Clinical trial results:
A prospective, randomised, placebo-controlled, double blind, multi-centre study of the effects of Irbesartan on aortic dilatation in Marfan syndrome

Summary

EudraCT number	2010-019302-16
Trial protocol	GB
Global end of trial date	12 March 2018

Results information

Result version number	v1 (current)
This version publication date	16 January 2020
First version publication date	16 January 2020
Summary attachment (see zip file)	AIMS_Publication (2010-019302-16_AIMS_Publication.pdf)

Trial information

Trial identification

Sponsor protocol code	2010GU001B

Additional study identifiers

ISRCTN number	ISRCTN90011794
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Royal Brompton and Harefield NHS Foundation Trust
Sponsor organisation address	Sydney Street, London, United Kingdom, SW3 6NP
Public contact	Chief Investigator, Bart’s Heart Centre St Bartholomew's Hospital West Smithfield, +44 02037658633, Michael.Mullen@bartshealth.nhs.uk
Scientific contact	Chief Investigator, Bart’s Heart Centre St Bartholomew's Hospital West Smithfield, +44 02037658633, Michael.Mullen@bartshealth.nhs.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	06 March 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	06 March 2018
Global end of trial reached?	Yes
Global end of trial date	12 March 2018
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

to determine whether giving patients with Marfan Syndrom treatment with Irbesartan reduces the annual rate of aortic dilatation compared to giving the placebo

Protection of trial subjects:

The Data Safety and Monitoring Committee reviews interim safety analysis

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	14 March 2012
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: 192
Worldwide total number of subjects	192
EEA total number of subjects	192

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)	40
Adolescents (12-17 years)	53
Adults (18-64 years)	99
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Recruitment Period 24 months

Pre-assignment

Screening details:

Screening visit
Date of assessment
Unique patient ID no.
Patient initials
Date of Birth
Gender
Height
Weight
Ethnic origin
Name of Hospital
Concomitant medications
SBP/DBP
Heart rate
ECG taken with detailed 12 leads quantitative measurements
Echocardiogram performed and recorded in digital format
75mg open label

Period 1

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

Arms

Are arms mutually exclusive?	Yes
Arm title	Irbesartan

Arm description: -

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

Dosage and administration details:

75 mg, 150 mg and 300 mg depending on tolerance

Arm title	Placebo

Arm description: -

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:

75 mg, 150 mg and 300 mg

Number of subjects in period 1	Irbesartan	Placebo
Started	104	88
Completed	104	88

Period 2	
Period 2 title	end of follow-up
Is this the baseline period?	No
Allocation method	Randomised - controlled
Blinding used	Double blind
Roles blinded	Subject, Investigator, Monitor, Data analyst, Carer, Assessor

Arms	
Are arms mutually exclusive?	Yes
Arm title	Ibesartan
Arm description: -	
Arm type	Active comparator
Investigational medicinal product name	Irbesartan
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use
Dosage and administration details: 75 mg, 150 mg, 300 mg	
Arm title	Placebo
Arm description: -	
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: 75 mg, 150 mg, 300 mg	

Number of subjects in period 2	Ibesartan	Placebo
Started	104	88
Completed	104	88

Baseline characteristics

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

Reporting group values	Irbesartan	Placebo	Total
Number of subjects	104	88	192
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			
median	18	18	
inter-quartile range (Q1-Q3)	12 to 28	12 to 28	-
Gender categorical Units: Subjects			
Female	57	42	99
Male	47	46	93

End points

End points reporting groups

Reporting group title	Irbesartan
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Reporting group title	Ibesartan
Reporting group description: -	
Reporting group title	Placebo
Reporting group description: -	
Subject analysis set title	end of follow-up analysis
Subject analysis set type	Intention-to-treat

Subject analysis set description:

At the end of follow-up, the data was analysed according to Intention-to-treat using mixed effects models to determine the rate of change in aortic z score, the primary endpoint.

Primary: the absolute difference in the mean annual rates of aortic root dilatation (measured by echocardiogram)

End point title	the absolute difference in the mean annual rates of aortic root dilatation (measured by echocardiogram)

End point description:

End point type	Primary

End point timeframe:

per year measured by echocardiogram

End point values	Ibesartan	Placebo		
Subject group type	Reporting group	Reporting group		
Number of subjects analysed	104	88		
Units: mm				
number (not applicable)	104	88		

Statistical analyses

Statistical analysis title	Statistical analysis

Statistical analysis description:

The primary analysis is the comparison of rates of change in aortic root diameter per year between the active Irbesartan and placebo arms of the trial. This will be carried out on the full analysis set based on the intention to treat principle. The mean annual rate of change in aortic root diamenter in each treatment group, together with the absolute difference between these rates (and its associated p value and 95% CI) will be estimated using a linear mixed effect model for repeated measur

Comparison groups	Ibesartan v Placebo

Number of subjects included in analysis	192
Analysis specification	Pre-specified
Analysis type	superiority
P-value	≤ 0.05
Method	Mixed models analysis
Parameter estimate	Mean difference (net)
Point estimate	-0.22
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.41
upper limit	-0.02
Variability estimate	Standard deviation

Adverse events

Adverse events information	
Timeframe for reporting adverse events: All SAE reported within 24 hours.	
Assessment type	Non-systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	16.1

Reporting groups	
Reporting group title	Irbesartan

Reporting group description: -

Serious adverse events	Irbesartan		
Total subjects affected by serious adverse events			
subjects affected / exposed	0 / 1 (0.00%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		

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

Non-serious adverse events	Irbesartan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	1 / 1 (100.00%)		
Vascular disorders			
Headache			
subjects affected / exposed	1 / 1 (100.00%)		
occurrences (all)	1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
26 October 2010	1.Changes to the study eligibility criteria, PIS and ICF. 2.Update of site list; Note: This amendment was approved by the REC on 26.10.2010 and MHRA on 08.11.2010.
25 January 2011	1.New sites added: Hear H, GOST; 2.Change of PI in: Golden Jubilee Hospital and Yorkhill Hospital Glasgow; Note: This amendment was approved by the REC on 25.01.2011. The amendment was not submitted to the MHRA at the time.
30 March 2011	1.Study label have been revised, V2/ 09.03.2011. Note: This amendment was approved by the MHRA on 30.03.2011.
13 October 2011	1.To notify changes of PI at: Middlesborough and Newcastle Note: This amendment was approved by the REC 13.10.2011 . The amendment was not submitted to the MHRA at the time.
26 October 2011	1.Notifying of the temporary halt Note: This amendment was approved by the REC on 15.11.2011 and MHRA on 26.10.2011.
05 December 2011	1.Following the notification of a Serious Breach, notification of recommencement of the trial. Note: This amendment was approved by the REC on 05.12.2011 and MHRA on 21.12.2011.
02 March 2012	1.Notification of addition of a new site: South Devon Healthcare NHS FT Note: This amendment was approved by the REC on 02.03.2011.
12 March 2012	1.Notifying: Parent/ Carer ICF (V3/ 24 Oct 2011) amendment to ensure consistency with the Adult ICF; correction of a typo error to the footer of the Genetics sub study adult ICF (V1/ 26 Feb 2010). Note: This amendment was approved by the REC on 12.03.2012.
12 March 2012	1.School letter (V1/11 Nov 2011) to explain absenteeism for paediatric patients entering the study. Note: This amendment was approved by the REC on 12.03.2012

08 June 2012	1.Addition of a new site: Cumberland Infirmary Note: This amendment was approved by the REC on 08.06.2012
30 October 2012	1.Change of PI at Royal Victoria Hospital Belfast Note: This amendment was approved by the REC on 30.10.2012.
07 February 2013	1.Add Invitation Reply Form V1/08.01.2013 2.AIMS Wikipedia Text entries 3.Addition of new site: Glenfield Hospital Leicester, PI Aidan Bolger Note: This amendment was approved by the REC on 07.02.2013.
28 March 2013	1.Change of PI at Southampton, Dr Aisling Carroll Note: This amendment was approved by the REC on 28.03.2013.
18 April 2013	1.Change of PI AT Heart Hospital London Note: This amendment was approved by the REC on 18.04.2013.
18 June 2013	1.Poster Note: This amendment was approved by the REC on 18.06.2013
05 August 2013	1.Web press release V1/23.07.2013 Note: This amendment was submitted to the REC on 05.08.2013.
22 October 2014	1.Change of PI at Sheffield Hospital Note: This amendment was submitted to the REC on 22.10.2014
16 January 2015	1.Addition of new site St Barholomew’s Hospital 2.Change of PI at Guy’s and St Thoma’s Hospital Note: This amendment was approved by the REC on 16.01.2015.
20 March 2015	1.Change of PI at Northern General Hospital Sheffield Note: This amendment was submitted to the REC on 20.03.2015.
11 May 2015	1.Suspended recruitment into AIMS study Note: This amendment was approved by the REC on 11.05.2015 and MHRA on 29.05.2015
02 February 2017	1.Protocol amended 2.SmPC Note: This amendment was approved by the REC 0n 13.01.2017 and MHRA on 07.02.2017

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported