Sponsor

Novartis

Generic Drug Name

LCI699

Therapeutic Area of Trial

Clinical pharmacology

Approved Indication

Investigational

Study Number

CLCI699A2215

Title

A phase II, randomized, double-blind, placebo controlled, multi-center study to evaluate the effects of LCI699 on cortisol in patients with hypertension

Phase of Development

Phase II

Study Start/End Dates

14-Jan-2009 to 12-Aug-2009

Study Design/Methodology

This study was a prospective, randomized, double-blind, placebo controlled study of LCI699 administered for 6 weeks to hypertensive patients. Patients with an established diagnosis of essential hypertension currently taking at least one anti-hypertensive treatment and demonstrating elevated blood pressure despite therapy were considered for this trial. Patients on a stable regime of anti-hypertensive medications (limited to ACE inhibitors, ARBs, thiazide diuretics, loop diuretics, beta-blockers, and/or CCBs) for four weeks prior to the screening visit were considered. Patients taking aldosterone receptor antagonists (i.e., spironolactone or eplerenone), direct renin inhibitors or potassium-sparing diuretics (e.g., triamterene or amiloride) within four weeks of screening were excluded from the study. This study was a sequential cohort, escalating dose design with up to 3 potential cohorts. Patients were randomized in a 1:2:2 manner to either placebo or one of two different LCI699 dose levels within a cohort, as follows: the first cohort (Cohort A: placebo, 0.5mg QD, 1.0mg QD); the second cohort (Cohort B1: placebo, 1.0mg BID, 2.0mg

QD); the third cohort (Cohort B: placebo, 1.5mg BID, 3.0mg QD). A dose at which 4 of 12 patients met the ACTH-stimulated cortisol stopping criterion (<400nM at 30 and 60 minutes for an ACTH test at a single visit or at either time point on two consecutive visits) was discontinued and was considered to be at or above the MTD. Upon reaching the MTD, higher dose cohorts were not initiated.

Centres

This study was performed at 9 centers in the United States and 1 center in Iceland.

Publication

In preparation

Objectives

Primary objective

To determine the maximally tolerated dose (MTD) of LCI699 with respect to cortisol suppression following ACTH stimulation in hypertensive patients.

Secondary objective(s)

- To characterize the LCI699 exposure-response relationship on cortisol levels following ACTH stimulation in hypertensive patients
- To characterize the pharmacokinetics of LCI699 in hypertensive patients
- To assess the safety and tolerability of LCI699 in hypertensive patients
- To explore the proportion of patients achieving a successful BP response and BP control

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

The patient's study medication dose was determined during randomization. LCI699 was supplied as 0.5mg and 1.0mg capsules. In the first cohort (A), patients were instructed to take study drug once daily in the morning. In the second cohort (B1), patients received a "Morning" bottle and "Evening" bottle to enable evaluation of once and twice daily dosing regimens. Morning doses were to be administered at approximately 09:00. Evening doses were to be administered at approximately 21:00. Patients were instructed to swallow the capsules whole. Study drug could be taken with or without food. No patients were enrolled into the third cohort (B) because a dose which met the pre-specified criteria in the protocol of an MTD was observed in the second cohort (B1).

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

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

Criteria for Evaluation

Primary variable

Cortisol level in response to ACTH stimulation was measured at, Run-in visit (Visit 2, between Day -14 and -2), and at Visit 5 (Day 7), Visit 6 (Day 28), and Visit 9 (Day 42). MTD was defined by the protocol as the dose at which 4 patients exhibited ACTH-stimulated cortisol results <400nmol/L.

Secondary variables

Office Blood Pressure (OBP) and heart rate were measured at all 12 scheduled office visits.

Safety and tolerability

Safety assessments consisted of collecting all adverse events (AEs), serious adverse events (SAEs) with their severity and relationship to study drug, and pregnancies. They included the regular monitoring of vital signs, height, waist circumference and weight, physical examinations, laboratory evaluations and ECG.

Bioanalytics

Blood samples were collected and processed to determine LCI699 plasma concentrations at various time points.

Statistical Methods

An assessment of differences in the distribution of baseline characteristics across treatments was performed using the chi-squared test for categorical variables (excluding medical histories of low prevalence) and a 1-way ANOVA (F-test) for continuous variables.

A mixed effects regression model was fit to cortisol concentrations following ACTH stimulation. This exposure-response model was used to determine the dose(s) at which no more than 20% of patients were expected to experience cortisol suppression below 400nM. Based on the estimated relationship between the LCI699 dose and cortisol response, the probability of failing the ACTH stimulation test at the time of peak study drug concentration was calculated (both point estimates and 90% prediction intervals) for the LCI699 doses and regimens of interest.

The incidence of adverse events was summarized by system organ classes and preferred term for all treatment groups. Laboratory data were summarized by visit using descriptive statistics, by shift tables describing most extreme values with respect to normal limits during double blind treatment, and by notable changes defined as percentage changes from baseline and pre-specified in the protocol. Furthermore, expanded ranges of interest for key safety parameters were summa-

rized as frequencies.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Able and willing to provide written informed consent prior to study participation.
2. An established diagnosis of hypertension with mean systolic and/or mean diastolic sitting OBP ≥140/90 mmHg and <180/110 mmHg on current antihypertensive treatment measured at Screening (Visit 1, between Days -28 and -14) and confirmed within 2 weeks of randomization at Run-in (Visit 2, between Day -14 and -2).
3. Male or female patients 18 to 75 years of age (inclusive)
   - Female patients of childbearing potential who were willing to use at least two barrier methods of contraception (i.e. IUD, condom with a spermicidal gel, diaphragm, sponge, cervical cap) throughout the study.
   - Female patients of childbearing potential who had a negative pregnancy test at screening and were willing to have a pregnancy test at the end of the study.

   OR:
   - Male subjects who were willing 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 (Visit 12), and refrain from fathering a child or donating sperm in the three (3) months following last study drug administration.
4. Subjects were to weigh at least 50 kg to participate in the study.
5. Morning plasma cortisol (sampled between 08:00 and 09:00) >250 nM and 30 or 60 min post-ACTH plasma cortisol >500 nM at the Run-in visit (Visit 2, between Days -14 and -2).
6. Ability to communicate and willingness to comply with all study requirements.

Exclusion criteria

1. 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).
2. Clinically significant cardiac conduction defects (e.g., 3rd degree atrioventricular [AV] block, left bundle branch block [LBBB], sick sinus syndrome, atrial fibrillation or flutter); familial long QT syndrome or torsades de pointe.
3. Patients with renal impairment (estimated creatinine clearance <50 mL/min by the MDRD formula).
4. Use of oral, parenteral, topical, inhaled or ophthalmic corticosteroids within 4 weeks of randomization.
5. Pregnant or nursing women, where pregnancy was confirmed by an hCG >5mIU/mL at screening (Visit 1, between Days -28 and -14).
6. Use of any of the following medications within four (4) weeks of randomization:
   - Aldosterone receptor inhibitors (i.e., eplerenone & spironolactone)
   - Potassium sparing diuretics (i.e., triamterene & amiloride)

- Direct renin inhibitors (i.e. aliskiren)
- Potassium supplements
- Thyroid medication (except on a stable regimen for at least 3 months prior to Visit 1 (between Days -28 and -14) and is not expected to change during the course of study), estrogen-based and/or androgen-based hormone replacement therapies.
- Cholestyramine and colestipol resins.
- Chronic administration (defined as >3 days per week) of systemically available non-steroidal anti-inflammatory agents (i.e. NSAIDs, COX-2 inhibitors) or >325mg total daily dose (TDD) of aspirin. Topical NSAIDs and daily low dose aspirin (<325mg/day) were allowed.
- Growth hormone or similar drugs
- Class Ia, Ib and Ic or III anti-arrhythmics
- Any antidepressant drugs in the MAO inhibitor class, tricyclics, and venafaxine, duloxetine, and bupropion. Other psychotropic drugs such as benzodiazepines and selective serotonin reuptake inhibitors (SSRIs) were allowed if well tolerated when previously taken and the patient had been on a stable dose for the previous 3 months.
- Chronic administration (defined as >3 days per week) of sympathomimetic drugs such as those found in nasal decongestants, oral decongestants, diet aids and bronchodilators. Doses of sympathomimetic drugs used occasionally were prohibited 24 hours prior to the study visit.
- Ergot and serotonin (5-hydroxytryptamine) receptor agonist preparations.
- Drugs for the treatment of attention deficit hyperactivity disorder (ADHD), including bupropion, desipramine, methylphenidate, amphetamine and atomoxetine.
- Nitrates of any kind.
- Sildenafil and vardenafil were disallowed within 24 hours prior to any scheduled visits. Tadalafil was disallowed within 48 hours prior to any scheduled visit. These drugs could be taken outside of this window.
- Any drug with a known and frequent toxicity to a major organ system within the past 3 months (i.e., cytostatic drugs)

7. Participation in any clinical investigation within 4 weeks prior to randomization or longer if required by local regulations.
8. Any blood donation or significant loss within 4 weeks of randomization; donation of plasma within 7 days prior to randomization.
9. History of malignancy of any organ system within the past 5 years with the exception of localized basal cell skin cancer.
10. Any surgical or medical condition which could significantly alter the absorption, of any drug substance, including 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, currently active inflammatory bowel syndrome.
11. Liver disease such as cirrhosis or chronic active hepatitis.
12. Any of the following significant laboratory abnormalities:

- Serum potassium ≥5.0mEq/L or ≤3.5mEq/L at screening (Visit 1, between Days -28 and -14).
- Serum sodium <135mEq/L at screening (Visit 1, between Days -28 and -14).
- ALT and AST >2.5X upper limit of normal (ULN) at screening (Visit 1, between Days -28 and -14).
- Bilirubin total >2X ULN at screening (Visit 1, between Days -28 and -14).
- Direct bilirubin >ULN at screening (Visit 1, between Days -28 and -14).
- Other clinically significant laboratory abnormalities at screening (Visit 1, between Days -28 and -14), confirmed by repeat measurement.

13. History of active substance abuse (including alcohol) within the past 2 years.
14. History of hypersensitivity to any of the study drugs or to components in the study drug.
15. 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).
16. History of heart failure (NYHA Class II-IV).
17. Clinically significant valvular heart disease.
18. Type 1 diabetes.
19. Type 2 diabetes mellitus with poor glucose control as defined by HbA1c >9%.
20. Any surgical or medical condition, which in the opinion of the investigator, could place the patient at higher risk from his/her participation in the study, or was likely to prevent the patient from complying with the requirements of the study, completing the study or jeopardize the evaluation of efficacy or safety.
21. Potent CYP3A4 inhibitors: Treatment with the following potent CYP3A4 inhibitors during the study period: ketoconazole, itraconazole, nefazodone, troleandomycin, clarithromycin, ritonavir and nelfinavir, as well as other drugs labeled as potent CYP3A4 inhibitors including consumption of grapefruit juice >1 quart/day (approximately 1 liter).
22. History or evidence of a secondary form of hypertension, including but not limited to any of the following: renal parenchymal hypertension, renovascular hypertension, coarctation of the aorta, primary hyperaldosteronism, unilateral or bilateral renal artery stenosis, Cushing's disease, pheochromocytoma, polycystic kidney disease, drug-induced hypertension, etc.
23. Arm circumference <24 or >42 cm (to facilitate ABPM assessment).
24. Subjects who performed alternating shift or night work.
25. Use of hormonal contraceptives.

Number of Subjects (Randomized set)

Disposition Reason	LCI699 0.5mg QD N=12 n (%)	LCI699 1.0mg QD N=12 n (%)	LCI699 1.0mg BID N=13 n (%)	LCI699 2.0mg QD N=13 n (%)	Placebo N=13 n (%)	Overall Total N=63 n (%)
Completed	10 (83.3)	9 (75.0)	9 (69.2)	1 (7.7)	11 (84.6)	40 (63.5)
Discontinued	2 (16.7)	3 (25.0)	4 (30.8)	12 (92.3)	2 (15.4)	23 (36.5)
Adverse Event(s)	1 (8.3)	1 (8.3)	1 (7.7)	0	0	3 (4.8)
Low ACTH-stimulated cortisol	0	1 (8.3)	2 (15.4)	4 (30.8)	0	7 (11.1)
Subject withdrew consent	1 (8.3)	1 (8.3)	0	0	0	2 (3.2)
Lost to follow-up	0	0	1 (7.7)	1 (7.7)	1 (7.7)	3 (4.8)
Dose arm exceeds MTD	0	0	0	7 (53.8)	0	7 (11.1)
Protocol deviation	0	0	0	0	1 (7.7)	1 (1.6)

Categories are mutually exclusive.

Demographic and Background Characteristics

Demographic variable	LCI699 0.5mg QD N=12	LCI699 1.0mg QD N=12	LCI699 1.0mg BID N=13	LCI699 2.0mg QD N=13	Placebo N=13	Overall Total N=63
Age (years)						
Mean	56.1	54.2	57.9	56.2	56.8	56.3
SD	6.37	16.01	9.09	10.37	10.08	10.52
Sex - n (%)						
Male	8 (66.7)	7 (58.3)	10 (76.9)	8 (61.5)	9 (69.2)	42 (66.7)
Female	4 (33.3)	5 (41.7)	3 (23.1)	5 (38.5)	4 (30.8)	21 (33.3)
Race - n (%)						
Caucasian	5 (41.7)	7 (58.3)	7 (53.8)	8 (61.5)	6 (46.2)	33 (52.4)
Black	5 (41.7)	4 (33.3)	5 (38.5)	5 (38.5)	6 (46.2)	25 (39.7)
Asian	2 (16.7)	1 (8.3)	1 (7.7)	0	1 (7.7)	5 (7.9)

Demo-graphic variable	LCI699 0.5mg QD N=12	LCI699 1.0mg QD N=12	LCI699 1.0mg BID N=13	LCI699 2.0mg QD N=13	Placebo N=13	Overall-Total N=63
Mean sitting systolic blood pressure (mmHg)						
Mean	151.1	149.4	145.2	146.2	140.2	146.3
SD	12.23	13.22	12.15	11.02	10.57	12.07
Mean sitting diastolic blood pressure (mmHg)						
Mean	87.8	90.4	88.9	85.6	86.8	87.8
SD	12.68	10.60	8.75	10.56	8.17	10.03
Mean sitting pulse (bpm)						
Mean	64.9	76.4	76.7	62.5	69.8	70.1
SD	12.98	12.30	10.95	4.94	11.08	11.95
Baseline GFR (mL/min)						
Mean	89.5	89.1	81.8	78.4	85.8	84.8
SD	18.90	18.46	17.08	18.03	28.15	20.38

Primary Objective Result(s)

Between treatment analysis for cortisol at 1hr after ACTH injection (Safety analysis set)

Visit	Treatment group	n	Mean	SE	95% CI
Day 7	LCI699 0.5mg QD	11	690.00	32.288	(625.27, 754.73)
	LCI699 1.0mg QD	12	669.40	30.903	(607.44, 731.35)
	LCI699 1.0mg BID	12	625.06	30.965	(562.98, 687.14)
	LCI699 2.0mg QD	13	562.04	30.325	(501.24, 622.84)
	Placebo	12	799.06	31.161	(736.59, 861.54)

	Pairwise comparisons vs Placebo	Difference of means	SE	95% CI	Two-sided P-value
	LCI699 0.5mg QD - Placebo	-109.06	44.703	(-198.69, -19.44)	0.018
	LCI699 1.0mg QD - Placebo	-129.67	44.031	(-217.95, -41.39)	0.005
	LCI699 1.0mg BID - Placebo	-174.00	43.689	(-261.59, -86.41)	<.001
	LCI699 2.0mg QD - Placebo	-237.02	44.098	(-325.43, -148.61)	<.001

Visit	Treatment group	n	Mean	SE	95% CI
Day 28	LCI699 0.5mg QD	10	634.87	32.181	(570.20, 699.54)
	LCI699 1.0mg QD	11	573.41	30.642	(511.83, 634.98)
	LCI699 1.0mg BID	12	554.79	29.466	(495.58, 614.01)
	LCI699 2.0mg QD	10	539.09	32.826	(473.12, 605.06)
	Placebo	12	804.86	29.786	(745.00, 864.71)

	Pairwise comparisons vs	Difference	SE	95% CI	Two-

	Placebo		of means			sided P-value
	LCI699 0.5mg QD - Placebo		-169.99	44.081	(-258.57, -81.41)	<.001
	LCI699 1.0mg QD - Placebo		-231.45	42.848	(-317.55, -145.34)	<.001
	LCI699 1.0mg BID - Placebo		-250.06	41.535	(-333.53, -166.60)	<.001
	LCI699 2.0mg QD - Placebo		-265.77	45.116	(-356.43, -175.10)	<.001

Visit	Treatment group	n	Mean	SE	95% CI
Day 30 (T)	LCI699 0.5mg QD	10	662.99	31.412	(599.72, 726.26)
	LCI699 1.0mg QD	10	628.28	31.382	(565.07, 691.48)
	LCI699 1.0mg BID	12	559.16	28.672	(501.41, 616.90)
	LCI699 2.0mg QD	8	560.98	35.212	(490.06, 631.90)
	Placebo	11	811.39	30.203	(750.56, 872.22)

	Pairwise comparisons vs Placebo	Difference of means	SE	95% CI	Two-sided P-value
	LCI699 0.5mg QD - Placebo	-148.40	43.849	(-236.71, -60.08)	0.001
	LCI699 1.0mg QD - Placebo	-183.11	43.785	(-271.30, -94.92)	<.001
	LCI699 1.0mg BID - Placebo	-252.23	41.388	(-335.59, -168.87)	<.001
	LCI699 2.0mg QD - Placebo	-250.41	46.771	(-344.61, -156.21)	<.001

Visit	Treatment group	n	Mean	SE	95% CI
Day 42	LCI699 0.5mg QD	8	647.51	45.593	(555.36, 739.65)

LCI699 1.0mg QD	8	626.08	45.441	(534.24, 717.92)
LCI699 1.0mg BID	12	539.68	37.146	(464.61, 614.76)
LCI699 2.0mg QD	7	479.91	48.865	(381.15, 578.67)
Placebo	11	812.91	39.096	(733.90, 891.93)

Pairwise comparisons vs Placebo	Difference of means	SE	95% CI	Two-sided P-value
LCI699 0.5mg QD - Placebo	-165.41	60.436	(-287.55, -43.26)	0.009
LCI699 1.0mg QD - Placebo	-186.84	60.116	(-308.34, -65.34)	0.003
LCI699 1.0mg BID - Placebo	-273.23	53.690	(-381.74, -164.72)	<.001
LCI699 2.0mg QD - Placebo	-333.00	63.068	(-460.47, -205.54)	<.001

Using analysis of covariance, adjusting for treatment as the factor and baseline value as the covariate.
Day 30 test was done prior to study drug dosing on that day. At all other visits the test was done 2 hours after study drug dosing (approx T_{max}).

Number (percent) of patients with cortisol levels below 400nmol/L at 1hr after ACTH injection (Safety set)

Visit	LCI699 0.5mg QD N=12 n/N (%)	LCI699 1.0mg QD N=12 n/N (%)	LCI699 1.0mg BID N=13 n/N (%)	LCI699 2.0mg QD N=13 n/N (%)	LCI699 Total N=50 n/N (%)	Placebo N=13 n/N (%)
Day 7	0/11 (0.0)	0/12 (0.0)	0/12 (0.0)	2/13 (15.4)	2/48 (4.2)	0/12 (0.0)
Day 28	0/10 (0.0)	0/11 (0.0)	0/12 (0.0)	0/10 (0.0)	0/43 (0.0)	0/12 (0.0)
Day 30 (trough)	0/10 (0.0)	0/10 (0.0)	0/12 (0.0)	0/ 8 (0.0)	0/40 (0.0)	0/11 (0.0)
Day 42	0/ 8 (0.0)	0/ 8 (0.0)	2/12 (16.7)	2/ 7 (28.6)	4/35 (11.4)	0/11 (0.0)
Any time during treatment	0/12 (0.0)	0/12 (0.0)	2/13 (15.4)	4/13 (30.8)	6/50 (12.0)	0/13 (0.0)

Day 30 test was done prior to study drug dosing on that day. At all other visits the test was done 2 hours after study drug dosing (approx T_{max}).

Secondary Objective Result(s)

Geometric mean (CV percent) LCI699 plasma concentrations three hours post LCI699 administration on Day 7

Treatment group	N	Geometric mean LCI699 concentration (ng/mL)
LCI699 0.5mg QD	11	1.51 (36%)
LCI699 1.0mg QD	12	2.88 (41%)
LCI699 1.0mg BID	13	3.92 (31%)
LCI699 2.0mg QD	13	6.73 (23%)

Between treatment analysis for change from baseline in mean sitting systolic blood pressure (MSSBP) at Day 43 LOCF (Full analysis set)

Treatment group	N	Mean change from baseline	SE	95% CI
LCI699 0.5mg QD	12	-11.2	3.95	(-19.1, -3.3)
LCI699 1.0mg QD	12	-12.4	3.91	(-20.2, -4.5)
LCI699 1.0mg BID	13	-14.9	3.73	(-22.3, -7.4)
LCI699 2.0mg QD	13	-13.3	3.73	(-20.7, -5.8)
Placebo	13	-2.4	3.84	(-10.0, 5.3)

Pairwise comparisons vs Placebo	Mean difference in change from baseline	SE	95% CI	Two-sided P-value
LCI699 0.5mg QD - Placebo	-8.8	5.62	(-20.1, 2.4)	0.122
LCI699 1.0mg QD - Placebo	-10.0	5.56	(-21.1, 1.1)	0.077
LCI699 1.0mg BID - Placebo	-12.5	5.33	(-23.2, -1.9)	0.022
LCI699 2.0mg QD - Placebo	-10.9	5.35	(-21.6, -0.2)	0.046

Using analysis of covariance, adjusting for treatment as the factor and baseline value as the covariate. P-values not adjusted for multiple comparisons.

Between treatment analysis for change from baseline in mean sitting diastolic blood pressure (MSDBP) at Day 43 LOCF (Full analysis set)

Treatment group	n	Mean change from baseline	SE	95% CI
LCI699 0.5mg QD	12	-3.9	2.42	(-8.7, 0.9)
LCI699 1.0mg QD	12	-8.5	2.43	(-13.4, -3.7)
LCI699 1.0mg BID	13	-8.6	2.33	(-13.3, -4.0)
LCI699 2.0mg QD	13	-3.9	2.34	(-8.6, 0.8)
Placebo	13	0.6	2.33	(-4.1, 5.2)

Pairwise comparisons vs Placebo	Mean difference in change from baseline	SE	95% CI	Two-sided P-value
LCI699 0.5mg QD - Placebo	-4.5	3.35	(-11.2, 2.3)	0.188
LCI699 1.0mg QD - Placebo	-9.1	3.37	(-15.9, -2.3)	0.009
LCI699 1.0mg BID - Placebo	-9.2	3.29	(-15.8, -2.6)	0.007
LCI699 2.0mg QD - Placebo	-4.5	3.29	(-11.1, 2.1)	0.179

Using analysis of covariance, adjusting for treatment as the factor and baseline value as the covariate.
P-values not adjusted for multiple comparisons.

Number (percent) of patients achieving a blood pressure response and blood pressure control at the Day 43 LOCF Visit (Full analysis set)

	LCI699 0.5mg QD N=12 n/N (%)	LCI699 1.0mg QD N=12 n/N (%)	LCI699 1.0mg BID N=13 n/N (%)	LCI699 2.0mg QD N=13 n/N (%)	Placebo N=13 n/N (%)
SBP Response (<140mmHg or reduction from baseline >=20mmHg)	7/12 (58.3)	6/12 (50.0)	9/13 (69.2)	10/13 (76.9)	8/13 (61.5)
DBP Response (<90mmHg or reduction from baseline >=10mmHg)	7/12 (58.3)	8/12 (66.7)	13/13 (100.0)	10/13 (76.9)	8/13 (61.5)
SBP Control (<140mmHg for non-diabetics and <130mHg for diabetics)	6/12 (50.0)	5/12 (41.7)	8/13 (61.5)	10/13 (76.9)	7/13 (53.8)

DBP Control (<90mmHg for non-diabetics and <80mHg for diabetics)	7/12 (58.3)	8/12 (66.7)	10/13 (76.9)	10/13 (76.9)	6/13 (46.2)
Both SBP and DBP Control	5/12 (41.7)	5/12 (41.7)	7/13 (53.8)	9/13 (69.2)	5/13 (38.5)

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

Summary of pharmacology

- LCI699 exposures increased with dose across the dose range studied.
- LCI699 suppressed ACTH-stimulated cortisol responses in an exposure-dependent and time-dependent manner, approaching steady-state by Day 28. The effects of LCI699 on ACTH-stimulated cortisol were reversible, with recovery apparent within one-to-two weeks. There was no reduction in basal cortisol levels and there were no signs/symptoms of adrenal insufficiency observed across the dose range of LCI699 studied.
- Given the protocol-defined MTD of 20% of patients experiencing ACTH-stimulated cortisol <400nmol/L, the MTD, based on the exposure-response analysis, is estimated to be 1.30mg QD with a 90% prediction interval of 0.88mg QD to 1.81mg QD.
- LCI699 showed statistically significant reductions from baseline in mean office blood pressures compared to placebo.

Safety Results

Adverse events overall and frequently affected system organ classes - n (percent) of patients (greater than or equal to 2 in any SOC) (Safety set)

System Organ Class	LCI699 0.5mg QD N=12 n (%)	LCI699 1.0mg QD N=12 n (%)	LCI699 1.0mg BID N=13 n (%)	LCI699 2.0mg QD N=13 n (%)	LCI699 Total N=50 n (%)	Placebo N=13 (%)
Total AEs for any primary system organ class	6 (50.0)	9 (75.0)	10 (76.9)	10 (76.9)	35 (70.0)	10 (76.9)
Nervous system disorders	3 (25.0)	4 (33.3)	6 (46.2)	2 (15.4)	15 (30.0)	4 (30.8)
Gastrointestinal disorders	2 (16.7)	3 (25.0)	6 (46.2)	1 (7.7)	12 (24.0)	4 (30.8)
Investigations	2 (16.7)	1 (8.3)	3 (23.1)	5 (38.5)	11 (22.0)	0
Infections and infestations	0	1 (8.3)	3 (23.1)	4 (30.8)	8 (16.0)	1 (7.7)
General disorders and site administration conditions	1 (8.3)	4 (33.3)	2 (15.4)	0	7 (14.0)	1 (7.7)

Musculoskeletal and connective tissue disorders	1 (8.3)	3 (25.0)	2 (15.4)	1 (7.7)	7 (14.0)	1 (7.7)
Metabolism and nutrition disorders	1 (8.3)	1 (8.3)	1 (7.7)	0	3 (6.0)	2 (15.4)
Psychiatric disorders	1 (8.3)	1 (8.3)	0	0	2 (4.0)	1 (7.7)

Adverse events overall and most frequently occurring AEs - n (percent) of patients (greater than or equal to 2 in any preferred term) (Safety set)

Preferred Term	LCI699 0.5mg QD N=12 n (%)	LCI699 1.0mg QD N=12 n (%)	LCI699 1.0mg BID N=13 n (%)	LCI699 2.0mg QD N=13 n (%)	LCI699 Total N=50 n (%)	Placebo N=13 n (%)
Total AEs for any preferred term	6 (50.0)	9 (75.0)	10 (76.9)	10 (76.9)	35 (70.0)	10 (76.9)
Headache	1 (8.3)	4 (33.3)	2 (15.4)	2 (15.4)	9 (18.0)	3 (23.1)
ACTH stimulation test abnormal	0	1 (8.3)	2 (15.4)	4 (30.8)	7 (14.0)	0
Dizziness	2 (16.7)	0	3 (23.1)	0	5 (10.0)	1 (7.7)
Diarrhea	0	1 (8.3)	2 (15.4)	0	3 (6.0)	3 (23.1)
Dyspepsia	1 (8.3)	1 (8.3)	0	1 (7.7)	3 (6.0)	1 (7.7)
Hyponatraemia	1 (8.3)	1 (8.3)	1 (7.7)	0	3 (6.0)	1 (7.7)
Nausea	1 (8.3)	1 (8.3)	1 (7.7)	0	3 (6.0)	0
Sinusitis	0	0	1 (7.7)	2 (15.4)	3 (6.0)	0
Arthritis	0	0	1 (7.7)	1 (7.7)	2 (4.0)	0
Back pain	0	1 (8.3)	1 (7.7)	0	2 (4.0)	0
Blood creatine phosphokinase increased	1 (8.3)	0	1 (7.7)	0	2 (4.0)	0
Chest discomfort	0	1 (8.3)	1 (7.7)	0	2 (4.0)	0
Fatigue	0	1 (8.3)	1 (7.7)	0	2 (4.0)	0
Nasopharyngitis	0	1 (8.3)	1 (7.7)	0	2 (4.0)	1 (7.7)
Vomiting	0	2 (16.7)	0	0	2 (4.0)	1 (7.7)

Patients with specified criteria in selected laboratory parameters by treatment group (safety set)

Abnormal values	LCI699 0.5mg QD N=12 n (%)	LCI699 1.0mg QD N=12 n (%)	LCI699 1.0mg BID N=13 n (%)	LCI699 2.0mg QD N=13 n (%)	LCI699 Total N=50 n (%)	Placebo N=13 n (%)
Sodium						
Total	12	12	13	13	50	13
<125mmol/L	0	0	0	0	0	0
≥125 and <130mmol/L	0	1 (8.3)	0	0	1 (2.0)	0
≥130 and <135mmol/L	1 (8.3)	0	2 (15.4)	0	3 (6.0)	1 (7.7)
>146mmol/L	0	0	0	0	0	0
Potassium						
Total	12	12	13	13	50	13
<3.5mmol/L	0	0	0	0	0	1 (7.7)
>5.5mmol/L	1 (8.3)	0	1 (7.7)	0	2 (4.0)	0
≥6.0mmol/L	0	0	0	0	0	0
Creatinine						
Total	12	12	13	13	50	13
>176.8 µmol/L	0	0	1 (7.7)	1 (7.7)	2 (4.0)	0
BUN						
Total	12	12	13	13	50	13
>14.28mmol/L	1 (8.3)	0	3 (23.1)	3 (23.1)	7 (14.0)	1 (7.7)

Most extreme post-baseline value is used.

Summary of safety

- The incidence of total AEs was similar for all LCI699 treatment groups and placebo.
- The incidence of hyperkalemia and hyponatremia was similar when comparing all doses of LCI699 to placebo.
- No deaths or serious adverse events were reported in this study.
- Nine patients (all randomized to LCI699) were discontinued from the study due to AEs, including 6 for the protocol-specified event of low ACTH-stimulated cortisol.

  Three others were discontinued for the lab abnormality of hyponatremia, one in combination with hyperkalemia, and another in combination with tremor.

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