Sponsor

Novartis

Generic Drug Name

LCI699

Therapeutic Area of Trial

Hypertension

Approved Indication

Investigational

Study Number

CLCI699A2216

Title

A phase II, randomized, double-blind, placebo and active controlled, parallel group, multi-center, dose ranging study to evaluate the efficacy and safety of LCI699 compared to placebo after 8 weeks treatment in patients with resistant hypertension

Phase of Development

Phase II

Study Start/End Dates

22-Dec-2008 to 13-Oct-2009

Study Design/Methodology

This was an exploratory (approximately 150 patients), prospective, randomized, double blind, placebo and active controlled, parallel group, multi-center, dose ranging study to compare the safety and efficacy of LCI699 in patients with resistant hypertension.

Patients taking at least three (3) anti-hypertensive treatments, one of which a diuretic, and demonstrating elevated blood pressure despite these therapies were eligible for the trial. Patients taking aldosterone receptor antagonists, direct renin antagonists or potassium-sparing diuretics within four weeks of screening were excluded from the study. Patients continued to take their background anti-hypertensive medications throughout the study.

Eligible patients had mean systolic blood pressures $\geq$ 140 and < 180 and met all other inclusion/exclusion criteria. After a 2-week single-blind run-in period of placebo, patients who continued to meet the entry criteria were randomized to placebo, LCI699 0.25 mg BID, LCI699 1.0

mg QD or eplerenone 50 mg BID for 8 weeks, or LCI699 0.5 mg BID for 4 weeks followed by LCI699 1.0 mg BID for 4 weeks.

Centres

This study was performed at 34 centers in the United States and 1 center in Iceland.

Publication

In discussion

Objectives

Primary objective

To explore the efficacy of three dose regimens (0.25 mg BID, 1.0 mg QD, and 0.5 mg BID titrated to 1 mg BID) of LCI699 in patients with resistant hypertension with respect to the change from baseline in mean sitting systolic blood pressure (MSSBP) compared to placebo after 8 weeks of treatment.

Secondary objective(s)

- To explore the efficacy LCI699 by testing the hypotheses that the change from baseline in mean sitting diastolic blood pressure (MSDBP) is superior to that of placebo.
- To explore the dose/exposure response relationship of LCI699 in the change from baseline in MSSBP and MSDBP.
- To explore whether the changes from baseline in mean 24 hour SBP and DBP with the three dose regimens of LCI699 are superior to that of placebo.
- To evaluate the safety and tolerability of LCI699 including, but not limited to: cortisol levels following ACTH stimulation, hyperkalemia, hyponatremia
- To assess the functional consequences of aldosterone inhibition by evaluating the efficacy and safety of LCI699 compared to eplerenone 50 mg BID.

Test Product (s), Dose(s), and Mode(s) of Administration

The patient's study medication dose was determined during randomization. All single-blind and double-blind medication was supplied as capsules in bottles. LCI699 was provided in 0.25 mg, 0.5 mg and 1.0 mg strengths. During each day of the single-blind run-in (2 weeks), and the double-blind treatment period (8 weeks), patients were asked to take by mouth 2 capsules (one from each bottle) with liquids, with or without food, in the morning and evening (a total of 4 capsules per diem), respectively, and approximately at the same time of each day during the course of study.

Reference Product(s), Dose(s), and Mode(s) of Administration

The following reference study medications were provided by the sponsor: placebo capsules matching LCI699 0.25 mg, 0.5 mg and 1.0 mg capsules, eplerenone 50 mg capsules and placebo capsules matching eplerenone 50 mg.

Criteria for Evaluation

Blood pressure assessments

Office Blood Pressure (OBP) and heart rate were measured using an automated blood pressure device at all scheduled office visits except for the Randomization Visit (Visit 4, Day 1).

Twenty-four (24) hour Ambulatory Blood Pressure Measurement (ABPM) was performed at the Final Run-in Visit (Visit 3, 1 day before initiating treatment), Visit 7 (Week 4) and at Visit 10 (Week 8).

Pharmacokinetic (PK) assessments

Blood samples were collected and processed to determine pre-dose (trough) LCI699 plasma concentrations at the Randomization Visit (Visit 4, Day 1), Visit 7 (Week 4), Visit 9 (Week 6) and Visit 10 (Week 8), and to determine a peak concentration measurement at Visit 10 (Week 8). For a subset of patients, high-resolution PK sampling was performed with LCI699 plasma concentrations measured just prior to and at 4 time points following dosing at Visit 9 (Week 6).

Safety assessments

Safety assessments consisted of monitoring and recording all adverse events with their severity and relationship to study drug. Safety monitoring also included laboratory evaluations of hematology, clinical blood chemistry, urinalysis, hormonal profile, regular assessments of vital signs, physical condition (including 12-lead electrocardiograms), and body weight.

Particular attention was given to serum levels of sodium, potassium, creatinine and BUN, since these laboratory tests may be altered by the active study drugs and other antihypertensive drugs.

Basal cortisol level (unstimulated) was measured at Visits 2 (between Day -14 and -2), 4 (Day 1), 10 (Week 8) and 11 (Week 10) and ACTH-stimulated cortisol was measured in a subset of patients prior to treatment with LCI699 at the Run-in Visit (Visit 2, between days -14 and -2) and again at the end of the treatment interval, at Visit 10 (Week 8).

Statistical Methods

The study's primary endpoint, the change from baseline to the Week 8 (LOCF) in MSSBP, was analyzed using a 2-way ANCOVA model with baseline MSSBP as the continuous covariate and with treatment and country as class effects. The change from baseline to the Week 4 (LOCF) in MSSBP was also analyzed using a 2-way ANCOVA model.

Each of the three LCI699 dose/regimens was compared against placebo, generating three two-sided p-values tested at the 10% level of significance. The 90% confidence interval of the mean difference (LCI699 - placebo) is presented for each LCI699 dose/regimen. A comparison between the 0.5 mg BID and 1.0 mg QD at week 4 was also undertaken to explore a potential regi-

men effect.

Safety Analyses: The incidence of adverse events were summarized by system organ classes and preferred term for all treatment groups. Laboratory data were summarized by visit using descriptive statistics and by notable changes defined as percentage changes from baseline and prespecified in the protocol. Furthermore, expanded ranges of interest for key safety parameters were summarized as frequencies. In addition, frequencies of ACTH stimulated cortisol measurements below relevant thresholds were summarized and descriptive statistics were provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. An established diagnosis of hypertension with MSSBP ≥140mmHg and <180mmHg on current antihypertensive treatment measured at Visits 1, 2 and 3 prior to randomization. This includes patients with diabetes and/or chronic kidney disease.
2. Resistant hypertension as defined by the failure to achieve blood pressure goals in patients adhering to optimal doses of a stable three-drug or more regimen that includes a diuretic for a period of at least 4 weeks.
3. Male or female patients 18 to 75 years of age (inclusive)
4. Female patients with childbearing potential were required to use at least two barrier methods of contraception (i.e. IUD, condom with a spermicidal gel, diaphragm, sponge, cervical cap) throughout the study.
5. Female patients with childbearing potential were required to have a negative pregnancy test at screening and be willing to take a pregnancy test at the end of the study.
6. Male patients were required to use a double-barrier local contraception, i.e., spermicidal gel plus condom, for the entire duration of the study, up to Study Completion visit, and refrain from fathering a child or donating sperm in the three (3) months following last study drug administration.
7. Morning serum cortisol (sampled between 07:00 a.m. and 010:00 a.m.) ≥200nM (7.3µg/dL)
8. Ability to provide written informed consent prior to study participation.
9. Ability to communicate with the investigator and willingness to comply with the requirements of the study.

Exclusion criteria

1. Severe hypertension (MSSBP >180mmHg or MSDBP >110mmHg) at screening.
2. Pregnant or nursing (lactating) women, with pregnancy confirmed by a positive Human Chorionic Gonadotropin (hCG) laboratory test (>5mIU/ml).
3. Recent history (within last 6 months) of myocardial infarction, heart failure, unstable angina, coronary artery bypass graft (CABG), percutaneous coronary intervention (PCI), hypertensive encephalopathy, cerebrovascular accident, or transient ischemic attack (TIA).
4. Clinically significant cardiac conduction defects (e.g., 3rd degree atrioventricular [AV] block, left bundle branch block [LBBB], sick sinus syndrome, atrial fibrillation or flutter).
5. Implanted cardioverter defibrillator (ICD) that had fired for any arrhythmia within 3 months of screening or implanted pacemakers.
6. Clinically significant valvular heart disease.
7. A history of secondary hypertension of any etiology (e.g., renal parenchymal hypertension, renovascular hypertension, coarctation of the aorta, primary hyperaldosteronism, unilateral or bilateral renal artery stenosis, Cushing's disease, pheochromocytoma, polycystic kidney disease, and drug-induced hypertension, obstructive sleep apnea, etc).
8. Known moderate or malignant retinopathy defined as: moderate (retinal signs of hemorrhage, microaneurysm, cotton-wool spots, hard exudates, or a combination thereof) or malignant (signs of moderate retinopathy plus swelling of the optic disk).

9. Type 1 diabetes.
10. Type 2 diabetes mellitus with poor glucose control as defined by HbA1c >9%.
11. Any of the following significant laboratory abnormalities seen at screening:
    a. Patients with serum potassium (>5.0mEq/L or <3.5mEq/L) or serum sodium (<135mEq/L).
    b. Patients with "significant" renal impairment (estimated creatinine clearance <50mL/min by the Modification of Diet in Renal Disease (MDRD) formula).
    c. Serum Alanine aminotransferase (ALT) or Aspartate aminotransferase (AST) >2.5X Upper Limit of Normal (ULN).
    d. Total bilirubin >2X ULN.
    e. Direct bilirubin >ULN.
12. Liver disease such as cirrhosis or chronic active hepatitis.
13. Any blood donation or significant loss within 4 weeks of randomization; donation of plasma within 7 days prior to randomization.
14. Anemia as defined by a hemoglobin level at screening or baseline ≤10g/dL.
15. History of familial long QT syndrome or family history of *torsade de pointe*.
16. Malignancy including leukemia and lymphoma (not including basal cell skin cancer) within the last 5 years.
17. Any surgical or medical condition which may significantly alter the absorption of any drug substance, but not limited to any of the following: history of major gastrointestinal tract surgery such as gastrectomy, gastroenterostomy, bowel resection, gastric bypass, gastric stapling, or gastric banding, or currently active inflammatory bowel syndrome.
18. Current obstruction of the urinary tract or difficulty in voiding (due to mechanical or inflammatory conditions) that is likely to require intervention during the course of the study, or is regarded as clinically meaningful by the investigator.
19. History of substance abuse (including alcohol) within the past 2 years.
20. History of hypersensitivity to any of the study drugs or to components in the study drug.
21. Upper arm less than 24cm or greater than 42cm to facilitate ABPM assessment.
22. Subjects who perform alternating shift or night work.
23. Use of any prohibited medication(s) listed within the protocol.
24. Participation in any clinical investigation within 4 weeks prior to randomization or longer if required by local regulations.
25. Any surgical or medical condition, which in the opinion of the investigator, may place the patient at higher risk from his/her participation in the study, or is likely to prevent the patient from complying with the requirements of the study or completing the study.
26. Patients taking aldosterone receptor antagonists (e.g., spironolactone or eplerenone), direct renin antagonists or potassium-sparing diuretics (e.g., triamterene or amiloride) within four (4) weeks of screening.

Patient disposition (Randomized set)

Disposition	LCI699 0.25mg BID N=32 n (%)	LCI699 1mg QD N=26 n (%)	LCI699 0.5/1mg BID N=31 n (%)	Eplerenone 50mg BID N=33 n (%)	Placebo N=33 n (%)	Overall Total N=155 n (%)
Completed	23 (71.9)	22 (84.6)	28 (90.3)	28 (84.8)	25 (75.8)	126 (81.3)
Discontinued	9 (28.1)	4 (15.4)	3 (9.7)	5 (15.2)	8 (24.2)	29 (18.7)
Reason for discontinuation						
Adverse Event(s)	1 (3.1)	0	0	1 (3.0)	1 (3.0)	3 (1.9)
Abnormal laboratory value(s)	1 (3.1) *	1 (3.8)	0	0	1 (3.0)	3 (1.9)
Subject withdrew consent	2 (6.3)	1 (3.8)	0	1 (3.0)	2 (6.1)	6 (3.9)
Lost to follow-up	0	1 (3.8)	0	1 (3.0)	0	2 (1.3)
Administrative problems	0	0	0	0	1 (3.0)	1 (0.6)
Death	0	0	0	0	0	0
Protocol deviation	5 (15.6)	1 (3.8)	3 (9.7)	2 (6.1)	3 (9.1)	14 (9.0)

* Patient 201002 (LCI699 0.25mg BID) was randomized into the study without first obtaining a basal serum cortisol level at Screening. Subsequently it was learned that the patient's basal serum cortisol on Day 1 was 190nmol/L, below the level required for inclusion (inclusion criterion #4, serum basal cortisol ≥200nmol/L). A second measurement on Day 8 of 188nmol/L was also below the minimum for participation in the study. Although not considered an AE, the patient was discontinued from the study after completing 5 days of double-blind treatment.

Demographic and Background Characteristics

Demographic summary by treatment group (Full analysis set)

Demographic variable	LCI699 0.25mg BID N=32	LCI699 1mg QD N=26	LCI699 0.5/1mg BID N=31	Eplerenone 50mg BID N=33	Placebo N=33	Overall Total N=155
Age (years)						
Mean	53.6	55.4	57.2	56.2	59.8	56.5
SD	10.36	9.58	10.77	7.70	9.33	9.69
Age group (years) – n (%)						
<65	28 (87.5)	23 (88.5)	23 (74.2)	30 (90.9)	20 (60.6)	124 (80.0)
>=65	4 (12.5)	3 (11.5)	8 (25.8)	3 (9.1)	13 (39.4)	31 (20.0)
Sex – n (%)						
Male	20 (62.5)	18 (69.2)	18 (58.1)	19 (57.6)	22 (66.7)	97 (62.6)
Female	12 (37.5)	8 (30.8)	13 (41.9)	14 (42.4)	11 (33.3)	58 (37.4)
Race – n (%)						
Caucasian	21 (65.6)	15 (57.7)	21 (67.7)	18 (54.5)	22 (66.7)	97 (62.6)
Black	11 (34.4)	9 (34.6)	10 (32.3)	14 (42.4)	11 (33.3)	55 (35.5)
Asian	0	0	0	0	0	0
Other	0	2 (7.7)	0	1 (3.0)	0	3 (1.9)
Duration of hypertension (years)						
Mean	14.1	11.7	13.9	13.0	15.5	13.7
SD	10.33	9.34	9.71	8.33	9.64	9.44

Number of anti-hypertensive medications – n (%)						
3	22 (68.8)	20 (76.9)	23 (74.2)	25 (75.8)	26 (78.8)	116 (74.8)
4	10 (31.3)	5 (19.2)	7 (22.6)	7 (21.2)	4 (12.1)	33 (21.3)
5	0	1 (3.8)	0	1 (3.0)	2 (6.1)	4 (2.6)
6	0	0	1 (3.2)	0	1 (3.0)	2 (1.3)
Baseline GFR (mL/min/SA)						
Mean	83.5	83.6	79.7	81.8	76.9	81.0
SD	16.64	20.77	14.80	14.49	16.65	16.62
Baseline MSSBP (mmHg)						
Mean	152.4	152.5	152.2	153.8	153.4	152.9
SD	11.21	9.79	7.58	8.92	9.61	9.39
Baseline MSDBP (mmHg)						
Mean	91.8	89.2	88.9	89.1	90.1	89.8
SD	11.68	9.56	11.89	9.84	11.65	10.92

Percentages are calculated using the Full Analysis Set as the denominator.

Primary Objective Result

Between treatment analysis for change from baseline in mean sitting systolic blood pressure (MSSBP) at Week 8 LOCF (Full analysis set)

Treatment group	n	Mean change from baseline	SE	95% CI
LCI699 0.25mg BID	31	-11.4	2.96	(-17.2, -5.5)
LCI699 1mg QD	26	-13.1	3.24	(-19.5, -6.7)
LCI699 0.5/1mg BID	31	-12.5	2.96	(-18.4, -6.7)
Eplerenone 50mg BID	32	-18.7	2.92	(-24.5, -12.9)
Placebo	33	-8.8	2.87	(-14.5, -3.1)

Comparisons vs. Placebo	Mean difference change from baseline	SE	90% CI	Two-sided P-value
LCI699 0.25mg BID – Placebo	-2.6	4.13	(-9.4, 4.3)	0.536
LCI699 1mg QD – Placebo	-4.3	4.33	(-11.5, 2.9)	0.323
LCI699 0.5/1mg BID – Placebo	-3.7	4.13	(-10.6, 3.1)	0.369
Eplerenone – Placebo	-9.9	4.09	(-16.7, -3.1)	0.017
Comparisons vs. Eplerenone				
LCI699 0.25mg BID – Eplerenone	7.3	4.16	(0.4, 14.2)	0.080
LCI699 1mg QD – Eplerenone	5.6	4.36	(-1.6, 12.8)	0.201
LCI699 0.5/1mg BID – Eplerenone	6.2	4.17	(-0.7, 13.1)	0.141

Using analysis of covariance, adjusting for treatment and country as factors and baseline value as the covariate.

P-values not adjusted for multiple comparisons.

LOCF, last observation carried forward.

Secondary Objective Result(s)

Between treatment analysis for change from baseline in mean sitting diastolic blood pressure (MSDBP) at Week 8 LOCF (Full analysis set)

Treatment group	n	Mean change from baseline	SE	95% CI
LCI699 0.25mg BID	31	-4.5	1.72	(-7.9, -1.1)
LCI699 1mg QD	26	-6.0	1.88	(-9.7, -2.3)
LCI699 0.5/1mg BID	31	-6.1	1.72	(-9.5, -2.7)
Eplerenone 50mg BID	32	-7.7	1.69	(-11.0, -4.3)
Placebo	33	-4.8	1.66	(-8.1, -1.5)

Comparisons vs. Placebo	Mean difference change from baseline	SE	90% CI	Two-sided P-value
LCI699 0.25mg BID – Placebo	0.3	2.39	(-3.6, 4.3)	0.894
LCI699 1mg QD – Placebo	-1.2	2.51	(-5.3, 3.0)	0.638
LCI699 0.5/1mg BID – Placebo	-1.2	2.39	(-5.2, 2.7)	0.604
Eplerenone – Placebo	-2.9	2.37	(-6.8, 1.1)	0.230
Comparisons vs. Eplerenone				
LCI699 0.25mg BID – Eplerenone	3.2	2.42	(-0.8, 7.2)	0.191
LCI699 1mg QD – Eplerenone	1.7	2.53	(-2.5, 5.9)	0.508
LCI699 0.5/1mg BID – Eplerenone	1.6	2.41	(-2.4, 5.6)	0.503

Using analysis of covariance, adjusting for treatment and country as factors and baseline value as the covariate.

P-values not adjusted for multiple comparisons.

LOCF, last observation carried forward.

Between treatment analysis of change from baseline in SBP at Week 8 LOCF as measured by ABPM (Full analysis set)

Variable	Treatment group	n	Mean change from baseline	SE	95% CI
24-hour mean SBP	LCI699 0.25mg BID	15	-4.4	3.22	(-10.8, 2.0)
	LCI699 1mg QD	19	-5.7	2.87	(-11.4, -0.0)
	LCI699 0.5/1mg BID	26	-6.3	2.47	(-11.2, -1.4)
	Eplerenone 50mg BID	23	-15.7	2.59	(-20.9, -10.6)
	Placebo	23	-1.0	2.59	(-6.1, 4.1)

Comparisons vs. Placebo	Mean difference change from BL	SE	90% CI	2-sided P-value
LCI699 0.25mg BID – Pbo	-3.4	4.14	(-10.3, 3.5)	0.412
LCI699 1mg QD – Pbo	-4.7	3.86	(-11.1, 1.7)	0.223
LCI699 0.5/1mg BID – Pbo	-5.3	3.59	(-11.3, 0.6)	0.142
Eplerenone – Pbo	-14.7	3.66	(-20.8, -8.6)	<.001

Using analysis of covariance, adjusting for treatment and country as factors and baseline value as the covariate.

Between treatment analysis of change from baseline in DBP at Week 8 LOCF as measured by ABPM (Full analysis set)

Variable	Treatment group	n	Mean change from baseline	SE	95% CI
24-hour mean DBP	LCI699 0.25mg BID	15	1.0	2.15	(-3.3, 5.2)
	LCI699 1mg QD	19	-3.4	1.94	(-7.2, 0.5)
	LCI699 0.5/1mg BID	26	-3.7	1.67	(-7.0, -0.3)
	Eplerenone 50mg BID	23	-9.6	1.74	(-13.1, -6.2)
	Placebo	23	-0.2	1.74	(-3.7, 3.2)

Comparisons vs. Placebo	Mean difference change from BL	SE	90% CI	2-sided P-value
LCI699 0.25mg BID – Pbo	1.2	2.77	(-3.4, 5.8)	0.660
LCI699 1mg QD – Pbo	-3.1	2.58	(-7.4, 1.2)	0.228
LCI699 0.5/1mg BID – Pbo	-3.4	2.44	(-7.5, 0.6)	0.166
Eplerenone – Pbo	-9.4	2.46	(-13.5, -5.3)	<.001

Using analysis of covariance, adjusting for treatment and country as factors and baseline value as the covariate.

LCI699 plasma pharmacokinetic parameter summary statistics (geometric mean, CV percent) following LCI699 administration on Day 43

Treatment group	N	Cmax (ng/mL)	Tmax* (hr)	AUC_{0-8} (ng*hr/mL)	$AUC_{0-\tau}$ (ng*hr/mL)	t1/2 (hr)
LCI699 0.25mg BID	5	1.04 (46%)	1.00 (1.0-3.0)	5.57 (45%)	6.97 (48%)	5.63 (34%)
LCI699 1mg QD	6**	3.81 (35%)	1.28 (1.0-3.0)	17.66 (34%)	25.18 (38%)	4.07 (17%)
LCI699 0.5/1mg BID	6**	4.25 (34%)	3.00 (1.0-4.0)	22.94 (30%)	31.84 (19%)	4.40 (9%)

* Median (Range)

** N is reduced by 1 for the $AUC_{0-\tau}$ and $t_{1/2}$ parameters

Summary of Efficacy

- None of the LCI699 MSSBP reductions at Week 8 LOCF (primary endpoint) was statistically different from placebo (p-value ≥ 0.10), but these reductions were numerically larger at total daily doses of 1 mg and 2 mg (4.3 mmHg and 3.7 mmHg, respectively, placebo-subtracted) than in the LCI699 0.25 mg BID group (2.6 mmHg).
- Mean reductions from baseline in MSSBP were largest in the eplerenone 50 mg BID group (9.9 mmHg, p = 0.017).
- LCI699 and eplerenone showed modest placebo-adjusted changes from baseline in MSDBP, which included both increases and decreases. However, none was statistically different from placebo (p-value ≥ 0.10).
- All 3 LCI699 dosing regimens showed modest placebo-adjusted mean reductions from baseline to Week 8 LOCF in 24-hour ambulatory SBP (placebo-subtracted reductions of 3.4 to 5.3 mmHg, p > 0.1) and DBP (maximum placebo-subtracted reduction of 3.4 mmHg).
- Placebo-adjusted reductions from baseline were largest in the eplerenone (50 mg BID) group; SBP/DBP decreased by 14.7/9.4 mmHg, p < 0.001 for both.

Safety Results

Number (percent) of patients with adverse events in the most frequently reported (greater than or equal to 2 percent of LCI699 patients) system organ classes (Safety set)

Primary system organ class	LCI699 0.25mg BID N=32 n (%)	LCI699 1mg QD N=26 n (%)	LCI699 0.5/1mg BID N=31 n (%)	LCI699 Total N=89 n (%)	Eplerenone 50mg BID N=33 n (%)	Placebo N=33 n (%)
Any system organ class	15 (46.9)	15 (57.7)	8 (25.8)	38 (42.7)	13 (39.4)	16 (48.5)
Gastrointestinal disorders	5 (15.6)	3 (11.5)	2 (6.5)	10 (11.2)	3 (9.1)	6 (18.2)
General disorders and administration site conditions	2 (6.3)	2 (7.7)	1 (3.2)	5 (5.6)	4 (12.1)	5 (15.2)
Infections and infestations	0	2 (7.7)	0	2 (2.2)	1 (3.0)	1 (3.0)
Injury, poisoning and procedural complications	2 (6.3)	1 (3.8)	0	3 (3.4)	0	3 (9.1)
Investigations	5 (15.6)	2 (7.7)	4 (12.9)	11 (12.4)	1 (3.0)	1 (3.0)
Metabolism and nutrition disorders	1 (3.1)	1 (3.8)	2 (6.5)	4 (4.5)	3 (9.1)	3 (9.1)
Musculoskeletal and connective tissue disorders	2 (6.3)	5 (19.2)	1 (3.2)	8 (9.0)	5 (15.2)	2 (6.1)
Nervous system disorders	1 (3.1)	3 (11.5)	2 (6.5)	6 (6.7)	5 (15.2)	4 (12.1)
Psychiatric disorders	1 (3.1)	1 (3.8)	1 (3.2)	3 (3.4)	1 (3.0)	0
Respiratory, thoracic and mediastinal disorders	3 (9.4)	1 (3.8)	0	4 (4.5)	1 (3.0)	1 (3.0)
Skin and subcutaneous tissue disorders	1 (3.1)	1 (3.8)	2 (6.5)	4 (4.5)	1 (3.0)	1 (3.0)

System organ classes (SOCs) are sorted alphabetically. A patient with multiple adverse events within an SOC is counted only once in the column.

Number (percent) of patients with most common adverse events (greater than or equal to 2 percent of LCI699 patients) by preferred term and treatment group (Safety set)

Preferred term	LCI699 0.25mg BID N=32 n (%)	LCI699 1mg QD N=26 n (%)	LCI699 0.5/1mg BID N=31 n (%)	LCI699 Total N=89 n (%)	Eplerenone 50mg BID N=33 n (%)	Placebo N=33 n (%)
Any preferred term	15 (46.9)	15 (57.7)	8 (25.8)	38 (42.7)	13 (39.4)	16 (48.5)
Hyponatremia*	2 (6.3)	0	3 (9.7)	5 (5.6)	2 (6.1)	0
Blood cortisol decreased	2 (6.3)	1 (3.8)	1 (3.2)	4 (4.5)	0	1 (3.0)
Diarrhea	3 (9.4)	0	0	3 (3.4)	2 (6.1)	1 (3.0)
Muscle spasms	1 (3.1)	2 (7.7)	0	3 (3.4)	4 (12.1)	0
Nausea	1 (3.1)	1 (3.8)	1 (3.2)	3 (3.4)	0	1 (3.0)
Abdominal pain upper	1 (3.1)	1 (3.8)	0	2 (2.2)	0	0
Blood creatinine increased	2 (6.3)	0	0	2 (2.2)	0	0
Blood glucose increased	0	1 (3.8)	1 (3.2)	2 (2.2)	0	0
Dizziness	1 (3.1)	1 (3.8)	0	2 (2.2)	4 (12.1)	1 (3.0)
Dyspepsia	1 (3.1)	0	1 (3.2)	2 (2.2)	0	1 (3.0)
Fatigue	0	1 (3.8)	1 (3.2)	2 (2.2)	3 (9.1)	2 (6.1)
Headache	0	1 (3.8)	1 (3.2)	2 (2.2)	0	2 (6.1)
Hyperhidrosis	0	0	2 (6.5)	2 (2.2)	0	0
Oedema peripheral	1 (3.1)	1 (3.8)	0	2 (2.2)	0	0

Preferred terms are sorted in descending frequency, as reported in column LCI699 Total column.
A patient with multiple adverse events is counted only once in the “Any preferred term” row.
A patient with multiple occurrences of an adverse event is only counted once for this event.
Also includes the code of “Blood sodium decreased”.

Number (%) of patients with deaths, serious adverse events (SAEs), adverse events leading to permanent treatment discontinuations (Safety set)

	LCI699 0.25 BID N=32 n (%)	LCI699 1.0 QD N=26 n (%)	LCI699 0.5/1 BID N=31 n (%)	LCI699 Total N=89 n (%)	Eplerenone 50 BID N=33 n (%)	Placebo N=33 n (%)
Patients with AE(s)	15 (46.9)	15 (57.7)	8 (25.8)	38 (42.7)	13 (39.4)	16 (48.5)
Serious and other significant events						
Deaths	0	0	0	0	0	0
SAEs	0	0	0	0	1 (3.0)	0
AE discontinuations	1 (3.1)	1 (3.8)	0	2 (2.2)	1 (3.0)	2 (6.1)

Dose quantities specified in the column headings are in mg.

Patients with serum potassium, serum sodium, creatinine, BUN and basal cortisol outside pre-specified criteria (Safety set)

Abnormal values*	LCI699 0.25mg BID N=32 n (%)	LCI699 1mg QD N=26 n (%)	LCI699 0.5/1mg BID N=31 n (%)	LCI699 Total N=89 n (%)	Eplerenone 50mg BID N=33 n (%)	Placebo N=33 n (%)
Sodium						
Total	31	26	31	88	32	33
<125mmol/L	0	0	0	0	0	0
<130 and ≥125mmol/L	0	0	0	0	1 (3.1)	0
<135 and ≥130mmol/L	3 (9.7)	2 (7.7)	7 (22.6)	12 (13.6)	3 (9.4)	2 (6.1)
>146mmol/L	0	0	0	0	0	2 (6.1)
Potassium						
Total	31	26	31	88	32	33
<3.5mmol/L	0	0	1 (3.2)	1 (1.1)	0	2 (6.1)
>5.5mmol/L	2 (6.5) †	0	0	2 (2.3) †	0	1 (3.0)
≥6.0mmol/L	2 (6.5) †	0	0	2 (2.3) †	0	0
Creatinine						
Total	31	26	31	88	32	33
>176.8 µmol/L	0	0	0	0	0	0
BUN						
Total	31	26	31	88	32	33
>14.28mmol/L	1 (3.2)	0	0	1 (1.1)	0	1 (3.0)
Cortisol (basal)						
Total	28	26	31	85	32	31
<150nmol/L	3 (10.7)	2 (7.7)	1 (3.2)	6 (7.1)	0	3 (9.7)

* Abnormality refers to extended normal range. The most extreme post-baseline value is used.

† Hemolysis of the sample is suspected. In both patients (3 instances total) a normal potassium (i.e., <5mmol/L) was observed in the subsequent measurements within a week later, while patients remained on study drug.

Number (percent) of patients with cortisol levels below 500 nmol/L at 1hr after ACTH injection at the Week 8 visit (ACTH stimulation test subset)

Threshold	LCI699 0.25mg BID n/N (%)	LCI699 1mg QD n/N (%)	LCI699 0.5/1mg BID n/N (%)	LCI699 Total n/N (%)	Eplerenone 50mg BID n/N (%)	Placebo n/N (%)
<500nmol/L	0/5 (0.0)	1/4 (25.0)	4/6 (66.7)	5/15 (33.3)	0/7 (0.0)	0/7 (0.0)

n=Number of patients meeting the criterion. N=number of patients with a valid result at the visit.

Safety summary

- There were no deaths, and only one serious adverse event (cerebrovascular accident, eplerenone 50 mg BID group) was reported among randomized patients.
- Overall, LCI699 was well tolerated. Five patients discontinued due to a treatment-emergent adverse event or abnormal laboratory value: 2 LCI699 patients (2.2%); 1 eplerenone patient (3.0%); 2 placebo patients (6.1%).
- The percent of patients experiencing an AE during double-blind treatment was comparable among the LCI699 (42.7%), eplerenone (39.4%) and placebo (48.5%) treatment groups. Hyponatremia, diarrhea and muscle spasms were reported more frequently with LCI699 and eplerenone treatment than placebo. Blood cortisol decreased and nausea were also more common with LCI699 treatment than with placebo.
- LCI699 suppressed ACTH-stimulated cortisol responses in a dose-related manner.

Conclusions

- The study suggested that the aldosterone synthase inhibitor LCI699, at total daily doses in the range of 0.5mg to 2.0mg, produced modest reductions in blood pressure in a resistant hypertensive patient population. However, given the sample size of the study, the treatment effects could not be estimated with precision.
- At the range of doses studied, the effects of LCI699 on blood pressure reductions were less than those observed with eplerenone 50 mg BID. Higher LCI699 doses may be necessary to produce blood pressure effects comparable to eplerenone 50 mg BID.
- Other than blunting of the ACTH-stimulated cortisol response, no safety results from the present study would preclude further evaluation of total daily doses up to 2.0 mg daily in a resistant hypertension patient population.

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