Efficacy and safety of macitentan tadalafil fixed dose combination in pulmonary arterial hypertension: results from the randomized controlled phase III A DUE study

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Background and objective

- In PAH, macitentan 10 mg and tadalafil 40 mg is recommended as combination therapy in newly diagnosed patients and in most patients at follow up[1,2]
- A fixed dose combination (FDC) of macitentan 10 mg and tadalafil 40 mg as a single-tablet combination therapy would offer a simplified treatment approach

Objective

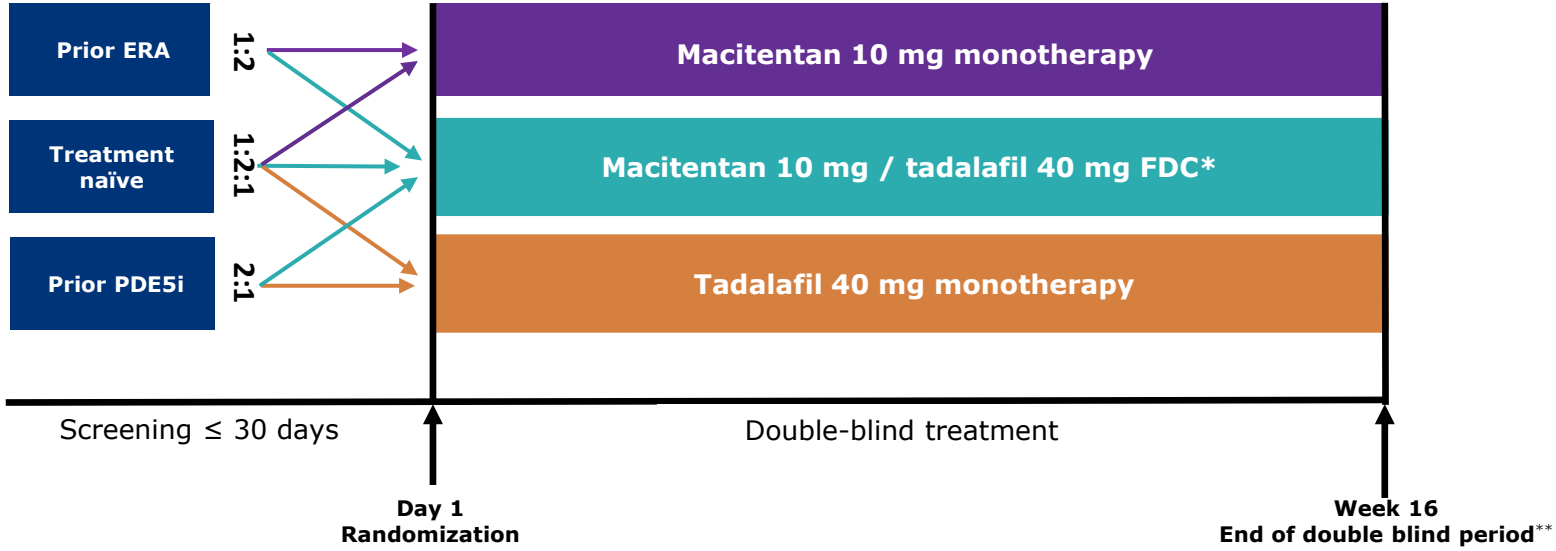
The A DUE trial evaluated the efficacy and safety of macitentan/tadalafil FDC versus macitentan and tadalafil monotherapies in patients with PAH

FDC: fixed-dose combination; PAH: pulmonary arterial hypertension

1. Humbert, *et al. Eur Heart J* 2022;43: 3618-3731;
2. Humbert, *et al. Eur Respir J* 2022;2200879.

Study design

- A DUE (NCT03904693): prospective, multicenter, double-blind, randomized, active-controlled, adaptive Phase III study



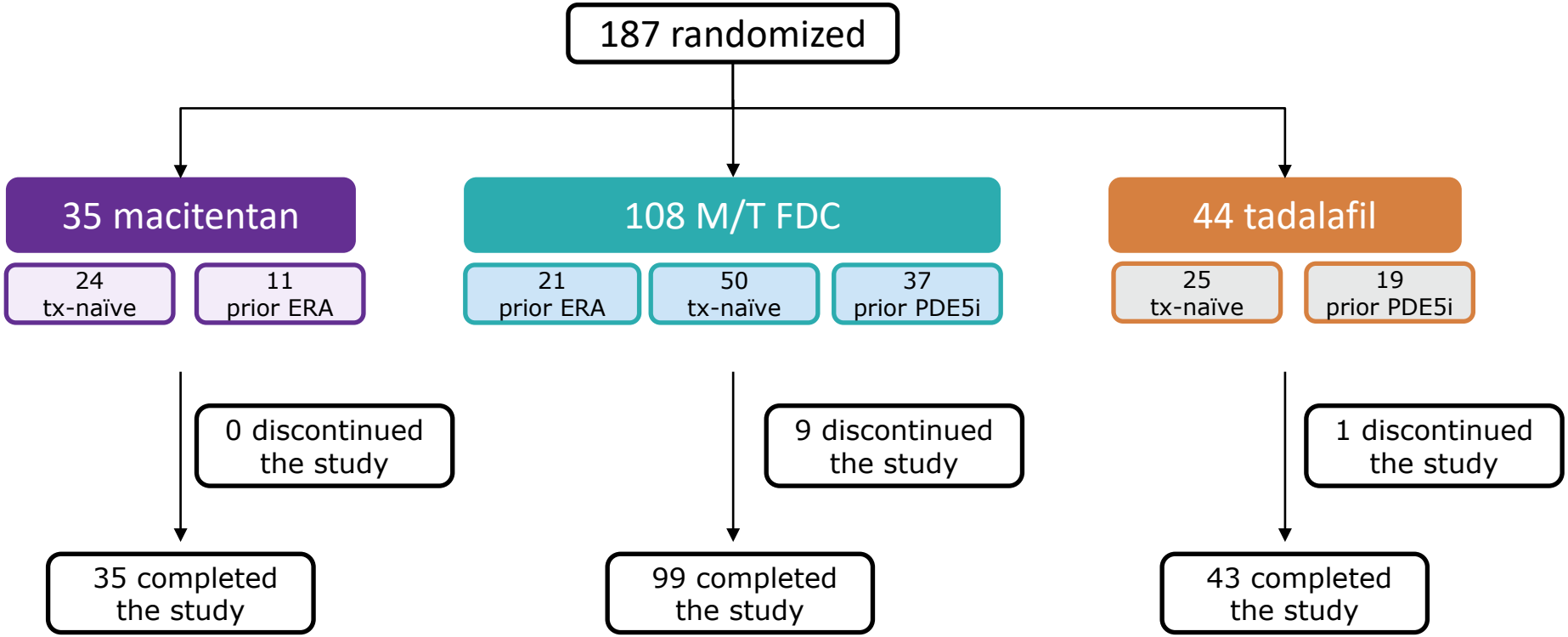
*Loose combination of macitentan 10 mg / tadalafil 20 mg given during Week 1 and macitentan 10 mg / tadalafil 40 mg during Week 2. From Day 15, M/T FDC given as a single tablet; tadalafil up-titration not performed in patients receiving prior PDE5i monotherapy. **After completion of the double-blind treatment period, M/T FDC to be administered open-label for 24 months. ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; PDE5i: phosphodiesterase type 5 inhibitor.

Patients and Outcome measures

- Adult PAH patients in WHO FC II or III
  - Treatment naïve
  - On stable dose (≥3 months) of an ERA (prior ERA) or a PDE5i (prior PDE5i)
- Efficacy endpoints at week 16:
  - **Primary endpoint**: Change in **PVR**, expressed as ratio of baseline
  - **Secondary endpoints** (hierarchical order): Change in **6MWD**, change in **PAH-SYMPACT** scores, absence of worsening in **WHO FC**
  - Treatment effects were calculated for
    - M/T FDC vs macitentan monotherapy
    - M/T FDC vs tadalafil monotherapy
- Safety and tolerability were monitored throughout the study

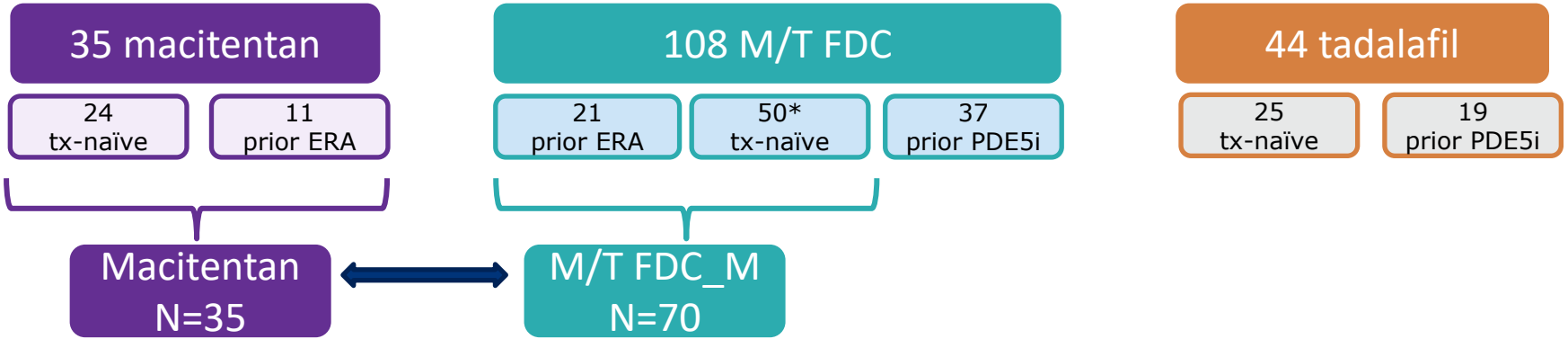
6MWD: six-minute walk distance; ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; PDE5i: phosphodiesterase type 5 inhibitor; WHO FC: World Health Organization Functional Class.

Patient disposition



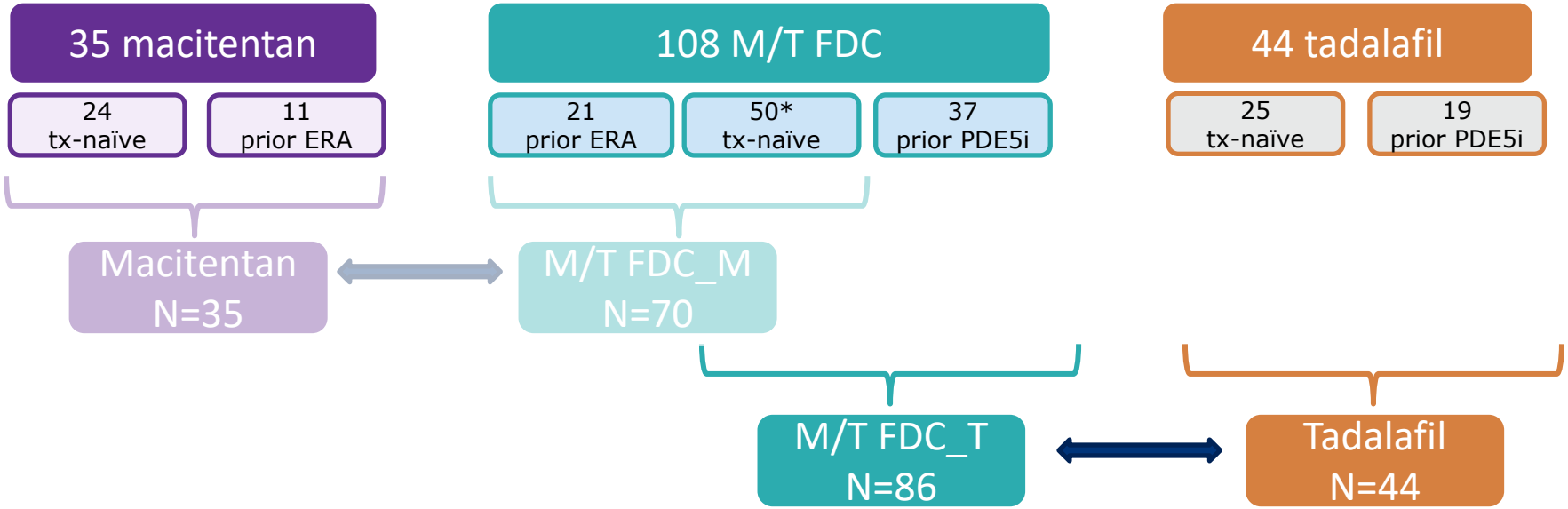
ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; PDE5i: phosphodiesterase type 5 inhibitor; tx naïve: treatment naïve.

M/T FDC versus monotherapies



*1 treatment-naïve patient did not receive any treatment and was not included in the M/T FDC_M group. ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; M/T FDC_M: M/T FDC group used for comparison vs macitentan; PDE5i: phosphodiesterase type 5 inhibitor; tx naïve: treatment naïve.

M/T FDC versus monotherapies



*1 treatment-naïve patient did not receive any treatment and was not included in the M/T FDC_T group. ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; M/T FDC_T: M/T FDC group used for comparison vs tadalafil; PDE5i: phosphodiesterase type 5 inhibitor; tx naïve: treatment naïve.

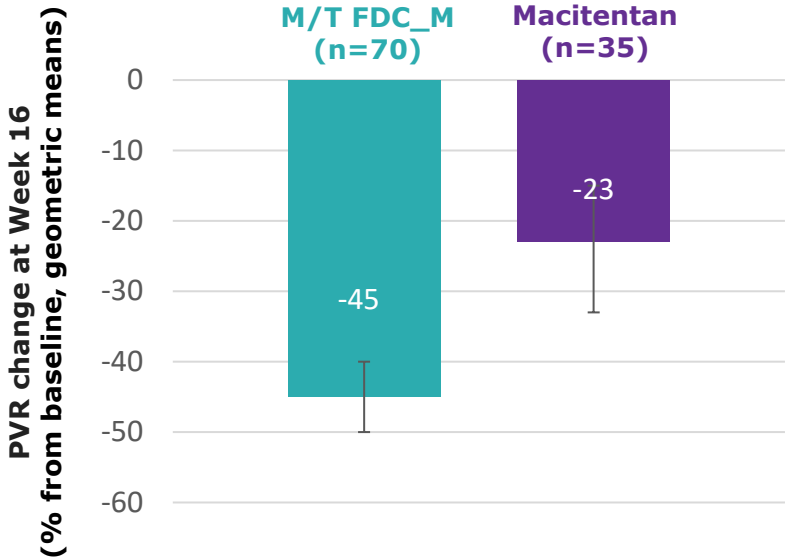
Demographics and baseline characteristics

Characteristic	M/T FDC_M (n=70)	Macitentan (n=35)	M/T FDC_T (n=86)	Tadalafil (n=44)
Female, n (%)	53 (75.7)	29 (82.9)	62 (72.1)	34 (77.3)
Age, mean ± SD, years	51.8 ±16.1	51.3 ± 15.9	48.7 ± 16.8	53.1 ± 13.7
Time from diagnosis of PAH, years				
Mean ± SD	1.49 ± 2.9	3.2 ± 6.2	1.4 ± 2.2	0.9 ± 2.3
Median (range)	0.14 (0.02; 14.8)	0.1 (0.03; 27.7)	0.16 (0.02; 10.7)	0.33 (0.02; 12.8)
PAH etiology, n (%)				
Idiopathic	36 (51.4)	16 (45.7)	47 (54.7)	20 (45.5)
PAH-CTD	27 (38.6)	13 (37.1)	29 (33.7)	16 (36.4)
6MWD, mean ± SD, m	354.3 ± 103.5	347.2 ± 88.8	351.0 ± 98.9	361.8 ± 70.4
WHO FC, n (%)				
II	42 (60.0)	11 (31.4)	51 (59.3)	19 (43.2)
III	28 (40.0)	24 (68.6)	35 (40.7)	25 (56.8)
PVR, dyn.sec/cm^5, mean ± SD	845.3 ± 636.6	827.2 ± 403.9	888.7 ± 639.1	812.4 ± 559
PAH therapy at baseline				
Treatment-naive, n (%)	49 (70%)	24 (68.5%)	49 (57%)	25 (57%)
Prior ERA/PDE5i, n(%)	21 (30%)	11 (31.5%)	37 (43%)	19 (43%)

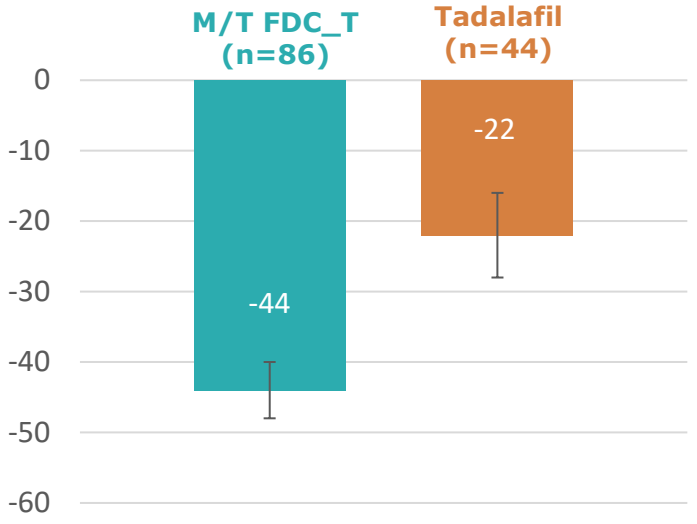
Data presented for the full analysis set. 6MWD: six-minute walk distance; ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; PAH: pulmonary arterial hypertension; PAH-CTD: PAH associated with connective tissue disease; PDE5i: phosphodiesterase type 5 inhibitor; PVR: pulmonary vascular resistance; WHO FC: World Health Organization Functional Class

Change in PVR from baseline at Week 16

M/T FDC_M vs Macitentan: PVR reduction 29%
Ratio of geometric means (95% CL):
0.71 (0.61, 0.82), **P≤0.0001**



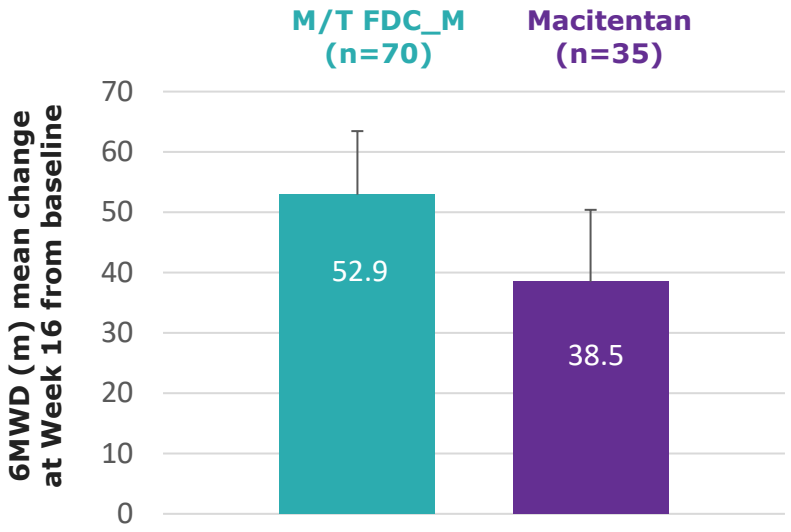
M/T FDC_T vs Tadalafil: PVR reduction 28%
Ratio of geometric means (95% CL):
0.72 (0.64, 0.80), **P≤0.0001**



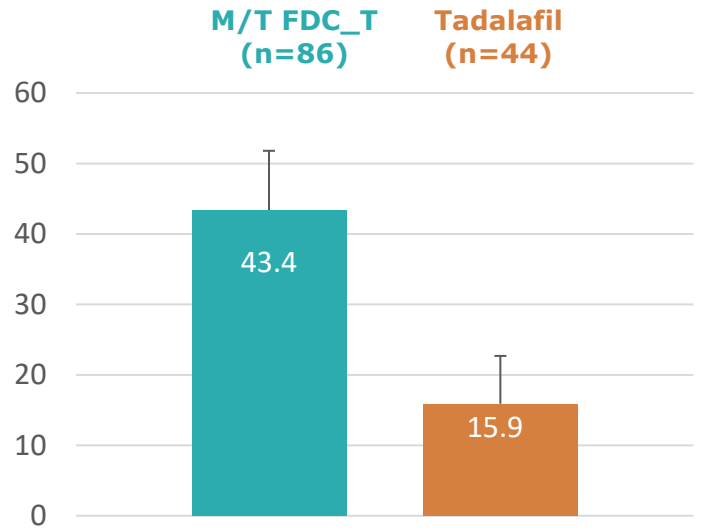
Median unbiased estimates and combination P-values with repeated CL and P-values adjusted for interim analysis are presented for the treatment effects. Geometric mean change and CL are presented on the figure. M/T FDC vs macitentan: M/T FDC_M group (n=70) comprised 49 treatment-naïve patients and 21 patients receiving prior ERA at randomization. M/T FDC vs tadalafil: M/T FDC_T group (n=86) comprised 49 treatment-naïve patients and 37 patients receiving prior PDE5i at randomization. CL: confidence limit; ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; M/T FDC_M: M/T FDC group used for comparison vs macitentan; M/T FDC_T: M/T FDC group used for comparison vs tadalafil; PDE5i: phosphodiesterase type 5 inhibitor; PVR: pulmonary vascular resistance.

Secondary endpoint: Change in 6MWD at Week 16

M/T FDC_M vs Macitentan:
Change in 6MWD (95% CL):
16.04m (-17.00, 49.08), P=0.380



M/T FDC_T vs Tadalafil:
Change in 6MWD (95% CL):
25.37m (-0.93, 51.59), P=0.059



Median unbiased estimates and combination P-values with repeated CL and P-values adjusted for interim analysis are presented for the treatment effects. Mean change and standard error is presented on the figure. M/T FDC vs macitentan: M/T FDC_M group (n=70) comprised 49 treatment-naïve patients and 21 patients receiving prior ERA at randomization. M/T FDC vs tadalafil: M/T FDC_T group (n=86) comprised 49 treatment-naïve patients and 37 patients receiving prior PDE5i at randomization. 6MWD: 6-minute walk distance; CL: confidence limit; ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed-dose combination; M/T FDC_M: M/T FDC group used for comparison vs macitentan; M/T FDC_T: M/T FDC group used for comparison vs tadalafil ; PDE5i: phosphodiesterase type 5 inhibitor; PVR: pulmonary vascular resistance.

Safety and tolerability

	M/T FDC (n=107)		Macitentan 10 mg (n=35)		Tadalafil 40 mg (n=44)	
Patients with ≥1 TAE*, n (%)	88 (82.2)		25 (71.4)		35 (79.5)	
Patients with ≥1 SAE, n (%)	15 (14.0)		3 (8.6)		4 (9.1)	
Patients with ≥1 AE leading to treatment discontinuation, n (%)	9 (8.4)		-		2 (4.5)	
Patients with ≥1 AESI, n (%)	**Any**	**Serious**	**Any**	**Serious**	**Any**	**Serious**
Edema / Fluid retention	22 (20.6)	1 (0.9)	5 (14.3)	-	7 (15.9)	-
Anemia / Hb decrease	20 (18.7)	1 (0.9)	1 (2.9)	-	1 (2.3)	-
Hypotension	8 (7.5)	1 (0.9)	-	-	-	-
Hepatic	1 (0.9)	-	1 (2.9)	-	4 (9.1)	-
ALT/AST, n (%)**						
≥3 x ULN	1 (1.0)		-		2 (4.5)	
Hemoglobin, n (%)**						
≤ 8 g/dL	2 (2.0)		-		-	
≤ 10 g/dL	11 (11.0)		1 (2.9)		-	

- Three patients died in the M/T FDC group (judged un-related to treatment)

Data presented for the safety set during the 16-week double blind period. *Most frequent TAEs: headache, edema, anemia, hemoglobin decrease, hypotension. **N=100 for M/T FDC group. AE: adverse event; AESI: AE of special interest; ALT: alanine aminotransferase; AST: aspartate aminotransferase; M/T FDC: macitentan/tadalafil fixed-dose combination; SAE: serious AE; TAE: treatment-emergent AE; ULN: upper limit of normal.

Conclusions

- **Primary endpoint met**: M/T FDC led to a highly significant and marked improvement in PVR vs macitentan and tadalafil monotherapies
- A trend for clinically relevant improvement in 6MWD in favor of M/T FDC was observed
- M/T FDC was well tolerated and consistent with the safety profile of macitentan and tadalafil
- A DUE supports M/T FDC, as a single-tablet combination therapy, for initial dual combination therapy and rapid escalation, in line with the ESC/ERS 2022 guidelines[1,2] on the use of dual combination therapy in PAH

6MWD: 6-minute walk distance; ESC/ERS: European Society of Cardiology/European Respiratory Society; M/T FDC: macitentan tadalafil fixed dose combination; PAH: pulmonary arterial hypertension; PVR: pulmonary vascular resistance

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