Results from the REPAIR study final analysis: Effects of macitentan on right ventricular (RV) remodelling in pulmonary arterial hypertension (PAH)

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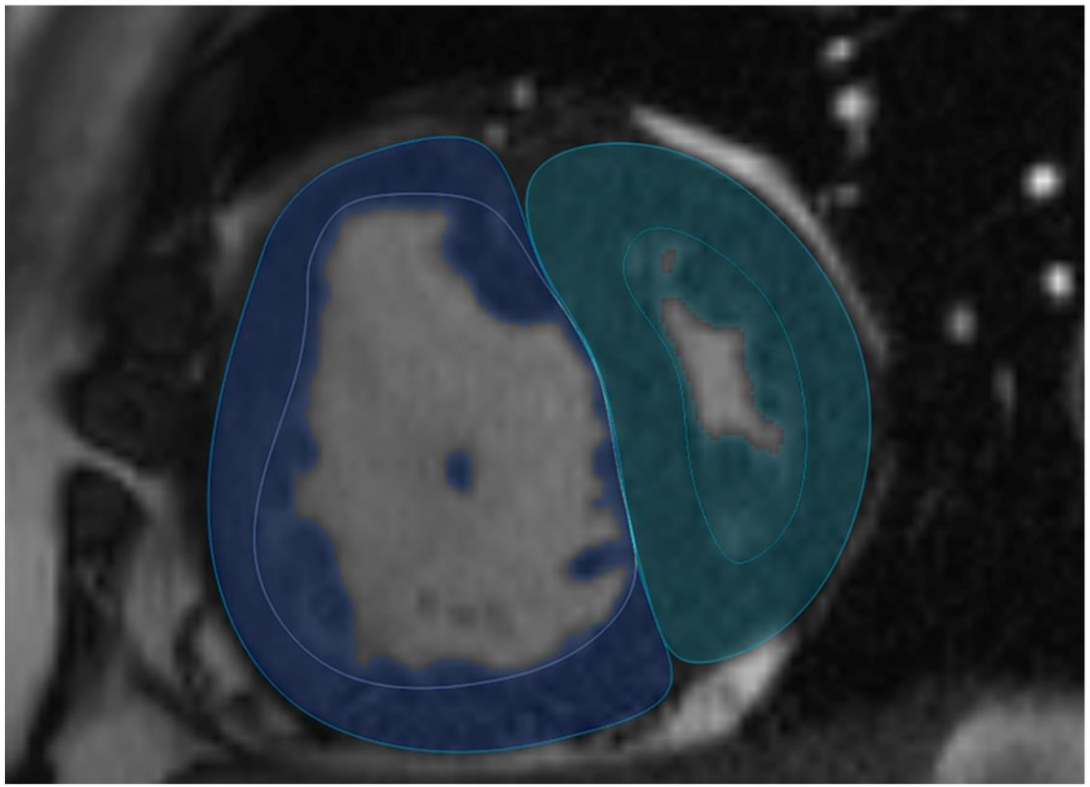
The role of the right ventricle in PAH



cMRI image from a 32-year-old female patient who received initial combination therapy with macitentan and a PDE5i in the REPAIR study

- In pulmonary arterial hypertension (PAH), increased pulmonary vascular resistance leads to remodelling of the right ventricle (RV)
- Prognosis in PAH is largely determined by RV function[1,2]
- RV failure is the primary cause of death in PAH[3]
- REPAIR is the first multicenter study in PAH to use an MRI assessment of RV function (RVSV) as a primary endpoint

1. D'Alonzo GE et al. Ann Intern Med 1991;115(5):343-9; 2. van Wolferen SA et al. Eur Heart J 2007;28(10):1250-7;
3. Vonk-Noordegraaf A et al. Eur Respir Rev 2011;20(122):243-253.

Study objectives

Primary objective

- To evaluate the effect of macitentan on RV and hemodynamic properties in patients with symptomatic PAH

Secondary objective

- To evaluate the safety and tolerability of macitentan in patients with symptomatic PAH

Efficacy endpoints

- **<u>Primary endpoints</u>, change from baseline to Week 26 in:**
  - RV stroke volume (RVSV)*, assessed by cardiac MRI (cMRI)
  - Pulmonary vascular resistance (PVR), measured by right heart catheterization
- **<u>Secondary endpoints</u>, change from baseline to Week 26 in:**
  - cMRI RV cavity volumes, myocardial mass and ejection fraction
  - 6-minute walk distance (6MWD)
  - WHO functional class (FC)
- **<u>Exploratory endpoints</u>, change from baseline to Week 26 in:**
  - Mean pulmonary arterial pressure, mean right atrial pressure, and cardiac index
  - NT-proBNP

*RVSV was determined by pulmonary artery blood flow

Main eligibility criteria

Main inclusion criteria

- Age: 18-74 years*
- Etiology: IPAH, HPAH, DPAH, CTD-PAH, CHD-PAH**
- WHO FC I to III
- 6MWD ≥ 150 m at screening
- PAH therapy at screening:
  - No PAH therapy (treatment naïve)
  - PDE-5i, stable dose for ≥ 3 months

Main exclusion criteria

- Prior use of:
  - ERAs
  - sGC stimulator
  - Prostacyclin/prostacyclin analogs

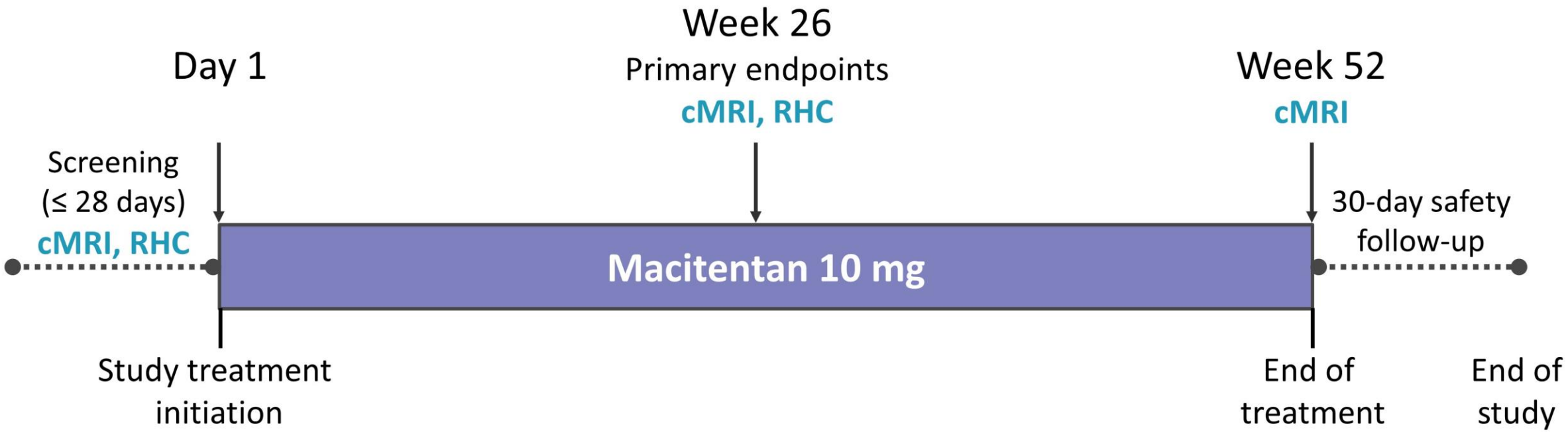
Macitentan (10 mg) initiated:

- In treatment-naïve patients
- In patients receiving stable background PDE5i
- In treatment-naïve patients as initial combination with a PDE5i

*Patients aged 65-74 were assessed for eligibility by scientific committee; **Simple, repaired defects only

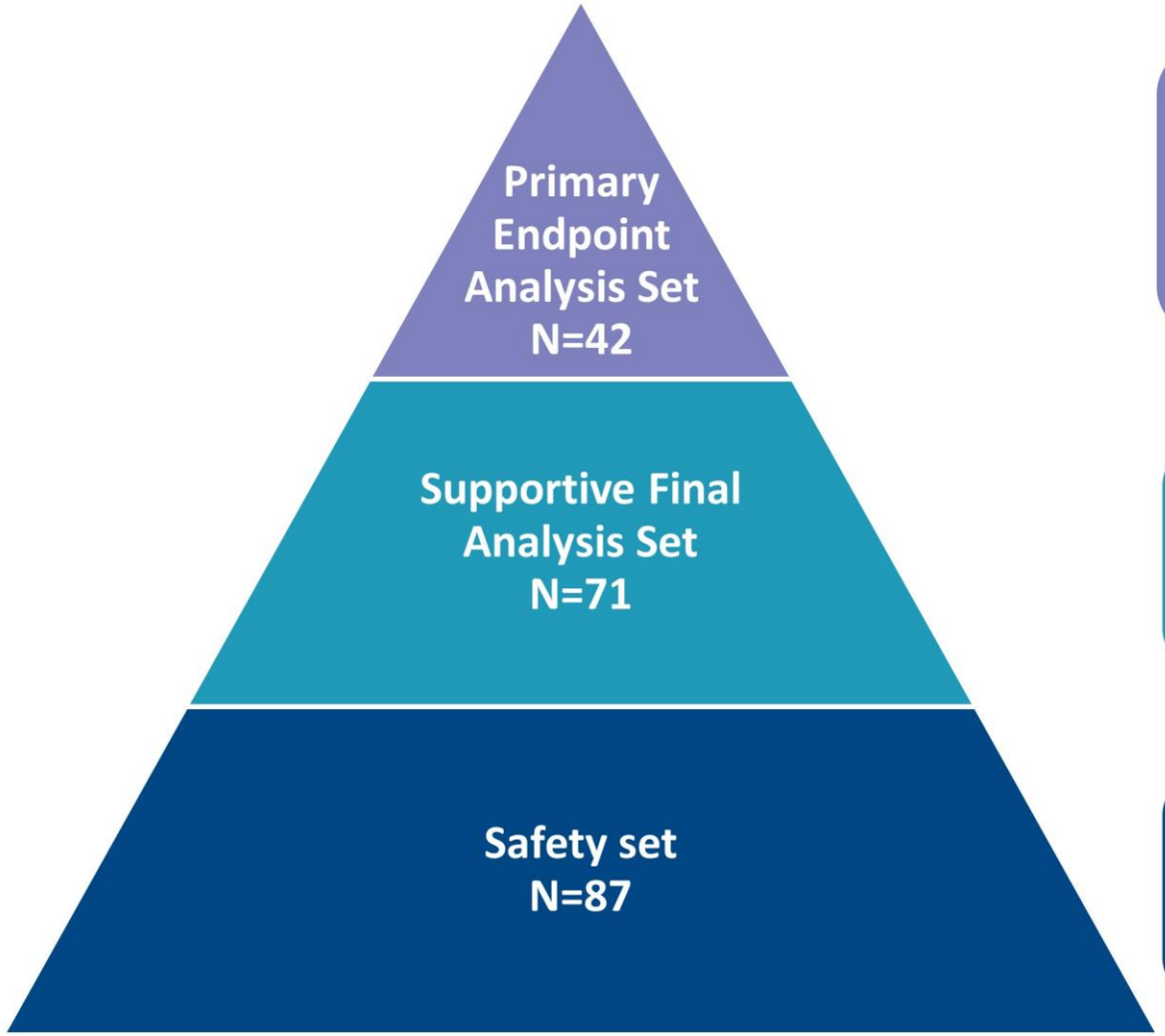
Study design

- Prospective, multicenter, single-arm, open-label, Phase 4 study



27 sites in 11 countries.

Analysis populations



- Pre-specified interim analysis of first 42 patients with RVSV and PVR measures at baseline and Week 26
- Interim analysis was positive for both primary endpoints → study declared positive, enrollment stopped

- All patients with RVSV and PVR measures at baseline and Week 26

- All patients who received ≥ 1 dose of macitentan, up to end of study +30 days

RVSV: right ventricular stroke volume; PVR: pulmonary vascular resistance

Baseline characteristics

	Safety Set (N = 87)
Sex, n (%), female	70 (81)
Age, mean (SD) years	46 (15)
WHO FC, n (%)*	
FC II	40 (46)
FC III	46 (53)
6MWD, median (range), m	390 (150-766)
Etiology, n (%)	
IPAH	48 (55)
CTD-PAH	27 (31)
CHD-PAH	5 (6)
HPAH/DPAH	7 (8)
PAH treatment strategy, n (%)	
Macitentan initiated:	
In treatment-naïve patients	22 (25)
In patients receiving stable background PDE5i	31 (36)
In treatment-naïve patients as initial combination therapy with a PDE5i	34 (39)

*One patient was WHO FC I at baseline

Primary efficacy endpoints

Primary Endpoint Analysis Set (N = 42; interim analysis)

	Baseline	Week 26	Change from baseline to Week 26
RVSV (mL), mean (SD)	50.7 (17.5)	67.3 (19.6)	16.6 (16.3)
Model-adjusted* LS mean change from baseline to Week 26 (96% CL)		**15.2 (9.3, 21.0)**	
P-value (2-sided)		<0.0001	
PVR (dyn.sec.cm^{-5}), mean (SD)	900 (458)	540 (312)	-360 (365)
Model-adjusted** geometric mean ratio Week 26:baseline (99% CL)		**0.63 (37% reduction) (0.54, 0.74)**	
P-value (2-sided)		<0.0001	

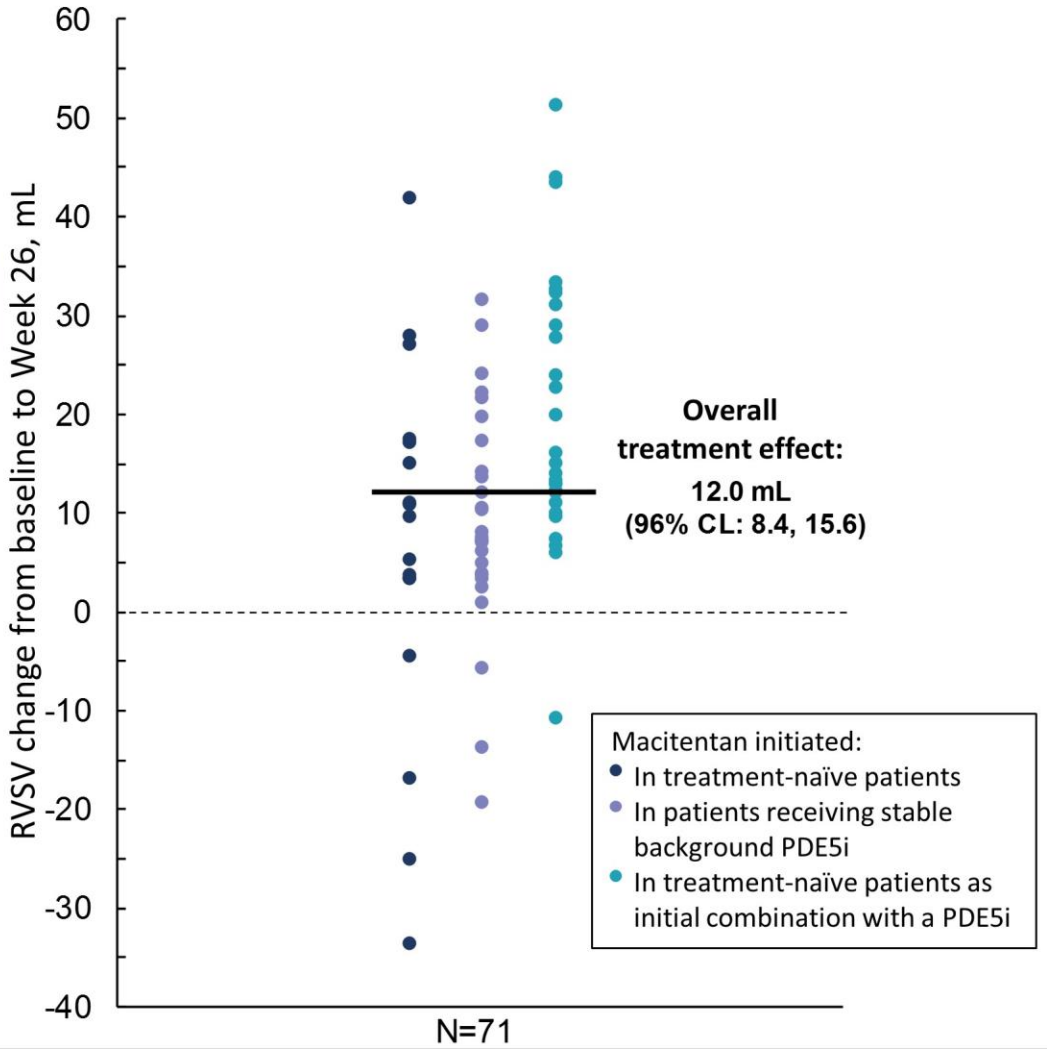
*From ANCOVA model on RVSV change from baseline with a factor for PAH treatment strategy and with RVSV at baseline as covariate. **From ANCOVA model on log-transformed ratio of baseline PVR with a factor for PAH treatment strategy and with log-transformed PVR at baseline as covariate. LS: least squares; RVSV: right ventricular stroke volume; PVR: pulmonary vascular resistance

Supportive final analyses for RVSV

RVSV change from baseline to Week 26

Supportive Final Analysis Set (N = 71)

	RVSV, mL
Baseline, mean (SD)	52.2 (17.2)
Week 26, mean (SD)	64.9 (19.0)
Treatment effect Model-adjusted* mean change from baseline to Week 26 (96% CL)	**+ 12.0 (8.4, 15.6)** p<0.0001



*From ANCOVA model on RVSV change from baseline with a factor for PAH treatment strategy and with RVSV at baseline as covariate. P-value is 2-sided.

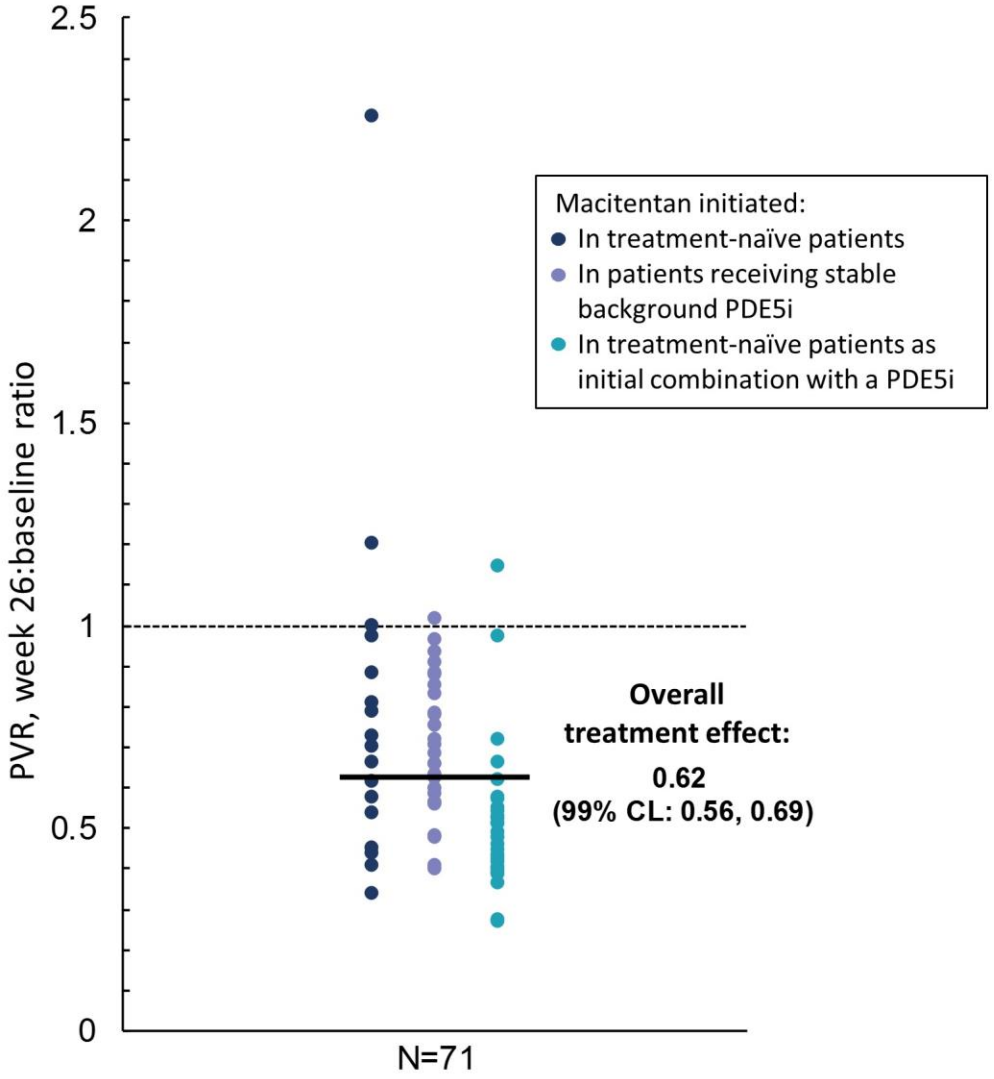
Supportive final analyses for PVR

PVR change from baseline to Week 26

Supportive Final Analysis Set (N = 71)

	PVR, dyn.sec.cm^{-5}
Baseline, mean (SD)	974.6 (679.0)
Week 26, mean (SD)	608.2 (446.3)
Treatment effect Model-adjusted* geometric mean ratio Week 26: baseline (99% CL)	**0.62 (0.56, 0.69)** p<0.0001

38% decrease



*From ANCOVA model on log-transformed ratio of baseline PVR with a factor for PAH treatment strategy and with log-transformed PVR at baseline as covariate. P-value is 2 sided

Secondary efficacy endpoints

RV parameters assessed by cMRI

Supportive Final Analysis Set (N = 71)

	n	Baseline Mean (SD)	Model-adjusted* change from baseline to Week 26	
			Mean change (95% CL)	P-value (2-sided)
RV end diastolic volume, mL	70	149.8 (49.1)	**-6.2** (-12.8, 0.4)	p=0.0659
RV end systolic volume, mL	70	90.2 (40.6)	**-16.1** (-20.0, -12.2)	p<0.0001
RV ejection fraction†, %	70	37.7 (14.3)	**10.6** (7.9, 13.3)	p<0.0001
RV mass, g	70	110.4 (47.5)	**-10.5** (-14.0, -7.1)	p<0.0001

*From ANCOVA model on RV parameter change from baseline with a factor for PAH treatment strategy and with RV parameter at baseline as covariate. †From pulmonary artery flow

Exploratory efficacy endpoints

Hemodynamic variables assessed by RHC

Supportive Final Analysis Set (N = 71)

	n	Baseline Mean (SD)	Model-adjusted* change from baseline to Week 26	
			LS mean change (95% CL)	P-value (2-sided)
Mean pulmonary arterial pressure, mmHg	71	53.5 (15.3)	**-7.73** (-10.0, -5.4)	p<0.0001
Mean right atrial pressure, mmHg	70	6.7 (4.0)	**-0.32** (-1.1, 0.5)	p=0.4272
Cardiac index, L/min/m^2	71	2.4 (0.7)	**0.54** (0.4, 0.7)	p<0.0001

*From ANCOVA model on parameter change from baseline with a factor for PAH treatment strategy and with baseline parameter value as covariate. LS: least squares

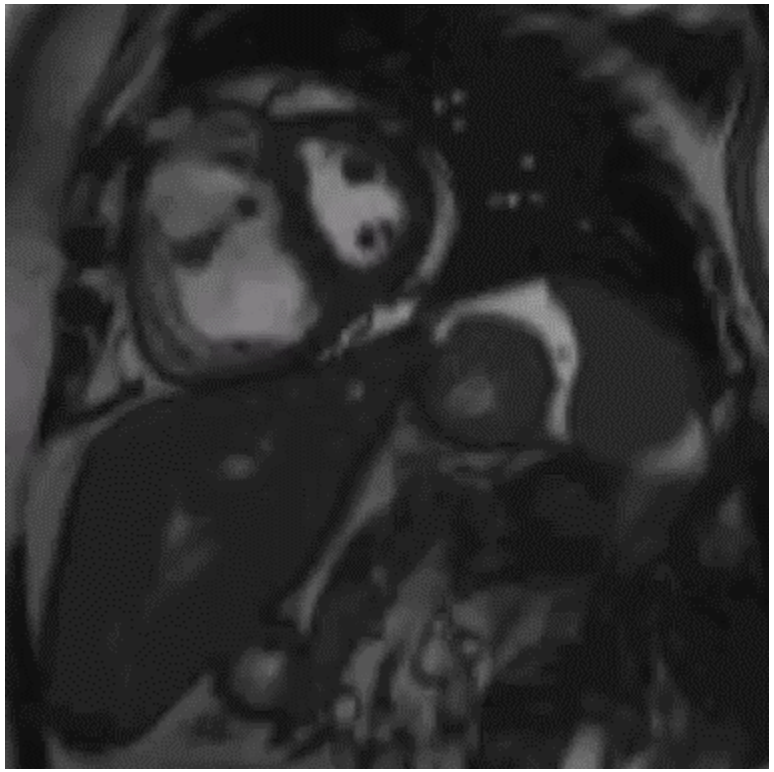
Secondary/exploratory endpoints

Supportive Final Analysis Set (N = 71)

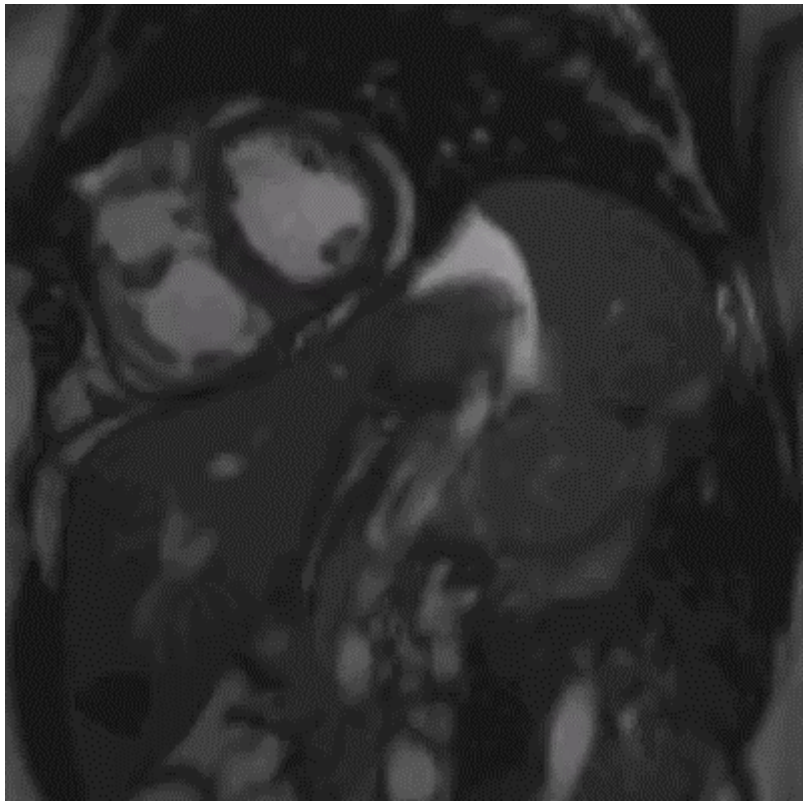
Secondary endpoints				
6MWD, m	**n**	**Baseline, mean (SD)**	**Model-adjusted* change from baseline to Week 26, LS mean (95% CL)**	**P-value (2-sided)**
	71	411.2 (120.5)	**+36** (19, 52)	p<0.0001
WHO FC	**n**	**Baseline, n (%)**	**Change from baseline to Week 26, n (%)**	**P-value (2-sided)**
	70	FC I: 1 (1.4) FC II: 34 (47.9) FC III: 36 (50.7)	Worsened: **0** No change: **30** (42.3) Improved: **40** (56.3)	NA**
Exploratory endpoints				
NT-proBNP, ng/L	**n**	**Baseline, mean (SD)**	**Model-adjusted* change from baseline to Week 26, geometric means ratio (95% CL)**	**P-value (2-sided)**
	60	846.7 (1006.7)	**0.45** (0.37, 0.54)	p<0.0001

*From ANCOVA model on parameter change from baseline with a factor for PAH treatment strategy and a covariate for baseline parameter value. **Not applicable; WHO FC was analysed as a proportion of patients who worsened.

RV changes with treatment



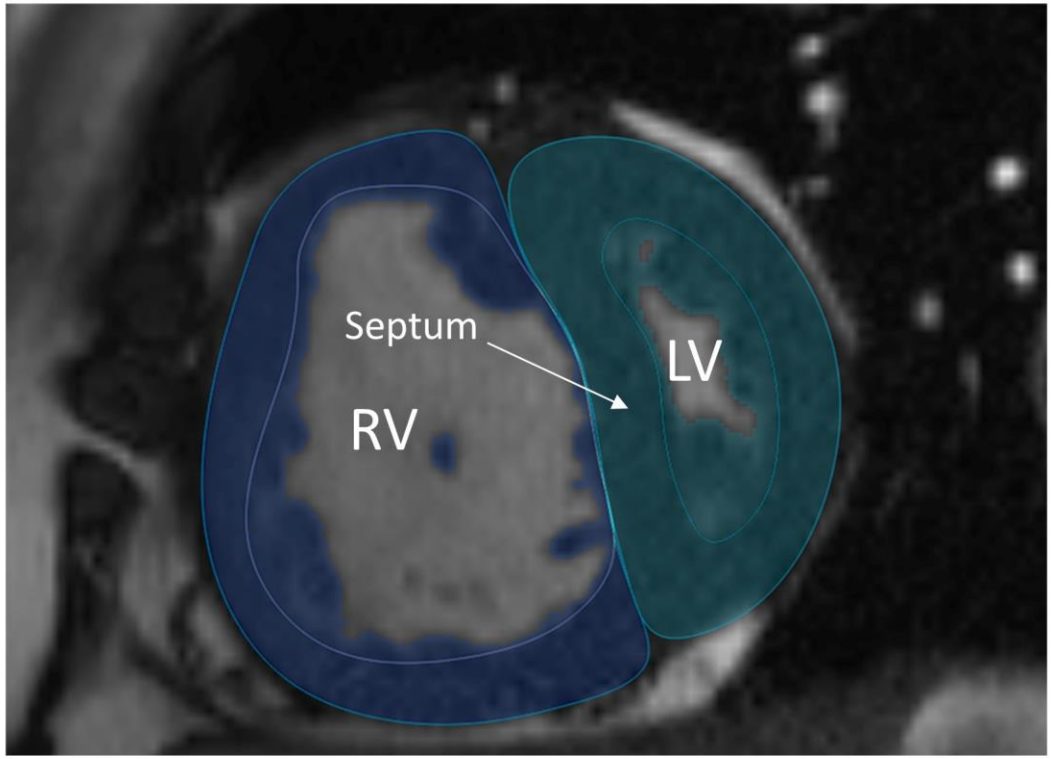
Screening

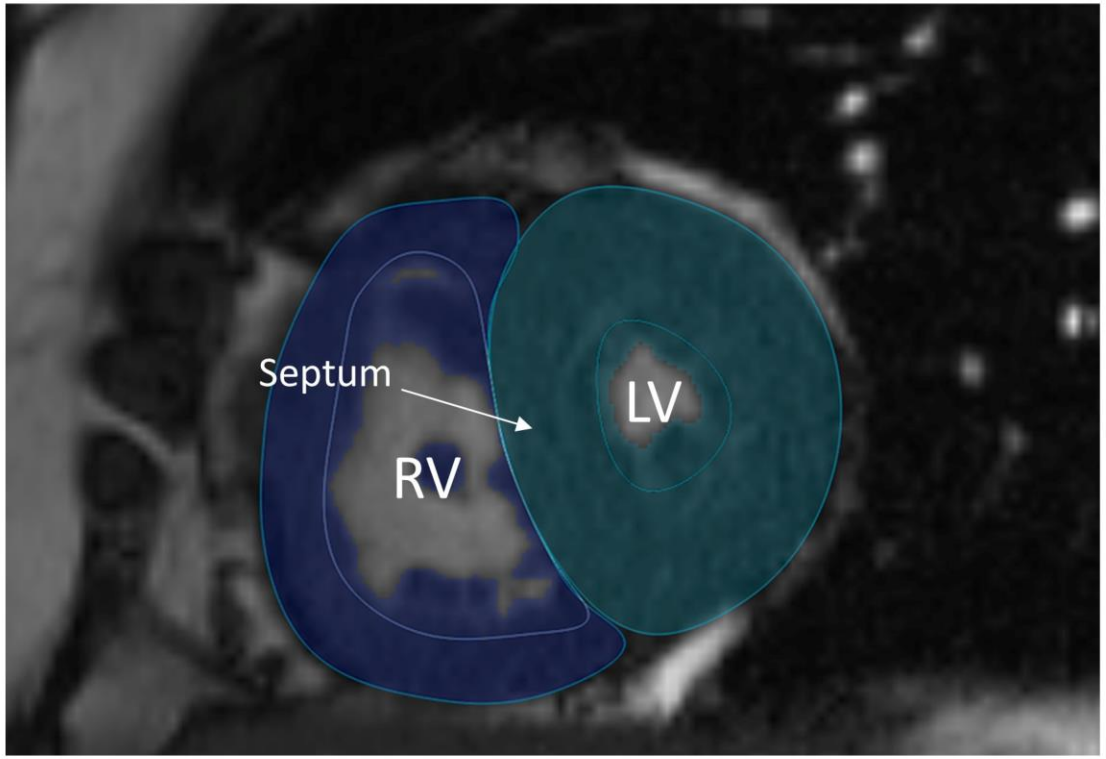


Week 26

cMRI videos from a 32-year-old female patient who received initial combination therapy with macitentan and a PDE5i in the REPAIR study

RV changes with treatment





Screening end systole

Week 26 end systole

cMRI image from a 32-year-old female patient who received initial combination therapy with macitentan and a PDE5i in the REPAIR study

Safety and tolerability

	Safety set (N = 87)
Patients with ≥1 AE, n (%)	75 (86)
Most common AEs (≥10% of patients), n (%)	
Peripheral edema	19 (22)
Headache	18 (21)
Dizziness	12 (14)
Cough	10 (12)
Hemoglobin decreased	10 (12)
Upper respiratory tract infection	10 (12)
Myalgia	9 (10)
Patients with ≥1 serious AE, n (%)	14 (16)
Patients with AEs leading to discontinuation of macitentan, n (%)	6 (7)
ALT/AST, n (%): ≥3 x ULN	5 (6)
≥3 x ULN and total bilirubin ≥2 x ULN	1 (1)
Hemoglobin, n (%): ≤ 8 g/dL	3 (3)
> 8 and ≤ 10 g/dL	7 (8)
Deaths, n (%)*	1 (1)

* 1 patient had a fatal serious adverse event of cardiac arrest. AE, adverse event; ALT: alanine aminotransferase; AST: aspartate aminotransferase; ULN: upper limit of normal.

Conclusions

- REPAIR is the first multicenter study in PAH to use an MRI assessment of RV function (RVSV) as a primary endpoint
- In REPAIR, macitentan treatment of patients with PAH led to improvements in the structure and function of the RV
- Macitentan treatment alone or in combination with a PDE5i led to significant, clinically-relevant improvements in RVSV and PVR at Week 26
  - Significant improvements in other RV, hemodynamic and functional parameters were also observed
- Safety and tolerability were consistent with the known profile for macitentan

REPAIR STUDY INVESTIGATORS

The Right Ventricular Remodeling in Pulmonary Arterial Hypertension (REPAIR) study principal investigators are:

France – A. Chaouat, N. Piriou, H. Bouvaist, P. Degroote, P. Moceri. **Germany** – E. Grünig; S. Konstantinides, D. Skowasch, S. Rosenkranz. **Hong-Kong** – D. Siu, A. Li, K Fan. **Israel** – Y. Raviv, T. Weitsman. **Italy** – C. Raineri. **Malaysia** – G. Kandavello. **The Netherlands** –A. van Dijk, K. Boomars, A. Vonk-Noordegraaf. **Russia –** T. Martynyuk, O. Moiseeva. **Singapore –** J. Yip; **UK –** A. Peacock; G. Coghlan. **USA** – C. McEvoy, M. Simon, K. Chin.