Clinical trial results:
Prospective, Multi-center, Single-arm, Open-label Long-term Study Assessing the Safety, Tolerability, and Effectiveness of Macitentan in Fontan-palliated Adult and Adolescent Subjects

Summary

EudraCT number	2018-002821-45
Trial protocol	FR DE GB DK PL CZ
Global end of trial date	18 January 2022

Results information

Result version number	v1 (current)
This version publication date	30 July 2022
First version publication date	30 July 2022

Trial information

Trial identification

Sponsor protocol code	AC-055H302

Additional study identifiers

ISRCTN number	-
ClinicalTrials.gov id (NCT number)	NCT03775421
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)	Yes
EMA paediatric investigation plan number(s)	EMEA-001032-PIP03-19
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	18 January 2022
Is this the analysis of the primary completion data?	No

Global end of trial reached?	Yes
Global end of trial date	18 January 2022
Was the trial ended prematurely?	Yes

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to assess the long-term safety and tolerability of macitentan in Fontan-palliated adult and adolescent subjects.

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	03 May 2019
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	Australia: 10
Country: Number of subjects enrolled	Canada: 4
Country: Number of subjects enrolled	China: 5
Country: Number of subjects enrolled	Czechia: 16
Country: Number of subjects enrolled	Denmark: 17
Country: Number of subjects enrolled	France: 7
Country: Number of subjects enrolled	United Kingdom: 3
Country: Number of subjects enrolled	New Zealand: 2
Country: Number of subjects enrolled	Poland: 23
Country: Number of subjects enrolled	Taiwan: 6
Country: Number of subjects enrolled	United States: 18
Worldwide total number of subjects	111
EEA total number of subjects	63

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37	0

wk	
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0
Adolescents (12-17 years)	12
Adults (18-64 years)	99
From 65 to 84 years	0
85 years and over	0

Subject disposition

Recruitment

Recruitment details: -

Pre-assignment

Screening details:

1 subject was enrolled twice with 2 different subjects IDs but only 111 subjects were enrolled in the study. Of these 111 enrolled subjects, 1 subject 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:

Subjects received macitentan 10 milligrams (mg) oral tablets once daily with or without food from Day 1 either until the end of the treatment (129 weeks) or when sponsor decided to stop this study.

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

Dosage and administration details:

Macitentan 10 mg tablet was administered once daily with or without food from Day 1 until the end of treatment (129 weeks) or when sponsor decided to stop this study.

Number of subjects in period 1	Macitentan 10 mg
Started	111
Completed	1
Not completed	110
Adverse event, serious fatal	1
Consent withdrawn by subject	10
Physician decision	2
Study terminated by sponsor	94
Adverse event, serious non-fatal	1
Lost to follow-up	2

Baseline characteristics

Reporting groups	
Reporting group title	Macitentan 10 mg
Reporting group description:	
Subjects received macitentan 10 milligrams (mg) oral tablets once daily with or without food from Day 1 either until the end of the treatment (129 weeks) or when sponsor decided to stop this study.	

Reporting group values	Macitentan 10 mg	Total	
Number of subjects	111	111	
Title for AgeCategorical Units: subjects			
Adolescents: 12-<18 yrs	12	12	
Adults: >= 18 yrs	99	99	
Title for AgeContinuous Units: years			
arithmetic mean	25.1		
standard deviation	± 7.04	-	
Title for Gender Units: subjects			
Female	34	34	
Male	77	77	

End points

End points reporting groups

Reporting group title	Macitentan 10 mg

Reporting group description:

Subjects received macitentan 10 milligrams (mg) oral tablets once daily with or without food from Day 1 either until the end of the treatment (129 weeks) or when sponsor decided to stop this study.

Primary: Number of Subjects with Treatment-emergent Adverse Events (TEAEs)

End point title	Number of Subjects with Treatment-emergent Adverse Events (TEAEs)[1]

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 end of treatment (EOT) (limits included) within the analysis set was considered to be treatment-emergent. The RUBATO open-label extension set (OLES) included all subjects who were enrolled in this study and received at least 1 dose of macitentan 10 milligrams (mg).

End point type	Primary

End point timeframe:

Up to 133 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	111			
Units: subjects	68			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with Treatment-emergent Serious AEs (SAEs)

End point title	Number of Subjects with Treatment-emergent Serious AEs (SAEs)[2]

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 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 SAE occurring at or after the study treatment start up to 30 days after end of treatment (EOT) (limits included) within the analysis set was considered to be treatment-emergent. The RUBATO OLES included all subjects who were enrolled in this study and received at least 1 dose of macitentan 10 mg.

End point type	Primary

End point timeframe:

Up to 133 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	111			
Units: subjects	18			

Statistical analyses

No statistical analyses for this end point

Primary: Number of Subjects with TEAEs Leading to Death

End point title	Number of Subjects with TEAEs Leading to Death[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. Any AE occurring at or after the study treatment start up to 30 days after end of treatment (EOT) (limits included) within the analysis set was considered to be treatment-emergent. The RUBATO OLES included all subjects who were enrolled in this study and received at least 1 dose of macitentan 10 mg.

End point type	Primary

End point timeframe:

Up to 133 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	111			
Units: subjects	1			

Statistical analyses

No statistical analyses for this end point

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

End point title	Number of Subjects with Treatment-emergent Marked Laboratory Abnormalities up to 30 Days After Study Treatment Discontinuation[4]

End point description:

Number of subjects with treatment-emergent marked laboratory abnormalities (Hemoglobin [gram/Litre{L}], Platelets [10^9/L], Leukocytes [10^9/L], Lymphocytes [10^9/L], Neutrophils [10^9/L], Prothrombin International Normalized Ratio [PINR; Ratio], Aspartate Aminotransferase [Units/L {U/L}], Bilirubin [micromoles/L {mcmol/L}], Alkaline Phosphatase [U/L], Glomerular Filtration Rate [millilitre/minute/1.73 metre square], Glucose [mmol/L], Potassium [mmol/L], Sodium [mmol/L], Triglycerides [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. RUBATO OLES: all subjects who were enrolled in this study and received at least 1 dose of macitentan 10mg. n=subjects who were analysed for specified categories; >=:greater than or equal to; <=:less than or equal to; ULN=upper limit of normal; L=Low, H=High, LLL=lower/worse than LL, HHH=higher/worse than HH.

End point type	Primary

End point timeframe:

Up to 133 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	111			
Units: subjects				
Hemoglobin: LL<100; n=111	1			
Platelets: LL (< 75); n=108	3			
Leukocytes: LLL (< 1.9); n=107	2			
Leukocytes: LL (< 3.0); n=107	10			
Lymphocytes: HH (> 4.0); n=106	1			
Neutrophils: LL (< 1.5); n=106	3			
PINR: HH (>=1.5 ULN); n=103	4			
PINR: HHH (>= 2.5 ULN); n=103	1			
Aspartate Aminotransferase: HH (>=3 ULN); n=111	1			
Bilirubin: HH (>=2 ULN); n=107	1			
Alkaline Phosphatase: HH (> 2.5 ULN); n=106	1			
Glomerular Filtration Rate: LL (< 60); n=106	1			
Glucose: LL (< 3.0); n=106	2			
Glucose: HH (> 8.9); n=106	3			
Potassium: HH (>5.5); n=106	1			
Sodium: LLL (<130); n=106	1			
Triglycerides: HH (>3.42); n=106	3			

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[5]

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 end of treatment (EOT) (limits included) within the analysis set was considered to be treatment-emergent. The RUBATO OLES included all subjects who were enrolled in this study and received at least 1 dose of macitentan 10 mg.

End point type	Primary

End point timeframe:

Up to 133 weeks

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	111			
Units: subjects	2			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hemoglobin Over Time

End point title	Change from Baseline in Hemoglobin Over Time[6]

End point description:

Change from baseline in hemoglobin over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	98			
Units: grams per litre (g/L)				
arithmetic mean (standard deviation)				
Week 26; n=98	-6.0 (± 9.94)			
Week 52; n=75	-4.0 (± 9.19)			
Week 78; n=42	-5.0 (± 7.20)			
Week 104; n=18	-2.4 (± 10.66)			
Week 130; n=3	5.7 (± 19.35)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Hematocrit Over Time

End point title	Change from Baseline in Hematocrit Over Time[7]

End point description:

Change from baseline in hematocrit over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	100			
Units: Litre/Litre (L/L)				
arithmetic mean (standard deviation)				
Week 26; n=100	-0.016 (± 0.0323)			
Week 52; n=74	-0.007 (± 0.0288)			
Week 78; n=42	-0.011 (± 0.0247)			
Week 104; n=18	-0.008 (± 0.0285)			
Week 130; n=3	0.010 (± 0.0624)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Leukocytes, Neutrophils, Lymphocytes, and Platelets Over Time

End point title	Change from Baseline in Leukocytes, Neutrophils, Lymphocytes, and Platelets Over Time[8]

End point description:

Change from baseline in leukocytes, neutrophils, lymphocytes, and platelets over time were reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	100			
Units: 10^9/L				
arithmetic mean (standard deviation)				
Leukocytes: Week 26; n=100	-0.358 (± 1.2966)			
Leukocytes: Week 52; n=75	-0.222 (± 1.3677)			
Leukocytes: Week 78; n=42	-0.300 (± 1.2868)			
Leukocytes: Week 104; n=18	-0.255 (± 1.2914)			
Leukocytes: Week 130; n=3	-0.560 (± 1.1186)			
Neutrophils: Week 26; n=98	-0.185 (± 1.0712)			
Neutrophils: Week 52; n=75	-0.074 (± 1.0624)			
Neutrophils: Week 78; n=42	-0.233 (± 1.0569)			
Neutrophils: Week 104; n=18	-0.105 (± 1.1060)			
Neutrophils: Week 130; n=3	-0.400 (± 1.0130)			
Lymphocytes: Week 26; n=98	-0.153 (± 0.3176)			
Lymphocytes: Week 52; n=75	-0.098 (± 0.5366)			
Lymphocytes: Week 78; n=42	-0.016 (± 0.3046)			
Lymphocytes: Week 104; n=18	-0.089 (± 0.3181)			
Lymphocytes: Week 130; n=3	-0.113 (± 0.2223)			
Platelets: Week 26; n=100	-9.2 (± 24.94)			
Platelets: Week 52; n=74	-4.3 (± 30.54)			
Platelets: Week 78; n=42	-8.1 (± 24.18)			
Platelets: Week 104; n=18	-11.1 (± 25.08)			
Platelets: Week 130; n=3	6.7 (± 12.74)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Systolic and Diastolic Arterial Blood Pressure (BP) Over Time

End point title	Change from Baseline in Systolic and Diastolic Arterial Blood Pressure (BP) Over Time[9]

End point description:

Change from baseline in systolic and diastolic arterial BP over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	101			
Units: millimeters of mercury (mmHg)				
arithmetic mean (standard deviation)				
Systolic BP: Week 26; n=101	-0.7 (± 13.00)			
Systolic BP: Week 52; n=75	-1.7 (± 14.81)			
Systolic BP: Week 78; n=43	-0.7 (± 14.79)			
Systolic BP: Week 104; n=18	0.7 (± 6.49)			
Systolic BP: Week 130; n=3	-12 (± 8.72)			
Diastolic BP: Week 26; n=101	-2.9 (± 12.63)			
Diastolic BP: Week 52; n=75	-0.9 (± 12.56)			
Diastolic BP: Week 78; n=43	-1.6 (± 11.61)			
Diastolic BP: Week 104; n=18	2.6 (± 9.65)			
Diastolic BP: Week 130; n=3	-0.7 (± 7.23)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Pulse Rate Over Time

End point title	Change from Baseline in Pulse Rate Over Time[10]

End point description:

Change from baseline in pulse rate over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	101			
Units: beats per minute (bpm)				
arithmetic mean (standard deviation)				
Week 26; n=101	-2.1 (± 10.48)			
Week 52; n=75	0.9 (± 10.95)			
Week 78; n=43	-1.3 (± 10.12)			
Week 104; n=18	-1.7 (± 8.78)			
Week 130; n=3	-0.3 (± 13.05)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Oxygen Saturation (SpO2) Over Time

End point title	Change from Baseline in Oxygen Saturation (SpO2) Over

End point description:

Change from baseline in SpO2 over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 analyzed at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	99			
Units: percentage of SpO2 (%)				
arithmetic mean (standard deviation)				
Week 26; n=99	0.2 (± 3.22)			
Week 52; n=75	0.2 (± 2.79)			
Week 78; n=43	-0.5 (± 2.52)			
Week 104; n=18	0.3 (± 2.44)			
Week 130; n=3	3.3 (± 2.31)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Body Weight Over Time

End point title	Change from Baseline in Body Weight Over Time[12]

End point description:

Change from baseline in body weight over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	102			
Units: kilograms (kg)				
arithmetic mean (standard deviation)				
Week 26; n=102	0.8 (± 2.89)			
Week 52; n=75	0.9 (± 4.23)			
Week 78; n=43	1.7 (± 3.65)			
Week 104; n=18	2.0 (± 4.17)			
Week 130; n=3	2.6 (± 5.54)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (AP), and Gamma Glutamyl Transferase (GGT) Over Time

End point title	Change from Baseline in Alanine Aminotransferase (ALT), Aspartate Aminotransferase (AST), Alkaline Phosphatase (AP), and Gamma Glutamyl Transferase (GGT) Over Time[13]

End point description:

Change from baseline in ALT, AST, AP, and GGT over time were reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	103			
Units: units per litre (U/L)				
arithmetic mean (standard deviation)				
ALT: Week 26; n=101	-2.0 (± 8.57)			
ALT: Week 52; n=75	-2.1 (± 10.40)			
ALT: Week 78; n=43	-2.7 (± 11.32)			
ALT: Week 104; n=18	-6.8 (± 15.72)			
ALT: Week 130; n=3	-13.7 (± 23.69)			
AST: Week 26; n=100	-1.3 (± 8.39)			
AST: Week 52; n=75	-1.7 (± 9.60)			
AST: Week 78; n=42	-3.0 (± 11.39)			
AST: Week 104; n=18	-6.1 (± 17.03)			
AST: Week 130; n=3	-21.3 (± 41.43)			
AP: Week 26; n=103	-7.7 (± 36.04)			
AP: Week 52; n=75	-1.9 (± 25.25)			
AP: Week 78; n=43	-6.6 (± 28.02)			
AP: Week 104; n=18	-21.8 (± 53.46)			
AP: Week 130; n=3	6.7 (± 6.03)			
GGT: Week 26; n=103	-1.2 (± 14.85)			
GGT: Week 52; n=75	1.2 (± 15.74)			
GGT: Week 78; n=43	-2.2 (± 18.26)			
GGT: Week 104; n=18	-3.2 (± 18.13)			
GGT: Week 130; n=3	1.0 (± 13.23)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Bilirubin, Direct Bilirubin, and Creatinine Over Time

End point title	Change from Baseline in Bilirubin, Direct Bilirubin, and Creatinine Over Time[14]

End point description:

Change from baseline in bilirubin, direct bilirubin, and creatinine over time were reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	103			
Units: micromoles per litre (mcmol/L)				
arithmetic mean (standard deviation)				
Bilirubin: Week 26; n=103	-0.9 (± 6.62)			
Bilirubin: Week 52; n=75	-1.1 (± 10.41)			
Bilirubin: Week 78; n=43	-0.5 (± 5.68)			
Bilirubin: Week 104; n=18	-0.8 (± 6.13)			
Bilirubin: Week 130; n=3	-1.3 (± 2.89)			
Direct Bilirubin: Week 26; n=101	-0.1 (± 1.14)			
Direct Bilirubin: Week 52; n=72	0.0 (± 1.29)			
Direct Bilirubin: Week 78; n=41	0.0 (± 1.00)			
Direct Bilirubin: Week 104; n=18	-0.2 (± 1.25)			
Direct Bilirubin: Week 130; n=3	-1.0 (± 1.00)			
Creatinine: Week 26; n=102	0.2 (± 9.27)			
Creatinine: Week 52; n=75	0.9 (± 9.16)			
Creatinine: Week 78; n=42	0.8 (± 8.22)			
Creatinine: Week 104; n=18	0.1 (± 8.10)			
Creatinine: Week 130; n=3	-0.7 (± 5.51)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Glomerular Filtration Rate (GFR) Over Time

End point title	Change from Baseline in Glomerular Filtration Rate (GFR) Over Time[15]

End point description:

Change from baseline in GFR over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	102			
Units: millilitres/minute/1.73 metre square				
arithmetic mean (standard deviation)				
Week 26; n=102	-0.9 (± 15.43)			
Week 52; n=75	-2.0 (± 15.22)			
Week 78; n=42	-0.5 (± 13.26)			

Week 104; n=17 Week 130; n=3	0.4 (± 17.00) -1.7 (± 7.57)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Prothrombin Time Over Time

End point title	Change from Baseline in Prothrombin Time Over Time[16]

End point description:

Change from baseline in prothrombin time over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	98			
Units: seconds				
arithmetic mean (standard deviation)				
Week 26; n=98	-0.31 (± 3.523)			
Week 52; n=73	-0.05 (± 4.038)			
Week 78; n=42	-0.38 (± 2.293)			
Week 104; n=18	-1.12 (± 3.317)			
Week 130; n=3	-0.57 (± 0.651)			

Statistical analyses

No statistical analyses for this end point

Primary: Change from Baseline in Prothrombin International Normalized Ratio Over Time

End point title	Change from Baseline in Prothrombin International Normalized Ratio Over Time[17]

End point description:

Change from baseline in prothrombin international normalized ratio over time was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Primary

End point timeframe:

Baseline up to Week 130

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	98			
Units: ratio				
arithmetic mean (standard deviation)				
Week 26; n=98	-0.06 (± 0.401)			
Week 52; n=73	-0.06 (± 0.456)			
Week 78; n=42	-0.12 (± 0.245)			
Week 104; n=18	-0.16 (± 0.379)			
Week 130; n=3	-0.07 (± 0.058)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Mean Count per Minute of Daily Physical Activity Measured by Accelerometer (PA-Ac)

End point title	Change from Baseline in Mean Count per Minute of Daily Physical Activity Measured by Accelerometer (PA-Ac)

End point description:

Change from baseline in mean count per minute of daily PA-Ac was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 26, Week 52, Week 78, and Week 104

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	42			
Units: mean count per minute				
arithmetic mean (standard deviation)				

Week 26; n=42	19.74 (± 131.622)			
Week 52; n=20	44.58 (± 153.196)			
Week 78; n=10	99.14 (± 165.965)			
Week 104; n=2	-62.87 (± 189.264)			

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Peak Oxygen Uptake/Consumption (VO2)

End point title	Change from Baseline in Peak Oxygen Uptake/Consumption (VO2)

End point description:

Change from baseline in peak VO2 was reported. The RUBATO OLES included all subjects who were enrolled in this study and 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 at specified timepoints.

End point type	Secondary

End point timeframe:

Baseline, Week 52, and Week 104

End point values	Macitentan 10 mg			
Subject group type	Reporting group			
Number of subjects analysed	71			
Units: Millilitres/kilogram/minute (mL/kg/min)				
arithmetic mean (standard deviation)				
Week 52; n=71	-0.82 (± 2.724)			
Week 104; n=12	-0.93 (± 1.968)			

Statistical analyses

No statistical analyses for this end point

Adverse events

Adverse events information

Timeframe for reporting adverse events:

Up to 133 weeks

Adverse event reporting additional description:

The RUBATO open-label extension set (OLES) included all subjects who were enrolled in this study and 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:

Subjects received macitentan 10 milligrams (mg) oral tablets once daily with or without food from Day 1 either until the end of the treatment (129 weeks) or when sponsor decided to stop this study.

Serious adverse events	Macitentan 10 mg		
Total subjects affected by serious adverse events			
subjects affected / exposed	18 / 111 (16.22%)		
number of deaths (all causes)	1		
number of deaths resulting from adverse events			
Neoplasms benign, malignant and unspecified (incl cysts and polyps)			
Hepatocellular Carcinoma			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pregnancy, puerperium and perinatal conditions			
Abortion Spontaneous			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
General disorders and administration site conditions			
Death			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 1		

Respiratory, thoracic and mediastinal disorders			
Hypoxia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Pleurisy			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Psychiatric disorders			
Anxiety			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Depression			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Mental Disorder			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Suicidal Ideation			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Investigations			
Sperm Concentration Decreased			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Spermatozoa Progressive Motility Decreased			

subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	1 / 1		
deaths causally related to treatment / all	0 / 0		
Injury, poisoning and procedural complications			
Anastomotic Stenosis			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Cardiac disorders			
Atrial Flutter			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Arrhythmia			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Nervous system disorders			
Cerebrovascular Accident			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Clonic Convulsion			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Epilepsy			
subjects affected / exposed	1 / 111 (0.90%)		
occurrences causally related to treatment / all	0 / 1		
deaths causally related to treatment / all	0 / 0		
Gastrointestinal disorders			
Colitis Ulcerative			

subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Abdominal Pain				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Incarcerated Inguinal Hernia				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Hepatobiliary disorders				
Hepatic Mass				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Musculoskeletal and connective tissue disorders				
Intervertebral Disc Protrusion				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Infections and infestations				
Cytomegalovirus Infection				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Covid-19				
subjects affected / exposed	1 / 111 (0.90%)			
occurrences causally related to treatment / all	0 / 1			
deaths causally related to treatment / all	0 / 0			
Pneumonia				
subjects affected / exposed	1 / 111 (0.90%)			
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	28 / 111 (25.23%)		
Cardiac disorders Palpitations subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 7		
Nervous system disorders Headache subjects affected / exposed occurrences (all)	8 / 111 (7.21%) 15		
General disorders and administration site conditions Fatigue subjects affected / exposed occurrences (all)	7 / 111 (6.31%) 8		
Infections and infestations Covid-19 subjects affected / exposed occurrences (all)	13 / 111 (11.71%) 13		

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
20 February 2019	The purpose of this amendment was to harmonize the RUBATO open-label (OL) protocol with the recently amended RUBATO double blind (DB) study. Changes were introduced to the RUBATO study to implement recommendations from the Fontan Advisory Board (meeting held on 19 September 2018) on ways to improve recruitment and compliance with study examinations. These measures were expected to reduce study subject burden while preserving the scientific and medical merit of the RUBATO study. Reducing the burden on subjects resulted in increased subject compliance with the evaluation and monitoring visits, hence enhanced the completeness of the efficacy and safety assessments.
16 July 2020	The purpose of this amendment was to update the exclusion criteria, initiation of forbidden medication and concomitant therapy sections pertaining to newly identified drug-drug interactions (DDI) between macitentan and fluconazole (a dual moderate inhibitor of cytochrome P450 [CYP]3A4 and CYP2C9) from a preclinical study on implications of role of CYP2C9 in the metabolism of macitentan.
21 July 2020	The purpose of this amendment was a preclinical study newly identified DDI between macitentan and fluconazole (a dual moderate inhibitor of CYP3A4 and CYP2C9), and concluded that there were implications on the role of CYP2C9 in the metabolism of macitentan. This led to the need for an amendment for an urgent safety measure (USM). At the time of the USM, there were sites who had implemented protocol version 1 and others were already on protocol version 2. As USM updates could not be combined with other updates to the protocol, a version 1.1 had to be created for regulatory submission and approval (for those on version 1) before transitioning those sites to version 3 (which combined version 2 and the USM information) as well.
19 November 2020	The purpose of this amendment was to align the study protocol with updates made for the AC-055H301 RUBATO double-blind study. a. Countries that did not enroll candidates for RUBATO open-label (OL) during the RUBATO study were removed from the section on acceptable methods of contraception; b. Study treatment supply and storage information was simplified was part of the Actelion and Janssen integration; c. The study duration was adapted to help ensure treatment with macitentan was available after the expected treatment duration of 2 years per subject; d. Global safety updates were made to align the protocol with Janssen processes as part of the Janssen and Actelion integration; e. Based on recent literature on the potential prognostic value of cardiopulmonary exercise testing (CPET) in Fontan-palliated subjects, the sponsor added 2 new exploratory efficacy endpoint variables that were not collected thus far but were already part of CPET assessments evaluated by the central leading facility. One of these variables, oxygen update/consumption at ventilatory anaerobic threshold, had also been claimed to be of interest in a recently completed study with a phosphodiesterase 5 inhibitor. Finally, an appendix was added to facilitate evaluation of exclusion criterion 3.3.

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.

The study was stopped prematurely because the main double-blind (DB) study did not meet the primary and secondary efficacy endpoints.

Notes: