Clinical trial results:
Effects of bosentan in a HOMogenEous population of SSc subjects with an early or active SSc nailfold capillaroscopic pattern (HOME II)

Summary

EudraCT number	2011-005303-32
Trial protocol	NL
Global end of trial date	03 June 2014

Results information

Result version number	v1 (current)
This version publication date	04 November 2018
First version publication date	04 November 2018

Trial information

Trial identification

Sponsor protocol code	AC-052-438

Additional study identifiers

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

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Nederland bv
Sponsor organisation address	Beneluxlaan 2b, Woerden, Netherlands, 3446 GR
Public contact	Medical Director, Actelion Pharmaceuticals Nederland bv, sjansen8@its.jnj.com
Scientific contact	Medical Director, Actelion Pharmaceuticals Nederland bv, sjansen8@its.jnj.com

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	02 March 2015
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	03 June 2014
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

Evaluate the effect of bosentan on the blood flow in the hands from baseline to 12 weeks, measured by laser Doppler imaging, in SSc subjects with an early or active SSc pattern, measured with nailfold capillaroscopy (NFM), with ongoing digital ulcer disease and a history of DU disease in the past 2 years.

Protection of trial subjects:

The clinical trial was designed and conducted in accordance with the ICH Harmonized Tripartite Guidelines for GCP, with applicable local regulations, including the European Directive 2001/20/EC, and with the ethical principles laid down in the Declaration of Helsinki.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 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	Netherlands: 44
Worldwide total number of subjects	44
EEA total number of subjects	44

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)	38
From 65 to 84 years	6
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Among the 55 screened patients, 44 were enrolled in the study.

Pre-assignment

Screening details:

Fifty-five patients with systemic sclerosis (SSc) and a history of digital ulcers (DU) in the past two years were screened by nailfold capillaroscopy (NFM) from seven sites in the Netherlands

Period 1

Period 1 title	Overall trial (overall period)
Is this the baseline period?	Yes
Allocation method	Not applicable
Blinding used	Not blinded

Arms

Arm title	Bosentan

Arm description:

All participants received bosentan for 3 months. They received 62.5 mg b.i.d of bosentan for the first 4 weeks followed by 125 mg b.i.d.during the next 8 weeks. Then they could continue to receive bosentan based on the clinical decision of the health care professional.

Arm type	Experimental
Investigational medicinal product name	Bosentan
Investigational medicinal product code	ACT-050088
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

tablets containing 62.5 mg or 125 mg of bosentan

Number of subjects in period 1	Bosentan
Started	44
Completed	33
Not completed	11
Consent withdrawn by subject	1
Adverse event, non-fatal	5
Lost to follow-up	4
subject abroad	1

Baseline characteristics

Reporting groups	
Reporting group title	Overall trial
Reporting group description: Overall trial	

Reporting group values	Overall trial	Total	
Number of subjects	44	44	
Age categorical Units: Subjects			
Age continuous Units: years			
arithmetic mean	50.5		
standard deviation	± 11.2	-	
Gender categorical Units:			
Male	14	14	
Female	30	30	
Systemic sclerosis (SSc) pattern Units: Subjects			
Early SSc pattern	13	13	
Active SSc pattern	31	31	
Systemic sclerosis (SSc) classification Units: Subjects			
Limited SSc	38	38	
Diffuse SSc	3	3	
Other	3	3	
Digital ulcer (DU) status Units: Subjects			
None	9	9	
Pitting scar	19	19	
DU < 3 months	7	7	
DU > 3 months	9	9	

End points

End points reporting groups

Reporting group title	Bosentan
Reporting group description:	
All participants received bosentan for 3 months. They received 62.5 mg b.i.d of bosentan for the first 4 weeks followed by 125 mg b.i.d.during the next 8 weeks. Then they could continue to receive bosentan based on the clinical decision of the health care professional.	
Subject analysis set title	Baseline efficacy data
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The baseline values of efficacy variables were used to assess the effects of bosentan on blood flow	
Subject analysis set title	12-week efficacy data
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
The values of efficacy variables at week 12 were compared to the baseline values for each subject because each subject was considered as his or her own control	

Primary: Change from baseline to week 12 in blood flow in the whole hand

End point title	Change from baseline to week 12 in blood flow in the whole hand
End point description:	
Blood flow in the hands was measured by laser Doppler Imaging at baseline and after 12 weeks of treatment with bosentan.	
End point type	Primary
End point timeframe:	
Baseline and Week 12	

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	60.75 (± 21.26)	66.60 (± 25.93)		

Statistical analyses

Statistical analysis title	Change from baseline to Week 12 in hand blood flow
Statistical analysis description:	
Change from baseline in hand blood flow was evaluated with a mixed model analysis	
Comparison groups	12-week efficacy data v Baseline efficacy data

Number of subjects included in analysis	88
Analysis specification	Pre-specified
Analysis type	superiority[1]
P-value	= 0.052
Method	ANCOVA
Confidence interval	
level	95 %
sides	2-sided
lower limit	-0.066
upper limit	12.265

Notes:

[1] - Each subject was considered as his/her own control (data at Week 12 were compared to baseline values for each subject). The blood flow of the hand was expected to be stable in time.

Secondary: Change from baseline to week 12 in blood flow in fingertips (ROI1)

End point title	Change from baseline to week 12 in blood flow in fingertips (ROI1)

End point description:

A change in blood flow was measured by laser Doppler Imaging in different regions of interest of the hand (ROI), including the fingertips (ROI1)

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	73.16 (± 32.45)	82.60 (± 38.80)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in blood flow in fingers (ROI2)

End point title	Change from baseline to week 12 in blood flow in fingers (ROI2)

End point description:

A change in blood flow was measured by laser Doppler Imaging in different regions of interest of the hand (ROI), including the fingers, excluding the tips (ROI2)

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	63.29 (± 23.01)	69.83 (± 28.16)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in blood flow in the palms of the hands (ROI3)

End point title	Change from baseline to week 12 in blood flow in the palms of the hands (ROI3)

End point description:

A change in blood flow was measured by laser Doppler Imaging in different regions of interest of the hand (ROI), including the palms of the hands (ROI3).

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	57.66 (± 19.69)	62.61 (± 22.35)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in blood flow in the whole hand of patients who never received iloprost

End point title	Change from baseline to week 12 in blood flow in the whole hand of patients who never received iloprost

End point description:

Blood flow in the hands measured by laser Doppler Imaging was analyzed separately for subjects with no history of iloprost use.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units				
arithmetic mean (standard deviation)	60.10 (± 22.79)	68.01 (± 28.01)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in ROI1 blood flow of patients who never received iloprost

End point title	Change from baseline to week 12 in ROI1 blood flow of patients who never received iloprost

End point description:

ROI1 (fingertips) Blood flow measured by laser Doppler Imaging was analyzed separately for subjects with no history of iloprost use.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	72.47 (± 32.84)	84.88 (± 39.53)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in ROI2 blood flow of patients who never received iloprost

End point title	Change from baseline to week 12 in ROI2 blood flow of patients who never received iloprost

End point description:

ROI2 (fingers, excluding tips) blood flow measured by laser Doppler Imaging was analyzed separately for subjects with no history of iloprost use.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	62.45 (± 23.45)	69.07 (± 29.87)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in ROI3 blood flow of patients who never received iloprost

End point title	Change from baseline to week 12 in ROI3 blood flow of patients who never received iloprost

End point description:

ROI3 (hand palms) blood flow measured by laser Doppler Imaging was analyzed separately for subjects with no history of iloprost use.

End point type	Secondary

End point timeframe:

Baseline and Week 12

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Perfusion units (PU)				
arithmetic mean (standard deviation)	56.26 (± 21.09)	63.70 (± 24.91)		

Statistical analyses

No statistical analyses for this end point

Secondary: Change from baseline to week 12 in number of digital ulcers and pitting scars

End point title	Change from baseline to week 12 in number of digital ulcers and pitting scars

End point description:

Photos were made of the hands of all patients using a digital camera to detect the presence of DUs or

pitting scars.
The sum of all DUs and pitting scars in all patients were reported at baseline and after 12 weeks of treatment with bosentan.

End point type	Secondary
End point timeframe:	
Baseline and Week 12	

End point values	Baseline efficacy data	12-week efficacy data		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	44	44		
Units: Number				
Sum of all DUs	23	8		
Sum of pitting scars	154	133		

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information	
Timeframe for reporting adverse events:	
From study drug initiation up to 52 weeks of treatment (whole study period)	
Assessment type	Systematic

Dictionary used	
Dictionary name	MedDRA
Dictionary version	21.0

Reporting groups	
Reporting group title	Bosentan
Reporting group description:	
43 Participants took at least one dose of bosentan, with 18 of them still on treatment at Week 52.	

Serious adverse events	Bosentan		
Total subjects affected by serious adverse events			
subjects affected / exposed	8 / 43 (18.60%)		
number of deaths (all causes)	0		
number of deaths resulting from adverse events	0		
Investigations			
Heart rate decreased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Alanine aminotransferase increased			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Aspartate aminotransferase increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatic enzyme abnormal			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

Blood alkaline phosphatase increased			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Surgical and medical procedures			
Vascular graft			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac pacemaker insertion			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrioventricular block			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Syncope			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Transient ischaemic attack			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Fatigue			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oedema			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pain			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Reduced vision			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal pain upper			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Nausea			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Skin and subcutaneous tissue disorders			
Pruritus			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Chromaturia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Metabolism and nutrition disorders			
Fluid retention			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Decreased appetite			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		

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

Non-serious adverse events	Bosentan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	11 / 43 (25.58%)		
Vascular disorders			
Hypotension			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Flushing			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Cardiac disorders			
Cyanosis			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Palpitations			

subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Nervous system disorders			
Headache			
subjects affected / exposed	2 / 43 (4.65%)		
occurrences (all)	2		
Dizziness			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Blood and lymphatic system disorders			
Lymphadenopathy			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Anaemia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
General disorders and administration site conditions			
Disease progression			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Drug ineffective			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Therapy non-responder			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Gastrointestinal disorders			
Oesophageal obstruction			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Dyspepsia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		
Dysphagia			
subjects affected / exposed	1 / 43 (2.33%)		
occurrences (all)	1		

Gastrointestinal motility disorder subjects affected / exposed occurrences (all) Nausea subjects affected / exposed occurrences (all) Diarrhoea subjects affected / exposed occurrences (all) Abdominal pain upper subjects affected / exposed occurrences (all)	1 / 43 (2.33%) 1 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1		
Skin and subcutaneous tissue disorders Skin ulcer subjects affected / exposed occurrences (all) Scar pain subjects affected / exposed occurrences (all)	 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1		
Musculoskeletal and connective tissue disorders Myalgia subjects affected / exposed occurrences (all) Pain in extremity subjects affected / exposed occurrences (all)	 1 / 43 (2.33%) 1 1 / 43 (2.33%) 1		
Infections and infestations Influenza subjects affected / exposed occurrences (all)	 2 / 43 (4.65%) 2		
Metabolism and nutrition disorders Fluid retention subjects affected / exposed occurrences (all)	 1 / 43 (2.33%) 1		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
22 May 2012	The main reason was to increase the time window of visit at Week 12 from +/- 5 days to +/- 7 days.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Due to slow recruitment the study was prematurely terminated and the long term effects of bosentan on vasculopathy and other secondary endpoints could not be assessed.

Notes: