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
Arm title	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 10^13 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.

Arm title	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.

Number of subjects in period 1	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 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 Units: years			
arithmetic mean	41	49	
full range (min-max)	29 to 69	49 to 49	-
Gender categorical Units: Subjects			
Female	1	0	1
Male	3	1	4
Ethnicity Units: Subjects			
White	4	0	4
Black	0	1	1
Not Recorded	0	0	0
Smoking History Units: Subjects			
Never	4	1	5
Not Recorded	0	0	0
Alcohol Consumption Units: Subjects			
None	1	0	1
≤1 alcoholic drink p/w	3	1	4
Not Recorded	0	0	0
Type of Heart Failure 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[1]
End point description:	
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:	
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:	
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:	
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.
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 %

Non-serious adverse events	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 subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 1 (0.00%) 0	
Product issues Device alarm issue subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 1 (0.00%) 0	
Infections and infestations Device related infection subjects affected / exposed occurrences (all)	2 / 4 (50.00%) 2	0 / 1 (0.00%) 0	
Metabolism and nutrition disorders Hyperkalaemia subjects affected / exposed occurrences (all)	1 / 4 (25.00%) 1	0 / 1 (0.00%) 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 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 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. 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 Protocol version 10 has been updated.
24 March 2015	Protocol version 12 Reasons for amendment • Clarification regarding trial samples including size of myocardial tissue samples, transfer and analysis • Update to IMPD to include clarification regarding manufacturing process, updated information on packaging operations and QP release • Change to IMP labelling due to extension of expiry date • Minor amendments have been made to the protocol and patient information sheet to correct typographical errors and administrative details
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	The Investigators and Trial Steering Committee have decided the following: • Recruitment to the trial will not recommence • 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. • 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

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? Yes

Date	Interruption	Restart date
01 May 2015	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). 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.	-

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: