Clinical trial results:
Phase II randomized, placebo-controlled, double blind clinical trial of valsartan for attenuating disease evolution in early sarcomeric HCM

Summary

EudraCT number	2015-002283-16
Trial protocol	DK
Global end of trial date	01 May 2020

Results information

Result version number	v1 (current)
This version publication date	20 December 2021
First version publication date	20 December 2021

Trial information

Trial identification

Sponsor protocol code	1P50HL112349

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01912534
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	National Institutes of Health
Sponsor organisation address	10 Center Dr, Bethesda, United States,
Public contact	Kristin Burns, Heart Development and Structural Diseases Branch / Division of Cardiovascular Sciences National Hea, 001 301-594-6859, kristin.burns@nih.gov
Scientific contact	Kristin Burns, Heart Development and Structural Diseases Branch / Division of Cardiovascular Sciences National Hear, 001 301-594-6859, kristin.burns@nih.gov

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	13 November 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	01 May 2020
Global end of trial reached?	Yes
Global end of trial date	01 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To assess the effect of Valsartan in young patients in an early stage of hypertrophic cardiomyopathy.

Protection of trial subjects:

The study was in compliance with the ethical principles derived from the Declaration of Helsinki and the International Conference on Harmonization (ICH) Good Clinical Practice (GCP) Guidelines. All the local regulatory requirements pertinent to safety of trial subjects were also followed during the conduct of the trial.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	01 July 2014
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	Denmark: 10
Country: Number of subjects enrolled	United States: 137
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	Brazil: 27
Worldwide total number of subjects	178
EEA total number of subjects	10

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)	10
Adolescents (12-17 years)	57
Adults (18-64 years)	111
From 65 to 84 years	0

85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Study was conducted at multiple centers in 4 countries between 1 July 2014 (first subject first visit) and 26 July 2019 (last subject last visit).

Pre-assignment

Screening details:

The most common reasons for not progressing to randomization were not meeting eligibility criteria (n=28) or consent withdrawal (n=19). In total, 178 subjects were randomized and received study treatment.

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Valsartan

Arm description:

Subjects entered into an active run-in phase during which increasing doses of valsartan were administered as
tolerated until reaching weight-based target dose (80–320 mg daily). Valsartan or placebo was thereafter administered for two years.

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

Dosage and administration details:

Subjects entered into an active run-in phase during which increasing doses of valsartan were administered as tolerated until reaching weight-based target dose (80–320 mg daily). Valsartan was thereafter
administered for two years.

Arm title	Placebo

Arm description:

Subjects entered into an active run-in phase during which increasing doses of valsartan were administered as tolerated until reaching weight-based target dose (80–320 mg daily). Placebo matched to valsartan was thereafter administered for two years

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

Dosage and administration details:

Subjects entered into an active run-in phase during which increasing doses of valsartan were administered as tolerated until reaching weight-based target dose (80–320 mg daily). Valsartan or placebo was thereafter
administered for two years.

Number of subjects in period 1	Valsartan	Placebo
Started	88	90
Completed	84	83
Not completed	4	7
Consent withdrawn by subject	3	6
Death in pedestrian accident	1	-
Adverse event, non-fatal	-	1

Baseline characteristics

Reporting groups

Reporting group title	Overall treatment period

Reporting group description: -

Reporting group values	Overall treatment period	Total	
Number of subjects	178	178	
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	23.3		
standard deviation	± 10.0	-	
Gender categorical Units: Subjects			
Female	69	69	
Male	109	109	

End points

End points reporting groups

Reporting group title	Valsartan

Reporting group description:

Subjects entered into an active run-in phase during which increasing doses of valsartan were administered as
tolerated until reaching weight-based target dose (80–320 mg daily). Valsartan or placebo was thereafter administered for two years.

Reporting group title	Placebo

Reporting group description:

Subjects entered into an active run-in phase during which increasing doses of valsartan were administered as tolerated until reaching weight-based target dose (80–320 mg daily). Placebo matched to valsartan was thereafter administered for two years

Primary: Primary composite end point

End point title	Primary composite end point

End point description:

The primary objective of VANISH was to investigate whether treatment with valsartan attenuated phenotypic progression in early sarcomeric HCM by assessing changes in multiple metrics of cardiac structure and function from baseline to end of study (Year 2). Metrics included BSA-indexed LV mass and BSA-indexed left atrial (LA) volume (decrease considered improvement), BSA-indexed LV end diastolic and end systolic volumes (increase considered improvement), BSA-adjusted maximal LV wall thickness (decrease considered improvement), age-adjusted age-adjusted mitral annulus diastolic (e') and systolic (s') velocities (increase considered improvement); and log-transformed serum TnT and NTproBNP levels (decrease considered improvement).
These changes were converted to z-scores for change for each metric and averaged together to produce the composite z-score for each patient, the prespecified primary outcome. A positive composite z-score indicates a greater than average improvement.

End point type	Primary

End point timeframe:

2 years

End point values	Valsartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	84	83		
Units: z-score				
median (inter-quartile range (Q1-Q3))	0.136 (0.049 to 0.223)	-0.095 (-0.192 to 0.002)		

Statistical analyses

Statistical analysis title	Primary endpoint

Statistical analysis description:

Our analyses of the composite z-score and its components were based on mixed model linear regressions, adjusting through random effects for clustering within sites and within families. Models compared changes in the outcome between the treatment groups and were adjusted for pre-specified patient characteristics.

Comparison groups	Valsartan v Placebo
Number of subjects included in analysis	167
Analysis specification	Pre-specified
Analysis type	superiority
P-value	< 0.05
Method	Mixed models analysis

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Adverse events are collected from First Patient First Visit (FPFV) until Last Patient Last Visit (LPLV).

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Valsartan
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	

Serious adverse events	Valsartan	Placebo	
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 88 (9.09%)	10 / 90 (11.11%)	
number of deaths (all causes)	1	0	
number of deaths resulting from adverse events	0	0	
Injury, poisoning and procedural complications			
Pedestrian accident	Additional description: Death (pedestrian accident) / unrelated to hypertrophic cardiomyopathy and study drug/ severity=5		
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	1 / 1	0 / 0	
deaths causally related to treatment / all	0 / 1	0 / 0	
Cardiac disorders			
ICD placement			
subjects affected / exposed	1 / 88 (1.14%)	3 / 90 (3.33%)	
occurrences causally related to treatment / all	0 / 1	0 / 3	
deaths causally related to treatment / all	0 / 0	0 / 0	
Syncope			
subjects affected / exposed	1 / 88 (1.14%)	2 / 90 (2.22%)	
occurrences causally related to treatment / all	0 / 1	0 / 2	
deaths causally related to treatment / all	0 / 0	0 / 0	
ICD malfunction			

subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Inducible ventricular tachycardia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
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	1 / 88 (1.14%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 1	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Palpitations			
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Premature ventricular complexes			
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	1 / 88 (1.14%)	0 / 90 (0.00%)	
occurrences causally related to treatment / all	0 / 1	0 / 0	
deaths causally related to treatment / all	0 / 0	0 / 0	
Blood and lymphatic system disorders			
Severe anemia			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Reproductive system and breast disorders			
Cervical cancer			

subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Hysterectomy			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Psychiatric disorders			
Depression			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
occurrences causally related to treatment / all	0 / 0	0 / 1	
deaths causally related to treatment / all	0 / 0	0 / 0	
Infections and infestations			
Viral syndrome			
subjects affected / exposed	0 / 88 (0.00%)	1 / 90 (1.11%)	
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 / 88 (1.14%)	0 / 90 (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: 0.5 %

Non-serious adverse events	Valsartan	Placebo	
Total subjects affected by non-serious adverse events			
subjects affected / exposed	52 / 88 (59.09%)	48 / 90 (53.33%)	
Cardiac disorders			
overall non-serious			
subjects affected / exposed	52 / 88 (59.09%)	48 / 90 (53.33%)	
occurrences (all)	52	48	

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
05 November 2013	1. Clarification of the visit information for subjects that may require a longer active-run phase; 2. Clarification of the visit information for children ≤16 years and <35 kg in the active-run; 3. Clarification of the dose adjustment guidelines for children who reach 17 years of age or whose body weight increases from <35 kg to ≥ 35 kg in the maintenance phase; 4. Clarification of the adverse event reporting timeframe to the DCC; 5. Clarification of the acquisition and handling of blood samples; 6. Clarification of the roles for the management of the investigational drugs; and 7. Clarification of the potential risk that valsartan administration may contribute to the development of obstructive physiology.

26 August 2014	1. Change in nomenclature to clarify that subjects designated as overt HCM may have borderline left ventricular hypertrophy and not meet standard clinical criteria for a diagnosis of HCM. The cohort previously designated "overt HCM" will now be designated "Group 1". The cohort previously designated as "preclinical HCM" will now be designated "Group 2". 2. Section 5.2: Clarification of Inclusion Criteria: All Group 1 subjects regardless of age may be eligible based on either LV wall thickness in mm (>/= 12 mm and </= 20 mm) or z score (>/= 3 and </=14) criteria. Group 1 z-score cap should be </=14 (not 10) to correlate with LVWT 20 mm. 3. Section 5.3: Subject Exclusion Criteria Addition of concomitant or prior use of Spironolactone, Lithium, or Aliskiren 4. Section 5.3: Subject Exclusion Criteria- Clarification prior ARB/ACE-use is permitted if medications have been discontinued or can be discontinued/ not needed for clinical care. A minimum 2-week washout period should be performed before proceeding to baseline studies. 5. Section 5.3: Subject Exclusion Criteria - Clarification of echocardiographic core lab eligibility 6. Section 5.3: Subject Exclusion Criteria - Clarify the exclusion for hypertension to exclude only those with uncontrolled, persistent hypertension (SBP>160 and/or DBP>90) 7. Section 7.7: Clarification of FitBit distribution 8. Section 8.2.2: Restrictions regarding concomitant treatment Addition of Spironolactone, Lithium, or Aliskiren to the list of restricted medications. 9. Section 9.1: Recording and Reporting of Adverse Events - Modification to remove independent medical monitor adjudication. 10. Section 10.4: Adjudication Procedures- Clarification of the process for adjudicating clinical events 11. Section 22.1 Appendix 1: Participating Sites Modifications to update the participating sites and investigators 12. We would like to expand our internet advertising strategy to include social media. We have included Face

23 February 2015	1. Minor grammatical/style changes were made throughout 2. Page 5, Section 1.2: Protocol Synopsis • Edited to reflect changes in eligibility (listed below) • Edited to reflect that baseline studies are considered current for up to six months 3. Page 14, Section 4.1 Trial Schema • Figure 4 updated to reflect changes in eligibility (listed below) 4. Page 15, Section 5.1: Subject Selection • Edited to reflect changes in group 2 eligibility (listed below) 5. Page 15-16, Section 5.2: Amendment of Inclusion Criteria • Genetic testing not performed by a laboratory not listed in the inclusion criteria will be reviewed by the Clinical Coordinating Center to determine eligibility. • The upper age range for Group 1 subjects will be increased from 30 to 45 years • The maximal LV wall thickness for Group 1 subjects will be increased from 20 to 25 mm or a z-score of 18 Rationale: Experience during the first 6 months of study enrollment indicated that the target population for this trial, as defined by original inclusion/exclusion criteria, is exceedingly rare. Even in the specialty HCM centers participating in the trial, the target population represents a very low prevalence group. As such, we recognize the need to modify eligibility criteria to facilitate enrollment. After detailed review of site screening logs, it was determined that allowing inclusion of subjects up to age 45 years, subjects with a maximal LV wall thickness of up 25mm, and subjects with primary prevention ICD devices will substantially increase the yield of eligible subjects without compromising study safety and design. • A LV wall thickness z-score of 1.5-2.9 combined with LV thickness to dimension ratio ≥0.19 (as determined by rapid assessment by the echocardiographic core laboratory) will qualify subjects for Group 2 Rationale: The combination of an upper normal LV wall thickness combined with an increased thickness:dimension ratio is anticipated to accurately discriminat
23 January 2017	Added additional performance sites
15 June 2018	The protocol has been updated in the following sections: -Section 1.2 - Protocol Synopsis -Section 6.1 - Subject Participation -Section 8.4 - Procedures for Monitoring Subject Compliance These changes relate to patients that have their Year 2 visit out of window and the timeframe in which they continue taking study drug. The protocol changes indicate that patients will continue taking study medication up until their Year 2 visit, even if the visit occurs out of window. If a patient has an out of window Year 2 visit, the patient should continue study medication until the visit occurs. This is to ensure that Year 2 studies are performed on therapy and preserve the reliability/interpretability of their results.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported

Online references

http://www.ncbi.nlm.nih.gov/pubmed/34556856