



Clinical trial results:

A multicenter, randomized, placebo-controlled, parallel group, double blind, dose-finding Phase II trial to study the efficacy, safety, pharmacokinetics and pharmacodynamic effects of the oral partial adenosine A1 receptor agonist neladenoson bialanate over 20 weeks in patients with chronic heart failure and preserved ejection fraction

Summary

EudraCT number	2016-004062-26
Trial protocol	BE DE ES BG PT GR AT IT
Global end of trial date	20 June 2018

Results information

Result version number	v1 (current)
This version publication date	05 July 2019
First version publication date	05 July 2019

Trial information

Trial identification

Sponsor protocol code	BAY1067197/17582
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Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03098979
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	20 June 2018
Is this the analysis of the primary completion data?	No
Global end of trial reached?	Yes
Global end of trial date	20 June 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

The objective of the study was to find the optimal dose of neladenoson bialanate for the Phase 3 trial by detecting and characterizing a significant dose-response relationship in the primary efficacy endpoint, absolute change from baseline in 6-minute walking distance (6MWD) at 20 weeks, in subjects with heart failure with preserved ejection fraction (HFpEF), and by characterizing the safety, tolerability and pharmacodynamic effects of the compound when given in addition to appropriate therapy for specific co-morbidities.

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: -

Evidence for comparator: -

Actual start date of recruitment	10 May 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: 32
Country: Number of subjects enrolled	Bulgaria: 49
Country: Number of subjects enrolled	Poland: 58
Country: Number of subjects enrolled	United States: 16
Country: Number of subjects enrolled	Austria: 31
Country: Number of subjects enrolled	Belgium: 8
Country: Number of subjects enrolled	Germany: 9
Country: Number of subjects enrolled	Spain: 15
Country: Number of subjects enrolled	Greece: 26
Country: Number of subjects enrolled	Israel: 17
Country: Number of subjects enrolled	Italy: 36
Country: Number of subjects enrolled	Portugal: 8
Worldwide total number of subjects	305
EEA total number of subjects	240

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)	41
From 65 to 84 years	236
85 years and over	28

Subject disposition

Recruitment

Recruitment details:

The study was conducted at 76 study centers in 12 countries, between 10 May 2017 (first patient first visit) and 20 June 2018 (last patient last visit)

Pre-assignment

Screening details:

A total of 339 subjects entered the screening period, of whom 34 withdrew before randomization. The remaining 305 subjects were randomized and received at least one dose of study drug

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 for 20 weeks

Arm type	Placebo
Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	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
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Arm description:

Subjects received 5 milligrams (mg) of neladenoson bialanate tablets orally 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
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Arm description:

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

Arm type	Experimental
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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
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Arm description:

Subjects received 20 mg of neladenoson bialanate tablets orally 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
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Arm description:

Subjects received 30 mg of neladenoson bialanate tablets orally 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
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Arm description:

Subjects received 40 mg of neladenoson bialanate tablets orally 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	76	27	50
Completed	70	25	46
Not completed	6	2	4
Adverse event, serious fatal	1	-	2

Consent withdrawn by subject	2	1	1
Physician decision	2	1	-
Adverse event, non-fatal	1	-	1
Non-compliance	-	-	-
Protocol deviation	-	-	-

Number of subjects in period 1	Neladenoson Bialanate 20 mg	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg
Started	51	50	51
Completed	46	41	47
Not completed	5	9	4
Adverse event, serious fatal	-	1	-
Consent withdrawn by subject	1	2	1
Physician decision	-	-	-
Adverse event, non-fatal	4	6	1
Non-compliance	-	-	1
Protocol deviation	-	-	1

Baseline characteristics

Reporting groups

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

Reporting group values	Placebo	Neladenoson Bialanate 5 mg	Neladenoson Bialanate 10 mg
Number of subjects	76	27	50
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age Continuous Units: Years			
arithmetic mean	73.1	74.3	73.5
standard deviation	± 8.0	± 9.3	± 9.9
Sex: Female, Male Units: Subjects			
Female	36	16	26
Male	40	11	24
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	9	3	6

Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	3	0	0
White	64	24	44
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	2	0	0
Not Hispanic or Latino	73	27	49
Unknown or Not Reported	1	0	1
NYHA class			
NYHA classes: I: No limitation of physical activity (PA). Ordinary PA does not cause undue fatigue, palpitation, dyspnea, or anginal pain II: Slight limitation of PA; comfortable at rest. Ordinary PA results in fatigue, palpitation, dyspnea, or anginal pain III: Marked limitation of PA; comfortable at rest. Less than ordinary PA causes fatigue, palpitation, dyspnea, or anginal pain IV: Inability to carry on any PA without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any PA is undertaken, discomfort is increased			
Units: Subjects			
Class II	61	23	37
Class III/IV	15	4	13
Medical history: diabetes			
Subjects with medical history of Type 2 diabetes mellitus			
Units: Subjects			
Medical history: diabetes	36	7	23
Medical history: no diabetes	40	20	27
Medical history: Atrial fibrillation			
Subjects with medical history of Atrial fibrillation			
Units: Subjects			
Medical history: Atrial fibrillation	28	10	18
Medical history: no Atrial fibrillation	48	17	32
Medical history: hypertension			
Subjects with medical history of hypertension			
Units: Subjects			
Medical history: hypertension	66	25	45
Medical history: no hypertension	10	2	5
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			
arithmetic mean	57.09	56.54	53.78
standard deviation	± 8.68	± 9.62	± 11.6
NT-proBNP			
N-terminal pro-hormone b-type natriuretic peptide			
Units: pg/ml			
median	882.0	1013.0	1000.0
full range (min-max)	54 to 3034	136 to 5709	116 to 3547
eGFR			
eGFR = estimated glomerular filtration rate			
Units: mL/min/1.73 square meter			
arithmetic mean	62.0	52.6	61.0
standard deviation	± 17.9	± 17.1	± 24.2
6MWD			

6MWD = six-minute walking distance			
Units: meter			
arithmetic mean	322.8	311.6	295.8
standard deviation	± 97.1	± 108.2	± 110.4

Reporting group values	Neladenoson Bialanate 20 mg	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg
Number of subjects	51	50	51
Age categorical			
Units: Subjects			
In utero			
Preterm newborn infants (gestational age < 37 wks)			
Newborns (0-27 days)			
Infants and toddlers (28 days-23 months)			
Children (2-11 years)			
Adolescents (12-17 years)			
Adults (18-64 years)			
From 65-84 years			
85 years and over			
Age Continuous			
Units: Years			
arithmetic mean	71.4	76	73.7
standard deviation	± 6.8	± 9.4	± 8.3
Sex: Female, Male			
Units: Subjects			
Female	21	32	29
Male	30	18	22
Race (NIH/OMB)			
Units: Subjects			
American Indian or Alaska Native	0	0	0
Asian	5	5	5
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	1	0	1
White	45	45	45
More than one race	0	0	0
Unknown or Not Reported	0	0	0
Ethnicity (NIH/OMB)			
Units: Subjects			
Hispanic or Latino	0	0	0
Not Hispanic or Latino	51	50	50
Unknown or Not Reported	0	0	1
NYHA class			
NYHA classes: I: No limitation of physical activity (PA). Ordinary PA does not cause undue fatigue, palpitation, dyspnea, or anginal pain II: Slight limitation of PA; comfortable at rest. Ordinary PA results in fatigue, palpitation, dyspnea, or anginal pain III: Marked limitation of PA; comfortable at rest. Less than ordinary PA causes fatigue, palpitation, dyspnea, or anginal pain IV: Inability to carry on any PA without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any PA is undertaken, discomfort is increased			
Units: Subjects			
Class II	41	31	39
Class III/IV	10	19	12

Medical history: diabetes			
Subjects with medical history of Type 2 diabetes mellitus			
Units: Subjects			
Medical history: diabetes	20	22	21
Medical history: no diabetes	31	28	30
Medical history: Atrial fibrillation			
Subjects with medical history of Atrial fibrillation			
Units: Subjects			
Medical history: Atrial fibrillation	19	20	21
Medical history: no Atrial fibrillation	32	30	30
Medical history: hypertension			
Subjects with medical history of hypertension			
Units: Subjects			
Medical history: hypertension	45	46	42
Medical history: no hypertension	6	4	9
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			
arithmetic mean	57.3	59.43	52.3
standard deviation	± 10.4	± 8.72	± 12.76
NT-proBNP			
N-terminal pro-hormone b-type natriuretic peptide			
Units: pg/ml			
median	834.5	626.0	886.5
full range (min-max)	173 to 6003	78 to 3043	60 to 8170
eGFR			
eGFR = estimated glomerular filtration rate			
Units: mL/min/1.73 square meter			
arithmetic mean	57.1	57.5	60.0
standard deviation	± 17.3	± 18.2	± 17.5
6MWD			
6MWD = six-minute walking distance			
Units: meter			
arithmetic mean	324.5	321.1	347.2
standard deviation	± 105	± 93.4	± 94.5

Reporting group values	Total		
Number of subjects	305		
Age categorical			
Units: Subjects			
In utero	0		
Preterm newborn infants (gestational age < 37 wks)	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)	0		
From 65-84 years	0		
85 years and over	0		

Age Continuous Units: Years arithmetic mean standard deviation	-		
Sex: Female, Male Units: Subjects			
Female	160		
Male	145		
Race (NIH/OMB) Units: Subjects			
American Indian or Alaska Native	0		
Asian	33		
Native Hawaiian or Other Pacific Islander	0		
Black or African American	5		
White	267		
More than one race	0		
Unknown or Not Reported	0		
Ethnicity (NIH/OMB) Units: Subjects			
Hispanic or Latino	2		
Not Hispanic or Latino	300		
Unknown or Not Reported	3		
NYHA class			
NYHA classes: I: No limitation of physical activity (PA). Ordinary PA does not cause undue fatigue, palpitation, dyspnea, or anginal pain II: Slight limitation of PA; comfortable at rest. Ordinary PA results in fatigue, palpitation, dyspnea, or anginal pain III: Marked limitation of PA; comfortable at rest. Less than ordinary PA causes fatigue, palpitation, dyspnea, or anginal pain IV: Inability to carry on any PA without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any PA is undertaken, discomfort is increased			
Units: Subjects			
Class II	232		
Class III/IV	73		
Medical history: diabetes			
Subjects with medical history of Type 2 diabetes mellitus			
Units: Subjects			
Medical history: diabetes	129		
Medical history: no diabetes	176		
Medical history: Atrial fibrillation			
Subjects with medical history of Atrial fibrillation			
Units: Subjects			
Medical history: Atrial fibrillation	116		
Medical history: no Atrial fibrillation	189		
Medical history: hypertension			
Subjects with medical history of hypertension			
Units: Subjects			
Medical history: hypertension	269		
Medical history: no hypertension	36		
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 arithmetic mean			

standard deviation	-		
NT-proBNP			
N-terminal pro-hormone b-type natriuretic peptide			
Units: pg/ml			
median			
full range (min-max)	-		
eGFR			
eGFR = estimated glomerular filtration rate			
Units: mL/min/1.73 square meter			
arithmetic mean			
standard deviation	-		
6MWD			
6MWD = six-minute walking distance			
Units: meter			
arithmetic mean			
standard deviation	-		

End points

End points reporting groups

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

Primary: Absolute change from baseline in 6-minute walking distance (6MWD) after 20 weeks of treatment

End point title	Absolute change from baseline in 6-minute walking distance (6MWD) after 20 weeks of treatment
End point description:	
The 6MWD test is designed to evaluate a subject's exercise capacity while performing an everyday activity.	
End point type	Primary
End point timeframe:	
Up to 20 weeks of treatment	

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	65	22	44	41
Units: meter				
arithmetic mean (standard deviation)				
Value at baseline	329 (± 95)	306 (± 117)	300 (± 109)	328 (± 105)
Change from baseline to Week 20	1.89 (± 49.5)	24.8 (± 72.4)	27.2 (± 90.0)	14.6 (± 54.1)

End point values	Neladenoson Bialanate 30	Neladenoson Bialanate 40		
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	mg	mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	37		
Units: meter				
arithmetic mean (standard deviation)				
Value at baseline	321 (± 101)	363 (± 83)		
Change from baseline to Week 20	16.3 (± 55.4)	10.7 (± 60.2)		

Statistical analyses

Statistical analysis title	Linear: Dose response test
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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.5183 ^[1]
Method	MCP-Mod method

Notes:

[1] - Linear dose-response shape: The multiple comparison procedures (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
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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.33 ^[2]
Method	MCP-Mod method

Notes:

[2] - Sigmoidal Emax 1 dose-response shape: 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
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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.6232 ^[3]
Method	MCP-Mod method

Notes:

[3] - Sigmoidal Emax 2 dose-response shape: The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Emax: Dose response test
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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.0918 ^[4]
Method	MCP-Mod method

Notes:

[4] - Emax dose-response shape: The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Statistical analysis title	Quadratic: Dose response test
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	243
Analysis specification	Pre-specified
Analysis type	superiority
P-value	= 0.2701 ^[5]
Method	MCP-Mod method

Notes:

[5] - Quadratic dose-response shape: The MCP approach was applied to calculate the adjusted one-sided p-values of the contrast test.

Secondary: Reported values and absolute change in AVIVO activity intensity from baseline to 20 weeks

End point title	Reported values and absolute change in AVIVO activity intensity from baseline to 20 weeks
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End point description:

AVIVO™ Mobile Patient Management System, a wearable wireless device worn by the subject, was used to monitor subjects' cardiovascular status. The patient's everyday physical activity e.g. duration, intensity, was also tracked by the AVIVO device

End point type	Secondary
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End point timeframe:

Up to 20 weeks of treatment

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	56	20	39	35
Units: % of weekly average activity intensity				
arithmetic mean (standard deviation)				
Value at visit Baseline	2.83 (± 1.03)	2.76 (± 0.72)	2.83 (± 0.95)	2.51 (± 0.91)
Change from baseline at Week 20	-0.19 (± 0.58)	-0.25 (± 0.51)	-0.12 (± 0.58)	-0.08 (± 0.67)

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
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Subject group type	Reporting group	Reporting group		
Number of subjects analysed	32	33		
Units: % of weekly average activity intensity				
arithmetic mean (standard deviation)				
Value at visit Baseline	2.61 (\pm 0.94)	2.43 (\pm 0.57)		
Change from baseline at Week 20	-0.18 (\pm 0.57)	-0.14 (\pm 0.57)		

Statistical analyses

No statistical analyses for this end point

Secondary: Measured values (log transformed) and absolute change in NT-proBNP from baseline to 20 weeks

End point title	Measured values (log transformed) and absolute change in NT-proBNP from baseline to 20 weeks
End point description:	
NT-proBNP = N-terminal pro-hormone b-type natriuretic peptide	
End point type	Secondary
End point timeframe:	
Up to 20 weeks of treatment	

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	62	21	44	39
Units: log (pg/ml)				
median (full range (min-max))				
Value at baseline	6.80 (4.0 to 8.0)	6.78 (4.9 to 8.1)	6.81 (4.8 to 8.2)	6.73 (5.2 to 8.7)
Absolute change from baseline to Week 20	-0.07 (-1.3 to 1.6)	0.08 (-3.0 to 0.9)	0.13 (-1.7 to 1.6)	0.06 (-1.2 to 2.3)

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	36		
Units: log (pg/ml)				
median (full range (min-max))				
Value at baseline	6.68 (4.5 to 8.0)	6.64 (4.1 to 8.8)		
Absolute change from baseline to Week 20	0.09 (-1.3 to 0.9)	0.19 (-1.0 to 2.9)		

Statistical analyses

No statistical analyses for this end point

Secondary: Measured values (log-transformed) and absolute change in High sensitivity troponin T (hs-TNT) from baseline to 20 weeks

End point title	Measured values (log-transformed) and absolute change in High sensitivity troponin T (hs-TNT) from baseline to 20 weeks
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End point description:

High sensitivity troponin T (hs-TNT) was measured

End point type	Secondary
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End point timeframe:

Up to 20 weeks of treatment

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	63	22	44	38
Units: log(pg/mL)				
median (full range (min-max))				
Value at baseline	2.92 (1.9 to 4.4)	3.25 (1.9 to 4.7)	2.95 (1.9 to 4.7)	2.76 (1.9 to 4.2)
Absolute change from baseline to Week 20	0.00 (-1.4 to 1.6)	0.02 (-0.9 to 0.9)	0.00 (-0.7 to 1.1)	0.12 (-0.8 to 1.5)

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	33	37		
Units: log(pg/mL)				
median (full range (min-max))				
Value at baseline	2.73 (1.9 to 3.9)	2.76 (1.9 to 4.8)		
Absolute change from baseline to Week 20	0.13 (-0.4 to 1.2)	0.01 (-0.8 to 0.9)		

Statistical analyses

Secondary: Measured values and absolute change in 3 scores from Kansas City cardiomyopathy questionnaire (KCCQ) from baseline to 20 weeks: Overall Summary Score, Physical Limitation Score and Total Symptom Score

End point title	Measured values and absolute change in 3 scores from Kansas City cardiomyopathy questionnaire (KCCQ) from baseline to 20 weeks: Overall Summary Score, Physical Limitation Score and Total Symptom Score
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End point description:

The KCCQ is the leading health-related quality-of-life measure for patients with chronic heart failure (CHF). It is a 23-item questionnaire that independently measures the impact of patient's heart failure (HF), or its treatment, on 7 distinct domains: 1) Symptom Frequency 2) Symptom Burden 3) Physical Limitation 4) Quality of Life 5) Social Limitations 6) Self-efficacy 7) Symptoms Stability. Summary scores are a combination of these domains: Overall summary score: symptom frequency + symptom burden+ physical limitation + quality of life + social limitation Total symptom score: symptom frequency + symptom burden. Positive change means improvement and negative change means deterioration.

End point type	Secondary
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End point timeframe:

Up to 20 weeks of treatment

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	65	22	44	41
Units: score				
arithmetic mean (standard deviation)				
Overall Summary Score Baseline	69.19 (± 18.02)	64.75 (± 23.99)	66.42 (± 21.21)	64.57 (± 20.73)
Overall Summary Score Change from baseline	3.38 (± 13.55)	7.04 (± 17.24)	-1.33 (± 20.61)	3.73 (± 13.03)
Physical Limitation Score Baseline	69.07 (± 19.43)	63.18 (± 25.24)	68.03 (± 22.79)	69.35 (± 22.64)
Physical Limitation Score Change from baseline	2.18 (± 17.54)	1.40 (± 17.62)	-1.34 (± 22.56)	0.92 (± 14.65)
Total Symptom Score Baseline	76.78 (± 19.64)	72.25 (± 21.73)	68.99 (± 23.13)	69.99 (± 20.18)
Total Symptom Score Change from baseline	2.96 (± 15.85)	5.82 (± 17.51)	0.14 (± 19.08)	3.56 (± 14.04)

End point values	Neladenoson Bialanate 30 mg	Neladenoson Bialanate 40 mg		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	34	37		
Units: score				
arithmetic mean (standard deviation)				
Overall Summary Score Baseline	63.67 (± 17.76)	64.65 (± 18.07)		
Overall Summary Score Change from baseline	0.27 (± 14.83)	2.25 (± 14.25)		

Physical Limitation Score Baseline	64.53 (± 22.47)	63.12 (± 23.44)		
Physical Limitation Score Change from baseline	-3.75 (± 22.10)	2.17 (± 17.32)		
Total Symptom Score Baseline	68.00 (± 20.09)	71.03 (± 18.80)		
Total Symptom Score Change from baseline	2.54 (± 16.79)	2.62 (± 16.04)		

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
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Dictionary used

Dictionary name	MedDRA
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Dictionary version	21.0
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Reporting groups

Reporting group title	Placebo
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Reporting group description:

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

Reporting group title	Neladenoson bialanate 5mg
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Reporting group description:

Subjects received 5 mg of neladenoson bialanate tablets orally for 20 weeks.

Reporting group title	Neladenoson bialanate 10mg
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Reporting group description:

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

Reporting group title	Neladenoson bialanate 20mg
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Reporting group description:

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

Reporting group title	Neladenoson bialanate 30mg
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Reporting group description:

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

Reporting group title	Neladenoson bialanate 40mg
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Reporting group description:

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

Serious adverse events	Placebo	Neladenoson bialanate 5mg	Neladenoson bialanate 10mg
Total subjects affected by serious adverse events			
subjects affected / exposed	21 / 76 (27.63%)	9 / 27 (33.33%)	11 / 50 (22.00%)
number of deaths (all causes)	2	0	2
number of deaths resulting from adverse events	1	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Colon cancer			

subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Lymphoma			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Metastases to liver			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Pancreatic carcinoma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Metastatic neoplasm			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Lung neoplasm			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Hypertensive crisis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Peripheral ischaemia			

subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Venous thrombosis limb			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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			
Hip arthroplasty			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Inguinal hernia repair			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Insertion of ambulatory peritoneal catheter			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Hysterosalpingectomy			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
General disorders and administration site conditions			
Oedema peripheral			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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			
Acute respiratory failure			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Asthma			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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	0 / 76 (0.00%)	1 / 27 (3.70%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory failure			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Product issues			
Device dislocation			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Investigations			
Arteriogram coronary			

subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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 glucose increased			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Influenza A virus test positive			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Injury, poisoning and procedural complications			
Femur fracture			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Atrial fibrillation			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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

Atrial flutter			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Bradycardia			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Cardiac arrest			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Cardiac failure			
subjects affected / exposed	2 / 76 (2.63%)	2 / 27 (7.41%)	3 / 50 (6.00%)
occurrences causally related to treatment / all	0 / 2	0 / 2	0 / 3
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			
subjects affected / exposed	1 / 76 (1.32%)	1 / 27 (3.70%)	0 / 50 (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 failure chronic			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 congestive			
subjects affected / exposed	3 / 76 (3.95%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences causally related to treatment / all	0 / 7	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Coronary artery disease			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Sinoatrial block			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Sinus arrest			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Sinus bradycardia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Tricuspid valve incompetence			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 tachycardia			
subjects affected / exposed	2 / 76 (2.63%)	0 / 27 (0.00%)	0 / 50 (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
Acute left ventricular failure			

subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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			
Cerebral haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Intraventricular haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Syncope			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Ischaemic stroke			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	1 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	1 / 1
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Ear and labyrinth disorders			

Vertigo			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Eye disorders			
Cataract			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Gastrointestinal disorders			
Ascites			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Gastrointestinal haemorrhage			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Intestinal obstruction			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Mallory-Weiss syndrome			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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			
Cholangitis acute			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Hepatic function abnormal			

subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 impairment			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 kidney disease			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute kidney injury			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Infections and infestations			
Bronchitis			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Influenza			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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
Otitis media chronic			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Pneumonia			
subjects affected / exposed	2 / 76 (2.63%)	1 / 27 (3.70%)	0 / 50 (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
Pneumonia pneumococcal			

subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Wound infection			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	0 / 50 (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
Pneumonia bacterial			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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			
Dehydration			
subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (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

Serious adverse events	Neladenoson bialanate 20mg	Neladenoson bialanate 30mg	Neladenoson bialanate 40mg
Total subjects affected by serious adverse events			
subjects affected / exposed	11 / 51 (21.57%)	14 / 50 (28.00%)	16 / 51 (31.37%)
number of deaths (all causes)	1	1	1
number of deaths resulting from adverse events	1	1	1

Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
B-cell lymphoma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Colon cancer			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Lymphoma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Metastases to liver			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Pancreatic carcinoma			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Metastatic neoplasm			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Lung neoplasm			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Vascular disorders			
Aortic stenosis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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

Hypertensive crisis			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Peripheral ischaemia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Venous thrombosis limb			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Peripheral arterial occlusive disease			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Hip arthroplasty			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Inguinal hernia repair			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Insertion of ambulatory peritoneal catheter			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Hysterosalpingectomy			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Oedema peripheral			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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, thoracic and mediastinal disorders			
Acute respiratory failure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Asthma			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Dyspnoea			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Epistaxis			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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
Pleural effusion			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Product issues			
Device dislocation			

subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 glucose increased			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Influenza A virus test positive			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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			
Femur fracture			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Spinal fracture			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac disorders			
Acute myocardial infarction			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	0 / 51 (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
Arteriosclerosis coronary artery			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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	1 / 51 (1.96%)	0 / 50 (0.00%)	2 / 51 (3.92%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Atrial flutter			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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
Bradycardia			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 arrest			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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	4 / 51 (7.84%)	2 / 50 (4.00%)	7 / 51 (13.73%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 8
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Cardiac failure acute			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 chronic			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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 congestive			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Mitral valve incompetence			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Sinoatrial block			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Sinus arrest			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Sinus bradycardia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tachycardia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Tricuspid valve incompetence			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Ventricular extrasystoles			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
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	0 / 51 (0.00%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Acute left ventricular failure			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Cerebral haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Haemorrhage intracranial			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Intraventricular haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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	0 / 51 (0.00%)	2 / 50 (4.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	1 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Ischaemic stroke			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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
Basal ganglia haemorrhage			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 and lymphatic system disorders			

Anaemia			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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
Ear and labyrinth disorders			
Vertigo			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Eye disorders			
Cataract			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 disorders			
Ascites			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Intestinal obstruction			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Mallory-Weiss syndrome			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Hepatobiliary disorders			
Cholangitis acute			

subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Hepatic function abnormal			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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 kidney disease			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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 kidney injury			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 4	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Bronchitis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Influenza			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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
Otitis media chronic			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia			

subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pneumonia pneumococcal			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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
Wound infection			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	0 / 51 (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
Pulmonary sepsis			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 bacterial			
subjects affected / exposed	0 / 51 (0.00%)	0 / 50 (0.00%)	0 / 51 (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 tract infection			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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			
Dehydration			
subjects affected / exposed	0 / 51 (0.00%)	1 / 50 (2.00%)	0 / 51 (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
Hyperkalaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
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 / 76 (31.58%)	13 / 27 (48.15%)	14 / 50 (28.00%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Vascular disorders			
Hypertension			
subjects affected / exposed	2 / 76 (2.63%)	1 / 27 (3.70%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	5 / 76 (6.58%)	0 / 27 (0.00%)	3 / 50 (6.00%)
occurrences (all)	5	0	3
Cardiac failure			
subjects affected / exposed	5 / 76 (6.58%)	2 / 27 (7.41%)	3 / 50 (6.00%)
occurrences (all)	5	3	3
Ventricular tachycardia			
subjects affected / exposed	3 / 76 (3.95%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences (all)	5	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 76 (1.32%)	1 / 27 (3.70%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences (all)	1	0	0
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	3 / 76 (3.95%)	0 / 27 (0.00%)	2 / 50 (4.00%)
occurrences (all)	3	0	2
Diarrhoea			

subjects affected / exposed	0 / 76 (0.00%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences (all)	0	0	0
Nausea			
subjects affected / exposed	0 / 76 (0.00%)	1 / 27 (3.70%)	1 / 50 (2.00%)
occurrences (all)	0	1	1
Respiratory, thoracic and mediastinal disorders			
Cough			
subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Dyspnoea			
subjects affected / exposed	3 / 76 (3.95%)	2 / 27 (7.41%)	2 / 50 (4.00%)
occurrences (all)	3	2	2
Skin and subcutaneous tissue disorders			
Pruritus			
subjects affected / exposed	2 / 76 (2.63%)	1 / 27 (3.70%)	1 / 50 (2.00%)
occurrences (all)	2	1	1
Renal and urinary disorders			
Renal impairment			
subjects affected / exposed	1 / 76 (1.32%)	1 / 27 (3.70%)	1 / 50 (2.00%)
occurrences (all)	1	1	1
Chronic kidney disease			
subjects affected / exposed	0 / 76 (0.00%)	2 / 27 (7.41%)	0 / 50 (0.00%)
occurrences (all)	0	2	0
Musculoskeletal and connective tissue disorders			
Arthralgia			
subjects affected / exposed	2 / 76 (2.63%)	1 / 27 (3.70%)	0 / 50 (0.00%)
occurrences (all)	2	1	0
Infections and infestations			
Nasopharyngitis			
subjects affected / exposed	5 / 76 (6.58%)	1 / 27 (3.70%)	3 / 50 (6.00%)
occurrences (all)	6	1	3
Metabolism and nutrition disorders			
Hyperkalaemia			
subjects affected / exposed	3 / 76 (3.95%)	2 / 27 (7.41%)	0 / 50 (0.00%)
occurrences (all)	3	2	0
Hyperuricaemia			

subjects affected / exposed	1 / 76 (1.32%)	0 / 27 (0.00%)	1 / 50 (2.00%)
occurrences (all)	1	0	1
Hypokalaemia			
subjects affected / exposed	4 / 76 (5.26%)	0 / 27 (0.00%)	0 / 50 (0.00%)
occurrences (all)	5	0	0

Non-serious adverse events	Neladenoson bicalanate 20mg	Neladenoson bicalanate 30mg	Neladenoson bicalanate 40mg
Total subjects affected by non-serious adverse events			
subjects affected / exposed	22 / 51 (43.14%)	17 / 50 (34.00%)	24 / 51 (47.06%)
Investigations			
Blood creatinine increased			
subjects affected / exposed	4 / 51 (7.84%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences (all)	4	2	1
Vascular disorders			
Hypertension			
subjects affected / exposed	4 / 51 (7.84%)	1 / 50 (2.00%)	1 / 51 (1.96%)
occurrences (all)	6	1	1
Cardiac disorders			
Atrial fibrillation			
subjects affected / exposed	1 / 51 (1.96%)	1 / 50 (2.00%)	4 / 51 (7.84%)
occurrences (all)	1	1	6
Cardiac failure			
subjects affected / exposed	6 / 51 (11.76%)	1 / 50 (2.00%)	3 / 51 (5.88%)
occurrences (all)	9	1	3
Ventricular tachycardia			
subjects affected / exposed	4 / 51 (7.84%)	0 / 50 (0.00%)	1 / 51 (1.96%)
occurrences (all)	4	0	1
Nervous system disorders			
Dizziness			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	1 / 51 (1.96%)
occurrences (all)	0	3	1
General disorders and administration site conditions			
Fatigue			
subjects affected / exposed	2 / 51 (3.92%)	3 / 50 (6.00%)	0 / 51 (0.00%)
occurrences (all)	2	4	0
Gastrointestinal disorders			

Constipation subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	5 / 50 (10.00%) 6	1 / 51 (1.96%) 1
Diarrhoea subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	3 / 50 (6.00%) 3	2 / 51 (3.92%) 2
Nausea subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	3 / 50 (6.00%) 3	2 / 51 (3.92%) 2
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)	0 / 51 (0.00%) 0	4 / 50 (8.00%) 4	0 / 51 (0.00%) 0
Dyspnoea subjects affected / exposed occurrences (all)	5 / 51 (9.80%) 6	3 / 50 (6.00%) 3	3 / 51 (5.88%) 3
Skin and subcutaneous tissue disorders Pruritus subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	0 / 50 (0.00%) 0	0 / 51 (0.00%) 0
Renal and urinary disorders Renal impairment subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	1 / 50 (2.00%) 2	5 / 51 (9.80%) 5
Chronic kidney disease subjects affected / exposed occurrences (all)	1 / 51 (1.96%) 1	0 / 50 (0.00%) 0	1 / 51 (1.96%) 1
Musculoskeletal and connective tissue disorders Arthralgia subjects affected / exposed occurrences (all)	4 / 51 (7.84%) 4	2 / 50 (4.00%) 3	1 / 51 (1.96%) 1
Infections and infestations Nasopharyngitis subjects affected / exposed occurrences (all)	3 / 51 (5.88%) 3	2 / 50 (4.00%) 3	4 / 51 (7.84%) 5
Metabolism and nutrition disorders			

Hyperkalaemia			
subjects affected / exposed	0 / 51 (0.00%)	3 / 50 (6.00%)	3 / 51 (5.88%)
occurrences (all)	0	4	4
Hyperuricaemia			
subjects affected / exposed	1 / 51 (1.96%)	0 / 50 (0.00%)	3 / 51 (5.88%)
occurrences (all)	1	0	3
Hypokalaemia			
subjects affected / exposed	2 / 51 (3.92%)	1 / 50 (2.00%)	0 / 51 (0.00%)
occurrences (all)	2	1	0

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported