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NEW RESEARCH PAPER

The REPAIR Study

Effects of Macitentan on RV Structure and Function in Pulmonary Arterial Hypertension

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ABSTRACT

OBJECTIVES The REPAIR (Right vEntricular remodeling in Pulmonary ArterIal hypeRtension) study evaluated the effect of macitentan on right ventricular (RV) and hemodynamic outcomes in patients with pulmonary arterial hypertension (PAH), using cardiac magnetic resonance (CMR) and right heart catheterization (RHC).

BACKGROUND RV failure is the primary cause of death in PAH. CMR is regarded as the most accurate noninvasive method for assessing RV function and remodeling and CMR measures of RV function and structure are strongly prognostic for survival in patients with PAH. Despite this, CMR is not routinely used in PAH clinical trials.

METHODS REPAIR was a 52-week, open-label, single-arm, multicenter, phase 4 study evaluating the effect of macitentan 10 mg, with or without phosphodiesterase type-5 inhibition, on RV remodeling and function and cardiopulmonary hemodynamics. Primary endpoints were change from baseline to week 26 in RV stroke volume, determined by CMR; and pulmonary vascular resistance, determined by RHC. Efficacy measures were assessed for all patients with baseline and week 26 data for both primary endpoints.

RESULTS At a prespecified interim analysis in 42 patients, both primary endpoints were met, enrollment was stopped, and the study was declared positive. At final analysis ($n = 71$), RV stroke volume increased by 12 mL (96% confidence level: 8.4-15.6 mL; $P < 0.0001$) and pulmonary vascular resistance decreased by 38% (99% confidence level: 31%-44%; $P < 0.0001$) at week 26. Significant positive changes were also observed in secondary and exploratory CMR (RV and left ventricular), hemodynamic, and functional endpoints at week 26. Improvements in CMR RV and left ventricular variables and functional parameters were maintained at week 52. Safety ($n = 87$) was consistent with previous clinical trials.

CONCLUSIONS In the context of this study, macitentan treatment in patients with PAH resulted in significant and clinically-relevant improvements in RV function and structure and cardiopulmonary hemodynamics. At 52 weeks, improvements in RV function and structure were sustained. (REPAIR: Right vEntricular remodeling in Pulmonary ArterIal hypeRtension [REPAIR]; NCT02310672) (J Am Coll Cardiol Img 2021;■:■-■) © 2021 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

6MWD = 6-minute walk distance

CMR = cardiac magnetic resonance

ERA = endothelin receptor antagonist

NT-proBNP = N-terminal pro-B-type natriuretic peptide

PAH = pulmonary arterial hypertension

PDE-5i = phosphodiesterase-type 5 inhibitor

PVR = pulmonary vascular resistance

RHC = right heart catheterization

RV = right ventricle

RVEF = right ventricular ejection fraction

RVSV = right ventricular stroke volume

WHO FC = World Health Organization functional class

Most deaths in pulmonary arterial hypertension (PAH) patients result from failure of the right ventricle (RV) (1). One defining feature of PAH is increased pulmonary vascular resistance (PVR), which results from obstructive remodeling of the pulmonary vasculature (1). In response to this elevated afterload, hypertrophy of the RV occurs as a compensatory mechanism to enhance contractility (1). For a time, this adaptive remodeling maintains key measures of cardiac function such as cardiac index; however, sustained pressure overload causes maladaptive remodeling, characterized by RV dilation, septal bowing, and impaired contractility (1). Consequently, cardiac index and right ventricular stroke volume (RVSV) begin to decrease, reflecting a decline in RV function that eventually results in RV failure and death (1). As such, reversing this maladaptive remodeling and maintaining RV function are important treatment goals in PAH. Beneficial RV remodeling, indicated by reduced RV mass and volume, has been observed in patients with PAH undergoing lung transplantation (2), and improvements in right heart function have also been noted following pulmonary endarterectomy in chronic thromboembolic pulmonary hypertension patients (3). Beneficial RV remodeling has additionally been reported in patients with PAH receiving PAH-targeted therapies (4-6).

Cardiac magnetic resonance (CMR) can provide detailed information relating to RV function and structure (7). It is regarded as the most accurate noninvasive method for assessing RV function and remodeling and provides complementary information to right heart catheterization (RHC) (7). Previous studies have demonstrated that CMR measures of RV function and structure, including RVSV index, right ventricular ejection fraction (RVEF), and right ventricular end-systolic volume (RVESV), are strongly prognostic for survival in patients with PAH (5,7-10), can improve risk stratification for mortality of patients with PAH (7), and may predict clinical worsening (10). Currently RVSV is the only RV CMR endpoint with a published threshold for clinically-relevant changes in PAH (11). CMR can also be used to measure changes in RV function and structure in response to therapy; in 91 patients with pulmonary hypertension, the EURO-MR (European Magnetic Resonance Imaging Study in PAH) study reported by Peacock et al (5) described significant improvements in CMR-assessed RVSV and RVEF after 12 months of PAH-targeted therapy. Furthermore, a study of 24 patients by Hassoun et al (6) with scleroderma-associated PAH showed significant improvements in CMR-assessed RV mass and RVEF after 36 weeks of treatment with ambrisentan and tadalafil (6). Despite this, CMR is not routinely used in PAH clinical trials.

Macitentan, an oral, dual endothelin receptor antagonist (ERA) approved for the long-term treatment of PAH, is recommended for use as monotherapy or combination therapy (12,13). In the pivotal SERAPHIN (Study with an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome) trial, once daily macitentan 10 mg reduced the risk of the composite morbidity/mortality primary endpoint by 45% compared with placebo (12). In addition, after 6 months of treatment, there was a significant decrease in PVR with cardiac index significantly increasing, indicating beneficial hemodynamic effects (14). Macitentan has also been shown to prevent maladaptive RV remodeling in animal models (15). The significant delay in disease progression and significantly reduced PVR shown in the SERAPHIN study suggests that macitentan treatment has a beneficial impact on RV function and structure.

The REPAIR (Right vEntricular remodeling in Pulmonary ArterIal hypeRtension) study aimed to evaluate the effect of macitentan on RV and hemodynamic outcomes in patients with symptomatic PAH, using CMR and RHC.

METHODS

STUDY DESIGN. REPAIR (NCT02310672) was a prospective, multicenter, single-arm, open-label, 52-week, phase 4 study (Supplemental Figure 1, Supplemental Table 1). Treatment with open-label macitentan 10 mg was initiated on day 1 and continued until week 52 (±7 days) or premature

The data sharing policy of Janssen Pharmaceutical Companies of Johnson & Johnson is available at https://www.janssen.com/clinical-trials/transparency. As noted on this site, requests for access to the study data can be submitted through Yale Open Data Access (YODA) Project site at http://yoda.yale.edu.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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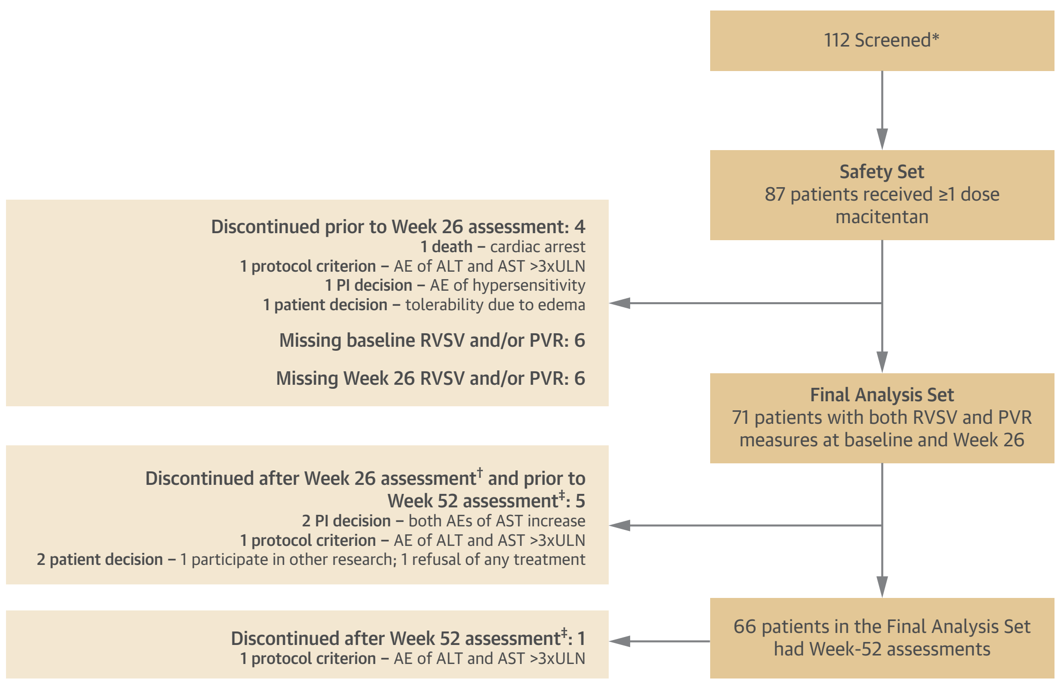
FIGURE 1 Patient Disposition



*For patients who screen failed, the most common inclusion criterion not met was the hemodynamic diagnosis of PAH, confirmed by RHC; the most common exclusion criteria met was related to the presence of moderate to severe restrictive lung disease or signs of relevant lung disease at screening. One patient who screen failed had "claustrophobia" reported. Two patients who screen failed had "atrial fibrillation, multiple premature ventricular or atrial contractions, or any other condition that would interfere with proper cardiac gating during MRI" reported. †Week 26 RHC and CMR assessments could be performed between weeks 16 and 30. ‡Week 52 assessments could be performed between weeks 42 and 62. AE = adverse event; ALT = alanine aminotransferase; AST = aspartate aminotransferase; BL = baseline; CMR = cardiac magnetic resonance; PI = principal investigator; PVR = pulmonary vascular resistance; RHC = right heart catheterization; RVSV = right ventricular stroke volume; ULN = upper limit of normal.

discontinuation of the study drug. Physicians had the option to additionally initiate phosphodiesterase type-5 inhibitor (PDE-5i) within the first 14 days of study drug treatment, in accordance with European Society of Cardiology/European Respiratory Society guidelines and recommendations from the Proceedings of the 6th World Symposium on Pulmonary Hypertension (16-18). Per protocol, initiation of rescue therapy prior to week 26 was permitted only in the event of disease progression, defined as any of the following: a decrease in 6-minute walk distance (6MWD) of more than 15%, associated with worsening in World Health Organization Functional Class (WHO FC); the need for subcutaneous or intravenous prostanoid therapy; or hospitalization for PAH. Initiation of rescue therapy did not require discontinuation of macitentan treatment. After week 26 RHC, treatment changes were permitted.

PATIENT POPULATION. Eligible patients were 18-74 years of age with idiopathic or heritable PAH; PAH related to connective tissue disease, drug use, or toxin exposure; or simple congenital systemic-to-pulmonary shunts at least 2 years after repair. RHC was required for confirmation of the diagnosis. At screening, patients were required to be PAH treatment-naïve or receiving a stable background PDE-5i for at least 3 months, have a 6MWD of ≥150 m, and be in WHO FC I-III. Full inclusion/exclusion criteria are available in the Supplemental Methods.

CLINICAL ASSESSMENTS. CMR was performed at screening, week 26, and week 52. At interim analysis, baseline and week 26 images were assessed for the first 42 patients with available data. CMR was performed using short-axis electrocardiographic (ECG)-gated steady-state free precession imaging with 6-mm slice thickness and at least 25 temporal phases. ECG-gated pulmonary arterial flow analysis was performed in an imaging plane orthogonal to the main pulmonary artery with a slice thickness of 6 to 8 mm, and with velocity encoding at 120 cm/s. No infolding

TABLE 1 Demographics and Baseline Disease Characteristics of Final Analysis Set (n = 71)

Sex	
Male	14 (19.7)
Female	57 (80.3)
Age, y	45 (19, 71)
Age at PAH diagnosis, y	40 (18, 71)
Time from PAH diagnosis to screening, y	2 ± 4
BMI, kg/m^2	25.3 ± 4.7
PAH etiology	
Idiopathic PAH	42 (59.2)
Heritable PAH	2 (2.8)
Drug and toxin-induced	2 (2.8)
PAH associated with congenital heart diseases[a]	5 (7.0)
PAH associated with connective tissue disease	20 (28.2)
WHO FC at baseline	
I	1 (1.4)
II	34 (47.9)
III	36 (50.7)
6MWD at baseline, m	411.2 ± 120.5
Treatment strategy	
Macitentan initiated in treatment-naïve patients as initial combination therapy with a PDE-5i	27 (38.0)
Macitentan initiated alone	44 (62.0)
In treatment-naïve patients	17 (23.9)
In patients receiving stable background PDE-5i	27 (38.0)

Values are n (%), median (min, max), or mean ± SD, unless otherwise indicated. [a]Only simple congenital systemic to pulmonary shunts at least 2 y post-surgical repair.

6MWD = 6-minute walk distance; BMI = body mass index; PAH = pulmonary arterial hypertension; PDE-5i = phosphodiesterase-type 5 inhibitor; WHO FC = World Health Organization functional class.

artefacts or aliasing of images were allowed. Additional details of the CMR protocol are included in the Supplemental Appendix.

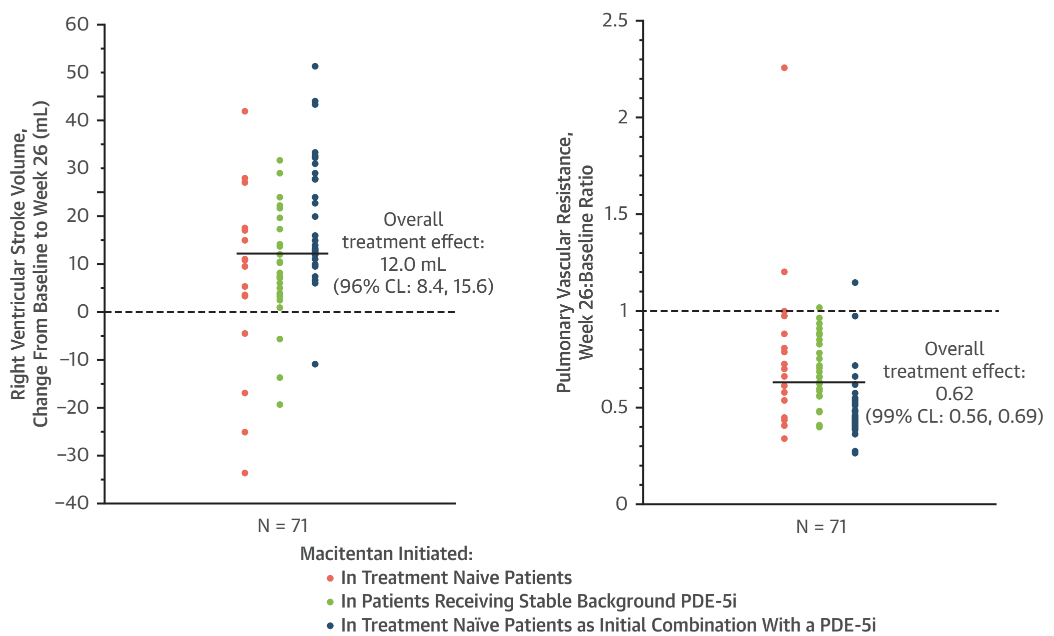
For the final analysis, all images for a given patient were analyzed at the same time by the same assessor, blinded to patient identity and date of image acquisition. Pulmonary artery flow imaging was used to measure RVSV to ensure reliable measurement of the blood volume going to the lungs. Assessment of PVR was performed by RHC at screening and week 26, and 6MWD, WHO FC, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were assessed at screening, week 26, and week 52. Analysis of plasma NT-proBNP was performed at a central laboratory.

OUTCOME MEASURES. The 2 primary endpoints were assessed at week 26: change in RVSV from baseline, as assessed by CMR (determined from pulmonary artery flow); and change in PVR from baseline, as assessed by RHC and expressed as the week 26 to baseline ratio. Secondary endpoints included change from baseline to week 26 in: RVEF (determined from pulmonary artery flow), RV end-diastolic volume, RVESV, and RV mass, measured by CMR; 6MWD; and WHO FC. Main exploratory endpoints included change from baseline to week 26 in: mean pulmonary arterial pressure (mPAP), mean right atrial pressure and cardiac index, assessed by RHC; left ventricular (LV) stroke volume (determined from aortic flow), left ventricular end-diastolic volume (LVEDV), LV end-systolic volume, LV ejection fraction (determined from aortic flow), and LV mass, assessed by CMR; and NT-proBNP. All endpoints (excluding variables assessed by RHC) were repeated at week 52 as exploratory endpoints. Adverse events (AEs), serious adverse events (SAEs) (defined in the Supplemental Appendix) and abnormal results from laboratory studies were monitored until 30 days after study drug discontinuation.

ANALYSIS SETS. The modified full analysis set (final analysis set) comprised all enrolled patients who received at least 1 dose of macitentan and had valid measurements for both primary endpoints at baseline and at week 26; the interim analysis set comprised the first 42 patients meeting these criteria. Primary efficacy analyses were performed using the interim and final analysis sets; secondary and exploratory efficacy analyses were performed using the final analysis set. The safety set comprised all screened patients who received at least one dose of macitentan.

STATISTICAL ANALYSES. The total sample size (n = 100) was based on the assumptions of an 8-mL increase in RVSV from baseline to week 26, an 18% decrease in PVR from baseline to week 26 (geometric mean for ratio of baseline = 0.82), an overall type I error $\alpha = 0.05$ (2-sided) split unequally between the 2 primary endpoints RVSV ($\alpha = 0.04$) and PVR ($\alpha = 0.01$), 90% power, and a protocol-specified interim analysis performed on the first 42 patients with assessments for both primary endpoints at week 26. The interim analysis used a hierarchical testing approach, whereby if the change from baseline to week 26 in RVSV was positive, the change in PVR would be assessed. If both tests were positive, patient enrollment was to be stopped and the study declared positive. If either test was negative, patient accrual was to continue until 100 patients were enrolled (Supplemental Table 1). For the primary endpoints, change from baseline in RVSV was analyzed using analysis of covariance (ANCOVA) (96% confidence level [CL]) with a factor for PAH-targeted therapy (macitentan initiated alone in treatment-naïve patients, on top of stable background PDE-5i, or as initial combination with a PDE-5i) and a covariate for baseline RVSV. The ratio of week 26 vs baseline PVR was log-transformed and analyzed using ANCOVA (99% CL) with a factor for PAH-targeted therapy and a covariate for baseline log PVR.

FIGURE 2 **Change From Baseline to Week 26 in RVSV and PVR in the Final Analysis Set (n = 71)**



CL = confidence limit; FC = functional class; PDE-5i = phosphodiesterase type-5 inhibitor; other abbreviations as in Figure 1.

Primary endpoints were also analyzed for the following subgroups using the ANCOVA models specified for the main analysis: PAH-targeted treatment strategy, WHO FC category at baseline (I/II vs III/IV), sex (male vs female), and age (<65 years vs ≥65 years).

Secondary and exploratory variables measured by CMR and RHC were summarized and analyzed as described for RVSV, using 95% CL. Change from baseline in 6MWD was analyzed by ANCOVA with a factor for PAH-targeted therapy and a covariate for baseline 6MWD and WHO FC, using 95% CL. Changes from baseline in WHO FC were dichotomized as worsening vs no change or improvement, with worsening analyzed using a logistic regression model with a factor for PAH-targeted therapy at baseline, using 95% CL. Change from baseline in NT-proBNP was analyzed as described for PVR, using 95% CL.

Secondary and exploratory efficacy analyses were performed with no correction for multiple testing; thus, all analyses are of an exploratory nature.

For all endpoints, analyses were based on observed data, and no imputations for missing data were performed. Images were assessed by independent imaging specialists, blinded to the patient identity and to the date and the time point of image acquisition.

MONITORING AND ETHICS STATEMENT. The study was designed by the Steering Committee in conjunction with the sponsor (Actelion Pharmaceuticals Ltd, a Janssen Pharmaceutical Company of Johnson & Johnson). Ethical approval was received from independent ethics committees/institutional review boards, and the study was conducted in compliance with the Declaration of Helsinki. Written informed consent was obtained from all patients. CMR and echocardiography results were assessed by a blinded central imaging committee.

RESULTS

PATIENT DISPOSITION AND INTERIM ANALYSIS. Patients were screened at 29 sites across 11 countries, with the protocol-specified interim analysis performed when both baseline and week 26 RVSV and PVR measurements were available for 42 patients (interim analysis set). As both primary endpoints were met, the study was declared positive and enrollment was stopped.

At cessation of enrollment, 112 patients had been screened with 87 patients receiving at least 1 dose of macitentan (safety set). The 71 patients with both baseline and week 26 PVR and RVSV measurements comprised the final analysis set (Figure 1). Reasons for

TABLE 2 Primary Endpoints of Change From Baseline to Week 26 in RVSV and PVR

	Interim Analysis Set (n = 42)			Final Analysis Set (n = 71)		
	Baseline	Change From Baseline to Week 26[a] LS Mean (96% CL)	*P* Value	Baseline	Change From Baseline to Week 26[a] LS Mean (96% CL)	*P* Value
RVSV, mL	50.7 ± 17.5	15.2 (9.3-21.0)	<0.0001[c]	52.2 ± 17.2	12.0 (8.4-15.6)	<0.0001[c]
	Baseline	Week 26/Baseline Ratio[b] Geometric Mean (99% CL)	*P* Value	Baseline	Week 26/Baseline Ratio[b] Geometric Mean (99% CL)	*P* Value
PVR, dyn•s/cm[5]	900.2 ± 457.6	0.63 (0.54-0.74)	<0.0001[c]	974.6 ± 679.0	0.62 (0.56-0.69)	<0.0001[c]

Baseline values are mean ± SD. [a]Adjusted change using an analysis of covariance model with a factor for PAH-targeted background therapy and a covariate for baseline parameter value. [b]Adjusted change using an analysis of covariance model with a factor for PAH-targeted background therapy and a covariate for baseline log PVR. [c]2-sided *P* value.

CL = confidence limit; LS = least squares; PVR = pulmonary vascular resistance; RVSV = right ventricular stroke volume.

patient exclusion from the final analysis set are shown in Supplemental Table 2. Patients with treatment changes during the study included 6 (6.9%) before and 8 (9.2%) after week 26 (Supplemental Table 3).

DEMOGRAPHICS AND BASELINE CHARACTERISTICS. Patients in the final analysis set had a median age of 45 years (range 19-71 years) at baseline, 80.3% were women, and 59.2% had idiopathic PAH. For these patients, mean ± SD 6MWD was 411.2 ± 120.5 m, and most were in WHO FC II (47.9%) or III (50.7%) at baseline (**Table 1**). Macitentan was initiated as monotherapy in 23.9% of patients, on top of stable background PDE-5i therapy in 38.0% of patients, and simultaneously with a PDE-5i in 38.0% of patients. Time from diagnosis to screening across the final analysis set, to the nearest year, is shown in Supplemental Table 4. Demographics and baseline characteristics for the interim analysis and safety sets are presented in Supplemental Table 5.

PRIMARY EFFICACY ENDPOINTS. For the primary efficacy endpoints, at final analysis (n = 71), mean RVSV increased from baseline to week 26 by 12.0 mL (96% CL: 8.4-15.6 mL; $P < 0.0001$) and PVR decreased by 38% from baseline to week 26 (model-adjusted geometric mean ratio: 0.62 [99% CL: 0.56-0.69; $P < 0.0001$]) (**Figure 2, Table 2**), confirming the positive results of the interim analysis (n = 42), where mean RVSV increased from baseline to week 26 by 15.2 mL (96% CL: 9.3-21.0 mL; $P < 0.0001$), and PVR decreased by 37% from baseline to week 26 (model-adjusted geometric mean ratio 0.63 [99% CL: 0.54-0.74; $P < 0.0001$]) (**Table 2**).

SUBGROUP ANALYSIS. Subgroup analyses (**Figure 3**) of the final analysis set demonstrated that the treatment effects for RVSV and PVR were generally consistent with the overall effect for all subgroups, with the exception of treatment strategy, for which the largest treatment effect was seen in treatment-naïve patients initiating macitentan in combination with a PDE-5i. As the study was not powered for tests in these subgroups, such results should be interpreted with caution.

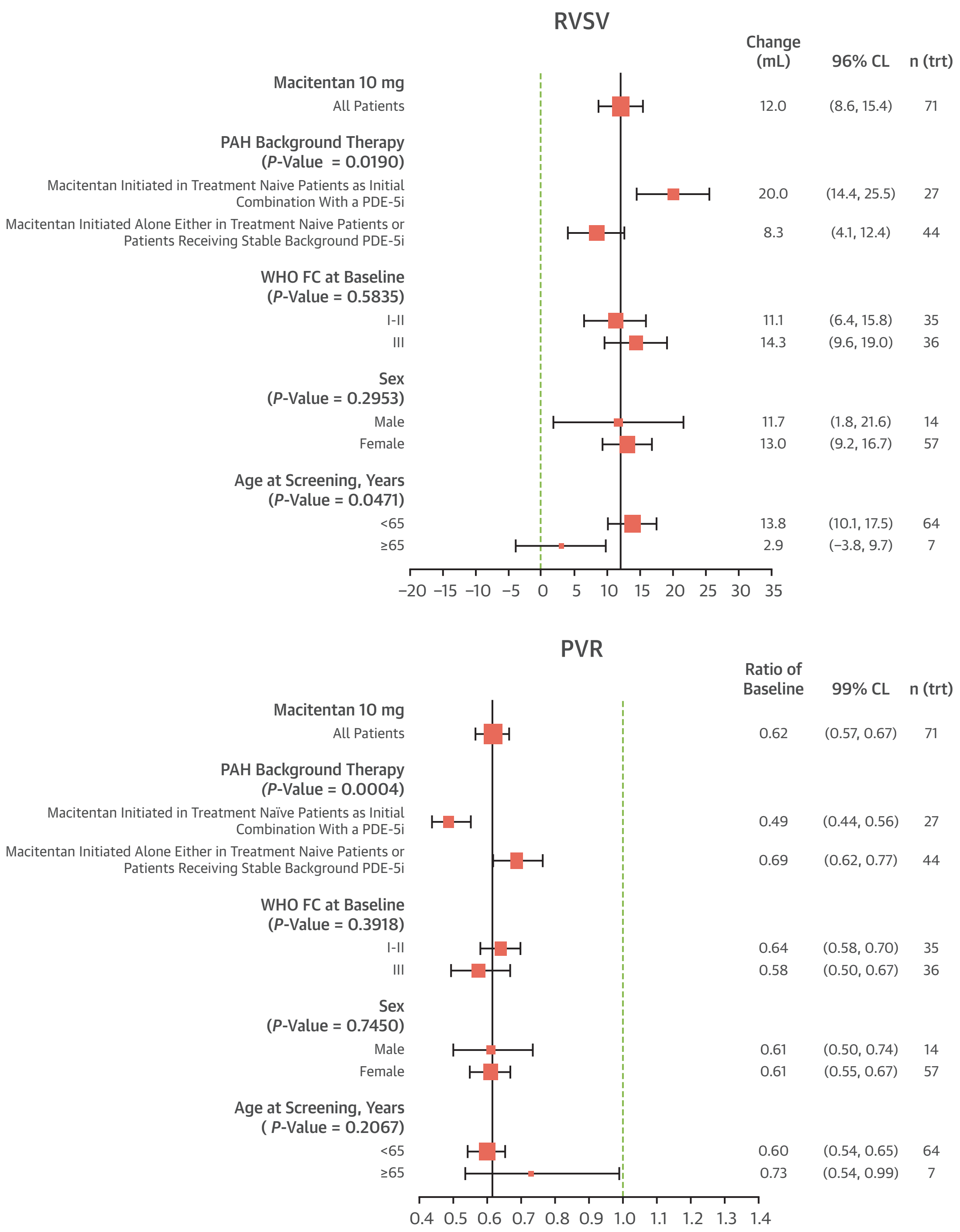
OTHER EFFICACY ENDPOINTS (SECONDARY AND EXPLORATORY). In addition to RVSV, significant improvements from baseline to week 26 were observed in the CMR secondary endpoints of RVESV, RVEF, and RV mass, and in the exploratory endpoints of LV stroke volume, LVEDV, LV ejection fraction, LV mass, and the RV/LV diastolic and systolic volume ratios (**Table 3**). Example CMR images from a female patient who received initial combination therapy with macitentan and a PDE-5i are shown in **Figure 4**. The improvements observed in these variables at week 26 were maintained and significant at week 52 (**Table 3**).

With respect to the change from baseline to week 26 in the exploratory hemodynamic endpoints, significant improvements were observed for mPAP (mean decrease of −7.7 mm Hg [95% CL: −10.0 to −5.4 mm Hg]) and cardiac index (mean increase of 0.5 L/min/m^2 [95% CL: 0.4-0.7 L/min/m^2]); mean right atrial pressure was not changed (**Table 4**).

Patients' 6MWD (n = 71) significantly increased from baseline to week 26 by a mean of 35.6 m (95% CL: 19-52 m), and this change was maintained at week 52 (mean increase of 38.2 m [95% CL: 19-57 m]; n = 65) (**Table 4**). Furthermore, at week 26, the majority (57.1%) of patients had improved WHO FC (n = 70) and no patients had worsened (1 patient had missing data) (**Table 4**). Similar results were observed at week 52 (n = 65; 52.3% of patients had improved; no patients had worsened) (**Table 4**).

Finally, NT-proBNP levels significantly decreased by 55% (95% CL: 46%-63%) (absolute change −425.1 ng/L [95% CL: −650.2 to −200.1 ng/L]; n = 60) from baseline to week 26, and this was maintained at Week 52 (decrease of 56% [95% CL:

FIGURE 3 **Subgroup Analysis of Change From Baseline to Week 26 in RVSV and PVR in the Final Analysis Set (n = 71)**



n(trt) = number of patients receiving macitentan; WHO FC = World Health Organization functional class; other abbreviations as in Figures 1 and 2.

TABLE 3 Change From Baseline to Weeks 26 and 52 in Primary, Secondary, and Exploratory CMR Endpoints in the Final Analysis Set (n = 71)

Parameter	Week 26 n	Week 26 Baseline	Change From Baseline to Week 26[a] LS Mean (95% CL)	Week 26 *P* Value	Week 52 n	Week 52 Baseline	Change From Baseline to Week 52[a] LS Mean (95% CL)	Week 52 *P* Value
			Primary Endpoint				**Exploratory Endpoint**	
RVSV, mL	71	52.2 ± 17.2	12.0 (8.4 to 15.6)[b]	<0.0001	63	52.2 ± 17.1	12.0 (8.4 to 15.6)	<0.0001
			Secondary Endpoints				**Exploratory Endpoints**	
RV end-diastolic volume, mL	70	149.8 ± 49.1	−6.2 (−12.8 to 0.4)	*ns*	63	149.3 ± 47.8	−5.3 (−12.0 to 1.4)	*ns*
RV end-systolic volume, mL	70	90.2 ± 40.6	−16.1 (−20.0 to −12.2)	<0.0001	63	89.2 ± 38.1	−17.0 (−22.1 to −12.0)	<0.0001
RVEF,[c] %	70	37.7 ± 14.3	10.6 (7.9 to 13.3)	<0.0001	62	37.9 ± 14.2	9.5 (7.0 to 12.0)	<0.0001
RV mass, g	70	110.4 ± 47.5	−10.5 (−14.0 to −7.1)	<0.0001	63	111.0 ± 49.1	−9.2 (−12.9 to −5.5)	<0.0001
			Exploratory Endpoints				**Exploratory Endpoints**	
LV stroke volume,[d] mL	67	47.5 ± 14.0	13.8 (10.7 to 16.9)	<0.0001	61	47.5 ± 14.4	13.8 (10.5 to 17.0)	<0.0001
LV end-diastolic volume, mL	70	87.2 ± 29.1	17.4 (12.4 to 22.5)	<0.0001	63	88.1 ± 30.0	17.0 (12.7 to 21.4)	<0.0001
LV end-systolic volume, mL	70	32.2 ± 16.1	1.7 (−1.0 to 4.4)	*ns*	63	32.7 ± 16.0	3.1 (0.6 to 5.6)	<0.05
LV ejection fraction,[d] %	66	56.3 ± 10.5	3.6 (1.1 to 6.1)	<0.01	61	55.9 ± 10.4	4.5 (2.0 to 7.0)	<0.001
LV mass, g	70	103.4 ± 23.7	3.8 (1.4 to 6.2)	<0.01	63	103.6 ± 24.6	4.0 (1.1 to 7.0)	<0.01

	Exploratory Endpoints n	Baseline	Geometric Means Ratio of Week 26 to Baseline[e] (95% CL)	*P* Value	Exploratory Endpoints n	Baseline	Geometric Means Ratio of Week 52 to Baseline[e] (95% CL)	*P* Value
RV/LV end-diastolic volume	70	1.8 ± 0.65	0.79 (0.76 to 0.83)	<0.0001	63	1.8 ± 0.65	0.80 (0.77 to 0.84)	<0.0001
RV/LV end-systolic volume	70	3.2 ± 1.62	0.78 (0.73 to 0.83)	<0.0001	63	3.1 ± 1.64	0.73 (0.67 to 0.80)	<0.0001

Baseline values are mean ± SD. [a]Analyzed using an analysis of covariance with a factor for PAH-targeted background therapy and a covariate for baseline parameter value. [b]96% CL. [c]From pulmonary artery flow. [d]From aortic flow. [e]From analysis of covariance model on log-transformed change ratio with baseline ratio as a covariate.

LV = left ventricular; *ns* = not significant; RV = right ventricular; RVEF = right ventricular ejection fraction; other abbreviations as in Table 2.

47%-64%]; absolute change −484.2 ng/L [95% CL: −692.1 to −276.3 ng/L]; n = 57) (**Table 4**).

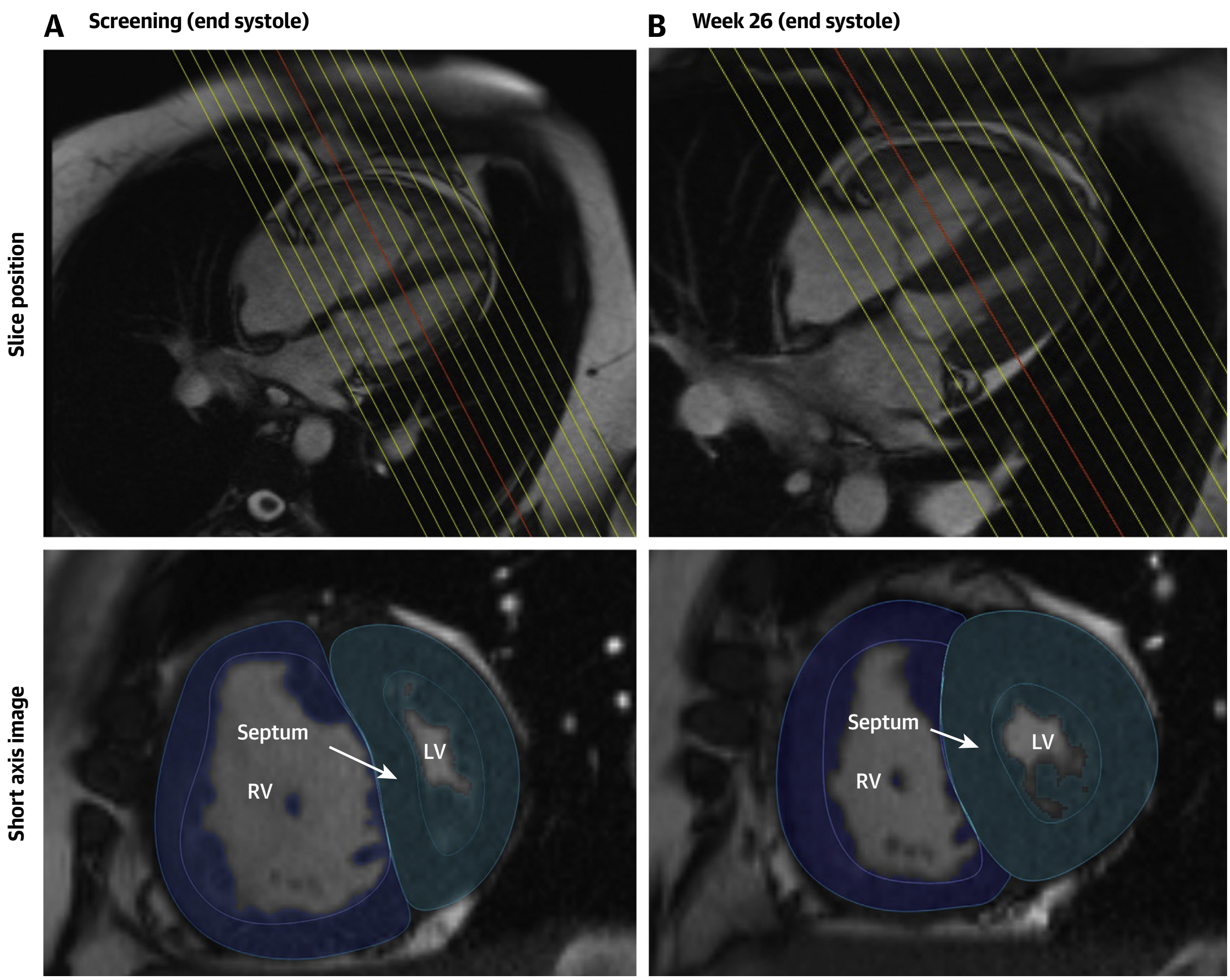
SAFETY AND TOLERABILITY. Safety and tolerability were assessed in the safety set (n = 87). Median (min, max) exposure time was 52.0 weeks (1.1, 58.3 weeks) (**Table 5**). There were 75 (86.2%) patients who reported at least 1 AE and 14 (16.1%) patients reported at least 1 SAE (**Table 5**, Supplemental Table 6). The most frequent AEs (≥20% of patients) were peripheral edema (n = 19, 21.8%) and headache (n = 18, 20.7%). For 26 (29.9%) patients, at least 1 treatment-emergent AE relating to edema and fluid retention was reported; 17 (19.5%) patients had at least 1 treatment-emergent AE relating to anemia (Supplemental Table 7); and 3 (3.5%) patients had hemoglobin decreases to ≤80 g/L (Supplemental Table 8).

There were 10 (11.5%) patients who discontinued macitentan treatment; 1 (1.1%) patient died, 3 (3.4%) patients discontinued because of meeting prespecified discontinuation criteria, 3 (3.4%) patients discontinued because of physician's decision, and 3 (3.4%) patients discontinued because of patient decision. The 1 death recorded was the result of a fatal SAE of cardiac arrest, which occurred after the patient experienced a pulmonary embolism (**Figure 1**). Laboratory abnormalities of alanine aminotransferase/aspartate aminotransferase ≥3× the upper limit of normal were reported for 5 (5.8%) patients in the safety set (Supplemental Table 8).

DISCUSSION

MACITENTAN IMPROVES RV FUNCTION AND STRUCTURE AS DETERMINED BY CMR AND HEMODYNAMIC PARAMETERS. REPAIR is one of the largest multicenter clinical trials in PAH to use a CMR variable as a primary endpoint. Here we show that macitentan treatment, alone or in combination with a PDE-5i, led to statistically significant and clinically relevant improvements in RVSV (11) and PVR at week 26, with improvements in RVSV maintained at week 52 (**Central Illustration**). Improvements were also seen in the majority of the secondary and exploratory CMR (RV and LV variables and the RV/LV volumetric ratios), hemodynamic, and functional endpoints. Improving RV function and structure is key to improving outcomes in patients with PAH. In REPAIR, the observed improvements in RVSV brought the mean to within the normal range (ie, between the 5th and 95th percentile in men [63-122 mL] and women [50-95 mL]) (19). This improvement was mirrored in the significant changes of RVEF and RVESV, both of which are strongly prognostic in PAH (7,20). That beneficial changes were observed for both RV function (RVSV and RVEF) and structure (RVESV and RV

FIGURE 4 **Example of RV (and LV) Changes in 1 Patient at Screening (End Systole) and Week 26 (End Systole)**



Images from a 49-year-old female who received initial combination therapy with macitentan and a phosphodiesterase-type 5 inhibitor at **(A)** screening (end systole) and **(B)** week 26 (end systole). Changes over time: right ventricular (RV) size reduced **(purple line)**, left ventricular (LV) size increased **(green line)**, septal bowing shift from left to right, reflecting pressure changes **(white arrows)**. Slice position indicated by **red line** in the **top panels**.

mass) suggests that macitentan contributes to beneficial remodeling of the RV in patients with PAH. In addition, significant improvements were observed for LV CMR variables, including LVEDV, which has been shown to have prognostic value in PAH (7). Together, these results suggest that macitentan-related improvements in RV structure and function are associated with improvements in LV function.

The REPAIR study showed that macitentan treatment also improved hemodynamic parameters with significant reductions in PVR, mPAP and an increase in cardiac index. This is consistent with previous studies reporting that macitentan significantly improves hemodynamics irrespective of WHO FC and background PAH-targeted therapy (12,14). Whether macitentan's effects on hemodynamics and RV structure are mechanistically linked remains unclear. The reduction in PVR induced by macitentan may indirectly lead to reverse remodeling of the RV by improving cardiac function; however, in vivo studies conducted in rats have also revealed that expression of genes related to RV remodeling are reduced after treatment with macitentan (15), suggesting a direct effect on RV structure.

TABLE 4 Change From Baseline to Week 26 in Exploratory RHC Endpoints, and From Baseline to Weeks 26 and 52 in Secondary and Exploratory Functional Endpoints in the Final Analysis Set (n = 71)

	Exploratory Endpoints			
Parameter	n	Baseline	Change From Baseline to Week 26[a] LS Mean (95% CL)	*P* Value
Mean pulmonary arterial pressure, mm Hg	71	53.5 ± 15.3	−7.7 (−10.0 to −5.4)	<0.0001
Mean right atrial pressure, mm Hg	70	6.7 ± 4.0	−0.3 (−1.1 to 0.5)	*ns*
Cardiac index, L/min/m^2	71	2.4 ± 0.7	0.5 (0.4 to 0.7)	<0.0001

	Secondary Endpoints				Exploratory Endpoints			
	n	Baseline	Change From Baseline to Week 26[b] LS Mean (95% CL)	*P* Value	n	Baseline	Change From Baseline to Week 52[b] LS Mean (95% CL)	*P* Value
6MWD, m	71	411.2 ± 120.5	35.6 (19.0 to 52.3)	<0.0001	65	414.6 ± 120.6	38.2 (19.0 to 57.4)	<0.001
	n	Baseline	Change From Baseline to Week 26	*P* Value	n	Baseline	Change From Baseline to Week 52	*P* Value
WHO FC	70	FC I: 1 (1.4) FC II: 34 (48.6) FC III: 35 (50.0)	0 worsened 30 (42.9) unchanged 40 (57.1) improved	*NA*	65	FC I: 1 (1.5) FC II: 33 (50.8) FC III: 31 (47.7)	0 worsened 31 (47.7) unchanged 34 (52.3) improved	*NA*

	Exploratory Endpoints				Exploratory Endpoints			
	n	Baseline	Geometric Means Ratio of Week 26 to Baseline[c] (95% CL)	*P* Value	n	Baseline	Geometric Means Ratio of Week 52 to Baseline[c] (95% CL)	*P* Value
NT-proBNP, ng/L	60	846.7 ± 1,006.7	0.45 (0.37 to 0.54)	<0.0001	57	780.1 ± 962.0	0.44 (0.36 to 0.53)	<0.0001

Baseline values are n, mean ± SD, or n (%). RHC assessments (mean pulmonary arterial pressure, mean right atrial pressure, cardiac index) were not performed at 52 wk. [a]From analysis of covariance (ANCOVA) model on parameter change from baseline with a factor for PAH-targeted treatment strategy and parameter at baseline as a covariate. [b]From ANCOVA model on parameter change from baseline with factors for PAH-targeted treatment strategy and baseline WHO FC, and parameter at baseline as a covariate. [c]From ANCOVA model on log-transformed N-terminal pro-B-type natriuretic peptide (NT-proBNP), with a factor for PAH-targeted treatment strategy and baseline log NT-proBNP level as a covariate.

NA = not applicable; other abbreviations as in Tables 2 and 3.

TABLE 5 Exposure and Overview of Safety

	Safety Set (n = 87)
Duration of study treatment, wk	
Mean ± SD	48.6 ± 11.3
Median (min, max)	52.0 (1.1, 58.3)
Adverse events and serious adverse events	
Patients with ≥1 treatment-emergent AE in ≥10% of patients	75 (86.2)
Peripheral edema	19 (21.8)
Headache	18 (20.7)
Dizziness	12 (13.8)
Cough	10 (11.5)
Hemoglobin decreased	10 (11.5)
Upper respiratory tract infection	10 (11.5)
Myalgia	9 (10.3)
Patients with ≥1 AE leading to discontinuation of study treatment	7 (8.0)
Aspartate aminotransferase increased	2 (2.3)
Transaminases increased	2 (2.3)
Hypersensitivity	1 (1.1)
Liver function test increased	1 (1.1)
Edema peripheral	1 (1.1)
Patients with ≥1 treatment-emergent SAE	14 (16.1)
Fatal TE serious AE	1 (1.1)

Values are n (%), unless otherwise indicated.

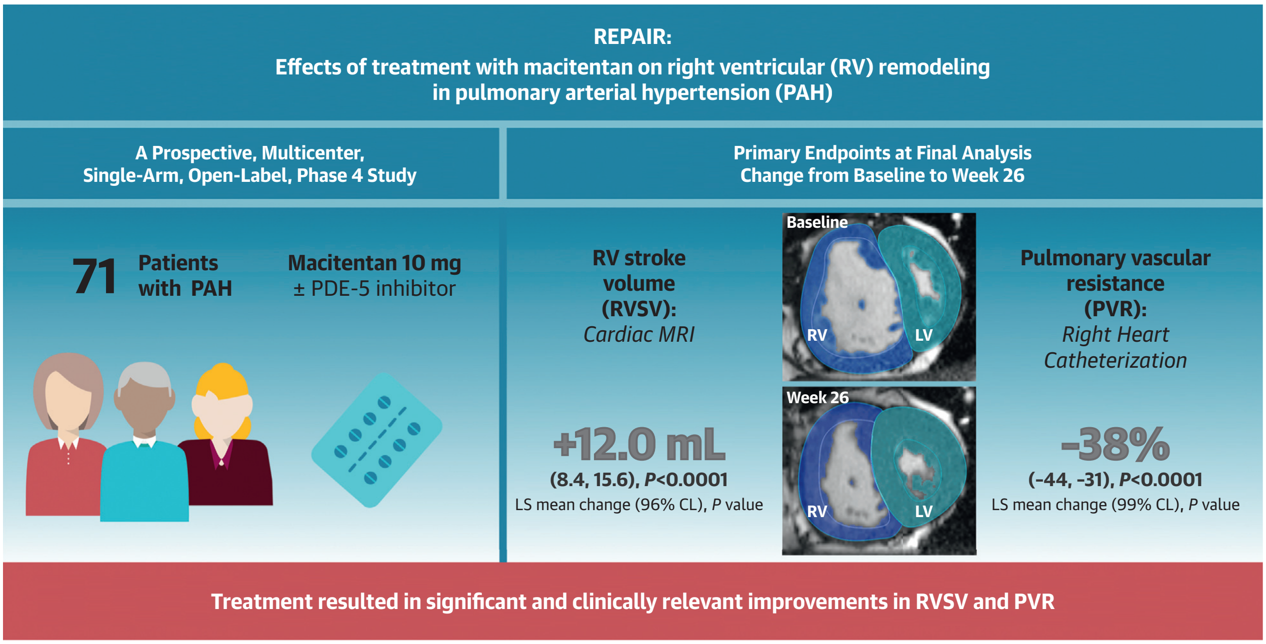
AE = adverse event; SAE = serious adverse event; TE = treatment emergent.

Patients who received macitentan as initial double combination therapy with a PDE-5i had numerically larger improvements than those initiating macitentan alone (either as monotherapy or sequential combination therapy), supporting the treatment approach recommended in the European Society of Cardiology/European Respiratory Society guidelines (16,17). However, there were major imbalances in baseline characteristics between the initial treatment regimen subgroups, and no formal statistical comparisons have been performed.

MACITENTAN TREATMENT LEADS TO LONG-TERM IMPROVEMENTS IN KEY CLINICAL PARAMETERS

Improvements were also seen in several key clinical parameters in the REPAIR study; 6MWD significantly increased from baseline to week 26, and the majority of patients had an improvement in WHO FC. In addition, NT-proBNP, a biomarker for cardiac overload (21) and prognostic for PAH (22), was significantly reduced. All of these improvements were maintained at week 52, supporting a sustained benefit of macitentan treatment beyond the

CENTRAL ILLUSTRATION REPAIR: Effects of Treatment With Macitentan on Right Ventricular Remodeling in Pulmonary Arterial Hypertension



Vonk Noordegraaf, A. et al. J Am Coll Cardiol Img. 2021;■(■):■-■.

REPAIR is the largest multicenter clinical trial in pulmonary arterial hypertension to use a cardiac magnetic resonance variable as a primary endpoint. Macitentan treatment, alone or in combination with a phosphodiesterase-type 5 inhibitor, led to statistically significant and clinically relevant improvements in right ventricular (RV) stroke volume and pulmonary vascular resistance at week 26, with improvements in RV stroke volume maintained at week 52.

typical 6-month observation period of PAH clinical studies.

The REPAIR study adds to the body of evidence supporting the efficacy of macitentan in PAH patients, including those receiving initial double combination therapy with macitentan and a PDE-5i (23), and reports safety data consistent with the known profile of macitentan (12,13).

CONSISTENT CMR RESULTS HIGHLIGHT THE CLINICAL RELEVANCE OF THIS NONINVASIVE IMAGING TECHNIQUE. RHC is the gold standard technique for measuring pressure (mPAP and pulmonary capillary wedge pressure) and calculating PVR (24). However, as the procedure is invasive and carries a small risk of complications, serial assessments are not routinely performed in clinical practice. By contrast, CMR is noninvasive, therefore lowering the risk for repeat assessments (24). Although CMR is more expensive and time-consuming than other noninvasive techniques such as echocardiography, the superior spatiotemporal resolution that CMR provides translates into an increased cost to benefit ratio (25). The clinical and cost benefits of CMR, including in patients with PH, has been further explored by Hegde et al (25).

As both REPAIR primary endpoints were positive and consistent with changes in hemodynamic (mPAP and cardiac index) and functional parameters (6MWD, WHO FC), this study provides further confidence in CMR-assessed endpoints and their potential use in future trials. In addition, CMR metrics have been shown to be reproducible, have prognostic value, and aid risk stratification in patients with PAH (5,7,26). The consistency of the CMR results presented here underline the clinical relevance of this imaging modality as a reliable noninvasive technique for monitoring disease status.

Previous studies in patients with PAH have used CMR parameters as endpoints to assess the effects of PH-targeted therapies on beneficial remodeling of the RV (27-29). The SERAPH (Sildenafil versus Endothelin Receptor Antagonist for Pulmonary Hypertension) randomized controlled trial (29) and a prospective observational study from van Wolferen et al (28) examined the addition of sildenafil to bosentan in patients with PAH; both reported decreases in RV mass of approximately 8-9 g with combination therapy. More recently, Hassoun et al (6) reported that combination therapy with ambrisentan and tadalafil resulted in a significant reduction in RV mass in treatment-naïve SSc-PAH patients (4.5 g). In contrast, an earlier study from Roeleveld et al (30) did not report significant changes in RV mass or RV end-diastolic volume measured by CMR in patients with PH treated with epoprostenol. Three clinical studies have also reported significant improvements in RVEF in patients with PH receiving PH-targeted therapies; van Wolferen et al (28) and van de Veerdonk et al (23) reported improvements following combination therapy with an ERA and PDE-5i, and the EURO-MR study (5) reported improvement with monotherapy (either ERA or PDE-5i). The COMPASS-3 study also supported the use of CMR in a clinical trial setting, with a number of CMR parameters found to predict clinical worsening/decline in patients with PAH (27). REPAIR extends these findings by showing that improvements were made for RV mass and RVEF in a multiregional PAH population receiving either macitentan monotherapy or combination therapy.

STUDY LIMITATIONS. Limitations of this study include its open-label design and the study size, which limited subgroup analyses.

CONCLUSIONS

The REPAIR study provides robust data to support the potential use of RVSV from CMR to assess RV cardiac function in future clinical trials in PAH. In addition to improving hemodynamic parameters (PVR, mPAP, cardiac index), PAH treatment with macitentan as monotherapy or part of combination therapy in this study resulted in improved RV function and structure, as shown by clinically relevant changes in CMR-measured RVSV, RVESV, RV mass, and RVEF, and in the corresponding LV parameters. Macitentan safety and tolerability were consistent with previous clinical trial data.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: The REPAIR study provides evidence that macitentan treatment significantly improves RV function and structure in patients with PAH, including those receiving initial double combination therapy with a PDE-5i. That these improvements were maintained for up to 52 weeks further supports the use of macitentan in PAH.

TRANSLATIONAL OUTLOOK: The consistent CMR results reported here, and in other studies, underscore the clinical relevance of this noninvasive imaging technique in monitoring PAH disease status and progression, and provide further confidence in CMR-assessed endpoints and their potential use in future trials.

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KEY WORDS cardiac magnetic resonance, hemodynamics, macitentan, pulmonary arterial hypertension, right ventricle

APPENDIX For an expanded Methods section as well as a supplemental figure and tables, please see the online version of this paper.