Clinical trial results:
A Multicenter, Randomized, Placebo-controlled, Parallel Group, Double Blind, Dose-finding Phase II Trial to Study the Efficacy, Safety, Pharmacokinetic and Pharmacodynamic Effects of the Oral Partial Adenosine A1 Receptor Agonist Neladenoson Bialanate Over 20 Weeks in Patients With Chronic Heart Failure With Reduced Ejection Fraction

Summary

EudraCT number	2016-003839-38
Trial protocol	DE NL ES BE GR BG IT
Global end of trial date	16 May 2018

Results information

Result version number	v1 (current)
This version publication date	28 March 2019
First version publication date	28 March 2019

Trial information

Trial identification

Sponsor protocol code	15128

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT02992288
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Bayer AG
Sponsor organisation address	Kaiser-Wilhelm-Allee, Leverkusen, Germany, D-51368
Public contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.com
Scientific contact	Therapeutic Area Head, Bayer AG, clinical-trials-contact@bayer.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	16 May 2018
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	16 May 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The primary objective of this trial was to find the optimal dose of neladenoson bialanate for the Phase III trial by detecting and characterizing a significant dose-response relationship in the two primary efficacy endpoints, absolute change from baseline in left ventricular ejection fraction (LVEF) and log-transformed N-terminal prohormone b-type natriuretic peptide (NTproBNP) at 20 weeks, in subjects with chronic heart failure with reduced ejection fraction (HFrEF), and by characterizing the safety, tolerability and pharmacodynamic effects of the compound when given in addition to standard therapy for HFrEF.

Protection of trial subjects:

The conduct of this clinical study met all local legal and regulatory requirements. The study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and the International Council for Harmonisation (ICH) guideline E6: Good Clinical Practice (GCP).

Background therapy:

Standard of care Heart Failure therapy as per local guidelines.

Evidence for comparator: -

Actual start date of recruitment	22 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	Japan: 24
Country: Number of subjects enrolled	Bulgaria: 53
Country: Number of subjects enrolled	Poland: 106
Country: Number of subjects enrolled	United States: 22
Country: Number of subjects enrolled	Belgium: 11
Country: Number of subjects enrolled	Germany: 38
Country: Number of subjects enrolled	Spain: 34
Country: Number of subjects enrolled	Greece: 60
Country: Number of subjects enrolled	Israel: 24
Country: Number of subjects enrolled	Italy: 44
Country: Number of subjects enrolled	Netherlands: 11
Worldwide total number of subjects	427
EEA total number of subjects	357

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)	159
From 65 to 84 years	255
85 years and over	13

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 11 countries between 22 February 2017 (first subject first visit) and 16 May 2018 (last subject last visit).

Pre-assignment

Screening details:

Overall, 462 subjects were enrolled of them, 35 subjects did not complete screening due to unmet eligibility criteria, consent withdrawal, adverse events and other unspecified reasons. In total, 427 subjects were randomized and 426 subjects received study treatment.

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	Subject, Investigator

Arms

Are arms mutually exclusive?	Yes
Arm title	Placebo

Arm description:

Subjects received placebo matched to neladenoson bialanate tablets orally once daily for 20 weeks.

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received placebo matched to neladenoson bialanate tablets.

Arm title	Neladenoson Bialanate 5 mg

Arm description:

Subjects received 5 milligrams (mg) of neladenoson bialanate tablets orally once daily for 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Neladenoson Bialanate
Investigational medicinal product code	BAY1067197
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received neladenoson bialanate tablets orally.

Arm title	Neladenoson Bialanate 10 mg

Arm description:

Subjects received 10 mg of neladenoson bialanate tablets orally once daily for 20 weeks.

Arm type	Experimental

Investigational medicinal product name	Neladenoson Bialanate
Investigational medicinal product code	BAY1067197
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received neladenoson bialanate tablets orally.

Arm title	Neladenoson Bialanate 20 mg

Arm description:

Subjects received 20 mg of neladenoson bialanate tablets orally once daily for 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Neladenoson Bialanate
Investigational medicinal product code	BAY1067197
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received neladenoson bialanate tablets orally.

Arm title	Neladenoson Bialanate 30 mg

Arm description:

Subjects received 30 mg of neladenoson bialanate tablets orally once daily for 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Neladenoson Bialanate
Investigational medicinal product code	BAY1067197
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received neladenoson bialanate tablets orally.

Arm title	Neladenoson Bialanate 40 mg

Arm description:

Subjects received 40 mg of neladenoson bialanate tablets orally once daily for 20 weeks.

Arm type	Experimental
Investigational medicinal product name	Neladenoson Bialanate
Investigational medicinal product code	BAY1067197
Other name	
Pharmaceutical forms	Coated tablet
Routes of administration	Oral use

Dosage and administration details:

Subjects received neladenoson bialanate tablets orally.

Number of subjects in period 1	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg
Started	106	37	70
Treated	106	37	70
Completed	89	32	63
Not completed	17	5	7

Adverse event, serious fatal	2	-	2
Physician decision	3	-	1
Consent withdrawn by subject	4	2	1
Adverse event, non-fatal	8	2	2
Non-compliance with study drug	-	1	1
Lost to follow-up	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Neladenoson Bialanate 20 mg	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg
Started	73	69	72
Treated	72	69	72
Completed	64	61	59
Not completed	9	8	13
Adverse event, serious fatal	1	2	-
Physician decision	-	-	1
Consent withdrawn by subject	5	3	4
Adverse event, non-fatal	2	2	7
Non-compliance with study drug	-	1	-
Lost to follow-up	1	-	-
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 5 mg
Reporting group description:	
Subjects received 5 milligrams (mg) of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 10 mg
Reporting group description:	
Subjects received 10 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 20 mg
Reporting group description:	
Subjects received 20 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 30 mg
Reporting group description:	
Subjects received 30 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 40 mg
Reporting group description:	
Subjects received 40 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	

Reporting group values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg
Number of subjects	106	37	70
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	66.9	66.6	66.4
standard deviation	± 9.4	± 10.5	± 11.2
Sex: Female, Male Units: Subjects			
Female	18	9	11
Male	88	28	59
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	6	3	3
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	2
White	98	32	65
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	0	1
Not Hispanic or Latino	105	37	69

Unknown or Not Reported	0	0	0
New York Heart Association (NYHA) Class			
NYHA classifies the extent of heart failure as Class I: Cardiac disease without resulting limitation of physical activity, Class II: Cardiac disease resulting in slight limitation of physical activity, Class III: Cardiac disease resulting in marked limitation of physical activity and Class IV: Cardiac disease resulting in inability to carry out any physical activity without discomfort.			
Units: Subjects			
Class I	0	0	1
Class II	62	23	38
Class III/IV	44	14	31
Medical history: Chronic heart failure etiology Units: Subjects			
Ischemic	65	25	45
Non-ischemic	41	12	24
Missing	0	0	1
Medical history: Atrial fibrillation Units: Subjects			
Medical history: Atrial fibrillation	44	14	27
Without Atrial fibrillation	62	23	43
Medication of interest: Beta-blocker Units: Subjects			
Medication of interest: Beta-blocker	103	37	66
Not used at Baseline	3	0	4
Medication of interest: Angiotensin-converting enzyme inhibitor Units: Subjects			
Angiotensin-converting enzyme inhibitor	58	19	41
Not used at Baseline	48	18	29
Medication of interest: Angiotensin receptor blocker Units: Subjects			
Angiotensin receptor blocker	15	6	11
Not used at Baseline	91	31	59
Medication of interest: Angiotensin receptor-neprilysin inhibitor Units: Subjects			
Angiotensin receptor-neprilysin inhibitor	20	7	9
Not used at Baseline	86	30	61
Medication of interest: Mineralocorticoid receptor antagonist Units: Subjects			
Mineralocorticoid receptor antagonist	93	33	56
Not used at Baseline	13	4	14
Left ventricular ejection fraction (LVEF)			
Left ventricular ejection fraction (LVEF) is defined as the fraction of blood being pumped out of the left ventricle of the heart with each contraction.			
Units: Percentage of LVEF			
arithmetic mean	28.24	26.22	27.58
standard deviation	± 10.67	± 7.99	± 8.92
N-terminal pro-hormone b-type natriuretic peptide (NT-proBNP)			

Units: Picograms per milliliter (pg/mL)			
median	2111.00	2071.00	2063.00
full range (min-max)	78.0 to 30428.0	155.0 to 17760.0	25.5 to 49896.0

Reporting group values	Neladenoson Bialanate 20 mg	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg
Number of subjects	73	69	72
Age categorical Units: Subjects			
Age Continuous Units: Years			
arithmetic mean	68.1	67.6	67.5
standard deviation	± 10.0	± 9.8	± 10.0
Sex: Female, Male Units: Subjects			
Female	14	12	7
Male	59	57	65
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	3	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	2	2	2
White	66	64	65
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	1	2	0
Not Hispanic or Latino	72	66	72
Unknown or Not Reported	0	1	0
New York Heart Association (NYHA) Class			
NYHA classifies the extent of heart failure as Class I: Cardiac disease without resulting limitation of physical activity, Class II: Cardiac disease resulting in slight limitation of physical activity, Class III: Cardiac disease resulting in marked limitation of physical activity and Class IV: Cardiac disease resulting in inability to carry out any physical activity without discomfort.			
Units: Subjects			
Class I	0	0	0
Class II	44	49	49
Class III/IV	29	20	23
Medical history: Chronic heart failure etiology Units: Subjects			
Ischemic	50	37	42
Non-ischemic	23	32	30
Missing	0	0	0
Medical history: Atrial fibrillation Units: Subjects			
Medical history: Atrial fibrillation	26	27	33
Without Atrial fibrillation	47	42	39

Medication of interest: Beta-blocker Units: Subjects			
Medication of interest: Beta-blocker	70	67	69
Not used at Baseline	3	2	3
Medication of interest: Angiotensin-converting enzyme inhibitor Units: Subjects			
Angiotensin-converting enzyme inhibitor	41	36	45
Not used at Baseline	32	33	27
Medication of interest: Angiotensin receptor blocker Units: Subjects			
Angiotensin receptor blocker	14	9	9
Not used at Baseline	59	60	63
Medication of interest: Angiotensin receptor-neprilysin inhibitor Units: Subjects			
Angiotensin receptor-neprilysin inhibitor	9	12	12
Not used at Baseline	64	57	60
Medication of interest: Mineralocorticoid receptor antagonist Units: Subjects			
Mineralocorticoid receptor antagonist	60	56	57
Not used at Baseline	13	13	15
Left ventricular ejection fraction (LVEF)			
Left ventricular ejection fraction (LVEF) is defined as the fraction of blood being pumped out of the left ventricle of the heart with each contraction.			
Units: Percentage of LVEF			
arithmetic mean	29.70	29.87	26.24
standard deviation	± 10.87	± 11.54	± 8.92
N-terminal pro-hormone b-type natriuretic peptide (NT-proBNP) Units: Picograms per milliliter (pg/mL)			
median	1894.50	2084.00	2419.00
full range (min-max)	56.0 to 13294.0	406.0 to 24551.0	60.0 to 13387.0

Reporting group values	Total		
Number of subjects	427		
Age categorical Units: Subjects			

Age Continuous Units: Years			
arithmetic mean			
standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	71		
Male	356		

Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	25		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	12		
White	390		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	5		
Not Hispanic or Latino	421		
Unknown or Not Reported	1		
New York Heart Association (NYHA) Class			
NYHA classifies the extent of heart failure as Class I: Cardiac disease without resulting limitation of physical activity, Class II: Cardiac disease resulting in slight limitation of physical activity, Class III: Cardiac disease resulting in marked limitation of physical activity and Class IV: Cardiac disease resulting in inability to carry out any physical activity without discomfort.			
Units: Subjects			
Class I	1		
Class II	265		
Class III/IV	161		
Medical history: Chronic heart failure etiology Units: Subjects			
Ischemic	264		
Non-ischemic	162		
Missing	1		
Medical history: Atrial fibrillation Units: Subjects			
Medical history: Atrial fibrillation	171		
Without Atrial fibrillation	256		
Medication of interest: Beta-blocker Units: Subjects			
Medication of interest: Beta-blocker	412		
Not used at Baseline	15		
Medication of interest: Angiotensin-converting enzyme inhibitor Units: Subjects			
Angiotensin-converting enzyme inhibitor	240		
Not used at Baseline	187		
Medication of interest: Angiotensin receptor blocker Units: Subjects			
Angiotensin receptor blocker	64		
Not used at Baseline	363		
Medication of interest: Angiotensin receptor-neprilysin inhibitor Units: Subjects			
Angiotensin receptor-neprilysin inhibitor	69		

Not used at Baseline	358		
Medication of interest: Mineralocorticoid receptor antagonist Units: Subjects			
Mineralocorticoid receptor antagonist	355		
Not used at Baseline	72		
Left ventricular ejection fraction (LVEF)			
Left ventricular ejection fraction (LVEF) is defined as the fraction of blood being pumped out of the left ventricle of the heart with each contraction.			
Units: Percentage of LVEF arithmetic mean standard deviation	- -		
N-terminal pro-hormone b-type natriuretic peptide (NT-proBNP) Units: Picograms per milliliter (pg/mL) median full range (min-max)	- -		

End points

End points reporting groups

Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 5 mg
Reporting group description:	
Subjects received 5 milligrams (mg) of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 10 mg
Reporting group description:	
Subjects received 10 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 20 mg
Reporting group description:	
Subjects received 20 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 30 mg
Reporting group description:	
Subjects received 30 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson Bialanate 40 mg
Reporting group description:	
Subjects received 40 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Subject analysis set title	Full analysis set (FAS)
Subject analysis set type	Full analysis
Subject analysis set description:	
FAS included all randomized subjects.	
Subject analysis set title	Per-protocol set LVEF (PPS LVEF)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
Per-protocol set (PPS) included all subjects without validity findings affecting efficacy evaluation. The subjects with invalid/missing baseline value or missing post-baseline values not due to cardiovascular (CV) death or heart failure (HF) hospitalization or with other major protocol deviation were excluded from PPS LVEF set.	
Subject analysis set title	Per-protocol set BNP (PPS BNP)
Subject analysis set type	Sub-group analysis
Subject analysis set description:	
PPS included all subjects without validity findings affecting efficacy evaluation. The subjects with invalid/missing baseline value or missing postbaseline value not due to CV death or HF hospitalization or with other major protocol deviation were excluded from the PPS BNP.	

Primary: Absolute Change From Baseline in Left Ventricular Ejection Fraction (LVEF) (%) at Week 20 Measured by Echocardiography

End point title	Absolute Change From Baseline in Left Ventricular Ejection Fraction (LVEF) (%) at Week 20 Measured by Echocardiography
End point description:	
Left ventricular ejection fraction (LVEF) was measured by echocardiography. Mean and standard deviation were reported.	
End point type	Primary
End point timeframe:	
Baseline, Week 20	

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[1]	19[2]	35[3]	47[4]
Units: Percentage of LVEF				
arithmetic mean (standard deviation)	-2.19 (± 8.39)	2.59 (± 8.48)	-3.01 (± 10.43)	0.13 (± 8.74)

Notes:

[1] - PPS LVEF

[2] - PPS LVEF

[3] - PPS LVEF

[4] - PPS LVEF

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[5]	38[6]		
Units: Percentage of LVEF				
arithmetic mean (standard deviation)	-2.45 (± 10.54)	1.53 (± 10.01)		

Notes:

[5] - PPS LVEF

[6] - PPS LVEF

Statistical analyses

Statistical analysis title	Linear: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the multiple comparison procedures (MCP)-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2297 [7]
Method	MCP-Mod method

Notes:

[7] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax 1: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4409 [8]
Method	MCP-Mod method

Notes:

[8] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax 2: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2842 [9]
Method	MCP-Mod method

Notes:

[9] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Emax: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2534 [10]
Method	MCP-Mod method

Notes:

[10] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Quadratic: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.3842 [11]
Method	MCP-Mod method

Notes:

[11] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Primary: Absolute Change From Baseline in log-transformed NT-pro b-type Natriuretic Peptide (BNP) at Week 20

End point title	Absolute Change From Baseline in log-transformed NT-pro b-type Natriuretic Peptide (BNP) at Week 20

End point description:

NT-pro b-type Natriuretic Peptide (BNP) was measured. Mean and standard deviation were reported.

End point type	Primary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[12]	29[13]	58[14]	59[15]
Units: log picograms per milliliter				
arithmetic mean (standard deviation)	-0.07 (± 0.70)	-0.24 (± 0.90)	-0.07 (± 0.52)	-0.07 (± 0.56)

Notes:

[12] - PPS BNP

[13] - PPS BNP

[14] - PPS BNP

[15] - PPS BNP

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[16]	56[17]		
Units: log picograms per milliliter				
arithmetic mean (standard deviation)	0.07 (± 0.55)	-0.08 (± 0.79)		

Notes:

[16] - PPS BNP

[17] - PPS BNP

Statistical analyses

Statistical analysis title	Linear: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo

Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8966 [18]
Method	MCP-Mod method

Notes:

[18] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax 1: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9233 [19]
Method	MCP-Mod method

Notes:

[19] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax 2: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9296 [20]
Method	MCP-Mod method

Notes:

[20] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Emax: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7357 [21]
Method	MCP-Mod method

Notes:

[21] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Quadratic: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9083 [22]
Method	MCP-Mod method

Notes:

[22] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Secondary: Change From Baseline in Left Ventricular End-Systolic Volume (LVESV) at Week 20

End point title	Change From Baseline in Left Ventricular End-Systolic Volume (LVESV) at Week 20

End point description:

LVESV was defined as the volume of blood in the left ventricle at the end of contraction, or systole and the beginning of filling or diastole. Mean and standard deviation were reported.

End point type	Secondary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[23]	19[24]	35[25]	47[26]
Units: Milliliters (mL)				
arithmetic mean (standard deviation)	-5.44 (± 33.29)	-21.41 (± 48.13)	-2.82 (± 35.12)	-4.32 (± 29.73)

Notes:

[23] - PPS LVEF

[24] - PPS LVEF

[25] - PPS LVEF

[26] - PPS LVEF

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[27]	38[28]		
Units: Milliliters (mL)				
arithmetic mean (standard deviation)	-3.12 (± 33.96)	-15.16 (± 39.65)		

Notes:

[27] - PPS LVEF

[28] - PPS LVEF

Statistical analyses

Statistical analysis title	Linear: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.4596 [29]
Method	MCP-Mod method

Notes:

[29] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax 1: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg v Placebo
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7859 [30]
Method	MCP-Mod method

Notes:

[30] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax2: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5562 [31]
Method	MCP-Mod method

Notes:

[31] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Emax: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5338 [32]
Method	MCP-Mod method

Notes:

[32] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test

Statistical analysis title	Quadratic: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.7303 [33]
Method	MCP-Mod method

Notes:

[33] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Secondary: Change From Baseline in Left Ventricular End-Diastolic Volume (LVEDV) at Week 20

End point title	Change From Baseline in Left Ventricular End-Diastolic Volume (LVEDV) at Week 20

End point description:

LVEDV was defined as the volume of blood in the left ventricle at end load or filling in diastole or the amount of blood in the ventricles just before systole. Mean and standard deviation were reported.

End point type	Secondary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	47[34]	19[35]	35[36]	47[37]
Units: Milliliters (mL)				
arithmetic mean (standard deviation)	-13.16 (± 40.23)	-21.65 (± 61.96)	-12.44 (± 39.84)	-5.92 (± 30.89)

Notes:

[34] - PPS LVEF

[35] - PPS LVEF

[36] - PPS LVEF

[37] - PPS LVEF

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	40[38]	38[39]		
Units: Milliliters (mL)				
arithmetic mean (standard deviation)	-11.17 (± 42.32)	-19.69 (± 48.38)		

Notes:

[38] - PPS LVEF

[39] - PPS LVEF

Statistical analyses

Statistical analysis title	Linear: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5703 [40]
Method	MCP-Mod method

Notes:

[40] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax1: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg

Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8253 [41]
Method	MCP-Mod method

Notes:

[41] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax2: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6506 [42]
Method	MCP-Mod method

Notes:

[42] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Emax: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6923 [43]
Method	MCP-Mod method

Notes:

[43] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Quadratic: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	226
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.8036 [44]
Method	MCP-Mod method

Notes:

[44] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Secondary: Change From Baseline in High Sensitivity Troponin T (hs-TNT) at Week 20

End point title	Change From Baseline in High Sensitivity Troponin T (hs-TNT) at Week 20

End point description:

High sensitivity troponin T (hs-TNT) was measured. Mean and standard deviation were reported.

End point type	Secondary

End point timeframe:

Baseline, Week 20

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[45]	29[46]	58[47]	59[48]
Units: Picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	0.13 (± 9.98)	6.46 (± 33.04)	3.77 (± 22.32)	7.43 (± 37.79)

Notes:

[45] - PPS BNP

[46] - PPS BNP

[47] - PPS BNP

[48] - PPS BNP

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[49]	56[50]		
Units: Picograms per milliliter (pg/mL)				
arithmetic mean (standard deviation)	2.59 (± 12.90)	7.03 (± 24.81)		

Notes:

[49] - PPS BNP

[50] - PPS BNP

Statistical analyses

Statistical analysis title	Linear: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg

Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9955 [51]
Method	MCP-Mod method

Notes:

[51] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax1: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9946 [52]
Method	MCP-Mod method

Notes:

[52] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Sigmoidal Emax2: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9913 [53]
Method	MCP-Mod method

Notes:

[53] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Emax: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9982 [54]
Method	MCP-Mod method

Notes:

[54] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Quadratic: Dose response test

Statistical analysis description:

Dose response relationship was assessed using the MCP-Mod method combining MCP principles with modeling techniques under model uncertainty.

Comparison groups	Placebo v Neladenoson Bialanate 5 mg v Neladenoson Bialanate 10 mg v Neladenoson Bialanate 20 mg v Neladenoson Bialanate 30 mg v Neladenoson Bialanate 40 mg
Number of subjects included in analysis	337
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.9959 [55]
Method	MCP-Mod method

Notes:

[55] - The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Secondary: Number of Subjects With Composite Efficacy Outcome

End point title	Number of Subjects With Composite Efficacy Outcome

End point description:

Composite efficacy outcome was the first occurrence of CV death, HF hospitalization or urgent visit for HF. Number of subjects with composite efficacy outcome were reported.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[56]	29[57]	58[58]	59[59]
Units: Subjects	10	4	10	9

Notes:

[56] - PPS BNP

[57] - PPS BNP

[58] - PPS BNP

[59] - PPS BNP

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[60]	56[61]		
Units: Subjects	7	8		

Notes:

[60] - PPS BNP

[61] - PPS BNP

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Cardiovascular (CV) Mortality

End point title	Number of Subjects With Cardiovascular (CV) Mortality

End point description:

Cardiovascular (CV) mortality was assessed. Number of subjects with CV mortality were reported.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[62]	29[63]	58[64]	59[65]
Units: Subjects	1	1	3	1

Notes:

[62] - PPS BNP

[63] - PPS BNP

[64] - PPS BNP

[65] - PPS BNP

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[66]	56[67]		
Units: Subjects	2	1		

Notes:

[66] - PPS BNP

[67] - PPS BNP

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Subjects With Heart Failure (HF) Hospitalization and Urgent Visits for Heart Failure (HF)

End point title	Number of Subjects With Heart Failure (HF) Hospitalization and Urgent Visits for Heart Failure (HF)

End point description:

Number of subjects with HF hospitalization and urgent visits for HF were reported.

End point type	Secondary

End point timeframe:

Baseline up to Week 26

End point values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg	Neladenoson Bialanate 20 mg
Subject group type	Reporting group	Reporting group	Reporting group	Reporting group
Number of subjects analysed	82[68]	29[69]	58[70]	59[71]
Units: Subjects	10	4	9	8

Notes:

[68] - PPS BNP

[69] - PPS BNP

[70] - PPS BNP

[71] - PPS BNP

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	53[72]	56[73]		
Units: Subjects	5	8		

Notes:

[72] - PPS BNP

[73] - PPS BNP

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From start of study drug administration up to 26 weeks	
Assessment type	Non-systematic
Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0
Reporting groups	
Reporting group title	Placebo
Reporting group description:	
Subjects received placebo matched to neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson bialanate 5mg
Reporting group description:	
Subjects received 5 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson bialanate 10mg
Reporting group description:	
Subjects received 10 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson bialanate 20mg
Reporting group description:	
Subjects received 20 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson bialanate 30mg
Reporting group description:	
Subjects received 30 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	
Reporting group title	Neladenoson bialanate 40mg
Reporting group description:	
Subjects received 40 mg of neladenoson bialanate tablets orally once daily for 20 weeks.	

Serious adverse events	Placebo	Neladenoson bialanate 5mg	Neladenoson bialanate 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	31 / 106 (29.25%)	13 / 37 (35.14%)	28 / 70 (40.00%)
number of deaths (all causes)	8	1	5
number of deaths resulting from adverse events	1	0	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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
Chronic lymphocytic leukaemia			

subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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 cancer metastatic			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Prostate cancer			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Vascular disorders			
Aortic aneurysm			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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	1 / 106 (0.94%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Thrombosis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Surgical and medical procedures			

Atrial septal defect repair			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Cardiac pacemaker insertion			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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 pacemaker replacement			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implantable defibrillator insertion			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular assist device insertion			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	2 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Implantable defibrillator replacement			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Cardiac resynchronisation therapy			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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
Colectomy			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
General disorders and administration site conditions			

Chest pain			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Sudden death			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Oedema due to cardiac disease			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Respiratory, thoracic and mediastinal disorders			
Chronic obstructive pulmonary disease			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Dyspnoea			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea exertional			

subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Pleural effusion			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Respiratory failure			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Sleep apnoea syndrome			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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			
Confusional state			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Delirium			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Product issues			
Device failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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

Investigations			
Arteriogram coronary			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood pressure decreased			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Device function test			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Hip fracture			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Joint dislocation			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Rib fracture			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Traumatic fracture			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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

Lower limb fracture			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Post-traumatic pain			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Toxicity to various agents			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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
Craniocerebral injury			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Angina pectoris			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Angina unstable			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Atrial fibrillation			
subjects affected / exposed	2 / 106 (1.89%)	0 / 37 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			

subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Cardiac failure			
subjects affected / exposed	15 / 106 (14.15%)	7 / 37 (18.92%)	12 / 70 (17.14%)
occurrences causally related to treatment / all	0 / 20	0 / 8	0 / 14
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 2
Cardiac failure acute			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
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 chronic			
subjects affected / exposed	5 / 106 (4.72%)	1 / 37 (2.70%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	2 / 8	0 / 1	0 / 2
deaths causally related to treatment / all	1 / 2	0 / 1	0 / 1
Cardiac failure congestive			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardio-respiratory arrest			

subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiogenic shock			
subjects affected / exposed	3 / 106 (2.83%)	0 / 37 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 2	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Low cardiac output syndrome			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Mitral valve incompetence			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Myocardial infarction			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Myocardial ischaemia			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Right ventricular failure			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Tachycardia			

subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular fibrillation			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ventricular tachycardia			
subjects affected / exposed	1 / 106 (0.94%)	1 / 37 (2.70%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Acute left ventricular failure			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Paraparesis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Presyncope			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Seizure			

subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Syncope			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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	2 / 106 (1.89%)	0 / 37 (0.00%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	1 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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
Diarrhoea			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastric haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Ileus			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Upper gastrointestinal haemorrhage			

subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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
Large intestinal haemorrhage			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Jaundice			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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			
Renal failure			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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 impairment			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	2 / 70 (2.86%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	2 / 106 (1.89%)	1 / 37 (2.70%)	0 / 70 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	2 / 106 (1.89%)	0 / 37 (0.00%)	0 / 70 (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
Endocrine disorders			

Hyperthyroidism			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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			
Pain in extremity			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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			
Infection			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Peritonitis			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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	2 / 106 (1.89%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Septic shock			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	0 / 70 (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
Serratia sepsis			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	0 / 70 (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

Metabolism and nutrition disorders			
Diabetes mellitus			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hyperkalaemia			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (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
Hypokalaemia			
subjects affected / exposed	2 / 106 (1.89%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

Serious adverse events	Neladenoson bialanate 20mg	Neladenoson bialanate 30mg	Neladenoson bialanate 40mg
Total subjects affected by serious adverse events			
subjects affected / exposed	22 / 72 (30.56%)	28 / 69 (40.58%)	26 / 72 (36.11%)
number of deaths (all causes)	1	2	2
number of deaths resulting from adverse events	0	1	0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Cervix carcinoma			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Chronic lymphocytic leukaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Rectal adenocarcinoma			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Renal cancer metastatic			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Prostate cancer			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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			
Aortic aneurysm			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypotension			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peripheral ischaemia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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
Thrombosis			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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
Surgical and medical procedures			
Atrial septal defect repair			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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 pacemaker insertion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Cardiac pacemaker replacement			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Implantable defibrillator insertion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Ventricular assist device insertion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Implantable defibrillator replacement			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Cardiac resynchronisation therapy			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Colectomy			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Sudden death			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Oedema due to cardiac disease			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Hypersensitivity			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Reproductive system and breast disorders			
Benign prostatic hyperplasia			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Dyspnoea exertional			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Pleural effusion			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary congestion			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Respiratory failure			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Sleep apnoea syndrome			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Psychiatric disorders			
Confusional state			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Delirium			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device failure			
alternative assessment type: Systematic			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Investigations			
Arteriogram coronary			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Blood pressure decreased			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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 function test			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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			
Fall			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Hip fracture			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Joint dislocation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Rib fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Traumatic fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Lower limb fracture			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Post-traumatic pain			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Toxicity to various agents			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Craniocerebral injury			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	1 / 1	0 / 0
Angina pectoris			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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
Angina unstable			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial fibrillation			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	3 / 72 (4.17%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial tachycardia			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Atrioventricular block complete			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac arrest			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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 failure			
subjects affected / exposed	6 / 72 (8.33%)	10 / 69 (14.49%)	11 / 72 (15.28%)
occurrences causally related to treatment / all	0 / 10	0 / 17	0 / 16
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure chronic			
subjects affected / exposed	3 / 72 (4.17%)	2 / 69 (2.90%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure congestive			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Cardio-respiratory arrest			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Cardiogenic shock			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Coronary artery disease			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Low cardiac output syndrome			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mitral valve incompetence			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Myocardial infarction			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Myocardial ischaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Right ventricular failure			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Tachycardia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Ventricular fibrillation			

subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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
Ventricular tachycardia			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac ventricular thrombosis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Acute left ventricular failure			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Paraparesis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Presyncope			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Seizure			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Syncope			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	1 / 72 (1.39%)	2 / 69 (2.90%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Gastric haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
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 haemorrhage			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (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
Ileus			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Upper gastrointestinal haemorrhage			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Large intestinal haemorrhage			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hepatobiliary disorders			
Hepatic function abnormal			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Jaundice			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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
Renal and urinary disorders			
Renal failure			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Renal impairment			
subjects affected / exposed	1 / 72 (1.39%)	2 / 69 (2.90%)	3 / 72 (4.17%)
occurrences causally related to treatment / all	0 / 1	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Chronic kidney disease			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 72 (1.39%)	1 / 69 (1.45%)	2 / 72 (2.78%)
occurrences causally related to treatment / all	1 / 1	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Endocrine disorders			
Hyperthyroidism			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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

Musculoskeletal and connective tissue disorders			
Pain in extremity			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	0 / 72 (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
Infections and infestations			
Infection			
subjects affected / exposed	0 / 72 (0.00%)	1 / 69 (1.45%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Peritonitis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Pneumonia			
subjects affected / exposed	2 / 72 (2.78%)	1 / 69 (1.45%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 2	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia legionella			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Septic shock			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Serratia sepsis			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Metabolism and nutrition disorders			
Diabetes mellitus			

subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	0 / 72 (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
Hyperkalaemia			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	1 / 72 (1.39%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Hypokalaemia			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences causally related to treatment / all	1 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0

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

Non-serious adverse events	Placebo	Neladenoson bialanate 5mg	Neladenoson bialanate 10mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 106 (22.64%)	10 / 37 (27.03%)	15 / 70 (21.43%)
Vascular disorders			
Hypotension			
subjects affected / exposed	0 / 106 (0.00%)	1 / 37 (2.70%)	5 / 70 (7.14%)
occurrences (all)	0	1	6
Cardiac disorders			
Cardiac failure			
subjects affected / exposed	9 / 106 (8.49%)	2 / 37 (5.41%)	2 / 70 (2.86%)
occurrences (all)	9	2	2
Nervous system disorders			
Dizziness			
subjects affected / exposed	3 / 106 (2.83%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences (all)	3	0	1
Headache			
subjects affected / exposed	3 / 106 (2.83%)	1 / 37 (2.70%)	2 / 70 (2.86%)
occurrences (all)	3	1	2
General disorders and administration site conditions			
Asthenia			

subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences (all)	2	0	1
Fatigue			
subjects affected / exposed	2 / 106 (1.89%)	2 / 37 (5.41%)	1 / 70 (1.43%)
occurrences (all)	2	2	1
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 106 (0.94%)	2 / 37 (5.41%)	1 / 70 (1.43%)
occurrences (all)	1	2	1
Nausea			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	0 / 70 (0.00%)
occurrences (all)	2	0	0
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 106 (0.00%)	0 / 37 (0.00%)	3 / 70 (4.29%)
occurrences (all)	0	0	3
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	6 / 106 (5.66%)	1 / 37 (2.70%)	0 / 70 (0.00%)
occurrences (all)	7	1	0
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	1 / 106 (0.94%)	0 / 37 (0.00%)	1 / 70 (1.43%)
occurrences (all)	1	0	1
Metabolism and nutrition disorders			
Hyperglycaemia			
subjects affected / exposed	2 / 106 (1.89%)	2 / 37 (5.41%)	0 / 70 (0.00%)
occurrences (all)	2	2	0

Non-serious adverse events	Neladenoson bialanate 20mg	Neladenoson bialanate 30mg	Neladenoson bialanate 40mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	18 / 72 (25.00%)	24 / 69 (34.78%)	19 / 72 (26.39%)
Vascular disorders			
Hypotension			
subjects affected / exposed	4 / 72 (5.56%)	3 / 69 (4.35%)	2 / 72 (2.78%)
occurrences (all)	4	3	2
Cardiac disorders			

Cardiac failure			
subjects affected / exposed	1 / 72 (1.39%)	3 / 69 (4.35%)	3 / 72 (4.17%)
occurrences (all)	1	3	6
Nervous system disorders			
Dizziness			
subjects affected / exposed	2 / 72 (2.78%)	4 / 69 (5.80%)	4 / 72 (5.56%)
occurrences (all)	2	4	4
Headache			
subjects affected / exposed	0 / 72 (0.00%)	6 / 69 (8.70%)	1 / 72 (1.39%)
occurrences (all)	0	8	1
General disorders and administration site conditions			
Asthenia			
subjects affected / exposed	2 / 72 (2.78%)	4 / 69 (5.80%)	0 / 72 (0.00%)
occurrences (all)	2	4	0
Fatigue			
subjects affected / exposed	2 / 72 (2.78%)	1 / 69 (1.45%)	0 / 72 (0.00%)
occurrences (all)	2	1	0
Gastrointestinal disorders			
Abdominal pain			
subjects affected / exposed	1 / 72 (1.39%)	0 / 69 (0.00%)	0 / 72 (0.00%)
occurrences (all)	3	0	0
Nausea			
subjects affected / exposed	0 / 72 (0.00%)	2 / 69 (2.90%)	5 / 72 (6.94%)
occurrences (all)	0	2	5
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	4 / 72 (5.56%)	3 / 69 (4.35%)	3 / 72 (4.17%)
occurrences (all)	6	3	3
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	4 / 72 (5.56%)	6 / 69 (8.70%)	7 / 72 (9.72%)
occurrences (all)	4	6	7
Infections and infestations			
Urinary tract infection			
subjects affected / exposed	0 / 72 (0.00%)	0 / 69 (0.00%)	4 / 72 (5.56%)
occurrences (all)	0	0	4
Metabolism and nutrition disorders			

Hyperglycaemia subjects affected / exposed occurrences (all)	1 / 72 (1.39%) 1	0 / 69 (0.00%) 0	0 / 72 (0.00%) 0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
17 February 2017	1. Justification of the study drug dose was included. 2. Exclusion criteria related to asthma, prohibited therapy and allergies or hypersensitivities were added. 3. Tablet combination for subjects in 10 mg and 20 mg dose arms was changed.

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.

Occurrence of "±" in relation to mean and standard deviation is auto generated.

Notes: