



## Clinical trial results:

### Investigation of the safety and feasibility of AAV1/SERCA2a gene transfer in patients with chronic heart failure and a left ventricular assist device

#### Summary

|                          |                   |
|--------------------------|-------------------|
| EudraCT number           | 2007-002809-48    |
| Trial protocol           | GB                |
| Global end of trial date | 19 September 2015 |

#### Results information

|                                |                 |
|--------------------------------|-----------------|
| Result version number          | v1 (current)    |
| This version publication date  | 05 October 2016 |
| First version publication date | 05 October 2016 |

#### Trial information

##### Trial identification

|                       |        |
|-----------------------|--------|
| Sponsor protocol code | CRO782 |
|-----------------------|--------|

##### Additional study identifiers

|                                    |                                   |
|------------------------------------|-----------------------------------|
| ISRCTN number                      | -                                 |
| ClinicalTrials.gov id (NCT number) | NCT00534703                       |
| WHO universal trial number (UTN)   | -                                 |
| Other trial identifiers            | Funder reference: SP/09/007/27920 |

Notes:

#### Sponsors

|                              |                                                                                               |
|------------------------------|-----------------------------------------------------------------------------------------------|
| Sponsor organisation name    | Imperial College London/ Joint Research Compliance Office                                     |
| Sponsor organisation address | Medical School Building, London, United Kingdom, W2 1PG                                       |
| Public contact               | Dr. Alexander Lyon , Imperial College London, +44 (0)207 351 8164, t.sasikaran@imperial.ac.uk |
| Scientific contact           | Dr. Alexander Lyon , Imperial College London, +44 (0) 207 351 8164, a.lyon@imperial.ac.uk     |

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                       | 23 June 2016      |
| Is this the analysis of the primary completion data? | Yes               |
| Primary completion date                              | 19 September 2015 |
| Global end of trial reached?                         | Yes               |
| Global end of trial date                             | 19 September 2015 |
| Was the trial ended prematurely?                     | Yes               |

Notes:

## General information about the trial

Main objective of the trial:

To determine the safety and feasibility of increasing the level of SERCA2a protein by viral gene transfer into patients with advanced heart failure who have had a mechanical pump (left ventricular assist device) that assists heart function implanted.

Protection of trial subjects:

Patients are diagnosed with advanced heart failure and have undergone recent LVAD insertion and it is possible they will have comprehension difficulties. Study staff ensured that a full understanding of the protocol and its implications was reached during the consent process.

Background therapy: -

Evidence for comparator: -

|                                                           |                           |
|-----------------------------------------------------------|---------------------------|
| Actual start date of recruitment                          | 23 June 2014              |
| Long term follow-up planned                               | Yes                       |
| Long term follow-up rationale                             | Safety, Regulatory reason |
| Long term follow-up duration                              | 10 Years                  |
| Independent data monitoring committee (IDMC) involvement? | Yes                       |

Notes:

## Population of trial subjects

### Subjects enrolled per country

|                                      |                   |
|--------------------------------------|-------------------|
| Country: Number of subjects enrolled | United Kingdom: 5 |
| Worldwide total number of subjects   | 5                 |
| EEA total number of subjects         | 5                 |

Notes:

### Subjects enrolled per age group

|                                           |   |
|-------------------------------------------|---|
| In utero                                  | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days)                      | 0 |
| Infants and toddlers (28 days-23 months)  | 0 |
| Children (2-11 years)                     | 0 |
| Adolescents (12-17 years)                 | 0 |
| Adults (18-64 years)                      | 4 |
| From 65 to 84 years                       | 1 |

|                   |   |
|-------------------|---|
| 85 years and over | 0 |
|-------------------|---|

## Subject disposition

### Recruitment

Recruitment details:

Potentially eligible patients have been identified by staff involved in managing advanced heart failure and transplantation in the collaborating institution. The patients who have agreed to take part in the study have signed the consent forms prior to taking part in the study.

### Pre-assignment

Screening details:

Patients with prior LVAD implantation have undergone screening assessments including a test to look for presence of AAV NABs.

### Period 1

|                              |                                                 |
|------------------------------|-------------------------------------------------|
| Period 1 title               | Overall period (overall period)                 |
| Is this the baseline period? | Yes                                             |
| Allocation method            | Randomised - controlled                         |
| Blinding used                | Double blind                                    |
| Roles blinded                | Subject, Investigator, Monitor, Carer, Assessor |

### Arms

|                              |              |
|------------------------------|--------------|
| Are arms mutually exclusive? | Yes          |
| <b>Arm title</b>             | AAV1/SERCA2A |

Arm description: -

|                                        |                       |
|----------------------------------------|-----------------------|
| 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:

1 x 10<sup>13</sup> DRP (dnase resistant particles). AAV1/SERCA2a is given as a single intracoronary infusion lasting approximately 10 minutes. Patients are followed up for 6 months (end of study) and there is an additional annual followup for 10 years for safety purposes.

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

Arm description: -

|                                        |                       |
|----------------------------------------|-----------------------|
| 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 is given as a single intracoronary infusion lasting approximately 10 minutes.

| <b>Number of subjects in period 1</b> | AAV1/SERCA2A | PLACEBO |
|---------------------------------------|--------------|---------|
| Started                               | 4            | 1       |
| Completed                             | 4            | 1       |

## Baseline characteristics

### Reporting groups

|                                |              |
|--------------------------------|--------------|
| Reporting group title          | AAV1/SERCA2A |
| Reporting group description: - |              |
| Reporting group title          | PLACEBO      |
| Reporting group description: - |              |

| Reporting group values                             | AAV1/SERCA2A | PLACEBO  | Total |
|----------------------------------------------------|--------------|----------|-------|
| Number of subjects                                 | 4            | 1        | 5     |
| Age categorical<br>Units: Subjects                 |              |          |       |
| In utero                                           | 0            | 0        | 0     |
| Preterm newborn infants (gestational age < 37 wks) | 0            | 0        | 0     |
| Newborns (0-27 days)                               | 0            | 0        | 0     |
| Infants and toddlers (28 days-23 months)           | 0            | 0        | 0     |
| Children (2-11 years)                              | 0            | 0        | 0     |
| Adolescents (12-17 years)                          | 0            | 0        | 0     |
| Adults (18-64 years)                               | 3            | 1        | 4     |
| From 65-84 years                                   | 1            | 0        | 1     |
| 85 years and over                                  | 0            | 0        | 0     |
| Age continuous<br>Units: years                     |              |          |       |
| arithmetic mean                                    | 41           | 49       |       |
| full range (min-max)                               | 29 to 69     | 49 to 49 | -     |
| Gender categorical<br>Units: Subjects              |              |          |       |
| Female                                             | 1            | 0        | 1     |
| Male                                               | 3            | 1        | 4     |
| Ethnicity<br>Units: Subjects                       |              |          |       |
| White                                              | 4            | 0        | 4     |
| Black                                              | 0            | 1        | 1     |
| Not Recorded                                       | 0            | 0        | 0     |
| Smoking History<br>Units: Subjects                 |              |          |       |
| Never                                              | 4            | 1        | 5     |
| Not Recorded                                       | 0            | 0        | 0     |
| Alcohol Consumption<br>Units: Subjects             |              |          |       |
| None                                               | 1            | 0        | 1     |
| ≤1 alcoholic drink p/w                             | 3            | 1        | 4     |
| Not Recorded                                       | 0            | 0        | 0     |
| Type of Heart Failure<br>Units: Subjects           |              |          |       |
| Dilated cardiomyopathy                             | 1            | 1        | 2     |
| Familial cardiomyopathy                            | 2            | 0        | 2     |

|                                                           |            |                |   |
|-----------------------------------------------------------|------------|----------------|---|
| Valvular Heart Disease                                    | 1          | 0              | 1 |
| Not Recorded                                              | 0          | 0              | 0 |
| Type of LVAD                                              |            |                |   |
| Units: Subjects                                           |            |                |   |
| Heartware HVAD                                            | 3          | 1              | 4 |
| Thoratec Heartmate 2                                      | 1          | 0              | 1 |
| Not Recorded                                              | 0          | 0              | 0 |
| Cardiac Transplant Waiting List?                          |            |                |   |
| If the patient on the waiting list for a heart transplant |            |                |   |
| Units: Subjects                                           |            |                |   |
| Yes                                                       | 4          | 1              | 5 |
| Not Recorded                                              | 0          | 0              | 0 |
| Subject History of Dislipidemia                           |            |                |   |
| IF the patient has a history of dislipidemia              |            |                |   |
| Units: Subjects                                           |            |                |   |
| No                                                        | 4          | 1              | 5 |
| Not Recorded                                              | 0          | 0              | 0 |
| Subject History of Thyroid Disorders                      |            |                |   |
| If the patient has a history of thyroid disorders         |            |                |   |
| Units: Subjects                                           |            |                |   |
| No                                                        | 4          | 1              | 5 |
| Not Recorded                                              | 0          | 0              | 0 |
| Subject History of Thoracic Radiation                     |            |                |   |
| If the patient has a history of thoracic radiation        |            |                |   |
| Units: Subjects                                           |            |                |   |
| No                                                        | 4          | 1              | 5 |
| Not Recorded                                              | 0          | 0              | 0 |
| Subject History of Hypertension                           |            |                |   |
| If the patient has a history of hypertension              |            |                |   |
| Units: Subjects                                           |            |                |   |
| No                                                        | 4          | 1              | 5 |
| Not Recorded                                              | 0          | 0              | 0 |
| Strata                                                    |            |                |   |
| Units: Subjects                                           |            |                |   |
| AAV -ve                                                   | 3          | 1              | 4 |
| AAV +ve                                                   | 1          | 0              | 1 |
| Not Recorded                                              | 0          | 0              | 0 |
| Height                                                    |            |                |   |
| Height of Patient in cm                                   |            |                |   |
| Units: cm                                                 |            |                |   |
| arithmetic mean                                           | 174.75     | 173            |   |
| full range (min-max)                                      | 164 to 185 | 173 to 173     | - |
| Weight                                                    |            |                |   |
| Weight of patient in cm                                   |            |                |   |
| Units: kg                                                 |            |                |   |
| arithmetic mean                                           | 73.05      | 102.5          |   |
| full range (min-max)                                      | 62 to 87.7 | 102.5 to 102.5 | - |
| BMI                                                       |            |                |   |
| BMI of patient in kg/m2                                   |            |                |   |
| Units: kg/m2                                              |            |                |   |
| arithmetic mean                                           | 23.795     | 34.25          |   |

|                               |                |                |   |
|-------------------------------|----------------|----------------|---|
| full range (min-max)          | 21.45 to 27.07 | 34.25 to 34.25 | - |
| Duration of Optimal HF Regime |                |                |   |
| Units: months                 |                |                |   |
| arithmetic mean               | 9.25           | 27             |   |
| full range (min-max)          | 1 to 19        | 27 to 27       | - |
| LDH                           |                |                |   |
| Units: U/L                    |                |                |   |
| arithmetic mean               | 593.5          | 395            |   |
| full range (min-max)          | 416 to 835     | 395 to 395     | - |
| Creatinine                    |                |                |   |
| Units: micromole(s)/litre     |                |                |   |
| arithmetic mean               | 85.75          | 128            |   |
| full range (min-max)          | 62 to 130      | 128 to 128     | - |
| 6MWT                          |                |                |   |
| Six-minute walk test          |                |                |   |
| Units: metres                 |                |                |   |
| arithmetic mean               | 531.75         | 563            |   |
| full range (min-max)          | 397 to 627     | 563 to 563     | - |
| Peak VO2                      |                |                |   |
| Units: mls/kg/min             |                |                |   |
| arithmetic mean               | 20.95          | 13.5           |   |
| full range (min-max)          | 15.6 to 28.3   | 13.5 to 13.5   | - |

## End points

### End points reporting groups

|                                |              |
|--------------------------------|--------------|
| Reporting group title          | AAV1/SERCA2A |
| Reporting group description: - |              |
| Reporting group title          | PLACEBO      |
| Reporting group description: - |              |

### Primary: Safety of administering AAV1/SERCA2a to LVAD patients

|                                                                                                                                                |                                                                      |
|------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------|
| End point title                                                                                                                                | Safety of administering AAV1/SERCA2a to LVAD patients <sup>[1]</sup> |
| End point description:<br>Safety is defined as incidence of death and major adverse cardiovascular events, and out of range laboratory values. |                                                                      |
| End point type                                                                                                                                 | Primary                                                              |
| End point timeframe:<br>From Baseline to 6 months                                                                                              |                                                                      |

Notes:

[1] - No statistical analyses have been specified for this primary end point. It is expected there is at least one statistical analysis for each primary end point.

Justification: The trial was terminated early with only 5 subjects enrolled. As a result full statistical analysis for both primary and secondary outcomes was impossible and a more pragmatic approach was undertaken to assess product safety.

| End point values            | AAV1/SERCA2A    | PLACEBO         |  |  |
|-----------------------------|-----------------|-----------------|--|--|
| Subject group type          | Reporting group | Reporting group |  |  |
| Number of subjects analysed | 4               | 1               |  |  |
| Units: events               |                 |                 |  |  |
| Death                       | 1               | 0               |  |  |

### Statistical analyses

No statistical analyses for this end point

### Secondary: Presence of SERCA DNA - Transplant

|                                                                                                                                                  |                                    |
|--------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------------|
| End point title                                                                                                                                  | Presence of SERCA DNA - Transplant |
| End point description:<br>AAV1/SERCA2a vector DNA presence in the heart by qPCR. Greatest value between the 4 samples per subject to be counted. |                                    |
| BLOD = Below Limit of Detection                                                                                                                  |                                    |
| End point type                                                                                                                                   | Secondary                          |
| End point timeframe:<br>From Baseline to 6 Months                                                                                                |                                    |

| End point values                               | AAV1/SERCA2A    | PLACEBO         |  |  |
|------------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                             | Reporting group | Reporting group |  |  |
| Number of subjects analysed                    | 4               | 1               |  |  |
| Units: subjects                                |                 |                 |  |  |
| No Sample Available                            | 2               | 1               |  |  |
| BLOD                                           | 1               | 0               |  |  |
| 20.0 - 49.9 ss DNA copy numbers/ µg human gDNA | 0               | 0               |  |  |
| 50.0 - 99.9 ss DNA copy numbers/ µg human gDNA | 1               | 0               |  |  |
| ≥ 100 ss DNA copy numbers/ µg human gDNA       | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Secondary: Presence of SERCA DNA - Biopsy

|                                                                                                                                   |                                |
|-----------------------------------------------------------------------------------------------------------------------------------|--------------------------------|
| End point title                                                                                                                   | Presence of SERCA DNA - Biopsy |
| End point description:                                                                                                            |                                |
| AAV1/SERCA2a vector DNA presence in the heart by qPCR: highest reading per subject to be used.<br>BLOD = Below Limit of Detection |                                |
| End point type                                                                                                                    | Secondary                      |
| End point timeframe:                                                                                                              |                                |
| From Baseline to 6 Months                                                                                                         |                                |

| End point values                               | AAV1/SERCA2A    | PLACEBO         |  |  |
|------------------------------------------------|-----------------|-----------------|--|--|
| Subject group type                             | Reporting group | Reporting group |  |  |
| Number of subjects analysed                    | 4               | 1               |  |  |
| Units: subjects                                |                 |                 |  |  |
| No sample taken                                | 3               | 1               |  |  |
| BLOD                                           | 0               | 0               |  |  |
| 20.0 - 49.9 ss DNA copy numbers/ µg human gDNA | 1               | 0               |  |  |
| 50.0 - 99.9 ss DNA copy numbers/ µg human gDNA | 0               | 0               |  |  |
| ≥ 100 ss DNA copy numbers/ µg human gDNA       | 0               | 0               |  |  |

## Statistical analyses

No statistical analyses for this end point

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From consent to 6 months follow-up

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

### Dictionary used

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

|                    |      |
|--------------------|------|
| Dictionary version | 19.1 |
|--------------------|------|

### Reporting groups

|                       |              |
|-----------------------|--------------|
| Reporting group title | AAV1/SERCA2A |
|-----------------------|--------------|

Reporting group description: -

|                       |         |
|-----------------------|---------|
| Reporting group title | PLACEBO |
|-----------------------|---------|

Reporting group description: -

| Serious adverse events                               | AAV1/SERCA2A   | PLACEBO       |  |
|------------------------------------------------------|----------------|---------------|--|
| Total subjects affected by serious adverse events    |                |               |  |
| subjects affected / exposed                          | 2 / 4 (50.00%) | 0 / 1 (0.00%) |  |
| number of deaths (all causes)                        | 1              | 0             |  |
| number of deaths resulting from adverse events       | 0              | 0             |  |
| Surgical and medical procedures                      |                |               |  |
| Heart transplant                                     |                |               |  |
| subjects affected / exposed                          | 1 / 4 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 0          | 0 / 0         |  |
| Cardiac disorders                                    |                |               |  |
| Cardiac failure                                      |                |               |  |
| subjects affected / exposed                          | 1 / 4 (25.00%) | 0 / 1 (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 |                |               |  |
| Death                                                |                |               |  |
| subjects affected / exposed                          | 1 / 4 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences causally related to treatment / all      | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all           | 0 / 1          | 0 / 0         |  |
| Product issues                                       |                |               |  |
| Device alarm issue                                   |                |               |  |

|                                                 |                |               |  |
|-------------------------------------------------|----------------|---------------|--|
| subjects affected / exposed                     | 1 / 4 (25.00%) | 0 / 1 (0.00%) |  |
| occurrences causally related to treatment / all | 0 / 1          | 0 / 0         |  |
| deaths causally related to treatment / all      | 0 / 0          | 0 / 0         |  |

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

| <b>Non-serious adverse events</b>                     | AAV1/SERCA2A    | PLACEBO         |  |
|-------------------------------------------------------|-----------------|-----------------|--|
| Total subjects affected by non-serious adverse events |                 |                 |  |
| subjects affected / exposed                           | 4 / 4 (100.00%) | 1 / 1 (100.00%) |  |
| Injury, poisoning and procedural complications        |                 |                 |  |
| Vessel puncture site haematoma                        |                 |                 |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                     | 1               | 0               |  |
| Cardiac disorders                                     |                 |                 |  |
| Myocarditis                                           |                 |                 |  |
| subjects affected / exposed                           | 0 / 4 (0.00%)   | 1 / 1 (100.00%) |  |
| occurrences (all)                                     | 0               | 1               |  |
| Atrial flutter                                        |                 |                 |  |
| subjects affected / exposed                           | 0 / 4 (0.00%)   | 1 / 1 (100.00%) |  |
| occurrences (all)                                     | 0               | 1               |  |
| Blood and lymphatic system disorders                  |                 |                 |  |
| Iron deficiency anaemia                               |                 |                 |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                     | 1               | 0               |  |
| General disorders and administration site conditions  |                 |                 |  |
| Medical device site bleeding                          |                 |                 |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                     | 1               | 0               |  |
| Malaise                                               |                 |                 |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                     | 1               | 0               |  |
| Respiratory, thoracic and mediastinal disorders       |                 |                 |  |
| Rhinitis                                              |                 |                 |  |
| subjects affected / exposed                           | 1 / 4 (25.00%)  | 0 / 1 (0.00%)   |  |
| occurrences (all)                                     | 1               | 0               |  |
| Skin and subcutaneous tissue disorders                |                 |                 |  |

|                                                                                                             |                     |                    |  |
|-------------------------------------------------------------------------------------------------------------|---------------------|--------------------|--|
| Skin lesion<br>subjects affected / exposed<br>occurrences (all)                                             | 1 / 4 (25.00%)<br>1 | 0 / 1 (0.00%)<br>0 |  |
| Product issues<br>Device alarm issue<br>subjects affected / exposed<br>occurrences (all)                    | 1 / 4 (25.00%)<br>1 | 0 / 1 (0.00%)<br>0 |  |
| Infections and infestations<br>Device related infection<br>subjects affected / exposed<br>occurrences (all) | 2 / 4 (50.00%)<br>2 | 0 / 1 (0.00%)<br>0 |  |
| Metabolism and nutrition disorders<br>Hyperkalaemia<br>subjects affected / exposed<br>occurrences (all)     | 1 / 4 (25.00%)<br>1 | 0 / 1 (0.00%)<br>0 |  |

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date             | Amendment                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
|------------------|-----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 15 November 2010 | Protocol Version 8<br>The following sections in the trial protocol have been amended. Section 1. Investigators, Section 2. Background and Rationale, Section 5. Eligibility Criteria, Section 6.1 Screening and enrolment of patients, Section 7.2 Delivery of the vector, Section 7.3.2. Hazards related to the AAV6 vector, Section 9. Study related investigations and follow-up, Section 12.3 Study funding, Section 12.4, Section 13.2 Data Collection and Section 14. Pharmacovigilance.                                                                                                                                                                                                                  |
| 20 December 2012 | Protocol version 9<br>The following sections in the protocol have been updated. Abbreviations, Section 1. Investigators, Section 3. Background and Rationale, Section 4. Aims of the study, Section 5. Trial design, Section 6. Eligibility Criteria, Section 7. Randomisation, Section 8. Delivery of the IMP, Section 10. IMP composition, Section 12. Study related Investigations, Section 13. Outcome measures, Section 13. Scientific studies after LVAD insertion, Section 14. Statistics, Section 15.4 Study funding, Section 16. Regulatory Issues and Section 17. Expected Serious Adverse Events/clinical outcomes                                                                                   |
| 21 August 2013   | Protocol version 10.<br>Following advice from the Principal Investigators at each of the participating centres, additional exclusion criteria have been added to the protocol to account for patients that are at a high risk of left ventricular assist device (LVAD) thrombosis and the effect of altering or temporarily stopping anticoagulation prior to administration of the gene therapy. Weekly visits during the month after gene transfer have been amended to reduce the need for patients to travel to hospital so frequently. Visits in week 1 and 3 will be conducted as home visits by a trained member of the study team at each hospital and weeks 2 and 4 will remain as visits to hospital. |
| 29 May 2014      | Protocol version 11<br>Protocol version 10 has been updated.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 24 March 2015    | Protocol version 12<br>Reasons for amendment <ul style="list-style-type: none"><li>• Clarification regarding trial samples including size of myocardial tissue samples, transfer and analysis</li><li>• Update to IMPD to include clarification regarding manufacturing process, updated information on packaging operations and QP release</li><li>• Change to IMP labelling due to extension of expiry date</li><li>• Minor amendments have been made to the protocol and patient information sheet to correct typographical errors and administrative details</li></ul>                                                                                                                                      |
| 15 May 2015      | The amendment is to temporarily halt recruitment to the trial . Results of the CUPID2 trial were announced by Celladon Corporation at the end of April in the form of a press release. Celladon Corporation is the IMP supplier for the SERCA-LVAD trial and the CUPID2 trial used the same IMP and administration protocol. The results of CUPID2 were negative, indicating that there is no evidence of benefit of AAV1/SERCA2a compared to placebo control. No safety concerns were raised for AAV1/SERCA2a (MYDICAR). The TSC advised a temporary halt to the trial as it is considered that the risk/benefit ratio is altered in light of the CUPID2 results.                                              |

|                   |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 02 September 2015 | <p>The Investigators and Trial Steering Committee have decided the following:</p> <ul style="list-style-type: none"> <li>• Recruitment to the trial will not recommence</li> <li>• Trial assessments that do not introduce an additional risk to patients will continue for existing patients (only one patient out of five still requires their 6-month follow-up visit). This is considered to be important for safety, scientific and ethical reasons as this is a safety trial and the data could be important for the individual patients and the study in general.</li> <li>• The end of the trial will be declared after the final patient's 6-month follow-up visit which is estimated to take place by the end of September</li> </ul> |
|-------------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|

Notes:

## Interruptions (globally)

Were there any global interruptions to the trial? Yes

| Date        | Interruption                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    | Restart date |
|-------------|-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|--------------|
| 01 May 2015 | <p>The trial was temporarily halted following the announcement of the CUPID 2 trial in May 2015. The results of CUPID2 were negative, indicating that there is no evidence of benefit of AAV1/SERCA2a compared to placebo control. No safety concerns were raised for AAV1/SERCA2a (MYDICAR).</p> <p>The Trial Steering Committee recommended that recruitment to the trial should be halted and that all existing patients (N=5) should be followed up until the 6-month follow-up visit, excluding any invasive tests and investigations.</p> | -            |

Notes:

## Limitations and caveats

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

The trial was terminated early with all existing patients (N=5) followed up until the 6-month follow-up visit, excluding any invasive tests and investigations. Full statistical analysis for both primary and secondary outcomes is no longer possible.

Notes: