



Clinical trial results:

A Multicenter, Open-label, Phase III Study to Assess the Efficacy, Safety, and Pharmacokinetics of Macitentan in Japanese Pediatric Patients (≥ 3 months to < 15 years) with Pulmonary Arterial Hypertension

Summary

| | |
|--------------------------|----------------|
| EudraCT number | 2023-000984-30 |
| Trial protocol | Outside EU/EEA |
| Global end of trial date | 04 March 2025 |

Results information

| | |
|--------------------------------|-----------------|
| Result version number | v1 (current) |
| This version publication date | 23 October 2025 |
| First version publication date | 23 October 2025 |

Trial information

Trial identification

| | |
|-----------------------|-----------------|
| Sponsor protocol code | 67896062PAH3001 |
|-----------------------|-----------------|

Additional study identifiers

| | |
|------------------------------------|-------------|
| ISRCTN number | - |
| ClinicalTrials.gov id (NCT number) | NCT05167825 |
| WHO universal trial number (UTN) | - |

Notes:

Sponsors

| | |
|------------------------------|---|
| Sponsor organisation name | Janssen Pharmaceutical K.K. |
| Sponsor organisation address | Nishi-kanda, Chiyoda-ku, Tokyo, Japan, 3-5-2 |
| Public contact | Clinical Registry Group, Janssen Pharmaceutical K.K., ClinicalTrialsEU@its.jnj.com |
| Scientific contact | Clinical Registry Group, Janssen Pharmaceutical K.K., ClinicalTrialsEU@its.jnj.com |

Notes:

Paediatric regulatory details

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

Notes:

Results analysis stage

| | |
|--|---------------|
| Analysis stage | Final |
| Date of interim/final analysis | 04 March 2025 |
| Is this the analysis of the primary completion data? | No |
| Global end of trial reached? | Yes |
| Global end of trial date | 04 March 2025 |
| Was the trial ended prematurely? | No |

Notes:

General information about the trial

Main objective of the trial:

The main objective of the trial was to evaluate the effect of macitentan on hemodynamic measures at Week 24.

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 | 14 November 2022 |
| Long term follow-up planned | No |
| Independent data monitoring committee (IDMC) involvement? | No |

Notes:

Population of trial subjects

Subjects enrolled per country

| | |
|--------------------------------------|----------|
| Country: Number of subjects enrolled | Japan: 7 |
| Worldwide total number of subjects | 7 |
| EEA total number of subjects | 0 |

Notes:

Subjects enrolled per age group

| | |
|---|---|
| In utero | 0 |
| Preterm newborn - gestational age < 37 wk | 0 |
| Newborns (0-27 days) | 0 |
| Infants and toddlers (28 days-23 months) | 2 |
| Children (2-11 years) | 4 |
| Adolescents (12-17 years) | 1 |
| Adults (18-64 years) | 0 |
| From 65 to 84 years | 0 |
| 85 years and over | 0 |

Subject disposition

Recruitment

Recruitment details:

A total of 7 participants were enrolled and treated in the study.

Pre-assignment

Screening details:

A total of 7 participants were enrolled and treated in 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 |

Blinding implementation details:

Not blinded

Arms

| | |
|-----------|------------|
| Arm title | Macitentan |
|-----------|------------|

Arm description:

Participants received macitentan 1 milligram (mg) or 2.5 mg tablets orally once daily based on age and body weight. Participants aged greater than or equal to (\geq) 3 months to less than ($<$) 6 months received daily dose of macitentan 1 mg, \geq 6 months to $<$ 2 years received daily dose of macitentan 2.5 mg. For participants above 2 years (inclusive) of age, daily doses of macitentan were 3.5 mg ($<$ 15 kilograms [kg] body weight [BW]), 5 mg (\geq 15 kg to $<$ 25 kg BW), 7.5 mg (\geq 25 kg to $<$ 50 kg BW), and 10 mg (\geq 50 kg BW). Treatment was administered from Day 1 to Week 52.

| | |
|--|--------------|
| Arm type | Experimental |
| Investigational medicinal product name | Macitentan |
| Investigational medicinal product code | |
| Other name | |
| Pharmaceutical forms | Tablet |
| Routes of administration | Oral use |

Dosage and administration details:

Participants aged between 3 months and 14 years, inclusive with PAH received macitentan 1 mg or 2.5 mg tablets orally once daily based on age and body weight. Participants aged \geq 3 months to $<$ 6 months received daily dose of macitentan 1 mg, \geq 6 months to $<$ 2 years received daily dose of macitentan 2.5 mg. For participants above 2 years (inclusive) of age, daily doses of macitentan were 3.5 mg ($<$ 15 kg BW), 5 mg (\geq 15 kg to $<$ 25 kg BW), 7.5 mg (\geq 25 kg to $<$ 50 kg BW), and 10 mg (\geq 50 kg BW). Treatment was administered from Day 1 to Week 52 followed by 30 days follow up after end of treatment.

| Number of subjects in period 1 | Macitentan |
|--------------------------------|------------|
| Started | 7 |
| Completed | 7 |

Baseline characteristics

Reporting groups

| | |
|-----------------------|------------|
| Reporting group title | Macitentan |
|-----------------------|------------|

Reporting group description:

Participants received macitentan 1 milligram (mg) or 2.5 mg tablets orally once daily based on age and body weight. Participants aged greater than or equal to (\geq) 3 months to less than ($<$) 6 months received daily dose of macitentan 1 mg, \geq 6 months to $<$ 2 years received daily dose of macitentan 2.5 mg. For participants above 2 years (inclusive) of age, daily doses of macitentan were 3.5 mg ($<$ 15 kilograms [kg] body weight [BW]), 5 mg (\geq 15 kg to $<$ 25 kg BW), 7.5 mg (\geq 25 kg to $<$ 50 kg BW), and 10 mg (\geq 50 kg BW). Treatment was administered from Day 1 to Week 52.

| Reporting group values | Macitentan | Total | |
|--|------------|-------|--|
| Number of subjects | 7 | 7 | |
| Age categorical | | | |
| Units: Subjects | | | |
| In Utero | 0 | 0 | |
| Preterm newborn infants (gestational age $<$ 37 wks) | 0 | 0 | |
| Newborns (0-27 days) | 0 | 0 | |
| Infants and toddlers (28 days - 23 months) | 2 | 2 | |
| Children (2 - 11 years) | 4 | 4 | |
| 12 - 17 years | 1 | 1 | |
| Adults (18 - 64 years) | 0 | 0 | |
| From 65 - 84 years | 0 | 0 | |
| 85 years and over | 0 | 0 | |
| Title for AgeContinuous | | | |
| Units: years | | | |
| arithmetic mean | 5.7 | | |
| standard deviation | \pm 5.12 | - | |
| Title for Gender | | | |
| Units: subjects | | | |
| Female | 3 | 3 | |
| Male | 4 | 4 | |

End points

End points reporting groups

| | |
|---|------------|
| Reporting group title | Macitentan |
| Reporting group description: | |
| Participants received macitentan 1 milligram (mg) or 2.5 mg tablets orally once daily based on age and body weight. Participants aged greater than or equal to (\geq) 3 months to less than ($<$) 6 months received daily dose of macitentan 1 mg, \geq 6 months to $<$ 2 years received daily dose of macitentan 2.5 mg. For participants above 2 years (inclusive) of age, daily doses of macitentan were 3.5 mg ($<$ 15 kilograms [kg] body weight [BW]), 5 mg (\geq 15 kg to $<$ 25 kg BW), 7.5 mg (\geq 25 kg to $<$ 50 kg BW), and 10 mg (\geq 50 kg BW). Treatment was administered from Day 1 to Week 52. | |

Primary: Fold Change from Baseline at Week 24 in Pulmonary Vascular Resistance Index (PVRI)

| | |
|-----------------|---|
| End point title | Fold Change from Baseline at Week 24 in Pulmonary Vascular Resistance Index (PVRI) ^[1] |
|-----------------|---|

End point description:

PVRI fold change at Week 24 was calculated as: $100 \times (\text{PVRI at Week 24} / \text{PVRI at baseline})$. PVR was determined by right heart catheterization. Efficacy analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|---------|
| End point type | Primary |
|----------------|---------|

End point timeframe:

Baseline (Day 1) and Week 24

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: Only descriptive statistics was planned for this endpoint. No inferential statistics was planned.

| End point values | Macitentan | | | |
|---|---------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: percent change | | | | |
| geometric mean (geometric coefficient of variation) | 59.43 (\pm 75.1) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Hemodynamic Variable: Pulmonary Vascular Resistance (PVR)

| | |
|-----------------|--|
| End point title | Change from Baseline to Week 24 in Hemodynamic Variable: Pulmonary Vascular Resistance (PVR) |
|-----------------|--|

End point description:

Change from baseline to Week 24 in hemodynamic variable: PVR was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Week 24

| | | | | |
|--------------------------------------|------------------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: wood units (WU) | | | | |
| arithmetic mean (standard deviation) | -3.734 (\pm 4.4971) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Hemodynamic Variable: Mean Right Atrial Pressure (mRAP)

| | |
|------------------------|---|
| End point title | Change from Baseline to Week 24 in Hemodynamic Variable: Mean Right Atrial Pressure (mRAP) |
| End point description: | Change from baseline to Week 24 in hemodynamic variable: mRAP was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention. |
| End point type | Secondary |
| End point timeframe: | From baseline (Day 1) up to Week 24 |

| | | | | |
|--------------------------------------|--------------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: millimeters of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | -2.9 (\pm 8.57) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Hemodynamic Variable: Mean Pulmonary Atrial Pressure (mPAP)

| | |
|------------------------|---|
| End point title | Change from Baseline to Week 24 in Hemodynamic Variable: Mean Pulmonary Atrial Pressure (mPAP) |
| End point description: | Change from baseline to Week 24 in hemodynamic variable: mPAP was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention. |
| End point type | Secondary |

End point timeframe:
From baseline (Day 1) up to Week 24

| | | | | |
|--------------------------------------|---------------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: millimeters of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | -8.0 (\pm 12.62) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Hemodynamic Variable: Cardiac Index (CI)

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 24 in Hemodynamic Variable: Cardiac Index (CI) |
|-----------------|---|

End point description:

Change from baseline to Week 24 in hemodynamic variable: CI was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Week 24

| | | | | |
|---|----------------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: liters/minute/meter square (L/min/m ²) | | | | |
| arithmetic mean (standard deviation) | -0.03 (\pm 1.019) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change from Baseline at Weeks 4, 8, 12, 16, 20, 24, 28, 40, and 52 in World Health Organization (WHO) Functional Class (FC)

| | |
|-----------------|---|
| End point title | Number of Participants With Change from Baseline at Weeks 4, 8, 12, 16, 20, 24, 28, 40, and 52 in World Health Organization (WHO) Functional Class (FC) |
|-----------------|---|

End point description:

WHO-FC for participants with pulmonary arterial hypertension (PAH) ranges: Class I (no limitation in

physical activity, ordinary physical activity did not cause undue dyspnea or fatigue, chest pain or near syncope), Class II (slight limitation of physical activity, comfortable at rest, ordinary physical activity caused undue dyspnea or fatigue, chest pain, or near syncope), Class III (marked limitation of physical activity, comfortable at rest, less than ordinary activity causes undue dyspnea or fatigue, chest pain, or near syncope) and Class IV (cannot perform a physical activity without any symptoms, signs of right heart failure, dyspnea and/or fatigue may be present even at rest, discomfort is increased by any physical activity). Participants who improve in WHO FC are reported below. Improvement was defined as reduction in FC. Analysis population included all participants greater than (>) 4 years of age.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, and 52 | |

| End point values | Macitentan | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Participants | | | | |
| Baseline | 0 | | | |
| Week 4 | 0 | | | |
| Week 8 | 0 | | | |
| Week 12 | 0 | | | |
| Week 16 | 0 | | | |
| Week 20 | 0 | | | |
| Week 24 | 0 | | | |
| Week 28 | 0 | | | |
| Week 40 | 0 | | | |
| Week 52 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Percent Change from Baseline to Week 24 in Hemodynamic Variable: Mixed Venous Oxygen Saturation (SvO[2])

| | |
|---|--|
| End point title | Percent Change from Baseline to Week 24 in Hemodynamic Variable: Mixed Venous Oxygen Saturation (SvO[2]) |
| End point description: | |
| Change from baseline to Week 24 in hemodynamic variable: SvO(2) was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention. | |
| End point type | Secondary |
| End point timeframe: | |
| From baseline (Day 1) up to Week 24 | |

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: percent change | | | | |
| arithmetic mean (standard deviation) | -2.9 (± 9.37) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Hemodynamic Variable: Cardiac Output (CO)

| | |
|-----------------|--|
| End point title | Change from Baseline to Week 24 in Hemodynamic Variable: Cardiac Output (CO) |
|-----------------|--|

End point description:

Change from baseline to Week 24 in hemodynamic variable: CO was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Week 24

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: liters per minute (L/min) | | | | |
| arithmetic mean (standard deviation) | 0.07 (± 0.743) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Week 24 in Hemodynamic Variable: Total Pulmonary Resistance (TPR)

| | |
|-----------------|---|
| End point title | Change from Baseline to Week 24 in Hemodynamic Variable: Total Pulmonary Resistance (TPR) |
|-----------------|---|

End point description:

Change from baseline to Week 24 in hemodynamic variable: TPR was reported. TPR was calculated as: (mPAP/CO)*80. Efficacy analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Week 24

| | | | | |
|--------------------------------------|-------------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: dynes second/centimeter^5 | | | | |
| arithmetic mean (standard deviation) | -243.0 (± 410.13) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Change from Baseline at Weeks 4, 8, 12, 16, 20, 24, 28, 40, and 52 in Panama Functional Class (FC)

| | |
|-----------------|--|
| End point title | Number of Participants With Change from Baseline at Weeks 4, 8, 12, 16, 20, 24, 28, 40, and 52 in Panama Functional Class (FC) |
|-----------------|--|

End point description:

Panama FC for PAH ranges: Class I (asymptomatic, growing normally, attending nursery/school regularly, no limitation of physical activity, playing sports with his/her classmates), Class II (slight limitation of physical activity, unduly dyspnoeic and fatigued when playing with his/her classmates, comfortable at rest, grow along own centiles, nursery/school attendance 75% normal, no chest pain), Class IIIa (marked limitation of physical activity, no attempt at sports, comfortable at rest, less than ordinary activity (eg: dressing) causes undue dyspnea, fatigue, syncope and/or presyncope or chest pain, nursery/schooling compromised <50% normal attendance), Class IIIb (growth compromised, poor appetite, supplemental feeding, same as class IIIa) and Class IV (cannot perform a physical activity without any symptoms, dyspnea at rest). Participants improved in were classified into Improved (reduction in FC), No change (no change in FC) and Worsened (increase in FC). Efficacy analysis set was used.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, and 52

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | | | | |
| Baseline | 0 | | | |
| Week 4 | 0 | | | |
| Week 8 | 0 | | | |
| Week 12 | 0 | | | |
| Week 16 | 0 | | | |
| Week 20 | 0 | | | |
| Week 24 | 0 | | | |
| Week 28 | 0 | | | |
| Week 40 | 0 | | | |
| Week 52 | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 24 and 52 in 6-minute Walk Distance (6MWD) as Measured by the 6-minute Walk Test (6MWT)

| | |
|-----------------|---|
| End point title | Change from Baseline to Weeks 24 and 52 in 6-minute Walk Distance (6MWD) as Measured by the 6-minute Walk Test (6MWT) |
|-----------------|---|

End point description:

Change from baseline to Weeks 24 and 52 in 6MWD as measured by 6MWT was reported. 6MWD was the distance that a participant could walk in 6 minutes. Rest periods were allowed if the participant could no longer continue. If the participant need to rest, he/she may pause, lean against the wall and continue walking whenever he/she feels able. The timer continued to run even if the participant stopped to rest. Analysis population included all participants greater than equal to (\geq) 6 years of age. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 24 and 52

| End point values | Macitentan | | | |
|--------------------------------------|--------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: meters | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 24 (n=3) | 4.897 (\pm 43.6657) | | | |
| Week 52 (n=2) | 24.710 (\pm 105.6559) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, 28, 40, and 52 in N-terminal Pro-brain Natriuretic Peptide (NT-proBNP)

| | |
|-----------------|--|
| End point title | Change from Baseline to Weeks 12, 24, 28, 40, and 52 in N-terminal Pro-brain Natriuretic Peptide (NT-proBNP) |
|-----------------|--|

End point description:

Change from baseline to Weeks 12, 24, 28, 40, and 52 in NT-proBNP was reported. Efficacy analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, 28, 40, and 52

| End point values | Macitentan | | | |
|---|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: picograms per milliliter (pg/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 (n=7) | 6.5911 (\pm 18.85065) | | | |
| Week 24 (n=7) | -3.7423 (\pm 7.79983) | | | |
| Week 28 (n=6) | -3.1663 (\pm 20.38136) | | | |
| Week 40 (n=7) | -5.7146 (\pm 14.23745) | | | |
| Week 52 (n=6) | -0.2360 (\pm 10.15074) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Tricuspid Annular Plane Systolic Excursion (TAPSE)

| | |
|-----------------|--|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Tricuspid Annular Plane Systolic Excursion (TAPSE) |
|-----------------|--|

End point description:

Change from baseline to Weeks 12, 24, and 52 in TAPSE was reported. It is calculated as: original TAPSE value/body surface area (BSA). TAPSE was a dimension used to evaluate Right Ventricle (RV) longitudinal systolic function; it measured the extent of systolic motion of the lateral portion of the tricuspid ring towards the apex. Efficacy analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|--|-----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: millimeters per meter square (mm/m ²) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 (n=7) | 2.766 (\pm 1.6763) | | | |

| | | | | |
|---------------|------------------|--|--|--|
| Week 24 (n=7) | 1.873 (± 1.0379) | | | |
| Week 52 (n=6) | 2.412 (± 1.3666) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Left Ventricular Eccentricity Index (LVEI)

| | |
|-----------------|--|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Left Ventricular Eccentricity Index (LVEI) |
|-----------------|--|

End point description:

Change from baseline to Weeks 12, 24, and 52 in LVEI was reported. It included diastolic (D) LVEI and systolic (S) LVEI. LV internal diameters were measured using the parasternal short axis view at the level of the papillary muscles: D1: LV internal diameter perpendicular to interventricular septum at end-diastole; D2: LV internal diameter parallel to interventricular septum, and at right angle from D1, at end-diastole; S1: LV internal diameter perpendicular to interventricular septum at end-systole; S2: LV internal diameter parallel to interventricular septum, and at a right angle from S1, at end-systole. The LVEI was a ratio that was calculated by sponsor as: LVEI diastole = D2/D1; LVEI systole = S2/S1. Efficacy analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Ratio | | | | |
| arithmetic mean (standard deviation) | | | | |
| Diastolic: Week 12 | 0.116 (± 0.1241) | | | |
| Diastolic: Week 24 | 0.125 (± 0.1491) | | | |
| Diastolic: Week 52 | 0.128 (± 0.0762) | | | |
| Systolic: Week 12 | 0.237 (± 0.1519) | | | |
| Systolic: Week 24 | 0.229 (± 0.2396) | | | |
| Systolic: Week 52 | 0.237 (± 0.1225) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Quality of Life (QoL) as Assessed by Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales Short Form (SF-15)

| | |
|-----------------|--|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Quality of Life (QoL) as Assessed by Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales Short Form (SF-15) |
|-----------------|--|

End point description:

Change from baseline to Weeks 12, 24, and 52 in QoL as assessed by PedsQL 4.0 generic core scales SF-15 was reported. The PedsQL 4.0 questionnaire generic core scales score SF-15 assessed general physical, emotional, social and school functioning on a 5-point Likert scale from 0 to 4 with 0= if it is never a problem, 1= if it is almost never a problem, 2= if it is sometime a problem, 3= if it is often a problem, 4 if it is almost always a problem. Scores were transformed on a scale from 0 to 100. Higher scores indicated better health related QoL. The QoL questionnaire was completed by parent(s)/caregiver(s) and by participants. Analysis population included all participants ≥ 2 years of age. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|---|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Total score parents/caregiver report: Week 12 (n=5) | 8.905 (\pm 6.1274) | | | |
| Total score parents/caregiver report: Week 24 (n=5) | 8.190 (\pm 11.3259) | | | |
| Total score parents/caregiver report: Week 52 (n=5) | 15.810 (\pm 7.8366) | | | |
| Total score - participant report: Week 12 (n=3) | 8.889 (\pm 3.4694) | | | |
| Total score - participant report: Week 24 (n=3) | -2.222 (\pm 17.8211) | | | |
| Total score - participant report: Week 52 (n=3) | 16.667 (\pm 20.2759) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Number of Hours of Daytime Activity

| | |
|-----------------|---|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Number of Hours of Daytime Activity |
|-----------------|---|

End point description:

Change from baseline to Weeks 12, 24, and 52 in physical activity as measured by accelerometry: number of hours of daytime activity was reported. Analysis population included all participants ≥ 2 years of age.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|--------------------------------------|------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: hours | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | -0.929 (\pm 0.9741) | | | |
| Week 24 | -0.280 (\pm 1.3553) | | | |
| Week 52 | 0.144 (\pm 0.4985) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Mean Count Per Minute of Daily Activity

| | |
|-----------------|---|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Mean Count Per Minute of Daily Activity |
|-----------------|---|

End point description:

Change from baseline to Weeks 12, 24, and 52 in physical activity as measured by accelerometry: mean count per minute of daily activity was reported. Analysis population included all participants ≥ 2 years of age.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|--------------------------------------|---------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: counts per minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | 73.946 (\pm 205.4249) | | | |
| Week 24 | 112.733 (\pm 219.3168) | | | |
| Week 52 | 125.427 (\pm 157.5824) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Mean Daily Time Spent in Light Physical Activity

| | |
|-----------------|--|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Mean Daily Time Spent in Light Physical Activity |
|-----------------|--|

End point description:

Change from baseline to Weeks 12, 24, and 52 in physical activity as measured by accelerometry: mean daily time spent in light physical activity was reported. Analysis population included all participants ≥ 2 years of age.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|--------------------------------------|-------------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | 1.600 (\pm 46.5857) | | | |
| Week 24 | 35.159 (\pm 92.2011) | | | |
| Week 52 | 38.852 (\pm 57.1818) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Mean Daily Time Spent in Moderate to Vigorous Physical Activity

| | |
|-----------------|---|
| End point title | Change from Baseline to Weeks 12, 24, and 52 in Physical Activity as Measured by Accelerometry: Mean Daily Time Spent in Moderate to Vigorous Physical Activity |
|-----------------|---|

End point description:

Change from baseline to Weeks 12, 24, and 52 in physical activity as measured by accelerometry: mean daily time spent in moderate to vigorous physical activity was reported. Analysis population included all participants ≥ 2 years of age.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From baseline (Day 1) up to Weeks 12, 24, and 52

| End point values | Macitentan | | | |
|--------------------------------------|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: minutes | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | 0.032 (± 0.4424) | | | |
| Week 24 | 0.169 (± 0.6058) | | | |
| Week 52 | 0.493 (± 1.5023) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Macitentan: Participants ≥ 2 Years Old

| | |
|--|---|
| End point title | Plasma Concentration of Macitentan: Participants ≥ 2 Years Old |
| End point description: Plasma concentration of macitentan was reported. Analysis population included all participants ≥ 2 years of age. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints. | |
| End point type | Secondary |
| End point timeframe: Day 11 (0, 1, 2, 4, 8, 12, 24 hours post-dose), Week 12 | |

| End point values | Macitentan | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 11: 0 hour (n=5) | 94.4 (± 28.9) | | | |
| Day 11: 1 hour (n=5) | 93.4 (± 27.7) | | | |
| Day 11: 2 hours (n=5) | 121 (± 55.1) | | | |
| Day 11: 4 hours (n=5) | 227 (± 38.5) | | | |
| Day 11: 8 hours (n=5) | 192 (± 93.2) | | | |
| Day 11: 12 hours (n=5) | 166 (± 75.5) | | | |
| Day 11: 24 hours (n=5) | 93.3 (± 26.9) | | | |
| Week 12 (n=4) | 85.6 (± 37.3) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Aprocitentan: Participants ≥ 2 Years Old

| | |
|-----------------|---|
| End point title | Plasma Concentration of Aprocitentan: Participants ≥ 2 Years Old |
|-----------------|---|

End point description:

Plasma concentration of aprocitentan was reported. Analysis population included all participants ≥ 2 years of age. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 11 (0, 1, 2, 4, 8, 12, 24 hours post-dose), Week 12

| End point values | Macitentan | | | |
|---|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 5 | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Day 11: 0 hour (n=5) | 993 (\pm 285) | | | |
| Day 11: 1 hour (n=5) | 789 (\pm 228) | | | |
| Day 11: 2 hours (n=5) | 763 (\pm 309) | | | |
| Day 11: 4 hours (n=5) | 944 (\pm 211) | | | |
| Day 11: 8 hours (n=5) | 773 (\pm 308) | | | |
| Day 11: 12 hours (n=5) | 789 (\pm 255) | | | |
| Day 11: 24 hours (n=5) | 929 (\pm 251) | | | |
| Week 12 (n=4) | 917 (\pm 266) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Macitentan: Participants < 2 Years Old

| | |
|-----------------|--|
| End point title | Plasma Concentration of Macitentan: Participants < 2 Years Old |
|-----------------|--|

End point description:

Plasma concentration of macitentan was reported. The data was not summarized since N=2, hence participants wise data was reported. Analysis population included all participants < 2 years of age. Here, "99999" refers to standard deviation not evaluable for single participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (2, 5, 24 hours post-dose), Weeks 4 and 8

| End point values | Macitentan | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Participant 1: Day 1 (2 hours) | 33.6 (± 99999) | | | |
| Participant 1: Day 1 (5 hours) | 120 (± 99999) | | | |
| Participant 1: Day 1 (24 hours) | 24.2 (± 99999) | | | |
| Participant 1: Week 4 | 55.1 (± 99999) | | | |
| Participant 1: Week 8 | 59.4 (± 99999) | | | |
| Participant 2: Day 1 (2 hours) | 81.4 (± 99999) | | | |
| Participant 2: Day 1 (5 hours) | 155 (± 99999) | | | |
| Participant 2: Day 1 (24 hours) | 61.1 (± 99999) | | | |
| Participant 2: Week 4 | 143 (± 99999) | | | |
| Participant 2: Week 8 | 83.5 (± 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Plasma Concentration of Aprocitentan: Participants <2 Years Old

| | |
|-----------------|---|
| End point title | Plasma Concentration of Aprocitentan: Participants <2 Years Old |
|-----------------|---|

End point description:

Plasma concentration of aprocitentan was reported. The data was not summarized since N=2, hence participants wise data was reported. Analysis population included all participants <2 years of age. Here, "99999" refers to standard deviation not evaluable for single participant.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Day 1 (2, 5, 24 hours post-dose), Weeks 4 and 8

| End point values | Macitentan | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 2 | | | |
| Units: nanograms per milliliter (ng/mL) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Participant 1: Day 1 (2 hours) | 7.98 (± 99999) | | | |
| Participant 1: Day 1 (5 hours) | 65.9 (± 99999) | | | |
| Participant 1: Day 1 (24 hours) | 162 (± 99999) | | | |
| Participant 1: Week 4 | 864 (± 99999) | | | |
| Participant 1: Week 8 | 982 (± 99999) | | | |
| Participant 2: Day 1 (2 hours) | 7.62 (± 99999) | | | |
| Participant 2: Day 1 (5 hours) | 29.2 (± 99999) | | | |
| Participant 2: Day 1 (24 hours) | 119 (± 99999) | | | |
| Participant 2: Week 4 | 662 (± 99999) | | | |
| Participant 2: Week 8 | 648 (± 99999) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change From Baseline to Week 24 and Week 52 in Borg Dyspnea Index

| | |
|-----------------|---|
| End point title | Change From Baseline to Week 24 and Week 52 in Borg Dyspnea Index |
|-----------------|---|

End point description:

Change from baseline to Weeks 24 and 52 in Borg dyspnea index was reported. BDI was a 10-point scale rating the maximum level of dyspnea experienced during the 6MWT. Scores ranged from 0 (no shortness of breath) to 10 (worst shortness of breath you have ever had). Higher score indicated worse outcome. Analysis population included all participants greater than equal to (\geq) 6 years of age. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 24 and 52

| End point values | Macitentan | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 3 | | | |
| Units: Score on a scale | | | | |
| arithmetic mean (standard deviation) | | | | |
| Before 6MWT: Week 24 (n=3) | 0.00 (\pm 0.000) | | | |
| Before 6MWT: Week 52 (n=2) | 0.00 (\pm 0.000) | | | |
| After 6MWT: Week 24 (n=3) | -1.17 (\pm 0.764) | | | |
| After 6MWT: Week 52 (n=2) | -1.00 (\pm 0.707) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Adverse Events (TEAEs)

| | |
|-----------------|---|
| End point title | Number of Participants With Treatment-emergent Adverse Events (TEAEs) |
|-----------------|---|

End point description:

Number of participants with TEAEs was reported. An adverse event (AE) was any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. TEAEs are defined as any AE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days. Safety analysis set included all participants who took at least 1 dose

of study intervention.

| | |
|-------------------------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| From Baseline (Day 1) up to Week 56 | |

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | 7 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Postbaseline Markedly Abnormal Hematology Laboratory Values

| | |
|-----------------|---|
| End point title | Number of Participants With Postbaseline Markedly Abnormal Hematology Laboratory Values |
|-----------------|---|

End point description:

Number of participants with postbaseline markedly abnormal hematology laboratory values was reported. Abnormality was judged at the discretion of investigator. Data is reported for categories where atleast one participant had abnormality. Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------------|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Weeks 20, 40, and 52 | |

| | | | | |
|--|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | | | | |
| Hematocrit: <0.28% of blood cells(<0.32M): Week 20 | 1 | | | |
| Hemoglobin: < 100 grams per liter (g/L): Week 20 | 1 | | | |
| Leukocytes: <3.0 10 ⁹ cells/L: Week 40 | 1 | | | |
| Leukocytes: <3.0 10 ⁹ cells/L: Week 52 | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With TEAEs of Special Interest

| | |
|-----------------|---|
| End point title | Number of Participants With TEAEs of Special Interest |
|-----------------|---|

End point description:

Number of participants with TEAEs of special interest was reported. It included anemia/decreased hemoglobin level, oedema/fluid retention, hepatic impairment and hypotension. Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Day 1) up to Week 56

| End point values | Macitentan | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Treatment-emergent Serious Adverse Events (TESAEs)

| | |
|-----------------|--|
| End point title | Number of Participants With Treatment-emergent Serious Adverse Events (TESAEs) |
|-----------------|--|

End point description:

Number of participants with TESAEs was reported. An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. A SAE is an AE resulting in any of the following outcomes or deemed significant for any other reason: death; initial or prolonged inpatient hospitalization; life-threatening experience (immediate risk of dying); persistent or significant disability/incapacity; congenital anomaly. TESAEs are defined as any SAE occurring at or after the initial administration of study intervention through the day of last dose plus 30 days. Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Day 1) up to Week 56

| End point values | Macitentan | | | |
|-----------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | 2 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With AEs Leading to Premature Discontinuation of Study Drug

| | |
|-----------------|--|
| End point title | Number of Participants With AEs Leading to Premature Discontinuation of Study Drug |
|-----------------|--|

End point description:

Number of participants with AEs leading to premature discontinuation of study drug was reported. An AE is any untoward medical occurrence in a clinical study participant administered a medicinal (investigational or non-investigational) product. An AE does not necessarily have a causal relationship with the intervention. Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

From Baseline (Day 1) up to Week 52

| | | | | |
|-----------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | 0 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Number of Participants With Postbaseline Markedly Abnormal Clinical Chemistry Laboratory Values

| | |
|-----------------|---|
| End point title | Number of Participants With Postbaseline Markedly Abnormal Clinical Chemistry Laboratory Values |
|-----------------|---|

End point description:

Number of participants with postbaseline markedly abnormal clinical chemistry laboratory values was reported. Abnormality was judged at the discretion of investigator. Data is reported for categories where atleast one participant had abnormality. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Weeks 4 and 28

| End point values | Macitentan | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Participants | | | | |
| Potassium: >6.0 mmol/L: Week 4 (n=7) | 1 | | | |
| Calcium: <1.75 mmol/L: Week 4 (n=7) | 1 | | | |
| ALP: > 2.5 * ULN: Week 28 (n=6) | 1 | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Vital Signs: Pulse Rate

| | |
|--|---|
| End point title | Change from Baseline in Vital Signs: Pulse Rate |
| End point description: Change from baseline in vital signs: pulse rate was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52 | |

| End point values | Macitentan | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: beats per minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=7) | -4.4 (± 7.87) | | | |
| Week 8 (n=7) | -1.7 (± 15.24) | | | |
| Week 12 (n=7) | -12.1 (± 7.45) | | | |
| Week 16 (n=7) | -13.4 (± 17.06) | | | |
| Week 20 (n=7) | -7.4 (± 17.50) | | | |
| Week 24 (n=7) | -2.4 (± 30.72) | | | |
| Week 28 (n=6) | -7.2 (± 12.42) | | | |
| Week 40 (n=7) | -10.3 (± 9.30) | | | |
| Week 52 (n=7) | -14.7 (± 9.62) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Vital Signs: Blood Pressure

| | |
|-----------------|---|
| End point title | Change from Baseline in Vital Signs: Blood Pressure |
|-----------------|---|

End point description:

Change from baseline in vital signs: blood pressure was reported. It included systolic blood pressure (SBP) and diastolic blood pressure (DBP). Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52

| End point values | Macitentan | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: millimeter of mercury (mmHg) | | | | |
| arithmetic mean (standard deviation) | | | | |
| SBP: Week 4 (n=7) | -5.3 (± 12.61) | | | |
| SBP: Week 8 (n=7) | -5.3 (± 14.86) | | | |
| SBP: Week 12 (n=7) | 0.4 (± 4.79) | | | |
| SBP: Week 16 (n=7) | -1.7 (± 10.29) | | | |
| SBP: Week 20 (n=7) | -1.1 (± 13.35) | | | |
| SBP: Week 24 (n=7) | -5.3 (± 9.79) | | | |
| SBP: Week 28 (n=6) | -5.5 (± 6.09) | | | |
| SBP: Week 40 (n=7) | -3.3 (± 9.05) | | | |
| SBP: Week 52 (n=7) | -9.3 (± 12.00) | | | |
| DBP: Week 4 (n=6) | -9.0 (± 9.06) | | | |
| DBP: Week 8 (n=6) | -4.5 (± 6.41) | | | |
| DBP: Week 12 (n=7) | -3.7 (± 11.83) | | | |
| DBP: Week 16 (n=7) | -6.1 (± 11.78) | | | |
| DBP: Week 20 (n=7) | 0.9 (± 19.04) | | | |
| DBP: Week 24 (n=7) | -7.1 (± 7.06) | | | |
| DBP: Week 28 (n=6) | -8.0 (± 8.32) | | | |
| DBP: Week 40 (n=7) | -0.7 (± 10.13) | | | |
| DBP: Week 52 (n=7) | -4.0 (± 16.93) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Electrocardiogram (ECG) Parameter: Heart Rate

| | |
|-----------------|---|
| End point title | Change from Baseline in Electrocardiogram (ECG) Parameter: Heart Rate |
|-----------------|---|

End point description:

Change from baseline in ECG: heart rate was reported. Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 12, 24, and 52

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: beats per minute | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 12 | -4.0 (± 19.04) | | | |
| Week 24 | -3.6 (± 25.48) | | | |
| Week 52 | -12.0 (± 8.91) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Electrocardiogram (ECG) Parameter: PR, QRS, QT, Corrected QT interval-Bazett's Formula (QTcB), and Corrected QT Interval-Fridericia's Formula (QTcF) Intervals

| | |
|-----------------|--|
| End point title | Change from Baseline in Electrocardiogram (ECG) Parameter: PR, QRS, QT, Corrected QT interval-Bazett's Formula (QTcB), and Corrected QT Interval-Fridericia's Formula (QTcF) Intervals |
|-----------------|--|

End point description:

Change from baseline in ECG: PR, QRS, QT, QTcB, and QTcF intervals was reported. Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 12, 24, and 52

| | | | | |
|--------------------------------------|-----------------|--|--|--|
| End point values | Macitentan | | | |
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: milliseconds (msec) | | | | |
| arithmetic mean (standard deviation) | | | | |
| PR Interval: Week 12 | 3.4 (± 10.94) | | | |
| PR Interval: Week 24 | 14.6 (± 15.10) | | | |
| PR Interval: Week 52 | 4.0 (± 7.57) | | | |
| QRS Interval: Week 12 | -0.3 (± 4.96) | | | |
| QRS Interval: Week 24 | 0.3 (± 4.19) | | | |
| QRS Interval: Week 52 | 0.3 (± 3.15) | | | |
| QT Interval: Week 12 | 16.1 (± 29.61) | | | |
| QT Interval: Week 24 | 12.4 (± 34.52) | | | |
| QT Interval: Week 52 | 32.1 (± 16.69) | | | |
| QTcB Interval: Week 12 | 10.6 (± 13.59) | | | |
| QTcB Interval: Week 24 | 4.0 (± 24.53) | | | |
| QTcB Interval: Week 52 | 11.4 (± 13.89) | | | |

| | | | | |
|------------------------|----------------|--|--|--|
| QTcf Interval: Week 12 | 12.6 (± 14.29) | | | |
| QTcf Interval: Week 24 | 6.7 (± 21.16) | | | |
| QTcf Interval: Week 52 | 19.0 (± 11.37) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hematology Parameters: Platelets, Leukocytes, Neutrophils Band Form (NBF), Lymphocytes, Monocytes, Eosinophils, and Basophils

| | |
|-----------------|---|
| End point title | Change from Baseline in Hematology Parameters: Platelets, Leukocytes, Neutrophils Band Form (NBF), Lymphocytes, Monocytes, Eosinophils, and Basophils |
|-----------------|---|

End point description:

Change from baseline in hematology parameters: platelets, leukocytes, NBF, lymphocytes, monocytes, eosinophils, and basophils was reported. Data for each parameters was planned to be reported at specified timepoints only. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints. Here, "99999" refers to standard deviation data was not calculated for single participant

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52

| End point values | Macitentan | | | |
|---|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: 10 ⁹ cells per liter (10 ⁹ /L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Platelets: Week 4 (n=7) | -20.4 (± 31.90) | | | |
| Platelets: Week 8 (n=7) | -47.9 (± 42.32) | | | |
| Platelets: Week 12 (n=7) | -23.3 (± 70.86) | | | |
| Platelets: Week 16 (n=7) | -41.3 (± 53.21) | | | |
| Platelets: Week 20 (n=7) | -42.4 (± 86.32) | | | |
| Platelets: Week 24 (n=7) | -42.6 (± 77.72) | | | |
| Platelets: Week 28 (n=6) | -22.0 (± 59.29) | | | |
| Platelets: Week 40 (n=7) | -40.3 (± 106.10) | | | |
| Platelets: Week 52 (n=7) | -56.7 (± 92.37) | | | |
| Leukocytes: Week 4 (n=7) | 0.031 (± 3.7398) | | | |
| Leukocytes: Week 8 (n=7) | 0.549 (± 3.4816) | | | |
| Leukocytes: Week 12 (n=7) | -0.131 (± 2.3574) | | | |

| | | | | |
|----------------------------|------------------------|--|--|--|
| Leukocytes: Week 16 (n=7) | -0.321 (\pm 1.5230) | | | |
| Leukocytes: Week 20 (n=7) | -1.256 (\pm 3.7745) | | | |
| Leukocytes: Week 24 (n=7) | 0.214 (\pm 3.6431) | | | |
| Leukocytes: Week 28 (n=6) | -0.347 (\pm 2.8012) | | | |
| Leukocytes: Week 40 (n=7) | -1.660 (\pm 3.0486) | | | |
| Leukocytes: Week 52 (n=7) | -0.541 (\pm 2.7583) | | | |
| NBF: Week 8 (n=1) | 0.120 (\pm 99999) | | | |
| NBF: Week 16 (n=1) | 0.480 (\pm 99999) | | | |
| NBF: Week 20 (n=2) | 0.055 (\pm 0.1485) | | | |
| NBF: Week 40 (n=1) | -0.050 (\pm 99999) | | | |
| NBF: Week 52 (n=1) | -0.030 (\pm 99999) | | | |
| Lymphocytes: Week 4 (n=7) | -0.144 (\pm 0.4446) | | | |
| Lymphocytes: Week 8 (n=7) | -0.240 (\pm 0.5289) | | | |
| Lymphocytes: Week 12 (n=7) | -0.451 (\pm 0.3151) | | | |
| Lymphocytes: Week 16 (n=7) | -0.294 (\pm 0.1784) | | | |
| Lymphocytes: Week 20 (n=7) | -0.286 (\pm 0.8204) | | | |
| Lymphocytes: Week 24 (n=7) | -0.224 (\pm 0.5638) | | | |
| Lymphocytes: Week 28 (n=6) | -0.255 (\pm 0.5392) | | | |
| Lymphocytes: Week 40 (n=7) | -0.649 (\pm 0.5258) | | | |
| Lymphocytes: Week 52 (n=7) | -0.411 (\pm 0.5227) | | | |
| Monocytes: Week 4 (n=7) | -0.029 (\pm 0.0807) | | | |
| Monocytes: Week 8 (n=7) | 0.070 (\pm 0.2063) | | | |
| Monocytes: Week 12 (n=7) | 0.033 (\pm 0.0925) | | | |
| Monocytes: Week 16 (n=7) | -0.046 (\pm 0.0382) | | | |
| Monocytes: Week 20 (n=7) | -0.081 (\pm 0.0928) | | | |
| Monocytes: Week 24 (n=7) | 0.017 (\pm 0.1042) | | | |
| Monocytes: Week 28 (n=6) | -0.052 (\pm 0.0884) | | | |
| Monocytes: Week 40 (n=7) | -0.103 (\pm 0.0911) | | | |
| Monocytes: Week 52 (n=7) | -0.086 (\pm 0.0988) | | | |
| Eosinophils: Week 4 (n=7) | -0.011 (\pm 0.0811) | | | |
| Eosinophils: Week 8 (n=7) | -0.009 (\pm 0.0795) | | | |

| | | | | |
|----------------------------|-------------------|--|--|--|
| Eosinophils: Week 12 (n=7) | 0.066 (± 0.1153) | | | |
| Eosinophils: Week 16 (n=7) | 0.030 (± 0.1606) | | | |
| Eosinophils: Week 20 (n=7) | 0.086 (± 0.1752) | | | |
| Eosinophils: Week 24 (n=7) | -0.016 (± 0.1066) | | | |
| Eosinophils: Week 28 (n=6) | -0.040 (± 0.1119) | | | |
| Eosinophils: Week 40 (n=7) | 0.000 (± 0.0693) | | | |
| Eosinophils: Week 52 (n=7) | 0.220 (± 0.6577) | | | |
| Basophils: Week 4 (n=7) | 0.016 (± 0.0162) | | | |
| Basophils: Week 8 (n=7) | 0.009 (± 0.0273) | | | |
| Basophils: Week 12 (n=7) | 0.016 (± 0.0270) | | | |
| Basophils: Week 16 (n=7) | 0.016 (± 0.0465) | | | |
| Basophils: Week 20 (n=7) | 0.000 (± 0.0183) | | | |
| Basophils: Week 24 (n=7) | 0.016 (± 0.0257) | | | |
| Basophils: Week 28 (n=6) | 0.008 (± 0.0256) | | | |
| Basophils: Week 40 (n=7) | -0.004 (± 0.0276) | | | |
| Basophils: Week 52 (n=7) | 0.053 (± 0.1073) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hematology Parameter: Hematocrit

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|-----------------|--|
| End point title | Change from Baseline in Hematology Parameter: Hematocrit |
|-----------------|--|

End point description:

Change from baseline in hematology parameter: hematocrit was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52

| End point values | Macitentan | | | |
|--------------------------------------|-------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Percentage of blood cells | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=7) | 0.009 (± 0.0204) | | | |
| Week 8 (n=7) | 0.016 (± 0.0223) | | | |
| Week 12 (n=7) | 0.004 (± 0.0230) | | | |
| Week 16 (n=7) | -0.006 (± 0.0299) | | | |
| Week 20 (n=7) | -0.004 (± 0.0282) | | | |
| Week 24 (n=7) | 0.006 (± 0.0355) | | | |
| Week 28 (n=6) | 0.010 (± 0.0237) | | | |
| Week 40 (n=7) | 0.010 (± 0.0216) | | | |
| Week 52 (n=7) | 0.010 (± 0.0404) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hematology Parameter: Hemoglobin

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|---|--|
| End point title | Change from Baseline in Hematology Parameter: Hemoglobin |
| End point description: | |
| Change from baseline in hematology parameter: hemoglobin was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints. | |
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52 | |

| End point values | Macitentan | | | |
|--------------------------------------|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: grams per liter (g/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=7) | 1.9 (± 9.12) | | | |
| Week 8 (n=7) | 2.3 (± 8.28) | | | |
| Week 12 (n=7) | -0.1 (± 9.60) | | | |
| Week 16 (n=7) | -3.0 (± 9.35) | | | |
| Week 20 (n=7) | -4.1 (± 5.84) | | | |
| Week 24 (n=7) | -0.3 (± 9.81) | | | |

| | | | | |
|---------------|---------------|--|--|--|
| Week 28 (n=6) | -2.7 (± 8.71) | | | |
| Week 40 (n=7) | 0.1 (± 8.91) | | | |
| Week 52 (n=7) | 0.7 (± 11.84) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Hematology Parameter: Erythrocytes

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|-----------------|--|
| End point title | Change from Baseline in Hematology Parameter: Erythrocytes |
|-----------------|--|

End point description:

Change from baseline in hematology parameter: erythrocytes was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52

| End point values | Macitentan | | | |
|---|-----------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: 10 ¹² cells per liter (10 ¹² /L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=7) | 0.03 (± 0.236) | | | |
| Week 8 (n=7) | 0.13 (± 0.309) | | | |
| Week 12 (n=7) | 0.04 (± 0.336) | | | |
| Week 16 (n=7) | -0.07 (± 0.269) | | | |
| Week 20 (n=7) | -0.06 (± 0.230) | | | |
| Week 24 (n=7) | 0.04 (± 0.299) | | | |
| Week 28 (n=6) | 0.07 (± 0.266) | | | |
| Week 40 (n=7) | 0.07 (± 0.335) | | | |
| Week 52 (n=7) | 0.04 (± 0.412) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Chemistry Parameters: Sodium, Potassium, Urea Nitrogen, Glucose, and Calcium

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|-----------------|--|
| End point title | Change from Baseline in Chemistry Parameters: Sodium, Potassium, Urea Nitrogen, Glucose, and Calcium |
|-----------------|--|

End point description:

Change from baseline in chemistry parameters: sodium, potassium, urea nitrogen, glucose, and calcium

was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

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|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52 | |

| End point values | Macitentan | | | |
|---|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: 10 ¹² cells per liter (10 ¹² /L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Sodium: Week 4 (n=7) | -0.1 (± 3.85) | | | |
| Sodium: Week 8 (n=7) | 0.1 (± 1.57) | | | |
| Sodium: Week 12 (n=6) | 0.2 (± 1.17) | | | |
| Sodium: Week 16 (n=7) | -0.7 (± 1.98) | | | |
| Sodium: Week 20 (n=7) | -0.1 (± 2.34) | | | |
| Sodium: Week 24 (n=7) | 0.3 (± 2.98) | | | |
| Sodium: Week 28 (n=6) | 1.5 (± 1.87) | | | |
| Sodium: Week 40 (n=7) | -0.1 (± 2.04) | | | |
| Sodium: Week 52 (n=7) | -0.7 (± 2.43) | | | |
| Potassium: Week 4 (n=7) | 0.46 (± 1.137) | | | |
| Potassium: Week 8 (n=7) | 0.03 (± 0.330) | | | |
| Potassium: Week 12 (n=6) | 0.10 (± 0.494) | | | |
| Potassium: Week 16 (n=7) | -0.09 (± 0.234) | | | |
| Potassium: Week 20 (n=7) | 0.03 (± 0.315) | | | |
| Potassium: Week 24 (n=7) | -0.09 (± 0.261) | | | |
| Potassium: Week 28 (n=6) | -0.07 (± 0.186) | | | |
| Potassium: Week 40 (n=7) | 0.07 (± 0.298) | | | |
| Potassium: Week 52 (n=7) | 0.04 (± 0.336) | | | |
| Urea Nitrogen: Week 4 (n=7) | -0.0510 (± 1.32665) | | | |
| Urea Nitrogen: Week 8 (n=7) | -0.3060 (± 1.32665) | | | |
| Urea Nitrogen: Week 12 (n=6) | 0.0000 (± 1.39184) | | | |
| Urea Nitrogen: Week 16 (n=7) | 0.3060 (± 1.19170) | | | |
| Urea Nitrogen: Week 20 (n=7) | -0.8160 (± 1.10448) | | | |
| Urea Nitrogen: Week 24 (n=7) | -0.1020 (± 1.14229) | | | |
| Urea Nitrogen: Week 28 (n=6) | -0.3570 (± 0.98418) | | | |
| Urea Nitrogen: Week 40 (n=7) | -0.8160 (± 1.40875) | | | |
| Urea Nitrogen: Week 52 (n=7) | -0.3060 (± 1.84847) | | | |
| Glucose: Week 4 (n=7) | 0.34099 (± 0.601656) | | | |

| | | | | |
|------------------------|-----------------------|--|--|--|
| Glucose: Week 8 (n=7) | 0.22204 (± 0.652101) | | | |
| Glucose: Week 12 (n=6) | 0.05548 (± 0.641615) | | | |
| Glucose: Week 16 (n=7) | 0.35684 (± 0.503536) | | | |
| Glucose: Week 20 (n=7) | 0.47580 (± 0.527417) | | | |
| Glucose: Week 24 (n=7) | 0.60266 (± 0.730401) | | | |
| Glucose: Week 28 (n=6) | 0.60133 (± 0.933768) | | | |
| Glucose: Week 40 (n=7) | 0.39649 (± 0.628362) | | | |
| Glucose: Week 52 (n=7) | 0.00791 (± 0.554573) | | | |
| Calcium: Week 4 (n=7) | -0.09980 (± 0.293456) | | | |
| Calcium: Week 8 (n=7) | -0.00357 (± 0.098172) | | | |
| Calcium: Week 12 (n=6) | -0.04158 (± 0.068184) | | | |
| Calcium: Week 16 (n=7) | -0.04634 (± 0.124293) | | | |
| Calcium: Week 20 (n=7) | -0.07486 (± 0.097716) | | | |
| Calcium: Week 24 (n=7) | -0.03564 (± 0.097564) | | | |
| Calcium: Week 28 (n=6) | -0.02495 (± 0.130142) | | | |
| Calcium: Week 40 (n=7) | -0.06416 (± 0.145380) | | | |
| Calcium: Week 52 (n=7) | -0.03563 (± 0.108627) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Chemistry Parameters: Creatinine (Jaffe Reaction), Bilirubin, and Direct Bilirubin,

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|--|---|
| End point title | Change from Baseline in Chemistry Parameters: Creatinine (Jaffe Reaction), Bilirubin, and Direct Bilirubin, |
| End point description: Change from baseline in chemistry parameters: creatinine, bilirubin, and direct bilirubin was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints. | |
| End point type | Secondary |
| End point timeframe: Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52 | |

| End point values | Macitentan | | | |
|---------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: micromoles per liter (mcmol/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Creatinine: Week 4 (n=6) | -0.2947 (± 4.92719) | | | |
| Creatinine: Week 8 (n=7) | -4.0411 (± 7.82156) | | | |
| Creatinine: Week 12 (n=6) | -1.9153 (± 11.69311) | | | |
| Creatinine: Week 16 (n=7) | -2.5257 (± 8.69784) | | | |
| Creatinine: Week 20 (n=7) | -2.5257 (± 10.36492) | | | |
| Creatinine: Week 24 (n=7) | 0.1263 (± 9.20703) | | | |
| Creatinine: Week 28 (n=6) | -3.5360 (± 8.69741) | | | |
| Creatinine: Week 40 (n=7) | -1.1366 (± 8.82104) | | | |
| Creatinine: Week 52 (n=7) | -1.2629 (± 11.22665) | | | |
| Bilirubin: Week 4 (n=7) | -0.733 (± 1.6688) | | | |
| Bilirubin: Week 8 (n=7) | 0.733 (± 2.9382) | | | |
| Bilirubin: Week 12 (n=6) | -0.570 (± 0.8830) | | | |
| Bilirubin: Week 16 (n=7) | -0.489 (± 0.8344) | | | |
| Bilirubin: Week 20 (n=7) | 0.489 (± 1.2926) | | | |
| Bilirubin: Week 24 (n=7) | 0.733 (± 1.6688) | | | |
| Bilirubin: Week 28 (n=6) | 0.285 (± 0.6981) | | | |
| Bilirubin: Week 40 (n=7) | 0.244 (± 1.1800) | | | |
| Bilirubin: Week 52 (n=7) | 0.733 (± 0.9140) | | | |
| Direct Bilirubin: Week 4 (n=5) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 8 (n=6) | 0.285 (± 0.6981) | | | |
| Direct Bilirubin: Week 12 (n=6) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 16 (n=6) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 20 (n=7) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 24 (n=6) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 28 (n=6) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 40 (n=7) | 0.000 (± 0.0000) | | | |
| Direct Bilirubin: Week 52 (n=5) | 0.000 (± 0.0000) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Chemistry Parameters: Creatinine Clearance

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| End point title | Change from Baseline in Chemistry Parameters: Creatinine Clearance |
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End point description:

Change from baseline in chemistry parameter: creatinine clearance was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52

| End point values | Macitentan | | | |
|--------------------------------------|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: milliliters per second (mL/s) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=6) | 0.08337 (± 0.227335) | | | |
| Week 8 (n=7) | 0.19291 (± 0.280068) | | | |
| Week 12 (n=6) | 0.13057 (± 0.353525) | | | |
| Week 16 (n=7) | 0.16670 (± 0.296181) | | | |
| Week 20 (n=7) | 0.23817 (± 0.382532) | | | |
| Week 24 (n=7) | 0.07384 (± 0.285638) | | | |
| Week 28 (n=6) | 0.23615 (± 0.307994) | | | |
| Week 40 (n=7) | 0.12623 (± 0.344860) | | | |
| Week 52 (n=7) | 0.21671 (± 0.540583) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Chemistry Parameters: Glomerular Filtration Rate (GFR) from Cystatin C Adjusted for Body Surface Area (BSA)

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|-----------------|---|
| End point title | Change from Baseline in Chemistry Parameters: Glomerular Filtration Rate (GFR) from Cystatin C Adjusted for Body Surface Area (BSA) |
|-----------------|---|

End point description:

Change from baseline in chemistry parameter: GFR from Cystatin C Adjusted for BSA was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

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|----------------|-----------|
| End point type | Secondary |
|----------------|-----------|

End point timeframe:

Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52

| End point values | Macitentan | | | |
|---|----------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: mL/second/meter square(mL/s/m ²) | | | | |
| arithmetic mean (standard deviation) | | | | |
| Week 4 (n=7) | 0.05670 (± 0.193047) | | | |
| Week 8 (n=7) | 0.11014 (± 0.233865) | | | |
| Week 12 (n=6) | 0.12838 (± 0.262144) | | | |
| Week 16 (n=7) | 0.05853 (± 0.181786) | | | |
| Week 20 (n=7) | 0.07144 (± 0.264242) | | | |
| Week 24 (n=7) | 0.04350 (± 0.180046) | | | |
| Week 28 (n=6) | 0.03373 (± 0.182168) | | | |
| Week 40 (n=7) | 0.06939 (± 0.205418) | | | |
| Week 52 (n=7) | 0.03863 (± 0.203820) | | | |

Statistical analyses

No statistical analyses for this end point

Secondary: Change from Baseline in Chemistry Parameters: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP)

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|-----------------|--|
| End point title | Change from Baseline in Chemistry Parameters: Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), and Alkaline Phosphatase (ALP) |
|-----------------|--|

End point description:

Change from baseline in chemistry parameters: AST, ALT, and ALP was reported. Safety analysis set included all participants who took at least 1 dose of study intervention. Here, "n" (number analyzed) refer to the number of participants evaluable at specified timepoints.

| | |
|--|-----------|
| End point type | Secondary |
| End point timeframe: | |
| Baseline (Day 1), Weeks 4, 8, 12, 16, 20, 24, 28, 40, 52 | |

| End point values | Macitentan | | | |
|--|------------------|--|--|--|
| Subject group type | Reporting group | | | |
| Number of subjects analysed | 7 | | | |
| Units: Enzyme units per liter (Enzyme U/L) | | | | |
| arithmetic mean (standard deviation) | | | | |
| AST: Week 4 (n=6) | 4.2 (± 5.60) | | | |
| AST: Week 8 (n=6) | 4.5 (± 10.33) | | | |
| AST: Week 12 (n=6) | -0.8 (± 1.94) | | | |
| AST: Week 16 (n=7) | -2.0 (± 4.97) | | | |
| AST: Week 20 (n=7) | 0.1 (± 4.78) | | | |
| AST: Week 24 (n=6) | 0.8 (± 1.47) | | | |
| AST: Week 28 (n=6) | -2.2 (± 4.49) | | | |
| AST: Week 40 (n=7) | 0.1 (± 9.75) | | | |
| AST: Week 52 (n=7) | -2.9 (± 4.22) | | | |
| ALT: Week 4 (n=7) | 3.3 (± 4.57) | | | |
| ALT: Week 8 (n=7) | 1.6 (± 3.69) | | | |
| ALT: Week 12 (n=6) | 1.2 (± 3.19) | | | |
| ALT: Week 16 (n=7) | -1.6 (± 3.31) | | | |
| ALT: Week 20 (n=7) | 0.0 (± 1.41) | | | |
| ALT: Week 24 (n=7) | 2.6 (± 5.74) | | | |
| ALT: Week 28 (n=6) | -1.2 (± 2.40) | | | |
| ALT: Week 40 (n=7) | 1.3 (± 6.21) | | | |
| ALT: Week 52 (n=7) | 0.4 (± 4.12) | | | |
| ALP: Week 4 (n=7) | -15.4 (± 47.60) | | | |
| ALP: Week 8 (n=7) | -12.3 (± 35.45) | | | |
| ALP: Week 12 (n=6) | -37.2 (± 27.75) | | | |
| ALP: Week 16 (n=7) | -12.0 (± 48.25) | | | |
| ALP: Week 20 (n=7) | -21.1 (± 39.81) | | | |
| ALP: Week 24 (n=7) | 20.7 (± 120.53) | | | |
| ALP: Week 28 (n=6) | 153.8 (± 436.62) | | | |
| ALP: Week 40 (n=7) | -37.0 (± 44.79) | | | |
| ALP: Week 52 (n=7) | -6.4 (± 29.79) | | | |

Statistical analyses

Adverse events

Adverse events information

Timeframe for reporting adverse events:

All-cause mortality: From screening (Day -30) up to Week 56; Serious and Non-serious AEs: From baseline (Day 1) up to Week 56

Adverse event reporting additional description:

Safety analysis set included all participants who took at least 1 dose of study intervention.

| | |
|-----------------|----------------|
| Assessment type | Non-systematic |
|-----------------|----------------|

Dictionary used

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|-----------------|--------|
| Dictionary name | MedDRA |
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| Dictionary version | 27.0 |
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Reporting groups

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|-----------------------|------------|
| Reporting group title | Macitentan |
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Reporting group description:

Participants received macitentan 1 milligram (mg) or 2.5 mg tablets orally once daily based on age and body weight. Participants aged greater than or equal to (\geq) 3 months to less than ($<$) 6 months received daily dose of macitentan 1 mg, \geq 6 months to $<$ 2 years received daily dose of macitentan 2.5 mg. For participants above 2 years (inclusive) of age, daily doses of macitentan were 3.5 mg ($<$ 15 kilograms [kg] body weight [BW]), 5 mg (\geq 15 kg to $<$ 25 kg BW), 7.5 mg (\geq 25 kg to $<$ 50 kg BW), and 10 mg (\geq 50 kg BW). Treatment was administered from Day 1 to Week 52.

| Serious adverse events | Macitentan | | |
|---|----------------|--|--|
| Total subjects affected by serious adverse events | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | | |
| number of deaths (all causes) | 0 | | |
| number of deaths resulting from adverse events | 0 | | |
| Infections and infestations | | | |
| Bacteraemia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Pneumonia Bacterial | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences causally related to treatment / all | 0 / 2 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Metapneumovirus Infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences causally related to treatment / all | 0 / 1 | | |
| deaths causally related to treatment / all | 0 / 0 | | |
| Bronchitis | | | |

| | | | |
|---|----------------|--|--|
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| 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 | | |
|---|-----------------|--|--|
| Total subjects affected by non-serious adverse events | | | |
| subjects affected / exposed | 7 / 7 (100.00%) | | |
| Vascular disorders | | | |
| Flushing | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| General disorders and administration site conditions | | | |
| Catheter Site Dermatitis | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Pyrexia | | | |
| subjects affected / exposed | 4 / 7 (57.14%) | | |
| occurrences (all) | 6 | | |
| Respiratory, thoracic and mediastinal disorders | | | |
| Obstructive Sleep Apnoea Syndrome | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Nasal Obstruction | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Asthma | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 2 | | |
| Investigations | | | |
| Crystal Urine Present | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Injury, poisoning and procedural complications | | | |

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|---|---------------------|--|--|
| Post-Traumatic Neck Syndrome subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Head Injury subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Fall subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Arthropod Bite subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | | |
| Congenital, familial and genetic disorders Ichthyosis subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Nervous system disorders Tongue Biting subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Blood and lymphatic system disorders Iron Deficiency Anaemia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Neutropenia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Eye disorders Conjunctivitis Allergic subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | | |
| Ocular Hyperaemia subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Strabismus | | | |

| | | | |
|--|---------------------|--|--|
| subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Gastrointestinal disorders | | | |
| Abdominal Pain subjects affected / exposed occurrences (all) | 2 / 7 (28.57%) 2 | | |
| Diarrhoea subjects affected / exposed occurrences (all) | 3 / 7 (42.86%) 4 | | |
| Faeces Soft subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Vomiting subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Skin and subcutaneous tissue disorders | | | |
| Haemorrhage Subcutaneous subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Dermatitis Allergic subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Acne subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Urticaria subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Rash subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Miliaria subjects affected / exposed occurrences (all) | 1 / 7 (14.29%) 1 | | |
| Musculoskeletal and connective tissue disorders | | | |

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|-----------------------------------|----------------|--|--|
| Arthralgia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Infections and infestations | | | |
| Viral Infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Upper Respiratory Tract Infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Streptococcal Infection | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | | |
| occurrences (all) | 3 | | |
| Pneumonia Viral | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Pneumonia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Paronychia | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Otitis Media | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 2 | | |
| Nasopharyngitis | | | |
| subjects affected / exposed | 6 / 7 (85.71%) | | |
| occurrences (all) | 24 | | |
| Adenovirus Infection | | | |
| subjects affected / exposed | 3 / 7 (42.86%) | | |
| occurrences (all) | 3 | | |
| Conjunctivitis | | | |
| subjects affected / exposed | 2 / 7 (28.57%) | | |
| occurrences (all) | 2 | | |
| Conjunctivitis Bacterial | | | |

| | | | |
|-----------------------------|----------------|--|--|
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Herpes Virus Infection | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |
| Influenza | | | |
| subjects affected / exposed | 1 / 7 (14.29%) | | |
| occurrences (all) | 1 | | |

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

| Date | Amendment |
|------------------|--|
| 02 November 2021 | The reason for this protocol amendment was to clarify that the treatment of pulmonary arterial hypertension (PAH) worsening is not limited to a specific drug, but within the scope of routine clinical practice. |
| 25 November 2021 | The reason for this protocol amendment was to modify the amount of blood collected and to add time points for blood collection in pediatric participants < 2 years. Minor corrections and editorial revisions were also implemented. |
| 09 March 2022 | The reason for this protocol amendment was to change the inclusion/exclusion criteria, to update the method of administration and to modify the definition prohibited concomitant therapy. Minor corrections and editorial revisions were also implemented. |
| 09 March 2023 | The reason for this protocol amendment was to add allowance for Day 1 and to add interpretation of exclusion criteria, and to also allow for the use of local laboratory data for eligibility assessment. Minor corrections and editorial revisions were also implemented. |

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 interpretation of study results was limited by small sample size of only 7 participants. Study was not controlled, hence no comparison to Standard of Care (or placebo) was possible.

Notes: