Long-term treatment with single-tablet combination of macitentan and tadalafil in pulmonary arterial hypertension (PAH): final results from the A DUE open-label extension

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Background

- ERA and PDE5i combination therapy is a core component of recommended treatment for patients with PAH across all risk groups[1,2]
- In the 16-week double-blind (DB) period, A DUE[3] evaluated a fixed-dose combination of macitentan 10 mg + tadalafil 40 mg (M/T FDC) in a once-daily, single tablet
  - M/T FDC significantly improved PVR (primary endpoint) vs each monotherapy
    - Treatment effect: 29% vs macitentan ($p<0.0001$)
    - Treatment effect: 28% vs tadalafil ($p<0.0001$)
  - Numerical improvements in 6MWD and decreases in NT-proBNP were observed
  - Safety was consistent with macitentan and tadalafil as individual tablets

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; 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* 2023;61: 2200879; 3. Grünig E, et al. *J Am Coll Cardiol* 2024;83: 473–484.

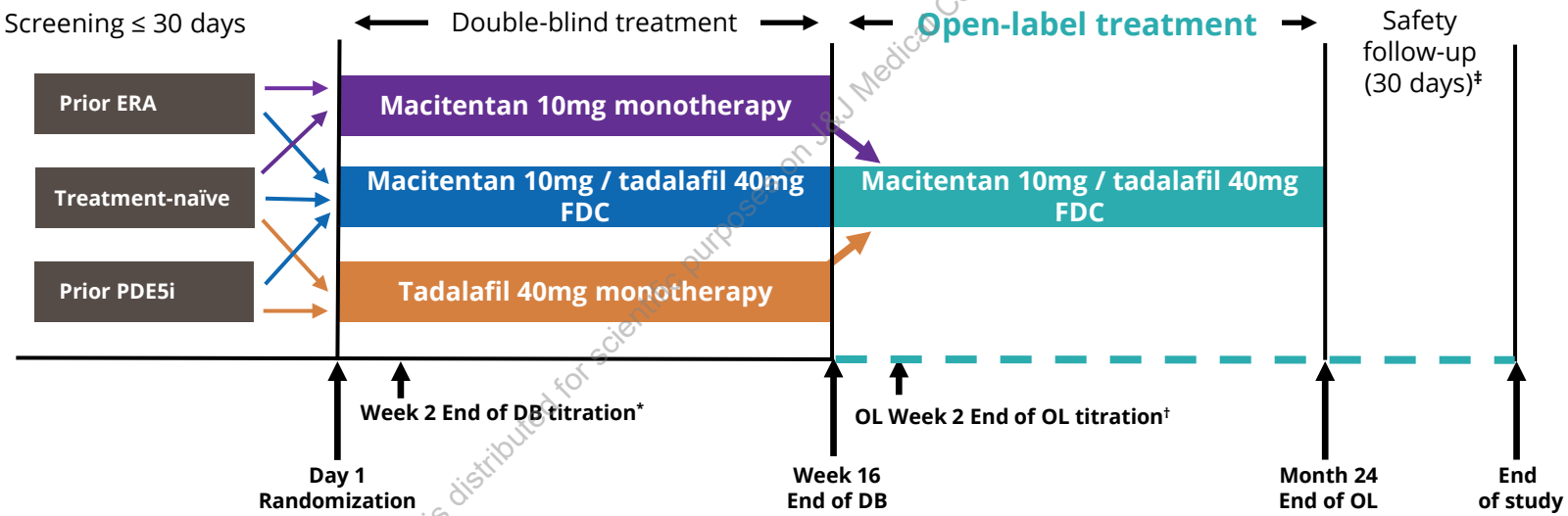
Objective

This final analysis of the A DUE open-label (OL) period evaluates the long-term effect of M/T FDC on survival, exercise capacity, reduction of NT-proBNP, hospitalizations, and safety/tolerability

OL: open-label.

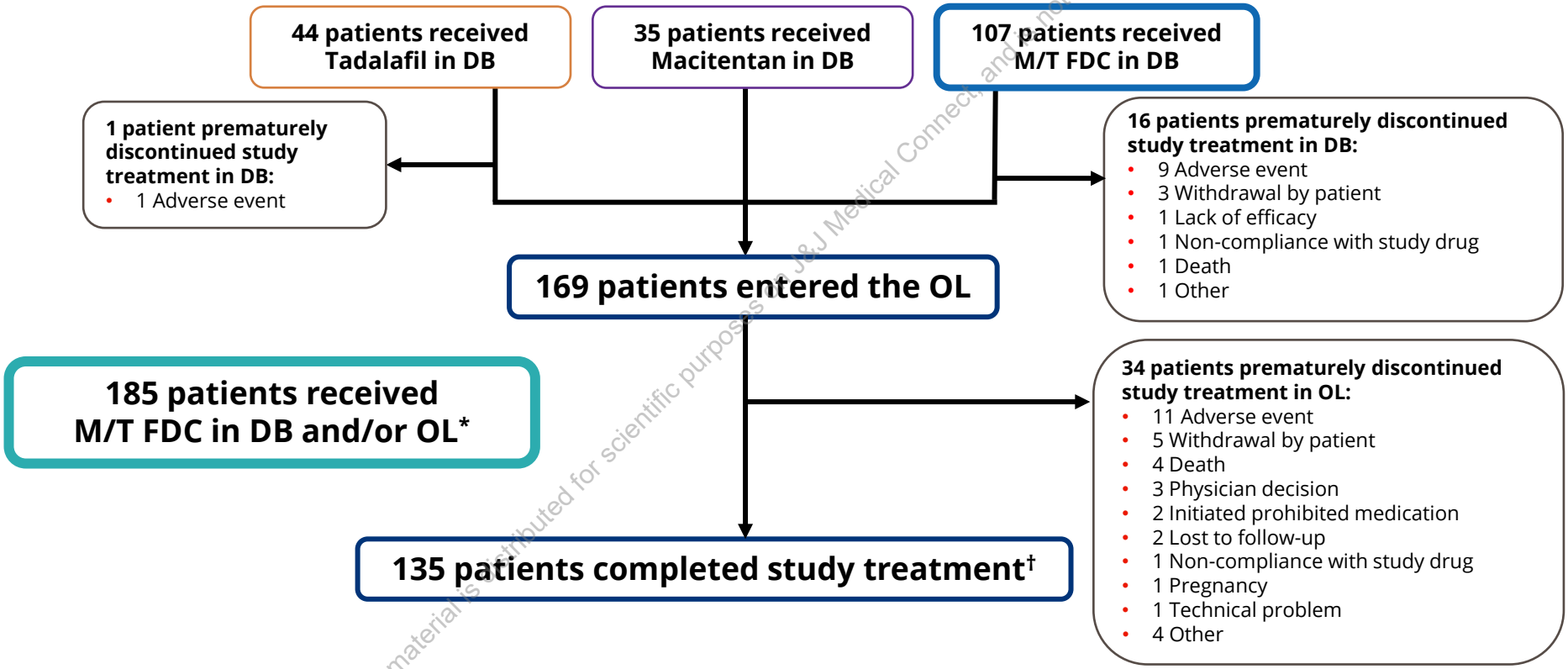
Methods and study design

- A DUE was a global, multicenter, double-blind, randomized, active-controlled, adaptive phase 3 study with a 16-week double-blind period and a 24-month open-label period (NCT03904693)



*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 DB 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 DB treatment received individual tablets of macitentan 10mg and tadalafil 40mg during Weeks 1 and 2 of OL; patients receiving M/T FDC in the DB remained on M/T FDC for the OL. ‡Patients who prematurely discontinued the DB study treatment continued until end of safety follow-up but did not receive OL treatment.

Patient disposition



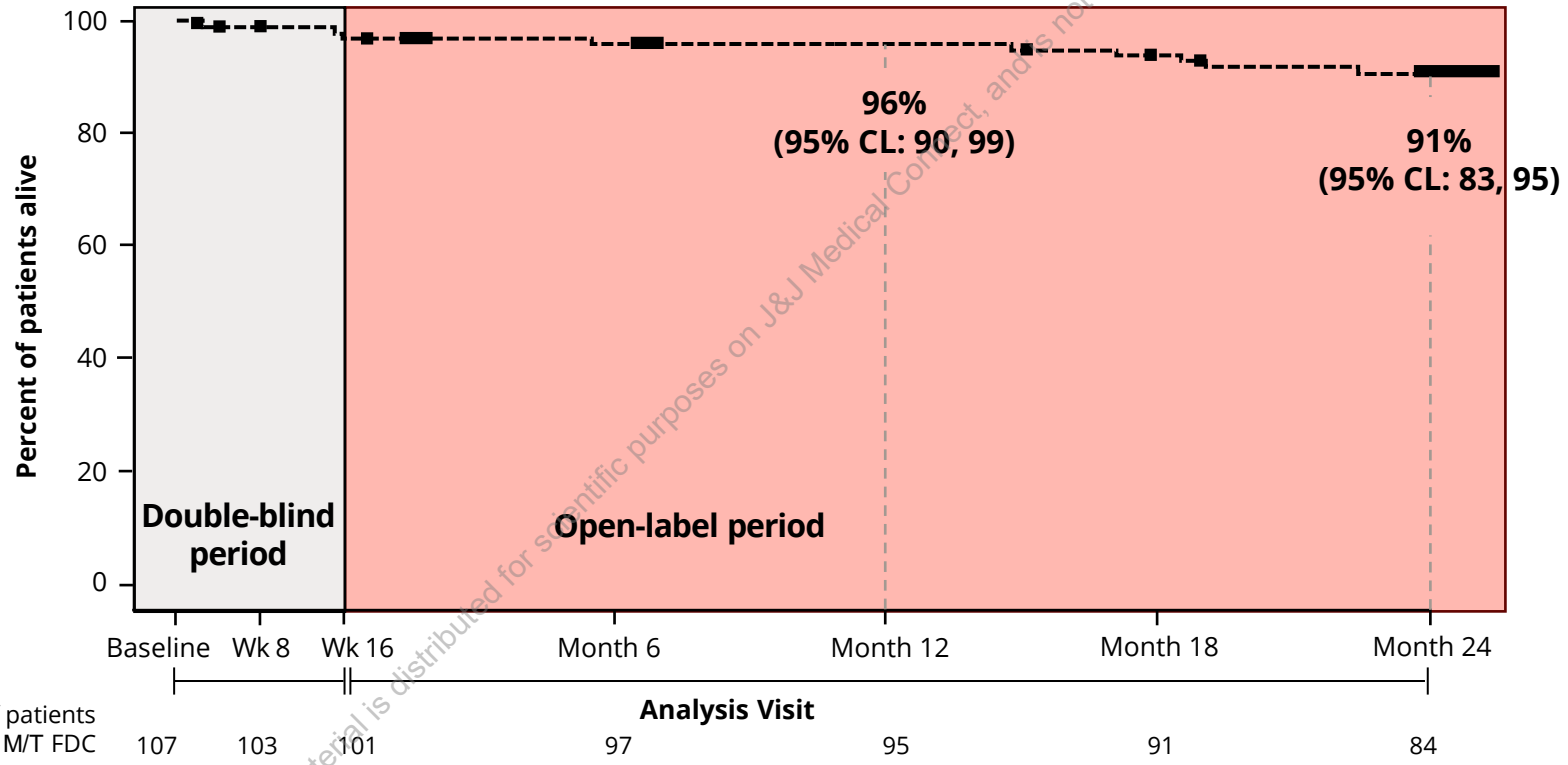
*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB and/or OL period. †Completed study treatment in the OL period: the patient took study drug up to Week 120.

Demographics and baseline characteristics

Characteristic	M/T FDC (DB and/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, 14.8)
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)

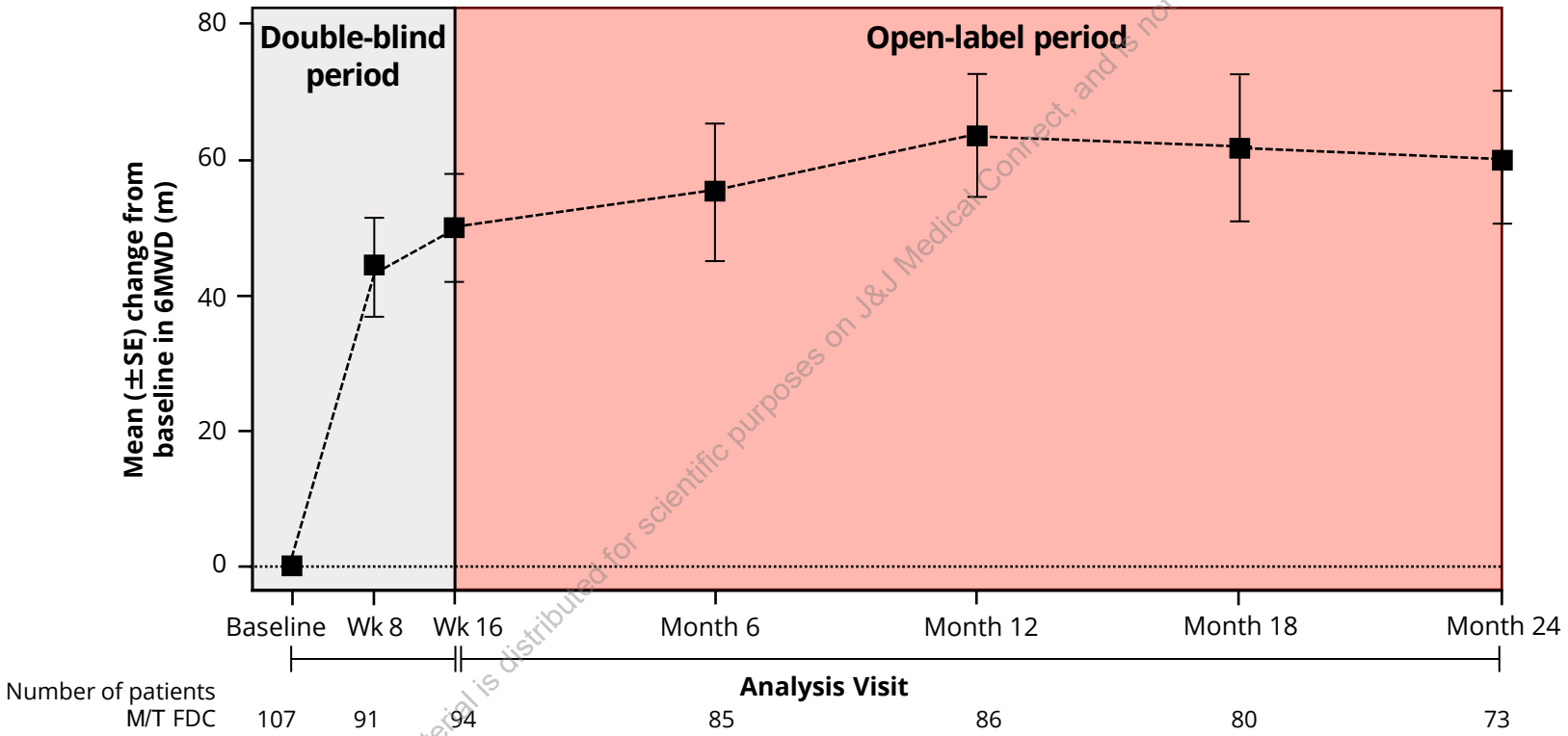
*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB and/or OL period; Baseline was defined as the last assessment prior to the first intake of M/T FDC (or titration dose) in either the DB or OL period. †Data are presented for patients who received at 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 and/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.

The majority of patients were alive at end of study



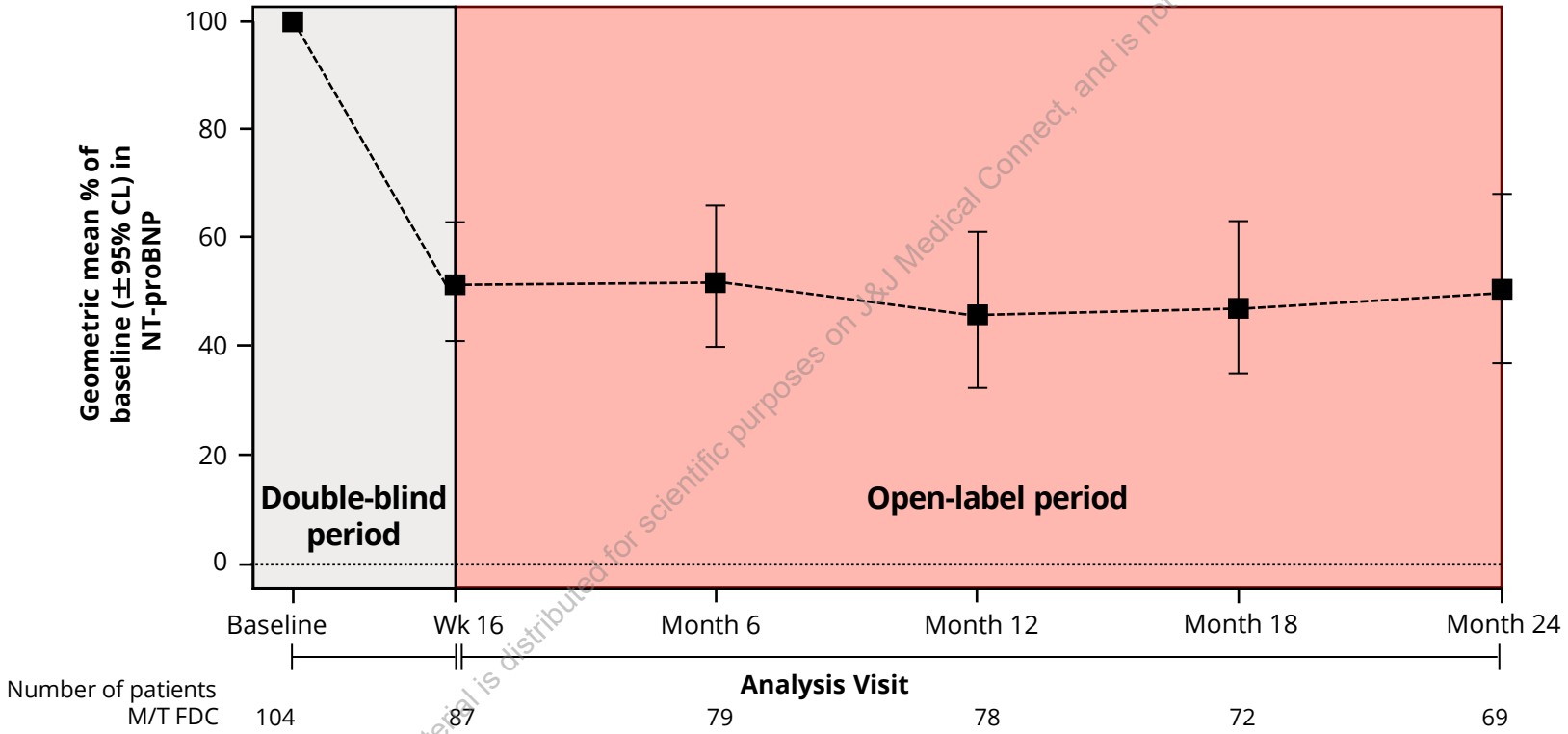
Kaplan-Meier curve for time to all cause death up to end of study, for patients who started treatment with M/T FDC in the DB period (N=107). Kaplan-Meier estimates (95% CL) are shown at 12 and 24 months.
CL: confidence limit; Wk: week of study.

Improvement in 6MWD was maintained over 24 months in the OL period



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

Improvement in NT-proBNP was maintained over 24 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 DB period (N=104).

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

	M/T FDC (in DB)* N=107
Patient-years in study	196.8
Exposure, weeks, median (range)	120.0 (0.6, 166.1)
All-cause hospitalizations	
Hospitalizations, per person-year	0.3
Inpatient hospital days, per person-year	2.6
PAH-related hospitalizations	
Hospitalizations, per person-year	0.1
Inpatient hospital days, per person-year	0.9

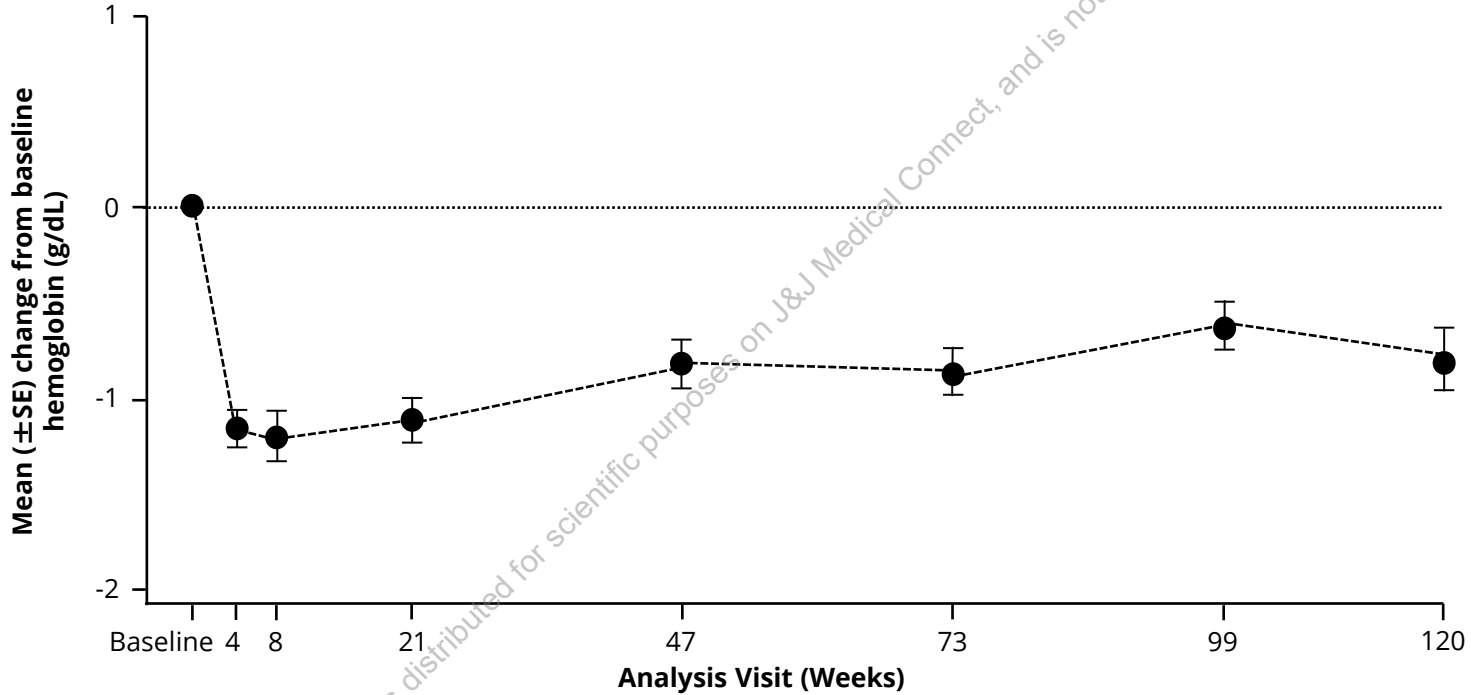
Medical encounters considered hospitalizations were: intensive care unit, hospice/palliative care unit, hospital inpatient department, long term care facility and rehabilitation center. Hospitalization events were not clinical event committee adjudicated. *Data are presented for patients who received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

Safety and tolerability (1)

	M/T FDC (DB and/or OL)* N=185
Exposure, weeks, median (range)	105.1 (0.6, 182.6)
Patients with ≥1 adverse event, n (%)	174 (94.1)
Patients with ≥1 serious adverse event, n (%)	62 (33.5)
Patients with ≥1 adverse event leading to premature discontinuation, n (%)	19 (10.3)
Adverse events (Preferred Term)†, n (%)	
COVID-19	47 (25.4)
Headache	28 (15.1)
Anemia	23 (12.4)
Peripheral edema	22 (11.9)
Patients with adverse events of special interest (Grouped Terms), n (%)	
Anemia	46 (24.9)
Edema and fluid retention	34 (18.4)
Hypotension	12 (6.5)
Hepatic disorders	11 (5.9)
Patients with low hemoglobin, n (%)‡	
<8 g/dL	5 (2.8)
<10 g/dL	28 (15.8)
Patients with liver abnormalities, n (%)**	
ALT/AST ≥3 x ULN	6 (3.4)

*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB and/or OL period. Treatment-emergent safety events with M/T FDC are described, with treatment-emergent defined as from first intake of M/T FDC treatment up to EOT, plus 30 days post- treatment. †Occurring in >10% patients. ‡n=177. **n=178. ALT: alanine aminotransferase; AST: aspartate aminotransferase; EOT: end of treatment; ULN: upper limit of normal.

Hemoglobin levels remained stable across the open-label period



Data are presented for patients with baseline and treatment-emergent assessments in the M/T FDC DB and/or OL group (N=185). The M/T FDC DB and/or OL group is the combination of DB-Macitentan, DB-Tadalafil, and DB-M/T FDC arms (i.e. covering treatment period with M/T FDC at any time). N is the number of patients with a non-missing value for the laboratory test at the specified time point and at baseline.

Safety and tolerability (2)

	M/T FDC (DB and/or OL)* N=185
Adverse events leading to death (Preferred Term), n (%)	7 (3.8)
Gastroenteritis clostridial (DB)	1 (0.5)
Cardiac failure (DB)	1 (0.5)
Respiratory failure (OL)	2 (1.1)
Right ventricular failure (OL)	1 (0.5)
Diverticulitis (OL)	1 (0.5)
Cardiac arrest (OL)	1 (0.5)

- In total, there were 7 deaths in patients receiving M/T FDC: all were evaluated as **unrelated to treatment**
- There were 7 additional deaths off-treatment (>30 days after end of treatment): 1 during the DB, 6 during the OL†

*Data are presented for the combined safety set of patients who received M/T FDC at any time in the DB and/or OL period. Treatment-emergent safety events with M/T FDC are described, with treatment-emergent defined as from first intake of M/T FDC treatment up to EOT, plus 30 days post- treatment. †All were evaluated as unrelated to treatment; Preferred Term (days after EOT): COVID-19 pneumonia (97), pulmonary arterial hypertension (113, 212), pulmonary hypertension (474), anal rectal cancer (368), cerebrovascular accident (398) and sudden cardiac death (667).

Conclusions from the A DUE Open-Label Study

- The majority of patients were alive at the end of the study
- Single-tablet combination therapy with macitentan and tadalafil led to sustained improvement in 6MWD at 24 months
- The cardiac biomarker NT-proBNP decreased during the DB period and remained stable over 24 months
- The PAH-related hospitalization rate was 0.1 per person-year
- Long term safety/tolerability of macitentan and tadalafil in a single tablet was in line with the known safety profiles of macitentan and tadalafil as separate tablets and no new or unexpected safety concerns were revealed

Open-label study endpoints and assessments

Outcomes (N=107; in patients receiving M/T FDC in the DB)

- Kaplan-Meier estimates of overall survival
- All-cause and PAH-related hospitalizations

Change in 6MWD and NT-proBNP

(N=107/N=104; in patients receiving in M/T FDC in the DB)

- Change in 6MWD from baseline to 24 months
- Change in NT-proBNP from baseline to 24 months

Safety and tolerability (N=185; in patients receiving M/T FDC in DB and/or OL)

- Adverse events
- Serious adverse events
- Adverse events leading to premature discontinuation of M/T FDC
- Adverse events leading to death