Circulation: Heart Failure

ORIGINAL ARTICLE

Macitentan for Heart Failure With Preserved or Mildly Reduced Ejection Fraction and Pulmonary Vascular Disease: Results of the SERENADE Randomized Clinical Trial and Open-Label Extension Study

Sanjiv J. Shah, MD; Diana Bonderman, MD; Barry A. Borlaug, MD; John G.F. Cleland, MD; Gabriela Lack, PhD; Wentao Lu, PhD; Adriaan A. Voors, MD; Faiez Zannad, MD; Mark T. Gladwin, MD

BACKGROUND: Despite favorable hemodynamic and neurohormonal effects, endothelin receptor antagonists have not improved outcomes in patients with heart failure (HF), possibly because they cause fluid retention.

METHODS: In this randomized, double-blind, multicenter trial (SERENADE [Macitentan in Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease]), we evaluated the effects of an endothelin receptor antagonist, macitentan, in patients with HF, left ventricular ejection fraction ≥40%, and pulmonary vascular disease. After a 4-week placebo run-in (to ensure clinical stability), followed by a 5-week single-blind macitentan run-in, patients who did not exhibit fluid retention were randomized to macitentan or placebo. The primary end point was change in NT-proBNP (N-terminal pro-B-type natriuretic peptide; baseline to 24 weeks); secondary end points included change in KCCQ (Kansas City Cardiomyopathy Questionnaire) clinical summary score (baseline to 24 weeks) and time to worsening HF by 52 weeks.

RESULTS: Of 230 patients enrolled, 28 were excluded during the placebo run-in, 60 excluded during the macitentan run-in, and 142 were randomized. Macitentan had no effect on change in NT-proBNP (geometric mean ratio [macitentan/placebo], 1.02 [90% CI, 0.88–1.19]; *P*=0.79) or on secondary end points (placebo-corrected change in KCCQ clinical summary score, −3.5 [90% CI, −8.2 to +1.2]; *P*=0.22). Worsening HF occurred in 20 (28%) patients assigned to macitentan and 13 (18%) assigned to placebo (hazard ratio, 1.48 [90% CI, 0.83–2.67]; *P*=0.24). More macitentan-treated patients developed fluid retention (16 [23%] versus 10 [14%]) and cardiac adverse events (33 [46%] versus 22 [31%]) versus placebo.

CONCLUSIONS: Despite a novel enrichment trial design to target pulmonary vascular disease and exclude treatment-related fluid retention in patients with HF and preserved/mildly reduced left ventricular ejection fraction, macitentan neither lowered NT-proBNP nor improved HF outcomes.

REGISTRATION: URL: https://www.clinicaltrials.gov; Unique identifiers: NCT03153111 and NCT03714815.

Key Words: endothelin receptor antagonist ■ pulmonary circulation ■ pulmonary hypertension ■ randomized controlled trial ■ right ventricular dysfunction

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Correspondence to: Sanjiv J. Shah, MD, Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, 676 N St. Clair St, Ste 730, Chicago, IL 60611. Email sanjiv.shah@northwestern.edu

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WHAT IS NEW?

- Previous clinical trials of heart failure (HF) suggest that endothelin receptor antagonists, an effective treatment for pulmonary arterial hypertension, might be beneficial in patients with left heart disease who have right-sided HF or in those who do not develop fluid retention soon after initiating an endothelin receptor antagonist.
- SERENADE (Macitentan in Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease) is the first placebo-controlled, randomized trial to investigate whether an endothelin receptor antagonist, macitentan, reduces natriuretic peptides, improves health status, and decreases HF events in patients with HF and left ventricular ejection fraction ≥40% with evidence of confirmed or probable pulmonary vascular disease.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Despite excluding patients who were clinically unstable during a placebo run-in period or who developed fluid retention during a subsequent macitentan run-in period, compared with placebo, macitentan neither reduced plasma concentrations of natriuretic peptides nor improved symptoms or quality of life. Compared with placebo, there were numerically more worsening HF events with macitentan, despite excluding those who developed fluid retention during the macitentan run-in phase. These findings indicate that endothelin receptor antagonists should not be used in patients with HF who have left ventricular ejection fraction ≥40% and pulmonary vascular disease.

Nonstandard Abbreviations and Acronyms

AE	adverse event
BNP	B-type natriuretic peptide
EF	ejection fraction
ERA	endothelin receptor antagonist
HF	heart failure
HFpEF	heart failure with preserved ejection fraction
KCCQ	Kansas City Cardiomyopathy Questionnaire
LA	left atrium
LV	left ventricle
NT-proBNP	N-terminal pro-B-type natriuretic peptide
PA	pulmonary artery
PVD	pulmonary vascular disease
PVR	pulmonary vascular resistance
RV	right ventricle
SAE	serious adverse event
SERENADE	Macitentan in Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease
SERENADE-OLE	SERENADE open-label extension
WU	Wood unit

Patients with heart failure with preserved ejection fraction (HFpEF) and pulmonary vascular disease (PVD) represent a distinct phenogroup,[1–9] but there are currently no approved treatments for such patients.[6] Endothelin is a potent vasoconstrictor implicated in the pathophysiology of PVD in heart failure (HF).[4,10] Clinical trials of endothelin receptor antagonists (ERAs) in patients with HF with reduced ejection fraction (EF) showed no benefit but were confounded by ERA-associated fluid retention.[11,12] Subsequent analyses suggested that patients without early fluid retention–related events had improved outcomes compared with placebo, and ERA treatment appeared to be more beneficial in patients with signs of right-sided HF.[12] These findings suggested that ERAs might be beneficial if administered in a more precision medicine–oriented approach, focusing on patients with advanced PVD and right-sided HF and excluding those who develop fluid retention on initial exposure to macitentan.

Sitaxentan improved exercise capacity in 1 trial in HFpEF,[13] but this ERA was subsequently withdrawn due to hepatotoxicity. In the MELODY-1 trial (Macitentan in Subjects With Combined Pre- and Post-Capillary Pulmonary Hypertension Due to Left Ventricular Dysfunction) (n=63), patients with HF and PVD were randomized to macitentan or placebo for 12 weeks.[14] Fluid retention was more frequent with macitentan than with placebo during the initial 4 weeks (6.4% versus 1.6%), with no between-group differences in fluid retention thereafter. Macitentan had no effect on pulmonary vascular resistance (PVR), but trends in reduced plasma NT-proBNP (N-terminal pro-B-type natriuretic peptide) concentrations and increased cardiac index were observed.[14]

Based on these data, we hypothesized that (1) enriching for patients with HF and PVD and (2) a run-in design to exclude patients with evidence of clinical instability or early fluid retention in response to macitentan might identify patients with a beneficial response to macitentan. We, therefore, conducted a phase 2b randomized trial to determine whether macitentan reduces plasma NT-proBNP and improves health status and physical activity—without worsening fluid retention—in patients with HF, EF ≥40%, and evidence of PVD, who did not develop early macitentan-induced fluid retention.

METHODS

The data sharing policy of Johnson & Johnson is available at https://www.jnj.com/about-jnj/policies-and-positions/our-position-on-clinical-trial-data-transparency. As noted on this site,

requests for access to the study data can be submitted through Yale Open Data Access Project site at http://yoda.yale.edu.

Objectives

The primary objective of SERENADE (Macitentan in Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease; https://www.clinicaltrials.gov; unique identifier: NCT03153111) was to compare the effects of macitentan 10 mg and placebo on plasma concentrations of NT-proBNP over 24 weeks in patients with HFpEF and PVD. Secondary outcomes included effects on health status (KCCQ [Kansas City Cardiomyopathy Questionnaire] clinical summary score), daily physical activity, and worsening HF. Effects on cardiovascular hospitalizations and deaths, New York Heart Association functional class, cardiac structure/function, safety, and tolerability were also recorded. Participants who completed the double-blind SERENADE trial were eligible to enter the long-term SERENADE-OLE study (SERENADE open-label extension; https://www.clinicaltrials.gov; unique identifier: NCT03714815). The aim of SERENADE-OLE was to assess long-term safety and tolerability of macitentan 10 mg in patients with HFpEF and PVD.

Trial Design and Participants

SERENADE was an international, multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase 2b trial conducted at 77 sites in 17 countries (Argentina, Austria, Brazil, Bulgaria, Czech Republic, Denmark, France, Germany, Hungary, Israel, Poland, Romania, Russia, Spain, Sweden, United Kingdom, and United States). The trial protocol was approved by the institutional review board or independent ethics committee at each participating site. Written informed consent was obtained from all trial participants. The trial steering committee designed the protocol with the trial sponsor. Throughout the trial, an independent data monitoring committee composed of cardiologists and a biostatistician periodically reviewed unblinded safety data.

Table S1 lists the inclusion and exclusion criteria for the trial. Key inclusion criteria included age ≥18 years with signs or symptoms of HF requiring treatment with at least 1 class of oral diuretic, New York Heart Association functional class II or III, left ventricular (LV) EF ≥40%, evidence of LV hypertrophy or left atrial (LA) enlargement on screening echocardiography, elevated plasma NT-proBNP or BNP (B-type natriuretic peptide) within 3 months of screening, and evidence of PVD. Due to concerns regarding feasibility of enrollment, we did not mandate invasive hemodynamic confirmation of PVD. Therefore, to enrich for likely PVD, patients who did not have PVD confirmed by right heart catheterization (PVR >3 Wood units [WU] or diastolic pulmonary gradient >5 mm Hg) were required to have echocardiographic (peak tricuspid regurgitation velocity >2.8 m/s or pulmonary artery [PA] systolic pressure >40 mm Hg) or invasive (mean PA pressure, ≥25 mm Hg) evidence of pulmonary hypertension, combined with echocardiographic evidence of right ventricular (RV) dysfunction (tricuspid annular plane systolic excursion <17 mm, RV fractional area change <35%, or RV tissue Doppler s′ velocity <9.5 cm/s). RV dysfunction was considered an appropriate surrogate for PVD in the setting of increased PA pressure because PVD ultimately leads to RV dysfunction. Echocardiographic evidence of LV EF ≥40% and markers of PVD and RV dysfunction were confirmed centrally by an independent echocardiography core laboratory.

Key exclusion criteria included any history of EF <40%; hemodynamically significant unrepaired primary valve disease; hypertrophic, restrictive, or infiltrative cardiomyopathy; pericardial disease; recent acute coronary syndrome or known indication of coronary revascularization; other causes of pulmonary hypertension or right-sided HF not associated with LV dysfunction (eg, significant chronic lung disease or recent history of pulmonary embolism); severe renal dysfunction (estimated glomerular filtration rate <30 mL/min per 1.73 m^2); severe hepatic impairment; and concurrent treatment with PA vasodilators (Table S1).

Patients who met the eligibility criteria entered a 4-week single-blind (ie, patient-blinded) placebo run-in period to ensure clinical stability, followed by a 5-week single-blind macitentan (10 mg daily) run-in period to exclude patients who developed fluid retention. Patients who did not meet any of the predefined run-in failure criteria (Table S2; Figure S1) were randomized to receive double-blind trial treatment for up to 52 weeks.

SERENADE-OLE was a multicenter, single-arm, open-label extension study of SERENADE conducted at 44 sites. The trial protocol was approved by the institutional review board or independent ethics committee at each participating site. Written informed consent was obtained from all trial participants. Only participants who completed the parent SERENADE trial per protocol were eligible to enter the SERENADE-OLE study.

Randomization and Blinding

The run-in periods were patient-blinded: patients were unaware of which order they would receive placebo and macitentan during run-in. During the double-blind period, patients, investigators, trial staff, and trial monitors remained blinded to treatment allocation until completion of the trial. Patients who were not excluded during the placebo and macitentan run-in periods were block randomized in a 1:1 ratio by an interactive voice response system to receive either macitentan 10 mg or placebo orally once daily, using the NT-proBNP value observed before entry in the macitentan run-in period as a stratification factor (<1000 versus ≥1000 pg/mL).

Trial Procedures

Key trial assessments included blood sampling for NT-proBNP (Elecsys proBNP II immunoassay for Cobas e601; Roche Diagnostics, Mannheim, Germany), daily physical activity measured by accelerometry (GT9X Link; Actigraph, Inc, Pensacola, FL), health status (KCCQ[15,16]), and comprehensive echocardiography, including Doppler and tissue Doppler imaging and RV assessment (read centrally by an echocardiography core laboratory [WorldCare Clinical, LLC, Boston, MA]). In-person follow-up visits were conducted at 4, 8, 16, 24, 36, and 52 weeks post-randomization and at 30 days after the end of treatment. In SERENADE-OLE, the focus was on the assessment of safety: in-person follow-up visits occurred at 1, 4, 8, 16, 24, 36, 52, 78, 104, and 130 weeks post-enrollment.

Efficacy and Safety End Points

The primary efficacy end point was change in NT-proBNP from baseline to week 24. Baseline was defined as the last

nonmissing value observed among all values measured during placebo and macitentan run-in periods, up to the day of randomization. Secondary end points included change from baseline to week 24 in KCCQ clinical summary score, change from baseline to week 24 in accelerometer-assessed proportion of time spent in light-to-vigorous physical activity (based on a threshold of >100 activity counts/min[17]), and time to a worsening HF event during 52 weeks of follow-up. Worsening HF was defined as either HF-related death, hospitalization for worsening HF, or an urgent visit to a health care facility for worsening HF. The latter 2 qualifying events must have been accompanied by new/worsening HF symptoms, objective evidence of worsening HF (eg, increase in NT-proBNP or BNP), and initiation/intensification of HF-specific treatment. For both SERENADE and SERENADE-OLE, key safety end points, evaluated from randomization to 30 days after treatment discontinuation, include all-cause mortality, treatment-emergent adverse events (AEs) and serious AEs (SAEs), treatment-emergent AEs of special interest, and AEs leading to premature discontinuation of trial treatment. Table S3 contains a full listing of the primary, secondary, exploratory, and safety end points evaluated in the trial. Only primary, secondary, and safety end points of SERENADE and safety end points of SERENADE-OLE are reported here.

Statistical Analysis

The sample size calculation for SERENADE was based on the primary end point (24-week change in NT-proBNP). A total number of 300 patients was determined adequate to detect a geometric mean ratio (macitentan/placebo) of 0.75, corresponding to a 25% greater reduction in NT-proBNP in macitentan versus placebo groups with a power of 80% and a 2-sided type I error of 0.10 when considering an SD of 1 in log scale and using the Wald test. The 2-sided type I error of 0.10 was used due to the phase 2, exploratory design of SERENADE. The SD of 1 for NT-proBNP was based on the PARAMOUNT trial,[18] in which the observed SD was 0.91 to 0.99 for the geometric mean ratio of week 12 to baseline NT-proBNP in the 2 treatment groups, and the MELODY-1 trial,[14,19] for which the SD of the geometric mean ratio was 0.82 in enrolled patients with baseline NT-proBNP ≥300 pg/mL. The targeted treatment effect of 0.75 was chosen based on MELODY-1 results.

We defined the full analysis set as all participants randomized to double-blind trial treatment. We defined the safety analysis set as all participants who received at least 1 dose of double-blind trial treatment. The primary results analysis in SERENADE was conducted using the full analysis set and the following outcome variable: log-transformed ratio of week 24 to baseline (prerandomization) NT-proBNP values, expressed as a percentage. We used an ANCOVA test adjusting for the log of the ratio of baseline (prerandomization) NT-proBNP to premacitentan run-in NT-proBNP. The treatment effect was expressed as the ratio of geometric means (macitentan divided by placebo values of the ratio of week 24 to baseline NT-proBNP). Its associated 90% 2-sided CI was estimated on the same model by inverse transformation using the exponential function of the least squares mean and 90% CIs obtained in log scale. For patients without available NT-proBNP data at week 24, missing data were imputed using last observation carried forward. A sensitivity analysis was performed by imputing missing NT-proBNP values at week 24 according to reason for dropout. To assess the consistency of the treatment effect across different patient subgroups for the primary end point, subgroup analyses (subgroup×treatment interaction testing) were performed for the following variables: geographic location, sex, age group, New York Heart Association functional class II versus III, history of atrial fibrillation, baseline renal function, obesity, and NT-proBNP (<1000 versus ≥1000 pg/mL).

ANCOVA was also applied (under assumptions of normal distribution) for change from baseline to week 24 in the KCCQ clinical summary score and in accelerometer-assessed proportion of time spent in light-to-vigorous physical activity based on a threshold of >100 activity counts per minute. Both analyses were adjusted for the baseline value of the variable and for the log of the ratio of baseline (prerandomization) to premacitentan run-in NT-proBNP.

The analysis of time to first occurrence of worsening HF was performed using a Cox proportional hazards model adjusting for the log of the ratio of baseline (prerandomization) to premacitentan run-in NT-proBNP. Kaplan-Meier estimates of the survival function for time-to-event variable were also calculated. All analyses were performed using SAS v.9.4 (SAS Institute, Cary, NC).

RESULTS

Patients were screened between August 2017 and December 2019, when the sponsor decided to cease further screening due to slow enrollment. Figure 1 displays the patient flowchart. A total of 437 patients were screened, of whom 230 (53%) entered the placebo run-in; 28 of these 230 (12%) patients met exclusion or run-in failure criteria during placebo run-in, and a further 60 (26%) patients were excluded during macitentan run-in. The remaining 142 (62%) patients were randomized to receive macitentan 10 mg (71 patients) or placebo (71 patients). A total of 91 patients were enrolled in SERENADE-OLE (46 patients from the macitentan group and 45 patients from the placebo group of the parent trial). Reasons for exclusion during run-in are listed in Figure 1.

The baseline characteristics were well balanced between randomized groups (Table 1). Table S4 lists the baseline characteristics of patients in the open-label period. Enrolled patients had characteristics typical of patients with HFpEF and PVD; they were older (median, 74 years), predominantly women (61%), with elevated plasma NT-proBNP (median, 1195 pg/mL) and Doppler echocardiography-estimated PA systolic pressure (median, 56 mm Hg), and high prevalence of comorbidities associated with metabolic syndrome (hypertension, 92%; type 2 diabetes, 42%; obesity, 58%). Of 142 randomized patients, 40% had available right heart catheterization data; the remaining 60% entered the study based on echocardiographic measurements. A total of 119 (84%) patients met the PVD criteria that combined elevated PA pressure with RV dysfunction, 20% met the elevated diastolic pulmonary gradient criteria, and 30%

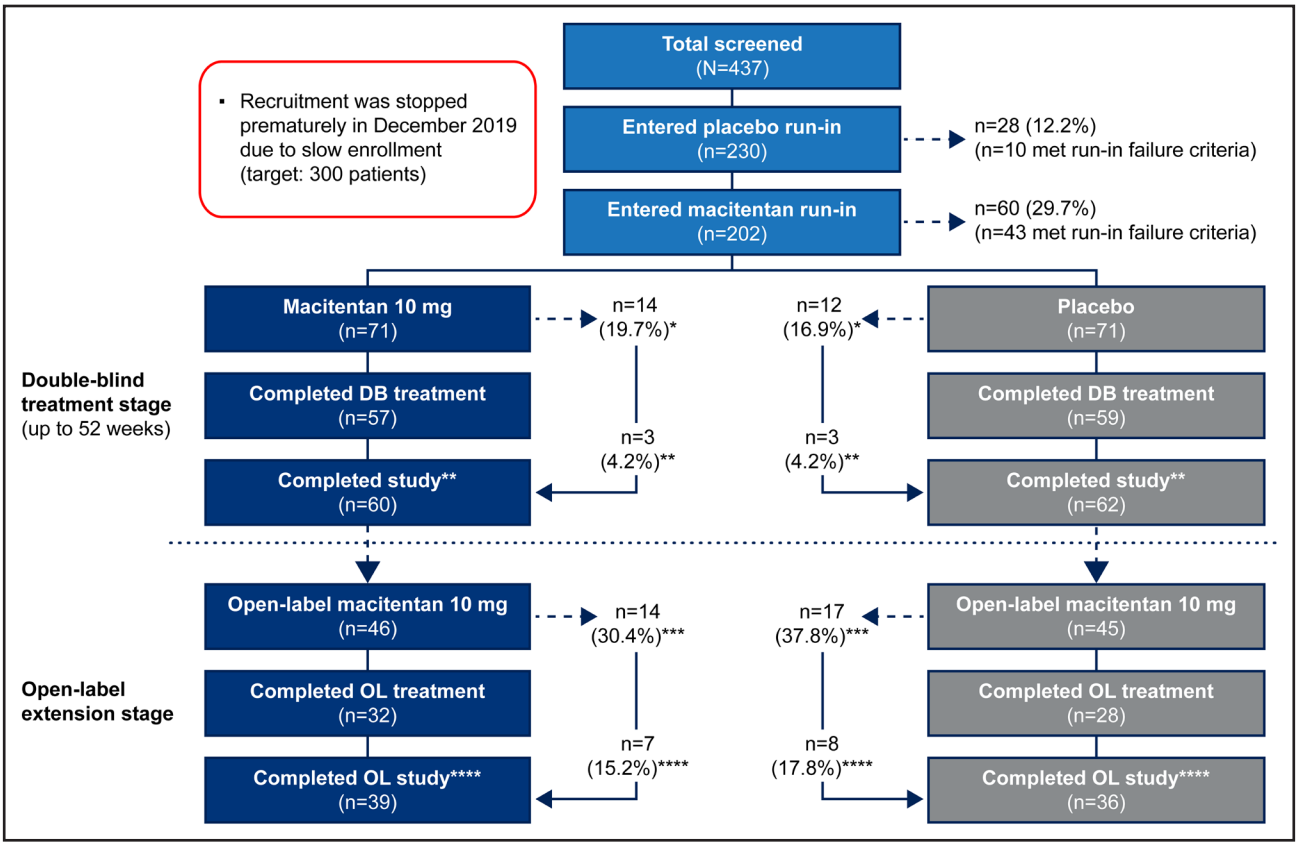

Figure 1. Study participant disposition flowchart.
Run-in failures by period: (1) placebo run-in (n [%]): predefined run-in exclusion criterion met, 10 (4.3); eligibility criteria not met*****, 5 (2.2); withdrawal by patient, 5 (2.2); other reason******, 8 (3.5); (2) macitentan predefined run-in exclusion criterion met, 43 (21.3); eligibility criteria not met*****, 10 (5.0); withdrawal by patient, 4 (2.0); other reason******, 3 (1.5). Predefined run-in exclusion criteria included: study treatment compliance <80%; decrease in hemoglobin by >5 g/dL from the screening value, hemoglobin <8 g/dL, or need for blood transfusion; or significant fluid retention or worsening of heart failure (HF) as evidenced by any 1 of the following: (1) administration of intravenous diuretics due to fluid retention; (2) addition of a high-potency thiazide diuretic (metolazone and indapamide) or torsemide; (3) ≥100% increase in loop diuretic dose to a total oral dose ≥120 mg of furosemide equivalents per day; (4) increase in body weight by ≥5% or ≥5 kg due to fluid overload; (5) worsening in New York Heart Association functional class; or (6) hospitalization for worsening HF. Patients could also be excluded from either run-in period for any adverse event (AE) that precluded continuation based on the site principal investigator's judgment criteria. *Reasons for double-blind (DB) treatment discontinuation include AEs, death, loss to follow-up, withdrawal of consent, or administrative reasons. **Patients completed the DB SERENADE study (Macitentan in Heart Failure With Preserved Ejection Fraction and Pulmonary Vascular Disease) if they remained in the study for 52 weeks (either on treatment or in posttreatment observation period) and completed the safety follow-up visit. ***Reasons for open-label (OL) treatment discontinuation include AEs, death, or lack of efficacy. ****Patients completed the SERENADE-OLE study (SERENADE open-label extension) if they remained on study treatment until termination of the study and completed the safety follow-up visit. *****Either eligibility not confirmed by central laboratory or exclusion criterion met during run-in. ******Other reasons: mainly inability to confirm eligibility by central echocardiogram reader (eg, ejection fraction not measurable).

met the elevated PVR criteria (patients could meet >1 PVD criteria). LA enlargement was present in nearly all patients (median LA volume index, 54 mL/m^2; normal value, <34 mL/m^2).

At week 24, the median (25th–75th percentile) change from baseline in NT-proBNP was +9 (−272 to +306) pg/mL in the macitentan group and +35 (−330 to +444) pg/mL in the placebo group. The geometric mean (median) percentage of baseline NT-proBNP at week 24 was 108.4 (102) in the macitentan group and 106.3 (105) in the placebo group. There was no statistically significant difference in NT-proBNP between the groups (Figure 2); the geometric mean ratio (macitentan over placebo) was 1.0 ([90% CI, 0.9–1.2] *P*=0.79), and the median ratio was also 1.0 (90% CI, 0.9–1.1). Prespecified subgroup analyses were consistent with the primary analysis. There were no statistically significant differences between macitentan and placebo in any subgroups (Figure 3).

Table 2 lists the results of the key secondary end points. There was no statistically significant difference between macitentan and placebo in change from baseline to week 24 in KCCQ clinical summary score (mean difference [macitentan−placebo], −3.5 [90% CI, −8.2 to +1.2]; *P*=0.22). Fewer than 50% of patients had evaluable accelerometry data due to poor compliance, defined as <4 complete days with at least 7 hours of data; among those with evaluable data, there

Table 1. Baseline Characteristics of Patients in the Main Study

Characteristic	Double-blind treatment period	
	Macitentan (n=71)	Placebo (n=71)
Age, y	74 (68–80)	74 (69–79)
Women, n (%)	46 (65)	41 (58)
Race, n (%)		
Black	3 (4)	1 (1)
Native American/Alaskan	0 (0)	1 (1)
White	68 (96)	67 (94)
Other	0 (0)	2 (3)
Enrollment region, n (%)		
Americas	15 (21)	12 (17)
Eastern Europe	30 (42)	28 (39)
Western Europe	26 (37)	31 (44)
New York Heart Association functional class, n (%)		
II	35 (49)	32 (45)
III	36 (51)	39 (55)
Time since the most recent HF hospitalization, y (n=37/37*)	0.1 (0.1–0.3)	0.3 (0.1–0.6)
LVEF (core laboratory measured), n (%)		
<40%	1 (1)	0 (0)
40%–49%	7 (10)	8 (11)
≥50%	62 (87)	63 (89)
Missing (not measurable)	1 (1)	0 (0)
PVD criteria, n (%)†		
Elevated PA pressure and evidence of RV dysfunction	61 (86)	58 (82)
Diastolic pulmonary gradient >5 mm Hg‡	12 (18)	15 (21)
PVR >3 WUs‡	23 (32)	19 (27)
Comorbidities, n (%)		
Hypertension	65 (92)	68 (96)
Obesity	42 (59)	40 (56)
Type 2 diabetes	25 (35)	30 (42)
Atrial fibrillation/flutter	50 (70)	60 (85)
Ischemic heart disease	17 (24)	31 (44)
Anemia	15 (21)	22 (31)
Chronic obstructive pulmonary disease	14 (20)	12 (17)
Obstructive sleep apnea	14 (20)	12 (17)
Medications, n (%)		
Angiotensin-converting enzyme inhibitor	28 (39)	22 (31)
Angiotensin receptor blocker	23 (32)	28 (39)
β-Blocker	54 (76)	52 (73)
Calcium channel blocker	18 (25)	23 (32)
Digoxin	9 (13)	6 (9)
Loop diuretic	60 (85)	60 (85)
Thiazide diuretic	6 (9)	8 (11)
Mineralocorticoid receptor antagonist	34 (48)	39 (55)
Sodium-glucose cotransporter 2 inhibitor	1 (1)	0 (0)
Anticoagulant	49 (69)	56 (79)
Antiplatelet	19 (27)	18 (25)
Physical exam		
Heart rate, bpm	74 (63–82)	72 (64–81)
Systolic blood pressure, mm Hg	127 (118–139)	128 (119–140)
Diastolic blood pressure, mm Hg	75 (67–79)	75 (70–81)
Weight, kg	79.5 (69.3–101.8)	84.0 (73.3–100.0)
Body mass index, kg/m²	31.2 (25.7–36.0)	30.4 (26.9–35.5)
Jugular venous distension, n (%)	18 (25)	17 (24)
Peripheral edema, n (%)	35 (49)	37 (52)
Laboratory data		
Hemoglobin, g/dL (n=69/68)	12.9 (11.8–13.6)	13.2 (12.2–14.6)
Estimated GFR, mL/min per 1.73 m² (n=70/70)	56 (41–71)	54 (42–62)
NT-proBNP in patients without atrial fibrillation, pg/mL (n=50/58)	902 (441–1200)	1091 (500–1623)
NT-proBNP in patients with atrial fibrillation, pg/mL (n=21/13)	1225 (788–1983)	1337 (772–1970)
Echocardiography		
LVEF, % units (n=70/71)	62 (56–66)	62 (57–66)
LV posterior wall thickness, mm (n=70/67)	11 (10–12)	10 (9–11)
LA volume index, mL/m² (n=69/71)	54 (43–69)	55 (42–69)
E/e′ ratio§ (n=60/65)	10.9 (8.3–14.4)	10.3 (7.6–14.3)
Estimated PA systolic pressure, mm Hg (n=66/68)	56 (44–76)	56 (46–68)
Estimated right atrial pressure, mm Hg (n=68/68)	15 (8–15)	15 (8–15)
Peak TR velocity, m/s (n=67/69)	3.3 (2.9–3.9)	3.3 (3.0–3.7)
TAPSE, mm (n=66/68)	14.6 (12.2–17.1)	14.6 (12.4–17.9)
RV fractional area change, % units (n=68/68)	32 (25–39)	33 (26–41)
RV s′ velocity, cm/s (n=66/68)	9 (8–11)	9 (7–11)
Hemodynamic parameters‖		
mPAP, mm Hg (n=30/27)	44.5 (36.3–48.8)	37 (31–44)
mRAP, mm Hg (n=30/27)	14 (10.3–16.8)	13 (9–14.5)
PVR, WU (n=30/25)	4.6 (3.4–6.3)	3.9 (3.1–6.4)

(*Continued*)

(*Continued*)

Table 1. Continued

Characteristic	Double-blind treatment period	
	Macitentan (n=71)	Placebo (n=71)
PAWP, mm Hg (n=27/24)	23 (18–26)	19.5 (16–22.3)
LVEDP, mm Hg (n=14/12)	19.5 (16.3–22.5)	19 (15.8–24.8)
TPG, mm Hg (n=27/24)	21 (15–25)	18 (14–26)
DPG, mm Hg (n=30/26)	4.5 (0.3–11.8)	6.5 (4–10)

Values represent median (25th–75th percentile) for continuous variables. For any variable where the number of participants with measurements available is <71, the n number is given in the left hand column as ($n_{macitentan}$/$n_{placebo}$). bpm indicates beats per minute; DPG, diastolic pressure gradient; EF, ejection fraction; GFR, glomerular filtration rate; HF, heart failure; LA, left atrial; LV, left ventricular; LVEDP, left ventricular end diastolic pressure; mPAP, mean pulmonary arterial pressure; mRAP, mean right atrial pressure; NT-proBNP, N-terminal pro-B-type natriuretic peptide; PA, pulmonary artery; PAWP, pulmonary artery wedge pressure; PVD, pulmonary vascular disease; PVR, pulmonary vascular resistance; RHC, right heart catheterization; RV, right ventricular; TAPSE, tricuspid annular plane systolic excursion; TPG, transpulmonary pressure gradient; TR, tricuspid regurgitation; and WU, Wood unit.

*In patients who were hospitalized within the last 12 mo (37 patients each in the macitentan and placebo groups).

†Patients could meet >1 criteria. Elevated PA pressure was defined as echocardiographic peak TR velocity >2.8 m/s, invasive mean PA pressure ≥25 mm Hg, or PA systolic pressure >40 mm Hg; RV dysfunction was defined as TAPSE <17 mm, RV fractional area change <35%, or tissue Doppler s′ velocity <9.5 cm/s. Diastolic pulmonary gradient=PA diastolic pressure—pulmonary capillary wedge pressure. PVR was calculated as mean PA pressure−PA wedge pressure divided by cardiac output.

‡Number of patients with available RHC data meeting the hemodynamic criteria for PVD.

§Calculated using e′ velocity measured at the lateral mitral annulus.

‖Historical (partial or complete) RHC data were available for 30 patients in the macitentan group and 27 patients in the placebo group. The number of patients with data available for each RHC variable (n) is shown in the left hand column as ($n_{macitentan}$/$n_{placebo}$).

was no statistically significant effect of macitentan on time spent in light/vigorous physical activity (mean difference [macitentan—placebo], −0.02 [90% CI, −0.05 to 0.02]; *P*=0.37). Figure 4 displays the Kaplan-Meier curves for time to first worsening HF event in the 2 treatment groups. During a median follow-up duration of 362 (25th–75th percentile, 175–374) days, there were 20 worsening HF events in the macitentan group and 13 worsening HF events in the placebo group (hazard ratio, 1.48 [90% CI, 0.83–2.67]; *P*=0.24); events were driven by HF hospitalization and urgent visits for worsening HF. One HF death reported in the placebo group contributed to this end point; the other 2 HF deaths (1 in the macitentan group and 1 in the placebo group) were preceded by another worsening HF event (HF hospitalization) and thus did not contribute to the time to first event end point.

The median (range) treatment duration, regardless of interruptions, was 42 (4–61) weeks with double-blind macitentan and 41 (3–60) weeks with placebo. Table 3 lists the most frequent AEs reported in SERENADE by treatment group (evaluated in the safety analysis set). SAEs were reported in 29 (41%) and 23 (32%) patients on macitentan and placebo, respectively. The most frequently reported SAEs (macitentan versus placebo) were RV failure (6 patients [8.5%] in each group), congestive cardiac failure (5 [7.0%] versus 0 patients), LV failure (3 [4.2%] versus 2 [2.8%] patients), and pneumonia (2 [2.8%] versus 3 [4.2%] patients). AEs of special interest (anemia and fluid retention/edema) were reported in 31 (44%) patients in the macitentan group and 16 (23%) patients in the placebo group. Twelve (16.9%) patients in the macitentan group and 5 (7.0%) in the placebo group experienced an AE leading to premature discontinuation of trial treatment; the main reasons were RV failure (4 patients [5.6%]) and fluid retention (2 patients [2.8%]) in the macitentan group and ischemic stroke (2 patients [2.8%]) in the placebo group. There was 1 death in the macitentan group and 5 in the placebo group during the trial.

Additional safety end points are presented in Table S5. In summary, the change from baseline to week 24 in glomerular filtration rate demonstrated a greater worsening (reduction) in patients receiving macitentan versus placebo (mean difference [macitentan—placebo], −3.5 [90% CI, −6.4 to −0.6]; *P*=0.05). Macitentan (compared

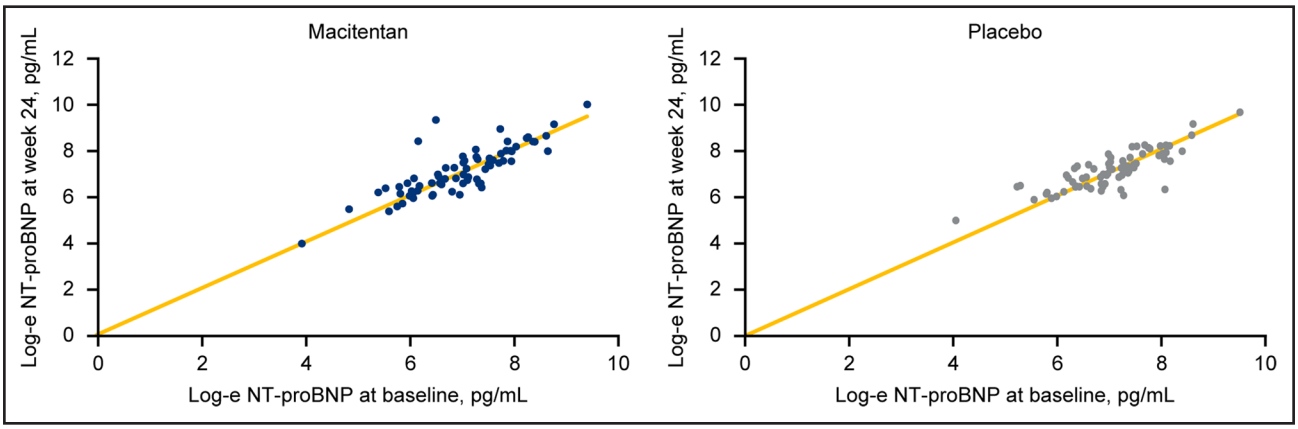

Figure 2. Scatterplots showing log NT-proBNP (N-terminal pro-B-type natriuretic peptide) at baseline vs week 24. **Left**, Macitentan arm; **right**, placebo arm. Orange line is the line of identity for NT-proBNP.

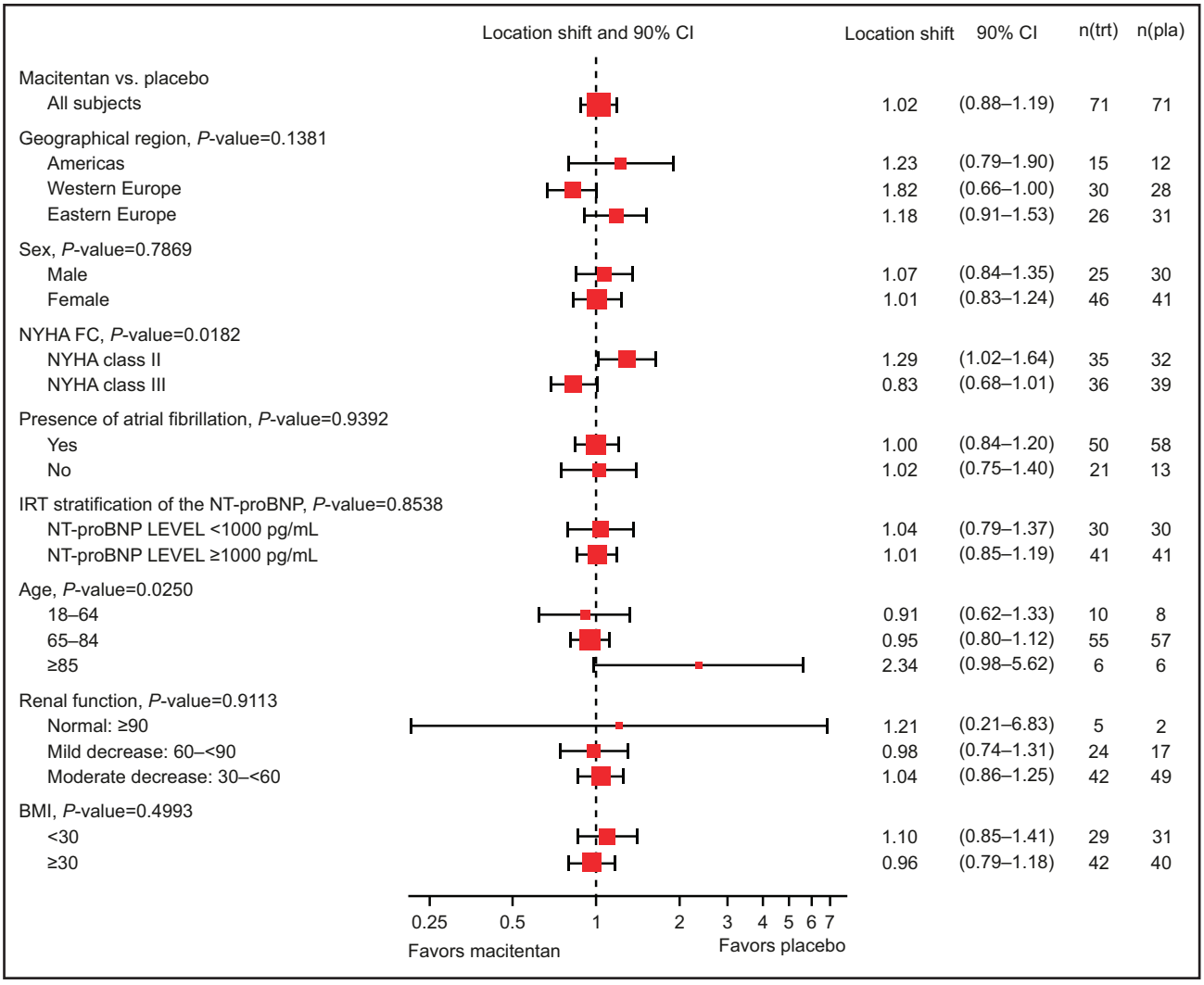

Figure 3. Forest plot of treatment effect (macitentan vs placebo) on the primary end point (change in NT-proBNP [N-terminal pro-B-type natriuretic peptide], baseline to 24 weeks) by prespecified subgroups.
BMI indicates body mass index; IRT, Interactive Response Technology; n(pla), number in placebo arm; n(trt), number in macitentan arm; NYHA, New York Heart Association; and NYHA FC, New York Heart Association functional class.

with placebo) resulted in a greater reduction in systolic blood pressure from baseline to week 24 (mean difference [macitentan—placebo], —4.2 [90% CI, —7.8 to —0.6]; *P*=0.06), but there was no difference in change in body weight between groups (mean difference [macitentan—placebo], —0.1 [90% CI, —1.1 to 0.9]; *P*=0.89).

Based on the main study results, the sponsor decided to stop SERENADE-OLE prematurely without option for continued access to macitentan. The median (range) duration of open-label extension treatment was 56 (0–126) weeks. Safety findings from SERENADE-OLE are listed in Table S6. SAEs were reported in 49 (53.8%) patients. The most frequently reported SAEs were congestive cardiac failure (6.6%), RV failure (5.5%), and acute kidney injury. AEs of special interest were reported in 14.3% (anemia), 13.2% (fluid retention/edema), and 5.5% (hepatic AEs of special interest) of patients. A total of 25 (27.5%) patients had AEs leading to discontinued open-label treatment, the most frequent of which were congestive cardiac failure and RV failure (3.3% each). Eleven deaths were reported during SERENADE-OLE (Table S6).

DISCUSSION

SERENADE is one of the first trials in HFpEF to use a precision medicine approach,[20] targeting a specific HFpEF phenotype (those with evidence of PVD) as an enrichment strategy while restricting randomization to patients without evidence of clinically overt fluid retention during a macitentan challenge. Because fluid retention was a major reason for the failure of prior trials of ERA in HF and based on the observation that fluid retention events typically occurred within the first 4 to 6 weeks of ERA initiation, the run-in design was intended to identify and exclude patients who were susceptible to developing fluid retention issues before randomization.

Table 2. Key Secondary End Point Results: KCCQ Clinical Summary Score and Accelerometry-Assessed Physical Activity

End point		Macitentan	Placebo
Change from baseline to week 24 in KCCQ clinical summary score	n	69	71
	Median	−3	+3
	Mean (SD)	−2 (16)	+1 (18)
	Between-treatment difference		
	LS mean (SE)	−3.5 (2.8)	
	90% CI	−8.2 to +1.2	
	P value	0.22	
Change from baseline to week 24 in proportion of time spent in light-to-vigorous physical activity*	n	30	31
	Median	0	0
	Mean (SD)	−0.02 (0.08)	−0.01 (0.10)
	Between-treatment difference		
	LS mean (SE)	−0.02 (0.02)	
	90% CI	−0.05 to +0.02	
	P value	0.37	

KCCQ indicates Kansas City Cardiomyopathy Questionnaire; and LS, least squares.

*Change from baseline to week 24 in accelerometer-assessed proportion of time spent in light-to-vigorous physical activity was based on a threshold of >100 activity counts per minute.

The trial was terminated early due to slow recruitment rate, but the absence of any positive trend in all efficacy measurements indicates that macitentan 10 mg would be unlikely to benefit patients with HFpEF and PVD. The open-label extension of SERENADE (SERENADE-OLE) was stopped based on results of the main study. The safety profile observed in the SERENADE studies was consistent with previous studies of ERAs in patient populations with HF. In SERENADE, AEs were more common in patients randomized to macitentan versus placebo. Fluid retention was nearly twice as common with macitentan than with placebo, despite the exclusion of patients with clinical instability or early fluid retention in response to macitentan in the run-in phases. Accordingly, worsening HF events (driven by HF hospitalizations) were numerically more common with macitentan than placebo, although the difference was not statistically significant, perhaps due to the small sample size. More deaths occurred in the placebo group versus macitentan; however, 3 of the 5 deaths in the placebo group had primary causes other than HF. The mechanism for fluid retention with ERAs is not clear, but recent studies showed that worsening congestion in this therapy setting is associated with increased risk for new-onset HF, despite slowing deterioration in renal function.[21] We now show that patients who develop worsening congestion may not be effectively identified even when challenged with several weeks' exposure to an ERA. The findings from SERENADE, coupled with those of the MELODY-1 trial,[14] do not support a role for ERAs in HFpEF-PVD, even in patients with no evidence of fluid retention in the weeks after initiation of an ERA.

Treatment of patients with HFpEF-PVD is challenging.[6,7] Pulmonary vasodilators, including phosphodiesterase-5 inhibitors,[22] soluble guanylate cyclase stimulators,[23,24] and ERAs,[19] have all failed to demonstrate convincing benefit in patients with HFpEF but have not focused specifically on those with PVD. Reasons for lack of efficacy might include withdrawal of interventions due to adverse reactions such as fluid retention; failure to enrich the population for PVD that may be more likely to benefit from pulmonary vasodilators (this was not done for trials of sildenafil[22] or soluble guanylate cyclase stimulators in HFpEF[23,24]); assessment of pulmonary hemodynamics and RV function at rest only; and targeting the wrong pathophysiology.

The recently published REDUCE LAP-HF II trial (A Study to Evaluate the Corvia Medical Inc IASD System II to Reduce Elevated Left Atrial Pressure in Patients With Heart Failure) of an interatrial shunt device in HFpEF[25] demonstrated the potential importance of dynamic changes in PVR during exercise. Those with peak exercise PVR <1.74 WU at baseline appeared to benefit from the device, while those with peak exercise PVR ≥1.74 WU appeared to do worse in terms of HF hospitalizations.[25,26] Interestingly, several patients with a PVR ≥1.74 WU at rest vasodilated with exercise, whereas several patients with PVR <1.74 WU at rest vasoconstricted during exercise.[26] Thus, future trials of patients with HFpEF may benefit from invasive exercise hemodynamic phenotyping to determine whether those with elevated PVR during exercise (which may not be apparent from resting PVR) benefit most from pulmonary vasodilators or whether those with greater capacity for pulmonary vasodilation are more likely to benefit. Exertional profiling may also provide greater insights, as symptoms develop during exercise and favorable drug effects may be stronger during exercise, as was observed in an acute, double-blind trial of albuterol in HFpEF. This trial found a reduction in PVR during exercise but not at rest.[27]

Autopsy studies have suggested that, in HFpEF, PVD resembles pulmonary veno-occlusive disease more so than pulmonary arterial hypertension, with a predominant pulmonary venopathy in addition to pulmonary arteriopathy.[28] Indeed, a recent pathophysiologic study showed that lung congestion during exercise was greater in patients with HFpEF-PVD, than in those with HFpEF but no PVD, even though LA pressures were similar between the groups.[8] With pulmonary vein remodeling, the venous component of PVR increases downstream of the capillaries, causing a greater increase in pulmonary capillary pressures for any LA pressure to drive forward flow, which would explain the greater increases in lung congestion observed. Therefore, pulmonary vasodilators acting exclusively on the arterial (precapillary) circulation might be less effective, or even detrimental, in HFpEF-PVD.

Alternatively, reducing stressed blood volume (ie, the dynamic shift of blood volume from the gut to the

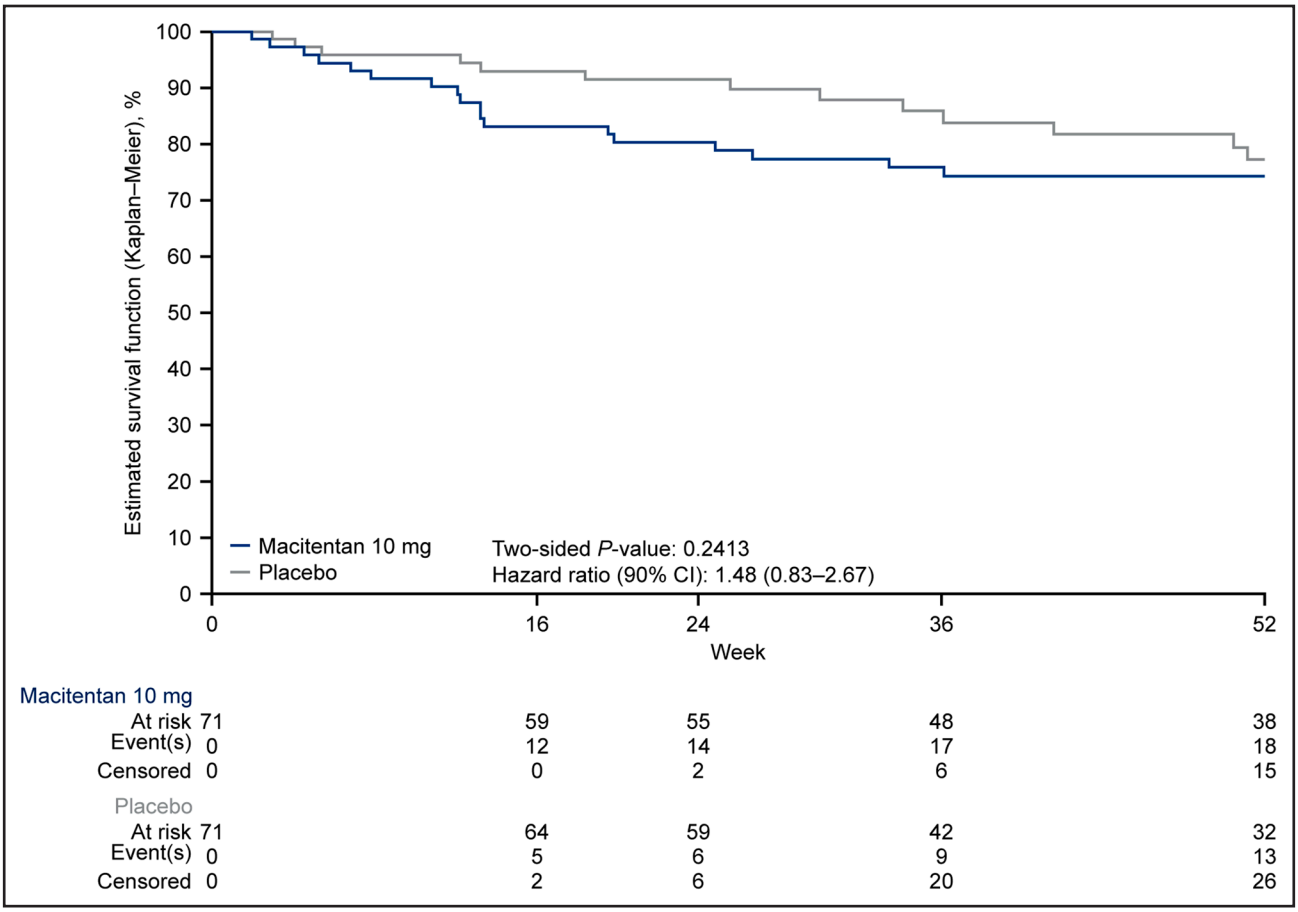

Figure 4. Kaplan-Meier estimates of worsening heart failure (HF) events among patients randomized to macitentan vs placebo. Median (25th–75th percentile) follow-up time: 364 (174–384) days in the macitentan group and 353 (175–371) days in the placebo group. Worsening HF was defined as either HF death, HF hospitalization, or an urgent visit for worsening HF, and the latter 2 qualifying events must have been accompanied by new/worsening HF symptoms, objective evidence of worsening HF (eg, increase in HF biomarker), and initiation or intensification of HF-specific treatment.

thorax during exercise)[29] while supporting RV inotropy (with pharmacological approaches such as levosimendan) is agnostic to the type of pulmonary vasculopathy and thus might be worthy of further investigation. Indeed, the results of the HELP-PH-HFpEF trial of levosimendan were promising given the ≈30-m improvement in 6-minute walk test, although the sample size was small (n=37).[30] Subsequent analyses of the trial demonstrated that the observed benefit might have been due to a reduction in stressed blood volume.[31] Additional treatment options in HFpEF-PVD under development include β-adrenergic agonists,[27,32] splanchnic nerve ablation (to reduce stress blood volume),[33] and an implantable system to increase central PA compliance (https://www.clinicaltrials.gov; unique identifier: NCT05001711).

Strengths and Limitations

Strengths of the SERENADE trial include its targeted, precision medicine design, which focused on patients with HFpEF with objective evidence of PVD and included placebo and macitentan run-in periods to enroll clinically stable patients without overt fluid retention in response to macitentan (thought to be a major reason why prior trials of ERAs in HF have failed). In addition, patients enrolled in SERENADE were required to have clear, objective evidence of HFpEF or HF with mildly reduced EF, elevated NT-proBNP, and evidence of LV hypertrophy or LA enlargement.

The early cessation of enrollment due to slow recruitment of patients into the trial is an important limitation. However, given the lack of benefit in the primary or secondary outcomes, and the numerically greater rate of fluid retention and worsening HF, these results show that macitentan is extremely unlikely to benefit patients with HFpEF-PVD. Sixty percent of patients entered the study based on echocardiographic measurements; while it is possible that some patients without PVD could have been included, these surrogate markers are well validated against direct invasive PVR measures, and this limitation would be unlikely to explain the absence of benefit observed in SERENADE. Nevertheless, future trials of therapies targeting the pulmonary vasculature in HFpEF may benefit from mandating right heart catheterization

Table 3. Most Frequent AEs (Including SAEs) in the Main Study

Double-blind treatment period	Macitentan (n=71)	Placebo (n=71)
Patients with ≥1 AE	63 (88.7)	61 (85.9)
Patients with ≥1 SAE	29 (40.8)	23 (32.4)
Patient with ≥1 AE leading to study treatment discontinuation	11 (15.5)	4 (5.6)
Most frequent AEs*		
RV failure	10 (14.1)	8 (11.3)
Peripheral edema	9 (12.7)	5 (7.0)
Congestive cardiac failure	8 (11.3)	1 (1.4)
Dyspnea	8 (11.3)	7 (9.9)
Gout	6 (8.5)	2 (2.8)
LV failure	6 (8.5)	2 (2.8)
Renal impairment†	6 (8.5)	1 (1.4)
Acute kidney injury†	5 (7.0)	4 (5.6)
Anemia	5 (7.0)	3 (4.2)
Fatigue	5 (7.0)	6 (8.5)
Atrial fibrillation	4 (5.6)	5 (7.0)
Pneumonia	4 (5.6)	8 (11.3)
Urinary tract infection	2 (2.8)	7 (9.9)
Renal failure†	2 (2.8)	5 (7.0)
AEs of special interest	31 (43.7)	16 (22.5)
Anemia	21 (29.6)	9 (12.7)
Edema/fluid retention	16 (22.5)	10 (14.1)
Total deaths	1 (1.4)	5 (7.0)
Primary AEs associated with death		
HF	1 (1.4)	2 (2.8)
Multiple organ failure after surgery	0	1 (1.4)
Septic shock	0	1 (1.4)
Stroke	0	1 (1.4)
Laboratory measurements of interest		
ALT/AST 3×ULN	1 (1.4)	0
Hemoglobin <10 g/dL	17 (23.9)	7 (9.9)
Hemoglobin <8 g/dL	3 (4.2)	1 (1.4)

Data are n (%). AE indicates adverse event; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HF, heart failure; LV, left ventricular; RV, right ventricular; SAE, serious adverse event; and ULN, upper limit of normal.

*Only AEs with total frequency ≥5.0% in 1/both groups are listed.

†Combining renal impairment, acute kidney injury, and renal failure AEs together, the frequency of renal events was 13 (18%) vs 10 (14%) in the macitentan and placebo groups, respectively.

in all patients to document the presence of PVD. Finally, given the early termination of the trial plus the lack of analyzable accelerometry data on a large proportion of the patients, we were underpowered to detect an effect of macitentan on physical activity.

Conclusions

Despite a novel precision medicine enrichment trial design to target PVD and exclude ERA-related fluid retention in patients with HF and preserved or mildly reduced EF, macitentan neither lowered NT-proBNP nor improved HF outcomes. ERAs should not be used in patients with HFpEF, even if there is evidence of PVD. Future clinical trials targeting patients with HFpEF and PVD should consider mandating invasive hemodynamic testing to document PVD in all patients.

ARTICLE INFORMATION

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Affiliations

Division of Cardiology, Department of Medicine, Northwestern University Feinberg School of Medicine, Chicago, IL (S.J.S.). Division of Cardiology, Favoriten Clinic, Wiener Gesundheitsverbund, Vienna, Austria (D.B.). Division of Circulatory Failure, Department of Cardiovascular Disease, Mayo Clinic and Foundation, Rochester, MN (B.A.B.). British Hearth Foundation Centre of Research Excellence, School of Cardiovascular & Metabolic Health, College of Medical, Veterinary and Life Sciences, University of Glasgow, United Kingdom (J.G.F.C.). R&D Cardiopulmonary Clinical Sciences, Johnson & Johnson, Allschwil, Switzerland (G.L.). Statistics & Decision Sciences, Johnson & Johnson, Raritan, NJ (W.L.). Department of Cardiology, University of Groningen, University Medical Center Groningen, the Netherlands (A.A.V.). Université de Lorraine, Inserm Centre d'Investigations Cliniques Plurithématique 1433 and CHRU, Nancy, France (F.Z.). Department of Medicine, University of Maryland School of Medicine, Baltimore (M.T.G.).

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Disclosures

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Supplemental Material

Tables S1–S6
Figure S1

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