



## Clinical trial results:

### A Phase 2b, Double-Blind, Placebo-Controlled, Multinational, Multicenter, Randomized Study Evaluating the Safety and Efficacy of Intracoronary Administration of MYDICAR® (AAV1/SERCA2a) in Subjects with Heart Failure

#### Summary

|                          |                         |
|--------------------------|-------------------------|
| EudraCT number           | 2012-001700-37          |
| Trial protocol           | SE DE GB BE PL NL DK HU |
| Global end of trial date | 26 February 2016        |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 06 January 2018 |
| First version publication date | 06 January 2018 |

#### Trial information

##### Trial identification

|                       |          |
|-----------------------|----------|
| Sponsor protocol code | CELL-004 |
|-----------------------|----------|

##### Additional study identifiers

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

Notes:

#### Sponsors

|                              |  |
|------------------------------|--|
| Sponsor organisation name    | Celladon Corporation   |
| Sponsor organisation address | 12707 High Bluff Drive, Suite 200, San Diego, United States, 92130                             |
| Public contact               | Vice President, Clinical Operations, Celladon Corporation, 1 858-432-7217 , jrudy@celladon.net |
| Scientific contact           | Vice President, Clinical Operations, Celladon Corporation, 1 858-432-7217 , jrudy@celladon.net |

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                       | 26 February 2016 |
| Is this the analysis of the primary completion data? | Yes              |
| Primary completion date                              | 27 February 2015 |
| Global end of trial reached?                         | Yes              |
| Global end of trial date                             | 26 February 2016 |
| Was the trial ended prematurely?                     | No               |

Notes:

## General information about the trial

Main objective of the trial:

To determine the efficacy of a single intracoronary infusion of 1 x 10<sup>13</sup> DNase Resistant Particles (DRP) MYDICAR® (AAV1/SERCA2a) added to an optimal heart failure (HF) regimen in subjects with ischemic or non-ischemic cardiomyopathy and moderate to advanced symptoms of HF by reducing the frequency of and/or delaying HF-related hospitalizations and episodes of ambulatory worsening HF (recurrent events) compared to placebo-treated subjects.

Protection of trial subjects:

All subjects provided written informed consent and the study was conducted according to the principles of the International Council on Harmonisation Guideline on Good Clinical Practice and the principles of the World Medical Association Declaration of Helsinki. All relevant approvals from Institutional Review Boards or Institutional Ethics Committees were obtained.

Only subjects that met all study inclusion criteria and none of the exclusion criteria were entered in the study. A subject could withdraw consent to participate in the study at any time without prejudice.

Background therapy: -

Evidence for comparator: -

|   |                  |
|---|------------------|
| Actual start date of recruitment                          | 01 July 2012     |
| Long term follow-up planned                               | Yes              |
| Long term follow-up rationale                             | Safety, Efficacy |
| Long term follow-up duration                              | 1 Years          |
| Independent data monitoring committee (IDMC) involvement? | Yes              |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                    |
|--------------------------------------|--------------------|
| Country: Number of subjects enrolled | Netherlands: 1     |
| Country: Number of subjects enrolled | Poland: 11         |
| Country: Number of subjects enrolled | Sweden: 15         |
| Country: Number of subjects enrolled | United Kingdom: 14 |
| Country: Number of subjects enrolled | Belgium: 8         |
| Country: Number of subjects enrolled | Denmark: 12        |
| Country: Number of subjects enrolled | Germany: 10        |
| Country: Number of subjects enrolled | Hungary: 8         |
| Country: Number of subjects enrolled | United States: 163 |
| Country: Number of subjects enrolled | Israel: 8          |
| Worldwide total number of subjects   | 250                |
| EEA total number of subjects         | 79                 |

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)                      | 162 |
| From 65 to 84 years                       | 88  |
| 85 years and over                         | 0   |

## Subject disposition

### Recruitment

Recruitment details:

Subjects were enrolled at 55 sites in the US, Israel and the EU including Sweden, UK, Denmark, Poland, Germany, Hungary, Belgium, and the Netherlands.

### Pre-assignment

Screening details:

From 09-Jul-2012 through 05-Feb-2014, 1558 subjects at 67 of the 69 initiated sites were pre-screened for adeno-associated virus serotype 1 neutralizing antibodies. Of the 1558 subjects pre-screened, 353 were further screened at 60 sites, of which 250 at 55 sites were ultimately randomized into the trial.

### Period 1

|                              |  |
|------------------------------|--|
| Period 1 title               | Active observation period (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 a single intracoronary administration of placebo.

|  |                       |
|--|-----------------------|
| Arm type                               | Placebo               |
| Investigational medicinal product name | Placebo               |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intracoronary use     |

Dosage and administration details:

Placebo was administered via antegrade epicardial coronary artery infusion. Intravenous nitroglycerin was administered before and during placebo infusion, with up-titration based on systolic blood pressure. Infusion of placebo was tailored to the subject's coronary anatomy and multiple infusion scenarios were possible depending on the extent and distribution of coronary artery stenoses, collateralization patterns and anatomic variations. Operators were instructed that in most cases it was expected that up to 3 infusions should be performed to capture the largest portion of left ventricular blood flow.

|                  |         |
|------------------|---------|
| <b>Arm title</b> | MYDICAR |
|------------------|---------|

Arm description:

Subjects received a single intracoronary administration of MYDICAR.

|  |                       |
|--|-----------------------|
| Arm type                               | Experimental          |
| Investigational medicinal product name | MYDICAR               |
| Investigational medicinal product code |                       |
| Other name                             |                       |
| Pharmaceutical forms                   | Solution for infusion |
| Routes of administration               | Intracoronary use     |

Dosage and administration details:

MYDICAR (1 x 10<sup>13</sup> DNase resistant particles) was administered via antegrade epicardial coronary artery infusion. Intravenous nitroglycerin was administered before and during MYDICAR infusion, with up-titration based on systolic blood pressure.

Infusion of MYDICAR was tailored to the subject's coronary anatomy and multiple infusion scenarios were possible depending on the extent and distribution of coronary artery stenoses, collateralization patterns and anatomic variations. Operators were instructed that in most cases it was expected that up to 3 infusions should be performed to capture the largest portion of left ventricular blood flow.

| <b>Number of subjects in period 1</b> | Placebo | MYDICAR |
|---------------------------------------|---------|---------|
| Started                               | 127     | 123     |
| Completed                             | 101     | 98      |
| Not completed                         | 26      | 25      |
| Agreed to phone follow-up only        | 4       | 2       |
| Consent withdrawn by subject          | 1       | 2       |
| Death                                 | 12      | 16      |
| Heart transplant                      | 3       | 3       |
| Unspecified                           | 1       | -       |
| Mechanical circulatory support device | 5       | 2       |

## Baseline characteristics

### Reporting groups

|   |         |
|---|---------|
| Reporting group title   | Placebo |
| Reporting group description:  |         |
| Subjects received a single intracoronary administration of placebo. |         |
| Reporting group title   | MYDICAR |
| Reporting group description:  |         |
| Subjects received a single intracoronary administration of MYDICAR. |         |

| Reporting group values                                | Placebo | MYDICAR | Total |
|---|---------|---------|-------|
| Number of subjects                                    | 127     | 123     | 250   |
| Age categorical<br>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                        |         |         |       |
| arithmetic mean                                       | 58.5    | 60.4    |       |
| standard deviation                                    | ± 12.33 | ± 9.73  | -     |
| Gender categorical<br>Units: Subjects                 |         |         |       |
| Female  | 25      | 21      | 46    |
| Male  | 102     | 102     | 204   |

## End points

### End points reporting groups

|  |  |
|--|--|
| Reporting group title  | Placebo                                |
| Reporting group description:<br>Subjects received a single intracoronary administration of placebo.              |  |
| Reporting group title  | MYDICAR                                |
| Reporting group description:<br>Subjects received a single intracoronary administration of MYDICAR.              |  |
| Subject analysis set title   | Modified intention-to-treat population |
| Subject analysis set type  | Modified intention-to-treat            |
| Subject analysis set description:<br>All randomized subjects who received the investigational medicinal product. |  |

### Primary: Recurrent heart failure-related hospitalizations and worsening heart failure

|   |  |
|---|--|
| End point title   | Recurrent heart failure-related hospitalizations and worsening heart failure |
| End point description:<br>The primary efficacy endpoint was the time to recurrent events (hospitalizations related to failure of the native heart that was not implanted with a mechanical circulatory support device [MCSD; left, right or biventricular assist device, total artificial heart] and ambulatory worsening failure of the native heart that was not implanted with an MCSD in the presence of terminal events (all-cause death, heart transplant, MCSD implantation) based on the joint frailty model. |  |
| End point type  | Primary  |
| End point timeframe:<br>Clinical events were collected until the Primary Analysis Data Cutoff was reached which was when all subjects had completed the 12-month Active Observation Period, or terminated early and at least 186 adjudicated primary endpoints had occurred in the ITT.   |  |

| End point values                               | Placebo         | MYDICAR         |  |  |
|--|-----------------|-----------------|--|--|
| Subject group type                             | Reporting group | Reporting group |  |  |
| Number of subjects analysed                    | 122             | 121             |  |  |
| Units: Recurrent event rate (per patient-year) |                 |                 |  |  |
| number (not applicable)                        | 0.74            | 0.63            |  |  |

### Statistical analyses

|                            |                       |
|----------------------------|-----------------------|
| Statistical analysis title | Hazard ratio analysis |
| Comparison groups          | Placebo v MYDICAR     |

|   |                   |
|---|-------------------|
| Number of subjects included in analysis | 243               |
| Analysis specification                  | Pre-specified     |
| Analysis type                           | superiority       |
| Parameter estimate                      | Hazard ratio (HR) |
| Point estimate                          | 0.93              |
| Confidence interval                     |                   |
| level                                   | 95 %              |
| sides                                   | 2-sided           |
| lower limit                             | 0.53              |
| upper limit                             | 1.65              |



## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

The reporting period for treatment-emerging adverse events started on the day of infusion with the investigational medicinal product (Day 0) and ended when a subject completed the 12-month active observation period or was terminated from the study.

Adverse event reporting additional description:

Non-serious adverse events were not analyzed separately; therefore, the list of non-serious adverse events also includes serious adverse events.

|                 |            |
|-----------------|------------|
| Assessment type | Systematic |
|-----------------|------------|

### Dictionary used

|                 |        |
|-----------------|--------|
| Dictionary name | MedDRA |
|-----------------|--------|

|                    |      |
|--------------------|------|
| Dictionary version | 18.0 |
|--------------------|------|

### Reporting groups

|                       |         |
|-----------------------|---------|
| Reporting group title | Placebo |
|-----------------------|---------|

Reporting group description:

Subjects received a single intracoronary administration of placebo.

|                       |         |
|-----------------------|---------|
| Reporting group title | MYDICAR |
|-----------------------|---------|

Reporting group description:

Subjects received a single intracoronary administration of MYDICAR.

| Serious adverse events                            | Placebo           | MYDICAR           |  |
|---|-------------------|-------------------|--|
| Total subjects affected by serious adverse events |                   |                   |  |
| subjects affected / exposed                       | 72 / 122 (59.02%) | 71 / 121 (58.68%) |  |
| number of deaths (all causes)                     | 20                | 25                |  |
| number of deaths resulting from adverse events    |                   |                   |  |
| Vascular disorders                                |                   |                   |  |
| Accelerated hypertension                          |                   |                   |  |
| subjects affected / exposed                       | 0 / 122 (0.00%)   | 1 / 121 (0.83%)   |  |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |
| Aortic aneurysm                                   |                   |                   |  |
| subjects affected / exposed                       | 0 / 122 (0.00%)   | 1 / 121 (0.83%)   |  |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |
| Arteriovenous fistula                             |                   |                   |  |
| subjects affected / exposed                       | 0 / 122 (0.00%)   | 1 / 121 (0.83%)   |  |
| occurrences causally related to treatment / all   | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all        | 0 / 0             | 0 / 0             |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Haematoma                                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypotension                                     |                 |                 |  |
| subjects affected / exposed                     | 4 / 122 (3.28%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Peripheral ischaemia                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Venous insufficiency                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Surgical and medical procedures                 |                 |                 |  |
| Cardiac ablation                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac pacemaker insertion                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 3 / 121 (2.48%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac resynchronisation therapy               |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Coronary arterial stent insertion               |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Heart transplant                                |                 |                 |  |

|  |                 |                 |  |
|--|-----------------|-----------------|--|
| subjects affected / exposed                          | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Implantable defibrillator insertion                  |                 |                 |  |
| subjects affected / exposed                          | 6 / 122 (4.92%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 6           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Medical device battery replacement                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Medical device change                                |                 |                 |  |
| subjects affected / exposed                          | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Percutaneous coronary intervention                   |                 |                 |  |
| subjects affected / exposed                          | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Pleurodesis  |                 |                 |  |
| subjects affected / exposed                          | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Tooth extraction                                     |                 |                 |  |
| subjects affected / exposed                          | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| Ventricular assist device insertion                  |                 |                 |  |
| subjects affected / exposed                          | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all           | 0 / 0           | 0 / 0           |  |
| General disorders and administration site conditions |                 |                 |  |
| Adverse drug reaction                                |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Asthenia  |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chest discomfort                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chest pain                                      |                 |                 |  |
| subjects affected / exposed                     | 6 / 122 (4.92%) | 4 / 121 (3.31%) |  |
| occurrences causally related to treatment / all | 0 / 7           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device lead issue                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Device malfunction                              |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Implant site oedema                             |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| medical device complication                     |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Necrosis  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Non-cardiac chest pain                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Oedema peripheral                               |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sudden cardiac death                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 2           |  |
| Sudden death                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Immune system disorders                         |                 |                 |  |
| Hypersensitivity                                |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 1 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory, thoracic and mediastinal disorders |                 |                 |  |
| Acute pulmonary oedema                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Acute respiratory failure                       |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Asthma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Chronic obstructive pulmonary disease           |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dyspnoea  |                 |                 |  |
| subjects affected / exposed                     | 5 / 122 (4.10%) | 4 / 121 (3.31%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 5           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Haemothorax                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleural effusion                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 10          | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pleuritic pain                                  |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary congestion                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary embolism                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary hypertension                          |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 122 (0.00%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pulmonary oedema                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory arrest                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Respiratory failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Psychiatric disorders                           |                 |                 |  |
| Confusional state                               |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Mental status changes                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Investigations                                  |                 |                 |  |
| Arthroscopy                                     |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Blood magnesium decreased                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ejection fraction decreased                     |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Heart rate increased                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| International normalised ratio increased        |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Scan abnormal                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Transplant evaluation                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury, poisoning and procedural complications  |                 |                 |  |
| Cardiac valve rupture                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Humerus fracture                                |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Injury  |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Rib fracture                                    |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Subdural haematoma                              |                 |                 |  |
| subjects affected / exposed                     | 3 / 122 (2.46%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Vascular pseudoaneurysm                         |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cardiac disorders                               |                 |                 |  |
| Angina pectoris                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Angina unstable                                 |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Arrhythmia                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial fibrillation                             |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 6 / 121 (4.96%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial flutter                                  |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Atrial tachycardia                              |                 |                 |  |

|   |                   |                   |  |
|---|-------------------|-------------------|--|
| subjects affected / exposed                     | 2 / 122 (1.64%)   | 0 / 121 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 3             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac arrest                                  |                   |                   |  |
| subjects affected / exposed                     | 0 / 122 (0.00%)   | 4 / 121 (3.31%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 5             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 3             |  |
| Cardiac failure                                 |                   |                   |  |
| subjects affected / exposed                     | 23 / 122 (18.85%) | 25 / 121 (20.66%) |  |
| occurrences causally related to treatment / all | 0 / 45            | 0 / 44            |  |
| deaths causally related to treatment / all      | 0 / 5             | 0 / 4             |  |
| Cardiac failure acute                           |                   |                   |  |
| subjects affected / exposed                     | 6 / 122 (4.92%)   | 11 / 121 (9.09%)  |  |
| occurrences causally related to treatment / all | 0 / 12            | 0 / 16            |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Cardiac failure chronic                         |                   |                   |  |
| subjects affected / exposed                     | 0 / 122 (0.00%)   | 1 / 121 (0.83%)   |  |
| occurrences causally related to treatment / all | 0 / 0             | 0 / 1             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiac failure congestive                      |                   |                   |  |
| subjects affected / exposed                     | 12 / 122 (9.84%)  | 8 / 121 (6.61%)   |  |
| occurrences causally related to treatment / all | 0 / 39            | 0 / 8             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Cardiogenic shock                               |                   |                   |  |
| subjects affected / exposed                     | 2 / 122 (1.64%)   | 2 / 121 (1.65%)   |  |
| occurrences causally related to treatment / all | 0 / 2             | 0 / 2             |  |
| deaths causally related to treatment / all      | 0 / 1             | 0 / 0             |  |
| Cardiomegaly                                    |                   |                   |  |
| subjects affected / exposed                     | 1 / 122 (0.82%)   | 0 / 121 (0.00%)   |  |
| occurrences causally related to treatment / all | 0 / 1             | 0 / 0             |  |
| deaths causally related to treatment / all      | 0 / 0             | 0 / 0             |  |
| Cardiomyopathy                                  |                   |                   |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ischaemic cardiomyopathy                        |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Mitral valve disease                            |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Myocardial infarction                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Palpitations                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular arrhythmia                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular failure                             |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular fibrillation                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 3 / 121 (2.48%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ventricular tachycardia                         |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 6 / 122 (4.92%) | 5 / 121 (4.13%) |  |
| occurrences causally related to treatment / all | 0 / 13          | 0 / 8           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nervous system disorders                        |                 |                 |  |
| Cerebrovascular accident                        |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 1           | 0 / 0           |  |
| Convulsion                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Dizziness                                       |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hemiplegia                                      |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoxic-ischaemic encephalopathy                |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Syncope   |                 |                 |  |
| subjects affected / exposed                     | 4 / 122 (3.28%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ear and labyrinth disorders                     |                 |                 |  |
| Vertigo   |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Eye disorders                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Amaurosis Fugax                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cataract  |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Glaucoma  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal disorders                      |                 |                 |  |
| Abdominal pain                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Abdominal pain upper                            |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Ascites   |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 3           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diarrhoea                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastrointestinal haemorrhage                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Nausea  |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 2 / 122 (1.64%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Pancreatitis relapsing                          |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Vomiting  |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hepatobiliary disorders                         |                 |                 |  |
| Liver injury                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal and urinary disorders                     |                 |                 |  |
| Nephropathy                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal artery stenosis                           |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Renal failure                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| renal failure acute                             |                 |                 |  |
| subjects affected / exposed                     | 6 / 122 (4.92%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 6           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocrine disorders                             |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| Hypothyroidism                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Inappropriate antidiuretic hormone secretion    |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Musculoskeletal and connective tissue disorders |                 |                 |  |
| Gouty arthritis                                 |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteoarthritis                                  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infections and infestations                     |                 |                 |  |
| Bronchitis                                      |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Cystitis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Endocarditis                                    |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Erysipelas                                      |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis                                 |                 |                 |  |
| subjects affected / exposed                     | 3 / 122 (2.46%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 3           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Gastroenteritis viral                           |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Implant site infection                          |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Infection                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Influenza                                       |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Lower respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Osteomyelitis                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 2 / 121 (1.65%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 2           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Pneumonia                                       |                 |                 |  |



|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 5 / 122 (4.10%) | 4 / 121 (3.31%) |  |
| occurrences causally related to treatment / all | 0 / 5           | 0 / 4           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 1           |  |
| Postoperative wound infection                   |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Sepsis  |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Upper respiratory tract infection               |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Urinary tract infection                         |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolism and nutrition disorders              |                 |                 |  |
| Dehydration                                     |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Diabetes mellitus inadequate control            |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyperkalaemia                                   |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypoglycaemia                                   |                 |                 |  |

|   |                 |                 |  |
|---|-----------------|-----------------|--|
| subjects affected / exposed                     | 1 / 122 (0.82%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hypokalaemia                                    |                 |                 |  |
| subjects affected / exposed                     | 1 / 122 (0.82%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Hyponatraemia                                   |                 |                 |  |
| subjects affected / exposed                     | 2 / 122 (1.64%) | 0 / 121 (0.00%) |  |
| occurrences causally related to treatment / all | 1 / 2           | 0 / 0           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |
| Metabolic acidosis                              |                 |                 |  |
| subjects affected / exposed                     | 0 / 122 (0.00%) | 1 / 121 (0.83%) |  |
| occurrences causally related to treatment / all | 0 / 0           | 0 / 1           |  |
| deaths causally related to treatment / all      | 0 / 0           | 0 / 0           |  |

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

| <b>Non-serious adverse events</b>                     | Placebo            | MYDICAR            |  |
|---|--------------------|--------------------|--|
| Total subjects affected by non-serious adverse events |                    |                    |  |
| subjects affected / exposed                           | 111 / 122 (90.98%) | 111 / 121 (91.74%) |  |
| Vascular disorders                                    |                    |                    |  |
| Hypotension   |                    |                    |  |
| subjects affected / exposed                           | 9 / 122 (7.38%)    | 11 / 121 (9.09%)   |  |
| occurrences (all)                                     | 15                 | 11                 |  |
| Cardiac disorders                                     |                    |                    |  |
| Atrial fibrillation                                   |                    |                    |  |
| subjects affected / exposed                           | 4 / 122 (3.28%)    | 8 / 121 (6.61%)    |  |
| occurrences (all)                                     | 4                  | 11                 |  |
| Cardiac failure                                       |                    |                    |  |
| subjects affected / exposed                           | 29 / 122 (23.77%)  | 31 / 121 (25.62%)  |  |
| occurrences (all)                                     | 57                 | 58                 |  |
| Cardiac failure acute                                 |                    |                    |  |
| subjects affected / exposed                           | 6 / 122 (4.92%)    | 11 / 121 (9.09%)   |  |
| occurrences (all)                                     | 12                 | 16                 |  |

|  |                         |                        |  |
|--|-------------------------|------------------------|--|
| Cardiac failure congestive<br>subjects affected / exposed<br>occurrences (all)   | 13 / 122 (10.66%)<br>42 | 10 / 121 (8.26%)<br>10 |  |
| Ventricular tachycardia<br>subjects affected / exposed<br>occurrences (all)  | 9 / 122 (7.38%)<br>17   | 10 / 121 (8.26%)<br>14 |  |
| Surgical and medical procedures<br>Implantable defibrillator insertion<br>subjects affected / exposed<br>occurrences (all) | 7 / 122 (5.74%)<br>7    | 0 / 121 (0.00%)<br>0   |  |
| Nervous system disorders<br>Dizziness<br>subjects affected / exposed<br>occurrences (all)                                  | 8 / 122 (6.56%)<br>8    | 9 / 121 (7.44%)<br>9   |  |
| Syncope<br>subjects affected / exposed<br>occurrences (all)  | 7 / 122 (5.74%)<br>10   | 2 / 121 (1.65%)<br>2   |  |
| General disorders and administration<br>site conditions<br>Asthenia<br>subjects affected / exposed<br>occurrences (all)    | 4 / 122 (3.28%)<br>4    | 7 / 121 (5.79%)<br>8   |  |
| Chest pain<br>subjects affected / exposed<br>occurrences (all)   | 7 / 122 (5.74%)<br>8    | 8 / 121 (6.61%)<br>10  |  |
| Fatigue<br>subjects affected / exposed<br>occurrences (all)  | 7 / 122 (5.74%)<br>8    | 8 / 121 (6.61%)<br>8   |  |
| Oedema peripheral<br>subjects affected / exposed<br>occurrences (all)  | 2 / 122 (1.64%)<br>2    | 7 / 121 (5.79%)<br>7   |  |
| Gastrointestinal disorders<br>Diarrhoea<br>subjects affected / exposed<br>occurrences (all)                                | 7 / 122 (5.74%)<br>7    | 4 / 121 (3.31%)<br>5   |  |
| Nausea   |                         |                        |  |

|   |                        |                       |  |
|---|------------------------|-----------------------|--|
| subjects affected / exposed<br>occurrences (all)  | 11 / 122 (9.02%)<br>11 | 6 / 121 (4.96%)<br>7  |  |
| Vomiting<br>subjects affected / exposed<br>occurrences (all)  | 7 / 122 (5.74%)<br>7   | 4 / 121 (3.31%)<br>4  |  |
| Respiratory, thoracic and mediastinal disorders<br>Dyspnoea<br>subjects affected / exposed<br>occurrences (all)   | 12 / 122 (9.84%)<br>14 | 9 / 121 (7.44%)<br>11 |  |
| Renal and urinary disorders<br>Renal failure acute<br>subjects affected / exposed<br>occurrences (all)            | 9 / 122 (7.38%)<br>10  | 5 / 121 (4.13%)<br>5  |  |
| Musculoskeletal and connective tissue disorders<br>Arthralgia<br>subjects affected / exposed<br>occurrences (all) | 4 / 122 (3.28%)<br>4   | 7 / 121 (5.79%)<br>7  |  |
| Infections and infestations<br>Bronchitis<br>subjects affected / exposed<br>occurrences (all)                     | 7 / 122 (5.74%)<br>7   | 5 / 121 (4.13%)<br>6  |  |
| Pneumonia<br>subjects affected / exposed<br>occurrences (all)   | 8 / 122 (6.56%)<br>8   | 7 / 121 (5.79%)<br>7  |  |
| Metabolism and nutrition disorders<br>Gout<br>subjects affected / exposed<br>occurrences (all)                    | 8 / 122 (6.56%)<br>9   | 6 / 121 (4.96%)<br>6  |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment  |
|------------------|--|
| 30 May 2012      | Exclusion criterion #10 was removed and text added as a new expanded section, "Section 4.3 Contraindications for Infusion of Investigational Medicinal Product".<br>Exclusion criterion #15 was added to exclude subjects with current history of malignancy except for basal cell carcinoma.<br>The collection of biopsies or specimens of myocardial tissue was added, if a subject received a left ventricular assist device or transplant, for qPCR analysis to determine presence of the vector transgene.<br>"Section 7.15 Clinical Events" was added.   |
| 14 February 2013 | Inclusion Criterion #2 was changed to exclude hypertrophic cardiomyopathy and include toxic and alcoholic myopathies if sufficient time had elapsed to rule out spontaneous recovery.<br>Inclusion Criterion #5 was changed to include New York Heart Association Class II.<br>Inclusion Criterion #6 was changed to specify that optimized HF therapy was to also be 'individualized' and 'appropriate to the individual subject'.<br>Inclusion Criterion #9 was added, which required all subjects to have a risk factor of either hospitalization within 6 months of Screening or elevated N-terminal prohormone brain natriuretic peptide/B-Type natriuretic peptide within 30 days of Screening.<br>Inclusion Criterion #10 was added regarding angiography.<br>Exclusion Criterion #2 was changed to include acute myocarditis.<br>Exclusion Criterion #13 was changed to define anemia as hemoglobin $\leq 9\text{g/dL}$ provided there was no evidence of bleeding.<br>Exclusion Criterion #15 was changed to specify "Diagnosis of, or treatment for, any cancer other than basal cell carcinoma within the last 5 years."<br>The end of study and Primary Analysis Date Cutoff definitions were changed.<br>"Discontinuation of the Study" was changed to "Discontinuation of Enrollment" and the reasons for discontinuing enrollment were restricted to the recommendation of the Data Monitoring Committee or in the event of bankruptcy.<br>Study medication storage conditions were updated for unopened vials to include 2-8°C for up to 3 months.<br>The table of "Commercially Available MYDICAR Device Delivery Products" was expanded. |
| 21 October 2013  | The number of subjects was increased from 200 to 250 (from 100 to 125 per treatment group) and the number of required primary endpoints was increased from 180 to 186 in order to declare the Primary Analysis Date Cutoff.<br>Appendix L was added to describe hospitalization and biohazard handling procedures in Hungary.  |
| 18 March 2014    | The duration of follow-up of subjects was extended from 2 to 5 years with the addition of the Extended Long-Term Follow-Up Period which encompassed quarterly telephonic visits.   |
| 01 December 2014 | The modified intention-to-treat (mITT) population (randomized subjects who received study medication) was defined as the analysis population for the primary efficacy analysis.<br>The mITT <sub>x</sub> analysis population was added, which excluded subjects who were adeno-associated virus serotype 1 neutralizing antibody positive or equivocal 1:2 at Baseline.  |
| 11 June 2015     | The extended long-term follow-up (LT-FUP) was eliminated.<br>LT-FUP quarterly visits were changed to telephone calls and collection of health status only.<br>Tissue collection was eliminated.<br>The collection of clinical events in the LT-FUP was eliminated.   |

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Notes:

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### **Interruptions (globally)**

Were there any global interruptions to the trial? No

### **Limitations and caveats**

None reported