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Randomized, Double-Blind, Placebo-Controlled Study of Sitaxsentan to Improve Impaired Exercise Tolerance in Patients With Heart Failure and a Preserved Ejection Fraction

Michael R. Zile, MD,* Robert C. Bourge, MD,† Margaret M. Redfield, MD,‡ Duo Zhou, MS,§ Catalin F. Baicu, PhD,* William C. Little, MD‖

Charleston, South Carolina; Birmingham, Alabama, Rochester, Minnesota; Groton, Connecticut; and Jackson, Mississippi

Objectives The purpose of this study was to evaluate the efficacy and safety of the selective endothelin type A (ET_A) receptor antagonist sitaxsentan in patients who have heart failure with preserved ejection fraction (HFpEF).

Background Fifty percent of heart failure (HF) patients have a preserved ejection fraction. No treatment has been shown to improve their clinical outcomes. Previous studies have suggested that ET_A receptor antagonists might improve diastolic function and exercise tolerance in some forms of HF.

Methods In all, 192 HFpEF patients (EF ≥50%) were randomly assigned 2:1 to sitaxsentan 100 mg/day (n = 128) versus placebo (n = 64) for 24 weeks. The primary endpoint was change in treadmill exercise time after 24 weeks of treatment. Secondary objectives included changes in left ventricular mass, transmitral inflow velocity to early diastolic mitral annulus velocity ratio, and Minnesota Living With Heart Failure questionnaire, and New York Heart Association functional class. Subjects were age 65 ± 11 years, 63% female, 29% non-Caucasian, and in functional class II (56.5%) or III (43.5%).

Results Subjects treated with sitaxsentan had an increase in median treadmill time (90 s) compared with placebo-treated subjects (37 s, p = 0.0302). There was no significant treatment differences in transmitral inflow velocity to early diastolic mitral annulus velocity ratio, left ventricular mass, Minnesota Living With Heart Failure questionnaire, New York Heart Association functional class, deaths, or HF hospital stay. The incidence of adverse events was similar for sitaxsentan and placebo.

Conclusions In HFpEF patients, treatment with a selective ET_A receptor antagonist increased exercise tolerance but did not improve any of the secondary endpoints such as left ventricular mass or diastolic function. Further studies will be necessary to determine whether ET_A receptor antagonists may be useful in the treatment of HFpEF. (A Study of the Effectiveness of Sitaxsentan Sodium in Patients With Diastolic Heart Failure; NCT00303498) (J Am Coll Cardiol HF 2014;2:123–30) © 2014 by the American College of Cardiology Foundation

Heart failure with preserved left ventricular ejection fraction (HFpEF) is a syndrome characterized by the signs and symptoms of heart failure (HF), a preserved ejection fraction (≥50%), and abnormal diastolic function (1). Patients with HFpEF are more commonly women, older, and have a history of systemic arterial hypertension (2–4). HFpEF patients have a devastating 5-year mortality rate (approaching 60%), costly morbidity (50%,

From the *Division of Cardiology, Medical University of South Carolina and RHJ Department of Veterans Affairs Medical Center, Charleston, South Carolina; †Department of Medicine, University of Alabama at Birmingham, Birmingham, Alabama; ‡Mayo Clinic, Rochester, Minnesota; §Pfizer, Inc., Groton, Connecticut; and the ‖Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi. Dr. Zile is supported by the Research Service of the Department of Veterans Affairs (5101CX000415-02 and 5101BX000487-04). Robyn J. Barst, MD, from Columbia University College of Physicians and Surgeons, New York, New York, now deceased, participated in the planning and conduction of this study but not in the analysis of the data or the preparation of the manuscript. This study was funded by Encysive Pharmaceuticals, Inc.; in June 2008, Encysive was acquired by Pfizer, Inc. Drs. Zile, Bourge, Redfield, and Little received research support from Encysive Pharmaceuticals, Inc. to participate in this study. Dr. Zhou is an employee of Pfizer, Inc. Dr. Baicu has reported that she has no relationships relevant to the contents of this paper to disclose.

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Abbreviations and Acronyms

BSLN = Baseline
E = transmitral inflow velocity
E' = early diastolic mitral annulus velocity
ET = endothelin
HF = heart failure
HFpEF = heart failure with preserved ejection fraction
ITT = intention-to-treat
LV = left ventricular
MLHF = Minnesota Living With Heart Failure
NYHA = New York Heart Association
QoL = quality of life
SCRN = screening

6-month hospital stay rate), and debilitating symptoms (maximal myocardial oxygen consumption averaging 14 ml/g/min) (5–9). However, there are no management strategies that have been proved to decrease morbidity or mortality in patients with HFpEF (1). Previous randomized clinical trials in HFpEF examining the efficacy of digitalis, angiotensin-converting enzyme (ACE) inhibitor, angiotensin-receptor blocker (ARB), β-adrenergic blocker, and phosphodiesterase type 5 inhibition have been largely neutral (10–15). Therefore, the search continues for novel approaches to the treatment of HFpEF. One such possibility is endothelin-1 receptor A (ET_A) antagonists.

Levels of ET-1 are elevated and predict mortality in HF patients (16–19). Two distinct ET receptor isoforms have been identified: type A (ET_A) and type B (ET_B). The adverse biologic effects of ET-1 are believed to be mediated principally through the ET_A receptor (20). These effects include arterial and pulmonary vasoconstriction, slowed left ventricular (LV) relaxation and stimulation of LV hypertrophy. Sitaxsentan is an ET receptor antagonist that has oral bioavailability in several species, a long duration of action, and high specificity for the ET_A receptor. The effects of treatment with a selective ET_A receptor antagonist on characteristics commonly found in patients with HFpEF such as pulmonary hypertension, diastolic dysfunction, and LV hypertrophy, raise the potential for its therapeutic application (21–29). However, to date, the long-term efficacy of ET receptor antagonists has not been examined in patients with HFpEF.

The purpose of this study was to determine whether blockade of ET_A receptors using sitaxsentan increased exercise time in subjects with HFpEF defined by signs and symptoms of chronic HF (New York Heart Association [NYHA] functional classes II to III) and an LVEF ≥50%. The present study was completed before the termination of clinical development and market withdrawal of sitaxsentan (Thelin Health Products, Sacramento, California) by the sponsor in December 2010 because of hepatic injury concerns (30). Therefore, the possible clinical importance of the results should be thought of as potentially applicable to ET_A receptor antagonists as a whole, not to sitaxsentan in isolation.

Methods

The current study was a randomized, double-blind, placebo-controlled exploratory efficacy study of sitaxsentan to improve impaired exercise tolerance in patients with HFpEF. One hundred ninety-two eligible subjects with HFpEF participated in this study: 64 in the placebo group and 128 in the active drug group. Patients were recruited from 65 sites in the United States and Canada (see Online Appendix A).

Study protocol. Eligible subjects were randomized to receive either sitaxsentan 100 mg or matching placebo orally once daily in a ratio of 1:2 (placebo vs. active drug). A 10-week run-in phase (R), R1 week to R10 weeks, was conducted before a 24-week maintenance phase (M), M1 week to M24 weeks. During the run-in phase, dosing commenced at 25 mg daily for 2 weeks, then increased to 50 mg daily for 2 weeks, to 75 mg daily for 2 weeks, and then to 100 mg daily for 2 weeks, with an additional 2-week stabilization period (10 weeks total) to a target study dose of 100 mg daily (Fig. 1). During the run-in phase, if a subject was not able to tolerate upward dose titration to the target dose of 100 mg, the investigator could elect to continue at

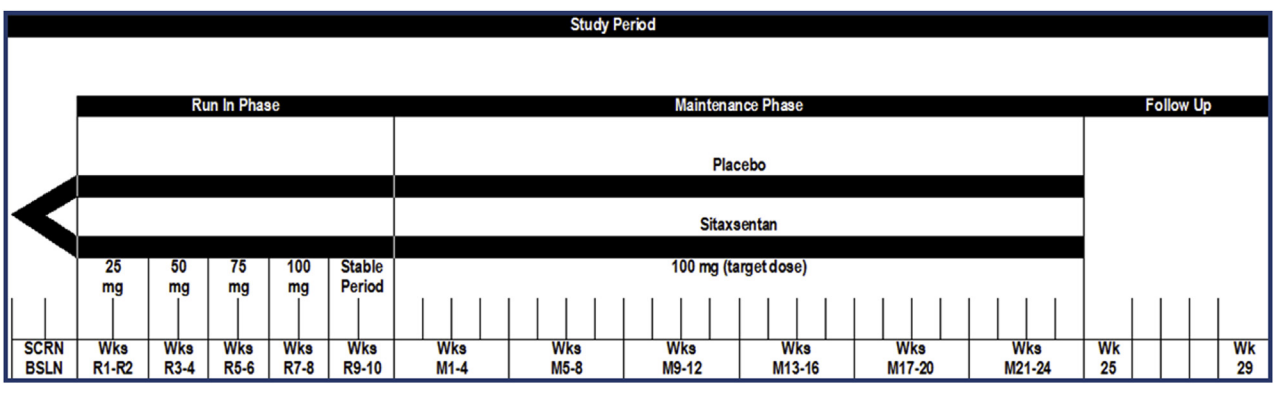

Figure 1 Study Protocol Scheme

Study protocol is depicted in schematic fashion. The time line for the run-in phase, maintenance phase, and follow-up is depicted for placebo versus sitaxsentan. BSLN = baseline; SCRN = screening; Wks = weeks.

the current dosage or reduced the dosage of sitaxsentan to the subject's immediate prior dose. The achieved dose was continued through the maintenance phase (M24). The end of study visit was conducted at the end of week M24 (±4 days) or early termination.

Efficacy endpoints. The primary efficacy endpoint was the change in treadmill exercise time after 24 weeks of continuous maintenance dose therapy with sitaxsentan using a Naughton protocol. Secondary efficacy endpoints included the change in the ratio of transmitral inflow velocity (E) as measured by Doppler echocardiography to early diastolic velocity of the mitral annulus (E') as measured by tissue Doppler imaging; the change in LV mass by echocardiography; the proportion of subjects who achieve improvement (>25 s increase) versus no change (≤25 s increase or decrease) or worsening (>25 s decrease) from baseline in the treadmill exercise time; the change in quality of life (QoL) as measured by the Minnesota Living With Heart Failure questionnaire (MLHF); and the change in New York Heart Association (NYHA) functional class.

Inclusion criteria. Patients were eligible for enrollment if they met all of the inclusion criteria listed here. Patients had signs and symptoms of chronic HF NYHA II or III and an LVEF ≥50% obtained by echocardiography, radionuclide imaging, or cardiac catheterization. Patients had a minimal treadmill exercise time of 120 s and a maximum of 720 s using a Naughton protocol on 2 treadmill exercise tests performed within 2 weeks before enrollment. Treadmill exercise tests were performed a maximum of 2 weeks between each assessment and exercise times agreed within ≤10%. For subjects with discordant exercise times, a third treadmill test was conducted within the 2-week screening and was concordant within ≤10% of 1 of the previous exercise test. Seven patients were excluded from randomization because they had discordant exercise test results of >10%. Patients had echocardiographic evidence of concentric remodeling and/or diastolic dysfunction as indicated by 1 or more of the following: LV mass ≥125 g/m^2, left atrial diameter ≥4.5 cm, wall thickness of ≥11 mm, relative wall thickness ≥0.45, tissue Doppler mitral annular E' ≤8 cm/s. The patient was taking a stable concomitant medication regimen for at least 4 weeks before enrollment that was not expected to have changed during the study period and follow-up. This applied to ARBs, ACE inhibitors, calcium-channel blockers, cardiac glycosides, and antihypertensive medications. For 4 weeks before study enrollment and through follow-up, these medications were not added to, deleted, or changed in dose; however, for acute emergency HF episodes, these medications could be initiated. Medications added or that underwent a dose change could not be administered for >14 continuous days and not within 7 days of an efficacy assessment. Changes in diuretics, potassium supplements, and/or nitrates, as needed during the study period, were allowed. The subject provided written informed consent and was age 18 years or older. Female subjects of childbearing potential agreed to use 2 forms of contraceptive therapy.

Exclusion criteria. Patients were not eligible to participate in the study if they had any of the following characteristics: atrial fibrillation or unstable angina within 4 weeks before screening; amyloidosis, hypertrophic obstructive cardiomyopathy, restrictive cardiomyopathy, constrictive pericarditis, significant valvular heart disease (greater than moderate); history of myocardial infarction, coronary artery bypass graft procedure, or percutaneous coronary intervention within the past 3 months; cerebrovascular accident or transient ischemic attack within the past 3 months; aspartate aminotransferase or alanine aminotransferase ≥1.5 times upper limit of normal, viral hepatitis, human immunodeficiency virus, anemia (hemoglobin concentration <10 g/dl); uncontrolled diabetes mellitus (glycosylated hemoglobin A_{1c} of ≥8.0%); exercise tolerance limited by noncardiac causes; uncontrolled systemic hypertension (blood pressure of ≥140/90 mm Hg if on no treatment or ≥160/90 mm Hg if on ≥2 medications); malignancy that required significant medical intervention within the past 3 months and/or was likely to result in death within the next 2 years; renal insufficiency (serum creatinine ≥2.5 mg/dl and/or required dialysis); treatment with warfarin, cyclosporine A; significant psychiatric, neurologic disease, or any other condition that would compromise ability to give informed consent; subject was lactating, breastfeeding, or pregnant; subject received any chronic prostacyclin, prostacyclin analogue, ET receptor antagonist, or phosphodiesterase inhibitor therapy within 30 days before study entry; subject received an investigational product or device within 30 days of screening.

Statistical analysis methods. All efficacy analyses were conducted on the intention-to-treat (ITT) study group, which was defined as all subjects who received at least 1 dose of study drug and had at least 1 valid treadmill test value at baseline and after baseline during maintenance phase. The primary efficacy endpoint was change from baseline to week M24 in treadmill exercise time in seconds. The last nonmissing, pre-randomization value for treadmill exercise test before the first dose was used as the baseline value. Missing values for treadmill exercise test were imputed using the last observation carried forward method.

In the protocol, the primary efficacy endpoint was planned to be analyzed using the parametric analysis of covariance (ANCOVA) controlling for the baseline treadmill exercise time. However, on the basis of the blinded data review, the primary efficacy endpoint data had some outliers; thus, the parametric ANCOVA may not be appropriate because of violation of the normality assumption. Therefore, in the final statistical analysis plan, the statistical method for the primary efficacy analysis was changed to nonparametric ANCOVA before treatment unblinding. Primary efficacy data are presented using a box and whisker plot format.

One interim efficacy analysis was conducted by an independent statistician who was not involved in the conduct of the trial when 35% of subjects had completed week M24 visit. The interim analysis results were only released to the chief scientific officer for the purpose of planning for future

studies. People who were involved in conduct of the study were blinded to interim analysis results. On the basis of the O'Brien-Fleming alpha spending function, the interim analysis spent an alpha of 0.0003 and left the final analysis with an alpha of 0.0497.

Changes from baseline to endpoint (week M24 or early termination) in the ratio of E/E' and LV mass, and MLHF QoL scores were analyzed using the parametric ANCOVA model with baseline value as the covariate. The Cochran-Mantel-Haenszel test adjusted for the baseline NYHA functional class was used to compare treatment difference in NYHA functional class change from baseline and categorical changes (improvement, no change, and worsening) in treadmill exercise time. The log-rank test was used to analyze the treatment difference in time to death or hospital stay due to HF. Missing values were not imputed for E/E' and LV mass, and the last nonmissing values were used for endpoint (week M24). Missing values for MLHF QoL scores and NYHA functional classes at week M24 were imputed using the last observation carried forward method.

All safety analyses were conducted on the safety study group, which was defined as all randomized subjects (n = 192) who received at least 1 dose of study drug (n = 191). Serious adverse events, including hospital stay and deaths were recorded up to 28 days after study discontinuation (last dose of administered study medication).

Study conduct, sites, and investigators. Please see Online Appendix A for details on study conduct, sites, and a list of investigators.

Results

Study subject characteristics. One hundred and ninety-two subjects were randomized, and 191 subjects received the study drug: 64 received placebo and 127 received sitaxsentan. Of 127 subjects who received sitaxsentan, 122 (96%) subjects achieved the target sitaxsentan dose level of 100 mg. Of 191 subjects who received study drug, 148 subjects had at least 1 valid treadmill test value at baseline and after baseline during maintenance phase, and thus met the definition for ITT study group: 52 in the placebo arm and 96 in the sitaxsentan arm (Fig. 2).

The demographic and baseline characteristics are summarized in Table 1. Of 191 subjects who received study drug, 63% were female, 71% were white, and 57% had baseline NYHA functional class II. Mean ± SD for systolic blood pressure was 126 ± 15 mm Hg, diastolic blood pressure was 73 ± 9 mm Hg, heart rate was 72 ± 13 beats/min, creatinine was 100 ± 28 μmol/l, sodium was 140 ± 3 mmol/l, and MLHF QoL score was 40 ± 25. The percent of subjects taking the following medications was 80% ACE-I or ARBs, 64% β-blockers, 77% diuretics, 73% antithrombotic agents, and 70% lipid-reducing agents. The percent of patients with LV hypertrophy (as judged by LV mass ≥51 g/m$^{2.7}$) was 53%, concentric remodeling (normal LV volume and mass, but relative wall thickness >0.42) was an additional 31%, and with left atrial enlargement (as judged by a left atrium dimension of >4.0 cm) was 67%. Fourteen patients (7%) had a hospital stay for acute decompensated HF within the year preceding randomization. For all 191 subjects, the mean age was 65 years, and the mean baseline treadmill exercise time was 423 s. There was no statistically significant difference in demographic and baseline characteristics between the 2 treatment arms in the safety and ITT populations.

Primary efficacy endpoint results. The changes from baseline in treadmill exercise time were summarized for the overall ITT study group and the subgroups by baseline NYHA functional class in Table 2. The median change from baseline to week M24 in treadmill exercise time was 37 s for

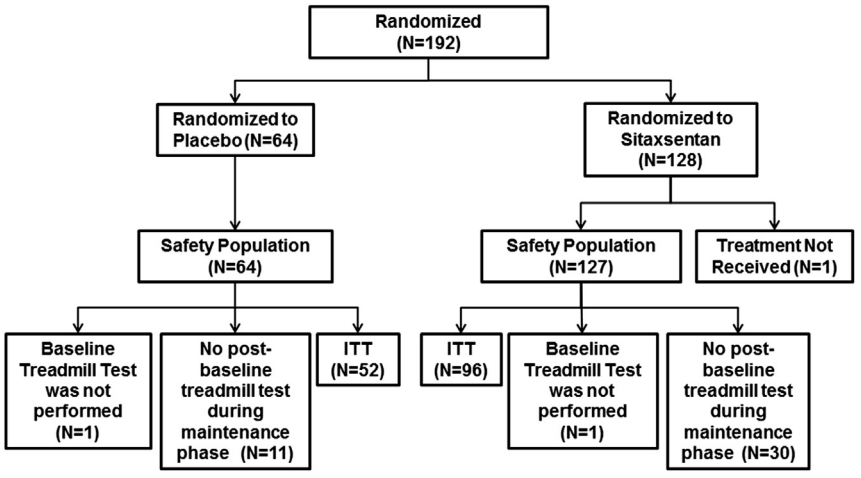

Figure 2 Flow Diagram

Flow diagram shows sample size distribution for safety population versus intention-to-treat (ITT) populations and causes for exclusion.

Table 1 Demographic and Baseline Characteristics

	Safety Study Group			ITT Study Group		
	Placebo (n = 64)	Sitaxsentan (n = 127)	Total (n = 191)	Placebo (n = 52)	Sitaxsentan (n = 96)	Total (n = 148)
Age, yrs						
Mean (SD)	65 (10)	65 (11)	65 (11)	64 (10)	64 (11)	64 (11)
Min, max	43, 86	34, 84	34, 86	43, 86	34, 84	34, 86
Sex, n (%)						
Male	19 (30)	51 (40)	70 (37)	16 (31)	40 (42)	56 (38)
Female	45 (70)	76 (60)	121 (63)	36 (69)	56 (58)	92 (62)
Race, n (%)						
White	42 (66)	94 (74)	136 (71)	34 (65)	74 (77)	108 (73)
Others	22 (34)	33 (26)	55 (29)	18 (35)	22 (23)	40 (27)
Treadmill time, s						
Mean (SD)	440 (158)	415 (164)	423 (162)	462 (147)	426 (166)	439 (160)
Median	461	416	428	485	425	450
Min, max	126, 693	120, 706	120, 706	126, 693	121, 706	121, 706
Functional class, n (%)						
Class II	36 (56)	72 (57)	108 (56)	27 (52)	58 (60)	85 (57)
Class III	28 (44)	55 (43)	83 (44)	25 (48)	38 (40)	63 (43)

ITT = intention-to-treat; Min, max = minimum, maximum.

placebo subjects (25th percentile, 28 s; 75th percentile, 110 s) and 90 s for sitaxsentan subjects (25th percentile, −5 s; 75th percentile, 154 s) (Fig. 3). The Hodge-Lehmann estimator of the median difference in the primary efficacy endpoint between the 2 treatment arms was 43 s, with a p value of 0.0302 on the basis of the nonparametric ANCOVA method controlling for baseline treadmill exercise time. The treatment effect was 10% of the median baseline treadmill exercise time, which is clinically meaningful and statistically significant (p = 0.0302) at the pre-specified alpha level of 0.0497. Heart rate and blood pressure both rose to a comparable degree from rest to peak exercise. There were no differences in these variables between baseline and week M24 or between placebo and sitaxsentan (please see Online Appendix F).

The treatment effect was numerically larger for functional class III subjects than for functional class II subjects. The median treatment effect was 11 s for NYHA functional II subjects and 77 s for NYHA functional III subjects.

The treadmill exercise time change from baseline was also categorized as improvement, no change, and worsening using the pre-specified 25 s as a cut-off for categorization. The categorical analysis of treadmill exercise time is

Table 2 Baseline Echocardiographic Data

Measurements	Total	Placebo	Sitaxsentan
Subjects, n	187	62	125
Body surface area, m^2	2.1 ± 0.3	2.1 ± 0.3	2.2 ± 0.3
LV EDD, cm	4.8 ± 0.5	4.9 ± 0.6	4.8 ± 0.5
LV EDV index, mL/m^2	52 ± 12	54 ± 12	50 ± 13
LV EF, %	61 ± 12	60 ± 13	62 ± 12
LV PWThD, cm	1.1 ± 0.3	1.2 ± 0.3	1.1 ± 0.3
LV mass index, g/m^2	105 ± 40	114 ± 45	101 ± 38
LV mass/EDV, g/ml	2.4 ± 1.0	2.2 ± 0.8	2.7 ± 1.3
LA dimension, cm	4.3 ± 0.6	4.3 ± 0.7	4.4 ± 0.6
E, m/s	0.84 ± 0.27	0.86 ± 0.28	0.83 ± 0.26
A, m/s	0.88 ± 0.24	0.87 ± 0.25	0.88 ± 0.24
E/A	1.0 ± 0.5	1.1 ± 0.5	1.0 ± 0.4
E′, cm/s	6.7 ± 2.6	6.3 ± 2.4	6.9 ± 2.7
E/E′	13.9 ± 6.6	14.9 ± 6.6	13.3 ± 6.6
TR peak velocity, m/s	2.7 ± 0.5	2.6 ± 0.6	2.7 ± 0.5

Values are mean ± SD. There were no statistical differences between sitaxsentan versus placebo for all echocardiography-derived values.

A = transmitral filling velocity resulting from atrial contraction; E = early transmitral filling velocity; E′ = early diastolic myocardial velocity; EDD = end-diastolic dimension; EDV = end-diastolic volume; EF = ejection fraction; LA = left atrial; LV = left ventricular; PWThD = posterior wall thickness; TR = tricuspid regurgitation.

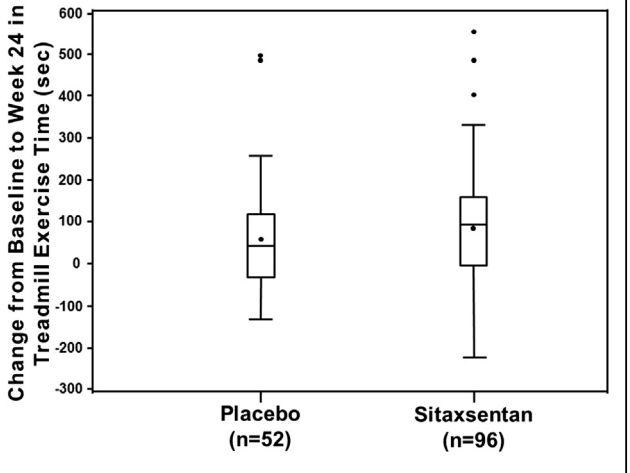

Figure 3 Primary Efficacy Endpoint Data

Primary efficacy endpoint data are presented in a box and whisker plot format. Median, 25th and 75th percentile, mean, 2 SDs from mean, and outliers are presented. Sitaxsentan increased median time on the treadmill after 24 weeks of treatment compared to placebo.

summarized in Table 3. For the overall ITT study group, there were more subjects with improvement and fewer subjects with worsening in the sitaxsentan arm than in the placebo arm, but the difference was not statistically significant at the significance level of 0.05.

Secondary efficacy endpoint results. Secondary efficacy endpoint analyses are summarized in Table 4. There were no statistically significant differences between the 2 treatment arms for any of the secondary efficacy endpoints, namely, change from baseline to endpoint in E/E′ ratio, LV mass, QoL scores, and NYHA functional class, and time to death or hospital stay due to HF (Table 5).

Safety results. There were no significant differences between the placebo and sitaxsentan groups with respect to safety endpoints, including discontinuation rate, adverse events, serious adverse events, and death. There were 2 deaths during the study; neither was considered to be related to study drug. These data are presented in Online Appendixes B to E.

Discussion

Data presented in the current study support 3 conclusions. First, in patients with HFpEF, treatment with the selective ET_A receptor antagonist sitaxsentan for 6 months significantly increased exercise tolerance as measured by time on the treadmill. Second, these results were not associated with any significant changes in LV structure or function. However, the short length of this study may not have been sufficient to adequately exclude such changes if treatment were sustained. Third, sitaxsentan use was not associated with any significant cardiovascular adverse events. Although sitaxsentan has been withdrawn from development, these results support the need for further studies using ET_A receptor antagonists in HFpEF patients.

ET-1 and ET_A antagonists in heart failure. Et-1 plays a pivotal role in cardiovascular physiology and pathophysiology by its direct effects on cardiomyocytes, vascular smooth muscle cells, and fibroblasts (16,19,20). ET-1 is continuously released by endothelial cells to maintain endogenous vascular tone (31). However, in response to external pathophysiologic stimuli, ET-1 production is increased and produces potent vasoconstrictor effects (20). Generation of ET-1 is increased by neurohormonal activation, increased myocardial stress, and free radicals that are common in antecedent disease processes that lead to the development of chronic HF. Synthesis of ET-1 is inhibited by nitric oxide, natriuretic peptides, and prostaglandins (20). There are 2 ET-1 receptors: type A (ET_A) and type B (ET_B); ET_A is the primary vasoconstrictor and growth promoting receptor; ET_B inhibits vasoconstriction and cell growth and functions as a clearance receptor. Thus, ET-1 binding to ET_A results in vasoconstriction, hypertension, hypertrophy, and fibrosis, all of which may lead to the development of diastolic dysfunction, and eventually, the transition to HF. This signaling pathway has been shown to be upregulated and ET-1 to be increased in HF with reduced ejection fraction (HFrEF), HFpEF, and pulmonary hypertension (17–19,26,32–37). Treatment with nonselective and ET_A selective endothelin receptor blockers has held significant promise in all 3 clinical syndromes. To date, treatment with endothelin antagonists have been demonstrated to be successful for pulmonary hypertension but not for HFrEF (19,32,37). The current study is the only study to selectively examine patients with HFpEF.

Lack of efficacy in HFrEF. Clinical studies of endothelin receptor antagonists in HFrEF demonstrated favorable acute and persistent hemodynamic effects with reduced

Table 3 Change From Baseline to Maintenance Phase Weeks 12 and 24 in Treadmill Exercise Time

	ITT Study Group		Functional Class II		Functional Class III	
Treadmill Exercise, s	Placebo (n = 52)	Sitaxsentan (n = 96)	Placebo (n = 27)	Sitaxsentan (n = 58)	Placebo (n = 25)	Sitaxsentan (n = 38)
Change from baseline to week M12						
Mean (SD)	47 (132)	66 (127)	74 (159)	75 (139)	19 (90)	52 (107)
Median	34	53	34	60	25	31
Minimum, maximum	−256, 493	−257, 549	−256, 493	−257, 549	−150, 266	−217, 246
Treatment effect						
Median		24		13		33
p value		0.2620		0.8790		0.2781
Change from baseline to week M24 (primary efficacy endpoint)						
Mean (SD)	52 (124)	87 (134)	77 (147)	76 (151)	24 (89)	104 (102)
Median	37	90	58	75	24	96
Minimum, maximum	−141, 490	−235, 549	−104, 490	−235, 549	−141, 260	−92, 332
Treatment effect						
Median		43		11		77
p value		0.0302		0.8053		0.0019

ITT = intention-to-treat.

Table 4 Change From Baseline to Maintenance Phase Week 24 in Treadmill Exercise Time

	Placebo (n = 52)	Sitaxsentan (n = 96)
Categorical change		
Improved (>25 s increase)	29 (56%)	64 (67%)
No change (≤25 s change)	10 (19%)	18 (19%)
Worsening (>25 s decrease)	13 (25%)	14 (14%)
p value for treatment difference		0.1361

pulmonary and systemic vascular resistance and increase cardiac output but not improved dyspnea (20,27,33–35,37). However, long-term oral application in a number of randomized clinical trials did not significantly reduce morbid or mortal outcomes (19,32). These include the REACH (Research on Endothelin Antagonism in Chronic Heart Failure), ENABLE (Endothelin Antagonist Bosentan for Lowering Cardiac Events in Heart Failure), EARTH (Endothelin A Receptor Antagonist Trial), and RITZ (Randomized Intravenous Tezosentan) studies. It appears that endothelin receptor antagonists will not be used in the treatment of HFrEF. However, their utility in HFpEF remains promising.

Potential application to HFpEF. Because there are significant differences in the pathophysiology of HFpEF versus HFrEF, there are also significant differences in the effectiveness of individual medical treatments of HFrEF versus HFpEF. For example, ACE-I/ARBs and beta-blockade clearly improve both morbidity and mortality in HFrEF but do not have similar efficacy in HFpEF. By contrast, whereas endothelin antagonists are not efficacious in treating HFrEF, there are a number of different pathophysiologic targets in HFpEF that make ET_A receptor antagonists potentially effective (21–29). For example, abnormalities in endothelial function, vascular compliance, pulmonary hypertension, diastolic relaxation, and myocardial fibrosis have all been implicated in the pathophysiology of HFpEF. The ET_A receptor antagonists may modify or correct each of these abnormalities. Both animal models and clinical studies have suggested that ET_A antagonism improves arterial compliance and pulse wave characteristics, decreases pulmonary artery pressure, improves myocardial relaxation, and modifies the profibrotic response. None of these specific pathophysiologic targets were directly examined in the current study. Indirect measurements such as E/E′ and LV mass were unchanged; however, whether longer term therapy would have altered these parameters was not tested. In general, these kind of structural and functional changes occur over a time frame that is usually longer than 6 months to be clearly apparent. However, increased exercise tolerance did occur with sitaxentan treatment in the current study, and that is singularly the most important symptom complaint in patients with HFpEF.

Study limitations. Two important factors limit the application of the results from this study. First, the study included a relatively small number of patients and the study time was relatively short. However, this remains the only study of ET_A receptor antagonists in HFpEF and was sufficiently large to show a statistically significant increase in exercise time. The lack of improvement in structural and functional parameters might be explained by the size and length of the study. In addition, the patients examined in this study were largely outpatient NYHA class II patients in stable condition; whether these effects would be larger or smaller in more symptomatic patients is yet to be tested. Second, hepatotoxicity prevented the further development of sitaxsentan. However, the possible clinical importance of the results should be potentially applicable to ET_A receptor antagonists as a whole, not sitaxsentan in isolation.

Table 5 Secondary Efficacy Endpoint Analysis

Efficacy Endpoint	Placebo (n = 52)	Sitaxsentan (n = 96)
Change from baseline to endpoint in E/E′ ratio		
N	48	66
Mean (SD)	0.6 (4.4)	−0.2 (4.1)
Minimum, maximum	−12.6, 12.1	−18.3, 8.3
Treatment effect		
Mean, p value		−0.9, 0.23
Change from baseline to endpoint in left ventricular mass		
N	25	46
Mean (SD)	−9.1 (42.8)	0.7 (42.1)
Minimum, maximum	−127.8, 56	−127.9, 84.3
Treatment effect		
Mean, p value		9.8, 0.37
Change from baseline to week M24 in MLHF QoL total scores		
N	51	91
Mean (SD)	−6.3 (18.9)	−8.2 (21.5)
Minimum, maximum	−57, 44	−76, 39
Treatment effect		
Mean, p value		−1.9, 0.89
Change from baseline to week M24 in NYHA functional class		
Improvement	18 (35%)	30 (31%)
No change	34 (65%)	60 (63%)
Deterioration		6 (6%)
p value for treatment difference		0.59
Time to death or hospital stay due to heart failure		
Number of subjects with event	5	5
Kaplan-Meier survival rate	90%	95%
Hazard ratio (95% CI)		0.5 (0.2–1.9)
p value based on log-rank test		0.32

CI = confidence interval; E = transmitral inflow velocity; E' = early diastolic mitral annulus velocity; M = maintenance phase; MLHF = Minnesota Living With Heart Failure questionnaire; NYHA = New York Heart Association; QoL = quality of life.

Conclusions

In HFpEF patients, treatment with a selective ET_A receptor antagonist increased exercise tolerance but did not improve

any of the secondary endpoints such as LV mass or diastolic function. Further studies will be necessary to determine whether ET_A receptor antagonists may be useful in the treatment of HFpEF.

Reprint requests and correspondence: Dr. Michael R. Zile, Division of Cardiology, Department of Medicine, Medical University of South Carolina, Ashley River Towers, 25 Courtenay Drive, Room 7067, Charleston, South Carolina 29425. E-mail: zilem@musc.edu.

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Key Words: ejection fraction ■ endothelin ■ heart failure.

APPENDIX

For supplemental information, please see the online version of this article.