnecessary delays in qualifying patients caused by the use of a single instrument. The exclusion criterion for minimum protein/calorie intake was revised to provide a choice of well accepted, valid methods for diet evaluation. In addition, the exclusion criteria were amended to identify a minimum body weight. Both of these changes could assist Investigators in identifying potential study patients and reduced the burden on patients who could not be enrolled. Because this amendment was necessary, an opportunity was taken to improve the clarity of certain text, correct a typographical error and update the risks section from data that became available after submission of the original protocol. These data were included in the the Investigator's Brochure (Edition 3). In addition, two lab parameters were added, but this did not require extra blood sampling. No patients was screened or enrolled in this study at the time of this amendment
16 July 2012	The primary purpose of this amendment was to address comments from the IRB, requesting additional exclusion criteria added relating to the optional muscle biopsies. The additional text clarified patient eligibility for this procedure to assist in patient safety and recruitment. A muscle symptoms log was added, to allow patients to record any symptoms related to their muscle throughout the study. To try to clarify and detail adverse events, a detailed dermatology assessment was added to the physical examination
03 September 2012	The purpose of this amendment was to update the blood log to adjust the blood volumes taken for safety and PK assessments. Some assessments listed in the biomarkers sections of the protocol, after this amendment, were done together with the safety lab samples, and other volumes adjusted to ensure a sufficient volume for the assay used. There were no changes to the safety, PK, or biomarker parameters being assessed
28 November 2012	The purpose of this amendment was to include the addition of an internal DMC separate from the BYM338 project team, which was being implemented in all new and ongoing phase I and IIa studies with BYM338. This DMC was introduced at the request of the US Food and Drug Administration (FDA) because of the new mode of action of BYM338, for which the safety profile was not fully characterized and because of safety concerns observed by FDA with a non-Novartis molecule with a similar mode of action. This amendment also added a second 30 mg/kg iv dose of BYM338 at Week 8 to the study design. Therefore, patients received two doses of BYM338 (Days 1 and 57) during the study period. This additional dosing was to provide drug exposure at a certain serum level over 16 continuous weeks rather than 8 weeks seen with a single dose. This additional exposure extended the treatment time to cover the estimated 16 weeks needed to see a measurable change in physical function, i.e., 6-MWD. Text was modified to clarify the NIRS assessment.
29 January 2013	Following a review of the protocol by Health Authorities and ECs, it was requested that an additional exclusion criteria be added, to specifically exclude immunocompromised patients. While most immunodeficient patients were excluded by their primary pathology or medication, i.e. rheumatoid arthritis, it was specified their exclusion to eliminate the possible risk of acquiring from or transmitting infections to other study patients. It was also requested that text included in the ICF section of the protocol regarding pregnancy was removed, as this study excluded women of child bearing potential

17 March 2014	The primary purpose of this amendment was to change the number of patients required for the second interim analysis. Following the first interim analysis, the protocol was updated to reflect the need for 50 patients at Week 16 for the second planned interim analysis. This was supported by simulations that showed that this sample size would provide sufficient power to declare that BYM338 significantly improves TMV at Week 8 compared to placebo. Minor administrative changes to the protocol were also included in this amendment.
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Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported