Clinical trial results:
A prospective, multicenter, open-label extension of FUTURE 3 to assess the safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension

Summary

EudraCT number	2010-021793-12
Trial protocol	DE HU CZ FR NL ES IT PL Outside EU/EEA
Global end of trial date	29 May 2020

Results information

Result version number	v3 (current)
This version publication date	12 December 2020
First version publication date	12 April 2015
Version creation reason	

Trial information

Trial identification

Sponsor protocol code	AC-052-374

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01338415
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd.
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	clinical trial disclosure desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@actelion.com
Scientific contact	clinical trial disclosure desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@actelion.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?	Yes

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	29 May 2020
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	29 May 2020
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To evaluate the long-term safety, tolerability and efficacy of the pediatric formulation of bosentan two versus three times a day in children with pulmonary arterial hypertension (PAH) and the objective of exceptional use treatment period (EUTP) was to assess the patients with bosentan beyond the initial 12-month treatment period of the FUTURE 3 extension and the long-term safety and tolerability of the pediatric formulation of bosentan in patients who completed the FUTURE 3 extension.

Protection of trial subjects:

This clinical study 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, the US CFR Title 21, and with the ethical principles laid down in the Declaration of Helsinki. Only patients who performed the end of study assessments of the FUTURE 3 core study, who tolerated bosentan 32 mg dispersible tablets (pediatric formulation) during the core study and for whom continuation of bosentan treatment was considered beneficial by the investigator, were offered the opportunity to participate in the FUTURE 3 Extension trial. Safety evaluations were based upon the adverse events (AEs), vital sign measurements, clinical laboratory test results, and physical examinations reported throughout the study.

Background therapy:

Patients receiving the commercial formulation of bosentan before entering the FUTURE 3 core study had to stop it and instead take the study drug (pediatric formulation of bosentan). Previous therapies for PAH were allowed at a stable regimen.

Evidence for comparator:

not applicable

Actual start date of recruitment	08 March 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	Poland: 5
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	Czechia: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Hungary: 3
Country: Number of subjects enrolled	Italy: 1
Country: Number of subjects enrolled	Australia: 2
Country: Number of subjects enrolled	South Africa: 6
Country: Number of subjects enrolled	China: 6

Country: Number of subjects enrolled	Israel: 2
Country: Number of subjects enrolled	Ukraine: 1
Country: Number of subjects enrolled	Belarus: 3
Country: Number of subjects enrolled	Russian Federation: 10
Country: Number of subjects enrolled	United States: 2
Country: Number of subjects enrolled	Serbia: 5
Country: Number of subjects enrolled	Mexico: 1
Country: Number of subjects enrolled	India: 3
Worldwide total number of subjects	64
EEA total number of subjects	23

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)	21
Children (2-11 years)	43
Adolescents (12-17 years)	0
Adults (18-64 years)	0
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

58 out of 64 patients randomized in the FUTURE 3 core study were enrolled in the FUTURE 3 extension study. Among 58 patients, 10 patients who entered and received bosentan during the exceptional use treatment period (EUTP) were included in the analysis.

Pre-assignment

Screening details:

Treatment groups assigned at randomization of FUTURE 3 core study (AC-052-373) were continued in the extension study (AC-052-374).

Period 1

Period 1 title	Period 1 (core+extension)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosentan 2mg/kg b.i.d.

Arm description:

Patients received 2 mg/kg bosentan twice daily (morning and evening) during the FUTURE 3 core period and continued with the same dose regimen during the extension period.

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

Dosage and administration details:

The body weight-adjusted dose of the dispersible tablet was dispersed in a teaspoon of water (not mixed with food) before being administered orally twice a day (morning and evening)

Arm title	Bosentan 2mg/kg t.i.d.

Arm description:

Patients received 2 mg/kg bosentan 3 times a day (morning, afternoon, evening) during the FUTURE 3 core period and continued with the same dose regimen during the extension period.

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

Dosage and administration details:

The body weight-adjusted dose of the dispersible tablet was dispersed in a teaspoon of water (not mixed with food) before being administered orally three times a day (morning, afternoon and evening)

Number of subjects in period 1	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.
Started	33	31
Completed	23	22
Not completed	10	9
Adverse event, serious fatal	2	1
Consent withdrawn by subject	1	1
Adverse event, non-fatal	6	5
PAH not the main etiology of PH	-	2
Administrative reason	1	-

Period 2

Period 2 title	Period2 Exceptional Use Treatment Period
Is this the baseline period?	No
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

Arms

Are arms mutually exclusive?	Yes
Arm title	Bosentan 2 mg/kg b.i.d.

Arm description:

Patients who entered the exceptional use treatment period (EUTP), continued receiving 2 mg/kg bosentan twice daily (b.i.d) up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d).

Arm type	Experimental
Investigational medicinal product name	Bosentan
Investigational medicinal product code	JNJ-39835770
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received bosentan 2 mg/kg tablet orally b.i.d.

Arm title	Bosentan 2 mg/kg t.i.d.

Arm description:

Patients who entered the EUTP, continued receiving 2 mg/kg bosentan 3 times a day (t.i.d) up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d.

Arm type	Experimental
Investigational medicinal product name	Bosentan
Investigational medicinal product code	JNJ-39835770
Other name	
Pharmaceutical forms	Dispersible tablet
Routes of administration	Oral use

Dosage and administration details:

Patients received bosentan 2 mg/kg tablet orally b.i.d or t.i.d.

Number of subjects in period 2[1]	Bosentan 2 mg/kg b.i.d.	Bosentan 2 mg/kg t.i.d.
Started	7	3
Completed	2	2
Not completed	5	1
Adverse event, serious fatal	1	-
Consent withdrawn by subject	1	-
Ongoing at the cut-off date of 19 nov 2019	3	-
Administrative reason	-	1

Notes:

[1] - The number of subjects starting the period is not consistent with the number completing the preceding period. It is expected the number of subjects starting the subsequent period will be the same as the number completing the preceding period.
Justification: The number of subjects starting the Exceptional Use Treatment Period (EUTP) is different from the extension period as per study design because only few patients opted to continue treatment in EUTP.

Baseline characteristics

Reporting groups	
Reporting group title	Bosentan 2mg/kg b.i.d.
Reporting group description:	
Patients received 2 mg/kg bosentan twice daily (morning and evening) during the FUTURE 3 core period and continued with the same dose regimen during the extension period.	
Reporting group title	Bosentan 2mg/kg t.i.d.
Reporting group description:	
Patients received 2 mg/kg bosentan 3 times a day (morning, afternoon, evening) during the FUTURE 3 core period and continued with the same dose regimen during the extension period.	

Reporting group values	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.	Total
Number of subjects	33	31	64
Age categorical			
Units: Subjects			
Infants and toddlers (28 days-23 months)	10	11	21
Children (2-11 years)	23	20	43
Adolescents (12-17 years)	0	0	0
Age continuous			
Age at randomization in the FUTURE 3 core study (AC-052-373)			
Units: years			
arithmetic mean	4.5	5.2	
standard deviation	± 3.35	± 3.81	-
Gender categorical			
Number of males and females randomized in the FUTURE 3 core study (AC-052-373)			
Units: Subjects			
Female	18	10	28
Male	15	21	36
Pulmonary Arterial Hypertension (PAH) etiology			
Number of subjects in each PAH category at randomization (before treatment initiation) in the FUTURE 3 core study (AC-052-373)			
Units: Subjects			
idiopathic	14	15	29
heritable	2	0	2
congenital heart disease	6	2	8
associated PAH (i.e.,PAH after surgery for CHD)	11	13	24
missing data	0	1	1
WHO functional class (FC)			
Number of subjects in each WHO FC at randomization (before treatment initiation) in the FUTURE 3 core study (AC-052-373)			
Units: Subjects			
FC I	9	10	19
FC II	12	15	27
FC III	12	6	18

Subject analysis sets	
Subject analysis set title	all treated set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

"All Randomized" analysis set includes all patients assigned to a study treatment in FUTURE 3. The "All Treated" analysis set comprised all patients in the FUTURE 3 core study who received at least one dose of the study drug. Because the same patients were included in the "All randomized " and the "All Treated" analysis sets, only the "All Treated analysis set was used.

Subject analysis set title	Bosentan 2 mg/kg b.i.d or t.i.d
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who entered the exceptional use treatment period (EUTP), continued receiving 2 mg/kg bosentan b.i.d or t.i.d up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d.

Reporting group values	all treated set	Bosentan 2 mg/kg b.i.d or t.i.d	
Number of subjects	64	10	
Age categorical Units: Subjects			
Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years)			
Age continuous			
Age at randomization in the FUTURE 3 core study (AC-052-373)			
Units: years arithmetic mean standard deviation	 4.8 ± 3.57	 ±	
Gender categorical			
Number of males and females randomized in the FUTURE 3 core study (AC-052-373)			
Units: Subjects			
Female Male			
Pulmonary Arterial Hypertension (PAH) etiology			
Number of subjects in each PAH category at randomization (before treatment initiation) in the FUTURE 3 core study (AC-052-373)			
Units: Subjects			
idiopathic heritable congenital heart disease associated PAH (i.e.,PAH after surgery for CHD) missing data	29 2 8 24 1		
WHO functional class (FC)			
Number of subjects in each WHO FC at randomization (before treatment initiation) in the FUTURE 3 core study (AC-052-373)			
Units: Subjects			
FC I FC II FC III	19 27 18		

End points

End points reporting groups

Reporting group title	Bosentan 2mg/kg b.i.d.

Reporting group description:

Patients received 2 mg/kg bosentan twice daily (morning and evening) during the FUTURE 3 core period and continued with the same dose regimen during the extension period.

Reporting group title	Bosentan 2mg/kg t.i.d.

Reporting group description:

Patients received 2 mg/kg bosentan 3 times a day (morning, afternoon, evening) during the FUTURE 3 core period and continued with the same dose regimen during the extension period.

Reporting group title	Bosentan 2 mg/kg b.i.d.

Reporting group description:

Patients who entered the exceptional use treatment period (EUTP), continued receiving 2 mg/kg bosentan twice daily (b.i.d) up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d).

Reporting group title	Bosentan 2 mg/kg t.i.d.

Reporting group description:

Patients who entered the EUTP, continued receiving 2 mg/kg bosentan 3 times a day (t.i.d) up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d.

Subject analysis set title	all treated set
Subject analysis set type	Intention-to-treat

Subject analysis set description:

"All Randomized" analysis set includes all patients assigned to a study treatment in FUTURE 3. The "All Treated" analysis set comprised all patients in the FUTURE 3 core study who received at least one dose of the study drug. Because the same patients were included in the "All randomized " and the "All Treated" analysis sets, only the "All Treated analysis set was used.

Subject analysis set title	Bosentan 2 mg/kg b.i.d or t.i.d
Subject analysis set type	Sub-group analysis

Subject analysis set description:

Patients who entered the exceptional use treatment period (EUTP), continued receiving 2 mg/kg bosentan b.i.d or t.i.d up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d.

Primary: Not applicable

End point title	Not applicable[1]

End point description:

no primary endpoint was defined. As it is an exploratory study, all efficacy endpoints were considered as exploratory endpoints

End point type	Primary

End point timeframe:

not applicable

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: No primary endpoint was defined. As it is an exploratory study, all efficacy endpoints were considered as exploratory endpoints.

End point values	all treated set			
Subject group type	Subject analysis set			
Number of subjects analysed	0[2]			
Units: not applicable				

Notes:

[2] - not applicable (no primary endpoint defined)

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extension Study: Change from baseline up to 18 months of treatment in Their World Health Organization (WHO) Functional Classification (FC)

End point title	Extension Study: Change from baseline up to 18 months of treatment in Their World Health Organization (WHO) Functional Classification (FC)

End point description:

This is the change from baseline up to 18 months of treatment with bosentan over FUTURE 3 core and extension studies in WHO FC. Baseline was defined as the last valid assessment performed prior to first study drug intake in the FUTURE 3 core study. The WHO FC indicates the severity of Pulmonary Arterial Hypertension: class I (none) to class IV (most severe).

End point type	Other pre-specified

End point timeframe:

Up to 18 months

End point values	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.	all treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	31	64	
Units: Percentage of patients				
Stable, Month 12	67	80	73	
Improved, Month 12	21	10	16	
Worsened, Month 12	12	10	11	
Stable, Month 18	76	80	78	
Improved, Month 18	9	10	9	
Worsened, Month 18	15	10	13	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extension Study: Change from baseline up to 18 months of treatment in the global clinical impression scale (GCIS)

End point title	Extension Study: Change from baseline up to 18 months of treatment in the global clinical impression scale (GCIS)

End point description:

This is the change from baseline up to 18 months of treatment with bosentan over FUTURE 3 core and extension studies in GCIS as assessed by both the physician and parents or legal representatives independently. Baseline was defined as the last valid assessment performed prior to first study drug intake in the FUTURE 3 core study. The GCIS is a scale used to rate the patient's current overall clinical

condition (“Very Good”, “Good”, “Neither Good or Bad”, “Bad”, and “Very Bad”).

End point type	Other pre-specified

End point timeframe:

Up to 18 months

End point values	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.	all treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33[3]	31[4]	64[5]	
Units: Percentage of patients				
Stable, Month 12 (Physician)	57	70	63	
Stable, Month 12 (Parents)	57	52	55	
Improved, Month 12 (Physician)	36	26	31	
Improved, Month 12 (Parents)	32	48	39	
Worsened, Month 12 (Physician)	7	4	6	
Worsened, Month 12(Parents)	11	0	6	
Stable, Month 18 (Physician)	47	67	57	
Stable, Month 18 (Parents)	42	39	41	
Improved, Month 18 (Physician)	32	28	30	
Improved, Month 18 (Parents)	32	55	43	
Worsened, Month 18 (Physician)	21	5	13	
Worsened, Month 18 (Parents)	26	6	16	

Notes:

[3] - No imputation performed; number of subjects analyzed = 28 at Month 12, 19 at Month 18

[4] - No imputation performed; number of subjects analyzed = 23 at Month 12, 18 at Month 18

[5] - No imputation performed; number of subjects analyzed = 41 at Month 12, 37 at Month 18

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extension Study: Percentage of patients with Pulmonary Arterial Hypertension (PAH) worsening components

End point title	Extension Study: Percentage of patients with Pulmonary Arterial Hypertension (PAH) worsening components

End point description:

Percentage of patients with PAH progression events (death, lung transplant or hospitalization due to PAH progression, initiation of new therapy for PAH or new/worsening right heart failure) up to the last day of treatment + 7 days in the two treatment groups.

End point type	Other pre-specified

End point timeframe:

Up to end of treatment + 7 days

End point values	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.	all treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33	31	64	
Units: Percentage of patients				
New or worsening RHF	24	10	17	
Death	18	13	16	
Hospitalization	12	10	11	
Initiation of new PAH therapy	6	7	6	

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extension Study: Pulmonary Arterial Hypertension (PAH) progression time

End point title	Extension Study: Pulmonary Arterial Hypertension (PAH) progression time

End point description:

Kaplan-Meier estimates for PAH worsening defined by time to any components of PAH progression (death, lung transplant, hospitalization due to PAH progression, initiation of new therapy for PAH or new / worsening right heart failure) in the 2 treatment groups

End point type	Other pre-specified

End point timeframe:

Up to end of treatment + 7 days

End point values	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.	all treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	29[6]	28[7]	57[8]	
Units: kaplan-Meier estimates				
number (confidence interval 95%)				
Month 12	74.9 (56.0 to 86.6)	88.9 (69.4 to 96.3)	81.4 (69.0 to 89.3)	
Month 18	68.2 (48.9 to 81.5)	81 (60.1 to 91.7)	74.1 (60.8 to 83.6)	

Notes:

[6] - patients at risk: n=23 at Month 12, n=5 at Month 18

[7] - patients at risk: n=23 at Month 12, n=5 at Month 18

[8] - patients at risk n=46 at Month 12, n=10 at Month 18

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Extension Study: Overall Survival

End point title	Extension Study: Overall Survival

End point description:

Kaplan-Meier estimates for overall survival defined by the time to death due to any cause up to end of

study (Month 18 survival follow-up) in the 2 treatment groups. Patients still alive at the time of the analysis were censored using their last contact date.

End point type	Other pre-specified

End point timeframe:

Up to the Month 18 survival follow-up

End point values	Bosentan 2mg/kg b.i.d.	Bosentan 2mg/kg t.i.d.	all treated set	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	33[9]	31[10]	64[11]	
Units: Kaplan-Meier estimates				
number (confidence interval 95%)	75.8 (57.3 to 87.1)	86.5 (68.0 to 94.7)	80.9 (68.7 to 88.6)	

Notes:

[9] - patients at risk = 17

[10] - patients at risk = 13

[11] - patients at risk = 30

Statistical analyses

No statistical analyses for this end point

Other pre-specified: Exceptional Use Treatment Period (EUTP): Percentage of Patients with Treatment-emergent Adverse Events (TEAEs) up to 7 days After Permanent Discontinuation of Study Drug

End point title	Exceptional Use Treatment Period (EUTP): Percentage of Patients with Treatment-emergent Adverse Events (TEAEs) up to 7 days After Permanent Discontinuation of Study Drug

End point description:

An adverse event (AE) is any untoward medical occurrence in a patient who received study drug without regard to possibility of causal relationship. TEAE are defined as AEs with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	8			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with Treatment-emergent Serious Adverse Events (SAEs) up to 7 days After Permanent Discontinuation of Study Drug

End point title	EUTP: Percentage of Patients with Treatment-emergent Serious Adverse Events (SAEs) up to 7 days After Permanent Discontinuation of Study Drug

End point description:

An adverse event (AE) is any untoward medical occurrence in a patient who received study drug without regard to possibility of causal relationship. TEAE are defined as AEs with onset during the treatment period or that are a consequence of a pre-existing condition that has worsened since baseline. A SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	4			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with AEs Leading to Premature Discontinuation of Study Drug

End point title	EUTP: Percentage of Patients with AEs Leading to Premature Discontinuation of Study Drug

End point description:

Percentage of Patients with AEs Leading to Premature Discontinuation of Study Drug were reported. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in

the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with SAEs from 7 up to 60 days After Permanent Discontinuation of Study Drug

End point title	EUTP: Percentage of Patients with SAEs from 7 up to 60 days After Permanent Discontinuation of Study Drug

End point description:

Percentage of patients with SAEs from 7 up to 60 days after permanent discontinuation of study drug were reported. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

From 7 up to 60 days after permanent discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with Deaths

End point title	EUTP: Percentage of Patients with Deaths

End point description:

Percentage of patients with deaths were reported. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	1			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with Adverse Events of Special Interest (AESI)

End point title	EUTP: Percentage of Patients with Adverse Events of Special Interest (AESI)

End point description:

Percentage of patients with AESI including liver abnormalities and anemia were reported. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	2			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with Treatment-emergent Marked Laboratory Abnormalities up to 7 days After Permanent Discontinuation of Study Drug

End point title	EUTP: Percentage of Patients with Treatment-emergent Marked Laboratory Abnormalities up to 7 days After Permanent Discontinuation of Study Drug

End point description:

Percentage of patients with treatment-emergent marked laboratory abnormalities: Alanine aminotransferase (ALT)> 3*upper limit of normal (ULN), aspartate aminotransferase (AST)> 3*ULN, ALT or AST> 3*ULN, ALT or AST> 3*ULN and Bilirubin (milligram per deciliter [mg/dL]) > 2*ULN and alkaline phosphatase <=2*ULN, ALT > 3*ULN and <= 5*ULN, ALT > 5*ULN and <= 8*ULN, ALT > 8*ULN, AST > 3*ULN and <= 5*ULN, AST > 5*ULN and<= 8*ULN and AST > 8*ULN were reported. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of patients with Liver Function Abnormalities

End point title	EUTP: Percentage of patients with Liver Function Abnormalities

End point description:

Percentage of patients with liver function abnormalities: Alanine aminotransferase (ALT) =>3*upper limit of normal (ULN), ALT/aspartate aminotransferase (AST) =>3*ULN, ALT /AST =>3*ULN and <5*ULN, ALT/AST =>5*ULN and <8*ULN, ALT/AST =>8*ULN and ALT/AST =>3*ULN and total bilirubin =>2*ULN were reported. Exceptional-use set included all patients who entered the EUTP. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to

global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	10			
Units: percentage of patients				
number (not applicable)	0			

Statistical analyses

No statistical analyses for this end point

Other pre-specified: EUTP: Percentage of Patients with Any time Occurrence of Hemoglobin <=10 gram per deciliter (g/dL) and <=8 g/dL, Between Baseline and up to 7 days After End of Treatment (EOT)

End point title	EUTP: Percentage of Patients with Any time Occurrence of Hemoglobin <=10 gram per deciliter (g/dL) and <=8 g/dL, Between Baseline and up to 7 days After End of Treatment (EOT)

End point description:

Percentage of patients with any time occurrence of Hgb (hemoglobin) less than or equal to (<=) 10 gram per deciliter (g/dL) and <=8 g/dL, between baseline and up to the last day of treatment + 7 days during EUTP were reported. Exceptional-use set included all patients who entered the EUTP. Here 'N' (number of subjects analyzed) signifies those subjects who were evaluable for this outcome measure. Due to change in study conduct, patients treated with bosentan t.i.d. switched to b.i.d. after local Amendment B to global protocol version 2 (17 March 2015 for Belarus and Ukraine, 1 April 2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the results were reported combined for bosentan b.i.d./t.i.d.

End point type	Other pre-specified

End point timeframe:

Up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

End point values	Bosentan 2 mg/kg b.i.d or t.i.d			
Subject group type	Subject analysis set			
Number of subjects analysed	9			
Units: percentage of patients				
number (not applicable)				
Hgb <= 10 g/dL	2			
Hgb <= 8 g/dL	0			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

From baseline up to end of treatment (and up to additional 60 days for serious adverse events and deaths), i.e. an average of 62 weeks and for EUTP: up to 7 days after discontinuation of study drug (approximately 3 years and 4 months)

Adverse event reporting additional description:

Adverse events (AEs) and deaths are reported cumulatively for both AC-052-373 and AC-052-374 (FUTURE 3 core & extension). Serious AEs with fatal outcome are not mutually exclusive (One death can be linked to more than one Serious AE). 5% threshold applied to total and individual frequent AEs.

Assessment type	Systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	17.0

Reporting groups

Reporting group title	bosentan 2mg/kg b.i.d.

Reporting group description:

2 mg/kg bosentan was administered twice daily for a cumulative mean (± SD) duration of 64.1 ± 3.38 weeks (FUTURE 3 core + extension studies)

Reporting group title	bosentan 2mg/kg t.i.d.

Reporting group description:

2 mg/kg bosentan was administered 3 times a day for a cumulative mean (± SD) duration of 60.4 ± 4.20 weeks (FUTURE 3 core + extension studies)

Reporting group title	bosentan 2mg/kg b.i.d or t.i.d. during EUTP

Reporting group description:

Patients who entered the exceptional use treatment period (EUTP), continued receiving 2 mg/kg bosentan b.i.d or t.i.d up to Amendment B. After implementation of Amendment B, all patients received 2 mg/kg bosentan b.i.d. Due to change in study conduct, patients treated with bosentan tid. switched to bid. after local Amendment B to global protocol version 2 (17-03-2015 for Belarus and Ukraine, 1-04-2015 for China) and displaying summaries in the EUTP period by dose were not significant. Therefore, the AEs were combined for bosentan bid. and tid.

Serious adverse events	bosentan 2mg/kg b.i.d.	bosentan 2mg/kg t.i.d.	bosentan 2mg/kg b.i.d or t.i.d. during EUTP
Total subjects affected by serious adverse events			
subjects affected / exposed	15 / 33 (45.45%)	13 / 31 (41.94%)	4 / 10 (40.00%)
number of deaths (all causes)	8	4	1
number of deaths resulting from adverse events			
Investigations			
Body temperature increased			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Oxygen saturation decreased			

subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Injury, poisoning and procedural complications			
Fall			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Head injury			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Congenital, familial and genetic disorders			
Mucopolysaccharidosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cardiac disorders			
Cardiopulmonary failure			
subjects affected / exposed	1 / 33 (3.03%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Cardiac arrest			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 2	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac failure acute			

subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Cyanosis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Surgical and medical procedures			
Atrial septal defect repair			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Cardiac operation			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Nervous system disorders			
Syncope			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 3	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Convulsion			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 4	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Loss of consciousness			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Migraine with aura			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
General disorders and administration			

site conditions			
Death			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Multi-organ failure			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pyrexia			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Immune system disorders			
Drug hypersensitivity			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastrointestinal disorders			
Gastrooesophageal reflux disease			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory, thoracic and mediastinal disorders			
Pulmonary arterial hypertension			
subjects affected / exposed	4 / 33 (12.12%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 4	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 4	0 / 2	0 / 0
Adenoidal hypertrophyhy			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Epistaxis			

subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Pulmonary embolism			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0
Pulmonary hypertensive crisis			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	2 / 10 (20.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 2
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 1
Respiratory distress			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Haemoptysis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 0	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infections and infestations			
Pneumonia			
subjects affected / exposed	1 / 33 (3.03%)	3 / 31 (9.68%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 1	0 / 3	0 / 1
deaths causally related to treatment / all	0 / 1	0 / 1	0 / 0
Bronchopneumonia			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 2	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 1	0 / 0
Bronchitis			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis			

subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis adenovirus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Gastroenteritis rotavirus			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Lower respiratory tract infection viral			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Respiratory tract infection viral			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	1 / 10 (10.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 1
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral infection			
subjects affected / exposed	0 / 33 (0.00%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 0	0 / 1	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Viral upper respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 0	0 / 0	0 / 0
Metabolism and nutrition disorders			
Metabolic disorder			

subjects affected / exposed	1 / 33 (3.03%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences causally related to treatment / all	0 / 1	0 / 0	0 / 0
deaths causally related to treatment / all	0 / 1	0 / 0	0 / 0

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

Non-serious adverse events	bosentan 2mg/kg b.i.d.	bosentan 2mg/kg t.i.d.	bosentan 2mg/kg b.i.d or t.i.d. during EUTP
Total subjects affected by non-serious adverse events			
subjects affected / exposed	24 / 33 (72.73%)	23 / 31 (74.19%)	7 / 10 (70.00%)
Vascular disorders			
Flushing			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Circulatory Collapse			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Hypotension			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
General disorders and administration site conditions			
Pyrexia			
subjects affected / exposed	5 / 33 (15.15%)	7 / 31 (22.58%)	3 / 10 (30.00%)
occurrences (all)	15	15	6
Oedema peripheral			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Chest Pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Exercise Tolerance Decreased			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Immune system disorders			
Seasonal allergy			

subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Hypersensitivity			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory, thoracic and mediastinal disorders			
Pulmonary arterial hypertension			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	2
Cough			
subjects affected / exposed	4 / 33 (12.12%)	3 / 31 (9.68%)	1 / 10 (10.00%)
occurrences (all)	4	3	4
Epistaxis			
subjects affected / exposed	0 / 33 (0.00%)	3 / 31 (9.68%)	1 / 10 (10.00%)
occurrences (all)	0	4	1
Rhinorrhoea			
subjects affected / exposed	3 / 33 (9.09%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	3	0	2
Nasal congestion			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Dyspnoea			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Oropharyngeal Pain			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory Failure			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Investigations			
Blood bilirubin increased			
subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	1 / 10 (10.00%)
occurrences (all)	2	1	1
Liver function test abnormal			

subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Injury, poisoning and procedural complications			
Accidental overdose			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Cardiac disorders			
Cyanosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Blood and lymphatic system disorders			
Thrombocytopenia			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	2	0	1
Anaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Splenomegaly			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Gastrointestinal disorders			
Vomiting			
subjects affected / exposed	4 / 33 (12.12%)	6 / 31 (19.35%)	0 / 10 (0.00%)
occurrences (all)	5	10	0
Diarrhoea			
subjects affected / exposed	2 / 33 (6.06%)	6 / 31 (19.35%)	0 / 10 (0.00%)
occurrences (all)	2	9	0
Constipation			
subjects affected / exposed	1 / 33 (3.03%)	3 / 31 (9.68%)	0 / 10 (0.00%)
occurrences (all)	1	4	0
Abdominal pain			
subjects affected / exposed	1 / 33 (3.03%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Abdominal Discomfort			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

Hepatobiliary disorders			
Hepatic Function Abnormal			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Skin and subcutaneous tissue disorders			
Rash			
subjects affected / exposed	1 / 33 (3.03%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Dermatitis allergic			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Urticaria			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Infections and infestations			
Upper respiratory tract infection			
subjects affected / exposed	9 / 33 (27.27%)	13 / 31 (41.94%)	2 / 10 (20.00%)
occurrences (all)	22	26	3
Nasopharyngitis			
subjects affected / exposed	6 / 33 (18.18%)	5 / 31 (16.13%)	1 / 10 (10.00%)
occurrences (all)	16	8	1
Viral upper respiratory tract infection			
subjects affected / exposed	4 / 33 (12.12%)	3 / 31 (9.68%)	0 / 10 (0.00%)
occurrences (all)	6	3	0
Gastroentiritis			
subjects affected / exposed	3 / 33 (9.09%)	3 / 31 (9.68%)	0 / 10 (0.00%)
occurrences (all)	3	3	0
Bronchitis			
subjects affected / exposed	3 / 33 (9.09%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	4	2	0
Viral infection			
subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences (all)	2	1	0
Lower respiratory tract infection			
subjects affected / exposed	1 / 33 (3.03%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	1	2	0
Otitis media			

subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	0 / 10 (0.00%)
occurrences (all)	5	1	0
Respiratory tract infection			
subjects affected / exposed	2 / 33 (6.06%)	1 / 31 (3.23%)	1 / 10 (10.00%)
occurrences (all)	3	2	2
Ear infection			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Influenza			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	2	0
Laryngitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences (all)	4	0	0
Otitis media chronic			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences (all)	2	0	0
Pharyngitis			
subjects affected / exposed	2 / 33 (6.06%)	0 / 31 (0.00%)	0 / 10 (0.00%)
occurrences (all)	3	0	0
Rhinitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	0 / 10 (0.00%)
occurrences (all)	0	3	0
Tonsilitis			
subjects affected / exposed	0 / 33 (0.00%)	2 / 31 (6.45%)	1 / 10 (10.00%)
occurrences (all)	0	2	1
Varicella			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
pneumonia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Respiratory Tract Infection Viral			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolism and nutrition disorders			

Hypoproteinaemia			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1
Metabolic Acidosis			
subjects affected / exposed	0 / 33 (0.00%)	0 / 31 (0.00%)	1 / 10 (10.00%)
occurrences (all)	0	0	1

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? No

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.

The main objective of exceptional use treatment period of FUTURE 3 extension was to provide patients with bosentan beyond 12-month treatment period of FUTURE 3 extension. No formal hypothesis was formulated therefore results were exploratory.

Notes: