Effects of a Novel Aldosterone Synthase Inhibitor for Treatment of Primary Hypertension

Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase 2 Trial

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Background—LCI699, a novel inhibitor of aldosterone synthase, reduces serum aldosterone, and may have benefit in the treatment of hypertension.

Methods and Results—We performed the first double-blind, randomized trial with LCI699 in patients with primary hypertension. We randomized 524 patients to LCI699 0.25 mg once daily (n=92), 0.5 mg once daily (n=88), 1.0 mg once daily (n=86), and 0.5 mg twice daily (n=97); eplerenone 50 mg twice daily (n=84); or placebo (n=77) for 8 weeks. Adrenocorticotropic hormone (250 μg IV) stimulation testing was performed in a subset of patients to quantify the selectivity of LCI699 for aldosterone synthase compared with 11-β-hydroxylase. Reductions in clinic diastolic blood pressure were significant for LCI699 1.0 mg (−7.1 mm Hg; P=0.0012) and eplerenone 50 mg twice daily (−7.9 mm Hg; P<0.0001) compared with placebo (−2.6 mm Hg) but not other doses of LCI699. Significant reductions in clinic systolic blood pressure were observed with all doses of LCI699 (P<0.005 or better) and eplerenone (P<0.0001). All doses of LCI699 significantly reduced 24-hour ambulatory blood pressure compared with placebo (P<0.01). Adrenocorticotropic hormone stimulation of cortisol was suppressed in ≈20% of subjects receiving LCI699 at a total daily dose of 1.0 mg. Safety and tolerability were similar among LCI699, placebo, and eplerenone.

Conclusions—Aldosterone synthase inhibition with LCI699 significantly lowered clinic and ambulatory blood pressure. A minority of subjects developed blunted adrenocorticotropic hormone–stimulated release of cortisol. These results support additional research to evaluate use of aldosterone synthase inhibition in primary hypertension and/or patients characterized by aldosterone excess.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00758524. (Circulation. 2011;124:00-00.)

Key Words: blood pressure ▪ hypertension ▪ inhibitors ▪ trials

Aldosterone, the principal mineralocorticoid in humans, is produced in the zona glomerulosa of the adrenal cortex by aldosterone synthase (CYP11B2). A key component of the renin-angiotensin-aldosterone system, aldosterone acts primarily at the renal distal convoluted tubules as a critical regulator of fluid and electrolyte homeostasis. Given the role that aldosterone plays in causing hypertension and in promoting vascular, renal, and myocardial disease, blockade of aldosterone represents an important option to lower blood pressure (BP) and potentially to mitigate the target-organ damage associated with hypertension.

Clinical Perspective on p ●●●

Mineralocorticoid receptor blockers such as spironolactone and eplerenone block the actions of aldosterone at the receptor level. Clinical trials indicate that spironolactone and eplerenone effectively lower BP, particularly in resistant hypertension, and improve outcomes in congestive heart failure.1–6 Use of these agents, particularly spironolactone, can be limited by adverse effects, and is associated with reactive increases in circulating aldosterone levels that could theoretically exacerbate any actions of aldosterone that are...
mediated independently of effects on gene transcription, ie, so-called nongenomic effects.\textsuperscript{7-9} Therefore, inhibition of aldosterone synthesis represents a novel approach to decreasing exposure of the cardiovascular system to aldosterone that may provide advantages in terms of tolerability and/or cardiovascular and renal protection.

LCI699 is a potent, orally administrated, first-in-class aldosterone synthase inhibitor. Studies in healthy volunteers showed that LCI699 was rapidly absorbed and well tolerated and suppressed both plasma and urinary aldosterone levels compared with placebo.\textsuperscript{10} In a recent study of 14 patients with primary aldosteronism, LCI699 1.0 mg twice daily suppressed plasma aldosterone by 75% and urinary aldosterone by 88%, and was associated with moderate reductions in 24-hour ambulatory systolic BP (SBP; \(-4.1 \text{ mm Hg}\)) and office SBP (\(-9.5 \text{ mm Hg}\)).\textsuperscript{11} The present study was undertaken to evaluate the efficacy and tolerability of LCI699 for the first time in patients with primary hypertension.

Methods

Study Design

This was a multicenter, randomized, double-blind, placebo- and active-controlled, parallel-group phase 2 study (Figure 1). The study protocol was approved by the independent ethics committee or institutional review board of each center, and the study was conducted in accordance with Good Clinical Practice guidelines and the ethical principles of the Declaration of Helsinki. All patients provided written informed consent before being enrolled. The trial is registered at www.ClinicalTrials.gov (identifier, NCT00758524).

Randomization and Masking

Patients were masked only during the single-blind run-in period. After this period, an interactive voice-response system was used to randomly assign patients to 1 of 6 treatment groups (defined below). Both patients and investigators were blinded to the treatment assigned at randomization. Randomization sequences were generated by the interactive voice-response system provider. A validated system automated the random assignment of patient numbers to treatment packs. Randomization was stratified by participation in the adrenocorticotropic hormone (ACTH) substudy and then by study center. The block size was 12 for patients not participating in the ACTH substudy (1:1:1:1:1:1 randomization ratio for the 6 treatment groups). For patients participating in the ACTH substudy, the block size was 10 (reflecting a 2:2:2:2:1:1 ratio; 2 for all LCI699 treatment groups, 1 for eplerenone and placebo) for the first 12 blocks (120 randomization codes) and a block size of 6 (1:1:1:1:1:1 ratio) for the rest of the blocks dedicated to the substudy. This was done to ensure some overalllocation to LCI699 treatment in the ACTH substudy, but to keep overall study balance, hence the restricted number of blocks that were weighted in favor of LCI699 treatment.

To evaluate the recovery in BP after the discontinuation of treatment, all patients entered a randomized withdrawal period at the end of the 8-week double-blind period. For this assessment, patients from each arm were randomized 1:1 to continue on either the same study treatment that they received during the 8-week period or placebo for 1 additional week.

Patients, investigators, people performing the assessments, and data analysts remained blinded to treatment assignments from the time of randomization until database lock. The identity of the treatments was concealed by the use of study drugs that were identical in packaging, labeling, schedule of administration, appearance, taste, and odor.

Patients

Eligible patients were between 18 and 75 years of age with stage 1 to 2 hypertension, either untreated or treated with \(\leq 2\) antihypertensive agents. Patients underwent a 2-week screening/washout period (only if previously on antihypertensive medication) followed by a 2-week placebo-controlled run-in period (Figure 1), after which they could be enrolled in the study if seated diastolic BP (DBP) was \(\geq 95\) and \(<110 \text{ mm Hg}\).

Women were required to be postmenopausal for 1 year, to be surgically sterile, or to be using an effective method of birth control other than hormonal contraceptives. Patients were excluded at screening if they had a history of severe hypertension (BP \(\geq 180/110 \text{ mm Hg}\)). Additional exclusion criteria included a history of diabetes mellitus; history of cardiovascular disease, including coronary artery disease, myocardial infarction, stroke, transient ischemic attack, any revascularization procedure, congestive heart failure, or hemodynamically significant carotid or peripheral arterial disease; an estimated glomerular filtration rate \(<60 \text{ mL} \cdot \text{min}^{-1} \cdot 1.73 \text{ m}^{-2}\); a serum potassium \(>5.2\) or \(<3.5 \text{ mEq/L}\); use of medications likely to affect BP, including nonsteroidal antiinflammatory drugs; or use of glucocorticoids, potent CYP3A4 inhibitors, or potassium supplements.

The study was conducted in participating clinics/physician’s offices in Argentina (n=55, 7 study centers), Australia (n=22, 6 centers), France (n=57, 12 centers), Germany (n=100, 15 centers), the Netherlands (n=63, 8 centers), Romania (n=9, 3 centers), Spain (n=61, 8 centers), Sweden (n=27, 7 centers), and the United States (n=130, 18 centers). Patients were recruited between September 11, 2008, and April 6, 2009, and treatment continued until July 2, 2009.
After a 2-week screening/washout period and a 2-week single-blind placebo-controlled run-in period to establish inclusive BP values, there was an 8-week double-blind double-dummy treatment period. Qualifying patients were randomly assigned to 1 of 6 treatment groups of double-blind treatment: LCI699 0.25 mg once daily, LCI699 0.5 mg once daily, LCI699 1.0 mg once daily, LCI699 0.5 mg twice daily, eplerenone 50 mg twice daily, or placebo. These doses were chosen on the basis of results from a phase 1 study that indicated that higher doses of LCI699 had the potential to inhibit 11-\beta-hydroxylase and to reduce cortisol synthesis. Patients randomized to LCI699 1.0 mg once daily received 0.5 mg once daily for 1 week and then were titrated to 1.0 mg daily for the remaining 7 weeks of the double-blind treatment period. Patients randomized to LCI699 0.5 mg twice daily or eplerenone twice daily started with the same dose once daily for 1 week and then were titrated to twice daily dosing for the remaining 7 weeks. All study procedures were conducted between 7 and 10 AM.

ACTH Stimulation Substudy
A subgroup of patients in 5 countries (Germany, the Netherlands, Spain, Sweden, and the United States) underwent ACTH stimulation cortisol testing at baseline (the day before randomization) and at the end of the 8-week double-blind treatment period (At Swedish sites, ACTH stimulation testing was also performed after 4 weeks of double-blind treatment). The objective was to detect even a minor impairment of cortisol synthesis if present. ACTH (250 \( \mu \)g IV) was administered 2 hours after the study drug was taken, and blood samples for cortisol determination were obtained 1 hour later (ie, 3 hours after study drug). ACTH stimulation was considered abnormal if the serum cortisol level remained below 500 nmol/L 1 hour after ACTH infusion.

Efficacy Assessments
The primary end point for this trial was mean sitting DBP. Secondary end points included mean sitting systolic BP and 24-hour ambulatory DBP and SBP.

Automated Clinic BP Determinations
Automated BP determinations were made in the clinic at each visit with an Omron BP monitor (model HEM705CP, HEM705INT, or HEM705IT, all with the same measurement algorithm; OMRON Healthcare Co Ltd, Kyoto, Japan) with an appropriately sized cuff in accordance with published guidelines. The arm with the higher DBP was used for the first and all subsequent visits. BPs were measured in triplicate at 2-minute intervals 23 to 26 hours after the morning dose and 11 to 14 hours after the evening dosing time. The BPs were calculated as the mean of the 3 clinic measurements.

Ambulatory BP Monitoring
Twenty-four hour ambulatory BP (ABP) monitoring was performed in all eligible patients at the completion of the single-blind run-in period before randomization and after 8 weeks of double-blind treatment. The nondominant arm of the patient was used for ABP measurement to avoid compliance issues. Measurements were recorded at 20-minute intervals during the daytime and nighttime. To be considered valid, the ABP recording was required to have at least 80% of the programmed measurements as evaluable, with no greater than 2 hours of contiguous loss of BP data. If an ABP recording did not meet these criteria, it could be repeated within 2 to 3 days of the initial study. If the second study did not meet quality control criteria, the ABP study was considered nonevaluable.

Hormonal Measurements
Aldosterone was measured with a liquid chromatography–tandem mass spectrometry method. Plasma renin activity was measured by radioimmunoassay (GammaCoat Plasma Renin Activity 125\( I\) radioimmunoassay kit; DiaSorin, Inc, Stillwater, MN) and cortisol by chemiluminescence ELISA (ADVIA Centaur cortisol assay; Siemens Healthcare Diagnostics, Deerfield, IL).

Safety Assessments
Key safety assessments included adverse events (AEs), serious AEs, and laboratory parameters (hematology, biochemistry, and a panel of hormones). Incidence rates of AEs were summarized by system organ classes and the preferred term for all treatment groups for both the core and randomized withdrawal periods.

Statistical Analyses
The primary efficacy variable for the trial was the change from baseline in trough mean seated DBP (23 to 26 hours after the morning dose and 11 to 14 hours after the dose [twice-daily regimen]) at the end of the 8-week double-blind treatment period.
This primary end point contained an assessment of 0.25-, 0.5-, and 1-mg once-daily doses and a 0.5-mg twice-daily dose of LCI699 compared with placebo. Response to treatment was defined as seated DBP <90 mm Hg or a reduction ≥10 mm Hg, and seated SBP <140 mm Hg or ≥20 mm Hg reduction at week 8.

The assessment of the primary objective of establishing superior efficacy of once-daily or twice-daily doses of LCI699 compared with placebo was evaluated by using a set of 6 optimal contrasts representing 5 prospectively defined dose-response shapes for once-daily or twice-daily dosing compared with placebo. A multiplicity adjustment applied to these multiple contrasts, using information on the correlation between the contrasts, kept the significance level of the global test of the primary objective at the 1-sided 2.5% level. This global test was performed to detect a dose-response signal in the reduction of mean sitting DBP (primary efficacy variable) used a multivariate t statistic as the reference distribution to adjust for the multiple assessments involving several doses compared with placebo.12

### Table 1. Demographic and Baseline Characteristics of the Patient Population

<table>
<thead>
<tr>
<th>LCI699</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.25 Once Daily</td>
<td>0.5 Once Daily</td>
</tr>
<tr>
<td>(n=92)</td>
<td>(n=87)</td>
</tr>
<tr>
<td>Age, mean (SD), y</td>
<td>53.9 (10.5)</td>
</tr>
<tr>
<td>&lt;65 y, n (%)</td>
<td>75 (81.5)</td>
</tr>
<tr>
<td>≥65 y, n (%)</td>
<td>17 (18.5)</td>
</tr>
<tr>
<td>Sex, n (%)</td>
<td>63 (68.5)</td>
</tr>
<tr>
<td>Male</td>
<td>29 (31.5)</td>
</tr>
<tr>
<td>Female</td>
<td>86 (93.5)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td>5 (5.4)</td>
</tr>
<tr>
<td>White</td>
<td>1 (1.1)</td>
</tr>
<tr>
<td>Asian</td>
<td>140.4 (10.5)</td>
</tr>
<tr>
<td>Clinic DBP, mean (SD)</td>
<td>160.1 (12.4)</td>
</tr>
<tr>
<td>Mean duration of hypertension, y</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Blood pressure, mm Hg

| SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ASBP, ambulatory SBP; ADBP, ambulatory DBP; and eGFR, estimated glomerular filtration rate. | SBP indicates systolic blood pressure; DBP, diastolic blood pressure; ASBP, ambulatory SBP; ADBP, ambulatory DBP; and eGFR, estimated glomerular filtration rate. |

| *P* values derived after this step do not share the adjustment for multiple comparisons and are only nominal. |

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### Results

#### Patients

Of the 903 subjects screened, 105 patients did not qualify for the study after washout, 274 patients failed the screening during the single-blind period, and 524 were randomly assigned to double-blind treatment. The most common reasons for screen failure were failure to meet diagnostic/severity criteria (45%), unacceptable test procedure results (22%), abnormal laboratory values (12%), and exclusionary medical conditions (7%). Of the randomized patients, 522 had postbaseline BP measurements, and 474 completed the 8-week double-blind period (Figure 2). The proportion of patients who discontinued during the double-blind treatment period was higher in the placebo group (13.0%, 10 of 77) compared with the 5 active treatment groups (values ranged from 6.8% [6 of 88] in the 0.5-mg once-daily LCI699 group to 10.7% [9/84] in the 50-mg twice-daily eplerenone group), primarily because of a lack of efficacy as judged by the investigator. All 474 patients completing the 8-week double-
blind treatment period continued into the 1-week randomized withdrawal period. During this final week of the study, 2 patients randomized to continue LCI 0.5 mg once daily and 1 randomized to continue LCI 0.25 mg once daily were withdrawn as a result of an unsatisfactory therapeutic response.

Baseline characteristics of the patients were similar among the treatment groups (Table 1). The study population was predominantly male (65%, 341 of 522) and white (90%, 467 of 522), and the mean age of patients was 55 years, with 15% (80 of 522) 65 years of age. Mean baseline BP was 157.9/100.2 mm Hg. The mean estimated glomerular filtration rate was 85 mL/min/1.73 m², which was comparable between treatment groups.

Efficacy Findings
Changes from baseline in clinic BPs for each of the treatment groups at the end of the double-blind treatment period (week 8) are shown in Figure 3. In a pairwise comparison, only the LCI699 1.0-mg once-daily dose was significantly more effective than placebo in reducing seated DBP (2-sided \( P<0.001 \)). Reductions in DBP with LCI699 1.0 mg once daily and eplerenone 50 mg twice daily were of a similar magnitude. Changes in SBP for each of the treatment groups are shown in Figure 3. In pairwise comparisons, all doses of LCI699 were significantly more effective in reducing SBP than placebo at 8 weeks (\( P=0.004 \) for 0.5 mg once daily and \( P<0.001 \) for all other doses). There were no differences in the changes in SBP with LCI699 1.0 mg once daily compared with eplerenone 50 mg twice daily (Figures 3 and 4).

Changes in 24-hour SBP and DBP after 8 weeks of treatment are shown in Figure 5. All doses of LCI699 produced a significant reduction in 24-hour SBP and DBP compared with placebo at 8 weeks (\( P<0.01 \) or better). Reductions from baseline in ABP with eplerenone 50 mg twice daily were similar to those with LCI699 1.0 mg once daily; however, they were greater than lower doses of LCI699. Additionally, reductions in 24-hour BP with LCI699 1.0 mg once daily and 0.5 mg twice daily were not significantly different from each other even by the pairwise \( P \) value criterion.

Changes in SBP and DBP were not significantly different from placebo during the 1-week randomized withdrawal period. Except for LCI699 0.5 mg once daily, patients rerandomized to placebo tended to have greater increases in clinic BP than those who remained on active treatment.

Response Rate
Response was defined as seated DBP \(<90\) mm Hg or a reduction \(\geq 10\) mm Hg and seated SBP \(<140\) mm Hg or \(\geq 20\) mm Hg reduction at week 8. The DBP response rates for the respective treatment groups were as follows: placebo, 28% (21 of 76); LCI699 0.25 mg once daily, 39% (36 of 92); LCI699 0.5 mg once daily, 34% (29 of 85); LCI699 1.0 mg
once daily, 50% (43 of 86); LCI699 0.5 mg twice daily, 34% (33 of 96); and eplerenone 50 mg twice daily, 49% (41 of 84). The SBP response rates were as follows: placebo, 17% (13 of 76); LCI699 0.25 mg once daily, 39% (36 of 92); LCI699 0.5 mg once daily, 38% (32 of 85); LCI699 1.0 mg once daily, 49% (42 of 86); LCI699 0.5 mg twice daily, 34% (33 of 96); and eplerenone 50 mg twice daily, 52% (49 of 84).

Effect on Aldosterone, Plasma Renin Activity, and Cortisol
At 0.5 mg twice daily, LCI699 modestly decreased aldosterone levels measured 12 hours after the last drug intake, whereas once-daily doses of LCI699 and placebo had little effect on plasma aldosterone concentrations measured 24 hours after the last drug intake (Table 2). As expected, eplerenone 50 mg twice daily increased aldosterone levels. Both LCI699 0.5 mg twice daily and eplerenone increased PRA compared with placebo, but this was not statistically significant with the once-daily doses of LCI699.

There was no change in mean morning cortisol levels in any of the treatment groups. A small number of patients (0%–2.2%, 0 of 84–2 of 91) had low morning cortisol levels (<150 nmol/L) while receiving LCI699, results that are similar to both placebo (1.4%, 1 of 71) and eplerenone (3.7%, 3 of 81). LCI699 also had no effect on total testosterone concentrations compared with placebo.

ACTH Stimulation Testing
At baseline, there were no differences in mean cortisol levels before and after ACTH stimulation among the different treatment groups (n=21–28; Table 3). After 8 weeks of treatment, LCI699 dose-dependently lowered cortisol levels at 1 hour after ACTH, and this effect achieved statistical significance for all doses of LCI699. At 8 weeks, mean cortisol values 1 hour after ACTH for LCI699 0.25 mg once daily, 0.5 mg once daily, 1.0 mg once daily, and 0.5 mg twice daily were 729±124 (mean± SD), 693±118, 604±125, and 609±108 nmol/L, respectively, compared with 802±134 and 823±116 nmol/L for eplerenone and placebo. Individual responses are shown in Figure I in the online-only Data Supplement.

ACTH-stimulated cortisol levels were also evaluated categorically. All patients had a normal ACTH response (pre-
specified as plasma cortisol >500 nmol/L 1 hour after ACTH infusion) at baseline. During active treatment with placebo, eplerenone, LC1699 0.25 mg, or LC1699 0.5 mg once daily, ACTH stimulation of cortisol remained normal in all patients. In contrast, 20.8% of patients (5 of 24) receiving LC1699 0.5 mg twice daily and 21.4% (6 of 28) treated with LC1699 1.0 mg once daily exhibited an attenuated cortisol response on ACTH stimulation. For those patients in whom the cortisol response to ACTH did not achieve 500 nmol/L, ACTH testing was repeated 1 to 2 weeks after treatment with LC1699 was stopped, and in all cases, the cortisol response returned to normal (ie, >500 nmol/L).

Safety and Tolerability
There were no deaths during the study. There were 2 serious AEs: 1 (retinal vein occlusion) in a patient receiving LC1699 0.25 mg once daily and 1 (hospitalization for abdominal pain and fever) in a patient receiving placebo.

The frequencies of patients reporting ≥1 AEs during the double-blind treatment period were similar across all treatment groups, ranging from 25% to 31% (the lowest being for LC1699 0.25 mg once daily [23 of 92] and the highest being for eplerenone 50 mg twice daily [26/84]). The most frequently reported AEs were headache, dizziness, and nasopharyngitis. Headache occurred more frequently with placebo (13%, 10 of 76), LC1699 0.5 mg once daily (4.6%, 4 of 87), and eplerenone 50 mg twice daily (3.6%, 3 of 84). Dizziness was most common with LC1699 0.5 mg twice daily (5.2%, 5 of 97). The majority of these AEs were categorized as mild to moderate in intensity.

Episodes of mild hyponatremia (≥130 and <135 mmol/L) were similar across the active treatment groups (0%–2.2%, 0 of 87–2 of 92) and placebo (2.7%, 2 of 76). One patient receiving LC1699 0.5 mg twice daily had an episode of hyponatremia <125 mmol/L, and 1 patient receiving LC1699 0.25 mg once daily had an episode of hyponatremia between ≥125 and <130 mmol/L. The incidence of hyperkalemia (>5.5 mmol/L) was similar across all LC1699 doses >0.25 mg and eplerenone (3.4%–4.8%, 3 of 87–4 of 84). There was 1 occurrence of hyperkalemia in the LC1699 0.25-mg once-daily group and none in the placebo group. One patient in each of the LC1699 treatment groups had an episode of hyperkalemia >6.0 mmol/L. In each case, the hyperkalemia was not present on repeat testing without any change in treatment status, and no patient was withdrawn from the study because of an abnormally high potassium concentration. There was a significant dose-response relationship for LC1699 and mean potassium concentration and change in potassium concentration. The placebo-subtracted changes in potassium concentration ranged from 0.01 to 0.28 mmol/L, which were similar to that of eplerenone. There

![Figure 5. Changes from baseline in 24-hour mean ambulatory diastolic (A) and systolic (B) blood pressures at week 8. Error bars represent SEM. DBP indicates diastolic blood pressure; SBP, systolic blood pressure; qd, once daily; and bid, twice daily.](image-url)
were no significant increases in creatinine with any of the doses of LCI699 or eplerenone.

**Discussion**

This is the first clinical study evaluating aldosterone synthase inhibition for the treatment of primary hypertension. The results indicate that LCI699 significantly lowered office and 24-hour BP and was well tolerated. Morning cortisol levels remained unchanged regardless of the dose of LCI699; however, ACTH stimulation of cortisol was suppressed in 20% of patients receiving the higher doses. Overall, the study suggests that aldosterone synthase inhibition may represent a new and effective means of treating hypertension.

A growing body of research has linked aldosterone to the development and progression of cardiovascular disease, including hypertension. In prospective analyses from the ongoing Framingham Offspring Study and in a middle-aged French population, serum aldosterone, plasma renin concentration, and the aldosterone/plasma renin ratio in normotensive subjects were prospectively related to development of hypertension or to BP progression (increase in severity). Specifically, rates of incident hypertension and BP progression rose across tertiles of increasing aldosterone levels.

Plasma aldosterone levels have also been associated with severity of hypertension, as indicated by cross-sectional studies of untreated hypertensive cohorts. More broadly, aldosterone is linked to the development and progression of cardioenral disease, including endothelial dysfunction, proteinuria, left ventricular hypertrophy, target-organ fibrosis and inflammation, congestive heart failure, stroke, and recently the severity of obstructive sleep apnea.

Mineralocorticoid receptor–blocking agents, such as spironolactone and eplerenone, prevent aldosterone from binding with the mineralocorticoid receptor. A large number of clinical studies have demonstrated their benefit in treating hypertension, particularly resistant hypertension, and in improving outcomes in patients with congestive heart failure. Smaller studies suggest benefit of these agents in improving endothelial function, regressing left ventricular hypertrophy, and reducing proteinuria. However, use of mineralocorticoid receptor–blocking agents can be complicated by adverse effects and reactive increases in circulating aldosterone levels. Experimental data suggest that some of the hemodynamic and cardiovascular effects of aldosterone may occur through possible nongenomic pathways, ie, independently of stimulation of the mineralocorticoid receptor and/or the classic steroid-receptor complex modulation of nuclear gene expression. If nongenomic pathways do contribute importantly to the effects induced by aldosterone, aldosterone synthase inhibitors such as LCI699 would potentially offer an

| Table 2. Aldosterone and Plasma Renin Activity at Baseline and After 8 Weeks of Treatment |
|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|----------------------------------|
|                                  | LCI699                           | Eplerenone 50                    |                                  |                                  |
|                                  | 0.25 Once Daily                  | 0.5 Once Daily                   | 1.0 Once Daily                   | 0.5 Twice Daily                  | Twice Daily                      | Placebo                          |
| Aldosterone, pmol/L             |                                  |                                  |                                  |                                  |                                  |
| Baseline 0.25                   |                                  |                                  |                                  |                                  |                                  |
| n                                | 79                               | 76                               | 76                               | 86                               | 73                               | 66                               |
| Geo mean                        | 164.7                            | 166.7                            | 199.7                            | 163.8                            | 189.7                            | 181.7                            |
| CV                              | 0.83                             | 0.82                             | 0.67                             | 0.67                             | 0.60                             | 0.77                             |
| Median                          | 194                              | 208                              | 250                              | 166                              | 222                              | 180                              |
| Week 8                          |                                  |                                  |                                  |                                  |                                  |                                  |
| n                                | 75                               | 72                               | 72                               | 80                               | 68                               | 60                               |
| Geo mean                        | 153.1                            | 166.8                            | 155.5                            | 108.0*                           | 379.8*                           | 172.3                            |
| CV                              | 0.64                             | 0.71                             | 1.15                             | 1.05                             | 0.83                             | 0.71                             |
| Median                          | 166                              | 194                              | 166                              | 111                              | 374.5                            | 194                              |
| PRA, μg·L⁻¹·h⁻¹                  |                                  |                                  |                                  |                                  |                                  |                                  |
| Baseline 0.25                   |                                  |                                  |                                  |                                  |                                  |                                  |
| n                                | 68                               | 64                               | 69                               | 75                               | 66                               | 59                               |
| Geo mean                        | 1.20                             | 1.10                             | 1.10                             | 1.10                             | 1.00                             | 1.10                             |
| CV                              | 1.14                             | 2.37                             | 1.57                             | 1.08                             | 1.05                             | 1.19                             |
| Median                          | 1.10                             | 0.70                             | 0.80                             | 0.90                             | 0.80                             | 1.00                             |
| Week 8                          |                                  |                                  |                                  |                                  |                                  |                                  |
| n                                | 68                               | 65                               | 69                               | 75                               | 61                               | 52                               |
| Geo mean                        | 1.60                             | 1.40                             | 1.70                             | 2.10*                            | 2.10*                            | 1.30                             |
| CV                              | 1.03                             | 1.12                             | 0.95                             | 1.44                             | 1.59                             | 1.96                             |
| Median                          | 1.70                             | 1.20                             | 1.40                             | 2.10                             | 2.30                             | 1.20                             |

Geo indicates geometric mean; CV, coefficient of variation; and PRA, plasma renin activity. The reference ranges for serum aldosterone and PRA are <776 pmol/L and <5.3 μg·L⁻¹·h⁻¹, respectively.

*P<0.05 for change from baseline versus placebo; all values are ~24 hours after once-daily dosing and 12 hours after twice-daily dosing.
advantage over mineralocorticoid receptor–blocking agents in preventing activation of both genomic and nongenomic pathways. Such a potential advantage, however, remains speculative because the present study was not designed to explore differences in mechanism of action at a receptor level.

In the present trial, all of the studied doses of LCI699 reduced SBP compared with placebo, whereas the 1.0-mg once-daily dose reduced DBP compared with placebo. LCI699 1.0 mg once daily lowered BP comparable to eplerenone 50 mg twice daily, the highest approved dose of eplerenone for the treatment of hypertension. It is unclear why LCI699 0.5 mg twice daily did not lower BP to the same extent as 1.0 mg once daily. It may represent a chance occurrence; however, additional assessment is needed to further evaluate whether a divided dose is less effective than a full dose given once daily. It is also noteworthy that LCI699 1.0 mg once daily induced a greater BP response than LCI699 dosed 0.5 mg once daily, indicating that we may not have observed the maximal antihypertensive effect of the drug.

Overall, LCI699 was well tolerated, with AE rates similar to that of placebo. Only 1 serious AE occurred with LCI699 dosing (retinal vein occlusion), and this was thought to be unrelated to medication exposure. The need to withdraw medication owing to an AE was low with all doses of LCI699 and comparable to that of eplerenone. Hyperkalemia (>5.5 mmol/L) with LCI699 occurred with an overall incidence of 3.1% (16 of 518). The highest incidence of hyperkalemia was observed with 0.5 mg once daily (4.8%, 4 of 84), which was similar to eplerenone (4.8%, 4 of 84) and was not present in any patient on retesting. These results suggest that in patients with normal renal function, hyperkalemia is unlikely but can occur, necessitating biochemical monitoring similar to that suggested for spironolactone and eplerenone.

LCI699 has a half-life of 4 hours in humans. Previous studies with this aldosterone synthesis inhibitor demonstrated a fall in plasma aldosterone that peaked 4 to 8 hours after dosing and was undetectable by 24 hours after drug intake. The results of the present study are consistent with this finding in that a decrease in plasma aldosterone was seen only when measured 12 hours after drug intake, as would have occurred in the LCI699 0.5-mg twice-daily group. Serial plasma levels or 24-hour urinary measurements might have been more successful in elucidating the relationship of dose of LCI699 with aldosterone response.

Phase 1 studies with LCI699 also showed no effect on baseline morning cortisol levels. Similar results were obtained in the present study. However, with the highest dose of LCI699 (1.0 mg either as a single dose or in divided doses), 20% of subjects had suppression of ACTH-induced cortisol release. This effect is likely attributable to partial inhibition of 11-β-hydroxylase (CYP11B1), the enzyme responsible for the final step in cortisol biosynthesis. The significance of the observed impaired ACTH-stress response is unknown. ACTH-mediated increases in cortisol release occur with stress and, in particular, may play an important role in mediating the response to hemorrhage, severe infection, hypotension, or acute myocardial infarction. Whether suppression of ACTH-stimulated release of cortisol to the degree observed in the present study (20%) would impair recovery from these clinical stress-mediated events needs

### Table 3. Effect of LCI699 on Adrenocorticotropic Hormone–Stimulated Cortisol Concentration

<table>
<thead>
<tr>
<th>Cortisol, nmol/L</th>
<th>LCI699 0.25 Once Daily</th>
<th>0.5 Once Daily</th>
<th>1.0 Once Daily</th>
<th>0.5 Twice Daily</th>
<th>Eplerenone 50 Twice Daily</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline Before ACTH</td>
<td>n=23</td>
<td>28</td>
<td>28</td>
<td>25</td>
<td>24</td>
<td>21</td>
</tr>
<tr>
<td>Mean</td>
<td>382</td>
<td>352</td>
<td>341</td>
<td>321</td>
<td>330</td>
<td>284</td>
</tr>
<tr>
<td>SD</td>
<td>173</td>
<td>98</td>
<td>181</td>
<td>105</td>
<td>114</td>
<td>108</td>
</tr>
<tr>
<td>1 h after ACTH n=23</td>
<td>27</td>
<td>27</td>
<td>26</td>
<td>24</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>Mean</td>
<td>812</td>
<td>774</td>
<td>803</td>
<td>778</td>
<td>770</td>
<td>789</td>
</tr>
<tr>
<td>SD</td>
<td>132</td>
<td>117</td>
<td>114</td>
<td>107</td>
<td>144</td>
<td>96</td>
</tr>
<tr>
<td>Week 8 Before ACTH</td>
<td>n=20</td>
<td>23</td>
<td>28</td>
<td>24</td>
<td>22</td>
<td>16</td>
</tr>
<tr>
<td>Mean</td>
<td>346</td>
<td>380</td>
<td>359</td>
<td>318</td>
<td>378</td>
<td>339</td>
</tr>
<tr>
<td>SD</td>
<td>109</td>
<td>135</td>
<td>117</td>
<td>88</td>
<td>128</td>
<td>114</td>
</tr>
<tr>
<td>1 h after ACTH</td>
<td>n=20</td>
<td>23</td>
<td>28</td>
<td>24</td>
<td>22</td>
<td>17</td>
</tr>
<tr>
<td>Mean</td>
<td>729*</td>
<td>693*</td>
<td>604*</td>
<td>609*</td>
<td>802</td>
<td>823</td>
</tr>
<tr>
<td>SD</td>
<td>124</td>
<td>118</td>
<td>125</td>
<td>108</td>
<td>134</td>
<td>116</td>
</tr>
</tbody>
</table>

ACTH indicates adrenocorticotropic hormone. Reference range for cortisol in the absence of ACTH stimulation is 119 to 618 nmol/L.

*P<0.05 vs placebo.
further study. Development of aldosterone synthase inhibitors that are more selective for aldosterone synthase may avoid this concern by leaving normal ACTH stimulation of cortisol release intact.

The present study results indicate that LCI699, the first-in-class aldosterone synthase inhibitor, effectively lowered clinic and 24-hour BP and was generally well tolerated. Despite the effect of LCI699 on cortisol synthesis and given the large body of evidence linking aldosterone to the development of hypertension and other cardiovascular diseases, the present findings support additional studies and the development of more selective compounds to determine whether inhibition of aldosterone synthesis provides advantages over other classes of antihypertensive agents in terms of tolerability and clinical benefit. Intuitively, such a class of agent would seem to be particularly appealing in treating high-risk cohorts strongly linked with aldosterone excess such as resistant hypertension, congestive heart failure, post–myocardial infarction, and chronic renal failure.

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This study was designed collaboratively by the academic authors and the sponsor, Novartis Pharma AG (Switzerland). The sponsor was responsible for collecting data from investigational sites to create the clinical database and for the data analysis. The analysis plan was developed in collaboration with the academic authors, who took responsibility for interpretation of the data and writing of the manuscript. All authors had full access to study results after unmasking of data.

Disclosures

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References


**CLINICAL PERSPECTIVE**

A growing body of literature links aldosterone to the development and/or progression of a variety of cardiovascular disease processes, including endothelial dysfunction, hypertension, ventricular remodeling, and congestive heart failure. Blockade of the mineralocorticoid receptor with antagonists such as spironolactone has shown benefit in blunting or reversing many of the unfavorable effects attributed to aldosterone. An alternative approach to blocking the effects of aldosterone is to prevent its production by inhibiting aldosterone synthase. The present findings indicate that inhibition of aldosterone synthase with the novel compound LCI699 significantly lowers blood pressure in patients with mild to moderate hypertension. The compound was safe and well tolerated. Aldosterone synthase inhibition with LCI699 was accompanied by suppression of adrenocorticotropic hormone–stimulated release of cortisol in a proportion of subjects, indicating partial inhibition of 11β-hydroxylase. Overall, the present results indicate that aldosterone synthase inhibition may represent a novel and effective approach to lowering high blood pressure. Additional studies are needed to determine whether there is differential antihypertensive and/or cardiovascular benefit of suppressing aldosterone production compared with blocking activation of the mineralocorticoid receptor. Such testing will need to include elucidation of the effects of partial suppression of cortisol synthesis.
Effects of a Novel Aldosterone Synthase Inhibitor for Treatment of Primary Hypertension: Results of a Randomized, Double-Blind, Placebo- and Active-Controlled Phase 2 Trial
David A. Calhoun, William B. White, Henry Krum, Weinong Guo, Georgina Bermann, Angelo Trapani, Martin P. Lefkowitz and Joël Ménard

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Figure S-1: Cortisol levels for each patient that participated in the ACTH test substudy at baseline (Week 0) and after 8 weeks of treatment. Within each panel, the values to the left represent cortisol concentrations prior to ACTH stimulation and the values to the right represent cortisol levels 1 hour after iv administration of ACTH. The yellow line demarks an ACTH concentration of 500 nmol/L.