



## 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 |
|-----------------------|------------------|

#### 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:

| <b>Subjects enrolled per age group</b>    |     |
|---|-----|
| 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     |
| <b>Arm title</b>             | 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.

|                  |                            |
|------------------|----------------------------|
| <b>Arm title</b> | Neladenoson Bialanate 5 mg |
|------------------|----------------------------|

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.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Neladenoson Bialanate 10 mg |
|------------------|-----------------------------|

Arm description:

Subjects received 10 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.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Neladenoson Bialanate 20 mg |
|------------------|-----------------------------|

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.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Neladenoson Bialanate 30 mg |
|------------------|-----------------------------|

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.

|                  |                             |
|------------------|-----------------------------|
| <b>Arm title</b> | Neladenoson Bialanate 40 mg |
|------------------|-----------------------------|

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.

| <b>Number of subjects in period 1</b> | 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           | - | - | - |

| <b>Number of subjects in period 1</b> | Neladenoson<br>Bialanate 20 mg | Neladenoson<br>Bialanate 30 mg | Neladenoson<br>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<br>Units: Subjects  |         |                            |                             |
| In utero<br>Preterm newborn infants (gestational age < 37 wks)<br>Newborns (0-27 days)<br>Infants and toddlers (28 days-23 months)<br>Children (2-11 years)<br>Adolescents (12-17 years)<br>Adults (18-64 years)<br>From 65-84 years<br>85 years and over |         |                            |                             |
| Age Continuous<br>Units: Years  |         |                            |                             |
| arithmetic mean   | 73.1    | 74.3                       | 73.5                        |
| standard deviation  | ± 8.0   | ± 9.3                      | ± 9.9                       |
| Sex: Female, Male<br>Units: Subjects  |         |                            |                             |
| Female  | 36      | 16                         | 26                          |
| Male  | 40      | 11                         | 24                          |
| Race (NIH/OMB)<br>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<br>Bialanate 20 mg | Neladenoson<br>Bialanate 30 mg | Neladenoson<br>Bialanate 40 mg |
|---|--------------------------------|--------------------------------|--------------------------------|
| Number of subjects  | 51                             | 50                             | 51                             |
| Age categorical   |                                |                                |                                |
| Units: Subjects   |                                |                                |                                |
| In utero  |                                |                                |                                |
| Preterm newborn infants<br>(gestational age < 37 wks)   |                                |                                |                                |
| Newborns (0-27 days)  |                                |                                |                                |
| Infants and toddlers (28 days-23<br>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<br>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<br>(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<br>Units: Years<br>arithmetic mean<br>standard deviation   | -   |  |  |
| Sex: Female, Male<br>Units: Subjects  |     |  |  |
| Female  | 160 |  |  |
| Male  | 145 |  |  |
| Race (NIH/OMB)<br>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)<br>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<br>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 |  |  |
|------------------|--------------------------|--------------------------|--|--|
|------------------|--------------------------|--------------------------|--|--|

|                                      | 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

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[1]</sup>  |
| 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.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[2]</sup>  |
| 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.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[3]</sup>  |
| 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.

|                                   |  |
|-----------------------------------|--|
| <b>Statistical analysis title</b> | 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 <sup>[4]</sup>                                   |
| 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.

|   |  |
|---|--|
| <b>Statistical analysis title</b>       | 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 <sup>[5]</sup>  |
| 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 |
| End point description:<br>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   |
| End point timeframe:<br>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 |  |  |
|------------------|-----------------------------|-----------------------------|--|--|
|------------------|-----------------------------|-----------------------------|--|--|

|   |                     |                     |  |  |
|---|---------------------|---------------------|--|--|
| 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 |
|-----------------|---|

End point description:

High sensitivity troponin T (hs-TNT) was measured

|                |           |
|----------------|-----------|
| 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              | 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 |
|-----------------|--|

## 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 |
|----------------|-----------|

## 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 |
|-----------------|----------------|

### 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 for 20 weeks.

|                       |                           |
|-----------------------|---------------------------|
| Reporting group title | Neladenoson bialanate 5mg |
|-----------------------|---------------------------|

Reporting group description:

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

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Neladenoson bialanate 10mg |
|-----------------------|----------------------------|

Reporting group description:

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

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Neladenoson bialanate 20mg |
|-----------------------|----------------------------|

Reporting group description:

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

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Neladenoson bialanate 30mg |
|-----------------------|----------------------------|

Reporting group description:

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

|                       |                            |
|-----------------------|----------------------------|
| Reporting group title | Neladenoson bialanate 40mg |
|-----------------------|----------------------------|

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          |
| <b>Investigations</b>                                 |                |                |                |
| 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          |
| <b>Injury, poisoning and procedural complications</b> |                |                |                |
| 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          |
| <b>Cardiac disorders</b>                              |                |                |                |
| 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 %

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

| <b>Non-serious adverse events</b>                     | Neladenoson<br>bilateral 20mg | Neladenoson<br>bilateral 30mg | Neladenoson<br>bilateral 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<br>subjects affected / exposed<br>occurrences (all)  | 1 / 51 (1.96%)<br>1 | 5 / 50 (10.00%)<br>6 | 1 / 51 (1.96%)<br>1 |
| Diarrhoea<br>subjects affected / exposed<br>occurrences (all)   | 3 / 51 (5.88%)<br>3 | 3 / 50 (6.00%)<br>3  | 2 / 51 (3.92%)<br>2 |
| Nausea<br>subjects affected / exposed<br>occurrences (all)  | 1 / 51 (1.96%)<br>1 | 3 / 50 (6.00%)<br>3  | 2 / 51 (3.92%)<br>2 |
| Respiratory, thoracic and mediastinal disorders<br>Cough<br>subjects affected / exposed<br>occurrences (all)      | 0 / 51 (0.00%)<br>0 | 4 / 50 (8.00%)<br>4  | 0 / 51 (0.00%)<br>0 |
| Dyspnoea<br>subjects affected / exposed<br>occurrences (all)  | 5 / 51 (9.80%)<br>6 | 3 / 50 (6.00%)<br>3  | 3 / 51 (5.88%)<br>3 |
| Skin and subcutaneous tissue disorders<br>Pruritus<br>subjects affected / exposed<br>occurrences (all)            | 3 / 51 (5.88%)<br>3 | 0 / 50 (0.00%)<br>0  | 0 / 51 (0.00%)<br>0 |
| Renal and urinary disorders<br>Renal impairment<br>subjects affected / exposed<br>occurrences (all)               | 1 / 51 (1.96%)<br>1 | 1 / 50 (2.00%)<br>2  | 5 / 51 (9.80%)<br>5 |
| Chronic kidney disease<br>subjects affected / exposed<br>occurrences (all)  | 1 / 51 (1.96%)<br>1 | 0 / 50 (0.00%)<br>0  | 1 / 51 (1.96%)<br>1 |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 4 / 51 (7.84%)<br>4 | 2 / 50 (4.00%)<br>3  | 1 / 51 (1.96%)<br>1 |
| Infections and infestations<br>Nasopharyngitis<br>subjects affected / exposed<br>occurrences (all)                | 3 / 51 (5.88%)<br>3 | 2 / 50 (4.00%)<br>3  | 4 / 51 (7.84%)<br>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

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported