Clinical trial results:
A Phase 2b randomised, double blind, placebo-controlled trial of trimetazidine therapy in patients with non-obstructive hypertrophic cardiomyopathy.

Summary

EudraCT number	2011-000038-12
Trial protocol	GB
Global end of trial date	30 April 2015

Results information

Result version number	v1 (current)
This version publication date	05 December 2018
First version publication date	05 December 2018

Trial information

Trial identification

Sponsor protocol code	10/0216

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01696370
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University College London
Sponsor organisation address	Joint UCLH/UCL Biomedical Research Unit, 1st Floor Maple House, 149 Tottenham Court Road, London, United Kingdom, W1T 7NF
Public contact	Margaret Norton, BRC Office Manager, Joint UCLH/UCL Biomedical Research Unit, 1st Floor Maple House, 149 Tottenham Court Road, London, +44 2031087907, m.norton@ucl.ac.uk
Scientific contact	Professor Perry Elliott, Chief Investigator, Joint UCLH/UCL Biomedical Research Unit, 1st Floor Maple House, 149 Tottenham Court Road, London, +44 2031087907, perry.elliott@ucl.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	04 July 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	30 April 2015
Global end of trial reached?	Yes
Global end of trial date	30 April 2015
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Principle question:
Does trimetazidine improve exercise capacity in patients with HCM?

We will test trimetazidine against placebo (dummy drug) in patients who have symptoms despite standard treatment.

Protection of trial subjects:

Adherence to Good Clinical Practice and UK clinical trials regulations

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 September 2011
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 51
Worldwide total number of subjects	51
EEA total number of subjects	51

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)	45

From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

recruitment at a single UK site. Participants were recruited between 31st may 2012 and 13th Aug 2014

Pre-assignment

Screening details:

Screening criteria:
able to consent, Age 18 or over, diagnosis of HCM, on optimal medical therapy, peak VO2 <= 80% predicted for age and gender, LVOT gradient < 50mmHg, NYHA Class >=2, resting heart rate < 90bpm, willing to use contraception.

Pre-assignment period milestones

Number of subjects started	51
Number of subjects completed	51

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Trimetazidine

Arm description: -

Arm type	Active comparator
Investigational medicinal product name	Trimetazidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

20 mg three times daily

Arm title	placebo

Arm description: -

Arm type	Placebo
Investigational medicinal product name	Trimetazidine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:

1 capsule three times daily

Investigational medicinal product name	Placebo
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule
Routes of administration	Oral use

Dosage and administration details:
1 capsule three times daily

Number of subjects in period 1	Trimetazidine	placebo
Started	27	24
Completed	26	23
Not completed	1	1
Physician decision	-	1
Protocol deviation	1	-

Baseline characteristics

Reporting groups	
Reporting group title	Trimetazidine
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Reporting group values	Trimetazidine	placebo	Total
Number of subjects	27	24	51
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
arithmetic mean	49	51	
standard deviation	± 13	± 14	-
Gender categorical Units: Subjects			
Female	9	6	15
Male	18	18	36
Ethnicity Units: Subjects			
Caucasian	17	19	36
Non-Caucasian	10	5	15

End points

End points reporting groups	
Reporting group title	Trimetazidine
Reporting group description: -	
Reporting group title	placebo
Reporting group description: -	

Primary: peak oxygen consumption	
End point title	peak oxygen consumption
End point description:	
End point type	Primary
End point timeframe:	
3 months	

End point values	Trimetazidine	placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	26	23		
Units: mls/kg/min				
arithmetic mean (standard deviation)	17.66 (± 3.53)	19.01 (± 4.68)		

Statistical analyses

Statistical analysis title	Primary end point
Comparison groups	Trimetazidine v placebo
Number of subjects included in analysis	49
Analysis specification	Pre-specified
Analysis type	non-inferiority
P-value	= 0.033
Method	Regression, Linear

Adverse events

Adverse events information	
Timeframe for reporting adverse events: From screening visit to 10 days after end of trial	
Assessment type	Systematic

Dictionary used	
Dictionary name	SNOMED CT
Dictionary version	1

Reporting groups	
Reporting group title	Trimetazidine
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Trimetazidine	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
number of deaths (all causes)	0	0	
number of deaths resulting from adverse events	0		
Cardiac disorders			
Chest pain	Additional description: Requiring hospital admission		
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences causally related to treatment / all	0 / 0	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	

Frequency threshold for reporting non-serious adverse events: 0 %

Non-serious adverse events	Trimetazidine	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	16 / 27 (59.26%)	12 / 24 (50.00%)	
Cardiac disorders			
Chest pain			
subjects affected / exposed	1 / 27 (3.70%)	2 / 24 (8.33%)	
occurrences (all)	1	2	
Palpitations			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	

Syncope			
subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
General disorders and administration site conditions			
Back pain			
subjects affected / exposed	0 / 27 (0.00%)	2 / 24 (8.33%)	
occurrences (all)	0	2	
Bite			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Dizziness			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Fall			
subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Headache			
subjects affected / exposed	3 / 27 (11.11%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Lethargy			
subjects affected / exposed	2 / 27 (7.41%)	4 / 24 (16.67%)	
occurrences (all)	2	4	
Peripheral swelling			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Tooth abscess			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Tooth extraction			
subjects affected / exposed	2 / 27 (7.41%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Eye disorders			
Conjunctival disorder			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Gastrointestinal disorders			

Abdominal pain			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Diarrhoea			
subjects affected / exposed	2 / 27 (7.41%)	1 / 24 (4.17%)	
occurrences (all)	2	1	
Nausea			
subjects affected / exposed	1 / 27 (3.70%)	0 / 24 (0.00%)	
occurrences (all)	1	0	
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	
Upper respiratory tract infection			
subjects affected / exposed	4 / 27 (14.81%)	6 / 24 (25.00%)	
occurrences (all)	7	6	
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	3 / 27 (11.11%)	1 / 24 (4.17%)	
occurrences (all)	4	1	
Renal and urinary disorders			
Urinary tract infection			
subjects affected / exposed	1 / 27 (3.70%)	1 / 24 (4.17%)	
occurrences (all)	1	1	
Musculoskeletal and connective tissue disorders			
Muscle spasms			
subjects affected / exposed	0 / 27 (0.00%)	1 / 24 (4.17%)	
occurrences (all)	0	1	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
09 August 2011	Changes to protocol V2.0: • Section 1 Trial Personnel: Updated investigator team telephone numbers. • Section 8.2. Delete "Minimisation will be used to balance groups according to age and gender. This will reduce the imbalance between the active treatment and placebo groups" This was removed as the investigator and the statistician decided minimisation was not necessary. • Section 8.2: Delete" Brecon Pharmaceuticals" and change "UCLH" to "The Heart Hospital, UCLH Pharmacy". Brecon Pharmaceuticals were left in the protocol in error as we had originally planned to use them. As per the CTA application form we will be using RFH Pharmacy Production. Changes to all other documents: Updated investigator team telephone numbers.
19 November 2012	Changes to protocol V3.0: Section 3.2.1 (Clinical Particulars): Updates made to therapeutic indications, contraindications and side effect table in light of updates to the SmPc Section 2.0 (Summary) and Section 6.1 (Inclusion Criteria): Updates made to the inclusion criteria to include patients with atrial fibrillation and also to clarify that patients who are fitted with a pacemaker are eligible. Expanded the inclusion criteria to include patients with atrial fibrillation as it is considered that this will increase recruitment by 10-20%. These individuals are usually asymptomatic and challenging to treat, so their inclusion is of clinical relevance. We have also clarified that patients with a pacemaker fitted are also eligible for the trial. Section 6.2 (Exclusion Criteria) Added 'Participant has Parkinson's disease or Parkinsonism' as an exclusion in line with the updated SmPc. Annex 1 updated in line with changes to protocol. Non-substantial amendment documents also sent.
10 April 2013	Protocol V4.0 Creation of advert and patient invitation letter to increase recruitment rate to the trial. Protocol updated to incorporate use of advert and recruitment plan.
15 January 2014	Changes to protocol V5.0: • Addition of 3 PIC sites to enhance the recruitment rate to the trial. Sites will potentially be • The Royal Brompton & Harefield NHS Foundation Trust • Barts Health NHS Trust • Guys and St Thomas' NHS Foundation Trust
01 April 2014	Protocol V6.0 Change to the inclusion criteria: • No significant left ventricular outflow tract obstruction on echocardiography at rest or during exercise (gradient < 50 mmHg) as determined at screening (if not done within previous 2 years).

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported