Effect on exercise capacity and long-term safety and tolerability of macitentan and tadalafil as a single-tablet combination in patients with pulmonary arterial hypertension from the A DUE open-label interim analysis

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Background and objective

- ERA and PDE5i combination therapy is recommended in PAH with low/intermediate risk[1,2]
- A DUE[3] evaluated a fixed-dose combination in a once-daily, single tablet of macitentan 10 mg + tadalafil 40 mg (M/T FDC)
  - M/T FDC significantly improved PVR (primary endpoint) vs monotherapy
    - Treatment effect: 29% vs macitentan ($p<0.0001$)
    - Treatment effect: 28% vs tadalafil ($p<0.0001$)
  - Numerical improvements in 6MWD and NT-proBNP
  - M/T FDC was well tolerated and adverse events were manageable

Objective
This interim analysis of the A DUE OL period evaluates the effect of M/T FDC on 6MWD, reduction of NT-proBNP and long-term safety/tolerability

6MWD: 6-minute walk distance; DB: double blind; ERA: endothelin receptor antagonist; M/T FDC: macitentan/tadalafil fixed dose combination; NT-proBNP: N-terminal pro-brain natriuretic peptide; OL: open-label; PAH: pulmonary arterial hypertension; PDE5i: phosphodiesterase 5 inhibitor; PVR: pulmonary vascular resistance. 1. Humbert M, et al. Eur Heart J 2022;43: 3618–3731; 2. Humbert M, et al. Eur Respir J 2022;61: 2200879; 3. Grünig E, et al. J Am Coll Cardiol 2024;83: 473–484.

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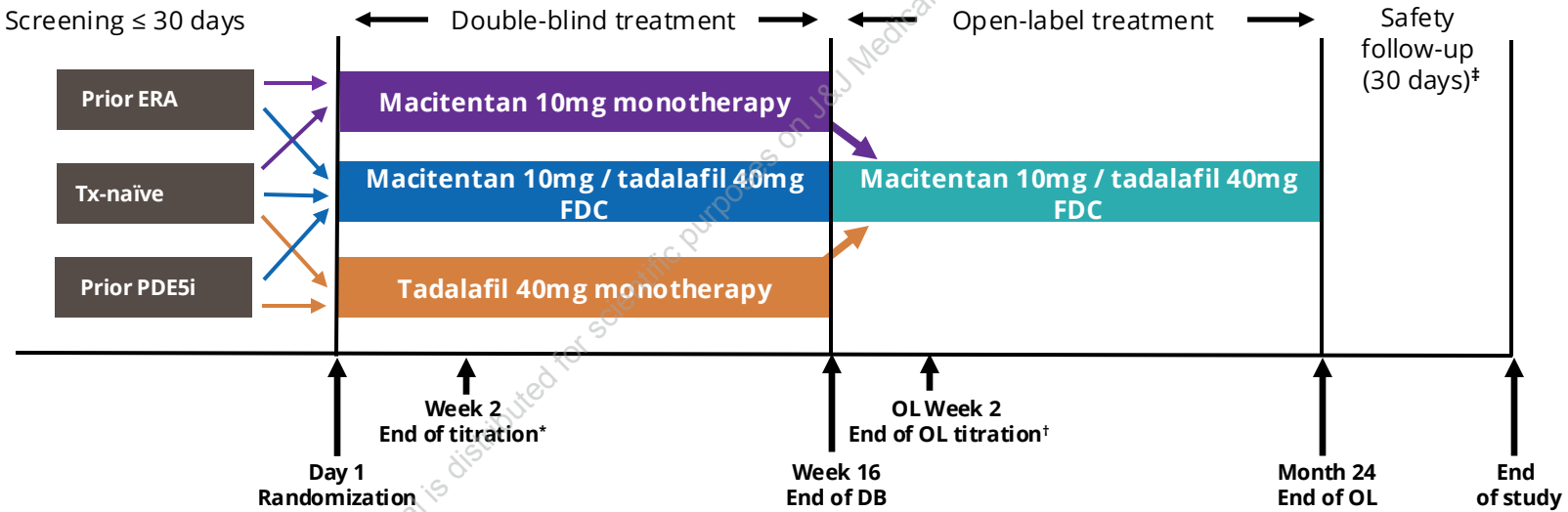
Methods and study design

- A DUE (NCT03904693) was a global, multicenter, double-blind, randomized, active-controlled, adaptive phase 3 study with a 16-week DB period (completed) and an ongoing 24-month OL period
- OL interim analysis: 28th April 2023



*Titration period: Individual tablets of macitentan 10mg and tadalafil 20mg given during Week 1 and macitentan 10mg and tadalafil 40mg 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. †OL titration period: Patients receiving macitentan 10 mg monotherapy during double-blind treatment received individual tablets of macitentan 10mg and tadalafil 20mg during Week 1 of OL, up-titrated to macitentan 10mg and tadalafil 40mg during Week 2; patients receiving tadalafil 40mg monotherapy during double-blind treatment received individual tablets of macitentan 10mg and tadalafil 40mg during Weeks 1 and 2 of OL. ‡Patients who prematurely discontinued double-blind study treatment continued until end of safety follow-up but did not receive open-label treatment. Tx-naïve: treatment naïve.

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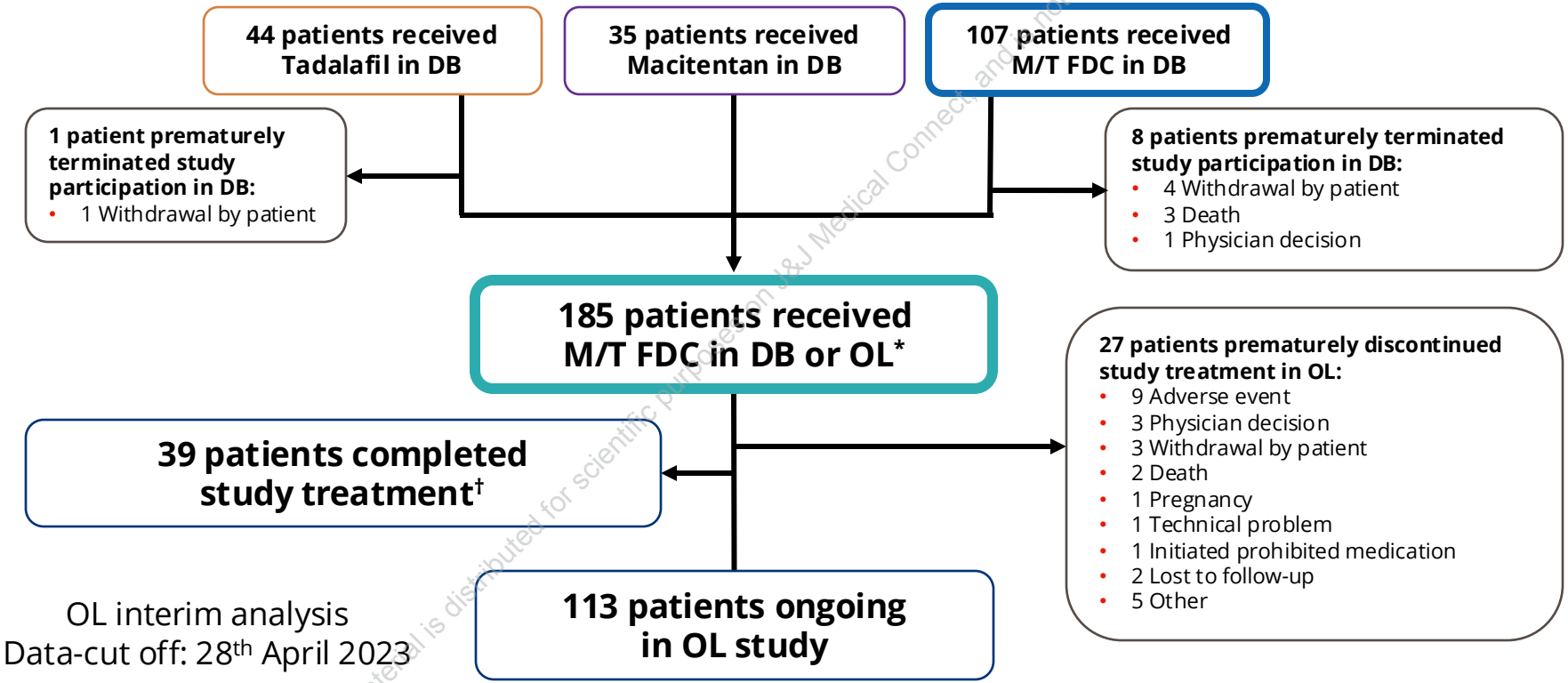
Patient disposition



OL interim analysis
Data-cut off: 28th April 2023

*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB or ongoing OL period. †Completed study treatment in the OL period: the patient took study drug up to Week 120.

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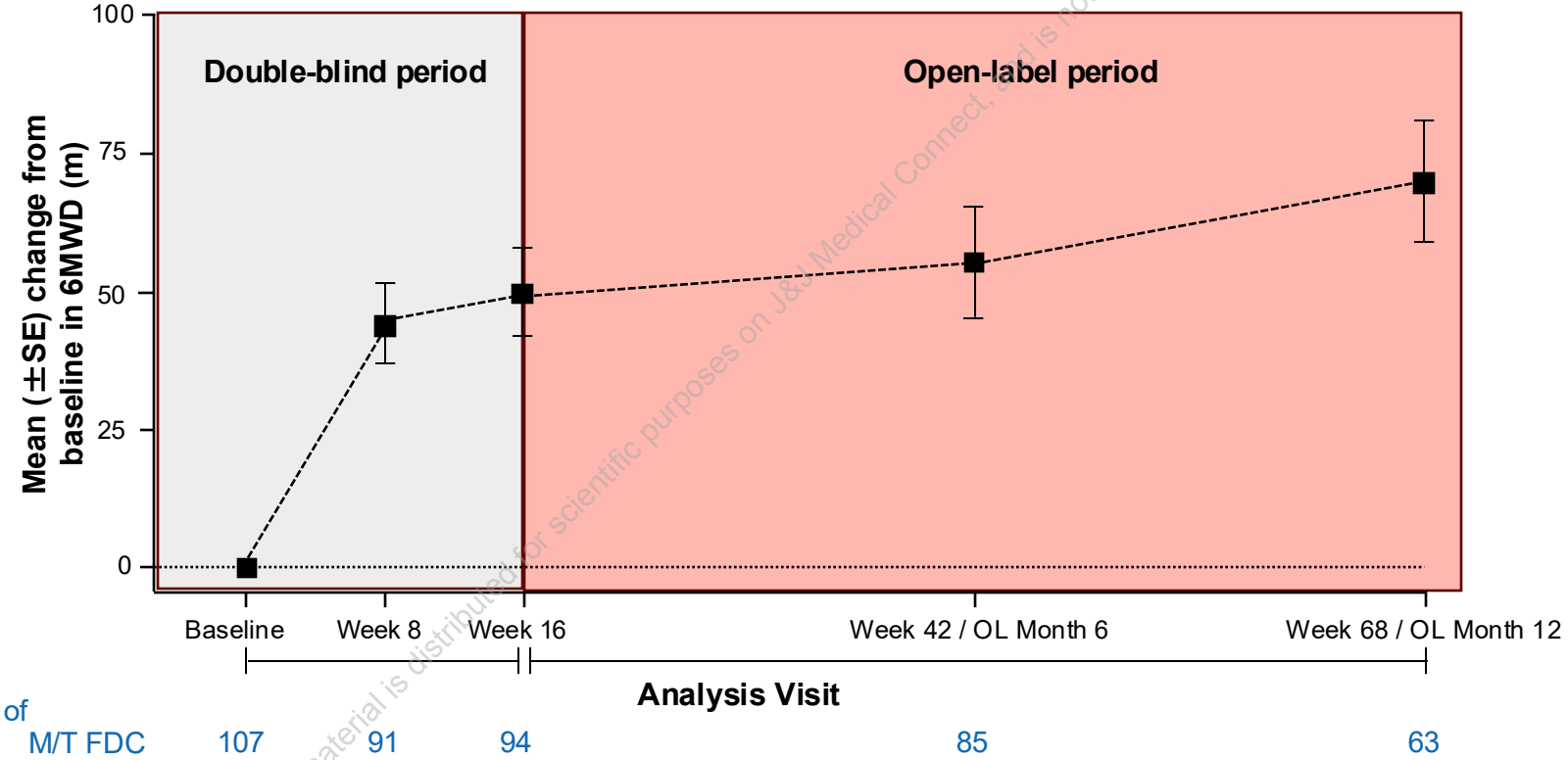
Demographics and baseline characteristics

Characteristic	M/T FDC (DB or OL)* N=185	M/T FDC (in DB)† N=107
Female, n (%)	144 (77.8)	82 (76.6)
Age, mean (SD), years	50.2 (15.4)	48.7 (15.8)
Time from diagnosis of PAH, years		
Mean (SD)	2.0 (3.6)	1.8 (2.8)
Median (range)	0.46 (0.02, 28.0)	0.41 (0.02, 14.84)
PAH etiology, n (%)		
Idiopathic	93 (50.3)	58 (54.2)
Heritable	9 (4.9)	4 (3.7)
Drug or toxin induced	3 (1.6)	1 (0.9)
Associated with		
CTD	65 (35.1)	36 (33.6)
HIV infection	6 (3.2)	4 (3.7)
Corrected CHD	6 (3.2)	3 (2.8)
Portal hypertension	3 (1.6)	1 (0.9)
6MWD, mean (SD), m	366 (91.4)	352 (96.1)
WHO FC, n (%)‡		
I	6 (3.2)‡	0
II	109 (58.9)	65 (60.7)
III	70 (37.8)	42 (39.3)
PVR, mean (SD), dyn.sec/cm^5	777 (548.0)	882 (627.2)
NT-proBNP, median (range), ng/L**	435 (51, 23662)	426 (51, 23662)

*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB or ongoing OL period (April 2023 data cut); Baseline was defined as the last assessment prior to the first intake of M/T FDC (or titration dose) in either the DB or OL period. †Data are presented for patients who received at least one dose of M/T FDC in the DB period[1]; Baseline was defined as the last non-missing assessment performed on or before the DB study treatment start date. ‡A DUE included patients in FC II and III only; FC I patients here reflect patients who improved while in the study. **M/T FDC (DB or OL) n=179; M/T FDC (in DB) n=104. CHD: congenital heart disease; CTD: connective tissue disease; HIV: human immunodeficiency virus, SD: standard deviation; WHO FC: World Health Organization Functional Class. 1. Grünig E, et al. J Am Coll Cardiol 2024;83: 473–484.

Sustained improvement in 6MWD at 12 months in the OL period



Data are presented for patients with non-missing values at both baseline and postbaseline who started treatment with M/T FDC in the double-blind period (N=107). SE: standard error.

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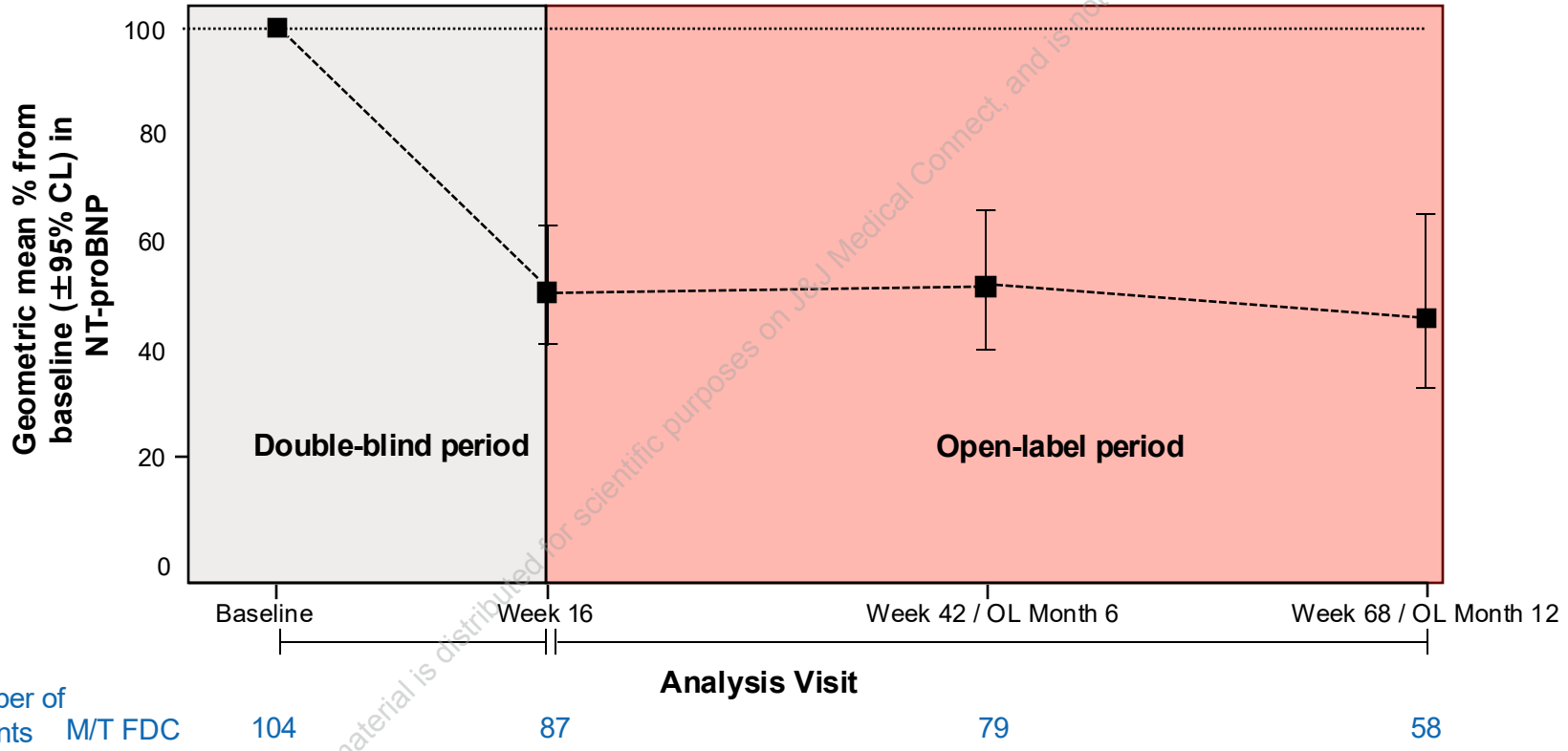
NT-proBNP was reduced during the DB and remained stable up to 12 months in the OL period



Data are presented for patients with non-missing values at both baseline and postbaseline who were randomized to receive M/T FDC for the double-blind period (N=104). CL: confidence limit.

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All-cause and PAH-related hospitalizations in the DB and OL period

	M/T FDC (in DB)* N=107
Patient-years in study	154.3
Exposure, weeks, median (range)	74.43 (0.6, 151.6)
All-cause hospitalizations	
Hospitalizations, per person-year	0.3
Inpatient hospital days, per person-year	2.8
PAH-related hospitalizations	
Hospitalizations, per person-year	0.1
Inpatient hospital days, per person-year	0.9

Medical encounters considered hospitalizations were: intensive care unit, hospice/palliative care unit, hospital inpatient department, long term care facility and rehabilitation center. Hospitalization events were not clinical event committee adjudicated. *Data are presented for patients who received at least one dose of M/T FDC in the DB period (April 2023 data cut).

Safety and tolerability (1)

	M/T FDC (DB or OL)* N=185
Exposure, weeks, median (range)	75.4 (0.6, 151.6)
Patients with ≥1 adverse event, n (%)	173 (93.5)
Patients with ≥1 serious adverse event, n (%)	49 (26.5)
Patients with ≥1 adverse event leading to premature discontinuation, n (%)	17 (9.2)
Adverse events (Preferred Term), n (%)†	
COVID-19	43 (23.2)
Headache	27 (14.6)
Peripheral edema	21 (11.4)
Anemia	20 (10.8)
Patients with adverse events of special interest (Grouped Terms), n (%)	
Anemia	43 (23.2)
Edema and fluid retention	34 (18.4)
Hypotension	12 (6.5)
Hepatic disorders	10 (5.4)

*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB or ongoing OL period. Treatment emergent safety events with M/T FDC are described; treatment-emergent defined as from first intake of study treatment up to end of treatment, + 30 days post- treatment. †Occurring in >10% patients.

Safety and tolerability (2)

	M/T FDC (DB or OL)* N=185
Patients with low hemoglobin, n (%)†	
<8 g/dL	4 (2.3)
<10 g/dL	26 (14.7)
Decrease from baseline ≥5g/dL	5 (2.8)
Patients with liver abnormalities, n (%)‡	
ALT/AST ≥3 x ULN	7 (3.9)
Deaths (Preferred Term), n (%)**	4 (2.2)
Gastroenteritis clostridial (DB)	1 (0.5)
Cardiac failure (DB)	1 (0.5)
Right ventricular failure (OL)	1 (0.5)
Respiratory failure (OL)	1 (0.5)

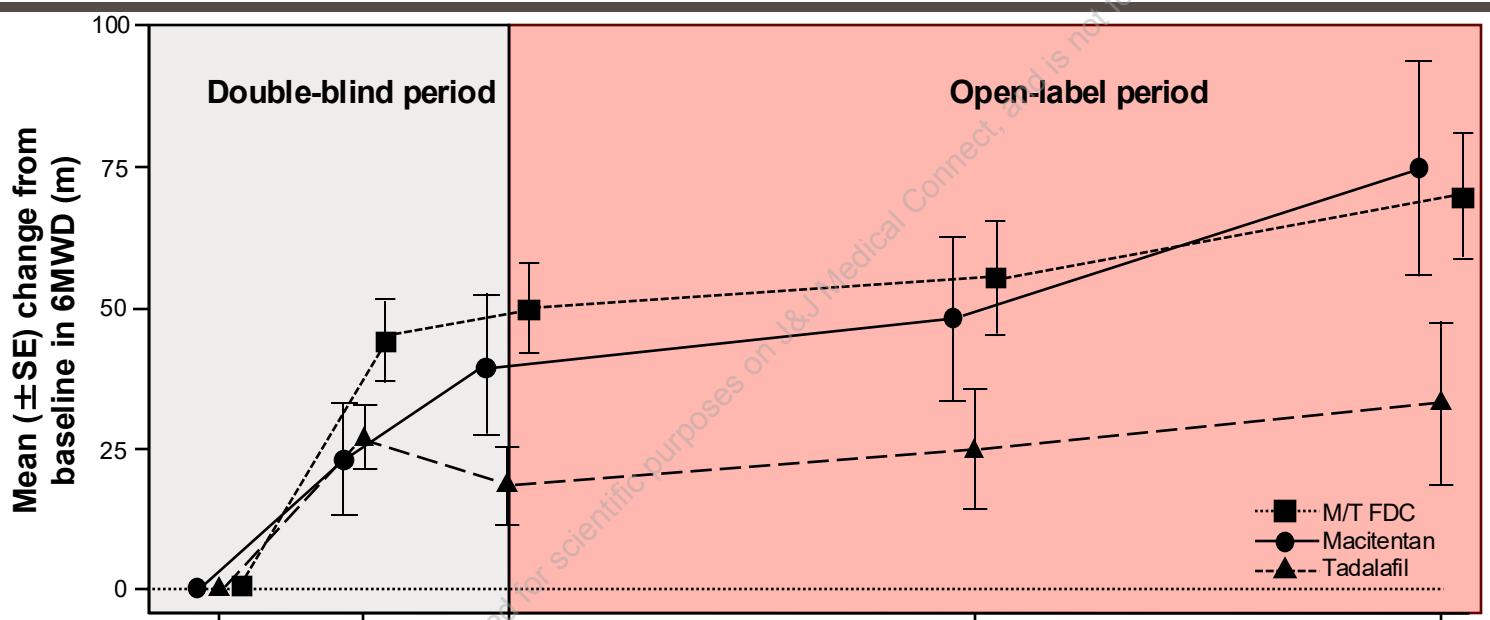
- In total, there were 6 deaths: all were evaluated as **unrelated to treatment** - 2 were non-treatment emergent

*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB or ongoing OL period. †n=177. ‡n=178. **Not including 2 deaths (COVID-19 pneumonia and cerebrovascular accident) that occurred >30 days after end of treatment (97 and 398 days, respectively). ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

Conclusions

- In the A DUE open-label interim analyses, single-tablet combination therapy with macitentan and tadalafil led to sustained improvement in 6MWD at 12 months in the OL period
- The cardiac biomarker NT-proBNP decreased during the DB period and remained stable up to 12 months in the OL period
- With M/T FDC the PAH-related hospitalization rate was 0.1 per person-year
- Long-term safety/tolerability of M/T FDC in these interim OL analyses was in line with the known safety profiles of macitentan and tadalafil as separate tablets and no new or unexpected safety concerns were revealed

Change from baseline in 6MWD



Number of patients	Baseline	Week 8	Week 16	Week 42 / OL Month 6	Week 68 / OL Month 12
M/T FDC	107	91	94	85	63
Macitentan	35	31	34	32	21
Tadalafil	44	42	43	36	25

Data are presented for patients with non-missing values at both baseline and postbaseline who were randomized to receive M/T FDC, macitentan or tadalafil for the double-blind period.

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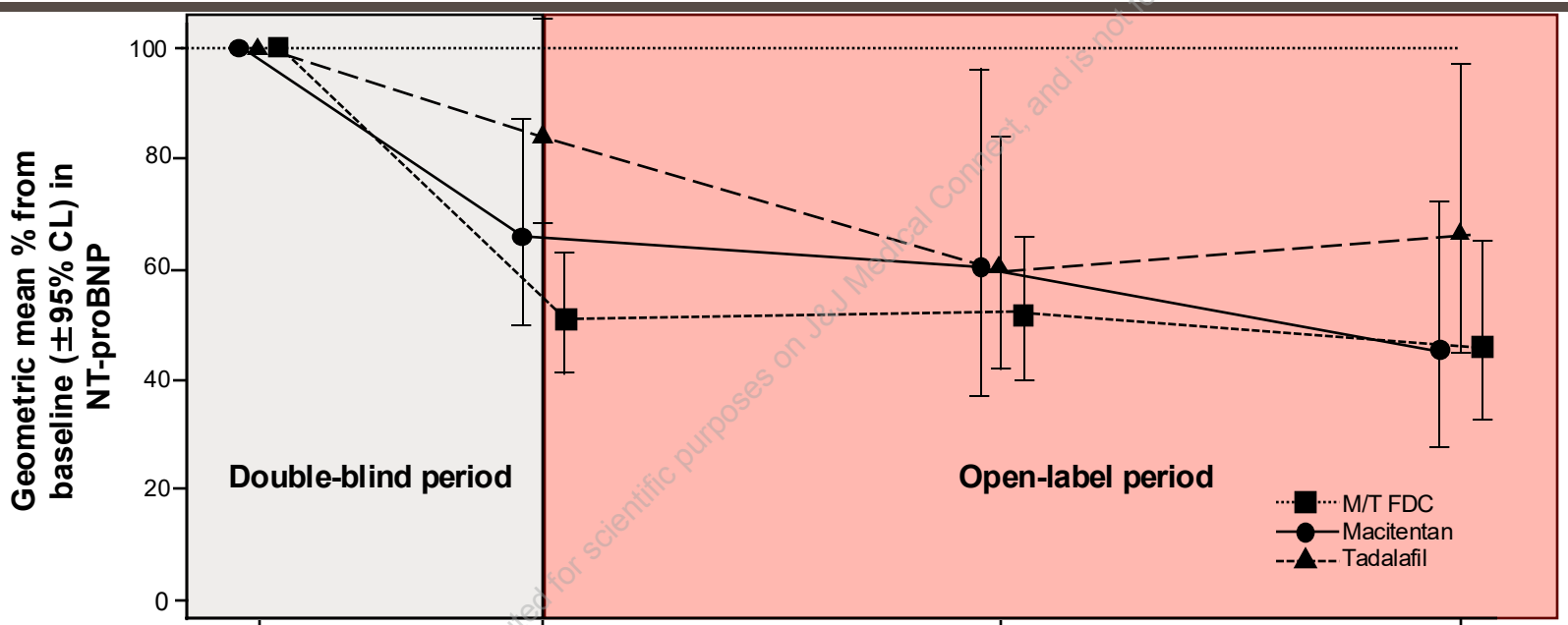
Change from baseline in NT-proBNP



Number of patients						
	M/T FDC	104	87	79	58	41
	Macitentan	30	27	28	21	14
	Tadalafil	42	41	35	26	20

Data are presented for patients with non-missing values at both baseline and postbaseline who were randomized to receive M/T FDC, macitentan or tadalafil for the double-blind period.

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All-cause and PAH-related hospitalizations in the DB and OL period

	Macitentan (in DB)* N=35	Tadalafil (in DB)* N=44†	M/T FDC (in DB)‡ N=107
Patient-years in study	58.1	72.4	154.3
Exposure, weeks, median (range)	71.29 (4.7, 120.0)	78.29 (1.0, 146.6)	74.43 (0.6, 151.6)
All-cause hospitalizations			
Hospitalizations, per person-year	0.33	0.33	0.34
Inpatient hospital days, per person-year	2.0	11.7	2.8
PAH-related hospitalizations			
Hospitalizations, per person-year	0.10	0.06	0.10
Inpatient hospital days, per person-year	0.5	10.3	0.9

Medical encounters considered hospitalizations were: intensive care unit, hospice/palliative care unit, hospital inpatient department, long term care facility and rehabilitation center. Hospitalization events were not clinical event committee adjudicated. *Data are presented for patients who received either macitentan or tadalafil monotherapy during the DB period, and M/T FDC upon entering the OL period (April 2023 data cut). †Includes one obese patient with ongoing asthma and hypothyroidism who entered a rehabilitation center to improve lung function and quality of life four weeks after treatment start for more than 700 days. ‡Data are presented for patients who received at least one dose of M/T FDC in the DB period (April 2023 data cut).