



## Clinical trial results:

### Long term, single-arm, open-label extension study of protocol AC-055-305 to assess the safety, tolerability and efficacy of macitentan in subjects with Eisenmenger Syndrome

#### Summary

EudraCT number	2012-004411-31
Trial protocol	IT BG GB DE AT PT ES HU CZ RO PL GR
Global end of trial date	12 January 2018

#### Results information

Result version number	v1 (current)
This version publication date	27 July 2018
First version publication date	27 July 2018

#### Trial information

##### Trial identification

Sponsor protocol code	AC-055-308
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##### Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT01739400
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@its.jnj.com
Scientific contact	Clinical Trial Disclosure Desk, Actelion Pharmaceuticals Ltd., clinical-trials-disclosure@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?	Yes

Notes:

## Results analysis stage

Analysis stage	Final
Date of interim/final analysis	22 January 2018
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 January 2018
Global end of trial reached?	Yes
Global end of trial date	12 January 2018
Was the trial ended prematurely?	Yes

Notes:

## General information about the trial

Main objective of the trial:

To assess the long-term safety and tolerability of macitentan in subjects with Eisenmenger Syndrome (ES) beyond the treatment of the AC-055-305/MAESTRO double-blind (DB) study (EudraCT number 2012-003335-33), and to assess the long-term efficacy of macitentan in this subject population.

Protection of trial subjects:

Prior to the start of the study, each study site consulted an Independent Ethics Committee (IEC) or Institutional Review Board (IRB), i.e., a review panel that was responsible for ensuring the protection of the rights, safety and well-being of human subjects involved in a clinical investigation. The study was conducted in compliance with the principles of the 'Declaration of Helsinki', the International Council for Harmonisation (ICH)-Good Clinical Practice (GCP) guidelines, and with the laws and regulations of the country in which the clinical research was conducted.

Both Actelion and the investigator had the right to terminate the study at any time, and in such a case, were responsible for protecting the subjects' interests. Prior to any study procedure and after adequate explanation of the aims, methods, objectives, and potential hazards of the study, written informed consent was obtained from each participating adult subject (including Down Syndrome subjects who were able to consent), as well as from the parent(s) or legal representative(s) of each participating minor, and from the parent(s)/legal representative(s) or caregiver(s) of each participating subject with Down Syndrome, who was not able to personally read and sign the informed consent. Additionally, written assent was obtained from each minor and each Down Syndrome subject who was unable to give written consent. All subjects who participated in the hemodynamic sub-study were required to sign a separate informed consent form (ICF). Informed consent/assent was obtained in accordance with the national laws or regulations.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	10 September 2013
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	No

Notes:

## Population of trial subjects

### Subjects enrolled per country

Country: Number of subjects enrolled	Austria: 3
Country: Number of subjects enrolled	Bulgaria: 5
Country: Number of subjects enrolled	Chile: 7
Country: Number of subjects enrolled	China: 68
Country: Number of subjects enrolled	France: 17
Country: Number of subjects enrolled	Germany: 3
Country: Number of subjects enrolled	Greece: 3
Country: Number of subjects enrolled	Malaysia: 3
Country: Number of subjects enrolled	Mexico: 29

Country: Number of subjects enrolled	Philippines: 2
Country: Number of subjects enrolled	Poland: 9
Country: Number of subjects enrolled	Portugal: 7
Country: Number of subjects enrolled	Romania: 8
Country: Number of subjects enrolled	Russian Federation: 19
Country: Number of subjects enrolled	Serbia: 9
Country: Number of subjects enrolled	Spain: 3
Country: Number of subjects enrolled	United Kingdom: 1
Country: Number of subjects enrolled	United States: 5
Country: Number of subjects enrolled	Vietnam: 16
Worldwide total number of subjects	217
EEA total number of subjects	59

Notes:

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### 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)	14
Adults (18-64 years)	200
From 65 to 84 years	3
85 years and over	0

## Subject disposition

### Recruitment

Recruitment details:

The study was conducted at 51 sites in 19 countries (geographical regions: Asia-Pacific, Eastern Europe, Latin America, North America and Western Europe).

### Pre-assignment

Screening details:

217 subjects from the AC-055-305/DB study (EudraCT 2012-003335-33) were enrolled in this open-label (OL) study without knowledge of their study treatment allocation (macitentan or placebo) in the DB study. As the DB study did not meet its primary endpoint, the sponsor decided to prematurely terminate this OL study.

### Period 1

Period 1 title	Overall study (overall period)
Is this the baseline period?	Yes
Allocation method	Non-randomised - controlled
Blinding used	Not blinded

### Arms

Arm title	Macitentan
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Arm description:

Macitentan 10 mg, film-coated tablet, oral use, once daily

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	ACT-064992
Other name	
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg, taken orally once daily

Number of subjects in period 1	Macitentan
Started	217
Completed	191
Not completed	26
Adverse event, serious fatal	7
Consent withdrawn by subject	14
Physician decision	3
Lost to follow-up	2

## Baseline characteristics

### Reporting groups

Reporting group title	Overall study
Reporting group description:	
Overall study	

Reporting group values	Overall study	Total	
Number of subjects	217	217	
Age categorical			
Units: Subjects			
12 - 17 years	14	14	
18 - 64 years	200	200	
65 - 84 years	3	3	
≥ 85 years	0	0	
Age continuous			
Units: years			
median	32.0		
full range (min-max)	12 to 82	-	
Gender categorical			
Units:			
Female	143	143	
Male	74	74	
Race			
Units: Subjects			
White	103	103	
Chinese	70	70	
Other Asian	22	22	
Other	22	22	
Ethnicity			
Units: Subjects			
Not Hispanic or Latino	177	177	
Hispanic or Latino	40	40	
Enrollment by geographical region			
Units: Subjects			
Asia-Pacific	89	89	
Eastern Europe	50	50	
Latin America	36	36	
North America	5	5	
Western Europe-Israel	37	37	
WHO functional class			
WHO functional class of subjects Class I: no symptoms with exercise or at rest. No limitation of activity. Class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing a flight of stairs, grocery shopping, or making the bed). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest (e.g. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure			
Units: Subjects			
class I	0	0	
class II	131	131	

class III	86	86	
class IV	0	0	
Down syndrome status			
Units: Subjects			
Yes	20	20	
No	197	197	
Body Mass Index (BMI)			
Units: kg/m2			
median	21.2		
full range (min-max)	11.9 to 42.2	-	

### Subject analysis sets

Subject analysis set title	All-enrolled analysis set
Subject analysis set type	Full analysis

Subject analysis set description:

The all-enrolled analysis set includes all subjects enrolled in AC-055-308 / OL, whether or not they took at least one dose of macitentan during the OL study.

Subject analysis set title	DB-macitentan
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received macitentan in the DB study (AC-055-305, EudraCT 2012-003335-33).

Subject analysis set title	DB-placebo
Subject analysis set type	Intention-to-treat

Subject analysis set description:

All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received placebo in the DB study (AC-055-305, EudraCT 2012-003335-33).

Reporting group values	All-enrolled analysis set	DB-macitentan	DB-placebo
Number of subjects	217	109	108
Age categorical			
Units: Subjects			
12 - 17 years	14	12	2
18 - 64 years	200	94	106
65 - 84 years	3	3	0
≥ 85 years	0	0	0
Age continuous			
Units: years			
median	32.0	33.0	31.5
full range (min-max)	12 to 82	12 to 82	14 to 62
Gender categorical			
Units:			
Female	143	77	66
Male	74	32	42
Race			
Units: Subjects			
White	103	52	51
Chinese	70	35	35
Other Asian	22	11	11
Other	22	11	11
Ethnicity			

Units: Subjects			
Not Hispanic or Latino	177	89	88
Hispanic or Latino	40	20	20
Enrollment by geographical region			
Units: Subjects			
Asia-Pacific	89	45	44
Eastern Europe	50	24	26
Latin America	36	18	18
North America	5	1	4
Western Europe-Israel	37	21	16
WHO functional class			
WHO functional class of subjects Class I: no symptoms with exercise or at rest. No limitation of activity. Class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing a flight of stairs, grocery shopping, or making the bed). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest (e.g. dyspnea and/or fatigue) and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure			
Units: Subjects			
class I	0	0	0
class II	131	66	65
class III	86	43	43
class IV	0	0	0
Down syndrome status			
Units: Subjects			
Yes	20	10	10
No	197	99	98
Body Mass Index (BMI)			
Units: kg/m2			
median	21.2	20.9	21.4
full range (min-max)	11.9 to 42.2	11.9 to 38.9	14.5 to 42.2

## End points

### End points reporting groups

Reporting group title	Macitentan
Reporting group description:	
Macitentan 10 mg, film-coated tablet, oral use, once daily	
Subject analysis set title	All-enrolled analysis set
Subject analysis set type	Full analysis
Subject analysis set description:	
The all-enrolled analysis set includes all subjects enrolled in AC-055-308 / OL, whether or not they took at least one dose of macitentan during the OL study.	
Subject analysis set title	DB-macitentan
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received macitentan in the DB study (AC-055-305, EudraCT 2012-003335-33).	
Subject analysis set title	DB-placebo
Subject analysis set type	Intention-to-treat
Subject analysis set description:	
All enrolled subjects treated with macitentan in the AC-055-308 / OL study who received placebo in the DB study (AC-055-305, EudraCT 2012-003335-33).	

### Primary: Change in exercise capacity as measured by 6-minute walking distance (6MWD) Month 6 and 12

End point title	Change in exercise capacity as measured by 6-minute walking distance (6MWD) Month 6 and 12
End point description:	
NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary safety endpoint here. All efficacy analyses were considered exploratory. The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in the OL study. For missing 6MWD values in the OL study, the following imputation rules were applied: If the reason for missing data was death, a distance of zero (0) meters was imputed for all 6MWD visits from the date of death. For any other reasons, the last available value was carried forward.	
End point type	Primary
End point timeframe:	
From baseline in DB study (AC-055-305) up to month 12 in this OL study.	

End point values	DB-macitentan	DB-placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	108		
Units: meter (m)				
arithmetic mean (standard deviation)				
6MWD at DB study baseline	370.6 (± 74.1)	381.6 (± 76.7)		
6MWD at Week 16 in DB study	395.1 (± 88.4)	399.9 (± 80.6)		
Change in 6MWD from DB study baseline to Week 16	24.4 (± 71.0)	18.2 (± 53.0)		
6MWD at Month 6 in OL study	396.8 (± 96.5)	425.0 (± 72.1)		
Change in 6MWD from DB study baseline to Month 6	26.2 (± 77.9)	43.4 (± 51.5)		



6MWD at Month 12 in OL study	397.1 ( $\pm$ 103.9)	421.5 ( $\pm$ 76.5)		
Change in 6MWD from DB study baseline to Month 12	26.5 ( $\pm$ 79.8)	39.9 ( $\pm$ 55.1)		

## Statistical analyses

Statistical analysis title	Analysis of exercise capacity
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Statistical analysis description:

The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented.

Comparison groups	DB-macitentan v DB-placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	other <sup>[1]</sup>
P-value	= 0
Method	no p-value as exploratory analysis

Notes:

[1] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

## Primary: Change in WHO functional class (FC) at Month 6 and 12

End point title	Change in WHO functional class (FC) at Month 6 and 12
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End point description:

NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary efficacy endpoint here. For missing WHO FC values in the OL study, the following imputation rules were applied: If the reason for missing data was death, class IV was imputed for all WHO visits from the date of death. For any other reasons, the last available value was carried forward. Class I: no symptoms with exercise or at rest. No limitation of activity. Class II: No symptoms at rest but slight limitation with ordinary activities causing symptoms (e.g. short of breath with climbing stairs). Class III: may not have symptoms at rest but activities greatly limited by shortness of breath, fatigue, or near fainting. Class IV: symptoms at rest and inability to carry out any physical activity without symptoms. Patients in class IV manifest signs of right heart failure.

End point type	Primary
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End point timeframe:

From baseline in DB study (AC-055-305) up to month 12 in this OL study.

End point values	DB-macitentan	DB-placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	108		
Units: subjects				
WHO functional class I at DB study baseline	0	0		
WHO functional class II at DB study baseline	66	65		
WHO functional class III at DB study baseline	43	43		
WHO functional class IV at DB study baseline	0	0		

WHO functional class I at Week 16 in DB study	3	1		
WHO functional class II at Week 16 in DB study	70	77		
WHO functional class III at Week 16 in DB study	36	30		
WHO functional class IV at Week 16 in DB study	0	0		
Improvement from DB study baseline to Week 16	10	15		
Worsening from DB study baseline to Week 16	0	1		
WHO functional class I at Month 6 in OL study	5	7		
WHO functional class II at Month 6 in OL study	74	79		
WHO functional class III at Month 6 in OL study	28	22		
WHO functional class IV at Month 6 in OL study	2	0		
Improvement from DB study baseline to Month 6	19	27		
Worsening from DB study baseline to Month 6	3	1		
WHO functional class I at Month 12 in OL study	5	7		
WHO functional class II at Month 12 in OL study	74	79		
WHO functional class III at Month 12 in OL study	28	22		
WHO functional class IV at Month 12 in OL study	2	0		
Improvement from DB study baseline to Month 12	20	31		
Worsening from DB study baseline to Month 12	4	3		

## Statistical analyses

<b>Statistical analysis title</b>	Analysis of change in WHO functional class
Statistical analysis description:	
The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented.	
Comparison groups	DB-macitentan v DB-placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	other <sup>[2]</sup>
P-value	= 0
Method	no p-value as exploratory analysis

Notes:

[2] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

## Primary: Change in Borg dyspnea score at Month 6 and 12

End point title	Change in Borg dyspnea score at Month 6 and 12
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**End point description:**

The Borg dyspnea score rates the severity of dyspnea (difficult or labored breathing) on a scale from 0 ('Nothing at all') to 10 ('Very, very severe – maximal'). NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary safety endpoint here. For missing Borg dyspnea index values in the OL study, the following imputation rules were applied: If the reason for missing data was death, a value of 10 was imputed for all Borg visits from the date of death. For any other reasons, the last available value was carried forward.

End point type	Primary
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**End point timeframe:**

From baseline in DB study (AC-055-305) up to month 12 in this OL study.

End point values	DB-macitentan	DB-placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109	108		
Units: Score on a scale				
arithmetic mean (standard deviation)				
Borg dyspnea score at DB study baseline	3.0 (± 1.9)	2.9 (± 1.8)		
Borg dyspnea score at Week 16 in DB study	2.7 (± 1.9)	1.9 (± 1.6)		
Change from DB study baseline to Week 16	-0.3 (± 1.4)	-0.2 (± 1.5)		
Borg dyspnea score at Month 6 in OL study	2.8 (± 2.0)	2.5 (± 1.8)		
Change from DB study baseline to Month 6	-0.1 (± 2.0)	-0.4 (± 1.5)		
Borg dyspnea score at Month 12 in OL study	2.9 (± 2.0)	2.6 (± 1.9)		
Change from DB study baseline to Month 12	-0.1 (± 2.1)	-0.3 (± 1.6)		

**Statistical analyses**

Statistical analysis title	Analysis of Borg dyspnea score
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**Statistical analysis description:**

The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented.

Comparison groups	DB-macitentan v DB-placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	other <sup>[3]</sup>
P-value	= 0
Method	no p-value as exploratory analysis

**Notes:**

[3] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

**Primary: Change in peripheral oxygen saturation (SpO2) at rest at Month 6 and 12**

End point title	Change in peripheral oxygen saturation (SpO2) at rest at
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End point description:

NOTE: The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. This exploratory efficacy outcome measure was selected to be reported as a primary efficacy endpoint here. No imputation of missing data for SpO2 was applied. Oxygen saturation assessed by pulse oximetry: peripheral oxygen saturation (SpO2) at rest before the 6-minute walk test (6MWT)

End point type Primary

End point timeframe:

From baseline in DB study (AC-055-305) up to month 12 in this OL study.

End point values	DB-macitentan	DB-placebo		
Subject group type	Subject analysis set	Subject analysis set		
Number of subjects analysed	109 <sup>[4]</sup>	108 <sup>[5]</sup>		
Units: percent (%)				
arithmetic mean (standard deviation)				
SpO2 at DB study baseline	84.2 (± 5.6)	85.4 (± 5.0)		
SpO2 at Week 16 in DB study	85.3 (± 5.8)	85.6 (± 5.4)		
Change in SpO2 from DB study baseline to Week 16	1.1 (± 4.0)	0.2 (± 4.5)		
SpO2 at Month 6 in OL study	85.9 (± 5.9)	87.4 (± 5.4)		
Change in SpO2 from DB study baseline to Month 6	1.5 (± 4.9)	2.0 (± 4.3)		
SpO2 at Month 12 in OL study	86.4 (± 6.3)	87.1 (± 5.0)		
Change in SpO2 from DB study baseline to Month 12	2.0 (± 4.4)	1.6 (± 4.9)		

Notes:

[4] - Out of 109 subjects 104 subjects were analyzed at month 6 and 92 subjects at month 12.

[5] - Out of 109 subjects 103 subjects were analyzed at month 6 and 84 subjects at month 12.

## Statistical analyses

Statistical analysis title	Analysis of peripheral oxygen saturation (SpO2)
Statistical analysis description:	
The MAESTRO-OL study was exploratory in nature and no primary efficacy and safety endpoint were defined in the clinical protocol. All efficacy analyses are considered exploratory. No hypothesis testing were defined, hence no p-values will be presented.	
Comparison groups	DB-macitentan v DB-placebo
Number of subjects included in analysis	217
Analysis specification	Pre-specified
Analysis type	other <sup>[6]</sup>
P-value	= 0
Method	no p-value as exploratory analysis

Notes:

[6] - The analyses of the exploratory efficacy endpoints focused on the absolute values and on the change from DB baseline to Week 16 in the DB study and to Month 6 and Month 12 in this OL study.

## Adverse events

### Adverse events information

Timeframe for reporting adverse events:

From OL study treatment initiation up to 30 days after study treatment discontinuation

Assessment type	Systematic
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### Dictionary used

Dictionary name	MedDRA
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Dictionary version	20
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### Reporting groups

Reporting group title	Macitentan
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Reporting group description:

Macitentan 10 mg to be taken daily, film-coated tablet, oral use

Serious adverse events	Macitentan		
Total subjects affected by serious adverse events			
subjects affected / exposed	62 / 217 (28.57%)		
number of deaths (all causes)	7		
number of deaths resulting from adverse events	1		
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Endometrial adenocarcinoma			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Glioblastoma			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	1 / 1		
Vascular disorders			
Arterial perforation			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Peripheral ischaemia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Surgical and medical procedures			
Drug therapy			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Surgery			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Pregnancy			
subjects affected / exposed	3 / 217 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Chest discomfort			
subjects affected / exposed	2 / 217 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Chest pain			
subjects affected / exposed	3 / 217 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
General physical health deterioration			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Immune system disorders			
Allergy to arthropod sting			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Reproductive system and breast disorders			

Ovarian cyst ruptured			
subjects affected / exposed	2 / 217 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Respiratory, thoracic and mediastinal disorders			
Bronchiectasis			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemoptysis			
subjects affected / exposed	9 / 217 (4.15%)		
occurrences causally related to treatment / all	0 / 11		
deaths causally related to treatment / all	0 / 0		
Hypoxia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pneumonia aspiration			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary alveolar haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary arterial hypertension			
subjects affected / exposed	4 / 217 (1.84%)		
occurrences causally related to treatment / all	0 / 4		
deaths causally related to treatment / all	0 / 1		
Pulmonary embolism			
subjects affected / exposed	3 / 217 (1.38%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 1		

Pulmonary haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pulmonary infarction			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Investigations			
Antineutrophil cytoplasmic antibody positive			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Oxygen saturation decreased			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Hip fracture			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Arrhythmia			



subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial fibrillation				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac arrest				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac failure				
subjects affected / exposed	3 / 217 (1.38%)			
occurrences causally related to treatment / all	0 / 4			
deaths causally related to treatment / all	0 / 0			
Cardiogenic shock				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Right ventricular failure				
subjects affected / exposed	6 / 217 (2.76%)			
occurrences causally related to treatment / all	3 / 7			
deaths causally related to treatment / all	0 / 0			
Supraventricular tachycardia				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ventricular arrhythmia				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Ventricular extrasystoles				

subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ventricular fibrillation			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Dizziness			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Haemorrhagic transformation stroke			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Ischaemic stroke			
subjects affected / exposed	2 / 217 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Syncope			
subjects affected / exposed	2 / 217 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Iron deficiency anaemia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Pancytopenia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Thrombocytopenia			

subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal artery embolism			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal distension			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Dyschezia			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Intestinal obstruction			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Upper gastrointestinal haemorrhage			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hepatobiliary disorders			
Cholecystitis			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Urinary retention			

subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral disc protrusion			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Rheumatoid arthritis			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Spinal disorder			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Appendicitis perforated			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Brain abscess			
subjects affected / exposed	2 / 217 (0.92%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Bronchitis viral			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Herpes zoster			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

Peritonitis				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	5 / 217 (2.30%)			
occurrences causally related to treatment / all	0 / 5			
deaths causally related to treatment / all	0 / 0			
Postoperative wound infection				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pyelonephritis acute				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Respiratory tract infection				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Sepsis				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Tuberculous pleurisy				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Upper respiratory tract infection				
subjects affected / exposed	1 / 217 (0.46%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Viral pharyngitis				

subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Wound infection			
subjects affected / exposed	1 / 217 (0.46%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		

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

<b>Non-serious adverse events</b>	Macitentan		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	152 / 217 (70.05%)		
Investigations			
Haemoglobin decreased			
subjects affected / exposed	20 / 217 (9.22%)		
occurrences (all)	29		
Nervous system disorders			
Dizziness			
subjects affected / exposed	18 / 217 (8.29%)		
occurrences (all)	20		
Headache			
subjects affected / exposed	29 / 217 (13.36%)		
occurrences (all)	34		
General disorders and administration site conditions			
Chest pain			
subjects affected / exposed	13 / 217 (5.99%)		
occurrences (all)	13		
Fatigue			
subjects affected / exposed	11 / 217 (5.07%)		
occurrences (all)	11		
Oedema peripheral			
subjects affected / exposed	14 / 217 (6.45%)		
occurrences (all)	15		
Gastrointestinal disorders			

Diarrhoea subjects affected / exposed occurrences (all)	18 / 217 (8.29%) 20		
Respiratory, thoracic and mediastinal disorders Cough subjects affected / exposed occurrences (all)  Haemoptysis subjects affected / exposed occurrences (all)	23 / 217 (10.60%) 28  24 / 217 (11.06%) 42		
Infections and infestations Bronchitis subjects affected / exposed occurrences (all)  Upper respiratory tract infection subjects affected / exposed occurrences (all)  Viral upper respiratory tract infection subjects affected / exposed occurrences (all)	20 / 217 (9.22%) 27  61 / 217 (28.11%) 119  21 / 217 (9.68%) 35		

## More information

### Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
03 April 2013	<p>Amendment 1 resulting in Global Protocol Version 2.</p> <p>Changes included:</p> <ul style="list-style-type: none"><li>- A summary of the potential risks associated with macitentan and the methodology for risk management were added.</li><li>- Sections related to study assessments (for e.g., review of the documents, order of assessments, 6MWT and Borg dyspnea index, etc.) were slightly modified in order to clarify the instructions relevant to the investigators.</li><li>- The "risks" section of the ICF was revised to account for the possibility of interruption or permanent discontinuation of study medication based on specific decreases in hemoglobin levels.</li><li>-The ICF was revised to include additional information about the potential risk of macitentan to align with updates to the Macitentan IB for non-oncology indications. The ICF was also updated to clarify the duties of the trial subjects following a change in the sponsor's insurance company.</li></ul>
19 September 2013	<p>Amendment 2 resulting in Global Protocol Version 3.</p> <p>Changes included:</p> <ul style="list-style-type: none"><li>- The number of study sites was increased to improve the rate of recruitment.</li><li>- Results of all protocol-mandated laboratory assessments to be collected in the database. A Central Laboratory was to be used for the analysis of all laboratory variables requested in the protocol.</li><li>- Monthly laboratory and safety monitoring at a site visit was added in order to improve sponsor oversight.</li><li>- The reason for permanent discontinuation was now documented in the eCRF.</li><li>- Throughout the protocol, upper limits for liver abnormality were updated to reflect the FDA guidance on DILI.</li><li>- For hemoglobin monitoring, clarification on re-tests for assessing hemoglobin change was provided.</li><li>- Collection of information on concomitant medication was extended to all visits.</li><li>- Instructions for collection and handling of local laboratory samples and, where applicable, reporting of results within the eCRF of local analyses of local laboratory samples were added.</li><li>- Instructions on performing and recording unscheduled visits were added.</li><li>- Updated definitions of alert flags for abnormal laboratory values were included in the appropriate appendix.</li><li>- The ICF was updated to reflect the increased number of planned study sites.</li><li>- The ICF was updated to reflect the expanded instructions for unscheduled visits.</li><li>- The risk section of the ICF was updated to account for the latest results of controlled studies.</li></ul>



16 May 2014	<p>Amendment 3 resulting in Global Protocol Version 4.</p> <p>Changes included:</p> <ul style="list-style-type: none"> <li>- The recruitment period was made consistent with the updated study planned duration of the AC-055-305 / MAESTRO study.</li> <li>- The number of study centers selected for the AC-055-305 / MAESTRO study was increased to improve recruitment speed. The same change was implemented in the MAESTRO-OL protocol.</li> <li>- Eligibility criteria was opened up to females of childbearing potential truly abstinent and to subjects with Down Syndrome (if they had support from a caregiver or family member).</li> <li>- To address anticipated difficulties in Down Syndrome subjects, adaptations were made to the 6MWT to accommodate these subjects and to safeguard study outcome.</li> <li>- Clarification regarding which prohibited concomitant treatments must lead to study treatment discontinuation was added.</li> <li>- Clarifications were added on when to perform the requested laboratory re-tests for hemoglobin monitoring.</li> <li>- The timeline to review the laboratory report was shortened in order to identify any potential clinically significant abnormality as early as possible.</li> <li>- Clarifications on medication errors and pre-existing medical conditions were added.</li> <li>- The ICF was updated to reflect the protocol changes.</li> </ul>
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Notes:

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## Interruptions (globally)

Were there any global interruptions to the trial? No

## Limitations and caveats

None reported