Macitentan in pediatric pulmonary arterial hypertension: results from the phase 3 randomized controlled TOMORROW study

Rolf M.F. Berger[1], Dunbar D. Ivy[2], Julian I. Borissoff[3], Sofija Cerovic[3], Dénes Csonka[3], Tatiana Remeňová[3], Dominik Richard[3], Matthieu Villeneuve[3], Maurice Beghetti[4]

1. Center for Congenital Heart Diseases, Pediatric Cardiology, Beatrix Children's Hospital, University Medical Center Groningen, University of Groningen, Groningen, Netherlands; 2. Division of Pediatric Cardiology, Children's Hospital Colorado, Denver, CO, USA; 3. Johnson & Johnson, Allschwil, Switzerland; 4. Paediatric Cardiology Unit, University Hospitals of Geneva, Geneva, Switzerland.

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Disclosures

- The UMCG contracts with Johnson & Johnson, GSK and MSD for advisory board and steering committee activities by Prof. Rolf M. F. Berger and Prof. Rolf M. F. Berger received IIS-grants from Johnson & Johnson
- The University of Colorado contracts with Johnson & Johnson, GSK, and Merck for Dr Dunbar D. Ivy to be a consultant. Dr Dunbar D. Ivy receives travel and meeting support from Johnson & Johnson and MSD. The University of Colorado receives grants from Johnson & Johnson, GSK, and Merck. Dr Dunbar D. Ivy is a board member of the Association for Pediatric Pulmonary Hypertension
- Prof. Maurice Beghetti has received speaker fees and honoraria from Johnson & Johnson, Bayer, AOP, Acceleron, Merck, GSK, MSD, Gossamer and Altavant and has received research and educational grants from Johnson & Johnson
- Julian I. Borissoff, Sofija Cerovic, Dénes Csonka, Tatiana Remeňová, Dominik Richard, and Matthieu Villeneuve are employees of Johnson & Johnson and own shares of stock/stock options in Johnson & Johnson

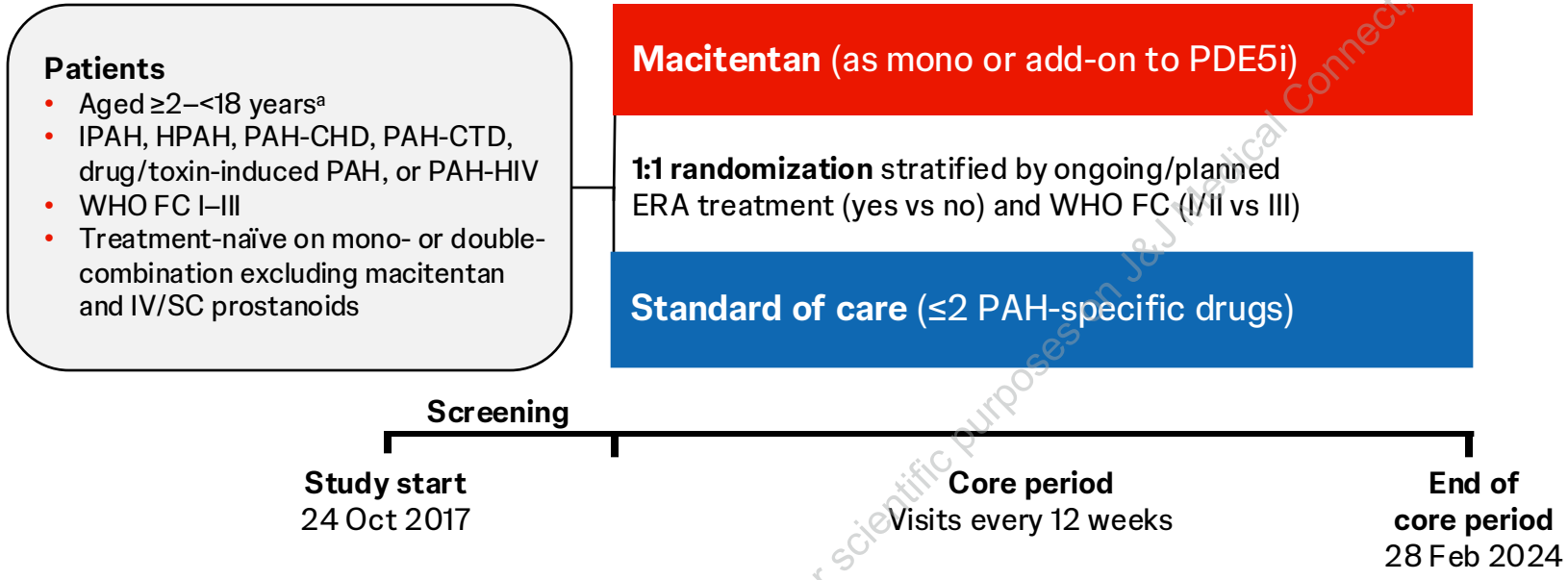
Background and Aim

- Pediatric PAH is a rare and life-threatening condition, and shows important similarities between adults and children[1–3]
- Despite several drugs being available, there remains an unmet medical need to improve outcomes in pediatric PAH[4,5]
- Macitentan 10 mg is an ERA that has been approved for the treatment of PAH in adult patients since 2013[6]
- **The TOMORROW study was designed to assess the pharmacokinetics of macitentan in pediatric patients and provide further information on efficacy and safety compared with standard of care**

1. Humbert et al. *Eur Heart J* 2022;43:3618–731; 2. Humbert et al. *Eur Respir J* 2022; 61:2200879; 3. Fleming et al. *Ther Innov Regul Sci* 2023;57:109–20; 4. Ploegstra et al. *Eur Heart J Qual Care Clin Outcomes* 2024;10:66–76; 5. Ivy et al. *Eur Respir J* 2024;2401345; 6. Opsumit SmPC 2024: https://www.ema.europa.eu/en/documents/product-information/opsumit-epar-product-information_en.pdf [Last accessed May 2025].
ERA, endothelin receptor antagonist; PAH, pulmonary arterial hypertension;.

TOMORROW (NCT02932410): macitentan vs standard of care in pediatric PAH

Prospective, multi-center, open-label, randomized, controlled, parallel-group, Phase 3 study



Following a disease progression event, background treatment could be escalated in both treatment arms, including use of IV or SC prostanoids, and patients in the standard of care arm could crossover to macitentan treatment

Primary endpoint (PK):

Steady state trough (pre-dose) plasma concentrations of macitentan and its active metabolite aprocitentan at Week 12

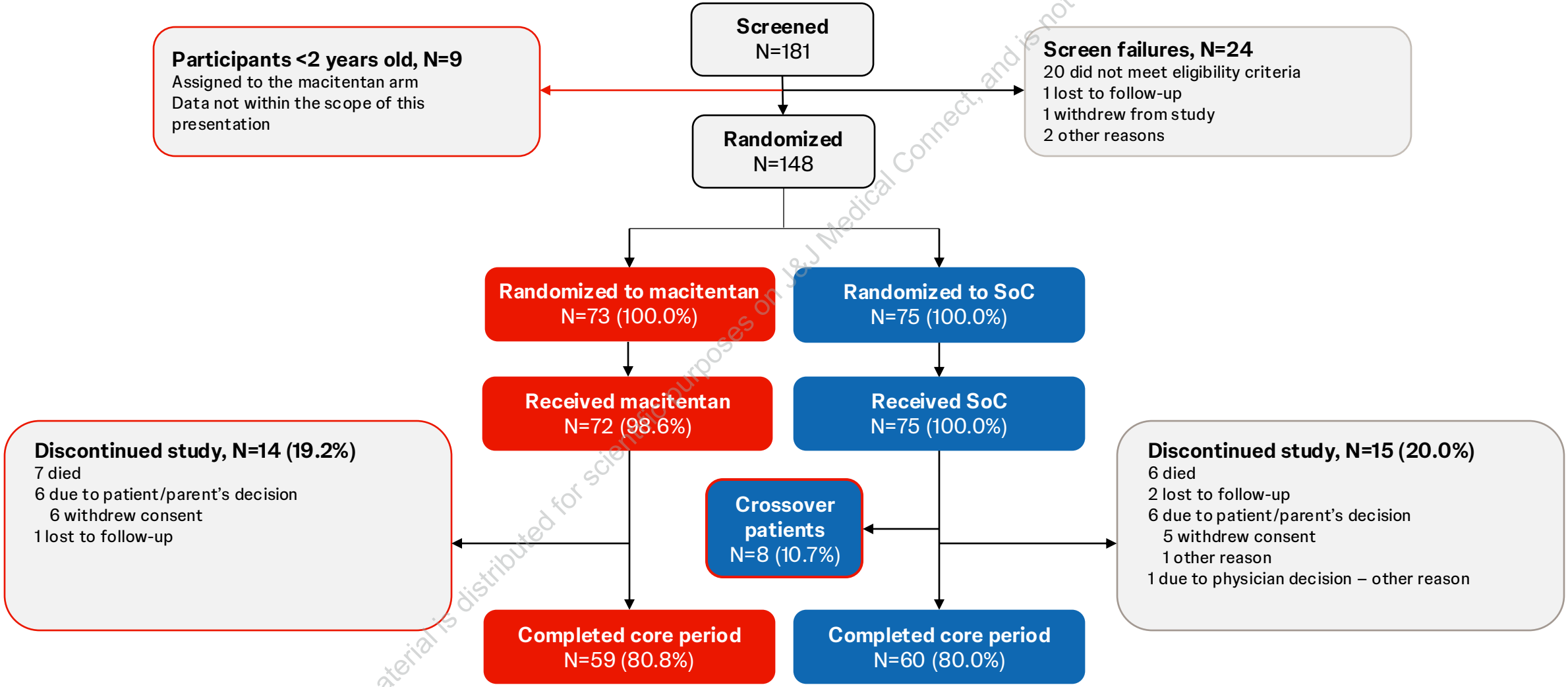
Secondary endpoints include:

- Time to first CEC-confirmed:
  - Disease progression
  - Hospitalization for PAH
  - Death due to PAH
- Time to first all-cause death
- Change from baseline to Week 24 in HRQoL (PedsQL™ v4.0 SF-15)
- Safety and tolerability

[a]Patients aged 1 month–<2 years were assigned as a cohort to the macitentan group without randomization and received 1 mg (1–<6 months) or 2.5 mg macitentan (6 months–<2 years). This presentation shows results in patients aged ≥2 years only.

CEC, clinical events committee; EOCP, end of core period; HPAH, hereditary PAH; HRQoL, health-related quality of life; IPAH, idiopathic PAH; IV, intravenous; PAH-CHD, PAH associated with congenital heart disease; PAH-CTD, PAH associated with connective tissue disease; PAH-HIV, PAH associated with human immunodeficiency virus; PDE5i, phosphodiesterase-5 inhibitor; PedsQL™ v4.0 SF15, PedsQL™ Pediatric Quality of Life Inventory version 4.0 short form 15; PK, pharmacokinetics; RHC, right heart catheterization; SC, subcutaneous; WHO FC, World Health Organization functional class.

Patient disposition



AE, adverse event; SoC, standard of care.

Demographics and baseline characteristics

Characteristic	Macitentan, N=73	Standard of care, N=75
Age category, n (%)		
≥2–<6 years	13 (17.8)	22 (29.3)
≥6–<12 years	29 (39.7)	32 (42.7)
≥12–<18 years	31 (42.5)	21 (28.0)
Female, n (%)	50 (68.5)	38 (50.7)
Race, n (%)		
White	44 (60.3)	32 (42.7)
Asian	15 (20.5)	22 (29.3)
Black or African American	1 (1.4)	1 (1.3)
Other	12 (16.4)	18 (24.0)
PAH etiology, n (%)		
Idiopathic PAH	35 (47.9)	36 (48.0)
Post-operative PAH	22 (30.1)	20 (26.7)
PAH with co-incidental CHD	14 (19.2)	12 (16.0)
PAH-CTD	1 (1.4)	2 (2.7)
Heritable PAH	1 (1.4)	5 (6.7)
Median (range) time from PAH diagnosis, years	1.34 (0.07–9.79)	0.94 (0.08–12.78)
WHO FC, n (%)		
I	19 (26.0)	18 (24.0)
II	41 (56.2)	42 (56.0)
III	13 (17.8)	15 (20.0)
Median (range) NT-proBNP[a], pmol/L	18.2 (2.4–3052.9)	21.2 (1.1–642.0)
Ongoing/planned treatment at randomization in ≥5% patients, n (%)		
ERA monotherapy	7 (9.6)	5 (6.7)
PDE5i monotherapy	39 (53.4)	36 (48.0)
ERA/PDE5i combination therapy	23 (31.5)	29 (38.7)

[a]NT-proBNP measurements were not available at baseline for seven patients in the macitentan arm and five patients in the standard of care arm.
CHD, congenital heart disease; NT-proBNP, N-terminal pro B-type natriuretic peptide.

Primary PK endpoint: Week 12

Overall		
Trough plasma concentration at steady state, ng/mL	**Macitentan, N=47**	**Aprocitentan, N=47**
Mean (SD)	185 (114.3)	983 (324.1)
Coefficient of variation, %	62	33
Median (range)	158 (6.8–581.0)	986 (339.0–1660.0)

Macitentan and aprocitentan exposure in this pediatric population was consistent with the known profile in adult patients[1]

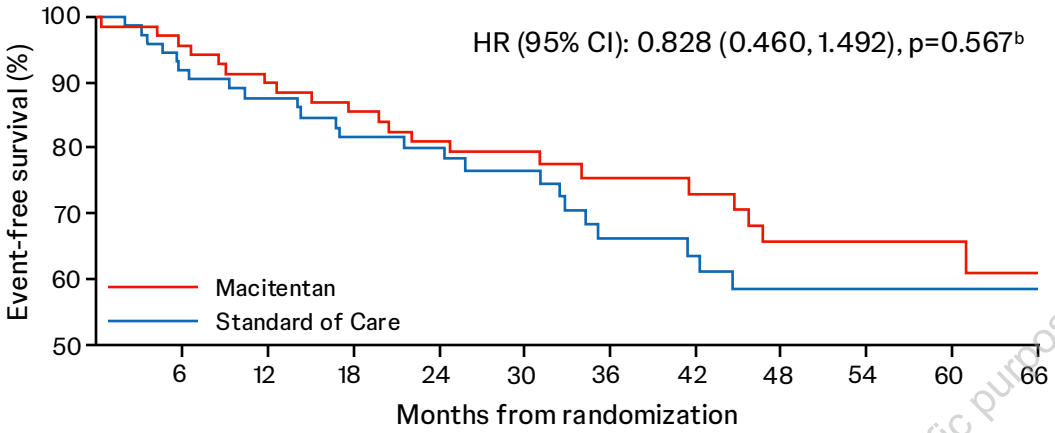
At steady-state conditions, PK samples were collected over 24 hours from patients ≥2 years old treated with macitentan. Collected PK data (both PK profiles and trough concentrations) were regularly assessed using non-linear mixed effects PK modelling during the course of the study to confirm the appropriateness of the selected dosing regimen in patients ≥2 years old.

1. Issac et al. *J Clin Pharmacol* 2017;57(8):997–1004.

SD, standard deviation.

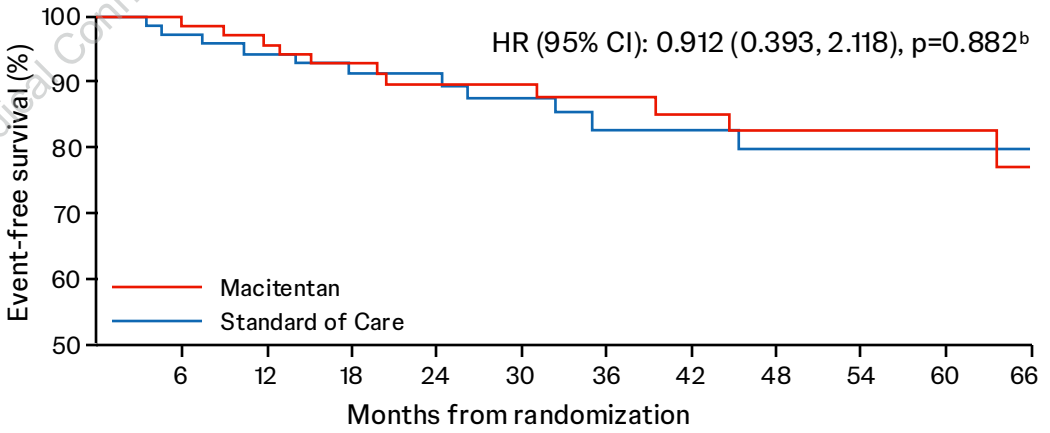
Secondary efficacy endpoints: morbidity

Kaplan–Meier curves of time to first CEC-confirmed disease progression[a] event



Macitentan											
at risk|	68	62	58	51	43	35	30	25	24	18	9
event(s)|	3	7	10	13	14	16	17	20	20	20	21
censored|	2	4	5	9	16	22	26	28	29	35	43
Standard of Care											
at risk|	67	60	54	48	41	28	25	19	17	11	4
event(s)|	6	9	13	14	16	21	22	24	24	24	24
censored|	2	6	8	13	18	26	28	32	34	40	47

Kaplan–Meier curves of time to first CEC-confirmed hospitalization for PAH



Macitentan											
at risk|	70	66	62	55	47	38	34	29	28	20	11
event(s)|	1	3	5	7	7	8	9	10	10	10	11
censored|	2	4	6	11	19	27	30	34	35	43	51
Standard of Care											
at risk|	71	63	59	50	43	30	29	23	21	13	5
event(s)|	2	4	6	6	8	10	10	11	11	11	11
censored|	2	8	10	19	24	35	36	41	43	51	59

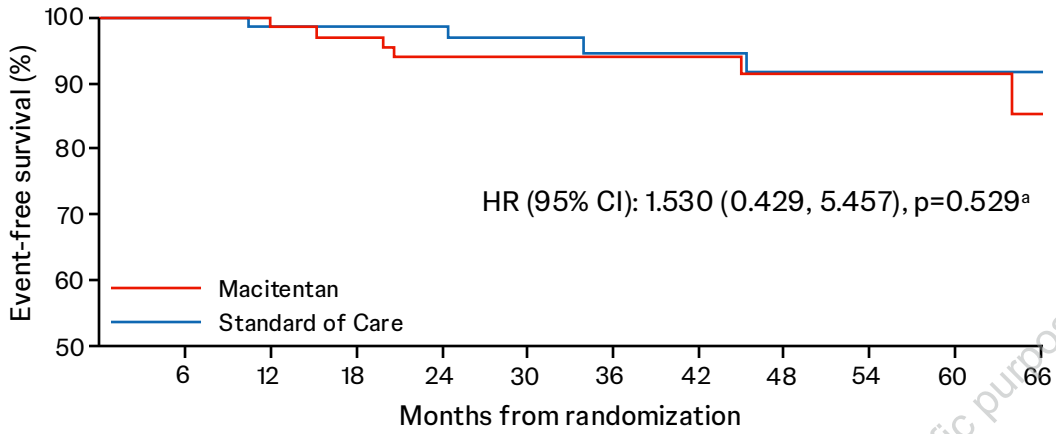
No statistically significant differences in these endpoints

HR for time to first CEC-confirmed disease progression event numerically in favor of macitentan

[a]Disease progression defined as death, atrial septostomy or Pott's anastomosis, or registration on lung transplant list, hospitalization due to worsening of PAH or clinical worsening of PAH, which was defined as need for, or initiation of, new PAH-specific therapy or intravenous diuretics or continuous oxygen use AND at least one of the following: worsening in WHO FC, or new occurrence or worsening of syncope (in frequency or severity as per medical judgment), or new occurrence or worsening of at least two PAH symptoms (i.e. dyspnea, chest pain, cyanosis, dizziness/near syncope or fatigue), or new occurrence or worsening of signs of right heart failure not responding to oral diuretics. [b]p values from a stratified log-rank test; HR from a Cox proportional hazards model adjusted for the two stratification factors.
CI, confidence interval; HR, hazard ratio.

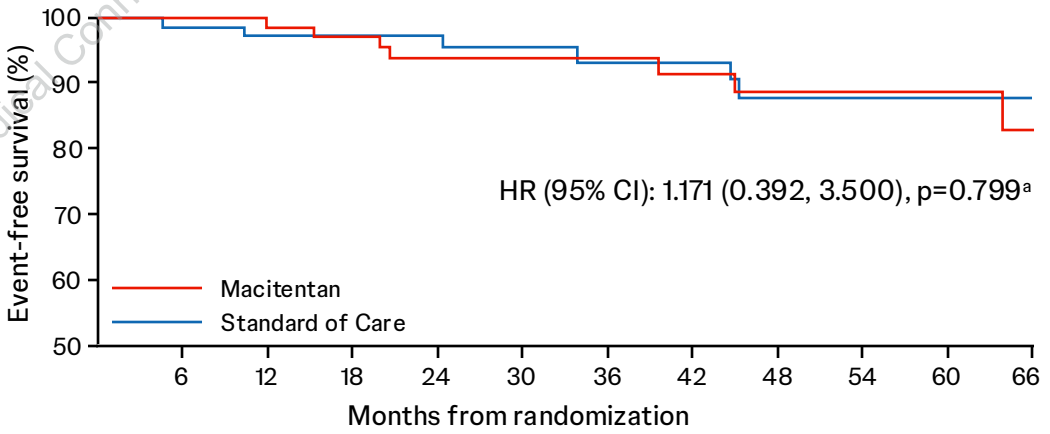
Secondary efficacy endpoints: mortality

Kaplan–Meier curves of time to CEC-confirmed death due to PAH



Macitentan											
at risk|	72	69	65	58	49	42	36	32	31	21	12
event(s)|	0	1	2	4	4	4	4	5	5	5	6
censored|	1	3	6	11	20	27	33	36	37	47	55
Standard of Care											
at risk|	73	70	65	58	50	38	36	30	28	17	8
event(s)|	0	1	1	1	2	3	3	4	4	4	4
censored|	2	4	9	16	23	34	36	41	43	54	63

Kaplan–Meier curves of time to all-cause death

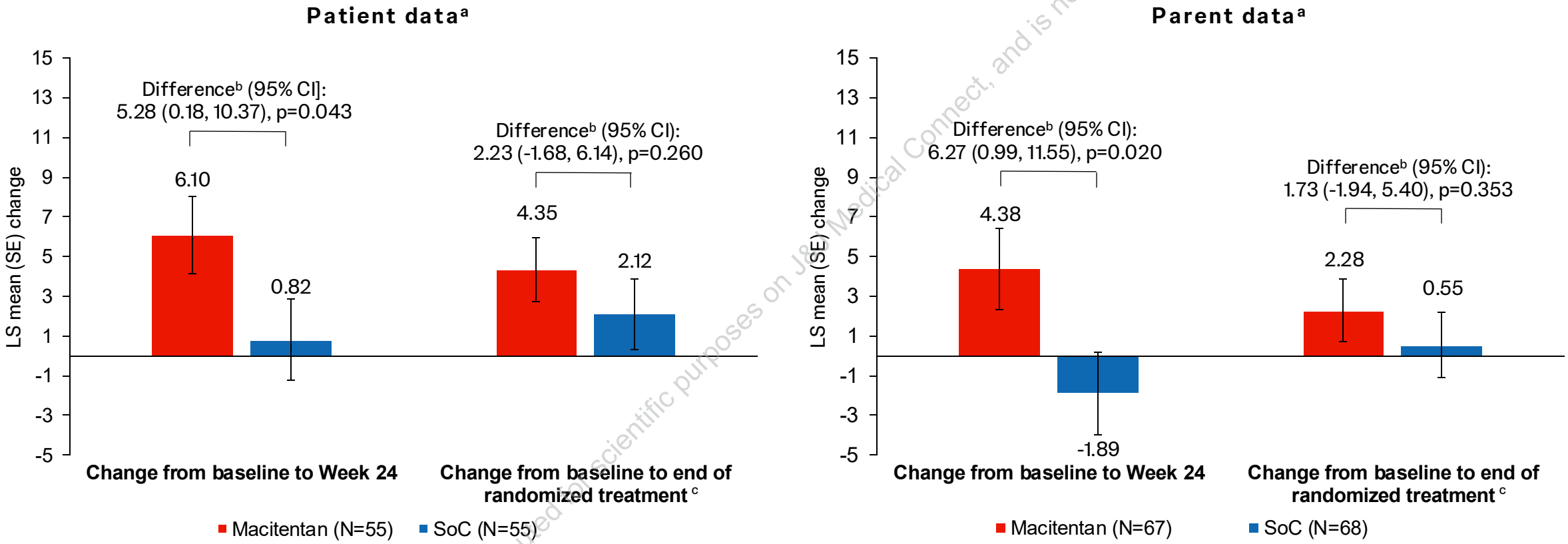


Macitentan											
at risk|	72	69	65	58	49	42	36	32	31	21	12
event(s)|	0	1	2	4	4	4	5	6	6	6	7
censored|	1	3	6	11	20	27	32	35	36	46	54
Standard of Care											
at risk|	73	70	65	58	50	38	36	30	28	17	8
event(s)|	1	2	2	2	3	4	4	6	6	6	6
censored|	1	3	8	15	22	33	35	39	41	52	61

No statistically significant differences in these endpoints
With limited number of patients, no difference in survival between groups

[a]p values from a stratified log-rank test. HR from a Cox proportional hazards model adjusted for the two stratification factors.

Secondary efficacy endpoints: Pediatric QoL Inventory version 4.0 SF15



Clinically meaningful improvements were observed in HRQoL for patients and parents at week 24

A positive change indicates improved quality of life.
[a]Treatment-by-visit interaction p value was statistically significant for parent data (p=0.049; patient p=0.086); [b]Repeated measures mixed model used with randomized treatment, visit, treatment-by-visit interaction, the two stratification factors (planned/ongoing ERA treatment [yes vs no) and WHO FC [I/II vs III] at randomization), and baseline value as fixed effects, and patient as random effect; [c]Change from baseline up to end of randomized treatment + 7 days or up to start of macitentan for crossover patients. This overall treatment effect is estimated using the same model excluding the treatment-by-visit interaction factor.
CI, confidence interval; LS, least squares; QoL SF15, quality of life short form 15; SE, standard error of the mean.

Safety profile

Consistent with the known profile in adults and/or background incidence in the target population

Characteristic	Macitentan, N=72	Standard of care, N=75
Exposure, patient-years	253.0	187.7
Patients with 1 or more of the following, n (%)		
AE	67 (93.1)	51 (68.0)
Macitentan-related AE[a]	15 (20.8)	N/A
Serious AE	26 (36.1)	16 (21.3)
Macitentan-related serious AE[a]	2 (2.8)	N/A
AE leading to death	0	1 (1.3)
AE leading to treatment discontinuation	4 (5.6)	2 (2.7)
Macitentan-related AE leading to treatment discontinuation[a]	4 (5.6)	N/A
COVID-19 associated AEs	12 (16.7)	8 (10.7)
Deaths[b], n (%)	7 (9.7)[b]	6 (8.0)
AEs observed with an exposure-adjusted incidence rate of ≥3 per 100 patient-years in macitentan arm (*post hoc*)		
Upper respiratory tract infection	9.09	6.39
Headache	5.53	4.79
Nasopharyngitis	5.53	5.86
COVID-19[c]	4.35	2.66
Gastroenteritis	3.16	0.53
Influenza	3.16	1.60
Exposure-adjusted incidence rates, per 100 patient-years (*post hoc*)		
Patients with 1 or more		
AEs and/or disease progression events	26.88	30.90
Serious AEs and/or serious disease progression events	11.86	10.66

Data are based on safety analysis set and on the period from randomization up to end of randomized macitentan or SoC + 30 days (or EOCP, whichever comes first), or, for crossover patients, up to start of macitentan or end of standard of care + 30 days, whichever comes first. [a]As assessed by the investigator; [b]None of the deaths were reported as related to macitentan; 6 deaths in the macitentan arm and 4 in the SoC arm were due to PAH disease progression confirmed by the CC. The primary cause of death in the macitentan arm were PAH (n=2), acute cardiac failure, congestive cardiac failure, hypertrophic cardiomyopathy, myocardial infarction and right ventricular failure (n=1 each). [c]Based on an additional analysis of all treatment-emergent AEs denoting COVID-19 infection, there was no meaningful difference between treatment arms.
COVID-19, coronavirus disease 2019.

Conclusions

- In the TOMORROW study, the primary endpoint (PK) confirmed the adequacy of the dosing regimen among pediatric patients with PAH
- TOMORROW was the first study in pediatric PAH to assess the long-term safety and efficacy of macitentan versus an active standard of care arm
  - The safety profile in pediatric patients with PAH was shown to be consistent with the known profile in adults
  - Although limited by patient numbers, there were no differences in time-to-event endpoints; the HR for time to first CEC-confirmed disease progression is numerically in favor of macitentan, suggesting a potential benefit
  - Clinically meaningful improvements in the quality-of-life for patients and parents were observed
- The TOMORROW study has provided evidence to confirm the dosing and safety of macitentan in pediatric PAH as well as potential efficacy signals