Clinical trial results:
A randomized, subject- and investigator-blinded, placebo-controlled study to assess the safety, pharmacokinetics and efficacy of intravenous bimagrumab in overweight and obese patients with type 2 diabetes

Summary

EudraCT number	2016-004124-26
Trial protocol	GB
Global end of trial date	08 May 2019

Results information

Result version number	v1 (current)
This version publication date	23 May 2020
First version publication date	23 May 2020

Trial information

Trial identification

Sponsor protocol code	CBYM338X2211

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03005288
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, Novartis.email@novartis.com
Scientific contact	Clinical Disclosure Office, Novartis Pharma AG, 41 613241111, Novartis.email@novartis.com

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	08 May 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	08 May 2019
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of the trial was to evaluate the treatment effect of bimagrumab on total body fat mass.

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	01 February 2017
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: 4
Country: Number of subjects enrolled	United States: 74
Worldwide total number of subjects	78
EEA total number of subjects	4

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)	54
From 65 to 84 years	24
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

The study was completed as planned.

Pre-assignment

Screening details:

Particpants were randomized to the study at 1:1 ratio to receive BYM338 10 mg/kg or placebo.

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, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	BYM338 10 mg/kg

Arm description:

intravenous infusion every four weeks

Arm type	Experimental
Investigational medicinal product name	Bimagrumab
Investigational medicinal product code	BYM338
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Bimagrumab 10 mg/kg up to maximum 1200 mg, every 4 weeks (12 doses)

Arm title	Placebo

Arm description:

intravenous infusion every four weeks

Arm type	Placebo
Investigational medicinal product name	N/A
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for infusion
Routes of administration	Intravenous use

Dosage and administration details:

Placebo, every 4 weeks (12 doses)

Number of subjects in period 1	BYM338 10 mg/kg	Placebo
Started	39	39
Safety analysis set	37	38
Pharmacodynamics (PD) analysis set	36	36
Completed	27	31
Not completed	12	8
Consent withdrawn by subject	7	5
Physician decision	-	1
Adverse event, non-fatal	5	-
Protocol deviation	-	1
Lost to follow-up	-	1

Baseline characteristics

Reporting groups	
Reporting group title	BYM338 10 mg/kg
Reporting group description: intravenous infusion every four weeks	
Reporting group title	Placebo
Reporting group description: intravenous infusion every four weeks	

Reporting group values	BYM338 10 mg/kg	Placebo	Total
Number of subjects	39	39	78
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)	27	27	54
From 65-84 years	12	12	24
85 years and over	0	0	0
Age Continuous Units: Years			
arithmetic mean	60.7	60.2	
standard deviation	± 7.50	± 8.02	-
Sex: Female, Male Units: participants			
Female	23	13	36
Male	16	26	42
Race/Ethnicity, Customized Units: Subjects			
Black Or African American	6	9	15
Other	1	0	1
White	32	28	60
Asian	0	1	1
Unknown	0	1	1
Race/Ethnicity, Customized Units: Subjects			
Hispanic Or Latino	28	26	54
Not Hispanic Or Latino	10	12	22
Not Reported	1	1	2

End points

End points reporting groups	
Reporting group title	BYM338 10 mg/kg
Reporting group description: intravenous infusion every four weeks	
Reporting group title	Placebo
Reporting group description: intravenous infusion every four weeks	

Primary: Change from baseline in total body fat mass by Dual energy X-ray absorptiometry (DXA) at week 48

End point title	Change from baseline in total body fat mass by Dual energy X-ray absorptiometry (DXA) at week 48
End point description: Dual energy X-ray absorptiometry (DXA) was used to assess changes in body composition, including total fat and lean body mass (FM and LBM) and appendicular skeletal fat and muscle mass (aFM and aLBM). DXA instruments had a source that generated x-rays split into two energies which measured bone mineral mass and soft tissue from which fat and fat-free mass (or lean body mass) were estimated.	
End point type	Primary
End point timeframe: Baseline, Week 48	

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: kg				
least squares mean (confidence interval 80%)	-7.49 (-8.33 to -6.64)	-0.18 (-0.99 to 0.63)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-7.31

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-8.48
upper limit	-6.14

Secondary: Change from baseline in total body fat mass by Dual energy X-ray absorptiometry (DXA) at week 24

End point title	Change from baseline in total body fat mass by Dual energy X-ray absorptiometry (DXA) at week 24

End point description:

Dual energy X-ray absorptiometry (DXA) was used to assess changes in body composition, including total fat and lean body mass (FM and LBM) and appendicular skeletal fat and muscle mass (aFM and aLBM). DXA instruments had a source that generated x-rays split into two energies which measured bone mineral mass and soft tissue from which fat and fat-free mass (or lean body mass) were estimated.

End point type	Secondary

End point timeframe:

Baseline, Week 24

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: kg				
least squares mean (confidence interval 80%)	-5.37 (-5.96 to -4.78)	-0.18 (-0.75 to 0.39)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-5.19
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.01
upper limit	-4.37

Secondary: Change from baseline in HbA1c at week 24 and 48

End point title	Change from baseline in HbA1c at week 24 and 48

End point description:

HbA1c reflects average glucose concentrations over the past 3 months and therefore provides a useful index of the glycemic control of bimagrumab over that time period. It is a standard endpoint used to assess the glycemic efficacy of any anti-diabetic medication. HbA1c is a key glycemic parameter which correlates with reduction of risk of diabetic complications.

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: percentage change				
least squares mean (confidence interval 80%)				
week 24	-0.85 (-1.06 to -0.64)	0.28 (0.08 to 0.48)		
week 48	-0.76 (-1.05 to -0.48)	0.04 (-0.23 to 0.31)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:

week 24

Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-1.13
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.42
upper limit	-0.83

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description: week 48	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.005
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.8
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.2
upper limit	-0.41

Secondary: The trough observed analyte concentration (Ctrough) of repeat doses of BYM338 10 mg/kg on day 84, 168, 252, 308 and 336

End point title	The trough observed analyte concentration (Ctrough) of repeat doses of BYM338 10 mg/kg on day 84, 168, 252, 308 and 336

End point description:

The trough observed analyte concentration (Ctrough) is the concentration that is just prior to the beginning of, or at the end of, a dosing interval (µg/mL).

End point type	Secondary

End point timeframe:

Day 84, 168, 252, 308, 336

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	0[1]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 84	25.3 (± 6.20)	()		
Day 168	27.5 (± 8.37)	()		
Day 252	31.0 (± 11.2)	()		
Day 308	29.9 (± 11.0)	()		
Day 336	27.8 (± 10.9)	()		

Notes:

[1] - PK samples were only obtained and evaluated for subjects treated with BYM338

Statistical analyses

No statistical analyses for this end point

Secondary: Maximum Observed Serum Concentration(Cmax) derived on day 1, 168 and 308

End point title	Maximum Observed Serum Concentration(Cmax) derived on day 1, 168 and 308

End point description:

Cmax is the observed maximum plasma concentration following administration (µg/mL).

End point type	Secondary

End point timeframe:

Day 1, 168, 308

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	0[2]		
Units: µg/mL				
arithmetic mean (standard deviation)				
Day 1	283 (± 32.0)	()		
Day 168	292 (± 45.3)	()		
Day 308	271 (± 31.1)	()		

Notes:

[2] - PK samples were only obtained and evaluated for subjects treated with BYM338

Statistical analyses

No statistical analyses for this end point

Secondary: Time to Reach the Maximum Concentration after Drug Administration (Tmax) derived on day 168 and 308

End point title	Time to Reach the Maximum Concentration after Drug Administration (Tmax) derived on day 168 and 308

End point description:

Tmax is the time to reach peak or maximum concentration (h).

End point type	Secondary

End point timeframe:

Day 1, 168, 308

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	0[3]		
Units: hr				
median (inter-quartile range (Q1-Q3))				
Day 1	0.750 (0.683 to 0.917)	(to)		
Day 168	0.750 (0.750 to 1.05)	(to)		
Day 308	0.750 (0.750 to 1.38)	(to)		

Notes:

[3] - PK samples were only obtained and evaluated for subjects treated with BYM338

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline in Body Mass Index (BMI)

End point title	Change from baseline in Body Mass Index (BMI)

End point description:

Body Mass Index (BMI) was determined by height and weight measurements at week 24 and 48. A negative change from baseline indicates improvement. BMI was calculated as (Body weight (kg)/ [Height (m)]^).

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: Kg/m^2				
least squares mean (confidence interval 80%)				
week 24	-1.50 (-1.77 to -1.23)	-0.17 (-0.43 to 0.10)		
week 48	-2.19 (-2.60 to -1.78)	-0.28 (-0.67 to 0.11)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:

week 24

Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-1.33

Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.71
upper limit	-0.95

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description:	
week 48	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-1.91
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-2.48
upper limit	-1.34

Secondary: Change from baseline in weight	
End point title	Change from baseline in weight
End point description:	
Body weight was measured to the nearest 0.1 kilogram (kg) in indoor clothing without shoes. A negative change from baseline indicates improvement.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24, Week 48	

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: Kg				
least squares mean (confidence interval 80%)				
week 24	-3.99 (-4.79 to -3.19)	-0.57 (-1.34 to 0.21)		
week 48	-5.90 (-7.08 to -4.71)	-0.79 (-1.92 to 0.33)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description: week 24	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-3.43
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-4.54
upper limit	-2.31

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description: week 48	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-5.1
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-6.74
upper limit	-3.47

Secondary: Change from baseline in lean body mass (LBM) measured by DXA

End point title	Change from baseline in lean body mass (LBM) measured by DXA

End point description:

Lean body mass (LBM) is a part of body composition defined as the difference between total body weight and body fat weight. This means that it counts the mass of all organs except body fat, including bones, muscles, blood, skin, and everything else.
Dual energy X-ray absorptiometry (DXA) was used to assess changes in body composition, including total fat and lean body mass (FM and LBM) and appendicular skeletal fat and muscle mass (aFM and aLBM). DXA instruments had a source that generated x-rays split into two energies which measured bone mineral mass and soft tissue from which fat and fat-free mass (or lean body mass) were estimated.

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 48

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: Kg				
least squares mean (confidence interval 80%)				
week 24	1.72 (1.25 to 2.19)	0.23 (-0.23 to 0.68)		
week 48	1.70 (1.14 to 2.26)	-0.44 (-0.97 to 0.09)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:

week 24

Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.003
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	1.49
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	0.82
upper limit	2.06

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:

week 48

Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	2.14
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	1.36
upper limit	2.93

Secondary: Change from baseline in waist circumference

End point title	Change from baseline in waist circumference

End point description:

Waist circumference is the length in cm of the circumference to the nearest 0.1 cm at the level of the umbilicus with the subject in the upright position. A negative change indicates improvement.

End point type	Secondary

End point timeframe:

Baseline, Week 24, Week 52

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: cm				
least squares mean (confidence interval 80%)				
week 24	-5.04 (-5.87 to -4.20)	-0.95 (-1.75 to -0.14)		
week 52	-9.00 (-10.3 to -7.68)	0.45 (-0.79 to 1.69)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:

week 24

Comparison groups	BYM338 10 mg/kg v Placebo

Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-4.09
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-5.26
upper limit	-2.92

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description:	
week 52	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-9.46
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-11.3
upper limit	-7.64

Secondary: Change from baseline in waist to hip ratio

End point title	Change from baseline in waist to hip ratio
End point description:	
Hip circumference was measured at the greatest protrusion of the buttocks. Combined with waist circumference, the waist-to-hip ratio was derived during data analysis.	
End point type	Secondary
End point timeframe:	
Baseline, Week 24, Week 52	

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: ratio				
least squares mean (confidence interval 80%)				
week 24	-0.02 (-0.03 to -0.01)	-0.01 (-0.01 to 0.00)		
week 52	-0.05 (-0.06 to -0.04)	0.01 (0.00 to 0.02)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description: week 24	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.062
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.02
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.03
upper limit	0

Statistical analysis title	Pharmacodynamic analysis set
Statistical analysis description: week 52	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	< 0.001
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.06
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-0.08
upper limit	-0.04

Secondary: Change from baseline in insulin resistance (HOMA2-IR)

End point title	Change from baseline in insulin resistance (HOMA2-IR)

End point description:

Blood samples were collected to analyze insulin resistance. HOMA2-IR is a derived insulin resistance index that was calculated based on measures of serum glucose and insulin, using an online calculator.

End point type	Secondary

End point timeframe:

Baseline. Week 12, Week 36

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	36	36		
Units: Insulin Resistance (IR) Score				
least squares mean (confidence interval 80%)				
week 12	0.10 (-0.17 to 0.37)	0.76 (0.50 to 1.02)		
week 36	-0.09 (-0.44 to 0.25)	0.57 (0.24 to 0.90)		

Statistical analyses

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:

week 12

Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.028
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.65
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.03
upper limit	-0.28

Statistical analysis title	Pharmacodynamic analysis set

Statistical analysis description:	
week 36	
Comparison groups	BYM338 10 mg/kg v Placebo
Number of subjects included in analysis	72
Analysis specification	Pre-specified
Analysis type	
P-value	= 0.081
Method	Mixed-Effect Model Repeated Measure
Parameter estimate	Mean difference (net)
Point estimate	-0.66
Confidence interval	
level	Other: 80 %
sides	2-sided
lower limit	-1.14
upper limit	-0.18

Secondary: Immunogenicity assessed by the number of participants developing anti-BYM338 antibodies during the trial

End point title	Immunogenicity assessed by the number of participants developing anti-BYM338 antibodies during the trial
End point description:	
Describes the number of participants tested positive for anti-BYM338 antibodies after the start of bimagrumab (BYM338) treatment. A validated bridging enzyme-linked immunosorbent assay (ELISA) was used for the confirmation of the presence of anti-BYM338 antibodies in human serum.	
End point type	Secondary
End point timeframe:	
392 days	

End point values	BYM338 10 mg/kg	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	37	38		
Units: participants				
Confirmed with positive immunogenicity	2	4		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events were collected throughout the study for 56 weeks which includes the treatment period of 48 weeks and the follow-up period of 8 weeks.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	22.0

Reporting groups

Reporting group title	Placebo

Reporting group description:

Placebo

Reporting group title	BYM338 10 mg/kg

Reporting group description:

BYM338 10 mg/kg

Serious adverse events	Placebo	BYM338 10 mg/kg	
Total subjects affected by serious adverse events			
subjects affected / exposed	3 / 38 (7.89%)	3 / 37 (8.11%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0	0	
Investigations			
Lipase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
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			
Thermal burn			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			
Acute coronary syndrome			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Acute myocardial infarction			

subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Impaired gastric emptying			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pancreatitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences causally related to treatment / all	0 / 0	1 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
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: 0 %

Non-serious adverse events	Placebo	BYM338 10 mg/kg	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	31 / 38 (81.58%)	31 / 37 (83.78%)	
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	

Hypertension			
subjects affected / exposed	1 / 38 (2.63%)	3 / 37 (8.11%)	
occurrences (all)	1	3	
Phlebitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Chest pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Early satiety			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Fatigue			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Influenza like illness			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Infusion site extravasation			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Non-cardiac chest pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Pain			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Peripheral swelling			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Immune system disorders			

Allergy to arthropod bite			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Food allergy			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Reproductive system and breast disorders			
Menorrhagia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Postmenopausal haemorrhage			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Dyspnoea exertional			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Epistaxis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Sinus congestion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Insomnia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Nervousness			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	

Investigations			
Alanine aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Amylase increased			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Aspartate aminotransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Blood alkaline phosphatase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Blood creatine phosphokinase MB increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Blood creatine phosphokinase increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Blood creatinine increased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Gamma-glutamyltransferase increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Lipase increased			
subjects affected / exposed	2 / 38 (5.26%)	4 / 37 (10.81%)	
occurrences (all)	2	4	
Pancreatic enzymes increased			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Weight decreased			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	

Weight increased			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Craniocerebral injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Ligament sprain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Rib fracture			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Skin laceration			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Congenital, familial and genetic disorders			
Type V hyperlipidaemia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Cardiac disorders			
Bundle branch block right			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Dysgeusia			

subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Headache			
subjects affected / exposed	5 / 38 (13.16%)	0 / 37 (0.00%)	
occurrences (all)	9	0	
Paraesthesia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Sciatica			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Syncope			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	3	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 38 (0.00%)	3 / 37 (8.11%)	
occurrences (all)	0	3	
Ear and labyrinth disorders			
Vertigo positional			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Eye disorders			
Cataract			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Diabetic retinopathy			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Macular oedema			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Abdominal pain upper			

subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Diarrhoea			
subjects affected / exposed	4 / 38 (10.53%)	15 / 37 (40.54%)	
occurrences (all)	6	17	
Dyspepsia			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Frequent bowel movements			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Nausea			
subjects affected / exposed	0 / 38 (0.00%)	4 / 37 (10.81%)	
occurrences (all)	0	5	
Tooth impacted			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Toothache			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Vomiting			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Hepatobiliary disorders			
Cholelithiasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Hepatic steatosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Hepatomegaly			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Skin and subcutaneous tissue disorders			
Acne			

subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Alopecia			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Blister			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	2	
Dermatitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Ecchymosis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Rash			
subjects affected / exposed	2 / 38 (5.26%)	2 / 37 (5.41%)	
occurrences (all)	2	2	
Skin ulcer			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Chromaturia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Dysuria			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Nephrolithiasis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Proteinuria			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	

Renal cyst			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Endocrine disorders			
Thyroid cyst			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Thyroid mass			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Back pain			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Coccydynia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Muscle fatigue			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	2	
Muscle spasms			
subjects affected / exposed	1 / 38 (2.63%)	15 / 37 (40.54%)	
occurrences (all)	1	23	
Muscle twitching			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Musculoskeletal stiffness			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Myalgia			
subjects affected / exposed	3 / 38 (7.89%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Neck mass			

subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Pain in extremity			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	3	0	
Plantar fasciitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Tendonitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Folliculitis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Gastroenteritis			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Helicobacter infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Hordeolum			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Influenza			
subjects affected / exposed	0 / 38 (0.00%)	2 / 37 (5.41%)	
occurrences (all)	0	2	
Pharyngitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Pneumonia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	

Rhinitis			
subjects affected / exposed	2 / 38 (5.26%)	0 / 37 (0.00%)	
occurrences (all)	2	0	
Sialoadenitis			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Sinusitis			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Tooth abscess			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Tooth infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Upper respiratory tract infection			
subjects affected / exposed	5 / 38 (13.16%)	6 / 37 (16.22%)	
occurrences (all)	5	6	
Urinary tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Urinary tract infection fungal			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Viral infection			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	
Viral upper respiratory tract infection			
subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Metabolism and nutrition disorders			
Decreased appetite			
subjects affected / exposed	1 / 38 (2.63%)	2 / 37 (5.41%)	
occurrences (all)	1	2	
Dehydration			

subjects affected / exposed	0 / 38 (0.00%)	1 / 37 (2.70%)	
occurrences (all)	0	1	
Diabetes mellitus			
subjects affected / exposed	1 / 38 (2.63%)	1 / 37 (2.70%)	
occurrences (all)	1	1	
Hyperglycaemia			
subjects affected / exposed	2 / 38 (5.26%)	1 / 37 (2.70%)	
occurrences (all)	2	1	
Hypoglycaemia			
subjects affected / exposed	1 / 38 (2.63%)	0 / 37 (0.00%)	
occurrences (all)	1	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
23 March 2017	Amendment 01: The purposes of this amendment were to: 1) align the study design with contemporary techniques for assessing dietary intake, physical activity, and insulin resistance; 2) integrate new safety data from recently completed bimagrumab studies; and 3) clarify the dietary intervention and overall assessment components of the study. At the time of this protocol amendment, no subjects were enrolled in the clinical study.
26 October 2017	Amendment 02: The primary purpose of this amendment was to present a new safety observation (transient elevations in lipase and amylase) in the bimagrumab development program and the resultant modifications to this protocol, to clarify language about laboratory evaluations required during the screening period, and to update eligibility criteria.
23 November 2017	Amendment 03: The primary purpose of this amendment was to include time points for the additional pancreatic enzyme safety monitoring that were inadvertently omitted from protocol amendment 02 and to clarify language related to treatment of adverse events and laboratory values.
12 March 2018	Amendment 04: The primary purpose of this amendment was to update the language related to the planned interim analyses and total sample size. More specifically: Interim Analysis #1 was removed as it was no longer needed for decision making. The assumed dropout rate was increased to 30% to reflect actual rate observed in the study, which increased the sample size to approximately 68 recruited. Additionally, this study began review by the program-level external Data Monitoring Committee (DMC).
17 January 2019	Amendment 05: The primary purpose of this amendment was to add an additional MRI at week 48 for subjects who had provided consent to this optional scan. Based on the results from the IA conducted after more than 50% of subjects had completed 24 weeks of treatment, this additional MRI scan was added to explore the effect of bimagrumab on MRI efficacy endpoints after 12 monthly doses.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported