University of Groningen

Effects of Elamipretide on Left Ventricular Function in Patients With Heart Failure With Reduced Ejection Fraction

Butler, Jonah; Khan, Muhammad Shahzeb; Anker, Stefan D.; Fonarow, Gregg C.; Kim, Raymond J.; Nodari, Savina; O'Connor, Christopher M.; Pieske, Burkert; Pieske-Kraigher, Elisabeth; Sabbah, Hani N.

Published in:
JOURNAL OF CARDIAC FAILURE

DOI:
[10.1016/j.cardfail.2020.02.001](https://doi.org/10.1016/j.cardfail.2020.02.001)

IMPORTANT NOTE: You are advised to consult the publisher's version (publisher's PDF) if you wish to cite from it. Please check the document version below.

Document Version
Publisher's PDF, also known as Version of record

Publication date:
2020

[Link to publication in University of Groningen/UMCG research database](#)

Citation for published version (APA):

Butler, J., Khan, M. S., Anker, S. D., Fonarow, G. C., Kim, R. J., Nodari, S., O'Connor, C. M., Pieske, B., Pieske-Kraigher, E., Sabbah, H. N., Senni, M., Voors, A. A., Udelson, J. E., Carr, J., Gheorghiade, M., & Filippatos, G. (2020). Effects of Elamipretide on Left Ventricular Function in Patients With Heart Failure With Reduced Ejection Fraction: The PROGRESS-HF Phase 2 Trial. *JOURNAL OF CARDIAC FAILURE*, 26(5), 429-437. <https://doi.org/10.1016/j.cardfail.2020.02.001>

Copyright

Other than for strictly personal use, it is not permitted to download or to forward/distribute the text or part of it without the consent of the author(s) and/or copyright holder(s), unless the work is under an open content license (like Creative Commons).

The publication may also be distributed here under the terms of Article 25fa of the Dutch Copyright Act, indicated by the "Taverne" license. More information can be found on the University of Groningen website: <https://www.rug.nl/library/open-access/self-archiving-pure/taverne-amendment>.

Take-down policy

If you believe that this document breaches copyright please contact us providing details, and we will remove access to the work immediately and investigate your claim.

Effects of Elamipretide on Left Ventricular Function in Patients With Heart Failure With Reduced Ejection Fraction: The PROGRESS-HF Phase 2 Trial

JAVED BUTLER, MD, MPH, MBA,¹ MUHAMMAD SHAHZEB KHAN, MD,² STEFAN D. ANKER, MD, PHD,³ GREGG C. FONAROW, MD,⁴ RAYMOND J. KIM, MD,⁵ SAVINA NODARI, MD,⁶ CHRISTOPHER M. O'CONNOR, MD,⁷ BURKERT PIESKE, MD,^{8,9} ELISABETH PIESKE-KRAIGHER, MD,^{8,9} HANI N. SABBAAH, PHD,¹⁰ MICHELE SENNI, MD,¹¹ ADRIAAN A. VOORS, MD,¹² JAMES E. UDELSON, MD,¹³ JIM CARR, PharmD,¹⁴ MIHAI GHEORGHIAD, MD,^{15,*} AND GERASIMOS FILIPPATOS, MD¹⁶

Jackson, Chicago, Los Angeles, Durham, Falls Church, Detroit, Boston, and USA; Berlin, Germany; Brescia, and Italy; the Netherlands; and Athens, Greece

ABSTRACT

Background: Elamipretide, a novel mitochondrial modulating agent, improves myocardial energetics; however, it is unknown whether this mechanistic benefit translates into improved cardiac structure and function in heart failure (HF) with reduced ejection fraction (HFrEF). The objective of this study was to evaluate the effects of multiple subcutaneous doses of elamipretide on left ventricular end systolic volume (LVESV) as assessed by cardiac magnetic resonance imaging.

Methods: We randomized 71 patients with HFrEF (LVEF $\leq 40\%$) in a double-blind, placebo-controlled trial in a 1:1:1 ratio to receive placebo, 4 mg or 40 mg elamipretide once daily for 28 consecutive days.

Results: The mean age (standard deviation) of the study population was 65 ± 10 years, 24% were females, and the mean EF was $31\% \pm 7\%$. The change in LVESV from baseline to week 4 was not significantly different between elamipretide 4 mg (89.4 mL to 85 mL; difference, -4.4 mL) or 40 mg (77.9 mL to 76.6 mL; difference, -1.2 mL) compared with placebo (77.7 mL to 74.6 mL; difference, -3.8 mL) (4 mg vs placebo: difference of means, -0.3 ; 95% CI, -4.6 to 4.0 ; $P = 0.90$; and 40 mg vs placebo: difference of means, 2.3 ; 95% CI, -1.9 to 6.5 ; $P = 0.28$). Also, no significant differences in change in LVESV and LVEF were observed between placebo and either of the elamipretide groups. Rates of any study drug-related adverse events were similar in the 3 groups.

Conclusions: Elamipretide was well tolerated but did not improve LVESV at 4 weeks in patients with stable HFrEF compared with placebo. (*J Cardiac Fail* 2020;26:429–437)

Key Words: Mitochondria, elamipretide, heart failure, cardiac MRI.

Despite advances in drug- and device-based therapies, patients with heart failure (HF) with reduced ejection fraction (HFrEF) continue to have poor quality of life and poor prognoses.^{1,2} HFrEF is a complex syndrome involving

multiple organ systems and altered physiologic mechanisms, resulting in increased myocardial energy demands.^{3,4} This higher demand for energy is coupled with mitochondrial dysfunction and reduced capacity to generate

From the ¹Department of Medicine, University of Mississippi Medical Center, Jackson, Mississippi, USA; ²Department of Medicine, Cook County Hospital, Chicago, Illinois, USA; ³Department of Cardiology (CVK), Berlin Institute of Health Center for Regenerative Therapies (BCRT), German Centre for Cardiovascular Research (DZHK) partner site Berlin, Charité Universitätsmedizin Berlin, Germany; ⁴Division of Cardiology, Department of Medicine, University of California, Los Angeles, Los Angeles, California, USA; ⁵Duke Cardiovascular Magnetic Resonance Center, Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA; ⁶Cardiology Section, Department of Clinical and Surgical Specialties, Radiological Sciences and Public Health, University of Brescia, Brescia, Italy; ⁷Inova Heart and Vascular Institute, Falls Church, Virginia, USA; ⁸Department of Internal Medicine and Cardiology, Charité Universitätsmedizin Berlin, Campus Virchow Klinikum, Berlin, Germany; ⁹Department of Internal Medicine and Cardiology, German Heart Center Berlin, and German Centre for Cardiovascular Research (DZHK), Partner site Berlin, and Berlin Institute of Health (BIH), Berlin, Germany; ¹⁰Division of Cardiovascular Medicine, Henry Ford Hospital, Detroit, Michigan, USA; ¹¹Cardiovascular Department, ASST Papa Giovanni XXIII, Bergamo, Italy; ¹²Department of Cardiology, University of Groningen, University Medical Center Groningen, Groningen, the Netherlands; ¹³Division of Cardiology and the Cardiovascular Center, Tufts Medical Center, Boston, Massachusetts, USA; ¹⁴Stealth BioTherapeutics, Newton, Massachusetts, USA; ¹⁵Department of Medicine, Bluhm Cardiovascular Institute, Northwestern University Feinberg School of Medicine, Chicago, Illinois, USA and ¹⁶National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece.

Manuscript received October 1, 2019; revised manuscript received February 5, 2020; revised manuscript accepted February 10, 2020.

Reprint requests: Gerasimos Filippatos, MD, National and Kapodistrian University of Athens, Attikon University Hospital, Athens, Greece; Fax: +30-210-6745222; Tel: +30 2105832196. E-mail: geros@otenet.gr

*Deceased.

See page 436 for disclosure information.

1071-9164/\$ - see front matter

© 2020 Published by Elsevier Inc.

<https://doi.org/10.1016/j.cardfail.2020.02.001>

adenosine trinucleotide phosphate (ATP) in HF, resulting in decreased myocardial efficiency and progressive worsening of cardiac function. The reduced energy capacity also results in exercise intolerance and impaired quality of life related to skeletal muscle dysfunction.^{5,6} Mitochondrial dysfunction is also seen in chronic kidney disease and insulin resistance, 2 comorbid conditions common in HF.^{7,8} Thus, mechanistic approaches that have impacts on myocardial metabolism are potentially useful for the treatment of HFrEF.⁹

Elamipretide (MTP-131, Bendavia) is a novel tetra-peptide that targets mitochondrial dysfunction in energy-depleted myocytes. Elamipretide crosses the outer membrane of the mitochondria and associates itself with cardiolipin, which is a phospholipid expressed only in the inner membrane of mitochondria. Cardiolipin has an integral role in mitochondrial stability and organization of respiratory complexes into super complexes for oxidative phosphorylation.^{10–12} Thus, elamipretide helps to enhance ATP synthesis in multiple organs of the body. Elamipretide has been shown to improve left ventricular ejection fraction (LVEF), LV end diastolic pressure, cardiac hypertrophy, myocardial fibrosis, and myocardial ATP synthesis in both animal models and humans.^{13–15} However, it is unknown whether this mechanistic benefit will translate into improved cardiac structure and function in patients with HFrEF and, subsequently, in clinical outcomes. In a previous small study,¹⁵ a single 4-hour infusion of elamipretide was shown to reduce echocardiographic LV volumes in patients with HFrEF. However, the confidence intervals were wide, with no change in corresponding biomarker data. Herein, we report the primary outcome results from a phase 2 trial designed to evaluate the effects of multiple subcutaneous doses of elamipretide on LV systolic and diastolic function as assessed by cardiac magnetic resonance imaging (MRI) and echocardiography over 4 weeks of dosing.

METHODS

This was a randomized, double-blinded, placebo-controlled, multiple-dose study that enrolled patients with stable HFrEF in 20 centers in Europe. Institutional review board approval was obtained at each study site. All patients provided written informed consent.

Study Population

The detailed inclusion and exclusion criteria of the trial can be found in Supplementary Table 1. Briefly, eligible patients aged ≥ 40 and < 80 years with an LVEF $\leq 40\%$ and with no hospitalization related to HF within 1 month prior to the screening visit and at least 3 dysfunctional but viable segments (hyperenhancement $\leq 25\%$) by a qualifying delayed gadolinium-enhanced cardiac MRI examination at screening were eligible. HF was considered to be stable if doses for HF treatment, including diuretics, had been stable for at least 1 month prior to the screening visit. Exclusion criteria included any contraindication to cardiac MRI

scanning; LV end diastolic diameter indexed to body surface area $> 45 \text{ mm/m}^2$ assessed by 2-dimensional echocardiography; coronary or peripheral revascularization procedures; valvular procedures; or any major surgical procedure within 3 months prior to the screening visit; and estimated glomerular filtration rate $< 30 \text{ mL/min}$.

Study Design

A treatment kit number was assigned to each patient on the basis of a centralized computer-generated randomization schedule. Treatment kits for placebo specified injection volumes of either 0.1 mL or 1 mL in order to maintain the blind. This was accomplished by administering a randomization schedule in randomized blocks of 6 with a ratio of 2:2:1:1 (elamipretide 4 mg [0.1 mL], elamipretide 40 mg [1 mL], placebo [0.1 mL], or placebo [1 mL]). This design was used to maintain the 1:1:1 ratio of elamipretide 4 mg, elamipretide 40 mg and placebo, in addition to ensuring the complete blind to study treatment. Patients who met selection criteria were randomized in a 1:1:1 ratio to receive placebo, 4 mg elamipretide or 40 mg elamipretide once daily by subcutaneous injection for 28 consecutive days. Total treatment duration was 4 weeks (visit 3), followed by a safety follow-up at 6 weeks after randomization.

Study Endpoints

The primary endpoint of this trial was change from baseline in left ventricular end systolic volume (LVESV) as assessed by cardiac MRI. Secondary endpoints included changes from baseline in LVEF and LV end diastolic volume (LVEDV) as assessed by MRI. Echocardiographic endpoints included changes in E/A ratio, E/e' ratio, LVEDV, LVESV, biplane EF, left atrial volume, LV mass, mitral and tricuspid regurgitation severity, LV global longitudinal strain, right ventricular (RV) fractional area change, and RV systolic pressure. Exploratory endpoints included changes in 6-minute walk test (6MWT), Kansas City Cardiomyopathy Questionnaire (KCCQ) summary score and levels of N-terminal pro-brain natriuretic peptide (NT-pro-BNP) levels. Echocardiographic assessments were performed at screening visit, day 1, week 4, and week 6. Cardiac MRI assessments were performed at screening visit, week 1 and week 4. KCCQ scores and 6MWT were measured at baseline and week 4. All 2-dimensional transthoracic echocardiograms and cardiac MRIs were analyzed by an independent core laboratory. Interpreting cardiologists were blinded to treatment allocation. Inter-reader reproducibility for these imaging parameters was high.

Statistical Analysis

A sample size of 22 patients per treatment group was estimated to provide 80% power to detect an 8 mL difference between treatment groups in LVESV by cardiac MRI, assuming a standard deviation of 9.4 mL. The intention-to-

treat population consisted of all subjects who were randomized and received at least 1 dose of treatment. The intention-to-treat population was used for the primary analysis for efficacy assessments. Additionally, changes in LVESV measurements of all 3 treatment groups together were analyzed by mixed model repeated measures (MMRM) in order to study trends in the treatment effects over 4 weeks, with the primary endpoint at week 4.

The model included treatment (4 mg elamipretide, 40 mg elamipretide or placebo), visit (week numbers), treatment-by-visit interaction, and ischemic/nonischemic as fixed effects, baseline LVESV, and baseline LVESV by visit interaction as covariates, and subject as a random effect. An unstructured covariance matrix was used to model the covariance of within-patient results. The Kenward-Roger method was used to compute the denominator degrees of freedom. All LVESV data at week 1 and week 4 were included in the MMRM model. All pairwise comparisons among treatment groups for change from baseline in LVESV and the corresponding 2-sided 95% CI were calculated based on the MMRM model. The subgroup analysis of the primary endpoint was performed with baseline ischemic/nonischemic status, high vs low baseline hs-troponin and NT-pro-BNP levels.

The echocardiography endpoints were analyzed using the same MMRM model as the primary endpoint, with the exception that week 4 and week 6 were included in the model instead of week 1 and week 4. Because of the high degree of measurement variability associated with echocardiography, only descriptive statistics were produced for selected echocardiography parameters. For the exploratory endpoints (KCCQ summary score and distance walked in 6MWT), an ANCOVA model was used instead of the repeated measures. Treatment difference estimates using

least square means along with the 95% CIs for the estimates were presented.

Safety assessment included all subjects who received at least 1 dose of the treatment. Safety analyses were conducted in the safety population according to the treatment received. No imputation was used for missing data. Data were summarized using descriptive statistics for continuous variables and using frequencies and percentages for discrete variables. Formal statistical tests were 2-sided and tested at the $\alpha = 0.05$ level of significance. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Cary, North Carolina, USA).

RESULTS

Baseline Characteristics

Of the 71 patients randomized, 70 completed the study without any major protocol deviation. One patient in the elamipretide 4 mg arm left the study early because of an adverse event. The mean age of patients was 64.8 ± 9.8 years; 24% were females and all were Caucasians. Clinical characteristics were generally well balanced in the groups at baseline. A large difference in NT-pro-BNP was noted in the groups. The placebo group had less diuretic usage and more frequent chronic kidney disease, whereas the elamipretide 4 mg group had more patients with diabetes. [Table 1](#) shows the demographic baseline characteristics of the cohort. None of the patients received angiotensin receptor neprilysin inhibitors.

Imaging Characteristics

The mean baseline LVEF was $31.2 \pm 6.9\%$, and 39% had ischemic cardiomyopathy as assessed by MRI. Baseline

Table 1. Baseline Clinical Characteristics

	Elamipretide 4 mg (n = 23)	Elamipretide 40 mg (n = 24)	Placebo (n = 24)
Age (years)	65.8 $\pm$ 10.8	62.0 $\pm$ 9.4	66.8 $\pm$ 9.8
Females (%)	4 (17%)	4 (17%)	9 (38%)
White (%)	23 (100%)	24 (100%)	24 (100%)
BMI (kg/m ²)	28.0 $\pm$ 5.0	28.8 $\pm$ 5.6	28.5 $\pm$ 5.4
Heart rate (bpm)	63.3 $\pm$ 13.2	64.3 $\pm$ 8.0	65.9 $\pm$ 7.9
Systolic BP (mmHg)	129.7 $\pm$ 18.3	124.8 $\pm$ 16.3	124.2 $\pm$ 17.6
Diabetes mellitus type 2	10 (43%)	5 (21%)	7 (29%)
Ischemic cardiomyopathy	9 (39%)	10 (42%)	9 (38%)
Hypertension	10 (43%)	13 (54%)	8 (33%)
Chronic kidney disease	5 (22%)	4 (17%)	10 (42%)
Hyperlipidemia	12 (52%)	11 (46%)	6 (25%)
eGFR (mL/min/1.73m ²)	70 $\pm$ 17.2	72.8 $\pm$ 17.6	61.7 $\pm$ 16.3
KCCQ score	79.5 $\pm$ 22.3	79.5 $\pm$ 17.4	76.8 $\pm$ 19.7
NT-pro BNP (ng/mL)	977.6 $\pm$ 718.8	2023.6 $\pm$ 6604.9	1024.8 $\pm$ 950.5
hsTroponin (ug/L)	0.008 $\pm$ 0.006	0.01 $\pm$ 0.006	0.009 $\pm$ 0.007
Distance (m) on 6MWT	437.8 $\pm$ 106.1	448.1 $\pm$ 105.7	374.8 $\pm$ 135.7
Medications at randomization			
Beta-blocker	23 (100%)	24 (100%)	24 (100%)
ACEI/ARB	23 (100%)	23 (96%)	22 (92%)
Diuretic	23 (100%)	19 (79%)	14 (58%)
Aldosterone antagonist	16 (70%)	16 (67%)	18 (75%)

ACEI, angiotensin converting enzyme; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BP, blood pressure; eGFR, estimated glomerular filtration rate; KCCQ, Kansas City Cardiomyopathy Questionnaire; 6MWT, six minute walk test.

Table 2. Baseline Imaging Characteristics

	Elamipretide 4 mg (n = 23)	Elamipretide 40 mg (n = 24)	Placebo (n = 24)
Cardiac MRI data			
LV end systolic volume (mL)	88.5 ± 38.3	77.9 ± 20.1	77.7 ± 38.9
LV ejection fraction (%)	30.9 ± 7.8	31.2 ± 5.7	31.5 ± 7.2
LV end diastolic volume (mL)	124.6 ± 42.0	112.6 ± 24.7	110.8 ± 44.7
Scarring of LV mass (%)	6.3 ± 6.7	8.7 ± 11.4	8.2 ± 12.3
Echocardiographic data			
E/A	0.86 ± 0.6	1.2 ± 1.0	1.05 ± 0.63
E/e'	11.3 ± 5.4	12.5 ± 5.0	12.6 ± 5.4
Biplane LV ejection fraction (%)	34.8 ± 9.1	36.4 ± 7.5	37.2 ± 9.6
LA volume (mL)	38.1 ± 12.6	37 ± 14	33.3 ± 8.9
LV mass (g)	140.1 ± 35	121.7 ± 26.2	136.6 ± 32.8
MR severity (cm ²)	4.1 ± 2.9	4.8 ± 2.7	7.3 ± 2.3
TR severity (cm ²)	3.3 ± 4.3	1.9 ± 1.2	3.7 ± 0.9
RV fractional area change (%)	46.2 ± 9.6	47.2 ± 10.9	43.5 ± 10.6
RV systolic pressure (mmHg)	26.9 ± 13.6	24.5 ± 10.1	33.8 ± 20.7

LA, left atrium; LV, left ventricle; MR, mitral regurgitation; MRI, magnetic resonance imaging; RV, right ventricle; TR, tricuspid regurgitation.

echocardiographic and cardiac MRI characteristics were generally similar across the 3 groups. LVESV was highest in the elamipretide 4 mg group. Table 2 shows the baseline imaging characteristics of the entire cohort.

Primary Endpoint

Fig. 1 shows the analysis of the primary endpoint. The change in LVESV from baseline to week 4 was not significantly different between elamipretide 4 mg (baseline, 89.5 mL; 4 weeks, 85 mL; difference, -4.4 ± 6.5 mL) and 40 mg (baseline, 77.9 mL; 4 weeks, 76.6 mL; difference, -1.2 ± 9.0 mL) compared with placebo (baseline, 77.7 mL; 4 weeks, 74.6 mL; difference, -3.8 ± 5.9 mL) (4 mg

vs placebo: difference of means, -0.3 ; 95% CI, -4.6 to 4.0 ; $P = 0.90$; and 40 mg vs placebo: difference of means, 2.3 ; 95% CI, -1.9 to 6.5 ; $P = 0.28$].

Exploratory subgroup analyses of the primary endpoint by baseline hs-troponin > 0.007 ng/mL, baseline NT-pro BNP > 700 ng/mL and ischemic cardiomyopathy showed no major differences in the treatment groups vs the placebo group (Supplementary Table 2).

Secondary Endpoints

Cardiac MRI parameters. No statistically significant increase in LVEF was observed in either the elamipretide 4 mg (difference of means, -0.1 ; 95% CI, -1.8 to 1.6 ;

Fig. 1. Analysis of the primary endpoint. The figure shows the mean change from baseline in left ventricular end systolic volume (LVESV) stratified by treatment group. The change in LVESV from baseline to week 4 was not significantly different between elamipretide and placebo. The error bars represent standard error.

$P = 0.90$) or the 40 mg group compared with placebo (difference of means, -0.8 ; 95% CI, -2.4 to 0.9 ; $P = 0.37$) (Fig. 2A) at 4 weeks. Similarly, there were no significant differences in change in LVEDV between placebo and either of the elamipretide groups (4 mg: difference of means, -0.1 ; 95% CI, -6.3 to 6.1 ; $P = 0.97$; 40 mg: difference of means, 2.3 ; 95% CI, -3.6 to 8.3 ; $P = 0.44$) (Fig. 2B).

Echocardiography parameters. Changes from baseline to week 4 in E/A, E/e' and LV global longitudinal strain were similar between the placebo and elamipretide groups (Table 3). The elamipretide 4 mg arm had significantly reduced left atrial volume compared with the placebo group at week 4 (difference of means, -4.3 ; 95% CI, -7.5 to -1.2 ; $P = 0.008$). However, no significant difference was observed between elamipretide 40 mg and placebo.

Exploratory Endpoints

Changes in NT-pro-BNP and distance walked in meters on 6MWT from baseline to 4 weeks were small and did not significantly differ between the 2 elamipretide dose arms and the placebo group (Table 3). There was a trend toward improvement in KCCQ summary scores with elamipretide 40 mg compared with placebo; however, it did not reach statistical significance (difference of means, 5.6 ; 95% CI, -0.5 to 11.6 ; $P = 0.07$).

Safety Outcomes

Safety outcomes were evaluated in all patients who received at least 1 dose of the drug. Table 4 shows the data regarding adverse events, serious adverse events and discontinuation due to the adverse events. Only 1 patient in the

Fig. 2. (A) Analysis of the secondary endpoint. The figure shows the mean change from baseline in left ventricular ejection fraction (LVEF) stratified by treatment group. No statistically significant increase in LVEF was observed in either elamipretide 4 mg or 40 mg group compared with placebo. The error bars represent standard error. (B) Analysis of the secondary endpoint. The figure shows the mean change from baseline in left ventricular end diastolic volume (LVEDV) stratified by treatment group. No statistically significant increase in LVEDV was observed in either elamipretide 4 mg or 40 mg group compared with placebo. The error bars represent standard error.

Fig. 2 Continued.

entire cohort (the elamipretide 4 mg group) had a treatment-related adverse event (nausea and fatigue) leading to discontinuation of involvement in the study. Similarly, only 1 patient (in the elamipretide 40 mg arm) had a serious treatment-emergent adverse event. Rates of any study drug-related adverse events were similar in the 3 groups. The most common adverse event was injection-site reactions in the elamipretide 40 mg arm. There were no significant changes in blood pressure, heart rate or ECG intervals in the groups.

DISCUSSION

In this study, elamipretide 4 mg or 40 mg did not significantly improve the primary endpoint of change in LVESV from baseline to week 4 compared with placebo in patients with stable HFrEF. Prespecified secondary analyses of LVEF and LVEDV also showed no significant difference between the treatment and placebo groups. There was a trend toward improvement in the KCCQ summary scores, with elamipretide 40 mg compared with placebo; however, it did not reach statistical significance. Other exploratory

endpoints of changes in NT-pro-BNP and distance walked in meters on 6MWT from baseline also did not significantly improve in the treatment group. Overall, elamipretide was well tolerated and showed similar rates of adverse events compared with placebo.

Although many studies^{13–15} based on human and animal models have reported benefit with mitochondrial agents, the results with this agent in patients with cardiovascular disease has been less convincing. In the EMBRACE STEMI (Evaluation of Myocardial Effects of Bendavia for Reducing Reperfusion Injury in Patients with Acute Coronary Events—ST-Segment Elevation Myocardial Infarction) trial,¹⁶ elamipretide did not improve any of the outcomes. However, in a previous small, randomized, controlled trial in patients with HFrEF, short-term treatment with elamipretide was shown to reduce LVEDV and LVESV significantly.¹⁵ It is important to note that these changes did not correspond with biomarker changes and had wide confidence intervals.

There could be several reasons to explain why animal studies, which were largely positive, were not confirmed in this human trial. In the human trial, there was an

Table 3. Secondary and Exploratory Endpoint Analyses

	Placebo	Elamipretide 4 mg	Elamipretide 40 mg	Elamipretide 4 mg vs placebo (95% CI) <i>P</i> value	Elamipretide 40 mg vs placebo (95% CI, <i>P</i> value)	Linear trend test <i>P</i> value
Echocardiography parameters						
E/A	-0.07 ± 0.5	-0.04 ± 0.2	-0.03 ± 0.3	-0.01 (-0.23, 0.21), 0.92	0.06 (-0.16, 0.27), 0.60	0.51
E/e'	-0.2 ± 4.3	-0.94 ± 3.2	0.47 ± 4.4	-1.14 (-3.5, 1.2), 0.33	0.46 (-1.8, 2.7), 0.69	0.31
LV EDV (mL)	2.9 ± 16.1	-3.2 ± 15.6	-3.7 ± 12.8	NR\$	NR	NR
LV ESV (mL)	0.6 ± 10.3	-1.9 ± 11.6	-0.5 ± 7.9	NR	NR	NR
LV GLS (%)	-1.5 ± 2.4	-1.8 ± 2.0	-1.5 ± 2.7	-0.13 (-3.3, 3.1), 0.93	-0.22 (-4.5, 4.1), 0.91	0.88
LA volume (mL)	1.6 ± 4.0	-3.4 ± 6.9	-0.2 ± 4.4	-4.3 (-7.5, -1.2), 0.008	-1.2 (-4.3, 1.9), 0.45	0.64
LVEF (%)	1.5 ± 4.2	1.8 ± 2.9	2.0 ± 2.8	NR	NR	NR
LV mass (g)	-0.7 ± 22	3 ± 18.3	-4.2 ± 18.6	NR	NR	NR
RVSP (mmHg)	-7 ± 25.6	5.7 ± 16.2	-1.5 ± 6.6	NR	NR	NR
RV fractional area change (%)	0.9 ± 8.9	0.1 ± 10.8	0.1 ± 8.8	NR	NR	NR
Other exploratory end points						
NT-pro BNP (ng/mL)	-73.4 ± 377	209 ± 511	-397 ± 1974	0.02(-0.09, 0.13), 0.71	0.02(-0.09, 0.12), 0.76	0.85
hsTroponin (ug/L)	0.005 ± 0.004	0.0007 ± 0.002	0.002 ± 0.01	0.0003 (-0.002, 0.003), 0.82	0.0008 (-0.002, 0.004), 0.57	0.69
KCCQ summary score	3.8 ± 12.5	3.8 ± 11.2	6.7 ± 12.5	2.6 (-3.5, 8.7), 0.40	5.6 (-0.5, 11.6), 0.07	0.09
Distance walked in 6MWT (m)	37.6 ± 52.7	23.1 ± 82.1	34.6 ± 67.4	2.8(-35.8, 41.4), 0.89	16.4 (-22.9, 55.7), 0.41	0.36

Note: Because of the high degree of measurement variability associated with echocardiography, only descriptive statistics were produced for these parameters (NR).

BNP, brain natriuretic peptide; EDV, end-diastolic volume; EF, ejection fraction; ESV, end systolic volume; GLS, global longitudinal strain; KCCQ, Kansas City Cardiomyopathy Questionnaire; LA, left atrium; LV, left ventricle; RV, right ventricle; RVSP, right ventricular systolic pressure; 6MWT, 6-minute walk test.

unexpected reverse modeling in the placebo group, with a reduction in LV volumes and increase in LVEF from baseline. This may have been caused by better treatment of the patients enrolled or regression to the mean, and with a small sample size, that may have had a major influence on the results. Moreover, some of the animal-model studies had used 3 months of elamipretide therapy. For cardiac remodeling and correction of abnormal mitochondrial dynamics in failing hearts, therapy with elamipretide during a term longer than 4 weeks might be required.¹⁷ It is also possible that the incremental benefit of improving mitochondrial function, if that occurred, is small and not detectable when

added to contemporary guideline-directed medical therapy or may be manifest only during times of higher demand, such as during exercise. It is important to note that elamipretide is just 1 of many treatments that have appeared to be effective in small animal models of HF but have failed to translate into clinical benefits in humans. Another possible explanation is that the effect of this agent may be the promotion of LV relaxation, as opposed to enhancement of contraction, as evidenced by the slight increase in LVEDV as assessed by cardiac MRI. A similar effect occurred in a small proof-of-concept trial in HFpEF. Likewise, echocardiogram results from a trial in Barth syndrome revealed a significant increase in stroke volume, resulting from increases in LV volumes.

It is well established that HF is a state of myocyte energy depletion due to changes that inhibit optimum production of ATP. Although targeting the mitochondria in HF makes sense physiologically, we lack evidence that this will help clinically. Previous attempts to restore myocardial energetics in HF have yielded inconsistent results. For instance, trimetazidine, an anti-ischemic (antianginal) metabolic agent that improves myocardial glucose utilization through inhibition of long-chain 3-ketoacyl coenzyme A thiolase activity, which results in a reduction in fatty-acid oxidation and a stimulation of glucose oxidation, has failed to show clinical benefits in patients with HF. Moreover, none of the antioxidants have proven to be beneficial in HF.^{18–21}

We believe that this study warrants a more general discussion regarding how better to design phase 2 trials in patients with HF. This study was based on the high

Table 4. Adverse Events (Safety Analysis Set)

	Elamipretide 4 mg (n = 22)	Elamipretide 40 mg (n = 25)	Placebo (n = 24)
Any AE	9 (41%)	16 (64%)	10 (42%)
Any study drug-related AE	5 (23%)	7 (28%)	4 (17%)
Any serious AE	0	1 (4%)	0
Any study drug-related serious AE	0	1 (4%)	0
Discontinuation of study drug due to AE	1 (4.5%)	0	0
Discontinuation of study drug due to serious AE	0	0	0
All-cause death	0	0	0
Injection-site reaction	1 (4.5%)	6 (24%)	0

AE, adverse event.

reproducibility of LV volumes as measured by cardiac MRI as well as on the hypothesis that changes in LV volumes and/or LVEF are predictive of effects on patients' outcomes. However, the hypothesis that surrogates of LV remodeling, such as natriuretic peptides, can be used as surrogates of drug effects on outcomes has not yet been proven.²² Thus, we are left with the question of whether a trial based on the assessment of the changes in LV volumes measured by an accurate tool such as cardiac MRI can be used to select drug treatment for patients with HFrEF.

One of the primary goals of HF treatment is to improve quality of life and reduce physical limitations. Physical limitation in HF is due to a combination of abnormal hemodynamics and skeletal-muscle weakness. Elamipretide has previously been shown to improve skeletal-muscle function and, subsequently, increase exercise tolerance. It has also been shown to increase significantly 6MWT distance in patients with mitochondrial myopathy.^{3,23–25} Although we observed a trend toward improvement in KCCQ summary scores with elamipretide 40 mg, we did not find any significant difference in the 6MWT distance in the placebo and elamipretide groups. Future studies should consider the association between elamipretide and subdomains of KCCQ, especially the physical-limitation score. Moreover, despite the neutral findings in patients with HF, there is evidence that elamipretide might be effective in patients with mitochondrial myopathy.

Elamipretide was well tolerated but did not have a statistically significant effect on change in LVESV at 4 weeks in stable patients with HFrEF compared with placebo. Further clinical trials of elamipretide in other HF phenotypes are needed to evaluate the potential role of targeting mitochondrial function in HF. Similarly, longer term studies in HFrEF may still be useful.

Disclosures

JB serves as a consultant for Abbott, Adrenomed, Amgen, Array, Astra Zeneca, Bayer, Boehringer Ingelheim, Bristol Myers Squibb, CVRx, G3 Pharmaceutical, Impulse Dynamics, Innolife, Janssen, LivaNova, Luitpold, Medtronic, Merck, Novartis, NovoNordisk, Relypsa, Roche, V-Wave Limited, and Vifor. SDA has received research support from Vifor International & Abbott Vascular, and fees for consultancy and/or speaking from Astra Zeneca, Bayer, Boehringer Ingelheim, Respicardia, Impulse Dynamics, Janssen, Novartis, Servier and Vifor International. GCF reports research funding from NIH and consultant to Abbott, Amgen, CHF solutions, Janssen, Medtronic, and Novartis. RJK has received grants from National Heart, Lung and Blood Institute and support from HeartIT. CC has served as a consultant for Bayer, Merck, Actelion, Bristol Myer Squibb, and NHLBI. BP has served as a consultant for or has received speaker's bureau fees from Bayer Healthcare, Merck, Novartis, Stealth Petides, Daiichi-Sankyo, Astra-Zeneca, BMS, and Servier. EPK has received support from the DZHK (German Centre for Cardiovascular Research) and personal fees from Bayer.

HNS reports receiving research support from Stealth BioTherapeutics, Bayer, Novartis, and Merck and is a consultant to Stealth BioTherapeutics and Bayer. MS reports no relevant disclosures. A.A.V. received consultancy fees and/or research grants from Amgen, AstraZeneca, Bayer, Boehringer Ingelheim, Cytokinetics, GSK, Myokardia, Novartis, Roche Diagnostics, Stealth and Servier. JEU has served as a consultant for Stealth BioTherapeutics, LivaNova, Imbria, Cardurion, Bayer, Committees for Pfizer/Merck. JC is an employee of Stealth BioTherapeutics, Newton, Massachusetts, USA. GF has received research grants from the European Union and participated in Committees of Trials and Registries sponsored by Medtronic, BI, Novartis, Vifor, Servier. MSK, SN have no relevant disclosures to report.

Acknowledgment

This study was funded by Stealth BioTherapeutics, Newton, Massachusetts, USA.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.cardfail.2020.02.001](https://doi.org/10.1016/j.cardfail.2020.02.001).

References

1. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. *Circulation* 2013;128:e240–327.
2. Roger VL, Weston SA, Redfield MM, et al. Trends in heart failure incidence and survival in a community-based population. *JAMA* 2004;292:344–50.
3. Ingwall JS. Energy metabolism in heart failure and remodeling. *Cardiovasc Res* 2009;81:412–9.
4. Katz AM, Rolett EL. Heart failure: when form fails to follow function. *Eur Heart J* 2016;37:449–54.
5. Brown DA, Perry JB, Allen ME, et al. Expert consensus document: mitochondrial function as a therapeutic target in heart failure. *Nat Rev Cardiol* 2016;14:238–50.
6. Abozguia K, Phan TT, Shivu GN, et al. Reduced in vivo skeletal muscle oxygen consumption in patients with chronic heart failure: a study using Near Infrared Spectrophotometry (NIRS). *Eur J Heart Fail* 2008;10:652–7.
7. Eirin A, Ebrahimi B, Zhang X, et al. Mitochondrial protection restores renal function in swine atherosclerotic renovascular disease. *Cardiovasc Res* 2014;103:461–72.
8. Anderson EJ, Lustig ME, Boyle KE, et al. Mitochondrial H₂O₂ emission and cellular redox state link excess fat intake to insulin resistance in both rodents and humans. *J Clin Invest* 2009;3:573–81.
9. Heggermont WA, Papageorgiou AP, Heymans S, Van Bilsen M. Metabolic support for the heart: complementary therapy for heart failure. *Eur J Heart Fail* 2016;18:1420–9.
10. Zhao K, Luo G, Zhao GM, Schiller PW, Szeto HH. Transcellular transport of a highly polar +3 net charge opioid tetrapeptide. *J Pharmacol Experim Therapeut* 2013;304:425–32.
11. Joshi AS, Thompson MN, Fei N, Huttermann M, Greenberg ML. Cardiolipin and mitochondrial phosphatidylethanolamine

- have overlapping functions in mitochondrial fusion in *Saccharomyces cerevisiae*. *J Biol Chem* 2012;287:17589–97.
12. DeVay RM, Dominguez-Ramirez L, Lackner LL, et al. Coassembly of mgm1 isoform requires cardiolipin and mediates mitochondrial inner membrane fusion. *J Cell Bio* 2009;186:793–803.
 13. Sabbah HN, Gupta RC, Kohli S, Wang M, Hachem S, Zhang K. Chronic therapy with elamipretide (MTP-131), a novel mitochondria-targeting peptide, improves left ventricular and mitochondrial function in dogs with advanced heart failure. *Circ Heart Fail* 2016;9:e002206.
 14. Shi J, Dai W, Hale SL, et al. Bendavia restores mitochondrial energy metabolism gene expression and suppresses cardiac fibrosis in the border zone of the infarcted heart. *Life Sci* 2015;141:170–8.
 15. Daubert MA, Yow E, Dunn G, et al. Novel mitochondria-targeting peptide in heart failure treatment: a randomized, placebo-controlled trial of elamipretide. *Circ Heart Fail* 2017;10:e004389.
 16. Gibson CM, Giugliano RP, Kloner RA, et al. EMBRACE STEMI study: a phase 2a trial to evaluate the safety, tolerability, and efficacy of intravenous MTP-131 on reperfusion injury in patients undergoing primary percutaneous coronary intervention. *Eur Heart J* 2016;37:1296–303.
 17. Chatfield KC, Sparagna GC, Chau S, et al. Elamipretide improves mitochondrial function in the failing human heart. *JACC Basic Transl Sci* 2019;4:147–57.
 18. Mann DL. Targeting myocardial energetics in the failing heart: are we there yet? *Circ Heart Fail* 2017;10:4658.
 19. Steggall A, Mordi IR, Lang CC. Targeting metabolic modulation and mitochondrial dysfunction in the treatment of heart failure. *Diseases* 2017;5:E14.
 20. Marchioli R, Levantesi G, Macchia A, et al. Vitamin E increases the risk of developing heart failure after myocardial infarction: results from the GISSI-Prevenzione trial. *J Cardiovasc Med (Hagerstown)* 2006;7:347–50.
 21. Bayeva M, Gheorghiade M, Ardehali H. Mitochondria as a therapeutic target in heart failure. *J Am Coll Cardio* 2013;61:599–610.
 22. Wessler BS, McCauley M, Morine K, Konstam MA, Udelson JE. Relation between therapy-induced changes in natriuretic peptide levels and long-term therapeutic effects on mortality in patients with heart failure and reduced ejection fraction. *Eur J Heart Fail* 2019;21:613–20.
 23. MMPOWER trial (A Study Investigating the Safety, Tolerability, and Efficacy of MTP-131 for the Treatment of Mitochondrial Myopathy), NCT02367014. *Mitochond Med* 2016. oral abstract presentation.
 24. Sabbah HN, Gupta RC, Singh-Gupta V, Zhang K. Effects of elamipretide on skeletal muscle in dogs with experimentally induce heart failure. *ESC Heart Fail* 2019;6:328–35.
 25. Karaa A, Haas R, Goldstein A, Vockley J, Weaver WD, Cohen BH. Randomized dose escalation of elamipretide in patients with primary mitochondrial myopathy. *Neurology* 2018;90:1212–21.