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Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

LCI699

Trial Indication(s)

Hypertension

Protocol Number

CLCI699A2216

Protocol Title

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

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

22-Dec-2008 to 13-0ct-2009

Reason for Termination

Not applicable.

Study Design/Methodology

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

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

Eligible patients had mean systolic blood pressures ≥ 140 and < 180 and met all other inclusion/ exclusion criteria. After a 2-week single-blind nm-in period of placebo, patients who continued to meet the entry criteria were randomized to placebo, LCI699 0.25 mg BID, LCI699 1.0 mg QD or eplerenone 50 mg BID for 8 weeks, or LCI699 0.5 mg BID for 4 weeks followed by LCI699 1.0 mg BID for 4 weeks.

Centers

35 centers in 2 countries: United States (34); Iceland (1)

Objectives:

Primary objective

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

Secondary objective(s)

- To explore the efficacy LCI699 by testing the hypotheses that the change from baseline in mean sitting diastolic blood pressure (MSDBP) is superior to that of placebo after 8 weeks of treatment.
- To explore the dose/exposure response relationship of LCI699 in the change from baseline in MSSBP and MSDBP after 8 weeks of treatment.
- To explore whether the changes from baseline in mean 24 hour SBP and DBP with the three dose regimens ofLCI699 are superior to that of placebo after 8 weeks of treatment.
- To evaluate the safety and tolerability of LCI699 including, but not limited to: cortisol levels following ACTH stimulation, hyperkalemia, hyponatremia

- To assess the functional consequences of aldosterone inhibition by evaluating the efficacy and safety of LCI699 compared to eplerenone 50 mg BID after 8 weeks of treatment.

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

LCI699 was supplied as 0.25mg, 0.5mg and 1.0mg capsules and matching placebo capsules. Eplerenone was supplied as 50mg capsules and matching placebo capsules

Statistical Methods

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

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

Study Population: Key Inclusion/Exclusion Criteria

Inclusion criteria

• Diagnosis of hypertension with mean sitting systolic blood pressure (MSSBP) ≥140 millimeters of mercury (mmHg) and <180 mmHg
• Stable on a three-drug regimen (including a diuretic) for at least 4 weeks for the treatment of resistant hypertension
• Male and female participants 18 to 75 years of age

Exclusion criteria:

• Recent history of myocardial infarction (MI), heart failure, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, hypertensive encephalopathy, cerebrovascular accident, or transient ischemic attack
• Clinically significant electrocardiography (ECG) findings related to cardiac conduction defects
• Type 1 diabetes or uncontrolled type 2 diabetes (haemoglobin A1c [HbA1c] >9%)
• Malignancies within the last 5 years (excluding basal cell skin cancer)
Other protocol-defined inclusion/exclusion criteria may apply.

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Participant Flow Table

Patient disposition – n (%) of patients (Randomized set)

Disposition	LCI699 0.25mg BID N=32 n (%)	LCI699 1.0mg QD N=26 n (%)	LCI699 0.5/1mg BID N=31 n (%)	Eplerenone 50mg BID N=33 n (%)	Placebo N=33 n (%)	Overall Total N=155 n (%)
Completed	23 (71.9)	22 (84.6)	28 (90.3)	28 (84.8)	25 (75.8)	126 (81.3)
Discontinued	9 (28.1)	4 (15.4)	3 (9.7)	5 (15.2)	8 (24.2)	29 (18.7)
Reason for discontinuation						
Adverse Event(s)	1 (3.1)	0	0	1 (3.0)	1 (3.0)	3 (1.9)
Abnormal laboratory value(s)	1 (3.1)[1]	1 (3.8)	0	0	1 (3.0)	3 (1.9)
Subject withdrew consent	2 (6.3)	1 (3.8)	0	1 (3.0)	2 (6.1)	6 (3.9)
Lost to follow-up	0	1 (3.8)	0	1 (3.0)	0	2 (1.3)
Administrative problems	0	0	0	0	1 (3.0)	1 (0.6)
Death	0	0	0	0	0	0
Protocol deviation	5 (15.6)	1 (3.8)	3 (9.7)	2 (6.1)	3 (9.1)	14 (9.0)

Categories are mutually exclusive.

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Baseline Characteristics

Demographic summary by treatment group (Full analysis set)

Demographic variable	LCI699 0.25mg BID N=32	LCI699 1mg QD N=26	LCI699 0.5/1mg BID N=31	Eplerenone 50mg BID N=33	Placebo N=33	Overall Total N=155
Age (years)						
n	32	26	31	33	33	155
Mean	53.6	55.4	57.2	56.2	59.8	56.5
SD	10.36	9.58	10.77	7.70	9.33	9.69
Median	54.0	58.0	58.0	56.0	62.0	57.0
Age group (years) – n (%)						
<65	28 (87.5)	23 (88.5)	23 (74.2)	30 (90.9)	20 (60.6)	124 (80.0)
>=65	4 (12.5)	3 (11.5)	8 (25.8)	3 (9.1)	13 (39.4)	31 (20.0)
Sex – n (%)						
Male	20 (62.5)	18 (69.2)	18 (58.1)	19 (57.6)	22 (66.7)	97 (62.6)
Female	12 (37.5)	8 (30.8)	13 (41.9)	14 (42.4)	11 (33.3)	58 (37.4)
Race – n (%)						
Caucasian	21 (65.6)	15 (57.7)	21 (67.7)	18 (54.5)	22 (66.7)	97 (62.6)
Black	11 (34.4)	9 (34.6)	10 (32.3)	14 (42.4)	11 (33.3)	55 (35.5)
Asian	0	0	0	0	0	0
Other	0	2 (7.7)	0	1 (3.0)	0	3 (1.9)
Baseline weight (kg)						
n	32	26	31	33	33	155
Mean	101.1	94.4	99.3	99.3	93.0	97.5
SD	20.25	16.08	21.70	18.86	21.73	19.96

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Demographic variable	LCI699 0.25mg BID N=32	LCI699 1mg QD N=26	LCI699 0.5/1mg BID N=31	Eplerenone 50mg BID N=33	Placebo N=33	Overall Total N=155
Median	101.4	95.4	90.9	96.8	90.0	95.4
Baseline BMI (kg/m^2)						
n	32	26	31	33	33	155
Mean	33.95	32.18	33.49	33.23	31.92	32.98
SD	5.918	5.286	8.128	5.519	7.785	6.632
Median	33.39	30.35	32.20	32.55	30.76	32.20
Baseline waist circumference (cm) (males)						
n	19	18	18	19	22	96
Mean	109.6	106.1	107.9	109.4	109.4	108.5
SD	12.58	7.16	11.11	12.29	11.98	11.10
Median	109.3	107.3	106.5	107.0	109.0	108.0
Baseline waist circumference (cm) (females)						
n	11	8	13	13	11	56
Mean	109.3	99.7	112.1	102.4	93.1	103.8
SD	14.33	19.24	17.13	13.93	17.45	17.15
Median	109.0	97.5	110.0	100.0	91.0	102.0

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

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Primary 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
LCI699 0.25mg BID	31	-11.4	2.96	(-17.2, -5.5)

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

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

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

P-values not adjusted for multiple comparisons.

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Secondary Outcome Result(s)

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

Treatment group	n	Mean change from baseline	SE	95% CI	
LCI699 0.25mg BID	31	-4.5	1.72	(-7.9, -1.1)	
LCI699 1mg QD	26	-6.0	1.88	(-9.7, -2.3)	
LCI699 0.5/1mg BID	31	-6.1	1.72	(-9.5, -2.7)	
Eplerenone 50mg BID	32	-7.7	1.69	(-11.0, -4.3)	
Placebo	33	-4.8	1.66	(-8.1, -1.5)	
Comparisons vs. Placebo		**Mean difference change from baseline**	**SE**	**90% CI**	**Two-sided P-value**
LCI699 0.25mg BID – Placebo		0.3	2.39	(-3.6, 4.3)	0.894
LCI699 1mg QD – Placebo		-1.2	2.51	(-5.3, 3.0)	0.638
LCI699 0.5/1mg BID – Placebo		-1.2	2.39	(-5.2, 2.7)	0.604
Eplerenone – Placebo		-2.9	2.37	(-6.8, 1.1)	0.230
Comparisons vs. Eplerenone					
LCI699 0.25mg BID – Eplerenone		3.2	2.42	(-0.8, 7.2)	0.191
LCI699 1mg QD – Eplerenone		1.7	2.53	(-2.5, 5.9)	0.508
LCI699 0.5/1mg BID – Eplerenone		1.6	2.41	(-2.4, 5.6)	0.503

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

P-values not adjusted for multiple comparisons.

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Number (percent) of patients achieving a blood pressure response and blood pressure control at Week 8 LOCF (Full analysis set)

	LCI699 0.25mg BID N=32 n/N (%)	LCI699 1mg QD N=26 n/N (%)	LCI699 0.5/1mg BID N=31 n/N (%)	Eplerenone 50mg BID N=33 n/N (%)	Placebo N=33 n/N (%)
SBP Response (<140mmHg or reduction from baseline >=20mmHg)	17/31 (54.8)	15/26 (57.7)	13/31 (41.9)	21/32 (65.6)	14/33 (42.4)
DBP Response (<90mmHg or reduction from baseline >=10mmHg)	21/31 (67.7)	19/26 (73.1)	22/31 (71.0)	23/32 (71.9)	19/33 (57.6)
SBP Control (<140mmHg for non-diabetics and <130mHg for diabetics)	16/31 (51.6)	13/26 (50.0)	10/31 (32.3)	17/32 (53.1)	12/33 (36.4)
DBP Control (<90mmHg for non-diabetics and <80mHg for diabetics)	17/31 (54.8)	17/26 (65.4)	18/31 (58.1)	18/32 (56.3)	18/33 (54.5)
Both SBP and DBP Control	13/31 (41.9)	12/26 (46.2)	8/31 (25.8)	14/32 (43.8)	11/33 (33.3)

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

Treatment group	n	Mean change from baseline	SE	95% CI	
LCI699 0.25mg BID	31	-4.5	1.72	(-7.9, -1.1)	
LCI699 1mg QD	26	-6.0	1.88	(-9.7, -2.3)	
LCI699 0.5/1mg BID	31	-6.1	1.72	(-9.5, -2.7)	
Eplerenone 50mg BID	32	-7.7	1.69	(-11.0, -4.3)	
Placebo	33	-4.8	1.66	(-8.1, -1.5)	
Comparisons vs. Placebo		**Mean difference change from baseline**	**SE**	**90% CI**	**Two-sided P-value**
LCI699 0.25mg BID – Placebo		0.3	2.39	(-3.6, 4.3)	0.894
LCI699 1mg QD – Placebo		-1.2	2.51	(-5.3, 3.0)	0.638
LCI699 0.5/1mg BID – Placebo		-1.2	2.39	(-5.2, 2.7)	0.604
Eplerenone – Placebo		-2.9	2.37	(-6.8, 1.1)	0.230
Comparisons vs. Eplerenone					
LCI699 0.25mg BID – Eplerenone		3.2	2.42	(-0.8, 7.2)	0.191
LCI699 1mg QD – Eplerenone		1.7	2.53	(-2.5, 5.9)	0.508
LCI699 0.5/1mg BID – Eplerenone		1.6	2.41	(-2.4, 5.6)	0.503

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

P-values not adjusted for multiple comparisons.

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Number (percent) of patients achieving a blood pressure response and blood pressure control at Week 8 LOCF (Full analysis set)

	LCI699 0.25mg BID N=32 n/N (%)	LCI699 1mg QD N=26 n/N (%)	LCI699 0.5/1mg BID N=31 n/N (%)	Eplerenone 50mg BID N=33 n/N (%)	Placebo N=33 n/N (%)
SBP Response (<140mmHg or reduction from baseline >=20mmHg)	17/31 (54.8)	15/26 (57.7)	13/31 (41.9)	21/32 (65.6)	14/33 (42.4)
DBP Response (<90mmHg or reduction from baseline >=10mmHg)	21/31 (67.7)	19/26 (73.1)	22/31 (71.0)	23/32 (71.9)	19/33 (57.6)
SBP Control (<140mmHg for non-diabetics and <130mHg for diabetics)	16/31 (51.6)	13/26 (50.0)	10/31 (32.3)	17/32 (53.1)	12/33 (36.4)
DBP Control (<90mmHg for non-diabetics and <80mHg for diabetics)	17/31 (54.8)	17/26 (65.4)	18/31 (58.1)	18/32 (56.3)	18/33 (54.5)
Both SBP and DBP Control	13/31 (41.9)	12/26 (46.2)	8/31 (25.8)	14/32 (43.8)	11/33 (33.3)

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

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

Treatment group	n	Mean change from baseline	SE	95% CI
LCI699 0.25mg BID	31	-11.4	2.96	(-17.2, -5.5)
LCI699 1.0mg QD	26	-13.1	3.24	(-19.5, -6.7)
LCI699 0.5/1mg BID	31	-12.5	2.96	(-18.4, -6.7)
Eplerenone 50mg BID	32	-18.7	2.92	(-24.5, -12.9)
Placebo	33	-8.8	2.87	(-14.5, -3.1)

Comparisons vs. Placebo	Mean difference change from baseline	SE	90% CI	Two-sided P-value
LCI699 0.25mg BID – Placebo	-2.6	4.13	(-9.4, 4.3)	0.536
LCI699 1.0mg QD – Placebo	-4.3	4.33	(-11.5, 2.9)	0.323
LCI699 0.5/1mg BID – Placebo	-3.7	4.13	(-10.6, 3.1)	0.369
Eplerenone – Placebo	-9.9	4.09	(-16.7, -3.1)	0.017

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

P-values not adjusted for multiple comparisons.

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

Treatment group	n	Mean change from baseline	SE	95% CI	
LCI699 0.25mg BID	31	-4.5	1.72	(-7.9, -1.1)	
LCI699 1mg QD	26	-6.0	1.88	(-9.7, -2.3)	
LCI699 0.5/1mg BID	31	-6.1	1.72	(-9.5, -2.7)	
Eplerenone 50mg BID	32	-7.7	1.69	(-11.0, -4.3)	
Placebo	33	-4.8	1.66	(-8.1, -1.5)	
Comparisons vs. Placebo		**Mean difference change from baseline**	**SE**	**90% CI**	**Two-sided P-value**
LCI699 0.25mg BID – Placebo		0.3	2.39	(-3.6, 4.3)	0.894
LCI699 1mg QD – Placebo		-1.2	2.51	(-5.3, 3.0)	0.638
LCI699 0.5/1mg BID – Placebo		-1.2	2.39	(-5.2, 2.7)	0.604
Eplerenone – Placebo		-2.9	2.37	(-6.8, 1.1)	0.230
Comparisons vs. Eplerenone					
LCI699 0.25mg BID – Eplerenone		3.2	2.42	(-0.8, 7.2)	0.191
LCI699 1mg QD – Eplerenone		1.7	2.53	(-2.5, 5.9)	0.508
LCI699 0.5/1mg BID – Eplerenone		1.6	2.41	(-2.4, 5.6)	0.503

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

P-values not adjusted for multiple comparisons.

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

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
24-hour mean SBP	LCI699 0.25mg BID	15	-4.4	3.22	(-10.8, 2.0)	
	LCI699 1mg QD	19	-5.7	2.87	(-11.4, -0.0)	
	LCI699 0.5/1mg BID	26	-6.3	2.47	(-11.2, -1.4)	
	Eplerenone 50mg BID	23	-15.7	2.59	(-20.9, -10.6)	
	Placebo	23	-1.0	2.59	(-6.1, 4.1)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		-3.4	4.14	(-10.3, 3.5)	0.412
	LCI699 1mg QD – Pbo		-4.7	3.86	(-11.1, 1.7)	0.223
	LCI699 0.5/1mg BID – Pbo		-5.3	3.59	(-11.3, 0.6)	0.142
	Eplerenone – Pbo		-14.7	3.66	(-20.8, -8.6)	<.001

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
Daytime mean SBP	LCI699 0.25mg BID	15	-4.9	3.29	(-11.4, 1.6)	
	LCI699 1mg QD	19	-6.0	2.92	(-11.8, -0.2)	
	LCI699 0.5/1mg BID	26	-6.3	2.52	(-11.3, -1.3)	
	Eplerenone 50mg BID	23	-15.7	2.65	(-21.0, -10.5)	
	Placebo	23	-1.6	2.65	(-6.9, 3.7)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		-3.3	4.24	(-10.3, 3.7)	0.439
	LCI699 1mg QD – Pbo		-4.4	3.94	(-10.9, 2.2)	0.271
	LCI699 0.5/1mg BID – Pbo		-4.7	3.67	(-10.8, 1.4)	0.206
	Eplerenone – Pbo		-14.1	3.74	(-20.3, -7.9)	<.001

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
Nighttime mean SBP	LCI699 0.25mg BID	15	-3.2	3.49	(-10.1, 3.8)	
	LCI699 1mg QD	19	-4.8	3.13	(-11.0, 1.4)	
	LCI699 0.5/1mg BID	26	-7.0	2.67	(-12.3, -1.7)	
	Eplerenone 50mg BID	23	-15.4	2.81	(-21.0, -9.9)	
	Placebo	23	0.4	2.81	(-5.2, 6.0)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		-3.6	4.48	(-11.0, 3.9)	0.430
	LCI699 1mg QD – Pbo		-5.2	4.20	(-12.2, 1.8)	0.218
	LCI699 0.5/1mg BID – Pbo		-7.4	3.88	(-13.8, -0.9)	0.060

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

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
24-hour mean DBP	LCI699 0.25mg BID	15	1.0	2.15	(-3.3, 5.2)	
	LCI699 1mg QD	19	-3.4	1.94	(-7.2, 0.5)	
	LCI699 0.5/1mg BID	26	-3.7	1.67	(-7.0, -0.3)	
	Eplerenone 50mg BID	23	-9.6	1.74	(-13.1, -6.2)	
	Placebo	23	-0.2	1.74	(-3.7, 3.2)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		1.2	2.77	(-3.4, 5.8)	0.660
	LCI699 1mg QD – Pbo		-3.1	2.58	(-7.4, 1.2)	0.228
	LCI699 0.5/1mg BID – Pbo		-3.4	2.44	(-7.5, 0.6)	0.166
	Eplerenone – Pbo		-9.4	2.46	(-13.5, -5.3)	<.001
Variable	**Treatment group**	**n**	**Mean change from baseline**	**SE**	**95% CI**	
Daytime mean DBP	LCI699 0.25mg BID	15	0.6	2.31	(-3.9, 5.2)	
	LCI699 1mg QD	19	-3.6	2.06	(-7.7, 0.5)	
	LCI699 0.5/1mg BID	26	-3.4	1.78	(-6.9, 0.1)	
	Eplerenone 50mg BID	23	-9.5	1.86	(-13.2, -5.9)	
	Placebo	23	-0.8	1.87	(-4.5, 2.9)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		1.4	2.97	(-3.5, 6.3)	0.636
	LCI699 1mg QD – Pbo		-2.8	2.77	(-7.4, 1.8)	0.316
	LCI699 0.5/1mg BID – Pbo		-2.6	2.61	(-7.0, 1.7)	0.316
	Eplerenone – Pbo		-8.8	2.64	(-13.2, -4.4)	0.001
Variable	**Treatment group**	**n**	**Mean change from baseline**	**SE**	**95% CI**	
Nighttime mean DBP	LCI699 0.25mg BID	15	1.9	2.17	(-2.4, 6.2)	
	LCI699 1mg QD	19	-2.5	1.98	(-6.4, 1.5)	
	LCI699 0.5/1mg BID	26	-4.6	1.69	(-8.0, -1.3)	
	Eplerenone 50mg BID	23	-9.6	1.75	(-13.1, -6.1)	
	Placebo	23	1.2	1.76	(-2.3, 4.7)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		0.7	2.80	(-3.9, 5.3)	0.804
	LCI699 1mg QD – Pbo		-3.6	2.62	(-8.0, 0.7)	0.168
	LCI699 0.5/1mg BID – Pbo		-5.8	2.46	(-9.9, -1.7)	0.020
	Eplerenone – Pbo		-10.8	2.49	(-14.9, -6.6)	<.001

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

NOVARTIS

Between treatment analysis of change from baseline in SBP at Week 4 as measured by ABPM (Full analysis set)

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
24-hour mean SBP	LCI699 0.25mg BID	12	-5.6	3.32	(-12.2, 1.0)	
	LCI699 1mg QD	18	-7.8	2.72	(-13.2, -2.4)	
	LCI699 0.5/1mg BID	26	-4.7	2.29	(-9.3, -0.2)	
	Eplerenone 50mg BID	19	-12.7	2.63	(-17.9, -7.5)	
	Placebo	22	-2.8	2.44	(-7.7, 2.0)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		-2.8	4.13	(-9.6, 4.1)	0.506
	LCI699 1mg QD – Pbo		-5.0	3.65	(-11.1, 1.1)	0.173
	LCI699 0.5/1mg BID – Pbo		-1.9	3.34	(-7.5, 3.6)	0.568
	Eplerenone – Pbo		-9.9	3.59	(-15.9, -3.9)	0.007
	BID vs. QD comparison					
	0.5mg BID - 1mg QD		3.1	3.59	(-2.9, 9.1)	0.391

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
Daytime mean SBP	LCI699 0.25mg BID	12	-6.5	3.30	(-13.1, 0.1)	
	LCI699 1mg QD	18	-8.1	2.69	(-13.5, -2.8)	
	LCI699 0.5/1mg BID	26	-5.3	2.27	(-9.8, -0.8)	
	Eplerenone 50mg BID	19	-12.7	2.62	(-17.9, -7.5)	
	Placebo	22	-3.8	2.43	(-8.6, 1.1)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		-2.7	4.10	(-9.6, 4.1)	0.506
	LCI699 1mg QD – Pbo		-4.4	3.62	(-10.4, 1.7)	0.232
	LCI699 0.5/1mg BID – Pbo		-1.5	3.33	(-7.1, 4.0)	0.646
	Eplerenone – Pbo		-8.9	3.57	(-14.8, -3.0)	0.014
	BID vs. QD comparison					
	0.5mg BID - 1mg QD		2.8	3.56	(-3.1, 8.7)	0.430

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
Nighttime mean SBP	LCI699 0.25mg BID	12	-3.4	3.85	(-11.0, 4.3)	
	LCI699 1mg QD	18	-6.8	3.17	(-13.1, -0.5)	
	LCI699 0.5/1mg BID	25	-4.5	2.70	(-9.9, 0.8)	
	Eplerenone 50mg BID	19	-12.5	3.04	(-18.6, -6.5)	
	Placebo	22	-0.6	2.83	(-6.2, 5.0)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**

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Between treatment analysis of change from baseline in DBP at Week 4 as measured by ABPM (Full analysis set)

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
24-hour mean DBP	LCI699 0.25mg BID	12	0.5	2.40	(-4.3, 5.2)	
	LCI699 1mg QD	18	-4.3	1.98	(-8.2, -0.4)	
	LCI699 0.5/1mg BID	26	-2.5	1.67	(-5.8, 0.9)	
	Eplerenone 50mg BID	19	-8.7	1.89	(-12.5, -4.9)	
	Placebo	22	-2.0	1.76	(-5.5, 1.5)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		2.4	2.98	(-2.5, 7.4)	0.415
	LCI699 1mg QD – Pbo		-2.3	2.64	(-6.7, 2.1)	0.379
	LCI699 0.5/1mg BID – Pbo		-0.5	2.44	(-4.6, 3.6)	0.842
	Eplerenone – Pbo		-6.7	2.59	(-11.0, -2.4)	0.011
	BID vs. QD comparison					
	0.5mg BID - 1mg QD		1.8	2.64	(-2.6, 6.2)	0.488

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
Daytime mean DBP	LCI699 0.25mg BID	12	-0.5	2.50	(-5.4, 4.5)	
	LCI699 1mg QD	18	-3.9	2.04	(-8.0, 0.2)	
	LCI699 0.5/1mg BID	26	-2.6	1.73	(-6.0, 0.9)	
	Eplerenone 50mg BID	19	-8.6	1.97	(-12.5, -4.7)	
	Placebo	22	-2.5	1.84	(-6.2, 1.1)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		2.1	3.10	(-3.1, 7.2)	0.505
	LCI699 1mg QD – Pbo		-1.4	2.74	(-5.9, 3.2)	0.618
	LCI699 0.5/1mg BID – Pbo		-0.0	2.54	(-4.2, 4.2)	0.994
	Eplerenone – Pbo		-6.1	2.69	(-10.5, -1.6)	0.027
	BID vs. QD comparison					
	0.5mg BID - 1mg QD		1.3	2.72	(-3.2, 5.9)	0.622

Variable	Treatment group	n	Mean change from baseline	SE	95% CI	
Nighttime mean DBP	LCI699 0.25mg BID	12	2.7	2.65	(-2.6, 7.9)	
	LCI699 1mg QD	18	-4.5	2.21	(-8.9, -0.1)	
	LCI699 0.5/1mg BID	25	-2.8	1.87	(-6.5, 0.9)	
	Eplerenone 50mg BID	19	-9.0	2.09	(-13.1, -4.8)	
	Placebo	22	-0.6	1.94	(-4.5, 3.3)	
	Comparisons vs. Placebo		**Mean difference change from BL**	**SE**	**90% CI**	**2-sided P-value**
	LCI699 0.25mg BID – Pbo		3.2	3.29	(-2.2, 8.7)	0.326
	LCI699 1mg QD – Pbo		-3.9	2.93	(-8.8, 0.9)	0.182
	LCI699 0.5/1mg BID – Pbo		-2.2	2.71	(-6.7, 2.3)	0.418

Number (percent) of patients with cortisol levels below 400nmol/L and 500nmol/L at 1hr after ACTH injection at the Week 8 visit ACTH stimulation test subset)

Threshold	LCI699 0.25mg BID n/N (%)	LCI699 1mg QD n/N (%)	LCI699 0.5/1mg BID n/N (%)	LCI699 Total n/N (%)	Eplerenone 50mg BID n/N (%)	Placebo n/N (%)
<400nmol/L	0/5 (0.0)	0/4 (0.0)	3/6 (50.0)	3/15 (20.0)	0/7 (0.0)	0/7 (0.0)
<500nmol/L	0/5 (0.0)	1/4 (25.0)	4/6 (66.7)	5/15 (33.3)	0/7 (0.0)	0/7 (0.0)

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

Analysis of covariance for percent change from baseline in renin-angiotensin-aldosterone-system (RAAS) biomarkers Full analysis set

Variable: Aldosterone at Week 8 LOCF

Treatment group	n	Geometric LSM (% change)	SE	95% CI
LCI699 0.25mg BID	27	-22.3	0.16	(-43.0, 6.0)
LCI699 1.0mg QD	23	-30.4	0.17	(-50.4, -2.4)
LCI699 0.5/1mg BID	29	-53.1	0.15	(-65.2, -36.7)
Eplerenone 50mg BID	31	115.0	0.15	(61.0, 187.1)
Placebo	27	-5.0	0.16	(-30.3, 29.6)

Pairwise comparisons vs Placebo	Difference of LSMs (%)	SE	90% CI	Two-sided p-value
LCI699 0.25mg BID / Placebo	-18.2	0.22	(-43.3, 18.0)	0.365
LCI699 1.0mg QD / Placebo	-26.8	0.23	(-50.2, 7.6)	0.182
LCI699 0.5/1mg BID / Placebo	-50.7	0.22	(-65.6, -29.2)	0.001
Eplerenone 50mg BID / Placebo	126.2	0.21	(58.5, 222.6)	<.001
Pairwise comparisons vs Eplerenone				
LCI699 0.25mg BID / Eplerenone	-63.8	0.21	(-74.7, -48.4)	<.001
LCI699 1.0mg QD / Eplerenone	-67.6	0.22	(-77.7, -53.0)	<.001
LCI699 0.5/1mg BID / Eplerenone	-78.2	0.21	(-84.6, -69.1)	<.001

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Variable: Plasma renin activity at Week 8 LOCF

Treatment group	n	Geometric LSM (% change)	SE	95% CI
LCI699 0.25mg BID	27	41.6	0.24	(-11.4, 126.2)
LCI699 1.0mg QD	20	74.3	0.28	(1.0, 200.6)
LCI699 0.5/1mg BID	27	107.7	0.24	(30.0, 231.8)
Eplerenone 50mg BID	31	414.1	0.22	(231.4, 697.5)
Placebo	26	-2.1	0.24	(-39.4, 58.2)

Pairwise comparisons vs Placebo	Difference of LSMs (%)	SE	90% CI	Two-sided p-value
LCI699 0.25mg BID / Placebo	44.7	0.34	(-17.5, 153.6)	0.278
LCI699 1.0mg QD / Placebo	78.1	0.37	(-3.2, 227.5)	0.119
LCI699 0.5/1mg BID / Placebo	112.2	0.34	(21.1, 272.1)	0.028
Eplerenone 50mg BID / Placebo	425.3	0.33	(204.0, 807.8)	<.001
Pairwise comparisons vs Eplerenone				
LCI699 0.25mg BID / Eplerenone	-72.5	0.32	(-83.9, -52.8)	<.001
LCI699 1.0mg QD / Eplerenone	-66.1	0.35	(-81.1, -39.1)	0.003
LCI699 0.5/1mg BID / Eplerenone	-59.6	0.32	(-76.4, -30.8)	0.006

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Variable: Active Renin at Week 8 LOCF

Treatment group	n	Geometric LSM (% change)	SE	95% CI
LCI699 0.25mg BID	27	73.1	0.24	(8.7, 175.6)
LCI699 1.0mg QD	21	72.8	0.27	(1.9, 192.8)
LCI699 0.5/1mg BID	28	156.4	0.23	(62.4, 304.7)
Eplerenone 50mg BID	30	430.6	0.22	(241.3, 725.0)
Placebo	26	26.3	0.24	(-21.4, 103.0)

Pairwise comparisons vs Placebo	Difference of LSMs (%)	SE	90% CI	Two-sided p-value
LCI699 0.25mg BID / Placebo	37.0	0.34	(-21.5, 139.2)	0.350
LCI699 1.0mg QD / Placebo	36.8	0.36	(-24.5, 147.6)	0.384
LCI699 0.5/1mg BID / Placebo	103.0	0.33	(17.0, 252.1)	0.035
Eplerenone 50mg BID / Placebo	320.0	0.33	(144.0, 623.1)	<.001
Pairwise comparisons vs Eplerenone				
LCI699 0.25mg BID / Eplerenone	-67.4	0.32	(-80.9, -44.2)	<.001
LCI699 1.0mg QD / Eplerenone	-67.4	0.35	(-81.7, -42.1)	0.002
LCI699 0.5/1mg BID / Eplerenone	-51.7	0.32	(-71.6, -17.8)	0.025

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Variable: Ratio of plasma aldosterone to PRA at Week 8 LOCF

Treatment group	n	Geometric LSM (% change)	SE	95% CI
LCI699 0.25mg BID	26	-46.7	0.26	(-67.8, -11.7)
LCI699 1.0mg QD	20	-50.0	0.29	(-71.9, -11.0)
LCI699 0.5/1mg BID	27	-78.3	0.25	(-86.8, -64.4)
Eplerenone 50mg BID	31	-57.1	0.23	(-73.0, -31.8)
Placebo	26	-5.1	0.26	(-42.8, 57.4)

Pairwise comparisons vs Placebo	Difference of LSMs (%)	SE	90% CI	Two-sided p-value
LCI699 0.25mg BID / Placebo	-43.8	0.36	(-69.1, 2.2)	0.113
LCI699 1.0mg QD / Placebo	-47.3	0.39	(-72.3, 0.1)	0.100
LCI699 0.5/1mg BID / Placebo	-77.1	0.36	(-87.4, -58.6)	<.001
Eplerenone 50mg BID / Placebo	-54.8	0.35	(-74.6, -19.6)	0.024
Pairwise comparisons vs Eplerenone				
LCI699 0.25mg BID / Eplerenone	24.2	0.35	(-30.0, 120.4)	0.533
LCI699 1.0mg QD / Eplerenone	16.5	0.37	(-37.4, 116.6)	0.684
LCI699 0.5/1mg BID / Eplerenone	-49.4	0.34	(-71.3, -10.8)	0.049

Safety Results

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

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

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

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

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

Preferred terms are sorted in descending frequency, as reported in column LCI699 Total column.

A patient with multiple adverse events is counted only once in the "Any preferred term" row.

A patient with multiple occurrences of an adverse event is only counted once for this event.

* Also includes the code of "Blood sodium decreased".

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Serious Adverse Events and Deaths

No deaths occurred during the study.

Serious adverse events during double-blind treatment, regardless of study drug relationship, by primary system organ class, preferred term and treatment group
Safety set

Primary system organ class Preferred term	LCI699 0.25mg BID N=32 n (%)	LCI699 1.0mg QD N=26 n (%)	LCI699 0.5/1mg BID N=31 n (%)	LCI699 Total N=89 n (%)	Eplerenone 50mg BID N=33 n (%)	Placebo N=33 n (%)
-Any primary system organ class						
-Total	0	0	0	0	1 (3.0)	0
Nervous system disorders						
-Total	0	0	0	0	1 (3.0)	0
Cerebrovascular accident	0	0	0	0	1 (3.0)	0

Conclusion:

The study suggested that the aldosterone synthase inhibitor LCI699, at total daily doses in the range of 0.5mg to 2.0mg, produced modest reductions in blood pressure in a resistant hypertensive patient population. However, given the sample size of the study, the treatment effects could not be estimated with precision.
At the range of doses studied, the effects of LCI699 on blood pressure reductions were less than those observed with eplerenone 50mg BID. Higher LCI699 doses may be necessary to produce blood pressure effects comparable to eplerenone 50mg BID.
LCI699 and eplerenone demonstrated effects on Renin Angiotensin Aldosterone System (RAAS) biomarkers consistent with their mechanisms of action.
Other than blunting of the Adrenocorticotropic Hormone (ACTH_-stimulated stress response, no safety results from the present study would preclude further evaluation of total daily doses up to 2.0mg daily in a resistant hypertension patient population.

Date of Clinical Trial Report

March 2, 2010