EU Clinical Trials Register

Clinical trial results:
A Long-term, Multicenter, Single-arm, Open-label Extension of the SERENADE Study, to Assess the Safety and Efficacy of Macitentan in Subjects with Heart Failure with Preserved Ejection Fraction and Pulmonary Vascular Disease

Summary

EudraCT number	2018-001603-37
Trial protocol	BG DE HU DK SE RO
Global end of trial date	12 October 2021

Results information

Result version number	v1 (current)
This version publication date	28 October 2022
First version publication date	28 October 2022

Trial information

Trial identification

Sponsor protocol code	AC-055G203

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03714815
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	Actelion Pharmaceuticals Ltd
Sponsor organisation address	Gewerbestrasse 16, Allschwil, Switzerland, 4123
Public contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com
Scientific contact	Clinical Registry Group, Actelion Pharmaceuticals Ltd, ClinicalTrialsEU@its.jnj.com

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	10 December 2021
Is this the analysis of the primary completion data?	Yes
Primary completion date	12 October 2021
Global end of trial reached?	Yes
Global end of trial date	12 October 2021
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of this trial was to describe the long-term safety of macitentan 10 milligrams (mg) in subjects with heart failure with preserved ejection fraction (HFpEF) and pulmonary vascular disease (PVD).

Protection of trial subjects:

This study was conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	21 December 2018
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	Argentina: 1
Country: Number of subjects enrolled	Austria: 2
Country: Number of subjects enrolled	Bulgaria: 8
Country: Number of subjects enrolled	Brazil: 2
Country: Number of subjects enrolled	Germany: 4
Country: Number of subjects enrolled	Denmark: 2
Country: Number of subjects enrolled	France: 5
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	Israel: 23
Country: Number of subjects enrolled	Poland: 7
Country: Number of subjects enrolled	Romania: 4
Country: Number of subjects enrolled	Russian Federation: 14
Country: Number of subjects enrolled	Sweden: 2
Country: Number of subjects enrolled	United States: 14
Worldwide total number of subjects	91
EEA total number of subjects	34

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	0
Adults (18-64 years)	14
From 65 to 84 years	69
85 years and over	8

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

Out of the 91 enrolled subjects, 76 subjects completed the study.

Period 1

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

Arms

Arm title	Macitentan 10 mg

Arm description:

Eligible subjects who remained in the main study (2016-003653-15) for at least 24 weeks after randomisation entered this open-label extension study to receive macitentan 10 milligrams (mg) tablet orally once daily until the end of the treatment (treatment exposure ranged from 0.4 to 126 weeks).

Arm type	Experimental
Investigational medicinal product name	Macitentan
Investigational medicinal product code	
Other name	JNJ-67896062 ACT-064992
Pharmaceutical forms	Film-coated tablet
Routes of administration	Oral use

Dosage and administration details:

Macitentan 10 mg tablet was administered once daily until the end of treatment (treatment exposure ranged from 0.4 to 126 weeks).

Number of subjects in period 1	Macitentan 10 mg
Started	91
Completed	76
Not completed	15
Adverse event, serious fatal	11
Physician decision	2
Consent withdrawn by subject	2

Baseline characteristics

Reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Eligible subjects who remained in the main study (2016-003653-15) for at least 24 weeks after randomisation entered this open-label extension study to receive macitentan 10 milligrams (mg) tablet orally once daily until the end of the treatment (treatment exposure ranged from 0.4 to 126 weeks).

Reporting group values	Macitentan 10 mg	Total	
Number of subjects	91	91	
Title for AgeCategorical			
Units: subjects			
Children (2-11 years)	0	0	
Adolescents (12-17 years)	0	0	
Adults (18-64 years)	14	14	
From 65 to 84 years	69	69	
85 years and over	8	8	
Title for AgeContinuous			
Units: years			
arithmetic mean	72.7		
standard deviation	± 9.21	-	
Title for Gender			
Units: subjects			
Female	59	59	
Male	32	32	

End points

End points reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Eligible subjects who remained in the main study (2016-003653-15) for at least 24 weeks after randomisation entered this open-label extension study to receive macitentan 10 milligrams (mg) tablet orally once daily until the end of the treatment (treatment exposure ranged from 0.4 to 126 weeks).

Primary: Number of Subjects with All-cause Deaths up to 30 Days After Study Treatment Discontinuation

End point title	Number of Subjects with All-cause Deaths up to 30 Days After Study Treatment Discontinuation[1]

End point description:

Number of subjects with all-cause deaths up to 30 days after study treatment discontinuation were reported. All-cause deaths are defined as all anticipated and unanticipated deaths due to any cause. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 milligrams (mg).

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 0.4 to 126 weeks)

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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: subjects	11			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with All-cause Hospital Admissions up to 30 Days After Study Treatment Discontinuation

End point title	Number of Subjects with All-cause Hospital Admissions up to 30 Days After Study Treatment Discontinuation[2]

End point description:

Number of subjects with all-cause hospital admissions up to 30 days after study treatment discontinuation were reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 0.4 to 126 weeks)

Notes:

[2] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: subjects	42			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) up to 30 Days After Study Treatment Discontinuation

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs) and Treatment-emergent Serious Adverse Events (TESAEs) up to 30 Days After Study Treatment Discontinuation[3]

End point description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. SAE is any AE that results in: death, persistent or significant disability/incapacity, requires inpatient hospitalization or prolongation of existing hospitalization, is a suspected transmission of any infectious agent via a medicinal product, is life-threatening experience, is a congenital anomaly/birth defect and may jeopardize subject and/or may require medical or surgical intervention to prevent one of the outcomes listed above. Any AE and SAE occurring at or after the study treatment start up to 30 days after end of treatment (EOT) within the analysis set was considered to be treatment-emergent. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 0.4 to 126 weeks)

Notes:

[3] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: subjects				
TEAEs	81			
TESAEs	49			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with TEAEs Leading to Premature Discontinuation of Study Treatment

End point title	Number of Subjects with TEAEs Leading to Premature Discontinuation of Study Treatment[4]

End point description:

An adverse event is any untoward medical event that occurs in a subject administered an investigational product, and it does not necessarily indicate only events with clear causal relationship with the relevant investigational product. Any AE occurring at or after the study treatment start up to 30 days after EOT within the analysis set was considered to be treatment-emergent. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 0.4 to 126 weeks)

Notes:

[4] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	91			
Units: subjects	25			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Systolic and Diastolic Arterial Blood Pressure (BP) at Week 24

End point title	Change from Baseline in Systolic and Diastolic Arterial Blood Pressure (BP) at Week 24[5]

End point description:

Change from baseline in systolic and diastolic arterial BP at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[5] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic BP	-5.01 (± 13.152)			
Diastolic BP	-3.34 (± 9.903)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Systolic and Diastolic Arterial BP at Week 52

End point title	Change from Baseline in Systolic and Diastolic Arterial BP at Week 52[6]

End point description:

Change from baseline in systolic and diastolic arterial BP at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[6] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: mmHg				
arithmetic mean (standard deviation)				
Systolic BP	-2.10 (± 20.855)			
Diastolic BP	-0.79 (± 11.685)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Pulse Rate at Week 24

End point title	Change from Baseline in Pulse Rate at Week 24[7]

End point description:

Change from baseline in pulse rate at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects

analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[7] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	62			
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)	0.59 (± 9.706)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Pulse Rate at Week 52

End point title	Change from Baseline in Pulse Rate at Week 52[8]

End point description:

Change from baseline in pulse rate at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[8] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	53			
Units: bpm				
arithmetic mean (standard deviation)	2.62 (± 18.441)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Body Weight at Week 24

End point title	Change from Baseline in Body Weight at Week 24[9]

End point description:

Change from baseline in body weight at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[9] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	64			
Units: kilograms (kg)				
arithmetic mean (standard deviation)	0.25 (± 6.353)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Body Weight at Week 52

End point title	Change from Baseline in Body Weight at Week 52[10]

End point description:

Change from baseline in body weight at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[10] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	56			
Units: kg				
arithmetic mean (standard deviation)	-0.16 (± 8.200)			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Marked Laboratory Abnormalities (MLAs) up to 30 Days After Study Treatment Discontinuation

End point title	Number of Subjects with Treatment-emergent Marked Laboratory Abnormalities (MLAs) up to 30 Days After Study Treatment Discontinuation[11]

End point description:

Number of subjects with treatment-emergent MLAs (Hemoglobin [grams/Litre{L}], Hematocrit [L/L], Leukocytes [10^9cells/L], Lymphocytes [10^9cells/L], Alanine Aminotransferase [Units/L {U/L}], Aspartate Aminotransferase [U/L], Bilirubin [micromoles/L {mcmol/L}], Alkaline Phosphatase [U/L], Creatinine [mcmol/L], Urea Nitrogen [mmol/L], Urate [mcmol/L], Potassium [mmol/L], Sodium [mmol/L], Magnesium [mmol/L], Calcium [mmol/L] were reported. Abnormalities that occurred after study treatment start and up to 30 days after study treatment discontinuation, that were not present at baseline, were treatment-emergent. SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. N=subjects evaluable for this endpoint; >:greater than; <:less than; ULN=upper limit of normal; L=Low, H=High, LL=low/low, HH=high/high LLL=lower/worse than LL, HHH=higher/worse than HH.

End point type	Primary

End point timeframe:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 0.4 to 126 weeks)

Notes:

[11] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	85			
Units: subjects				
Hemoglobin:LL<100	10			
Hematocrit: LL(<0.28-females;<0.32-males)	5			
Leukocytes: HH (>20.0)	1			
Lymphocytes: LLL (<0.5)	1			
Lymphocytes: LL (<0.8)	10			
Alanine Aminotransferase: HH (>3 ULN)	1			
Aspartate Aminotransferase: HH (>3 ULN)	1			
Alkaline Phosphatase: HH (>2.5 ULN)	1			
Bilirubin: HH (>2 ULN)	1			
Bilirubin: HHH (>5 ULN)	1			
Creatinine: HH (>1.5 ULN)	2			
Urea Nitrogen: HH (>2.5 ULN)	3			
Urate: HH (>590)	15			
Urate: HHH (>720)	3			
Sodium: LLL (<130)	3			
Potassium: LLL (<3.0)	1			
Potassium: LL (<3.2)	5			
Potassium: HH (>5.5)	5			
Magnesium: HHH (>1.23)	1			
Calcium: LLL (<1.75)	1			
Calcium: LL (<2.0)	2			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hemoglobin at Week 24

End point title	Change from Baseline in Hemoglobin at Week 24[12]

End point description:

Change from baseline in hemoglobin at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[12] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: grams per litre (g/L)				
arithmetic mean (standard deviation)	-4.13 (± 11.324)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Leukocytes and Platelets at Week 24

End point title	Change from Baseline in Leukocytes and Platelets at Week

End point description:

Change from baseline in leukocytes and platelets at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[13] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Leukocytes	-0.078 (± 1.6871)			

Platelets	1.39 (± 36.102)				

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hemoglobin at Week 52

End point title	Change from Baseline in Hemoglobin at Week 52[14]

End point description:

Change from baseline in hemoglobin at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[14] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg				
Subject group type	Reporting group				
Number of subjects analysed	51				
Units: g/L					
arithmetic mean (standard deviation)	-1.10 (± 13.241)				

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Leukocytes and Platelets at Week 52

End point title	Change from Baseline in Leukocytes and Platelets at Week

End point description:

Change from baseline in leukocytes and platelets at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[15] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: 10^9 cells/L				
arithmetic mean (standard deviation)				
Leukocytes	-0.503 (± 1.5090)			
Platelets	-9.02 (± 37.285)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Alanine Aminotransferase and Aspartate Aminotransferase at Week 24

End point title	Change from Baseline in Alanine Aminotransferase and Aspartate Aminotransferase at Week 24[16]

End point description:

Change from baseline in alanine aminotransferase and aspartate aminotransferase at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint; "n" specifies those subjects who were analysed for specified categories.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[16] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: units per litre (U/L)				
arithmetic mean (standard deviation)				
Alanine Aminotransferase; n=59	-0.49 (± 7.590)			
Aspartate Aminotransferase; n=58	-0.2 (± 7.76)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Alanine Aminotransferase and Aspartate Aminotransferase at Week 52

End point title	Change from Baseline in Alanine Aminotransferase and Aspartate Aminotransferase at Week 52[17]

End point description:

Change from baseline in alanine aminotransferase and aspartate aminotransferase at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[17] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: U/L				
arithmetic mean (standard deviation)				
Alanine Aminotransferase	0.10 (± 7.529)			
Aspartate Aminotransferase	1.2 (± 6.52)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Bilirubin at Week 24

End point title	Change from Baseline in Bilirubin at Week 24[18]

End point description:

Change from baseline in bilirubin at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[18] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	58			
Units: micromoles per litre (mcmol/L)				
arithmetic mean (standard deviation)	-0.0970 (± 4.20548)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Bilirubin at Week 52

End point title	Change from Baseline in Bilirubin at Week 52[19]

End point description:

Change from baseline in bilirubin at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[19] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	49			
Units: mcmol/L				
arithmetic mean (standard deviation)	0.2041 (± 4.65018)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 24

End point title	Change from Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 24[20]

End point description:

Change from baseline in eGFR rate at Week 24 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 24

Notes:

[20] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	59			
Units: millilitres/minute/1.73 metre square				
arithmetic mean (standard deviation)	-4.05 (± 11.766)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 52

End point title	Change from Baseline in Estimated Glomerular Filtration Rate (eGFR) at Week 52[21]

End point description:

Change from baseline in eGFR rate at Week 52 was reported. The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 mg. Here, "N" (number of subjects analysed) specifies number of subjects evaluable for this endpoint.

End point type	Primary

End point timeframe:

Baseline and Week 52

Notes:

[21] - 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 inferential statistics was planned for this primary endpoint.

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	51			
Units: millilitres/minute/1.73 metre square				
arithmetic mean (standard deviation)	-1.80 (± 13.510)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 30 days after study treatment discontinuation (treatment exposure ranged from 0.4 to 126 weeks)

Adverse event reporting additional description:

The SERENADE OL safety analysis set included all subjects who received at least 1 dose of macitentan 10 milligrams (mg).

Assessment type	Non-systematic

Dictionary used

Dictionary name	MedDRA
Dictionary version	24.0

Reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Eligible subjects who remained in the main study (2016-003653-15) for at least 24 weeks after randomisation entered this open-label extension study to receive macitentan 10 milligrams (mg) tablet orally once daily until the end of the treatment (treatment exposure ranged from 0.4 to 126 weeks).

Serious adverse events	Macitentan 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	49 / 91 (53.85%)		
number of deaths (all causes)	11		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Colon Cancer			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Malignant Neoplasm of Unknown Primary Site			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Plasma Cell Myeloma			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Metastases to Peritoneum			

subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small Intestine Carcinoma				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Uterine Neoplasm				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Surgical and medical procedures				
Cardiac Pacemaker Replacement				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cholecystectomy				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Small Intestinal Resection				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Thyroidectomy				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
General disorders and administration site conditions				
Chest Pain				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Death				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
No Adverse Event				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Non-Cardiac Chest Pain				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Ulcer Haemorrhage				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Respiratory, thoracic and mediastinal disorders				
Acute Respiratory Failure				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Haemoptysis				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Dyspnoea Exertional				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			

Pleural Effusion				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Hypertension				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pulmonary Embolism				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Investigations				
Blood Potassium Increased				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
International Normalised Ratio Increased				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Sars-Cov-2 Test Positive				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Injury, poisoning and procedural complications				
Limb Injury				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Subcutaneous Haematoma				

subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Wound Dehiscence				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac disorders				
Acute Left Ventricular Failure				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Angina Pectoris				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 3			
deaths causally related to treatment / all	0 / 0			
Atrioventricular Block Complete				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	1 / 1			
deaths causally related to treatment / all	0 / 0			
Atrial Fibrillation				
subjects affected / exposed	2 / 91 (2.20%)			
occurrences causally related to treatment / all	0 / 2			
deaths causally related to treatment / all	0 / 0			
Bradycardia				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Cardiac Arrest				
subjects affected / exposed	1 / 91 (1.10%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 1			
Cardiac Failure Acute				

subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	2 / 2		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Chronic			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac Failure Congestive			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences causally related to treatment / all	3 / 10		
deaths causally related to treatment / all	0 / 1		
Left Ventricular Failure			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences causally related to treatment / all	2 / 3		
deaths causally related to treatment / all	0 / 0		
Sinus Node Dysfunction			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Right Ventricular Failure			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences causally related to treatment / all	2 / 5		
deaths causally related to treatment / all	1 / 1		
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Ischaemic Stroke			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Radiculopathy			

subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	1 / 2		
deaths causally related to treatment / all	0 / 0		
Eye disorders			
Retinal Vein Thrombosis			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Abdominal Incarcerated Hernia			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Ascites			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Duodenal Ulcer Haemorrhage			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal Haemorrhage			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Ileus			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Hepatobiliary disorders			
Cholecystitis Acute			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Renal and urinary disorders			
Acute Kidney Injury			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences causally related to treatment / all	1 / 5		
deaths causally related to treatment / all	0 / 1		
Urinary Retention			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Renal Impairment			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 0		
Musculoskeletal and connective tissue disorders			
Intervertebral Disc Protrusion			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Infections and infestations			
Cellulitis			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Covid-19			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		
Herpes Zoster			

subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Covid-19 Pneumonia			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia			
subjects affected / exposed	3 / 91 (3.30%)		
occurrences causally related to treatment / all	0 / 3		
deaths causally related to treatment / all	0 / 0		
Pneumonia Viral			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Sepsis			
subjects affected / exposed	2 / 91 (2.20%)		
occurrences causally related to treatment / all	0 / 2		
deaths causally related to treatment / all	0 / 1		
Metabolism and nutrition disorders			
Fluid Retention			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperglycaemia			
subjects affected / exposed	1 / 91 (1.10%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Hyperkalaemia			
subjects affected / exposed	1 / 91 (1.10%)		
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 %

Non-serious adverse events	Macitentan 10 mg		
Total subjects affected by non-serious adverse events			
subjects affected / exposed	45 / 91 (49.45%)		
Investigations			
Weight Increased			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	6		
Haemoglobin Decreased			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	5		
Vascular disorders			
Hypotension			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	5		
Cardiac disorders			
Right Ventricular Failure			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences (all)	6		
Nervous system disorders			
Dizziness			
subjects affected / exposed	7 / 91 (7.69%)		
occurrences (all)	9		
Blood and lymphatic system disorders			
Anaemia			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences (all)	6		
General disorders and administration site conditions			
Oedema Peripheral			
subjects affected / exposed	7 / 91 (7.69%)		
occurrences (all)	13		
Gastrointestinal disorders			
Constipation			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences (all)	6		
Nausea			

subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	6		
Respiratory, thoracic and mediastinal disorders			
Dyspnoea			
subjects affected / exposed	11 / 91 (12.09%)		
occurrences (all)	12		
Musculoskeletal and connective tissue disorders			
Back Pain			
subjects affected / exposed	7 / 91 (7.69%)		
occurrences (all)	7		
Pain in Extremity			
subjects affected / exposed	6 / 91 (6.59%)		
occurrences (all)	7		
Infections and infestations			
Upper Respiratory Tract Infection			
subjects affected / exposed	5 / 91 (5.49%)		
occurrences (all)	5		
Urinary Tract Infection			
subjects affected / exposed	9 / 91 (9.89%)		
occurrences (all)	9		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
02 August 2018	The purpose of this amendment was to correct the description of the investigational medicinal product used in the study.
16 May 2019	The purpose of this amendment was to: introduce a new efficacy endpoint, the 6-minute walk distance (6MWD), assessed by the 6-minute walk test (6MWT), as part of a substudy to assess the change from baseline in exercise capacity; include the collection of mid-regional pro-atrial natriuretic peptide (MR-proANP) and a research biomarker (optional) sample at scheduled visits and at the time of a fluid retention or worsening heart failure event to continue the analysis from the main study; include the collection of N-terminal pro-brain natriuretic peptide (NT-proBNP) at the time of fluid retention or worsening heart failure event to support the clinical event committee (CEC) review.
06 February 2020	The purpose of this amendment was to: align the strategy for subject enrollment into this open-label (OL) extension study due to premature termination of recruitment into the main study (AC-055G202/ SERENADE)-eligible subjects could enroll into this OL extension study after remaining in the main study for at least 24 weeks; remove evaluation of the efficacy assessments (that is, Kansas City cardiomyopathy questionnaire, accelerometry, echocardiography, and blood sample collection for NT-proBNP, MR-proANP, and biomarkers) in an effort to simplify the study and reduce assessment burden for subjects and study site personnel; stop the substudy assessments (6MWT and Borg Dyspnea Index), as number of subjects participating in the substudy was too low to allow for meaningful interpretation of results; remove CEC adjudication in line with the main study global protocol Version 6. The CEC was appointed to review and adjudicate in a blinded fashion worsening heart failure event, the reasons for hospitalization, and causes of death. The rationale was based on the reduction of the double-blind treatment period from 52 weeks to 24 weeks coupled with the low occurrence of clinical events, which did not allow meaningful conclusions to be drawn. However, the investigator assessment of worsening heart failure events was continued. Removal of the CEC did not affect safety monitoring and therefore, the decision was also endorsed by the independent data monitoring committee; created a single version of the SERENADE OL AC-055G203 protocol by incorporating voluntary harmonization procedure (VHP)-mandated changes into the global protocol version.
16 July 2020	The purpose of this amendment was to update the exclusion criteria and concomitant therapy sections pertaining to new information regarding a drug-drug-interaction of macitentan with moderate dual cytochrome P450 (CYP)3A4 and CYP2C9 inhibitors or co-administration of a combination of moderate CYP3A4 inhibitors and moderate CYP2C9 inhibitors.
26 November 2020	The purpose of this amendment was to adapt to changed internal safety language and reporting processes to align with TransCelerate template, to update information about post-treatment access program, study treatment storage conditions, forbidden medications, Actelion's policy for study data disclosure, and to make minor editorial revisions and corrections.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

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

Limited number of efficacy parameters were assessed in an exploratory manner. Study was stopped prematurely as main double-blind study did not meet the primary efficacy endpoint.

Notes: