Sponsor

Novartis

Generic Drug Name

LCI699

Therapeutic Area of Trial

Stage 1-2 hypertension

Approved Indication

Investigational

Study Number

CLCI699A2201

Title

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

Phase of Development

Phase II

Study Start/End Dates

11-Sep-2008 to 02-Jul-2009

Study Design/Methodology

This was an 8-week multicenter, randomized, double-blind, placebo and active controlled, parallel group study in patients with seated diastolic blood pressures (BP) of ≥ 95 and < 110 mm Hg. Ambulatory BP monitoring was also performed at baseline and at 8 weeks. Following a 2-week washout and a two-week single blind placebo run-in period, 524 patients were randomized 1:1:1:1:1:1 to LCI699 0.25 mg QD, 0.5 mg QD, 1.0 mg QD, 0.5 mg BID, eplerenone 50 mg BID, or placebo for 8 weeks. The primary objective was to evaluate the effects of LCI699 on clinic diastolic blood pressure versus placebo. Following the 8-week double-blind period, patients were re-randomized in a 1:1 ratio to either continue the originally randomized treatment or receive placebo for one week.

Centres

84 study centers in 9 countries: Argentina (7), Australia (6), France (12), Germany (15), Netherlands (8), Romania (3), Spain (8), Sweden (7), United States (18).

Publication

Ongoing

Objectives

Primary objective

To evaluate the efficacy of any of 4 dose regimens (0.25 mg QD, 0.5 mg QD, 1.0 mg QD and 0.5 mg BID) of LCI699 in patients with essential hypertension by testing the hypothesis that the reduction in mean sitting diastolic blood pressure (MSDBP) 23-26 hours post dose (11-14 hours post BID dosing) with LCI699 is superior to that with placebo after 8 weeks treatment.

Secondary objective(s)

- To evaluate the efficacy of any of 4 dose regimens of LCI699 by testing the hypothesis that the reduction in mean sitting systolic blood pressure (MSSBP) 23-26 hours post dose (11-14 hours post BID dosing) with LCI699 is superior to that with placebo after 8 weeks treatment.
- To evaluate the safety and tolerability of 4 dose regimens of LCI699 compared to placebo over 8 weeks treatment.
- To evaluate the dose-response relationship of LCI699 in the reduction in MSDBP and MSSBP after 8 weeks treatment.
- To evaluate whether the changes in mean 24 hours, mean daytime and mean nighttime SBP and DBP with 4 dose regimens of LCI699 are superior to those with placebo after 8 weeks treatment.
- To assess the functional consequences of aldosterone inhibition by evaluating the efficacy and safety of LCI699 compared to eplerenone 50 mg BID after 8 weeks treatment.

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), the double-blind treatment period (8 weeks), and the double-blind randomized withdrawal period (1 week) of the trial, 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

Primary variables

The following efficacy assessments were performed:

Automated arterial BP determinations were made with an automated BP device (such as the Omron BP monitor) in accordance with the Guidelines for management of hypertension: report of the 4th working party of the British Hypertension Society, 2004-BHS IV. Sitting and standing BP measurements were performed at screening through the end of study at every visit. Standing BP measurements were used for safety analysis only. Sitting and standing BP measurements were performed at trough (23-26 hours post morning dose or 11-14 hours post bid dosing).

Secondary variables

Twenty-four hour ambulatory blood pressure monitoring was performed in all eligible patients twice during the study. The first monitoring period began at the completion of the single-blind run-in period prior to randomization and the second after 8 weeks of double-blind treatment. BP and heart rate were measured using the ABPM device at study specified intervals. ABPM readings/data was analyzed by a central laboratory.

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 (including hormonal profile and ACTH stimulation cortisol testing) and ECG.

Pharmacology

None

Other

Bioanalytics: Sparse blood sampling was performed in a subset of patients (approximately 20 patients per treatment arm) participating in the ACTH stimulation cortisol test sub-study. Blood samples (1 mL each) were drawn at 3 time points from each patient. There were two sampling days; the first 2 samples were collected during the second ACTH stimulation test performed up to 7 days prior to Visit 7 and the last sample was collected on the day of Visit 7: Sample 1: 0 to 2 hr post dose but before ACTH injection (Pre-ACTH). Sample 2: 3 hr post dose or 1 hr post ACTH injection (Post-ACTH). Sample 3: 12 hr post 0.5 mg BID, or 24 hr post 0.25 mg QD, 0.5 mg QD or 1 mg QD (Trough).

Statistical Methods

The analysis of the primary objective used a multiplicity adjusted comparison of optimal contrasts for five candidate shapes of dose-response or efficacy of the single BID arm compared to placebo to establish efficacy of treatment with LCI699 compared to placebo. This evaluation established a significant dose-response signal of treatment with LCI699 dosed QD compared to placebo, but treatment with LCI699 dosed BID failed to reach significance. Estimates of the efficacy response for all treatments and comparisons between these treatments were derived from the best fitting model, including baseline and region as covariates. This method was applied to the evaluation of changes in MSDBP (primary efficacy variable) for both Full Analysis and Per Protocol sets as well as to MSSBP (secondary efficacy variable).

Secondary efficacy analyses: Evaluation of all BP change measurements using Analysis of Covariance, including the same covariates as for the primary analysis.

All efficacy measurements imputed missing data by using the Last Observation Carried Forward. In order to evaluate the sensitivity of results to this method of handling missing data, the primary efficacy analysis was repeated using multiple imputations.

Safety Analyses: Incidence of adverse events were summarized by system organ classes and preferred term for all treatment groups, both for the core and randomized withdrawal periods. 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 summarized as frequencies. These analyses were performed for measurements collected during the core treatment period and when applicable during randomized withdrawal. In addition, frequencies of ACTH stimulated cortisol measurements below relevant thresholds were summarized and descriptive statistics were provided. An additional analysis which compared LCI699 to non-LCI699 groups to evaluate the dose-response signal of cortisol levels after ACTH stimulation using the last on drug value collected was also provided.

Study Population: Inclusion/Exclusion Criteria and Demographics

Inclusion criteria

1. Male and non-fertile females.
2. Age from 18 up to 75 years inclusive.
3. Patients with mild-to-moderate uncomplicated essential hypertension, untreated including newly diagnosed and/or those with known hypertension history but who have not been treated for at least 4 weeks prior to Visit 1, or treated who are currently taking antihypertensive therapy (monotherapy or combination therapy of 2 drugs). Therapy with a fixed dose combination of two active substances is considered 2 drugs
4. Untreated or treated patients must meet the following office BP criteria:
   - Untreated patients must have a MSDBP ≥ 95 mm Hg and < 110 mmHg at Visits 1-3.
   - Treated patients must have a MSDBP ≥ 90 mmHg and < 110 mmHg at Visits 1 (screening) & 2 (after washout) and a MSDBP ≥ 95 mmHg and < 110 mmHg at Visit 3.
5. Ability to communicate and comply with all study requirements and demonstrating a good medication compliance (≥ 80% compliance rate) during the run-in period.

Exclusion criteria

1. Women of child bearing potential, pregnant or nursing women or women on hormone replacement therapy.
2. Severe hypertension (MSDBP ≥ 110 mmHg and/or MSSBP ≥ 180 mmHg).
3. History or evidence of a secondary form of hypertension.
4. Known moderate or malignant retinopathy.
5. History of angina pectoris, myocardial infarction, coronary bypass surgery, ischemic heart disease, surgical or percutaneous arterial intervention of any kind (coronary, carotid or peripheral vessels), stroke, transient ischemic attack (TIA), carotid artery stenosis, aortic aneurysm or peripheral arterial disease.
6. Type 1 or type 2 diabetes mellitus.
7. The following cardiac related conditions: clinically significant valvular heart disease, previous or current diagnosis of congestive heart failure (NYHA class II-IV), history or current diagnosis of the following cardiac electric abnormalities indicating significant risk of safety for patients participating in the study such as: second or third degree AV block without a pacemaker, concomitant clinically significant cardiac arrhythmias, history of familial long QT syndrome or family history of *torsade de pointe*.
8. History of malignancy of any organ system, treated or untreated, within the past 5 years, whether or not there was evidence of local recurrence or metastases, with the exception of localized basal cell carcinoma of the skin.
9. Liver disease such as cirrhosis or chronic active hepatitis.
10. Any surgical or medical conditions that may have significantly altered the absorption, distribution, metabolism or excretion of any drug substance,
11. Any surgical or medical conditions, not identified in the protocol that in the opinion of the investigator or the Novartis monitor placed 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 or completing the trial period.

12. Patients unwilling or not able to discontinue safely the use of current antihypertensive medications during the study period, as required by the protocol. Administration of any agent indicated for the treatment of hypertension after Visit 1, with the permitted exception of those antihypertensive medications requiring tapering down commencing at Visit 1 and completing by Visit 2.
13. Any contraindication or history of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.
14. Chronic oral or parenteral corticosteroid treatment (≥ 7 consecutive days of treatment) within 4 weeks prior to Visit 1.
15. Treatment with potassium supplement or potassium sparing diuretics (e.g. amiloride, spironolactone, triamterene) required during the course of study.
16. 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).
17. Use of other investigational drugs at Visit 1, or within 30 days or 5 half-lives of Visit 1, whichever was longer, unless local health authority guidelines mandated a longer period.
18. Any of the following significant laboratory abnormalities: serum potassium > 5.2 mEq/L or < 3.5 mEq/L at Visit 1, serum sodium < 132 mEq/L at Visit 1, ALT or AST > 2 times the upper limit of the normal range (ULN) at Visit 1, bilirubin (total) > 1.5 x ULN at Visit 1, MDRD (Modification of Diet in Renal Disease) eGFR < 60 ml/min/1.73 m^2 at Visit 1. Other clinically significant laboratory abnormalities, confirmed by repeated measurements, at Visit 1.
19. History of active substance abuse (including alcohol) within the past 2 years and potentially unreliable patients.
20. Patients with night-shift employment.
21. Persons directly involved in the execution of this clinical study.
22. Arm circumference <24 cm or > 42 cm, due to ABPM assessment.

Number of Subjects (Randomized set)

Disposition	LCI699 0.25 QD N=92 n (%)	LCI699 0.5 QD N=88 n (%)	LCI699 1.0 QD N=86 n (%)	LCI699 0.5 BID N=97 n (%)	Eple-renone 50 BID N=84 n (%)	Placebo N=77 n (%)	Total N=524 n (%)
Continue into Randomized withdrawal pe-riod	84 (91.3)	81 (92.0)	77 (89.5)	90 (92.8)	75 (89.3)	67 (87.0)	474 (90.5)
Discontinued Total	8 (8.7)	6 (6.8)	9 (10.5)	7 (7.2)	9 (10.7)	10 (13.0)	49 (9.4)
Reason for discontinuation							
Unsatisfactory therapeutic ef-fect	3 (3.3)	2 (2.3)	4 (4.7)	0	3 (3.6)	5 (6.5)	17 (3.2)
Subject with-drew consent	3 (3.3)	0	2 (2.3)	3 (3.1)	1 (1.2)	3 (3.9)	12 (2.3)
Adverse Event(s)	2 (2.2)	1 (1.1)	1 (1.2)	3 (3.1)	2 (2.4)	1 (1.3)	10 (1.9)
Lost to follow-up	0	2 (2.3)	1 (1.2)	0	2 (2.4)	1 (1.3)	6 (1.1)
Administrative problems	0	0	1 (1.2)	1 (1.0)	0	0	2 (0.4)
Abnormal labor-atory value(s)	0	0	0	0	1 (1.2)	0	1 (0.2)
Abnormal test procedure re-sult(s)	0	1 (1.1)	0	0	0	0	1 (0.2)

Dose quantities specified in the column headings are in mg. Percentages are calculated using the randomized set as the denominator. Only one reason for discontinuation is selected for each patient in the row discontinued total.

Demographic and Background Characteristics

	LCI699 0.25 QD (N=92)	LCI699 0.5 QD (N=87)	LCI699 1.0 QD (N=86)	LCI699 0.5 BID (N=96)	Eplerenone 50 BID (N=84)	Placebo (N=77)
Age (years) - (Mean [SD])	53.9 (10.5)	54.8 (7.8)	54.5 (9.7)	54.4 (10.8)	55.3 (9.1)	53.9 (8.7)
< 65 years – *n* (%)	75 (81.5)	79 (90.8)	75 (87.2)	78 (81.3)	68 (81.0)	67 (87.0)
≥ 65 years – *n* (%)	17 (18.5)	8 (9.2)	11 (12.8)	18 (18.8)	16 (19.0)	10 (13.0)
Gender – *n* (%)						

Male	63 (68.5)	58 (66.7)	55 (64.0)	63 (65.6)	56 (66.7)	46 (59.7)
Female	29 (31.5)	29 33.3)	31 (36.0)	3 (34.4)	28 (33.3)	31 (40.3)
Race – *n* (%)						
Caucasian	86 (93.5)	76 (87.4)	77 (89.5)	85 (88.5)	73 (86.9)	70 (90.9)
Black	5 (5.4)	11 (12.6)	8 (9.3)	10 (10.4)	10 (11.9)	5 (6.5)
Asian	1 (1.1)	0	1 (1.2)	1 (1.0)	1 (1.2)	1 (1.3)
Blood Pressures – (mm Hg)						
Clinic SBP – mean (SD)	157.7 (12.2)	157.0 (11.6)	159.2 (10.4)	158.5 (11.0)	158.2 (10.9)	156.7 (10.1)
Clinic DBP – mean (SD)	100.4 (3.9)	99.9 (3.3)	100.0 (3.6)	100.2 (3.4)	100.4 (3.6)	100.5 (3.8)
	N=62	N=59	N=68	N=70	N=57	N=52
24-h ambulatory SBP – mean (SD)	140.6 (10.5)	139.8 (13.3)	142.6 (11.0)	142.0 (10.8)	143.1 (14.3)	141.6 (12.5)
24-h ambulatory DBP – mean (SD)	89.4 (9.3)	88.8 (8.3)	90.4 (7.7)	91.2 (8.3)	90.8 (9.4)	89.5 (10.4)
Mean Duration of hyperten-sion (yrs)	6.3	6.7	7.3	6.2	8.1	5.3
eGFR (mL/min/ 1.73 m^2) – mean (SD)	86.3 (15.6)	84.5 (15.1)	82.1 (14.4)	86.5 (17.0)	84.2 (12.8)	85.4 (15.2)

Primary Objective Result(s)

Mean change in sitting diastolic blood pressure after 8 weeks

Treatment group	n	Mean mmHg change from baseline (SE)	95% CI
Placebo[1]	76	-3.22 (0.87)	(-4.93, -1.51)
LCI699 0.25QD[1]	92	-4.47 (0.60)	(-5.66, -3.28)
LCI699 0.50QD[1]	85	-5.50 (0.57)	(-6.62, -4.38)
LCI699 1.0QD[1]	86	-7.11 (0.88)	(-8.84, -5.39)
LCI699 0.50BID[2]	96	-4.25 (0.95)	(-6.12, -2.39)
Eplerenone 50BID[2]	84	-7.49 (0.97)	(-9.39, -5.58)

Pairwise comparison	Mean mmHg difference in change from baseline (SE)	95% CI for Mean difference	Two-sided p-value*
LCI699 0.25QD - Placebo	-1.25 (0.43)	(-2.10, -0.40)	0.0040
LCI699 0.50QD - Placebo	-2.28 (0.79)	(-3.82, -0.73)	0.0040
LCI699 1.0QD - Placebo	-3.89 (1.34)	(-6.53, -1.25)	0.0040
LCI699 0.50BID - Placebo	-1.03 (1.31)	(-3.61, 1.55)	0.4318
Eplerenone 50BID - Placebo	-4.26 (1.33)	(-6.88, -1.65)	0.0014
LCI699 1.0QD - Eplerenone 50BID	0.37 (1.33)	(-2.24, 2.99)	0.7793

If the Week 8 measurement was missing, the last post-baseline measurement during the double-blind period was carried forward.

[1] Derived from dose-response model fit.

[2] Derived from ANCOVA.

p-values not adjusted for multiple comparisons. SE=Standard Error, CI= Confidence Interval, n= non-missing data points. Covariates and factors used in all estimations are baseline levels and treatment/dose and region.

Dose quantities specified in the row headings are in mg.

Secondary Objective Result(s)

Mean change in sitting systolic blood pressure after 8 weeks

Treatment group	n	Mean mmHg change from baseline (SE)	95% CI
Placebo[1]	76	-2.93 (1.68)	(-6.24, 0.38)
LCI699 0.25QD[1]	92	-9.00 (1.40)	(-11.76, -6.25)
LCI699 0.50QD[1]	85	-10.69 (0.98)	(-12.61, -8.76)
LCI699 1.0QD[1]	86	-11.93 (1.44)	(-14.77, -9.10)
LCI699 0.50BID[2]	96	-9.10 (1.45)	(-11.97, -6.24)
Eplerenone 50BID[2]	84	-13.31 (1.48)	(-16.23, -10.39)

Pairwise comparison	Mean mmHg difference in change from baseline (SE)	95% CI for Mean difference	Two-sided p-value*
LCI699 0.25QD - Placebo	-6.07 (2.07)	(-10.14, -2.01)	0.0035
LCI699 0.50QD - Placebo	-7.76 (1.87)	(-11.44, -4.07)	< 0.000
LCI699 1.0QD - Placebo	-9.01 (2.11)	(-13.15, -4.86)	< 0.000
LCI699 0.50BID - Placebo	-6.18 (2.26)	(-10.61, -1.74)	0.0064
Eplerenone 50BID - Placebo	-10.38 (2.28)	(-14.86, -5.90)	< 0.000
LCI699 1.0QD - Eplerenone 50BID	1.38 (2.12)	(-2.79, 5.54)	0.5162

If the Week 8 measurement was missing, the last post-baseline measurement during the double-blind period was carried forward.

[1] Derived from dose-response model fit.

[2] Derived from ANCOVA.

p-values not adjusted for multiple comparisons. SE=Standard Error, CI= Confidence Interval, n= non-missing data points. Covariates and factors used in all estimations are baseline levels and treatment/dose and region. Dose quantities specified in the row headings are in mg.

Mean change in 24-hour ambulatory diastolic blood pressure at 8 weeks

Treatment group	n	LS Mean change from baseline (mmHg)	SE	95% CI
Placebo	52	1.03	0.99	(-0.91, 2.98)
LCI699 0.25QD	62	-4.03	0.91	(-5.82, -2.24)
LCI699 0.50QD	59	-2.44	0.92	(-4.25, -0.63)
LCI699 1.00QD	68	-4.96	0.86	(-6.64, -3.28)
LCI699 0.50BID	70	-2.75	0.86	(-4.45, -1.06)
Eplerenone 50BID	57	-6.03	0.94	(-7.89, -4.17)

Pairwise comparison	LS Mean difference in change from baseline (mmHg)	SE	95% CI for Mean difference	Two-sided p-value*
LCI699 0.25QD - Placebo	-5.06	1.30	(-7.62, -2.51)	0.0001
LCI699 0.50QD - Placebo	-3.47	1.32	(-6.06, -0.88)	0.0087
LCI699 1.00QD - Placebo	-5.99	1.28	(-8.50, -3.49)	<0.0001

LCI699 0.50BID - Placebo	-3.79	1.27	(-6.28, -1.30)	0.0030
Eplerenone 50BID - Placebo	-7.06	1.33	(-9.67, -4.45)	<0.0001
LCI699 1.00QD - Eplerenone 50BID	1.07	1.24	(-1.37, 3.51)	0.3901

Only subjects with available ABPM measurements are included. P-values not adjusted for multiple comparisons. LSM = Least Squares Mean, SE = standard error of the mean, CI = confidence interval, n = non-missing data points. Dose quantities specified in the row headings are in mg.

Mean change in 24-hour ambulatory systolic blood pressure at 8 weeks

Treatment group	n	LS Mean change from baseline (mmHg)	SE	95% CI
Placebo	52	1.11	1.30	(-1.45, 3.68)
LCI699 0.25QD	62	-7.15	1.20	(-9.51, -4.78)
LCI699 0.50QD	59	-4.90	1.22	(-7.30, -2.51)
LCI699 1.00QD	68	-7.73	1.13	(-9.95, -5.51)
LCI699 0.50BID	70	-6.18	1.14	(-8.41, -3.95)
Eplerenone 50BID	57	-10.52	1.25	(-12.97, -8.07)

Pairwise comparison	LS Mean difference in change from baseline (mmHg)	SE	95% CI for Mean difference	Two-sided p-value*
LCI699 0.25QD - Placebo	-8.26	1.71	(-11.63, -4.89)	<0.0001
LCI699 0.50QD - Placebo	-6.02	1.74	(-9.43, -2.60)	0.0006
LCI699 1.00QD - Placebo	-8.85	1.68	(-12.15, -5.54)	<0.0001
LCI699 0.50BID - Placebo	-7.29	1.67	(-10.58, -4.01)	<0.0001
Eplerenone 50BID - Placebo	-11.63	1.75	(-15.07, -8.19)	<0.0001
LCI699 1.00QD - Eplerenone 50BID	2.79	1.64	(-0.44, 6.01)	0.0900

Only subjects with available ABPM measurements are included. P-values not adjusted for multiple comparisons. (1) LSM = Least Squares Mean, SE = standard error of the mean, CI = confidence interval, n = non-missing data points. Dose quantities specified in the row headings are in mg.

Safety Results

Number (%) of patients with overall adverse events in core period by primary system organ class and treatment group (Safety set)

	LCI699 0.25 QD (N=92)	LCI699 0.5 QD (N=87)	LCI699 1.0 QD (N=87)	LCI699 0.5 BID (N=97)	LCI699 total (N=363)	Eplerenone 50 BID (N=84)	Placebo (N=76)
Primary system organ class	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**	**n (%)**
Any primary system organ class	23 (25.0)	22 (25.3)	24 (27.6)	27 (27.8)	96 (26.4)	26 (31.0)	23 (30.3)
Primary system organ class							
Cardiac disorders	3 (3.3)	1 (1.1)	2 (2.3)	0	6 (1.7)	1 (1.2)	2 (2.6)
Congenital, familial and genetic disorders	0	0	1 (1.1)	0	1 (0.3)	0	0
Ear and labyrinth disorders	0	0	0	2 (2.1)	2 (0.6)	0	0
Eye disorders	2 (2.2)	1 (1.1)	1 (1.1)	1 (1.0)	5 (1.4)	0	1 (1.3)
Gastrointestial disorders	4 (4.3)	4 (4.6)	5 (5.7)	7 (7.2)	20 (5.5)	4 (4.8)	6 (7.9)
General disorders and administration site conditions	4 (4.3)	1 (1.1)	2 (2.3)	4 (4.1)	11 (3.0)	1 (1.2)	4 (5.3)
Hepatobiliary disorders	0	0	0	2 (2.1)	2 (0.6)	0	1 (1.3)
Immune system disorders	0	0	1 (1.1)	0	1 (0.3)	1 (1.2)	0
Infections and infestations	5 (5.4)	9 (10.3)	9 (10.3)	5 (5.2)	28 (7.7)	8 (9.5)	6 (7.9)
Injury, poisoning and procedural complications	3 (3.3)	0	3 (3.4)	0	6 (1.7)	0	2 (2.6)
Investigations	0	0	0	0	0	1 (1.2)	0
Metabolism and nutrition disorders	2 (2.2)	1 (1.1)	0	0	3 (0.8)	2 (2.4)	1 (1.3)
Musculoskeletal and connective tissue disorders	3 (3.3)	0	3 (3.4)	5 (5.2)	11 (3.0)	5 (6.0)	3 (3.9)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	1 (1.2)	0
Nervous system disorders	3 (3.3)	6 (6.9)	4 (4.6)	7 (7.2)	20 (5.5)	5 (6.0)	10 (13.2)
Psychiatric disorders	1 (1.1)	0	0	0	1 (0.3)	2 (2.4)	3 (3.9)
Renal and urinary disorders	0	0	0	0	0	1 (1.2)	0
Reproductive system and breast disorders	0	0	1 (1.1)	0	1 (0.3)	1 (1.2)	0
Respiratry, thoracic and medias-	1 (1.1)	5 (5.7)	2 (2.3)	2 (2.1)	10 (2.8)	2 (2.4)	1 (1.3)

tinal disorders							
Skin and sub-cutaneous tissue disorders	2 (2.2)	3 (3.4)	3 (3.4)	2 (2.1)	10 (2.8)	2 (2.4)	2 (2.6)
Vascular disorders	1 (1.1)	0	0	1 (1.0)	2 (0.6)	0	1 (1.3)

Dose quantities specified in the column headings are in mg. Primary system organ classes are sorted alphabetically. A patient with multiple adverse events
within a primary system organ class is counted only once in the total column.

Number (%) of patients with most common adverse events (greater than or 2% in any group) in core period by preferred term and treatment group (Safety set)

Preferred term	LCI699 0.25 QD (N=92) n (%)	LCI699 0.5 QD (N=87) n (%)	LCI699 1.0 QD (N=87) n (%)	LCI699 0.5 BID (N=97) n (%)	LCI699 total (N=363) n (%)	Eplerenone 50 BID (N=84) n (%)	Placebo (N=76) n (%)
Any Adverse Events							
Total	23 (25.0)	22 (25.3)	24 (27.6)	27 (27.8)	96 (26.4)	26 (31.0)	23 (30.3)
Nasopharyngitis	1 (1.1)	2 (2.3)	3 (3.4)	1 (1.0)	7 (1.9)	4 (4.8)	3 (3.9)
Sinusitis	0	1 (1.1)	2 (2.3)	0	3 (0.8)	1 (1.2)	0
Dizziness	0	0	2 (2.3)	5 (5.2)	7 (1.9)	1 (1.2)	0
Headache	1 (1.1)	4 (4.6)	1 (1.1)	2 (2.1)	8 (2.2)	3 (3.6)	10 (13.2)
Influenza	0	2 (2.3)	1 (1.1)	1 (1.0)	4 (1.1)	1 (1.2)	1 (1.3)
Joint sprain	2 (2.2)	0	1 (1.1)	0	3 (0.8)	0	1 (1.3)
Fatigue	1 (1.1)	0	1 (1.1)	2 (2.1)	4 (1.1)	0	1 (1.3)
Back pain	1 (1.1)	0	1 (1.1)	1 (1.0)	3 (0.8)	1 (1.2)	2 (2.6)
Nausea	1 (1.1)	0	1 (1.1)	1 (1.0)	3 (0.8)	0	2 (2.6)
Oropharyngeal pain	1 (1.1)	0	1 (1.1)	0	2 (0.6)	2 (2.4)	0

Dose quantities specified in the column headings are in mg. Preferred terms are sorted in descending frequency, as reported in column LCI699 1 mg QD. A patient with multiple adverse events is counted only once in the total row. A patient with multiple occurrences of an adverse event is only counted once for this event.

Number (%) of patients with deaths, serious adverse events (SAEs), adverse events and abnormal laboratory values leading to permanent treatment discontinuations in core period (Safety set)

	LCI699 0.25 QD (N=92) n (%)	LCI699 0.5 QD (N=87) n (%)	LCI699 1.0 QD (N=87) n (%)	LCI699 0.5 BID (N=97) n (%)	LCI699 Total (N=363) n (%)	Eplerenone 50 BID (N=84) n (%)	Placebo (N=76) n (%)
Patients with AE(s)	23 (25.0)	22 (25.3)	24 (27.6)	27 (27.8)	96 (26.4)	26 (31.0)	23 (30.3)
Serious and other significant events							
Deaths	0	0	0	0	0	0	0
SAEs	1 (1.1)	0	0	0	1 (0.3)	0	1 (1.3)
AE discontinuations	2 (2.2)	1 (1.1)	1 (1.1)	2 (2.1)	6 (1.7)	2 (2.4)	0
Discontinuations for abnormal lab values	0	0	0	0	0	1 (1.2)	0

Dose quantities specified in the column headings are in mg.

* abnormality refers to extended normal range/notable range. Most extreme post-baseline value is used.

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

Abnormal values*	LCI699 0.25 QD (N=92) n (%)	LCI699 0.5 QD (N=87) n (%)	LCI699 1.0 QD (N=87) n (%)	LCI699 0.5 BID (N=97) n (%)	Eplerenone 50 BID (N=84) n (%)	Placebo (N=76) n (%)	Total (N=523) n (%)
Sodium							
Total	92 (100.0)	84 (100.0)	87 (100.0)	96 (100.0)	84 (100.0)	75 (100.0)	518 (100.0)
<125 mmol/L	0	0	0	1 (1.0)	0	0	1 (0.2)
≥125 and <130 mmol/L	0	1 (1.2)	0	0	0	0	1 (0.2)
≥130 and <135 mmol/L	2 (2.2)	1 (1.2)	0	2 (2.1)	1 (1.2)	2 (2.7)	8 (1.5)
>146 mmol/L	1 (1.1)	0	0	1 (1.0)	1 (1.2)	0	3 (0.6)
Potassium							
Total	92 (100.0)	84 (100.0)	87 (100.0)	96 (100.0)	84 (100.0)	75 (100.0)	518 (100.0)
<3.5 mmol/L	0	0	0	0	0	1 (1.3)	1 (0.2)
>5.5 mmol/L	1 (1.1)	4 (4.8)	3 (3.4)	4 (4.2)	4 (4.8)	0	16 (3.1)
≥6.0 mmol/L	1 (1.1)	1 (1.2)	1 (1.1)	1 (1.0)	0	0	4 (0.8)
Creatinine							
Total	92 (100.0)	84 (100.0)	87 (100.0)	96 (100.0)	84 (100.0)	75 (100.0)	518 (100.0)
>176.8 umol/L	0	0	0	0	0	0	0
BUN							
Total	92 (100.0)	84 (100.0)	87 (100.0)	96 (100.0)	84 (100.0)	75 (100.0)	518 (100.0)
>14.28 mmol/L	0	0	0	0	0	0	0
Cortisol							
Total	91 (100.0)	84 (100.0)	86 (100.0)	95 (100.0)	81 (100.0)	71 (100.0)	508 (100.0)
<150 nmol/L	2 (2.2)	0	1 (1.2)	1 (1.1)	3 (3.7)	1 (1.4)	8 (1.6)

Dose quantities specified in the column headings are in mg.

* abnormality refers to extended normal range/notable range. Most extreme post-baseline value is used.

Number (%) of patients with cortisol levels below 500 nmol/L at 1 hour after ACTH injection in the ACTH stimulated cortisol test (ACTH substudy)

Time of ACTH-stimulated cortisol test	LCI699 0.25 QD n/N (%)	LCI699 0.5 QD n/N (%)	LCI699 0.5 BID n/N (%)	LCI699 1.0 QD n/N (%)	LCI699 Total n/N (%)	EPL 50 BID n/N (%)	Placebo n/N (%)
Baseline	0/2 3 (0.0)	0/27 (0.0)	0/26 (0.0)	0/27 (0.0)	0/103 (0.0)	0/24 (0.0)	0/21 (0.0)
Post-treatment any time*	0/21 (0.0)	0/23 (0.0)	5/24 (20.8)	6/28 (21.4)	11/96 (11.5)	0/22 (0.0)	0/17 (0.0)

Dose quantities specified in the column headings are in mg.

* 99% of patients evaluated in the ACTH stimulation cortisol test post baseline were tested at 8 weeks.

Summary of safety

- Overall, LCI699 was well tolerated.
- The incidence of total AEs and discontinuations due to AEs were similar for LCI699, eplerenone and placebo. There was 1 SAE on 0.25 mg QD LCI699 and 1 on placebo; neither was suspected to be study drug related.
- The incidence of hyperkalemia (> 5.5 mmol/L) was similar across doses of LCI699 ≥ 0.5 mg and eplerenone (3-5% with 0% for placebo).
- Infrequent abnormalities in serum sodium with LCI699 were observed.
- There were no adverse effects on renal function
- There was a 20% incidence of an impaired ACTH-stimulated cortisol response (< 500 nmol/L) with a daily dose of 0.5 mg BID or 1 mg QD LCI699, with no abnormal tests for lower doses of LCI699, eplerenone or placebo. 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.

Date of Clinical Trial Report

23 June 2010

Date Inclusion on Novartis Clinical Trial Results Database

25 June 2010

Date of Latest Update

16 June 2010