Effects of the Novel Long-Acting GLP-1 Agonist, Albiglutide, on Cardiac Function, Cardiac Metabolism, and Exercise Capacity in Patients With Chronic Heart Failure and Reduced Ejection Fraction

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ABSTRACT

OBJECTIVES This study sought to determine if glucagon-like peptide (GLP)-1 ameliorates myocardial metabolic abnormalities in chronic heart failure.

BACKGROUND Albiglutide (GSK716155) is a GLP-1 agonist indicated for type 2 diabetes.

METHODS We performed a randomized, placebo-controlled study evaluating 12 weeks of albiglutide in New York Heart Association II or III subjects with ejection fraction <40%. Subjects received weekly placebo (n = 30) or albiglutide 3.75 mg (n = 12), 15 mg (n = 13), or 30 mg (n = 27). The primary comparison was between albiglutide 30 mg and placebo. Assessments included echocardiography, 6-minute-walk test, and peak oxygen consumption. In a subgroup of patients, myocardial glucose and oxygen use were assessed. Endpoints are reported as change from baseline/C6 SE.

RESULTS Albiglutide 30 mg compared with placebo did not improve change from baseline in left ventricular ejection fraction (2.4% [1.1%] vs. 4.4% [1.1%]; p = 0.22), 6-min walk test (18 [12] m vs. 9 [11] m; p = 0.58), myocardial glucose use (p = 0.59), or oxygen use (p = 0.25). In contrast, albiglutide 30 mg versus placebo improved change from baseline in peak oxygen consumption (0.9 [0.5] ml/kg/min vs. -0.6 [0.5] ml/kg/min; p = 0.02). Albiglutide was well tolerated.

CONCLUSIONS Although there was no detectable effect of albiglutide on cardiac function or myocardial glucose use, there was a modest increase in peak oxygen consumption, which could have been mediated by noncardiac effects.

(A Multi-center, Placebo-controlled Study to Evaluate the Safety of GSK716155 and Its Effects on Myocardial Metabolism, Myocardial Function, and Exercise Capacity in Patients With NYHA Class II/III Congestive Heart Failure; NCT01357850) (J Am Coll Cardiol HF 2016;4:559–66) © 2016 by the American College of Cardiology Foundation.
A n increasing body of evidence indicates that advanced heart failure with reduced ejection fraction (HFrEF) is characterized by an impaired capacity of the myocardium to metabolize fatty acids. Furthermore, the changes in metabolism are associated with a reduction in high-energy phosphate content, changes in mitochondrial function, and increased dependence on glucose as a substrate (1). The basis for this shift toward glucose metabolism is unknown; however, it may serve as a compensatory mechanism for the generation of adequate adenosine triphosphate in the face of metabolic decompensation (2–4). Despite this shift, stores of high-energy phosphates decline and correspond to reductions in myocardial insulin sensitivity (5,6). This myocardial energy depletion is thought to be a key contributor to the progressive impairment in myocardial systolic function that characterizes HFrEF.

Glucagon-like peptide (GLP)-1 receptor activation leads to insulinotropic and insulinomimetic effects in various tissues including the myocardium and has demonstrated beneficial effects on myocardial glucose uptake (7–10). Improved glucose uptake associated with GLP-1 administration has been shown to increase myocardial contractility in preclinical models of heart failure and in patients with HFrEF (8,10,11). In several small studies, a continuous infusion of GLP-1 peptide increased exercise capacity (peak oxygen consumption [VO₂] and 6-min walk test [6MW]) and left ventricular ejection fraction (LVEF) in subjects with chronic heart failure (12), improved LVEF in patients with acute myocardial infarction (10), and reduced the need for administration of intravenous pressor agents in patients following cardiac surgery (13). However, improvement in myocardial glucose uptake in HFrEF has been demonstrated using metabolically active agents that nonetheless have been reported to have adverse clinical effects (14,15). Whether the putative benefit of GLP-1 mimetics will translate into clinical benefit is of interest, and is under study in several clinical trials (NCT01425580, NCT01800968, NCT00766857).

Albiglutide is a novel, long-acting GLP-1 mimetic consisting of 2 tandem copies of modified human GLP-1 fused to human albumin and has recently been approved in the United States and European Union for the treatment of type 2 diabetes (16).

We hypothesized that the administration of albiglutide to patients with HFrEF would improve left ventricular (LV) function and exercise performance, mediated at least in part by promoting myocardial glucose uptake and use.

**METHODS**

**STUDY DESIGN.** This was a multicenter, randomized, parallel arm, placebo-controlled study to evaluate the safety and efficacy of 12 weeks of treatment with albiglutide in subjects with stable, chronic heart failure (diagnosis ≥6 months, stable medications ≥3 months). Eligible subjects had New York Heart Association functional class II or III HFrEF (ejection fraction <40%). Key exclusion criteria included diabetes mellitus, myocardial infarction, or unstable angina within 12 mos, or coronary revascularization within 6 mos.

Approval from Institutional Review Boards/Ethics Committees was obtained, and written informed consent was obtained before each subject could participate in the study. The study was conducted in accordance with “good clinical practice” and all applicable regulatory requirements, including the 2008 version of the Declaration of Helsinki and the Institutional Ethics Committee, and the study was registered on clinicaltrials.gov (NCT01357890). Academic investigators had full access to the final data.

Subjects were randomized to 12 weeks’ subcutaneous placebo or albiglutide 3.75 mg, 15 mg, or 30 mg. Subjects, investigators, and sponsor staff at the study sites were blinded to treatment allocation; sponsor internal staff and staff from the contract research organization (Pharmaceutical Product Development, Wilmington, North Carolina) were unblinded.

Subjects came to their respective study sites weekly for subcutaneous injections and study assessments, with final assessments performed at Week 13, and a follow-up visit 28 days after the last dose (Figure 1).

A total of 100 subjects were planned to complete this study (25 per treatment arm). In-stream assessments were used to gauge the use of continued randomization into dose levels not achieving sufficient pharmacodynamic effects, on the basis of the difference from placebo in point estimates for LVEF, LV volumes, and peak VO₂.

**BIOMARKERS OF HEART FAILURE SEVERITY AND GLUCOSE METABOLISM.** Blood samples for analysis of fasting levels of brain natriuretic peptide, glucose, insulin, and free fatty acids and for calculation of Homeostasis Model Assessment index were collected at Weeks 1, 7, and 13; glucose was also collected at Weeks 2, 4, 6, 8, 10, and 12.
ECHOCARDIOGRAPHY. LV structure and function were evaluated with echocardiography at baseline and Week 13. All echocardiographic studies were read independently by 2 expert echocardiographers from the Washington University Echocardiography Core Laboratory who were blinded to all clinical parameters and treatment group. All reported measurements represent the average of 3 consecutive cardiac cycles. The intraclass correlation coefficient for measurements of LV volume was 0.88.

VO2 UPTAKE. Peak VO2 was measured by bicycle ergometry at baseline and Week 13 according to standard methodology (17).

6MW. The 6MW was performed at baseline and Week 13 according to standard methodology (18). All patients were given standardized instructions and the distance walked was measured.

PATIENT-REPORTED QUALITY OF LIFE. Patient-reported quality of life was measured at baseline and Week 13 using a validated instrument, the Minnesota Living with Heart Failure Questionnaire (19,20).

POSITRON EMISSION TOMOGRAPHY IMAGE ACQUISITION AND ANALYSIS. At selected sites, imaging was performed on commercially available positron emission tomography (PET)/computed tomography (CT) systems at baseline and Week 13 to assess myocardial glucose utilization with 18F-fluorodeoxyglucose and myocardial oxygen consumption with 11C-acetate using standard techniques (21,22).

PHARMACOKINETICS. Trough plasma pharmacokinetic samples were taken at each clinic visit. Plasma concentrations of albiglutide were determined using a validated enzyme-linked immunosorbent assay. Within-run precision ranged between 7.4 and 11.6%. Bias ranged between -11.1 and -3.1%.

STATISTICAL ANALYSIS. A sample size of 100 subjects (25 subjects per arm) provided at least 90% power to detect a targeted increase (compared with placebo) in myocardial glucose use (15.2 μmol/100 g/min) (23,24), myocardial efficiency (1.4 × 10^6 mm Hg · ml/min^2) (25), peak VO2 (1.5 ml/kg/min) (26), and LVEF (6%); and 61% power to detect a 50-m improvement in 6MW (27). The endpoints, after natural log transformation as appropriate, were analyzed using a mixed effects analysis of variance model, fitting terms for treatment, visit, and interaction of treatment and visit, with subject as random effects. Point estimates, 95% confidence intervals, and p values were obtained for each variable for the comparisons of Week 13 versus Week 1 for each treatment arm, and for the comparison of change from baseline in active drug versus change from baseline in placebo. For the log transformed endpoints, the point estimates and 95% confidence intervals were then back transformed so that the estimates for ratios (percent change) could be obtained.

RESULTS

SUBJECT DISPOSITION. Review of data from an early in-stream analysis suggested limited efficacy in subjects receiving albiglutide 3.75 or 15 mg weekly. Accordingly, per protocol, randomization into these arms was discontinued, and all subsequent subjects were randomized in a 1:1 fashion to either albiglutide 30 mg weekly or placebo until the target enrollment in these treatment arms was complete. Eighty-one of 82 randomized subjects (97%) completed the study. One placebo-treated subject withdrew before the follow-up visit. No subjects were withdrawn because of adverse events (AEs) (Table 1).

DEMOGRAPHICS AND BASELINE CHARACTERISTICS. Subject characteristics were balanced across all treatment groups. Background medical management was consistent with recommendations for standard of care (Table 2).

Efficacy

BIOMARKERS OF HEART FAILURE SEVERITY AND MEASURES OF GLUCOSE METABOLISM. Brain natriuretic peptide. There were no clinically meaningful changes in brain natriuretic peptide within or between treatment groups (Table 3).

Metabolic parameters. At Week 13, weight increased significantly (0.75 kg; p = 0.04) in subjects treated with placebo, whereas weight decreased significantly (0.84 kg; p = 0.03) in subjects treated with albiglutide 30 mg. Homeostasis Model Assessment, plasma glucose, and insulin levels did not change in either the placebo or albiglutide 30-mg
groups. Free fatty acids decreased similarly in both treatment groups, with statistical significance in placebo-treated subjects (Table 3).

**Clinical Measures.** Clinical efficacy results are summarized in Table 4 as changes from baseline to Week 13 for albiglutide 30 mg compared with placebo. Results for change from baseline for the discontinued albiglutide 3.75-mg and 15-mg weekly dosing arms are presented in Online Table 1. Baseline measures of myocardial structure and function, exercise performance, and quality of life did not differ significantly between the 2 treatment groups. Subjects receiving placebo and albiglutide 30 mg had statistically significant changes in left ventricular end-diastolic volume, left ventricular end-systolic volume, and LVEF compared with baseline, but administration of albiglutide 30 mg weekly for 13 weeks did not result in a change from baseline in LV size and function, 6MW, or quality of life versus placebo. However, subjects receiving albiglutide 30 mg demonstrated a numeric improvement in peak VO2 at Week 13 versus baseline (0.9 ml/kg/min; p = 0.07) and had a modest but significant increase in peak VO2 of 1.5 ml/kg/min (p = 0.024) compared with placebo.

**PET/CT: Myocardial Glucose Use, O2 Consumption, and Efficiency Index.** The results of 18F-fluorodeoxyglucose PET/CT to measure myocardial glucose use and of 11C-acetate PET to derive myocardial oxygen consumption are shown in Table 5. Note that only a subset of randomized subjects underwent PET/CT, and not all eligible subjects underwent both 18F-fluorodeoxyglucose and 11C-acetate PET/CT. With the exception of an increase in myocardial oxygen consumption for placebo-treated patients, neither regimen had any significant impact on these parameters at Week 13 versus baseline. Furthermore, the data show no meaningful changes in myocardial glucose use, myocardial efficiency, or O2 consumption on albiglutide 30 mg versus placebo.

**Subgroup Analyses.** Subgroup analyses on the basis of baseline demographic and clinical characteristics (including sex, ischemic/nonischemic etiology, baseline ejection fraction, baseline peak VO2) were performed but did not suggest albiglutide efficacy in any subgroup.

**Pharmacokinetics.**

The original analysis plan for the pharmacokinetic data was to use Bayesian methodology to incorporate previous knowledge of albiglutide pharmacokinetics in patients with type 2 diabetes mellitus (25). However, on receipt of the data, an unexpected shift in albiglutide plasma concentrations was observed, resulting in approximately 1.5 to 2 times higher concentrations than expected. This shift was later found to be caused by a change from manual to robotic pipetting, but at the time the analysis was performed, the cause was unknown. Despite several attempts to analyze the data as planned, the analysis could not be performed successfully. A summary of the achieved steady state trough concentrations by dose is provided in Online Table 2. Good dose separation, in terms of observed exposures between the dose groups, was achieved. Steady state was achieved by Week 5.
The observed albiglutide plasma concentrations and peak VO$_2$ levels were modeled using a standard baseline $E_{\text{max}}$ model to determine if a relationship exists between albiglutide plasma concentrations and the peak VO$_2$ response. The results (Online Figure 1) suggest no relationship between albiglutide exposure and peak VO$_2$.

**SAFETY AND AEs**

There were a total of 69 subjects with AEs: placebo, 25 of 30 (83%); 3.75 mg, 12 of 12 (100%); 15 mg, 12 of 13 (95%); and 30 mg, 20 of 27 (74%). Subjects reported gastrointestinal disorders, including diarrhea, vomiting, and nausea most commonly: placebo, 13 of 30 (43%); 3.75 mg, 4 of 12 (33%); 15 mg, 5 of 13 (38%); and 30 mg, 10 of 27 (37%). Seven subjects had treatment-emergent serious AEs (3 on placebo, 2 on 3.75 mg, and 2 on 15 mg); these are detailed in Online Table 3. There were no drug-related serious AEs and no serious AEs in subjects receiving albiglutide 30 mg. No treatment-emergent AEs of renal impairment, pancreatitis, thyroid tumors, systemic allergic reactions, or hypoglycemia were reported. Blood pressure and heart rate were not different between albiglutide- and placebo-treated subjects.

**DISCUSSION**

This is the first study to evaluate the safety and efficacy of the GLP-1 mimetic, albiglutide, in patients with HFrEF. Following 12 weeks of albiglutide 30 mg weekly, there was a nonsignificant improvement in peak VO$_2$ from baseline (p = 0.07) and a significant

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<td>Brain natriuretic peptide, ng/l</td>
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<td>Weight, kg</td>
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<td>Insulin, pmol/l</td>
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<td>Glucose, mmol/l</td>
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<td>Free fatty acids, mmol/l</td>
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Values are mean ± SE.
BL = baseline; HOMA = Homeostasis Model Assessment.

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<th>TABLE 4 Clinical Measures of Efficacy</th>
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<td>LVEF, %</td>
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<td>LVEDV, ml</td>
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<td>Peak VO$_2$, ml/kg/min</td>
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<td>6MW, m</td>
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<td>QoL score</td>
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Values are mean ± SE.
6MW – 6 min walk test; LVEDV = left ventricular end-diastolic volume; LVEF = left ventricular ejection fraction; LVESV = left ventricular end-systolic volume; peak VO$_2$ = peak oxygen consumption; QoL = quality of life; other abbreviations as in Table 3.
improvement compared with placebo at 13 weeks. Albiglutide versus placebo did not impact myocardial glucose use, myocardial O₂ consumption, cardiac efficiency, LV size and function, 6MW distance, or quality of life. Because the results of the study do not demonstrate an effect of albiglutide on resting cardiac functional or metabolic measures, the influence of albiglutide on peak VO₂ suggests the potential for extracardiac GLP-1 effects, or an effect on cardiac performance (e.g., contractile reserve, relaxation reserve, or metabolic reserve) evident only during stress or exercise.

Although the major physiologic function of GLP-1 is systemic glycemic regulation, increasing evidence indicates that GLP-1 may also play a direct role in cardiovascular physiology. GLP-1 receptors are expressed in cardiomycocytes and in vascular endothelium and smooth muscle cells, and GLP-1 receptor agonists exert a wide range of cardiovascular effects including increased myocardial glucose uptake, vasodilation, and activation of cyclic adenosine monophosphate (6). In addition, GLP-1 has been shown to function as an insulinomimetic in the heart, directly modulating glucose metabolism (8). Most importantly, it has been reported that a short-term infusion of GLP-1 significantly improves cardiac function in patients with heart failure, suggesting GLP-1 and mimetics may be used as a novel therapeutic approach for heart failure (10).

However, the results from this study do not support the hypothesis that albiglutide improves myocardial glucose use and thereby increases cardiac performance. The apparent lack of drug effect may be the result of assay sensitivity, high assay variability, suboptimal dosing, or insufficient treatment duration to demonstrate clinical benefit. In addition, it is possible that functional myocardial effects would only be evident during high cardiac demand, such as during exercise or dobutamine infusion; however, this was not assessed because of technical limitations. Importantly, although this approach to treat HFrEF was directed toward improving myocardial glucose use in a population of patients with presumably insulin-resistant myocardium, it was observed in another study where subjects with heart failure that was considered “mild to moderate” exhibited no underlying myocardial insulin resistance and in fact had increased myocardial fatty acid oxidation (23). Thus, the population recruited for this study may not have had a disease burden sufficient to derive benefit from GLP-1 agonism. Finally, targeting GLP-1 as a means to reverse the metabolic abnormalities in HFrEF may be inadequate given the possibility that multiple mechanisms are contributing to the underlying defects.

The mechanism of the demonstrated benefit on peak VO₂ is not clear. Because there was no apparent relationship between peak VO₂ and measures of myocardial metabolic function including myocardial glucose utilization, myocardial oxygen consumption, and myocardial efficiency (Online Figure 2), the observed effect on peak VO₂ is unlikely to be related to an improvement in myocardial function. Of note, the improvement in peak VO₂ over placebo was not associated with a corresponding relative improvement in 6MW distance or quality of life, suggesting the potential for a spurious finding. The possibility that the improvement in peak VO₂ is a spurious finding is also supported by the pharmacokinetic/pharmacodynamic modeling, which indicated no relationship between albiglutide exposure and peak VO₂. However, it is also possible that the effects of the drug on functional capacity are only realized at maximal or near maximal efforts, mediated by a cardiac effect under stress, or by improved skeletal muscle performance. In that case, one would not expect any improvement in measurements of submaximal effort (i.e., 6MW) or quality of life. Similar findings have been demonstrated with inotropic therapy. Small studies have demonstrated an increase

### Table 5: Positron Emission Tomography Data

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<th>Placebo (n = 10) Change From BL</th>
<th>Albiglutide 30 mg (n = 11) Change From BL</th>
<th>Albiglutide 30 mg Versus Placebo</th>
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<td>BL Week 13 p Value</td>
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<td>Myocardial glucose use</td>
<td>0.03 ± 0.02</td>
<td>0.05 ± 0.02</td>
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<td>0.09 ± 0.02</td>
<td>0.09 ± 0.02 0.006 ± 0.02 0.72</td>
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<td>0.01 ± 0.02</td>
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<tr>
<td>Myocardial efficiency, mm Hg l/min²</td>
<td>9.611 ± 1.036</td>
<td>8.559 ± 0.901</td>
<td>-1.052 ± 1.022 0.31</td>
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<td>9.232 ± 0.945</td>
<td>-871 ± 93.06 0.36</td>
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<td>181 ± 1.384</td>
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<td>Myocardial O₂ consumption, l/min</td>
<td>0.039 ± 0.004</td>
<td>0.047 ± 0.004</td>
<td>0.008 ± 0.003 0.01</td>
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<td>0.046 ± 0.004</td>
<td>0.049 ± 0.003 0.003 ± 0.003 0.29</td>
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Values are mean ± SE.
Abbreviation as in Table 3.
in peak VO₂ with milrinone (28). However, in the PROMISE trial of oral milrinone, multiple measures of submaximal exercise or quality of life all demonstrated no improvement versus placebo (29). The safety data demonstrated that albiglutide up to 30 mg weekly was generally well tolerated in nondiabetic patients with heart failure, and no new safety concerns were identified.

**STUDY LIMITATIONS.** This study has several important limitations imposed by the study design. The number of subjects studied was small, and the duration of treatment may not have been sufficient to maximize the potential benefits of therapy. The mechanistic assessment by PET/CT was also limited by small numbers and higher than expected variability in the data. Furthermore, the requirement for weekly visits for study drug administration skewed enrollment toward patients with lower disease severity, and a potential benefit may be more difficult to detect in this population. In addition, weekly assessments and associated careful clinical management may have contributed to a greater than expected benefit in the placebo-treated patients; there could have obscured any effect of drug.

Although there was no robust clinical effect shown by activation of the GLP-1 receptor with albiglutide in this study, the need for additional treatment in HFrEF persists, especially in those with concomitant diabetes. Accordingly, future studies of therapies directed toward improving myocardial metabolism should be pursued.

**REFERENCES**


patients treated with rosiglitazone or pioglitazone. JAMA 2010;304:411-8.


KEY WORDS albiglutide, glucagon-like peptide-1 (GLP-1), heart failure

APPENDIX For supplemental tables and figures, please see the online version of this article.