Heart Failure

Riociguat for Patients With Pulmonary Hypertension Caused by Systolic Left Ventricular Dysfunction

A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study

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Background—Pulmonary hypertension caused by systolic left ventricular dysfunction is associated with significant morbidity and mortality; however, no treatment is approved for this indication. We hypothesized that riociguat, a novel soluble guanylate cyclase stimulator, would have beneficial hemodynamic effects in patients with pulmonary hypertension caused by systolic left ventricular dysfunction.

Methods and Results—Overall, 201 patients with heart failure resulting from pulmonary hypertension caused by systolic left ventricular dysfunction were randomized to double-blind treatment with oral placebo or riociguat (0.5, 1, or 2 mg 3 times daily) for 16 weeks in 4 parallel arms. The primary outcome was the placebo-corrected change from baseline at week 16 in mean pulmonary artery pressure. Although the decrease in mean pulmonary artery pressure in the riociguat 2 mg group (−6.1±1.3 mm Hg; P<0.0001 versus baseline) was not significantly different from placebo (P=0.10), cardiac index (0.4 L·min⁻¹·m⁻²; 95% confidence interval, 0.2–0.5; P=0.0001) and stroke volume index (5.2 mL·m⁻²; 95% confidence interval, 2.0–8.4; P=0.0018) were significantly increased without changes in heart rate or systemic blood pressure compared with placebo. Both pulmonary (−46.6 dynes·s⁻¹·cm⁻⁴; 95% confidence interval, −89.4 to −3.8; P=0.03) and systemic vascular resistance (−239.3 dynes·s⁻¹·cm⁻⁵; 95% confidence interval, −363.4 to −115.3; P=0.0002) were significantly reduced with riociguat 2 mg. Riociguat reduced the Minnesota Living With Heart Failure score (P=0.0002). Discontinuation of treatment was similar between treatment groups.

Conclusions—Although the primary end point of the study was not met, riociguat was well tolerated in patients with pulmonary hypertension caused by systolic left ventricular dysfunction and improved cardiac index and pulmonary and systemic vascular resistance.


Key Words: clinical trial □ heart failure, systolic □ hypertension, pulmonary □ riociguat □ soluble guanylate cyclase

Pulmonary hypertension (PH) caused by systolic left ventricular dysfunction (sLVD) is associated with high levels of morbidity and mortality in patients with heart failure (HF).1 Established HF therapies such as angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, and diuretics may be effective by improving left ventricular (LV) function and reducing LV filling pressure, but currently available agents do not affect the pulmonary circulation.1

To date, randomized trials of agents targeted at the pulmonary vasculature either have failed to demonstrate benefit in patients with PH-sLVD or have not been adequately powered to detect changes in morbidity or mortality,2-8 highlighting an urgent unmet medical need.

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Riociguat is a novel soluble guanylate cyclase (sGC) stimulator that is under investigation as a new approach to treat PH.\(^6\) HF- and PH-related diseases are characterized by endothelial dysfunction with a concomitant decrease in availability of nitric oxide.\(^1,7,8\) Riociguat has a dual mode of action: It sensitizes sGC to endogenous nitric oxide and directly stimulates sGC independently of nitric oxide.\(^9\) Riociguat induces vasodilation, and results from animal studies have demonstrated additional antifibrotic, antiproliferative, and anti-inflammatory effects.\(^6,9\) In a hemodynamic study in patients with reduced LV ejection fraction (≤45%) and mean pulmonary artery pressure (mPAP) ≥25 mm Hg, single doses of the sGC stimulator BAY 60-4552 reduced mPAP, pulmonary capillary wedge pressure, systemic vascular resistance (SVR), and pulmonary vascular resistance (PVR) and decreased systemic arterial blood pressure (BP).\(^10,11\) Thus, riociguat may be a promising novel treatment for PH-sLVD in patients with HF.

To characterize the long-term hemodynamic and clinical effects, safety, and tolerability of chronic sGC stimulator therapy in HF patients with PH-sLVD, we studied the effects of 16 weeks of riociguat treatment in a multicenter clinical trial, the Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT).\(^12\)

**Methods**

**Study Population**

Patients were recruited between April 2010 and January 2012. The main study was completed in August 2012. Men and women 18 to 80 years of age were eligible if they had HF resulting from ischemic or nonischemic causes, LV ejection fraction ≤40%, and mPAP ≥25 mm Hg at rest (measured by right heart catheterization) and were symptomatic despite optimized medical therapy according to published guidelines at a stable dose regimen for >30 days before randomization.\(^1\) Further details of the inclusion and exclusion criteria are provided in the online-only Data Supplement. The distribution of patients with regard to prespecified dichotomized subgroup strata is provided in Table I in the online-only Data Supplement.

Local ethics committees approved the research protocol, and written informed consent was obtained from patients in accordance with the Declaration of Helsinki. The trial is registered at www.ClinicalTrials.gov (unique identifier: NCT01065454).

A data safety monitoring committee reviewed trial data (unblinded in closed sessions) for patient safety at 2-month intervals.

**Outcome Measures**

The primary efficacy variable was the change in mPAP from baseline to week 16. Secondary variables included changes in hemodynamic and echocardiography parameters. Exploratory clinical outcomes included the composite of the incidence of clinical worsening (defined in the online-only Data Supplement), the dual composite of incidence of cardiovascular death or hospitalization, quality of life (QoL; evaluated with the Minnesota Living With Heart Failure and EuroQol 5-Dimensions questionnaires), World Health Organization/New York Heart Association functional class, 6-minute walking distance, and N-terminal prohormone of brain natriuretic peptide.

**Study Design**

The LEPHT study design has been published previously.\(^1,2\) Briefly, LEPHT was a 16-week, randomized, double-blind, placebo-controlled, parallel-group, phase IIb study conducted in 84 centers across 18 countries. During the titration phase, patients were randomized 2:1:1:2 to 4 treatment arms: placebo, riociguat 0.5 mg 3 times daily, riociguat 1 mg 3 times daily, or riociguat 2 mg 3 times daily. Details of the riociguat dosing regimen are provided in the online-only Data Supplement.

**Core Laboratory Evaluations**

As described previously,\(^1,2\) to ensure comparability of hemodynamic data, participating investigators were instructed in transducer leveling, zeroing, and acquiring pressure curves at the end of expiration. Centers were certified for the study only if adequacy of hemodynamic tracings was confirmed by 2 independent central adjudicators. In addition, all hemodynamic data were reviewed in the hemodynamic core laboratory (Kerckhoff Klinik, Bad Nauheim, Germany). Cardiac index was measured by thermodilution (mean of 3 measurements). Stable diuretic therapy was required for at least 1 week before baseline right heart catheterization was performed. Hemodynamic variables were calculated from standard formulas.\(^13\) The analysis of echocardiographic examinations was performed at a central echocardiography laboratory by a single experienced echocardiographer to ensure consistent measurement methodology. Measurements were made in accordance with the recommendations of the American Society of Echocardiography.\(^14\)

**Statistical Analysis**

As described previously,\(^1,2\) assuming a standard deviation of 8.6, a power of 82%, and a 2-sided significance level of 5%, 50 patients valid for safety/intention-to-treat (ITT) in each of the highest target dose and placebo groups were required to detect a placebo-adjusted difference of 5 mm Hg. The 2 lower target doses required 25 patients per group. Thus, it was predicted that 150 subjects valid for the efficacy analysis were required in total.

The primary analysis was performed in the per-protocol (PP) population, with supportive analysis in patients valid for safety/ITT. The primary variable was assessed with an ANCOVA model with baseline mPAP as a covariate and treatment group and region as main effects. The primary comparison was a 2-sided test at the 5% significance level for the difference in treatment effect compared sequentially between treatment groups and placebo (starting from the highest target dose). Secondary analyses were exploratory. Supportive analysis was performed in the ITT population according to imputation methods outlined in the online-only Data Supplement. The secondary and QoL variables measured on a semicontinuous scale were analyzed with the use of the same methods as for the primary variable. Differences between groups are given as least squares mean, ie, adjusted for baseline. The incidence of clinical worsening was analyzed with the Mantel-Haenszel test. The safety analyses were performed descriptively in the safety/ITT population of patients. Within-treatment group analyses were performed by use of paired \(t\) tests on the changes between baseline and visit 6.

In addition, patients were analyzed by protocol-prespecified subgroups as defined in the online-only Data Supplement. Within subgroups, changes from baseline between riociguat 2 mg and placebo were compared by ANCOVA as described above.

Data are presented as mean±SEM unless stated otherwise.

**Results**

**Patients**

Of the 301 patients screened, 202 were eligible for randomization and 201 were allocated to treatment (Figure 1). Of the 201 patients who were included in the ITT and safety populations, 160 underwent a second right heart catheterization at 16 weeks and were valid for analysis and included in the PP population. Reasons for withdrawal are summarized in Figure 1.

Demographic, clinical, and hemodynamic characteristics were well balanced across treatment groups at baseline (Table I in the online-only Data Supplement [PP]). Overall, nearly half of the patients had marked or severe limitation of physical activity (World Health Organization/New York Heart Association functional class III or IV) and a baseline 6-minute walking distance ≤400 m. Baseline hemodynamic characteristics underlined the severe disease in the
study population, with 75% of patients having an mPAP >30 mm Hg. Mean transpulmonary gradient at baseline ranged from 12.6 to 15.3 mm Hg across the treatment groups, indicating a significant passive contribution to PH. In accordance with the protocol, patients were receiving standard medical or device therapy at baseline, indicated by angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and β-blocker treatment in >90% and aldosterone antagonists in >70% of patients.

Right Heart Hemodynamics
The primary variable, placebo-corrected change from baseline to week 16 in mPAP, was not met because there was a decrease of 6.1±1.3 mm Hg in the riociguat 2 mg group (P<0.0001 for change from baseline) compared with a decrease of 4.0±1.2 mm Hg in the placebo group (P=0.0014 for change from baseline; P=0.10 for pairwise comparison of riociguat 2 mg versus placebo in change from baseline using ANCOVA; Table 2 and Figure 2). Riociguat 2 mg significantly increased cardiac index (P<0.0001) and stroke volume index (P=0.0018) with no change in heart rate (P=0.83) or systolic BP (SBP) (P=0.99; diastolic BP: P=0.41) compared with placebo. Both PVR (P=0.03) and SVR (P=0.0002) decreased compared with placebo (Figure 2). The decreases in pulmonary capillary wedge pressure (P=0.16) and transpulmonary gradient (P=0.17) and increase in mixed venous oxygen saturation (1.9%; 95% confidence interval, −0.8 to 4.6; P=0.17; riociguat 2 mg: n=49 at baseline and n=50 at week 16; placebo: n=53 and n=49, respectively) in the riociguat 2 mg group did not reach statistical significance compared with placebo. Mean right atrial pressure was low at baseline in all groups, and small further decreases from baseline at 16 weeks were not significantly different between the 2 mg and placebo groups (P=0.95; Table 2).

In the riociguat 0.5 and 1.0 mg groups, lower dose-dependent increases in cardiac index and stroke volume index and decreases in SVR and PVR were not statistically significantly different compared with placebo (Table 2).

The results in the ITT population were consistent with those in the PP population. Cardiac index (P=0.0004) and stroke volume index (P=0.003) were significantly increased and PVR (P=0.04) and SVR (P=0.0018) were decreased at the last visit.

Echocardiography
Riociguat 2 mg did not significantly alter echocardiographic LV ejection fraction, LV end-diastolic volume, and LV end-systolic volume in patients with PH-sLVD (Table III in the online-only Data Supplement). Echocardiographically estimated systolic pulmonary arterial pressure was 53.7±2.4 mm Hg at baseline and 49.0±2.4 mm Hg at week 16 in the riociguat 2 mg group and 53.8±1.7 and 52.1±2.0 mm Hg, respectively, in the placebo group (least squares mean difference, −2.3 mm Hg; 95% confidence interval, −6.3 to 1.8 mm Hg; P=0.27).

Clinical and Biomarker Variables
In accordance with the study protocol, data for clinical variables and biomarkers relating to safety are presented for the

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**Figure 1.** Patient flow. Only the primary reasons for withdrawal are listed. AE indicates adverse event.

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*This patient was mistakenly randomized and was ineligible for the study; no treatment was allocated.
†Valid for intention-to-treat/safety population.
‡n=1 invalid due to prohibited medication (nitrates).
§n=1 invalid due to a second right heart catheterization not being performed.
ITV population and those relating to efficacy for the PP population. Treatment with riociguat 2 mg reduced (indicating improvement) the Minnesota Living With Heart Failure questionnaire total score in the ITT (Figure 3) and PP populations (28.7±0.7 at baseline versus 28.2±0.8 at week 16; \( \bar{P} =0.027 \) versus placebo), and the placebo-corrected difference in EuroQoL 5-Dimensions score was 0.07 (95% confidence interval, –0.03 to 0.17; ITT \( \bar{P} =0.19 \)). There were similar numbers of clinical worsening events in the placebo and riociguat 2 mg groups (Table IV in the online-only Data Supplement; ITT \( \bar{P} =0.93 \)).

Likewise, the incidence of the composite end point of cardiovascular death or hospitalization was similar in the placebo and riociguat 2 mg groups (Table IV in the online-only Data Supplement; ITT \( \bar{P} =0.87 \)). Biomarker and functional capacity data are shown in Table 3. There was no significant difference in the change in New York Heart Association functional class from baseline to the last visit between the riociguat 2 mg and placebo groups (\( \bar{P} =0.91 \); Figure I in the online-only Data Supplement); similar numbers of patients progressed to New York Heart Association functional class IV symptoms. The glomerular filtration rate decreased by –4.1±2.1 mL·min\(^{-1}\)·1.73 m\(^{-2}\) with placebo versus –3.2±1.5 mL·min\(^{-1}\)·1.73 m\(^{-2}\) in the riociguat 2 mg group (ITT).

**Prespecified Subgroups**

Analysis of subgroups dichotomized by baseline mPAP, transpulmonary gradient, pulmonary vascular gradient, LV ejection fraction, 6-minute walking distance, and etiology showed no
adverse changes with riociguat in any of the prespecified subgroups, including no increase in pulmonary capillary wedge pressure (Figure II in the online-only Data Supplement).

**Safety and Tolerability**

Most adverse events (AEs) were of mild or moderate intensity in all treatment groups (Table 4). The commonest treatment-emergent AEs in the riociguat 2 mg group were diarrhea (18% versus 7% with placebo), dizziness (16% versus 10% with placebo), and nausea (16% versus 7% with placebo). Treatment-emergent study drug-related AEs were reported in 43% and 22% of patients in the riociguat 2 mg and placebo groups, respectively. The majority of episodes of hypotension occurred during the titration phase and were addressed by downtitration of dose. Treatment-emergent drug-related serious AEs were reported in 4 patients (6%) in the riociguat 2 mg group (cardiac failure, ventricular tachycardia, syncope, and hypotension) and in 2 patients (3%) in the placebo group (ventricular tachycardia and lobar pneumonia, syncope, and hypotension). Study treatment was discontinued because of serious AEs in 2 patients (3%) in the 2 mg riociguat group (cardiac decompensation [drug related] and worsening of HF) and 5 patients (7%) in the placebo group (heart transplantation, worsening of HF [n=2], cardiac decompensation, and ischemic stroke). There was 1 death in the riociguat 2 mg group resulting from suspicion of ventricular fibrillation (investigator term) on day 106 of study drug intake; 1 death each in the 1 mg (pneumonia) and 0.5 mg groups (cardiac arrest/gastrointestinal hemorrhage/critical illness polyneuropathy/hypoxic-ischemic encephalopathy/heart transplantation).

### Table 2. Hemodynamic Results From Right Heart Catheterization (Per-Protocol Population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=56)</th>
<th>0.5 mg (n=22)</th>
<th>1 mg (n=28)</th>
<th>2 mg (n=54)</th>
<th>Placebo-Corrected LS Mean Difference (95% CI), Riociguat 2 mg vs Placebo</th>
<th>P Value, Riociguat 2 mg vs Placebo*</th>
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<tbody>
<tr>
<td>Mean pulmonary artery pressure, mmHg</td>
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<tr>
<td>Baseline</td>
<td>40.4±1.2</td>
<td>37.9±2.2</td>
<td>35.2±1.8</td>
<td>38.1±1.3</td>
<td>−2.7 (−6.0 to 0.6)</td>
<td>0.10</td>
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<tr>
<td>Week 16</td>
<td>36.4±1.4</td>
<td>33.4±2.4</td>
<td>34.5±2.2</td>
<td>32.0±1.6</td>
<td>−0.1 (−1.9 to 1.7)</td>
<td>0.95</td>
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<td>Pulmonary capillary wedge pressure, mmHg</td>
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<tr>
<td>Baseline</td>
<td>9.7±0.8</td>
<td>10.2±1.0</td>
<td>9.7±1.2</td>
<td>8.8±0.7</td>
<td>−2.1 (−5.0 to 0.8)</td>
<td>0.16</td>
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<tr>
<td>Week 16</td>
<td>8.6±0.7</td>
<td>8.1±1.2</td>
<td>10.3±1.1</td>
<td>8.2±0.7</td>
<td>−1.3 (−3.1 to 0.5)</td>
<td>0.17</td>
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<td>Transpulmonary gradient, mmHg</td>
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<tr>
<td>Baseline</td>
<td>15.2±1.0</td>
<td>14.0±1.7</td>
<td>12.5±1.3</td>
<td>14.2±1.0</td>
<td>−0.95 (−4.4 to 2.5)</td>
<td>0.59</td>
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<td>Mean arterial pressure, mmHg</td>
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<tr>
<td>Baseline</td>
<td>89.2±1.7</td>
<td>87.1±2.8</td>
<td>85.2±1.4†</td>
<td>89.0±1.8</td>
<td>0.4 (0.2 to 0.5)</td>
<td>0.0001</td>
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<tr>
<td>Week 16</td>
<td>84.9±1.7</td>
<td>86.0±2.3</td>
<td>86.8±2.1</td>
<td>84.0±1.4†</td>
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<tr>
<td>Cardiac index, L·min⁻¹·m⁻²</td>
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<tr>
<td>Baseline</td>
<td>2.2±0.07</td>
<td>2.3±0.1</td>
<td>2.3±0.1†</td>
<td>2.2±0.1</td>
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<tr>
<td>Week 16</td>
<td>2.2±0.07</td>
<td>2.4±0.1</td>
<td>2.5±0.1</td>
<td>2.6±0.1</td>
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<td>Stroke volume index, mL·m⁻²</td>
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<tr>
<td>Baseline</td>
<td>30.2±1.1</td>
<td>33.1±1.8</td>
<td>33.3±2.0‡</td>
<td>30.6±1.0</td>
<td>5.2 (2.0 to 8.4)</td>
<td>0.0018</td>
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<tr>
<td>Week 16</td>
<td>31.6±1.2</td>
<td>36.9±2.5</td>
<td>37.6±2.9†</td>
<td>37.1±1.3</td>
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<tr>
<td>Pulmonary vascular resistance, dyne·s⁻¹·cm⁻⁵</td>
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<tr>
<td>Baseline</td>
<td>304.9±23.3</td>
<td>274.9±35.7</td>
<td>223.1±23.5</td>
<td>291.3±24.1</td>
<td>−46.6 (−89.4 to −3.8)</td>
<td>0.03</td>
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<tr>
<td>Week 16</td>
<td>267.9±16.2</td>
<td>223.5±32.9</td>
<td>190.0±15.9</td>
<td>213.1±26.1†</td>
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<tr>
<td>Systemic vascular resistance, dyne·s⁻¹·cm⁻⁵</td>
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<td></td>
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<tr>
<td>Baseline</td>
<td>1591.0±66.8</td>
<td>1470.1±99.2</td>
<td>1396.8±80.3‡</td>
<td>1593.4±57.1</td>
<td>−239.3 (−363.4 to −115.3)</td>
<td>0.0002</td>
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<tr>
<td>Week 16</td>
<td>1496.5±60.5</td>
<td>1402.6±108.0</td>
<td>1273.0±60.2</td>
<td>1262.2±47.1†</td>
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<td>Pulmonary vascular resistance/systemic vascular resistance ratio</td>
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<tr>
<td>Baseline</td>
<td>0.20±0.014</td>
<td>0.18±0.019</td>
<td>0.17±0.022‡</td>
<td>0.19±0.014</td>
<td>−0.01 (−0.04 to 0.01)</td>
<td>0.32</td>
</tr>
<tr>
<td>Week 16</td>
<td>0.19±0.011</td>
<td>0.16±0.020</td>
<td>0.16±0.014†</td>
<td>0.17±0.017§</td>
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</tbody>
</table>

Data are mean±SEM. CI indicates confidence interval; and LS, least squares.
*Analysis of covariance for change from baseline to week 16 (per-protocol analysis set); pairwise comparison.
†n=53.
‡n=27.
§n=52.

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nontreatment-emergent) occurred during the follow-up phase and were not considered to be related to the study drug by the investigator. There were no deaths in the placebo group.

No clinically relevant changes were seen in vital signs or ECG or laboratory variables.

Because uptitration of the study drug dose was based on SBP, 61% of patients in the riociguat 2 mg group were receiving a dose of 2 mg, 24% were receiving a dose of 1 mg, and 15% were receiving a dose of 0.5 mg at week 16.

**Discussion**

LEPHT is the first study to assess the hemodynamic effects of an oral sGC stimulator in patients with PH-sLVD. The primary end point, placebo-corrected change from baseline to week 16 in mPAP, was not met. Consequently, interpretation of secondary end points requires caution. However, treatment with riociguat 2 mg 3 times daily for 16 weeks in addition to standard HF therapy improved cardiac index, PVR, SVR, and health-related QoL, without altering heart rate and BP compared with placebo. Importantly, riociguat was also well tolerated and had a favorable safety profile.

Treatment of PH in patients with HF represents an important therapeutic target given the epidemiology of PH-sLVD and its prognostic impact.\(^1,15-17\) However, despite the approval of several classes of drug for the treatment of precapillary pulmonary arterial hypertension, application of these drugs to patients with HF has so far proven unsuccessful. Several trials of prostacyclin analogs and endothelin receptor antagonists in congestive HF have shown no improvement or worsening of clinical outcomes.\(^2,18\) In 2 more recent studies with sildenafil, improvements were evident in resting and exercise hemodynamics, echocardiographic signs of diastolic dysfunction, exercise capacity, and QoL.\(^4,19\) However, both were small single-center trials, and the results require confirmation in large, multicenter, randomized, clinical trials. Current practice guidelines therefore discourage the use of pulmonary vasoselective agents in patients with HF.\(^1\)

Impaired nitric oxide synthesis and signaling through the nitric oxide–sGC–cGMP pathway are involved in the pathogenesis of PH.\(^6\) Riociguat is the first of a novel class of therapeutics called sGC stimulators that are being investigated...
to treat PH.6,9,10 Because of its promising preclinical profile and effectiveness in reducing PVR and SVR in a single-dose hemodynamic study,11,20 we hypothesized that riociguat may improve right heart hemodynamics, an as-yet unmet target in patients with HF and PH.12

LEPHT was a first-of-its-kind phase IIb trial that explored the hemodynamic effects of an sGC stimulator in a unique HF patient population: those with secondary PH who had not previously been exposed to vasoactive treatment in a large-scale, multicenter trial. Given the lack of previous studies and the dearth of information on the potential hemodynamic consequences of sGC stimulators in this specific population, we believed that change in mPAP would be the most robust hemodynamic parameter to reflect changes in the pulmonary circulation. High mPAP at baseline is associated with right ventricular dysfunction and increased morbidity and mortality in patients with sLVD.15–21,24 Therefore, we chose change in mPAP as a relevant hemodynamic parameter to assess the effects of riociguat. Compared with patients assigned to placebo, patients in the riociguat 2 mg group failed to achieve a significant reduction in mPAP after 16 weeks of treatment. The primary end point was therefore not met despite a reduction in mPAP of $6$ mmHg compared with baseline because mPAP also decreased by $4$ mmHg in the placebo group. Such an observation not only was unexpected but also is difficult to explain. A rapidly deteriorating clinical course despite exhausted avenues for maximal individual background therapy in a population of patients with advanced HF might have contributed to this observation in the placebo group. However, because LEPHT is the first randomized, controlled, multicenter study to assess invasively measured right heart hemodynamic changes in patients with PH-sLVD over 16 weeks, no data in the literature are available to support progressive hemodynamic deterioration during short-term follow-up of such patients, although a posteriori we should recognize that a subtle decrease in mPAP was also observed in the placebo group in a study performed in PH-sLVD by Lewis et al.4

The lessons learned from the characterization of the LEPHT patient population may assist in planning future studies in this indication.

Riociguat 2 mg significantly improved cardiac index in the absence of any significant change in heart rate or SBP compared with placebo, indicating that this improvement was not attributable to reflex sympathetic activation elicited by a decrease in SBP. The improvement in cardiac function was

Table 3. Laboratory and Clinical Results

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=56)</th>
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<th>1 mg (n=28)</th>
<th>2 mg (n=54)</th>
<th>Placebo-Corrected LS Mean Difference (95% CI), Riociguat 2 mg vs Placebo</th>
<th>P Value for Change From Baseline, Riociguat 2 mg vs Placebo</th>
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</thead>
<tbody>
<tr>
<td>Troponin T, ng·mL$^{-1}$ (PP)</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>0.028±0.003 (n=59)</td>
<td>0.034±0.012 (n=26)</td>
<td>0.031±0.007 (n=27)</td>
<td>0.027±0.004 (n=48)</td>
<td>–612 (–1060 to –164)</td>
<td>0.008</td>
</tr>
<tr>
<td>Week 8</td>
<td>0.029±0.003 (n=48)</td>
<td>0.021±0.003 (n=19)</td>
<td>0.023±0.003 (n=27)</td>
<td>0.029±0.004 (n=39)</td>
<td>–407 (–1055 to 241)</td>
<td>0.22</td>
</tr>
<tr>
<td>Last visit</td>
<td>0.029±0.003 (n=63)</td>
<td>0.031±0.01 (n=27)</td>
<td>0.025±0.003 (n=29)</td>
<td>0.029±0.006 (n=52)</td>
<td>0 (–0.01 to 0.01)</td>
<td>0.61</td>
</tr>
<tr>
<td>6-min walking distance, m (PP)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>396±15 (n=56)</td>
<td>434±21 (n=22)</td>
<td>395±20 (n=28)</td>
<td>380±18 (n=54)</td>
<td>–612 (–1060 to –164)</td>
<td>0.008</td>
</tr>
<tr>
<td>Week 8</td>
<td>420±15 (n=54)</td>
<td>433±19 (n=20)</td>
<td>433±20 (n=25)</td>
<td>403±16 (n=51)</td>
<td>–407 (–1055 to 241)</td>
<td>0.22</td>
</tr>
<tr>
<td>Week 16</td>
<td>414±16 (n=55)</td>
<td>431±25 (n=22)</td>
<td>420±19 (n=28)</td>
<td>411±15 (n=54)</td>
<td>10 (–18 to 39)</td>
<td>0.48</td>
</tr>
</tbody>
</table>

Data are mean±SEM. Last visit is the last observed value (not including follow-up) as defined in the Methods section. CI indicates confidence interval; ITT, intention-to-treat; LS, least squares; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; and PP, per-protocol.

*ANCOVA for change from baseline to last visit (ITT) or week 16 (per-protocol analysis set); pairwise comparison at week 16/last visit. 

Figure 3. Minnesota Living With Heart Failure questionnaire total scores at baseline and last visit (intention-to-treat population). *Pairwise comparison of change from baseline (ANCOVA) for riociguat 2 mg group vs placebo, $P=0.002$. Last visit indicates the last observed value (not including follow-up) as defined in the online-only Data Supplement.
to an increase in LV filling pressure as a result of a shift of blood volume from the pulmonary arterial to the pulmonary venous compartment.\textsuperscript{25,26} In any case, even if predominantly or exclusively systemic effects unload the pulmonary circuit secondary to decreased LV filling pressures, the resulting improvement in hemodynamics without an increase in heart rate or a decrease in systemic BP may be just as promising for future studies in patients with HF.

Importantly, the clinical relevance of the hemodynamic changes observed in the riociguat group was paralleled by favorable exploratory clinical outcomes and a low frequency of AEs. Despite the trial not being powered for clinical outcomes, health-related QoL improved. The incidence of clinical worsening and the composite of cardiovascular death and cardiovascular hospitalization were also similar between the riociguat and placebo groups, indicating no adverse effect of riociguat. The fact that N-terminal prohormone of brain natriuretic peptide decreased significantly at 8 weeks and showed a trend toward a decrease at 16 weeks may also support the notion of hemodynamic improvement. Thus, although changes in the primary hemodynamic variable, mPAP, were not significant, statistically significant changes or trends toward improvement were evident in some of the domains studied in this exploratory phase IIb study compared with placebo, including cardiac index, PVR, SVR, symptom- and health-related QoL, and serum biomarkers.

With all riociguat doses, most AEs were of mild or moderate severity, and there were no clinically relevant changes in laboratory values. The decrease in SBP at 16 weeks was smaller in the riociguat 2 mg group than with placebo, coupled with minimal changes in mean arterial pressure and diastolic BP; a decrease in SBP in normotensive and hypotensive patients with HF is known to be prognostically unfavorable. Although minor decreases in BP were noted during the up titration phase (data not shown), these small decreases were well tolerated and diminished over time, suggesting a potential for stabilization of BP with riociguat treatment. Subgroup analysis showed no negative effects of riociguat in any of the prespecified subgroups.

The present study has several limitations. The observed changes in flow were assessed by a single method (ie, thermodilution), which may be inaccurate in patients with severe tricuspid regurgitation,\textsuperscript{27} and oximetry-based calculations of cardiac output were not collected. However, only 14 patients (7\%) in the safety analysis population had tricuspid valvular disorders that may have been associated with severe tricuspid regurgitation reported in their medical history. Furthermore, the thermodilution technique, which strongly correlates with the Fick oxygen technique,\textsuperscript{28} was consistently used to measure cardiac output at baseline and after 16 weeks of study drug therapy. We cannot exclude the possibility that the pulmonary vasodilator effect of riociguat was accompanied by the development of ventilation/perfusion mismatching and that some of the increase in cardiac index observed in patients receiving riociguat occurred to mitigate that effect and to maintain peripheral oxygen delivery.

The assessment of changes in vascular tone from calculated vascular resistance is limited when cardiac output itself changes because cardiac output is included in the calculation.

<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (n=69)</th>
<th>0.5 mg (n=32)</th>
<th>1 mg (n=33)</th>
<th>2 mg (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any AE</td>
<td>57 (83)</td>
<td>26 (81)</td>
<td>28 (85)</td>
<td>61 (91)</td>
</tr>
<tr>
<td>Dyspnea</td>
<td>9 (13)</td>
<td>3 (9)</td>
<td>4 (12)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Blood creatinine increased</td>
<td>8 (12)</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cardiac failure</td>
<td>7 (10)</td>
<td>2 (6)</td>
<td>3 (9)</td>
<td>9 (13)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>7 (10)</td>
<td>5 (16)</td>
<td>4 (12)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Headache</td>
<td>7 (10)</td>
<td>1 (3)</td>
<td>4 (12)</td>
<td>10 (15)</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>7 (10)</td>
<td>0</td>
<td>2 (6)</td>
<td>2 (3)</td>
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<tr>
<td>Diarrhea</td>
<td>5 (7)</td>
<td>0</td>
<td>5 (15)</td>
<td>12 (18)</td>
</tr>
<tr>
<td>Nausea</td>
<td>5 (7)</td>
<td>2 (6)</td>
<td>2 (6)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Peripheral edema</td>
<td>5 (7)</td>
<td>4 (13)</td>
<td>4 (12)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Hypotension*</td>
<td>4 (6)</td>
<td>3 (9)</td>
<td>5 (15)</td>
<td>8 (12)</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>4 (6)</td>
<td>2 (6)</td>
<td>3 (9)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>4 (6)</td>
<td>0</td>
<td>2 (6)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>3 (4)</td>
<td>3 (9)</td>
<td>0</td>
<td>4 (6)</td>
</tr>
<tr>
<td>Anemia</td>
<td>2 (3)</td>
<td>0</td>
<td>5 (15)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Cough</td>
<td>2 (3)</td>
<td>4 (13)</td>
<td>3 (9)</td>
<td>5 (7)</td>
</tr>
<tr>
<td>Constipation</td>
<td>2 (3)</td>
<td>4 (13)</td>
<td>1 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>International normalized ratio increased†</td>
<td>1 (1)</td>
<td>1 (3)</td>
<td>4 (12)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Gastroenteritis</td>
<td>1 (1)</td>
<td>3 (9)</td>
<td>1 (3)</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Dyspepsia</td>
<td>0</td>
<td>2 (6)</td>
<td>6 (18)</td>
<td>6 (9)</td>
</tr>
<tr>
<td>AF‡</td>
<td>0</td>
<td>1 (3)</td>
<td>0</td>
<td>6 (9)</td>
</tr>
</tbody>
</table>

AE indicates adverse event; and AF, atrial fibrillation.

*In the riociguat 2 mg group, 2 events of hypotension were mild and 6 moderate; in the placebo group, 2 were mild, 1 moderate, and 1 severe. AEs reported as hypotension included asymptomatic and symptomatic hypotension.

†No serious AEs of bleeding, hemato ma, or hemorrhage were reported.

‡In 1 patient, AF occurred de novo; in all other patients, it was present in their previous medical history. At baseline, AF was present in 9 patients in the riociguat 2 mg group and 9 patients in the placebo group; at week 16, 5 patients in the riociguat 2 mg group and 6 in the placebo group were in AF according to resting 12-lead ECG.

paralleled by a decrease in PVR and SVR, although there was no effect of riociguat on simultaneous echocardiographic measures of cardiac function or N-terminal prohormone of brain natriuretic peptide. Although the relative decrease in PVR slightly exceeded the decrease in SVR in the riociguat 2 mg group, PVR/SVR was unchanged and no major decrease in transpulmonary gradient was found compared with placebo owing to the parallel decrease in pulmonary capillary wedge pressure at 16 weeks. The contribution of pulmonary arteriole relaxation secondary to decreases in left atrial pressure as opposed to a direct drug effect on the pulmonary vasculature is not resolved by our study. On the basis of our data, riociguat may be hypothesized to induce a relatively similar vasodilator effect on the pulmonary and the systemic circulation in patients with sLVD, a characteristic that could be considered important for drug efficacy in these patients. Indeed, a purely pulmonary vasodilation in patients with HF could lead...
of vascular resistance. As for prior studies with sildenafil, the effects of riociguat on pulmonary and systemic arterial pressure at different levels of blood flow should clarify the effects of sGC stimulation on vascular resistance.

There are also limitations associated with the baseline observation carried forward approach used to deal with missing data in the ITT population, which assumes that patients receiving placebo would not improve and patients receiving riociguat would not deteriorate.

The favorable safety profile of riociguat, particularly at the highest dose of 2 mg, suggests that higher doses might have been tolerated in some patients with PH-sLVD. Furthermore, the minimal effects on SBP suggest that it might be well tolerated in patients with an SBP <100 mm Hg using an adapted titration scheme. Comparison of baseline criteria between groups shows slightly less severe disease in the riociguat 0.5 and 1 mg groups compared with placebo and 2 mg riociguat, and the former groups were powered with only half the sample size. Dose dependency was not analyzed because we focused on the comparison between placebo and riociguat 2 mg, but for the evaluation of dose dependence, these baseline differences and smaller sample size should be considered. Because the majority of the study population can be characterized as having sLVD with high left heart filling pressure and would be investigating their effects in patients with HF having sLVD with high left heart filling pressure and would be investigated in the ITT population, which assumes that patients receiving placebo would not improve and patients receiving riociguat would not deteriorate.

The primary end point, placebo-corrected change from baseline to week 16 in mPAP, was not met. Nevertheless, riociguat was well tolerated and resulted in significant improvements in the secondary end points of cardiac index, PVR, and SVR without significantly changing mean pulmonary artery or systemic arterial pressure. Future studies are required to validate the mechanism of the increase in cardiac index and its clinical implications.

Acknowledgments
Editorial assistance was provided by Adelphi Communications Ltd (Bollington, UK), supported by Bayer HealthCare Pharmaceuticals (Berlin, Germany).

Sources of Funding
This study was supported by Bayer HealthCare Pharmaceuticals (Berlin, Germany).

Disclosures
Dr Bonderman has received a research grant from Bayer; honoraria from Bayer, Actelion, AOP, and Pfizer; and consultancy/advisory board fees from Bayer, Actelion, and United Therapeutics. Dr Ghio has received honoraria from Lilly, Pfizer, Actelion, GlaxoSmithKline, and Bayer. Dr Felix has received research grants from Bayer, Biotronik, and Medtronic; drugs from Bayer; honoraria from Bayer and Cardiorentis; and speaking fees from Bayer, Berlin-Chemie, Boehringer Ingelheim, Biotronik, Daiichi Sanyko, Fresenius, MSD, Medtronic, Novartis, Pfizer, Sanofi Aventis, and Servier. He also received consultancy fees as a member of the LEPHT Study Steering Committee. Dr Ghofrani has received research grants from Actelion, Ergonex, Bayer, and Pfizer; speaking fees from Actelion, Bayer, Ergonex, Gilead, GlaxoSmithKline, Novartis, and Pfizer; honoraria from Actelion, Bayer, Ergonex, GlaxoSmithKline, Merck, Pfizer, and Novartis; and consultancy/advisory board fees from Actelion, Bayer, Ergonex, GlaxoSmithKline, and Novartis. Dr Mitrovic has received research support from Novartis and Bayer; honoraria from Bayer, Novartis, and GlaxoSmithKline; and expert witness fees from Novartis and Bayer. Dr Michelakis has received consultancy fees as a member of the LEPHT Study Steering Committee. Dr Oudiz has received research grants from Actelion, Bayer, Gilead, Ikaria, Lung LLC, Novartis, Pfizer, and United Therapeutics; speaking fees from Gilead, Lung LLC, and United Therapeutics; and consultant/advisory board fees from Actelion, Bayer, Gilead, Lung LLC, Novartis, and United Therapeutics. Dr Semigran received a research grant as the principal investigator of the LEPHT study. Drs Roessig, Scalise, and Boateng are full-time employees of Bayer Pharma AG, Bayer Hispania SL, and Bayer HealthCare Pharmaceuticals, respectively.

References
Pulmonary hypertension caused by systolic left ventricular dysfunction is one of the most common forms of pulmonary hypertension and is associated with considerable morbidity and mortality in patients with heart failure. Currently, no approved heart failure therapies target the pulmonary vasculature of heart failure patients with pulmonary hypertension caused by systolic left ventricular dysfunction, highlighting an urgent unmet medical need in this population. Riociguat is a novel soluble guanylate cyclase stimulator and pulmonary vasodilator currently under investigation as a therapy for pulmonary hypertension caused by systolic left ventricular dysfunction after a single dose of the soluble guanylate cyclase stimulator BAY 60-4552, the present study investigated the chronic hemodynamic effects and safety of riociguat in heart failure patients with pulmonary hypertension caused by systolic left ventricular dysfunction. Patients were randomized to double-blind treatment with oral placebo or riociguat (0.5, 1, or 2 mg 3 times daily) for 16 weeks in 4 parallel arms. Despite the primary end point, placebo-corrected change from baseline to week 16 in mean pulmonary artery pressure, not being met, riociguat was well tolerated and improved cardiac index, stroke volume index, and both pulmonary and systemic vascular resistance without significantly changing systemic arterial pressure or heart rate. These hemodynamic changes were accompanied by favorable exploratory clinical outcomes, including an improvement in quality of life as measured by the Minnesota Living With Heart Failure score. Future studies are required to validate the mechanism of the increase in cardiac index seen with riociguat and its clinical implications.
Hypertension Riociguat Trial (LEPHT) Study Group

Lothar Roessig and Marc J. Semigran

on behalf of the Left Ventricular Systolic Dysfunction Associated With Pulmonary Hypertension Riociguat Trial (LEPHT) Study Group

Riociguat for Patients With Pulmonary Hypertension Caused by Systolic Left Ventricular Dysfunction: A Phase IIb Double-Blind, Randomized, Placebo-Controlled, Dose-Ranging Hemodynamic Study

Diana Bonderman, Stefano Ghio, Stephan B. Felix, Hossein-Ardeshir Ghofrani, Evangelos Michelakis, Veselin Mitrovic, Ronald J. Oudiz, Francis Boateng, Andrea-Viviana Scalise, Lothar Roessig and Marc J. Semigran

Circulation. 2013;128:502-511; originally published online June 17, 2013; doi: 10.1161/CIRCULATIONAHA.113.001458

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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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SUPPLEMENTAL MATERIAL

Supplemental Methods

Inclusion and exclusion criteria

The key inclusion criteria for the LEPHT trial were:

- Men and women aged 18–80 years
- Heart failure due to ischemic or non-ischemic causes
- Left ventricular ejection fraction ≤40%
- Mean pulmonary artery pressure ≥25 mmHg at rest (measured by right heart catheterization)
- Symptomatic despite optimized medical therapy according to published guidelines at a stable dose regimen for >30 days before randomization.

The key exclusion criteria for the LEPHT trial were:

- Pulmonary hypertension in groups other than Group 2.1 according to Dana Point classification
- Cardiac decompensation ≤30 days before randomization
- Systemic blood pressure <100 mmHg at baseline
- Severe renal impairment (glomerular filtration rate <30 mL·min\(^{-1}\))
- Patients with cardiac ischemia in whom percutaneous coronary intervention or bypass surgery was planned were not considered eligible
Riociguat dosing regimen

At Weeks 2 and 4, dose titration (from a starting dose of riociguat 0.5 mg three-times daily) was based on patients’ symptoms and trough systolic blood pressure (SBP) in accordance with the following algorithm: if SBP was ≥100 mmHg, the dose was increased (doubled); if SBP was 90–99 mmHg without symptoms of hypotension, the dose was maintained; if SBP was <90 mmHg without symptoms of hypotension, study treatment was stopped; but if SBP recovered to ≥90 mmHg after 24 hours, and no clinical symptoms of hypotension were present, study treatment was resumed with a reduced (halved) dose. For any cases of SBP <100 mmHg with clinical symptoms of hypotension, study treatment was stopped and only resumed after 24 hours at a reduced (halved) dose. Depending on their randomized treatment group, patients underwent sham or verum uptitration. For example, when the starting dose of 0.5 mg was increased to 1 mg in the 1 mg and 2 mg groups at 2 weeks, a sham titration was performed in a double-blind fashion in the 0.5 mg group, thus maintaining the starting dose of 0.5 mg.
Definition of clinical worsening

The first occurrence of the following events was included in the composite endpoint of time to clinical worsening:

- All-cause mortality
- First hospitalization for a cardiovascular event
- Upgrade of heart transplantation status
- Need for intravenous diuretics
- Persistent decline of World Health Organization or New York Heart Association functional class
Statistical analysis – imputation rules

For supportive analysis in the intention-to-treat population, last visit was defined as the last observed value (not including follow-up) for patients who completed the study or withdrew. When a patient died or withdrew due to clinical worsening without a termination visit or a measurement at that termination visit, the following imputed values were used: baseline observation carried forward for hemodynamic parameters and biomarkers; 0 meters for 6-minute walking distance; withdrawal due to clinical worsening was imputed as New York Heart Association (NYHA) functional class IV and death as NYHA functional class V; 0.594 for EuroQoL 5-Dimensions questionnaire score; and 105 for Minnesota Living with Heart Failure questionnaire score.
Statistical analysis – subgroup analysis

Patients were analyzed by protocol-prespecified subgroups according to the following baseline criteria: mean pulmonary artery pressure (≤30 mmHg and >30 mmHg), transpulmonary pressure gradient (≤15 mmHg and >15 mmHg), left ventricular ejection fraction (<30% and ≥30%), and 6-minute walking distance (≤400 m and >400 m). Additional subgroup analyses included a comparison of patients with ischemic heart disease underlying systolic left ventricular dysfunction versus non-ischemic cardiomyopathy.
**LEPHT investigators**

The authors would like to thank all investigators who participated in the LEPHT trial, including those who randomized 5 or more patients: Professor E. Erdmann, Professor S. Rosenkranz (Uniklinik Köln, Köln, Germany), Professor H. Lapp (HELIOS Klinikum Erfurt, Erfurt, Germany), Dr T. Palecek (Vseobecna fakultni nemocnice, Prague, Czech Republic), Dr L. Scelsi and Dr A.S. Pazzano (IRCCS Policlinico San Matteo, Pavia, Italy), Dr G. Lewis (Massachusetts General Hospital, Boston, USA), Dr L. Almenar Bonet (Hospital La Fe, Valencia, Spain), Dr F. Bauer (CHRU de Rouen, Rouen, France), Dr J. Krejci (Fakultni nemocnice u sv. Anny, Brno, Czech Republic), Professor A. Keogh (St Vincent’s Hospital, Sydney, Australia), Dr S. Chaparro (University of Miami, Miami, USA), and Dr A. van Dijk (U.M.C.St. Radboud, Nijmegen, The Netherlands).

**Study team**

We also thank Dr Susanne Hoischen, Caroline Gomo, Veronique Smets, Vanessa Desavoye, Juliette Dehay, and Liubov Shatkina for clinical project, study and data management.
### Supplemental Table 1. Baseline hemodynamic and echocardiographic characterization (safety population)

<table>
<thead>
<tr>
<th>Hemodynamics, n (%)</th>
<th>Placebo (n=69)</th>
<th>Riociguat (n=201)</th>
<th>Total (n=201)</th>
</tr>
</thead>
<tbody>
<tr>
<td>mPAP ≤30 mmHg</td>
<td>11 (16)</td>
<td>9 (28)</td>
<td>18 (27)</td>
</tr>
<tr>
<td>mPAP &gt;30 mmHg</td>
<td>58 (84)</td>
<td>23 (72)</td>
<td>49 (73)</td>
</tr>
<tr>
<td>TPG ≤15 mmHg</td>
<td>35 (51)</td>
<td>22 (69)</td>
<td>28 (42)</td>
</tr>
<tr>
<td>TPG &gt;15 mmHg</td>
<td>34 (49)</td>
<td>12 (36)</td>
<td>34 (51)</td>
</tr>
<tr>
<td>LVEF ≤30%</td>
<td>41 (59)</td>
<td>22 (69)</td>
<td>34 (51)</td>
</tr>
<tr>
<td>LVEF &gt;30%</td>
<td>24 (35)</td>
<td>10 (31)</td>
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LVEF indicates left ventricular ejection fraction; mPAP, mean pulmonary artery pressure; TPG, transpulmonary pressure gradient.
### Supplemental Table 2. Patient demographics and baseline characteristics

(per-protocol population)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo (n=56)</th>
<th>Riociguat 0.5 mg (n=22)</th>
<th>Riociguat 1.0 mg (n=28)</th>
<th>Riociguat 2.0 mg (n=54)</th>
<th>Total (n=160)</th>
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<tr>
<td>Gender, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Male</td>
<td>50 (89)</td>
<td>18 (82)</td>
<td>25 (89)</td>
<td>43 (80)</td>
<td>136 (85)</td>
</tr>
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<td>Mean age, years (range)</td>
<td>58.8 (33–75)</td>
<td>57.1 (36–78)</td>
<td>56.9 (34–74)</td>
<td>58.7 (26–76)</td>
<td>58.2 (26–78)</td>
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<td>Mean body mass index, kg·m⁻² (SEM)</td>
<td>28.5 (0.8)</td>
<td>29.4 (0.9)</td>
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<td>29.0 (0.8)</td>
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<tr>
<td>6MWD, m (SEM)</td>
<td>396.4 (15.5)</td>
<td>434.3 (21.1)</td>
<td>395.1 (19.5)</td>
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<td></td>
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<tr>
<td>LVEF, % (SEM)</td>
<td>27.3 (0.7)</td>
<td>26.4 (1.1)</td>
<td>28.7 (0.9)</td>
<td>28.5 (0.8)</td>
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<td>Etiology, n (%)</td>
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<td></td>
<td></td>
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</tr>
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<td>Ischemic cardiomyopathy</td>
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<td>8 (36)</td>
<td>11 (39)</td>
<td>24 (44)</td>
<td>70 (44)</td>
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<td>Non-ischemic cardiomyopathy</td>
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<td>Class</td>
<td>n (%)</td>
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<td>III</td>
<td>IV</td>
<td>Diabetes mellitus (including subtypes), n (%)</td>
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<td>4 (18)</td>
<td>10 (36)</td>
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</tr>
<tr>
<td></td>
<td></td>
<td>1 (2)</td>
<td>0</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>25 (45)</td>
<td>8 (36)</td>
<td>9 (32)</td>
<td>23 (43)</td>
</tr>
<tr>
<td>Atrial fibrillation, n (%)*</td>
<td>8 (16)</td>
<td>2 (10)</td>
<td>2 (7)</td>
<td>5 (11)</td>
<td>–</td>
</tr>
<tr>
<td>Atrial flutter, n (%)*</td>
<td>0</td>
<td>1 (5)</td>
<td>0</td>
<td>0</td>
<td>–</td>
</tr>
<tr>
<td>Pacemaker rhythm, n (%)*</td>
<td>14 (28)</td>
<td>3 (15)</td>
<td>9 (33)</td>
<td>14 (30)</td>
<td>–</td>
</tr>
<tr>
<td>Baseline drug and device therapy, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Cardiac devices†</td>
<td>32 (57)</td>
<td>14 (64)</td>
<td>15 (54)</td>
<td>32 (59)</td>
<td>93 (58)</td>
</tr>
<tr>
<td>ACE inhibitors</td>
<td>36 (64)</td>
<td>15 (68)</td>
<td>20 (71)</td>
<td>40 (74)</td>
<td>111 (69)</td>
</tr>
<tr>
<td>ARBs</td>
<td>15 (27)</td>
<td>7 (32)</td>
<td>8 (29)</td>
<td>15 (28)</td>
<td>45 (28)</td>
</tr>
<tr>
<td>Aldosterone antagonists</td>
<td>40 (71)</td>
<td>16 (73)</td>
<td>22 (79)</td>
<td>37 (69)</td>
<td>115 (72)</td>
</tr>
<tr>
<td>Beta-blockers‡</td>
<td>27 (48)</td>
<td>15 (68)</td>
<td>14 (50)</td>
<td>24 (44)</td>
<td>80 (50)</td>
</tr>
<tr>
<td>Beta-blockers with alpha-blocking activity</td>
<td>26 (46)</td>
<td>7 (32)</td>
<td>13 (46)</td>
<td>24 (44)</td>
<td>70 (44)</td>
</tr>
<tr>
<td>Drug Class</td>
<td>0.5 mg (n=20)</td>
<td>1.0 mg (n=27)</td>
<td>2.0 mg (n=46)</td>
<td>5.0 mg (n=50)</td>
<td>10 mg (n=52)</td>
</tr>
<tr>
<td>-----------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>---------------</td>
<td>--------------</td>
</tr>
<tr>
<td>Loop diuretics</td>
<td>55 (98)</td>
<td>20 (91)</td>
<td>26 (93)</td>
<td>50 (93)</td>
<td>151 (94)</td>
</tr>
<tr>
<td>Thiazide diuretics</td>
<td>7 (13)</td>
<td>6 (27)</td>
<td>3 (11)</td>
<td>6 (11)</td>
<td>22 (14)</td>
</tr>
<tr>
<td>Cardiac glycosides</td>
<td>23 (41)</td>
<td>3 (14)</td>
<td>9 (32)</td>
<td>17 (32)</td>
<td>52 (33)</td>
</tr>
<tr>
<td>Oral anticoagulants</td>
<td>25 (45)</td>
<td>12 (55)</td>
<td>14 (50)</td>
<td>27 (50)</td>
<td>78 (49)</td>
</tr>
<tr>
<td>Amiodarone</td>
<td>6 (11)</td>
<td>3 (14)</td>
<td>2 (7)</td>
<td>7 (13)</td>
<td>18 (11)</td>
</tr>
</tbody>
</table>

6MWD indicates 6-minute walk distance; ACE, angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; GFR, glomerular filtration rate; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; SEM, standard error of the mean; TPG, transpulmonary pressure gradient; WHO, World Health Organization.

*Data available for n=50 (placebo), n=20 (0.5 mg), n=27 (1.0 mg), n=46 (2.0 mg).

†Includes implantable cardioverter defibrillator, cardiac resynchronization therapy, and conventional pacemaker.

‡Includes atenolol, bisoprolol, metoprolol, nebivolol, and sotalol (1 patient in the 0.5 mg group), excludes carvedilol.
<table>
<thead>
<tr>
<th>Parameter</th>
<th>Placebo</th>
<th>Riociguat 0.5 mg</th>
<th>Riociguat 1.0 mg</th>
<th>Riociguat 2.0 mg</th>
<th>Placebo-corrected LS mean difference (95% CI): riociguat 2.0 mg vs placebo</th>
<th>Pairwise comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td>Week 16</td>
<td>(n=56)</td>
<td>(n=22)</td>
<td>(n=28)</td>
<td>(n=54)</td>
<td>Placebo-corrected LS mean difference (95% CI): riociguat 2.0 mg vs placebo</td>
<td>Pairwise comparison</td>
</tr>
<tr>
<td>Left ventricular ejection fraction, %</td>
<td>0.7±0.3†</td>
<td>0.9±0.4</td>
<td>1.4±0.3‡</td>
<td>1.1±0.3§</td>
<td>0.5 (–0.2 to 1.2)</td>
<td>0.17</td>
</tr>
<tr>
<td>Left ventricular end diastolic volume, mL</td>
<td>11.1±6.0†</td>
<td>5.5±10.3</td>
<td>12.7±8.0‡</td>
<td>6.6±6.0§</td>
<td>–4.3 (–21.1 to 12.6)</td>
<td>0.62</td>
</tr>
<tr>
<td>Left ventricular end systolic volume, mL</td>
<td>7.3±4.5†</td>
<td>1.5±7.3</td>
<td>6.4±5.5‡</td>
<td>1.8±4.4§</td>
<td>–5.1 (–17.3 to 7.2)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Data are mean±standard error of the mean. CI indicates confidence interval; LS, least squares.

†n=53 at baseline and n=54 at Week 16.

*Analysis of covariance for change from baseline to Week 16 (per-protocol analysis set); pairwise comparison.
‡n=27 at baseline and n=28 at Week 16.

§n=54 at baseline and n=52 at Week 16.
<table>
<thead>
<tr>
<th>Event, n (%)</th>
<th>Placebo (n=69)</th>
<th>Riociguat 0.5 mg (n=32)</th>
<th>Riociguat 1.0 mg (n=33)</th>
<th>Riociguat 2.0 mg (n=67)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clinical worsening</td>
<td>15 (22)</td>
<td>5 (16)</td>
<td>5 (15)</td>
<td>15 (22)</td>
</tr>
<tr>
<td>First hospitalization for a CV event</td>
<td>12 (17)</td>
<td>3 (9)</td>
<td>4 (12)</td>
<td>11 (16)</td>
</tr>
<tr>
<td>Need for IV diuretics</td>
<td>2 (3)</td>
<td>1 (3)</td>
<td>0</td>
<td>1 (1)</td>
</tr>
<tr>
<td>Persistent worsening of WHO functional class</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Upgrade of heart transplant status</td>
<td>1 (1)</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Death</td>
<td>0</td>
<td>1 (3)</td>
<td>1 (3)</td>
<td>1 (1)</td>
</tr>
<tr>
<td>CV death or hospitalization</td>
<td>12 (17)</td>
<td>3 (9)</td>
<td>3 (9)</td>
<td>11 (16)</td>
</tr>
</tbody>
</table>

CV denotes cardiovascular; IV, intravenous; WHO, World Health Organization.
Supplemental Figure 1.

% of patients

NYHA functional class
- IV
- III
- II
- I

Baseline
Placebo (n=56)
Week 16

Baseline
Riociguat 0.5 mg (n=22)
Week 16

Baseline
Riociguat 1.0 mg (n=28)
Week 16

Baseline
Riociguat 2.0 mg (n=54)
Week 16

61 33
6 19

28 59
28 19

61 27
6 27

2 46
46 31

18 9
45 9

(n=56) (n=22) (n=28) (n=54)
Supplemental Figure 2.
Supplemental Figure Legends

Supplemental Figure 1. Proportion of patients in each NYHA functional class at baseline and last visit. There was no significant difference in the change from baseline in NYHA functional class between the placebo and riociguat 2 mg groups ($P=0.91$).

NYHA indicates New York Heart Association;

Supplemental Figure 2. Forest plots of hemodynamic and echocardiographic parameters in subgroups of patients: (A) mPAP, (B) PCWP, (C) CI, (D) LVEF, (E) LVEDV, and (F) LVESV.

6MWD indicates 6-minute walking distance; CI, cardiac index; ICM, ischemic cardiomyopathy; LVEDV, left ventricular end-diastolic volume; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; mPAP, mean pulmonary artery pressure; NICM, non-ischemic cardiomyopathy; PCWP, pulmonary capillary wedge pressure; PVG, pulmonary vascular gradient; TPG, transpulmonary pressure gradient. Data shown are placebo corrected least squares mean difference at Week 16 (95% confidence interval).
Supplemental References