Clinical trial results:
A 24-week double-blind treatment and 24-week follow-up, randomized, multicenter, placebo-controlled, phase IIa/IIb study to evaluate safety and efficacy of i.v. bimagrumab on total lean body mass and physical performance in patients after surgical treatment of hip fracture

Summary

EudraCT number	2013-003439-31
Trial protocol	BE GB DE HU CZ AT
Global end of trial date	25 October 2018

Results information

Result version number	v1 (current)
This version publication date	02 November 2019
First version publication date	02 November 2019

Trial information

Trial identification

Sponsor protocol code	CBYM338D2201

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02152761
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Novartis Pharma AG
Sponsor organisation address	CH-4002, Basel, Switzerland,
Public contact	Study Director, Novartis Pharma AG, 41 613241111, novartis.email@novartis.com
Scientific contact	Study Director, Novartis Pharmaceuticals, 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	15 April 2019
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	25 October 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to assess the efficacy of at least one dose of bimagrumab given intravenously (IV) every 4 weeks on total lean body mass (LBM) measured by dual emission X-ray absorptiometry (DXA), as assessed by change from baseline at Week 24 relative to placebo in subjects with disuse atrophy after surgical treatment of hip fracture.

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	16 September 2014
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	Argentina: 9
Country: Number of subjects enrolled	Australia: 3
Country: Number of subjects enrolled	Austria: 1
Country: Number of subjects enrolled	Belgium: 18
Country: Number of subjects enrolled	Chile: 5
Country: Number of subjects enrolled	Colombia: 3
Country: Number of subjects enrolled	Czech Republic: 27
Country: Number of subjects enrolled	France: 2
Country: Number of subjects enrolled	Germany: 18
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Hungary: 28
Country: Number of subjects enrolled	Japan: 26
Country: Number of subjects enrolled	Mexico: 10
Country: Number of subjects enrolled	Russian Federation: 15
Country: Number of subjects enrolled	Spain: 25
Country: Number of subjects enrolled	Taiwan: 18
Country: Number of subjects enrolled	Turkey: 3
Country: Number of subjects enrolled	United States: 36

Worldwide total number of subjects	250
EEA total number of subjects	122

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)	25
From 65 to 84 years	186
85 years and over	39

Subject disposition

Recruitment

Recruitment details:

384 subjects were screened, and 252 subjects completed Screening period. One was lost to follow-up after screening and did not attend any visits for treatment epoch therefore, 251 were recruited to study. 2 subjects died during Screening epoch (1 was reported as discontinued and 1 was reported as a screen failure)

Pre-assignment

Screening details:

251 subjects entered treatment epoch and were randomized to one of the three bimagrumab dose groups (70 mg, 210 mg and 700 mg) or the placebo group. 1 from the 210 mg group was randomized in error and did not receive study drug. Of the 250 subjects who were randomized and treated, 207 completed the 24 weeks treatment epoch.

Pre-assignment period milestones

Number of subjects started	250
Number of subjects completed	250

Period 1

Period 1 title	Epoch: Treatment epoch
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Investigator, Monitor, Subject

Arms

Are arms mutually exclusive?	Yes
Arm title	bimagrumab 700 mg

Arm description:

bimagrumab 700mg administered via intravenous infusion from Day 1 until Week 20

Arm type	Experimental
Investigational medicinal product name	BYM338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravascular use , Intravenous use

Dosage and administration details:

bimagrumab 700 mg administered via intravenous infusion from Day 1 until Week 20

Arm title	bimagrumab 210 mg

Arm description:

bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20

Arm type	Experimental
Investigational medicinal product name	BYM338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:

bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20

Arm title	bimagrumab 70 mg
Arm description:	
bimagrumad 70 mg administered via intravenous infusion starting Day 1 until Week 20	
Arm type	Experimental
Investigational medicinal product name	BYM338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Concentrate and solvent for concentrate for solution for infusion, Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
bimagrumab 70 mg administered via intravenous infusion from Day 1 until Week 20	

Arm title	Placebo
Arm description:	
placbo administered via intravenous infusion from Day 1 until Week 20	
Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use
Dosage and administration details:	
placebo administered via intravenous infusion from Day 1 until Week 20	

Number of subjects in period 1	bimagrumab 700 mg	bimagrumab 210 mg	bimagrumab 70 mg
Started	75	69	34
Completed	64	50	29
Not completed	11	19	5
Adverse event, serious fatal	-	3	1
Consent withdrawn by subject	7	8	3
Adverse event, non-fatal	3	6	1
Technical problems	-	-	-
Non-compliance with treatment	1	1	-
Lost to follow-up	-	1	-

Number of subjects in period 1	Placebo
Started	72
Completed	64
Not completed	8
Adverse event, serious fatal	-
Consent withdrawn by subject	5
Adverse event, non-fatal	2
Technical problems	1

Non-compliance with treatment	-
Lost to follow-up	-

Period 2	
Period 2 title	Epoch: Post-treatment follow-up epoch
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor

Arms	
Are arms mutually exclusive?	No
Arm title	bimagrumab 700 mg

Arm description:
bimagrumab 700mg administered via intravenous infusion from Day 1 until Week 20

Arm type	Experimental
Investigational medicinal product name	BYM338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
bimagrumab 700 mg administered via intravenous infusion from Day 1 until Week 20

Arm title	bimagrumab 210 mg

Arm description:
bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20

Arm type	Experimental
Investigational medicinal product name	BYM338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20

Arm title	bimagrumab 70 mg

Arm description:
bimagrumad 70 mg administered via intravenous infusion starting Day 1 until Week 20

Arm type	Experimental
Investigational medicinal product name	BYM338
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
bimagrumab 70 mg administered via intravenous infusion from Day 1 until Week 20

Arm title	placebo

Arm description:
placbo administered via intravenous infusion from Day 1 until Week 20

Arm type	Placebo
Investigational medicinal product name	placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Infusion
Routes of administration	Intravenous use

Dosage and administration details:
placebo administered via intravenous infusion from Day 1 until Week 20

Number of subjects in period 2	bimagrumab 700 mg	bimagrumab 210 mg	bimagrumab 70 mg
Started	67	54	30
Completed	63	47	30
Not completed	4	7	0
Adverse event, serious fatal	1	-	-
Consent withdrawn by subject	1	3	-
Adverse event, non-fatal	1	-	-
Lost to follow-up	1	4	-

Number of subjects in period 2	placebo
Started	68
Completed	66
Not completed	2
Adverse event, serious fatal	1
Consent withdrawn by subject	1
Adverse event, non-fatal	-
Lost to follow-up	-

Baseline characteristics

Reporting groups	
Reporting group title	bimagrumab 700 mg
Reporting group description:	
bimagrumab 700mg administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 210 mg
Reporting group description:	
bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 70 mg
Reporting group description:	
bimagrumad 70 mg administered via intravenous infusion starting Day 1 until Week 20	
Reporting group title	Placebo
Reporting group description:	
placbo administered via intravenous infusion from Day 1 until Week 20	

Reporting group values	bimagrumab 700 mg	bimagrumab 210 mg	bimagrumab 70 mg
Number of subjects	75	69	34
Age, Customized			
Actual number of subjects enrolled in the study by age category (Full Analysis Set)			
Units: Subjects			
< 65 years	9	9	4
65 - 74 years	22	23	10
75 - 84 years	30	26	16
=>85 years	14	11	4
Age Continuous			
average age of participants			
Units: years			
arithmetic mean	76.1	74.8	76.1
standard deviation	± 8.58	± 8.94	± 8.59
Sex: Female, Male			
Units: Subjects			
Female	54	48	21
Male	21	21	13
Race/Ethnicity, Customized			
Units: Subjects			
Caucasian	57	58	26
Black	0	0	0
Asian	13	8	6
Pacific Islander	0	0	0
Other	5	3	2

Reporting group values	Placebo	Total	
Number of subjects	72	250	
Age, Customized			
Actual number of subjects enrolled in the study by age category (Full Analysis Set)			
Units: Subjects			
< 65 years	3	25	

65 - 74 years	27	82	
75 - 84 years	32	104	
=>85 years	10	39	
Age Continuous			
average age of participants			
Units: years			
arithmetic mean	76.4		
standard deviation	± 7.88	-	
Sex: Female, Male Units: Subjects			
Female	53	176	
Male	19	74	
Race/Ethnicity, Customized Units: Subjects			
Caucasian	53	194	
Black	0	0	
Asian	17	44	
Pacific Islander	0	0	
Other	2	12	

End points

End points reporting groups

Reporting group title	bimagrumab 700 mg
Reporting group description: bimagrumab 700mg administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 210 mg
Reporting group description: bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 70 mg
Reporting group description: bimagrumad 70 mg administered via intravenous infusion starting Day 1 until Week 20	
Reporting group title	Placebo
Reporting group description: placbo administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 700 mg
Reporting group description: bimagrumab 700mg administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 210 mg
Reporting group description: bimagrumab 210 mg administered via intravenous infusion from Day 1 until Week 20	
Reporting group title	bimagrumab 70 mg
Reporting group description: bimagrumad 70 mg administered via intravenous infusion starting Day 1 until Week 20	
Reporting group title	placebo
Reporting group description: placbo administered via intravenous infusion from Day 1 until Week 20	

Primary: Change from baseline in total lean body mass measured by DXA (Dual-energy X-ray absorptiometry) at weeks 12 and 24

End point title	Change from baseline in total lean body mass measured by DXA (Dual-energy X-ray absorptiometry) at weeks 12 and 24[1]
End point description: Mixed Model for Repeated Measures (MMRM) of change from baseline in total LBM (kg) by treatment and visit	
End point type	Primary
End point timeframe: Weeks 12 and 24	

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: Stats analysis not planned

End point values	bimagrumab 700 mg	bimagrumab 210 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	69	72	
Units: kg				
least squares mean (standard error)				

week 12	1.066 (± 0.0107)	1.052 (± 0.0109)	1.009 (± 0.0103)	
week 24	1.064 (± 0.0113)	1.042 (± 0.0115)	0.996 (± 0.0109)	

Statistical analyses

Statistical analysis title	Analysis of Change in total LBM measured by DXA
Comparison groups	bimagrumab 700 mg v bimagrumab 210 mg v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	< 0.001 [2]
Method	Mixed models analysis
Parameter estimate	Treatment Group Ratio
Point estimate	1.058
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.04
upper limit	1.076

Notes:

[2] - Active Total Efficacy (AT:E) vs placebo

Secondary: Change from baseline in gait speed at week 24

End point title	Change from baseline in gait speed at week 24[3]

End point description:

Change from baseline to Week 24 in gait speed (meters/sec) Mixed Model for Repeated Measures (MMRM) of change from baseline in derived gait speed (m/sec) by treatment and visit MMRM: change from baseline in derived gait speed (m/sec) = treatment group + Baseline derived gait speed + region + treatment date + fracture fixation type + history of falls + use of mobility aid + visit + treatment group*visit + Baseline derived gait speed*visit + region*visit + treatment date*visit + fracture fixation type*visit + history of falls*visit + use of mobility aid*visit. Baseline is defined as the last available assessment (scheduled or unscheduled) prior to the start of the first infusion of study drug, including pre-dose assessments at Day 1. # p-value lower than the respective type-1 error in the testing procedure.

End point type	Secondary

End point timeframe:

Baseline, Week 24

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: Stats analysis not planned

End point values	bimagrumab 700 mg	bimagrumab 210 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	69	72	
Units: meters per second				
least squares mean (standard error)	0.268 (± 0.0599)	0.350 (± 0.0617)	0.339 (± 0.0607)	

Statistical analyses

Statistical analysis title	Analysis of Change from baseline in gait speed
Comparison groups	bimagrumab 700 mg v bimagrumab 210 mg v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5218 [4]
Method	Mixed models analysis
Parameter estimate	Treatment Group Difference
Point estimate	-0.03
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.121
upper limit	0.095

Notes:

[4] - Active Total Efficacy (AT:E) vs placebo

Secondary: Change from baseline in short physical performance battery at weeks 24

End point title	Change from baseline in short physical performance battery at weeks 24[5]

End point description:

Change from baseline to Week 24 and week 48 and in physical performance as measured by the Short Physical Performance Battery (SPPB) which is an assessment tool for evaluating lower extremity functioning in older persons Scores range from 0 (worst performance) to 12 (best performance) Mixed Model for Repeated Measures (MMRM) of change from baseline in total SPPB score by treatment and visit

End point type	Secondary

End point timeframe:

Week 24

Notes:

[5] - 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: Stats analysis not planned

End point values	bimagrumab 700 mg	bimagrumab 210 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	69	72	
Units: scores on a scale				
least squares mean (standard error)	2.331 (± 0.5436)	3.535 (± 0.5623)	2.702 (± 0.5516)	

Statistical analyses

Statistical analysis title	Analysis of Change in short SPPB test
Comparison groups	bimagrumab 700 mg v bimagrumab 210 mg v Placebo
Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other
P-value	= 0.5802 [6]
Method	Mixed models analysis
Parameter estimate	Treatment Group Difference
Point estimate	0.231
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.591
upper limit	1.053

Notes:

[6] - Active Total Efficacy (AT:E) vs placebo

Secondary: Falls rate at Final Update Analysis

End point title	Falls rate at Final Update Analysis[7]

End point description:

Group falls rate The frequency of having at least one fall up to Week 48 was summarized by treatment groups

End point type	Secondary

End point timeframe:

Week 48

Notes:

[7] - 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: Stats analysis not planned

End point values	bimagrumab 700 mg	bimagrumab 210 mg	Placebo	
Subject group type	Reporting group	Reporting group	Reporting group	
Number of subjects analysed	75	69	72[8]	
Units: Number of falls (Falls rate ratio)				
number (confidence interval 95%)	1.08 (0.53 to 2.21)	1.58 (0.78 to 3.18)	0 (0 to 0)	

Notes:

[8] - Confidence Interval (95%) is not eavluable

Statistical analyses

Statistical analysis title	Analysis of Falls Rate at Final Update Analysis
Comparison groups	bimagrumab 700 mg v bimagrumab 210 mg v Placebo

Number of subjects included in analysis	216
Analysis specification	Pre-specified
Analysis type	other[9]
P-value	= 0.3999 [10]
Method	Negative binomial regression
Parameter estimate	Falls rate ratio
Point estimate	1.31
Confidence interval	
level	95 %
sides	2-sided
lower limit	0.7
upper limit	2.43

Notes:

[9] - rate of falls varied between treatment groups

[10] - Active Total Efficacy (AT:E) vs placebo

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
AEs and SAEs were collected for the maximum duration of treatment and follow up for a participant per protocol for approximately 48 weeks. All cause mortality (on-treatment deaths) was collected for as long as participants could be contacted	
Adverse event reporting additional description:	
Any sign or symptom that occurs during the study treatment plus the # days post treatment	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.1

Reporting groups	
Reporting group title	BYM338 700 mg
Reporting group description:	
BYM338 700 mg	
Reporting group title	BYM338 210 mg
Reporting group description:	
BYM338 210 mg	
Reporting group title	BYM338 70 mg
Reporting group description:	
BYM338 70 mg	
Reporting group title	AT:S
Reporting group description:	
AT:S	
Reporting group title	Placebo
Reporting group description:	
Placebo	

Serious adverse events	BYM338 700 mg	BYM338 210 mg	BYM338 70 mg
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 75 (20.00%)	17 / 69 (24.64%)	9 / 34 (26.47%)
number of deaths (all causes)	1	3	1
number of deaths resulting from adverse events	0	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholangiocarcinoma			

subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematoma			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypertension			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Varicose vein			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Oedema peripheral			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Pyrexia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	1 / 75 (1.33%)	1 / 69 (1.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia aspiration			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Pulmonary embolism			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary oedema			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Psychiatric disorders			
Depression			

subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device breakage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device dislocation			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device extrusion			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	2 / 75 (2.67%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower limb fracture			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lumbar vertebral fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Radius fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Spinal fracture			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Thoracic vertebral fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tibia fracture			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 75 (1.33%)	1 / 69 (1.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cerebrovascular accident			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Transient ischaemic attack			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Leukocytosis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diarrhoea			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Duodenogastric reflux			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspepsia			

subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haematochezia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cholelithiasis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Osteoarthritis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Osteonecrosis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pseudarthrosis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 75 (1.33%)	1 / 69 (1.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Diverticulitis			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Empyema			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Enterobacter infection			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Erysipelas			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Escherichia urinary tract infection			

subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 1	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Salpingo-oophoritis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urinary tract infection			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Urosepsis			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	1 / 34 (2.94%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Metabolism and nutrition disorders			
Hypokalaemia			

subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyponatraemia			
subjects affected / exposed	1 / 75 (1.33%)	0 / 69 (0.00%)	0 / 34 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	AT:S	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	41 / 178 (23.03%)	9 / 72 (12.50%)	
number of deaths (all causes)	5	1	
number of deaths resulting from adverse events	0	0	
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Bladder cancer			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholangiocarcinoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Vascular disorders			
Deep vein thrombosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematoma			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypertension			

subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hypotension			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Varicose vein			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
General disorders and administration site conditions			
Multiple organ dysfunction syndrome			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Oedema peripheral			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pyrexia			
subjects affected / exposed	1 / 178 (0.56%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	3 / 178 (1.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia aspiration			

subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 1	
Pulmonary congestion			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Pulmonary embolism			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pulmonary oedema			
subjects affected / exposed	2 / 178 (1.12%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Respiratory failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Product issues			
Device breakage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device dislocation			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Device extrusion			

subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
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			
Hip fracture			
subjects affected / exposed	2 / 178 (1.12%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 2	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lower limb fracture			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Lumbar vertebral fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Radius fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Spinal fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Thoracic vertebral fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Tibia fracture			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac disorders			

Atrial fibrillation			
subjects affected / exposed	3 / 178 (1.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cardiac failure congestive			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Nervous system disorders			
Cerebral infarction			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cerebrovascular accident			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Transient ischaemic attack			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Leukocytosis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Eye disorders			
Retinal haemorrhage			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diarrhoea			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Duodenogastric reflux			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Dyspepsia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastrooesophageal reflux disease			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Haematochezia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

Hepatobiliary disorders			
Cholecystitis acute			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Cholelithiasis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Renal and urinary disorders			
Acute kidney injury			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteoarthritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Osteonecrosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pseudarthrosis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Bronchitis			

subjects affected / exposed	3 / 178 (1.69%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 3	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Diverticulitis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Empyema			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Enterobacter infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Erysipelas			
subjects affected / exposed	1 / 178 (0.56%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Escherichia urinary tract infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Gastroenteritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Peritonitis			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pneumonia			

subjects affected / exposed	2 / 178 (1.12%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	1 / 2	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Salpingo-oophoritis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Septic shock			
subjects affected / exposed	0 / 178 (0.00%)	1 / 72 (1.39%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urinary tract infection			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Urosepsis			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Metabolism and nutrition disorders			
Hypokalaemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hyponatraemia			
subjects affected / exposed	1 / 178 (0.56%)	0 / 72 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	

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

Non-serious adverse events	BYM338 700 mg	BYM338 210 mg	BYM338 70 mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	47 / 75 (62.67%)	34 / 69 (49.28%)	15 / 34 (44.12%)
Investigations			
Weight decreased			
subjects affected / exposed	4 / 75 (5.33%)	4 / 69 (5.80%)	1 / 34 (2.94%)
occurrences (all)	4	4	1
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	3 / 75 (4.00%)	1 / 69 (1.45%)	0 / 34 (0.00%)
occurrences (all)	3	1	0
Fall			
subjects affected / exposed	14 / 75 (18.67%)	12 / 69 (17.39%)	6 / 34 (17.65%)
occurrences (all)	17	17	8
Vascular disorders			
Hypertension			
subjects affected / exposed	3 / 75 (4.00%)	2 / 69 (2.90%)	2 / 34 (5.88%)
occurrences (all)	3	3	2
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	1 / 75 (1.33%)	4 / 69 (5.80%)	0 / 34 (0.00%)
occurrences (all)	1	4	0
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	9 / 75 (12.00%)	3 / 69 (4.35%)	1 / 34 (2.94%)
occurrences (all)	10	3	1
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	7 / 75 (9.33%)	4 / 69 (5.80%)	0 / 34 (0.00%)
occurrences (all)	9	4	0
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 75 (4.00%)	0 / 69 (0.00%)	2 / 34 (5.88%)
occurrences (all)	3	0	3
Musculoskeletal and connective tissue disorders			
Arthralgia			

subjects affected / exposed	8 / 75 (10.67%)	6 / 69 (8.70%)	5 / 34 (14.71%)
occurrences (all)	10	6	6
Back pain			
subjects affected / exposed	4 / 75 (5.33%)	5 / 69 (7.25%)	1 / 34 (2.94%)
occurrences (all)	4	5	1
Muscle spasms			
subjects affected / exposed	12 / 75 (16.00%)	17 / 69 (24.64%)	2 / 34 (5.88%)
occurrences (all)	15	23	3
Pain in extremity			
subjects affected / exposed	2 / 75 (2.67%)	1 / 69 (1.45%)	2 / 34 (5.88%)
occurrences (all)	2	1	3
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 75 (0.00%)	1 / 69 (1.45%)	2 / 34 (5.88%)
occurrences (all)	0	1	2
Nasopharyngitis			
subjects affected / exposed	5 / 75 (6.67%)	1 / 69 (1.45%)	2 / 34 (5.88%)
occurrences (all)	6	1	2
Urinary tract infection			
subjects affected / exposed	8 / 75 (10.67%)	3 / 69 (4.35%)	2 / 34 (5.88%)
occurrences (all)	8	3	3
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	0 / 75 (0.00%)	0 / 69 (0.00%)	2 / 34 (5.88%)
occurrences (all)	0	0	2

Non-serious adverse events	AT:S	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	96 / 178 (53.93%)	30 / 72 (41.67%)	
Investigations			
Weight decreased			
subjects affected / exposed	9 / 178 (5.06%)	1 / 72 (1.39%)	
occurrences (all)	9	1	
Injury, poisoning and procedural complications			
Contusion			
subjects affected / exposed	4 / 178 (2.25%)	5 / 72 (6.94%)	
occurrences (all)	4	5	

Fall			
subjects affected / exposed	32 / 178 (17.98%)	13 / 72 (18.06%)	
occurrences (all)	42	16	
Vascular disorders			
Hypertension			
subjects affected / exposed	7 / 178 (3.93%)	4 / 72 (5.56%)	
occurrences (all)	8	4	
Nervous system disorders			
Cognitive disorder			
subjects affected / exposed	5 / 178 (2.81%)	0 / 72 (0.00%)	
occurrences (all)	5	0	
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	13 / 178 (7.30%)	4 / 72 (5.56%)	
occurrences (all)	14	4	
Gastrointestinal disorders			
Diarrhoea			
subjects affected / exposed	11 / 178 (6.18%)	1 / 72 (1.39%)	
occurrences (all)	13	1	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	5 / 178 (2.81%)	0 / 72 (0.00%)	
occurrences (all)	6	0	
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	19 / 178 (10.67%)	5 / 72 (6.94%)	
occurrences (all)	22	6	
Back pain			
subjects affected / exposed	10 / 178 (5.62%)	2 / 72 (2.78%)	
occurrences (all)	10	2	
Muscle spasms			
subjects affected / exposed	31 / 178 (17.42%)	6 / 72 (8.33%)	
occurrences (all)	41	6	
Pain in extremity			
subjects affected / exposed	5 / 178 (2.81%)	1 / 72 (1.39%)	
occurrences (all)	6	1	
Infections and infestations			

Bronchitis			
subjects affected / exposed	3 / 178 (1.69%)	1 / 72 (1.39%)	
occurrences (all)	3	1	
Nasopharyngitis			
subjects affected / exposed	8 / 178 (4.49%)	2 / 72 (2.78%)	
occurrences (all)	9	2	
Urinary tract infection			
subjects affected / exposed	13 / 178 (7.30%)	2 / 72 (2.78%)	
occurrences (all)	14	2	
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 178 (1.12%)	0 / 72 (0.00%)	
occurrences (all)	2	0	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
01 February 2014	Central laboratory serology testing, including hepatitis B virus (HBV), hepatitis C virus (HCV), and HIV, as well as urine drug testing was added at the screening visit. Exclusion criteria 26 (chronic active hepatitis) was clarified and distinguished from exclusion criteria 33 (chronic active virus or bacterial infection). Inclusion of rectal, external genitalia, breast, and pelvic exams in physical exam, if deemed necessary by the Investigator, was clarified. Temperature was added to the vital sign assessments.
02 June 2015	Bimagrumab 70 mg group was added in the study to facilitate an adequate dose selection. The dosing regimen was changed from weight-based to fixed-dose. The 24-Week treatment period was extended by a 24-Week follow-up without treatment. The window of eligibility assessment was extended by 2 weeks. The age limit was decreased from 65 to 60 years. Several exclusion criteria of conditions affecting the subject's mobility were merged into one unique criterion focusing on the potentially confounding symptoms rather than a list of diagnoses. Stable psychiatric conditions were allowed if they do not affect the ability of the subject to comply with the study procedures. The restriction pertaining to ischemic heart disease was modified. The criterion was reduced to the exclusion of ongoing unstable angina pectoris and history of myocardial infarction in the past 3 months prior to randomization. The vitamin D related exclusion criterion was modified to exclude only those vitamin deficient subjects who did not receive adequate vitamin D3 supplementation prior to randomization. Minimum requirements for physical exercising were modified to minimum 4 weeks with at least 2 sessions and inclusion of strength / resistance components with focus on hip and thigh muscles. The list of forbidden medication was adjusted and the use of anti-estrogens was allowed. The tri-axial accelerometer device use was removed from the assessment. Dedicated monitoring of coagulation parameters was considered as unnecessary and was removed from the assessment schedule. Some of the exploratory biomarkers were removed from the assessment due to the diminished importance of some of these markers or the delayed/challenged development of some of the assays. The use of electronic (e) -diaries for falls and exercise was removed from the study.

03 April 2017	Regular echocardiography was deemed unnecessary to be further included for the monitoring of new subjects while the rest of the cardiac monitoring (vital signs and ECG) remained untouched. The conservative exclusion criteria with 450 and 460 msec thresholds was considered as unnecessary. Consequently, the threshold was lifted up to 500 msec for both genders. Closer body weight monitoring was included as a part of assessment. Serology (HIV, HCV, Hepatitis B surface antigen [HbsAg]) and 25-OH vitamin D measurements were excluded from eligibility criteria, but considered as important baseline characteristics or background information. The role of the Orthopedic Adjudication Committee (Department of Traumatology, Innsbruck University, Austria) was deemed redundant and reference to the potential operational involvement of this committee was removed from the protocol. A novel PRO measure called the HIP was included in the study along with the PGIS and PGIC, as well as the PROMIS.
04 February 2018	A new safety monitoring guidance for subjects with an increase of lipase and/or amylase was added. The evaluation of the effects of bimagrumab vs. placebo on the incidence of falls was added as a new secondary endpoint. Falls were also added to the testing strategy and analysis strategy for secondary endpoints (SPPB and gait speed) was amended to increase power of the study. Evaluation of a new responder (binary) variable was added as one of exploratory objectives. The responder was defined as subjects with physical performance improvement without falls. The statistical section was updated to include data from the new safety monitoring guidance. Also clarifications were added on the blinding handling at the time of the interim DBL.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

Limitations of the trial such as small numbers of subjects analysed or technical problems leading to unreliable data.

As there were no statistically significant improvements in functional measures (i.e. gait speed, SPPB) at week 24, the need to test for sustained improvement at wk 48 became irrelevant. So, wk 48 treatment differences were not evaluated

Notes: