

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	
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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: -

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	enroll	led per	country	1
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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

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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
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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)

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

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 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.

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)		

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:	

Notes:

Baseline up to Week 130

[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
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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.

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)		

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
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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.

EU-CTR publication date: 30 July 2022

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)		

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.

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)		

No statistical analyses for this end point

Primary: Change from Baseline in Glomerular Filtration Rate (GFR) Over Time	
	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	0.4 (± 17.00)		
Week 130; n=3	-1.7 (± 7.57)		

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

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, a	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)		

No statistical analyses for this end point

Secondary: Change from Baselin	e 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
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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 occurrences causally related to treatment / all deaths causally related to treatment / all		T	ı	1
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility	1 ' '			
occurrences causally related to treatment / all deaths causally related to treatment / all subjects affected / exposed occurrences causally related to treatment / all deaths causally related to tre	Hypoxia			
treatment / all deaths causally related to treatment / all o/ 0 Pleurisy subjects affected / exposed occurrences causally related to treatment / all o/ 0 Psychiatric disorders Anxiety subjects affected / exposed occurrences causally related to treatment / all o/ 0 Psychiatric disorders Anxiety subjects affected / exposed occurrences causally related to treatment / all o/ 0 Depression subjects affected / exposed occurrences causally related to treatment / all o/ 0 Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/ 0 Mental Disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/ 0 Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/ 0 Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all o/ 0 Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all o/ 0 Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all o/ 0 Spermatozoa Progressive Motility		1 / 111 (0.90%)		
Pleurisy subjects affected / exposed		0 / 1		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all		0 / 0		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all	Pleurisy			
treatment / all deaths causally related to treatment / all		1 / 111 (0.90%)		
reatment / ali		0 / 1		
Anxiety subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		0 / 0		
Anxiety subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility	Psychiatric disorders			
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility				
treatment / all deaths causally related to treatment / all Depression subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all		1 / 111 (0.90%)		
treatment / all 0 / 0 Depression subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 Mental Disorder subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 Suicidal Ideation subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all 0 / 0 Suicidal Ideation subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all 0 / 0 Investigations Sperm Concentration Decreased subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 Spermatozoa Progressive Motility		0 / 1		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Mental Disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		0/0		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Mental Disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility	Depression		I	
treatment / all deaths causally related to treatment / all Mental Disorder subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		1 / 111 (0.90%)		
treatment / all 0 / 0 Mental Disorder subjects affected / exposed 1 / 111 (0.90%) occurrences 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 / 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 0 / 0 Sperm Concentration Decreased 1 / 111 (0.90%) occurrences causally related to treatment / all 0 / 0 Spermatozoa Progressive Motility		0 / 1		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		0/0		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility	Mental Disorder			
treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Suicidal Ideation subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		1 / 111 (0.90%)		
treatment / all 0 / 0 Suicidal Ideation subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all 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 deaths causally related to treatment / all deaths causally related to treatment / all 0 / 0 Spermatozoa Progressive Motility		0 / 1		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		0 / 0		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility	Suicidal Ideation	1]	i İ
treatment / all deaths causally related to treatment / all Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		1 / 111 (0.90%)		
Investigations Sperm Concentration Decreased subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		0 / 1		
Sperm Concentration Decreased subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 Spermatozoa Progressive Motility		0 / 0		
Sperm Concentration Decreased subjects affected / exposed 1 / 111 (0.90%) occurrences causally related to treatment / all deaths causally related to treatment / all 0 / 0 Spermatozoa Progressive Motility	Investigations	Ī		
subjects affected / exposed occurrences causally related to treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility	_			
treatment / all deaths causally related to treatment / all Spermatozoa Progressive Motility		1 / 111 (0.90%)		
treatment / all 0 / 0 Spermatozoa Progressive Motility		1/1		
		0/0		
		İ		

subjects affected / exposed	1 / 111 (0.90%)		1
occurrences causally related to	1/11 (0.50 %)		
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	I]
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	Ī	<u>. </u>	<u> </u>
Colitis Ulcerative			
1	1	I	ı

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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-actions of reporting non-serious duverse events. 5 70				
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	7 / 111 (6.31%)			
occurrences (all)	7			
Nervous system disorders				
Headache				
subjects affected / exposed	8 / 111 (7.21%)			
occurrences (all)	15			
General disorders and administration site conditions				
Fatigue				
subjects affected / exposed	7 / 111 (6.31%)			
occurrences (all)	8			
Infections and infestations				
Covid-19				
subjects affected / exposed	13 / 111 (11.71%)			
occurrences (all)	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.

EU-CTR publication date: 30 July 2022

Notes: