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Novartis Clinical Trial Results

Sponsor

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Generic Drug Name

LCI699

Trial Indication(s)

Stage 1-2 hypertension

Protocol Number

CLCI699A2201

Protocol 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

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

11-Sep-2008 to 02-Jul-2009

Reason for Termination

Not applicable.

Study Design/Methodology

This was a multi-center, randomized, double-blind, placebo and active controlled, parallel group study. Patients with mild-to-moderate uncomplicated essential hypertension were randomized equally across the following 6 treatment groups: LCI699 0.25 mg QD, 0.5 mg QD, 1.0 mg QD, 0.5 mg BID, eplerenone 50 mg BID and placebo.

Centers

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

Objectives:

Primary objective(s)

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 evaluate the trough/peak ratios of reduction in MSDBP and MSSBP with 4 dose regimens of LCI699 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.

• To evaluate the proportion of patients achieving a successful BP response and BP control in all treatment groups for 23–26-hour post dose (11–14-hour post dose for BID regimen) MSDBP and MSSBP after 8 weeks treatment.

• To compare the efficacy and safety of two dose regimens of 1 mg LCI699, i.e., administered as 1 mg QD versus 0.5 mg BID, after 8 weeks treatment.

• To evaluate the potential off-target effect of 4 dose regimens of LCI699 on cortisol synthesis after 8 weeks treatment, including assessment of ACTH-stimulation cortisol test in a subset of patients.

• To evaluate the additional changes in MSDBP and MSSBP at week 9 after randomized withdrawal at week 8.

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.

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: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Males and non-fertile females.

• 18-75 years inclusive.

• Participants with mild-to-moderate uncomplicated essential hypertension.

Exclusion Criteria:

• All women of childbearing potential.

• Female participants on hormone replacement therapy.

• Severe hypertension.

• History or evidence of a secondary form of hypertension.

• Known moderate or malignant retinopathy.

• 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.

• Type 1 or type 2 diabetes mellitus.

• Clinically significant valvular heart disease.

• Congestive heart failure (New York Heart Association [NYHA] class II-IV).

• Cardiac electrical abnormalities indicating significant risk of safety for participant taking part in the study.

• History of malignancy of any organ system, treated or untreated, within the past 5 years.

• Liver disease such as cirrhosis or chronic active hepatitis.

• Any surgical or medical conditions that may significantly alter the absorption, distribution, metabolism, or excretion of any drug substance

• Any surgical or medical conditions, not identified in the protocol that in the opinion of the investigator or the monitor, place the participant at higher risk from his/her participation in the study, or is likely to prevent the participant from complying with the requirements of the study or completing the trial period.

• Participant unwilling or not able to discontinue safely the use of current antihypertensive medications during the study period

• Any contraindication or history of hypersensitivity to any of the study drugs or to drugs with similar chemical structures.

• Chronic oral or parenteral corticosteroid treatment.

• Treatment with potassium supplement or potassium sparing diuretics.

• Treatment with potent cytochrome P450 3A4 (CYP3A4) inhibitors during the study period.

• Use of other investigational drugs at Visit 1, or within 30 days or 5 half-lives of Visit 1, whichever is longer, unless local health authority guidelines mandate a longer period.

• Serum potassium > 5.2 milliequivalents per liter (mEq/L) or < 3.5 mEq/L at Visit 1.

• Serum sodium < 132 mEq/L at Visit 1.

• Aspartate aminotransferase (ALT) or alanine aminotransferase (AST) > 2 times the upper limit of the normal range (ULN) at Visit 1.

• Bilirubin (total) > 1.5 x ULN at Visit 1.

• Modification of diet in renal disease estimated glomerular filtration rate (MDRD eGFR) < 60 milliliters per minute (ml/min)/1.73 m^2 at Visit 1.

• Other clinically significant laboratory abnormalities, confirmed by repeat measurements, at Visit 1.

• History of active substance abuse (including alcohol).

• Participants with night-shift employment.

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Participant Flow Table

Patient disposition during the core period by treatment (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 period	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 effect	3 (3.3)	2 (2.3)	4 (4.7)	0	3 (3.6)	5 (6.5)	17 (3.2)
Subject withdrew 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 laboratory value(s)	0	0	0	0	1 (1.2)	0	1 (0.2)
Abnormal test procedure result(s)	0	1 (1.1)	0	0	0	0	1 (0.2)

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Baseline Characteristics

Patient demographics by treatment group (Full analysis set)

	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)	Total (N=522)
Age (yrs)							
N	92	87	86	96	84	77	522
Mean	53.9	54.8	54.5	54.4	55.3	53.9	54.5
SD	10.48	7.85	9.66	10.78	9.13	8.70	9.50
Median	55.0	56.0	56.0	54.0	55.0	54.0	55.0
Min	29	25	22	33	25	37	22
Max	74	69	75	75	75	74	75
Age Group - n (%)							
< 65 yrs	75 (81.5)	79 (90.8)	75 (87.2)	78 (81.3)	68 (81.0)	67 (87.0)	442 (84.7)
≥ 65 yrs	17 (18.5)	8 (9.2)	11 (12.8)	18 (18.8)	16 (19.0)	10 (13.0)	80 (15.3)
Sex - n (%)							
Male	63 (68.5)	58 (66.7)	55 (64.0)	63 (65.6)	56 (66.7)	46 (59.7)	341 (65.3)
Female	29 (31.5)	29 (33.3)	31 (36.0)	33 (34.4)	28 (33.3)	31 (40.3)	181 (34.7)
Race - n (%)							
Caucasian	86 (93.5)	76 (87.4)	77 (89.5)	85 (88.5)	73 (86.9)	70 (90.9)	467 (89.5)
Black	5 (5.4)	11 (12.6)	8 (9.3)	10 (10.4)	10 (11.9)	5 (6.5)	49 (9.4)
Asian	1 (1.1)	0	1 (1.2)	1 (1.0)	1 (1.2)	1 (1.3)	5 (1.0)
Native American	0	0	0	0	0	0	0
Pacific Islander	0	0	0	0	0	0	0
Other	0	0	0	0	0	1 (1.3)	1 (0.2)

	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)	Total (N=522)
Ethnicity - n (%)							
Hispanic or Latino	15 (16.3)	14 (16.1)	13 (15.1)	16 (16.7)	13 (15.5)	17 (22.1)	88 (16.9)
Chinese	0	0	1 (1.2)	0	0	0	1 (0.2)
Indian (India Subcontinent)	0	0	0	0	0	0	0
Japanese	0	0	0	0	0	0	0
Mixed ethnicity	1 (1.1)	0	1 (1.2)	0	0	1 (1.3)	3 (0.6)
Other	76 (82.6)	73 (83.9)	71 (82.6)	80 (83.3)	71 (84.5)	59 (76.6)	430 (82.4)
Height (cm)							
N	91	87	86	96	84	77	521
Mean	170.6	171.0	170.9	170.7	171.1	169.7	170.7
SD	9.52	9.96	9.79	10.78	9.58	8.96	9.77
Median	171.0	174.0	171.5	170.5	172.0	170.0	172.0
Min	147	146	144	144	148	153	144
Max	190	193	196	200	188	190	200
Weight (kg)							
N	92	87	86	96	84	77	522
Mean	88.51	90.07	88.46	88.43	86.93	85.01	87.98
SD	19.196	17.889	14.224	18.801	17.784	14.206	17.228
Median	87.05	88.00	86.00	87.10	83.95	84.50	86.00
Min	57.0	54.0	60.0	53.0	51.0	56.0	51.0
Max	151.3	132.0	134.3	141.5	145.9	147.0	151.3

	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)	Total (N=522)
BMI (kg/m^2)							
N	91	87	86	96	84	77	521
Mean	30.286	30.765	30.337	30.208	29.600	29.460	30.127
SD	5.4343	5.5295	4.5443	4.8313	4.8298	3.9810	4.9030
Median	29.750	29.700	29.905	29.535	28.830	28.910	29.410
Min	20.80	19.05	21.26	19.49	19.68	20.08	19.05
Max	44.26	47.50	46.43	43.36	42.64	42.95	47.50
BMI ≤25 kg/m^2	17 (18.5)	11 (12.6)	9 (10.5)	13 (13.5)	13 (15.5)	6 (7.8)	69 (13.2)
BMI >25 and <30 kg/m^2	30 (32.6)	35 (40.2)	34 (39.5)	40 (41.7)	36 (42.9)	44 (57.1)	219 (42.0)
BMI ≥30 kg/m^2	44 (47.8)	41 (47.1)	43 (50.0)	43 (44.8)	35 (41.7)	27 (35.1)	233 (44.6)
Waist circumference (cm)							
Males							
N	62	57	54	63	56	46	338
Mean	104.26	103.14	103.03	104.79	101.93	103.41	103.47
SD	12.813	11.402	8.956	12.424	13.225	10.424	11.673
Median	102.50	101.60	102.00	103.00	101.00	103.00	102.00
Min	83.5	76.2	75.0	76.0	66.0	86.0	66.0
Max	142.2	138.0	128.0	143.0	138.0	143.0	143.0

	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)	Total (N=522)
Females							
N	29	28	31	32	28	31	179
Mean	93.96	101.13	98.07	98.25	93.46	94.33	96.55
SD	13.047	13.408	13.464	10.946	9.951	8.106	11.799
Median	92.00	102.50	100.00	96.00	93.50	92.00	96.00
Min	65.0	74.0	72.0	80.0	73.0	78.0	65.0
Max	119.0	124.0	132.0	126.0	114.0	110.0	132.0

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Primary Outcome Result(s)

Between treatment analysis for change from baseline in mean sitting diastolic blood pressure (MSDBP) at week 8 LOCF including dose response estimates (Full analysis set)

Treatment group	n	Mean 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)

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Secondary Outcome Result(s)

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
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)

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

Between treatment analysis for change from baseline in mean sitting diastolic blood pressure (MSDBP) at week 8 LOCF including dose response estimates (Full analysis set)

Treatment group	n	Mean 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)

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
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)

Between treatment analysis for change from baseline in 24 hours mean ambulatory systolic blood pressure (Full analysis set)

Treatment Group	n	LSMean change from baseline	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)

Between treatment analysis for change from baseline in 24 hours mean ambulatory diastolic blood pressure at Week 8 (Full analysis set)

Treatment group	n	LSMean change from baseline	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)

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Trough-to-hour ratios for method 1 in using ambulatory blood pressure at week 8 endpoint by treatment group (Full analysis set)

Variable: diastolic blood pressure (mmHg)

	LSM (SE) for change from baseline in MADBP (mmHg)									
Hour	Placebo N=77		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	
1	7.11	(1.588)	3.91	(1.466)	2.95	(1.541)	0.27	(1.389)	3.87	(1.404)	0.17	(1.544)
2	6.28	(1.586)	1.44	(1.452)	1.85	(1.488)	0.17	(1.397)	3.44	(1.381)	-1.65	(1.529)
3	4.99	(1.585)	1.16	(1.477)	1.13	(1.502)	-0.36	(1.387)	4.01	(1.369)	-2.42	(1.528)
4	7.02	(1.584)	0.51	(1.452)	2.91	(1.488)	0.35	(1.386)	2.64	(1.378)	-1.39	(1.541)
5	4.31	(1.584)	1.11	(1.463)	-0.02	(1.513)	-1.69	(1.385)	1.45	(1.377)	-2.91	(1.514)
6	1.82	(1.585)	-1.18	(1.451)	-2.36	(1.487)	-3.01	(1.386)	1.20	(1.367)	-4.86	(1.513)
7	3.62	(1.599)	-1.85	(1.463)	-0.95	(1.487)	-2.63	(1.406)	1.21	(1.366)	-3.70	(1.513)
8	2.65	(1.616)	-3.01	(1.464)	-1.38	(1.487)	-2.43	(1.396)	2.09	(1.366)	-2.30	(1.514)
9	3.30	(1.600)	-1.24	(1.464)	-0.07	(1.487)	-2.25	(1.386)	3.27	(1.366)	-2.81	(1.515)
10	3.86	(1.585)	-0.59	(1.452)	2.60	(1.487)	-1.65	(1.385)	0.49	(1.378)	-2.43	(1.515)
11	2.38	(1.585)	-1.02	(1.451)	1.72	(1.487)	-1.54	(1.386)	1.54	(1.367)	-1.93	(1.514)
12	3.24	(1.584)	-1.60	(1.451)	2.53	(1.487)	-3.10	(1.385)	-1.06	(1.367)	-3.20	(1.527)
13	1.52	(1.584)	-4.32	(1.451)	-1.20	(1.487)	-5.31	(1.385)	-1.45	(1.366)	-5.35	(1.513)
14	-0.90	(1.584)	-6.47	(1.451)	-3.29	(1.487)	-7.38	(1.385)	-2.96	(1.376)	-7.64	(1.513)
15	-1.01	(1.586)	-8.34	(1.452)	-5.82	(1.488)	-8.89	(1.386)	-6.10	(1.377)	-9.03	(1.527)
16	-1.61	(1.587)	-8.92	(1.465)	-8.37	(1.491)	-10.50	(1.387)	-9.54	(1.369)	-12.55	(1.528)
17	-4.20	(1.604)	-10.26	(1.454)	-10.99	(1.492)	-12.71	(1.398)	-10.38	(1.380)	-12.88	(1.516)
18	-6.89	(1.587)	-10.68	(1.456)	-11.73	(1.492)	-11.88	(1.389)	-11.85	(1.379)	-13.49	(1.529)

Variable: diastolic blood pressure (mmHg)

	LSM (SE) for change from baseline in MADBP (mmHg)									
Hour	Placebo N=77		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	
19	-5.84	(1.587)	-10.13	(1.456)	-10.12	(1.493)	-9.74	(1.388)	-10.78	(1.369)	-10.13	(1.517)
20	-5.21	(1.602)	-10.73	(1.454)	-8.06	(1.504)	-10.43	(1.408)	-10.49	(1.369)	-10.47	(1.516)
21	-4.12	(1.586)	-9.31	(1.453)	-7.68	(1.489)	-9.66	(1.386)	-8.22	(1.377)	-10.51	(1.514)
22	-1.09	(1.585)	-7.90	(1.452)	-4.93	(1.487)	-5.37	(1.385)	-6.35	(1.386)	-7.60	(1.513)
23	1.82	(1.599)	-4.94	(1.475)	-1.93	(1.487)	-1.18	(1.385)	-2.67	(1.377)	-5.54	(1.513)
24	1.98	(1.617)	-0.21	(1.477)	1.45	(1.501)	0.29	(1.397)	1.36	(1.370)	-2.78	(1.529)

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Trough-to-hour ratios for method 1 in using ambulatory blood pressure at week 8 endpoint by treatment group (Full analysis set)

Variable: systolic blood pressure (mmHg)

	LSM (SE) for change from baseline in MASBP (mmHg)					
Hour	Placebo N=77	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
1	8.23 (1.915)	-0.54 (1.767)	0.09 (1.859)	-4.51 (1.674)	-1.42 (1.690)	-5.33 (1.863)
2	6.48 (1.913)	-1.59 (1.752)	0.15 (1.795)	-3.56 (1.685)	-0.57 (1.663)	-5.90 (1.844)
3	4.60 (1.912)	-2.11 (1.781)	-1.53 (1.811)	-4.86 (1.672)	0.91 (1.649)	-5.89 (1.843)
4	4.68 (1.912)	-2.06 (1.752)	-1.18 (1.794)	-4.15 (1.672)	1.50 (1.661)	-5.12 (1.859)
5	2.78 (1.912)	-4.29 (1.766)	-3.09 (1.825)	-3.47 (1.671)	-1.70 (1.660)	-7.22 (1.826)
6	1.42 (1.912)	-4.21 (1.751)	-3.12 (1.794)	-5.88 (1.672)	-1.02 (1.648)	-7.91 (1.826)
7	2.25 (1.930)	-4.95 (1.766)	-2.10 (1.794)	-5.40 (1.697)	-0.76 (1.649)	-8.70 (1.826)
8	3.76 (1.950)	-5.28 (1.766)	-4.69 (1.794)	-5.30 (1.684)	-3.02 (1.649)	-8.06 (1.827)
9	2.39 (1.931)	-3.98 (1.766)	-1.59 (1.795)	-4.78 (1.672)	-1.87 (1.649)	-7.46 (1.828)
10	2.54 (1.913)	-3.69 (1.752)	-0.30 (1.794)	-3.40 (1.672)	-1.73 (1.662)	-7.35 (1.828)
11	3.51 (1.913)	-2.47 (1.751)	-0.43 (1.795)	-4.22 (1.672)	-1.74 (1.649)	-5.75 (1.827)
12	4.69 (1.912)	-5.19 (1.752)	0.73 (1.794)	-4.35 (1.671)	-3.92 (1.650)	-6.25 (1.843)
13	3.20 (1.912)	-6.45 (1.751)	-2.30 (1.794)	-7.25 (1.671)	-4.05 (1.649)	-8.81 (1.826)
14	0.75 (1.912)	-7.37 (1.751)	-5.68 (1.794)	-9.33 (1.671)	-6.12 (1.660)	-10.91 (1.826)
15	0.02 (1.912)	-10.61 (1.752)	-8.28 (1.795)	-11.26 (1.672)	-9.78 (1.661)	-12.04 (1.842)
16	-0.33 (1.914)	-11.71 (1.767)	-10.01 (1.797)	-12.63 (1.672)	-13.03 (1.651)	-16.68 (1.843)
17	-3.03 (1.933)	-13.71 (1.754)	-11.96 (1.799)	-15.46 (1.685)	-13.72 (1.664)	-19.59 (1.828)
18	-6.35 (1.915)	-14.49 (1.756)	-14.37 (1.800)	-14.54 (1.675)	-15.60 (1.664)	-18.55 (1.844)

Variable: systolic blood pressure (mmHg)

	LSM (SE) for change from baseline in MASBP (mmHg)					
Hour	Placebo N=77	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
19	-6.98 (1.914)	-13.78 (1.756)	-13.08 (1.801)	-12.85 (1.674)	-15.93 (1.652)	-15.49 (1.830)
20	-6.53 (1.934)	-13.92 (1.756)	-13.22 (1.814)	-12.54 (1.699)	-15.47 (1.652)	-16.09 (1.829)
21	-3.89 (1.914)	-14.33 (1.754)	-10.06 (1.797)	-12.78 (1.672)	-13.63 (1.662)	-15.34 (1.827)
22	-0.94 (1.912)	-13.46 (1.752)	-8.35 (1.794)	-7.52 (1.671)	-10.55 (1.673)	-12.47 (1.826)
23	2.18 (1.930)	-7.88 (1.780)	-6.23 (1.794)	-5.77 (1.671)	-6.73 (1.661)	-9.02 (1.826)
24	0.70 (1.951)	-3.16 (1.781)	-0.64 (1.810)	-3.45 (1.685)	-3.76 (1.651)	-8.90 (1.844)

Hormonal profile (Aldosterone, 11-deoxycorticosterone, active renin and PRA) results by laboratory parameter, treatment group at week 8 (safety set)

			LCI699				Eplerenone	Placebo
			0.25 QD	0.5 QD	1.0 QD	0.5 BID	50 BID	
Aldosterone (pmol/L)		n/N	(71/75)	(69/72)	(70/73)	(76/79)	(64/68)	(54/58)
	Baseline	mean	215	238	245	212	252	252
		SD	182	177	173	141	141	201
		median	194	222	208	166	222	180
	Week 8	**mean**	**189**	**220**	**233**	**163**	**517**	**230**
		change	**-21.5**	**-20.0**	**-9.9**	**-47.5**	**277.1**	**-28.8**
		SD	122	156	266	170	429	163
		median	166	194	166	111	375	194

Number (%) of responders in mean sitting systolic blood pressure (MSSBP) (less than 140 mmHg or greater than or equal to 20 mmHg reduction) at Week 8 LOCF by treatment group (Full analysis set)

Treatment group	N	Number of responders n / N (%)	Estimated odds	95% CI for odds
LCI699 0.25QD	92	36 (39.1)	0.68	(0.44, 1.05)
LCI699 0.50QD	85	32 (37.6)	0.63	(0.40, 0.98)
LCI699 1.00QD	86	42 (48.8)	1.02	(0.66, 1.57)
LCI699 0.50BID	96	33 (34.4)	0.56	(0.36, 0.87)
Eplerenone 50BID	84	44 (52.4)	1.17	(0.75, 1.82)
Placebo	76	13 (17.1)	0.21	(0.12, 0.39)

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Proportion of BP control (Full analysis set)

Variable: diastolic BP control (MSDBP<90mmHg) at week 8 LOCF by treatment group

Treatment group	N	Number of responders n / N (%)	Estimated odds	95% CI for odds
LCI699 0.25QD	92	30 (32.6)	0.40	(0.25, 0.64)
LCI699 0.50QD	85	25 (29.4)	0.33	(0.20, 0.54)
LCI699 1.00QD	86	36 (41.9)	0.59	(0.38, 0.94)
LCI699 0.50BID	96	28 (29.2)	0.32	(0.20, 0.52)
Eplerenone 50BID	84	38 (45.2)	0.70	(0.44, 1.12)
Placebo	76	14 (18.4)	0.18	(0.10, 0.33)

Number (%) of responders in mean sitting diastolic blood pressure (MSDBP) (less than 90 mmHg or greater than or equal to 10 mmHg reduction) at Week 8 LOCF by treatment group (Full analysis set)

Treatment group	N	Number of responders n / N (%)	Estimated odds	95% CI for odds
LCI699 0.25QD	92	36 (39.1)	0.54	(0.35, 0.85)
LCI699 0.50QD	85	29 (34.1)	0.44	(0.28, 0.71)
LCI699 1.00QD	86	43 (50.0)	0.87	(0.56, 1.35)
LCI699 0.50BID	96	33 (34.4)	0.43	(0.27, 0.67)
Eplerenone 50BID	84	41 (48.8)	0.82	(0.52, 1.28)
Placebo	76	21 (27.6)	0.32	(0.19, 0.54)

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Proportion of BP control (Full analysis set)

Variable: systolic BP control (MSSBP<140mmHg) at week 8 LOCF by treatment group

Treatment group	N	Number of responders n / N (%)	Estimated odds	95% CI for odds
LCI699 0.25QD	92	29 (31.5)	0.45	(0.28, 0.72)
LCI699 0.50QD	85	23 (27.1)	0.34	(0.20, 0.57)
LCI699 1.00QD	86	35 (40.7)	0.76	(0.48, 1.20)
LCI699 0.50BID	96	24 (25.0)	0.33	(0.20, 0.55)
Eplerenone 50BID	84	37 (44.0)	0.83	(0.52, 1.33)
Placebo	76	12 (15.8)	0.17	(0.09, 0.32)

ACTH stimulation test cortisol levels by visit and hour, treatment group and visit (Safety set-ACTH SubStudy)

Variable: ACTH Stimulated Cortisol (nmol/L)

Visit	Statistics	LCI699 0.25 QD (N=24)	LCI699 0.5 QD (N=28)	LCI699 1.0 QD (N=29)	LCI699 0.5 BID (N=27)	Eplerenone 50 BID (N=24)	Placebo (N=21)
Visit 7 (Pre)	n	20	23	28	24	22	16
	Mean	346.10	379.70	358.64	317.83	378.18	338.63
	SD	109.185	134.878	117.147	88.481	128.046	114.120
	Median	353.00	401.00	360.00	335.00	374.00	347.00
	Minimum	108.0	166.0	190.0	160.0	190.0	149.0
	Maximum	563.0	650.0	734.0	472.0	685.0	517.0
Visit 7 (Post)	n	20	23	28	24	22	17
	Mean	729.20	692.74	604.46	609.21	802.32	822.65
	SD	123.753	117.645	125.017	107.923	134.497	116.041
	Median	717.50	703.00	608.00	589.50	786.50	825.00
	Minimum	536.0	522.0	428.0	450.0	616.0	555.0
	Maximum	1027.0	938.0	930.0	788.0	1184.0	1007.0

Between treatment analysis for change from week 8 in mean sitting diastolic blood pressure (MSDBP) at week 9 (Randomized withdrawal set)

Treatment group	n	LSMean change from week 8	SE	95% CI
LCI699 0.25QD/Active	45	0.5	0.99	(-1.5, 2.4)
LCI699 0.25QD/Placebo	38	0.5	1.08	(-1.6, 2.6)
LCI699 0.50QD/Active	43	1.6	1.01	(-0.4, 3.6)
LCI699 0.50QD/Placebo	37	-0.2	1.09	(-2.3, 2.0)
LCI699 1.00QD/Active	41	-0.5	1.03	(-2.5, 1.5)
LCI699 1.00QD/Placebo	36	2.5	1.11	(0.4, 4.7)
LCI699 0.50BID/Active	45	1.3	1.00	(-0.7, 3.3)
LCI699 0.50BID/Placebo	44	1.3	1.02	(-0.7, 3.3)
Eplerenone 50BID/Active	39	-1.2	1.06	(-3.3, 0.9)
Eplerenone 50BID/Placebo	36	0.4	1.11	(-1.8, 2.6)
Placebo/Placebo	67	1.6	0.83	(0.0, 3.3)

Between treatment analysis for change from week 8 in mean sitting systolic blood pressure (MSSBP) at week 9 (Randomized withdrawal set)

Treatment group	n	LSMean change from week 8	SE	95% CI
LCI699 0.25QD/Active	45	0.3	1.66	(-3.0, 3.6)
LCI699 0.25QD/Placebo	38	3.3	1.80	(-0.2, 6.8)
LCI699 0.50QD/Active	43	0.5	1.69	(-2.9, 3.8)
LCI699 0.50QD/Placebo	37	2.5	1.82	(-1.1, 6.1)
LCI699 1.00QD/Active	41	0.4	1.72	(-3.0, 3.8)
LCI699 1.00QD/Placebo	36	5.3	1.85	(1.6, 8.9)
LCI699 0.50BID/Active	45	1.6	1.68	(-1.7, 4.9)
LCI699 0.50BID/Placebo	44	4.4	1.69	(1.0, 7.7)
Eplerenone 50BID/Active	39	-1.5	1.79	(-5.0, 2.1)
Eplerenone 50BID/Placebo	36	2.7	1.86	(-1.0, 6.3)
Placebo/Placebo	67	1.8	1.39	(-1.0, 4.5)

Adverse Events by System Organ Class

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

Primary system organ class	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 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)
Gastrointestinal 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)

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Primary system organ class	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 (%)
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
Respiratory, thoracic and mediastinal disorders	1 (1.1)	5 (5.7)	2 (2.3)	2 (2.1)	10 (2.8)	2 (2.4)	1 (1.3)
Skin and subcutaneous 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)

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Number (%) of patients with overall adverse events in randomized withdrawal period by primary system organ class and treatment group (Randomized withdrawal safety set)

Primary system organ class	LCI699 0.25 QD /Active (N=46) n (%)	LCI699 0.25 QD /Placebo (N=38) n (%)	LCI699 0.5 QD /Active (N=44) n (%)	LCI699 0.5 QD /Placebo (N=37) n (%)	LCI699 1.0 QD /Active (N=41) n (%)	LCI699 1.0 QD /Placebo (N=37) n (%)
Any primary system organ class	2 (4.3)	1 (2.6)	1 (2.3)	0	3 (7.3)	5 (13.5)
Primary system organ class						
Cardiac disorders	0	0	0	0	0	0
Gastrointestinal disorders	0	0	0	0	0	1 (2.7)
General disorders and administration site conditions	0	1 (2.6)	0	0	0	0
Infections and infestations	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	1 (2.4)	1 (2.7)
Metabolism and nutrition disorders	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (2.2)	0	0	0	0	1 (2.7)
Nervous system disorders	0	0	0	0	0	2 (5.4)
Renal and urinary disorders	1 (2.2)	0	0	0	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (2.6)	0	0	2 (4.9)	0
Skin and subcutaneous tissue disorders	0	0	1 (2.3)	0	0	0

Primary system organ class	LCI699 0.5 BID /Active (N=45) n (%)	LCI699 0.5 BID /Placebo (N=45) n (%)	LCI699 total /Active (N=176) n (%)	LCI699 total /Placebo (N=157) n (%)	Eplerenone 50 BID /Active (N=39) n (%)	Eplerenone 50 BID /Placebo (N=36) n (%)	Placebo /Placebo (N=66) n (%)
Any primary system organ class	4 (8.9)	3 (6.7)	10 (5.7)	9 (5.7)	2 (5.1)	0	3 (4.5)
Primary system organ class							
Cardiac disorders	0	1 (2.2)	0	1 (0.6)	0	0	0
Gastrointestinal disorders	0	0	0	1 (0.6)	0	0	0
General disorders and administration site conditions	0	0	0	1 (0.6)	0	0	0
Infections and infestations	1 (2.2)	1 (2.2)	1 (0.6)	1 (0.6)	0	0	1 (1.5)
Injury, poisoning and procedural complications	0	0	1 (0.6)	1 (0.6)	0	0	0
Metabolism and nutrition disorders	0	1 (2.2)	0	1 (0.6)	0	0	0
Musculoskeletal and connective tissue disorders	1 (2.2)	0	2 (1.1)	1 (0.6)	2 (5.1)	0	1 (1.5)
Nervous system disorders	1 (2.2)	1 (2.2)	1 (0.6)	3 (1.9)	0	0	1 (1.5)
Renal and urinary disorders	0	0	1 (0.6)	0	0	0	0
Respiratory, thoracic and mediastinal disorders	1 (2.2)	0	3 (1.7)	1 (0.6)	0	0	0
Skin and subcutaneous tissue disorders	0	0	1 (0.6)	0	0	0	0

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Number (%) of patients with most common adverse events (greater than or 2% in any group) in core period by 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
Abdominal pain upper	0	2 (2.3)	0	0	2 (0.6)	0	0
Diarrhoea	2 (2.2)	1 (1.1)	0	0	3 (0.8)	0	2 (2.6)
Palpitations	1 (1.1)	1 (1.1)	0	0	2 (0.6)	1 (1.2)	2 (2.6)

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 (%)
Non-cardiac chest pain	2 (2.2)	0	0	0	2 (0.6)	0	0
Urinary tract infection	2 (2.2)	0	0	0	2 (0.6)	1 (1.2)	0
Vomiting	1 (1.1)	0	0	1 (1.0)	2 (0.6)	0	2 (2.6)
Asthenia	0	0	0	2 (2.1)	2 (0.6)	1 (1.2)	1 (1.3)
Insomnia	0	0	0	0	0	0	2 (2.6)

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Number (%) of patients with most common adverse events (greater than or 2% in any group) in randomized withdrawal period by treatment group (Randomized withdrawal safety set)

Preferred term	LCI699 0.25 QD /Active (N=46) n (%)	LCI699 0.25 QD /Placebo (N=38) n (%)	LCI699 0.5 QD /Active (N=44) n (%)	LCI699 0.5 QD /Placebo (N=37) n (%)	LCI699 1.0 QD /Active (N=41) n (%)	LCI699 1.0 QD /Placebo (N=37) n (%)
Any Adverse Events						
Total	2 (4.3)	1 (2.6)	1 (2.3)	0	3 (7.3)	5 (13.5)
Contusion	0	0	0	0	1 (2.4)	0
Cough	0	0	0	0	1 (2.4)	0
Epistaxis	0	1 (2.6)	0	0	1 (2.4)	0
Rash	0	0	1 (2.3)	0	0	0
Back pain	1 (2.2)	0	0	0	0	0
Urinary incontinence	1 (2.2)	0	0	0	0	0
Cervicobrachial syndrome	0	0	0	0	0	0
Nasopharyngitis	0	0	0	0	0	0
Oropharyngeal pain	0	0	0	0	0	0
Spinal disorder	0	0	0	0	0	0
Abdominal pain lower	0	0	0	0	0	1 (2.7)
Angina pectoris	0	0	0	0	0	0
Arthralgia	0	0	0	0	0	0

Preferred term	LCI699 0.25 QD /Active (N=46) n (%)	LCI699 0.25 QD /Placebo (N=38) n (%)	LCI699 0.5 QD /Active (N=44) n (%)	LCI699 0.5 QD /Placebo (N=37) n (%)	LCI699 1.0 QD /Active (N=41) n (%)	LCI699 1.0 QD /Placebo (N=37) n (%)
Headache	0	0	0	0	0	1 (2.7)
Hypertriglyceridaemia	0	0	0	0	0	0
Joint sprain	0	0	0	0	0	1 (2.7)
Myalgia	0	0	0	0	0	1 (2.7)
Oedema peripheral	0	1 (2.6)	0	0	0	0
Syncope	0	0	0	0	0	1 (2.7)
Tachycardia	0	0	0	0	0	0

NOVARTIS

Number (%) of patients with most common adverse events (greater than or 2% in any group) in randomized withdrawal period by treatment group (Randomized withdrawal safety set) (ctd)

Preferred term	LCI699 0.5 BID /Active (N=45) n (%)	LCI699 0.5 BID /Placebo (N=45) n (%)	LCI699 total /Active (N=176) n (%)	LCI699 total /Placebo (N=157) n (%)	Eplerenone 50 BID /Active (N=39) n (%)	Eplerenone 50 BID /Placebo (N=36) n (%)	Placebo /Placebo (N=66) n (%)
Any Adverse Events							
Total	4 (8.9)	3 (6.7)	10 (5.7)	9 (5.7)	2 (5.1)	0	3 (4.5)
Contusion	0	0	1 (0.6)	0	0	0	0
Cough	0	0	1 (0.6)	0	0	0	0
Epistaxis	0	0	1 (0.6)	1 (0.6)	0	0	0
Rash	0	0	1 (0.6)	0	0	0	0
Back pain	0	0	1 (0.6)	0	1 (2.6)	0	0
Urinary incontinence	0	0	1 (0.6)	0	0	0	0
Cervicobrachial syndrome	1 (2.2)	0	1 (0.6)	0	0	0	0
Nasopharyngitis	1 (2.2)	1 (2.2)	1 (0.6)	1 (0.6)	0	0	0
Oropharyngeal pain	1 (2.2)	0	1 (0.6)	0	0	0	0
Spinal disorder	1 (2.2)	0	1 (0.6)	0	0	0	0
Abdominal pain lower	0	0	0	1 (0.6)	0	0	0
Angina pectoris	0	1 (2.2)	0	1 (0.6)	0	0	0
Arthralgia	0	0	0	0	1 (2.6)	0	0

Preferred term	LCI699 0.5 BID /Active (N=45) n (%)	LCI699 0.5 BID /Placebo (N=45) n (%)	LCI699 total /Active (N=176) n (%)	LCI699 total /Placebo (N=157) n (%)	Eplerenone 50 BID /Active (N=39) n (%)	Eplerenone 50 BID /Placebo (N=36) n (%)	Placebo /Placebo (N=66) n (%)
Headache	0	1 (2.2)	0	2 (1.3)	0	0	0
Hypertriglyceridaemia	0	1 (2.2)	0	1 (0.6)	0	0	0
Joint sprain	0	0	0	1 (0.6)	0	0	0
Myalgia	0	0	0	1 (0.6)	0	0	0
Oedema peripheral	0	0	0	1 (0.6)	0	0	0
Syncope	0	0	0	1 (0.6)	0	0	0
Tachycardia	0	1 (2.2)	0	1 (0.6)	0	0	0

NOVARTIS

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

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

	LCI699 0.25 QD /Active (N=46) n (%)	LCI699 0.25 QD /Placebo (N=38) n (%)	LCI699 0.5 QD /Active (N=44) n (%)	LCI699 0.5 QD /Placebo (N=37) n (%)	LCI699 1.0 QD /Active (N=41) n (%)	LCI699 1.0 QD /Placebo (N=37) n (%)
Patients with AE(s)	2 (4.3)	1 (2.6)	1 (2.3)	0	3 (7.3)	5 (13.5)
Serious and other significant events						
Deaths	0	0	0	0	0	0
SAEs	0	0	0	0	0	0
AE discontinuations	0	0	0	0	0	0
Discontinuations for abnormal lab values	0	0	0	0	0	0

	LCI699 0.5 BID /Active (N=45) n (%)	LCI699 0.5 BID /Placebo (N=45) n (%)	LCI699 total /Active (N=176) n (%)	LCI699 total /Placebo (N=157) n (%)	Eplerenone 50 BID /Active (N=39) n (%)	Eplerenone 50 BID /Placebo (N=36) n (%)	Placebo /Placebo (N=66) n (%)
Patients with AE(s)	4 (8.9)	3 (6.7)	10 (5.7)	9 (5.7)	2 (5.1)	0	3 (4.5)
Serious and other signif. events							
Deaths	0	0	0	0	0	0	0
SAEs	0	0	0	0	0	0	0
AE discontinuations	0	0	0	0	0	0	0
Discontinuations for abnormal lab values	0	0	0	0	0	0	0

Conclusion:

- The study achieved its primary objective of demonstrating a reduction in BP with LCI699 compared to placebo.
- This was the first clear demonstration of efficacy with an aldosterone synthase inhibitor (ASI) in patients with mild-moderate essential hypertension.
- BID dosing of LCI699 appeared to offer no clinical advantage compared to once daily dosing.
- At the doses evaluated, there is no evidence that LCI699 is superior in BP lowering toeplerenone (50 mg BID) in mild-moderate hypertension.
- The effects of LCI699 and eplerenone on potassium disposition, as assessed by the incidence of hyperkalemia and changes in mean potassium concentration, were similar in this study population with normal renal function.
- The clinical significance of the observed effect of LCI699 on the cortisol axis is unknown. However, these results would appear to limit the therapeutic index of this ASI.
- Based on the predicted narrow therapeutic index, further development of LCI699 in general or broad hypertension needs to be re-evaluated.
- LCI699 may be considered for other indications where low doses may be effective, or where suppression of both aldosterone and stimulated cortisol may be of benefit

Date of Clinical Trial Report

17-Jun-2010