NOVARTIS

Novartis Clinical Trial Results

Sponsor

Novartis

Generic Drug Name

LCI699

Trial Indication(s)

Hypertension

Protocol Number

CLCI699A2215

Protocol Title

A Phase II, Randomized, Double-blind, Placebo Controlled, Multi-center Study to Evaluate the Effects of LCI699 on Cortisol in Patients With Hypertension

Clinical Trial Phase

Phase II

Phase of Drug Development

Phase II

Study Start/End Dates

January 14, 2009 to August 12, 2009

Reason for Termination

Not applicable.

Study Design/Methodology

This study was a prospective, randomized, double-blind, placebo controlled study of LCI699 administered for 6 weeks to hypertensive patients. Up to 90 patients with an established diagnosis of essential hypertension currently taking at least one (1) anti-hypertensive treatment and demonstrating elevated blood pressure despite therapy were considered for this trial. Patients on a stable regime of anti-hypertensive medications (limited to ACE inhibitors, ARBs, thiazide diuretics, loop diuretics, BB, and/or CCBs) for four (4) weeks prior to the screening visit were considered. Patients taking aldosterone receptor antagonists (i.e., spironolactone or eplerenone), direct renin inhibitors or potassium-sparing diuretics (e.g., triamterene or amiloride) within four (4) weeks of screening were excluded from the study. This study was a sequential cohort, escalating dose design with up to 3 potential cohorts, each with approximately 30 patients. Patients were randomized in a 1:2:2 manner to either placebo or one of 2 different LCI699 dose levels within a cohort, as follows: the first cohort (Cohort A: placebo, 0.5mg QD, 1.0mg QD); the second cohort (Cohort B1: placebo, 1.0mg BID, 2.0mg QD); the third cohort (Cohort B: placebo, 1.5mg BID, 3.0mg QD). A dose at which 4 of 12 patients met the ACTH-stimulated cortisol stopping criterion (<400nM at 30 and 60 minutes for an ACTH test at a single visit or at either time point on two consecutive visits) was discontinued and was considered to be at or above the MTD. Upon reaching the MTD, higher dose cohorts were not initiated.

Centers

10 centers in 2 countries: United States (9); Iceland (1)

Objectives:

Primary objective

Primary Objective: The primary objective of this study was to determine the maximally tolerated dose (MTD) of LCI699 with respect to cortisol suppression following ACTH stimulation in hypertensive patients.

Secondary objective(s)

The secondary objectives were to characterize the LCI699 exposure-response relationship on cortisol levels following ACTH stimulation, to characterize the pharmacokinetics, to assess the safety and tolerability of LCI699 and to explore the proportion of patients achieving a BP response and control.

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

LCI699 was supplied as 0.5mg and 1.0mg capsules and matching placebo capsules.

Statistical Methods

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

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

Study Population: Key Inclusion/Exclusion Criteria

Inclusion Criteria:

• Diagnosis of hypertension with blood pressure ≥ 140/90 millimeters of mercury (mmHg) and < 180/110 mmHg on current antihypertensive treatment

• Male and female participants 18-75 years of age

• Participants must weigh at least 50 kilograms (kg)

Exclusion Criteria:

• Recent history of myocardial infarction, heart failure, unstable angina, coronary artery bypass graft, percutaneous coronary intervention, hypertensive encephalopathy, cerebral 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)

• Liver disease

Other protocol-defined inclusion/exclusion criteria may apply.

NOVARTIS

Participant Flow Table

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

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

Categories are mutually exclusive.

NOVARTIS

Baseline Characteristics

Demographic summary by treatment group (Full analysis set)

Demographic variable	LCI699 0.5mg QD N=12	LCI699 1.0mg QD N=12	LCI699 1.0mg BID N=13	LCI699 2.0mg QD N=13	Placebo N=13	Overall Total N=63
Age (years)						

n	12	12	13	13	13	63
Mean	56.1	54.2	57.9	56.2	56.8	56.3
SD	6.37	16.01	9.09	10.37	10.08	10.52
Median	56.5	54.0	62.0	55.0	57.0	57.0
Minimum	46.0	22.0	37.0	37.0	39.0	22.0
Maximum	68.0	74.0	69.0	74.0	69.0	74.0
Age group (years) - n (%)						
<65	11 (91.7)	7 (58.3)	10 (76.9)	9 (69.2)	8 (61.5)	45 (71.4)
>=65	1 (8.3)	5 (41.7)	3 (23.1)	4 (30.8)	5 (38.5)	18 (28.6)
Sex - n (%)						
Male	8 (66.7)	7 (58.3)	10 (76.9)	8 (61.5)	9 (69.2)	42 (66.7)
Female	4 (33.3)	5 (41.7)	3 (23.1)	5 (38.5)	4 (30.8)	21 (33.3)
Race - n (%)						
Caucasian	5 (41.7)	7 (58.3)	7 (53.8)	8 (61.5)	6 (46.2)	33 (52.4)
Black	5 (41.7)	4 (33.3)	5 (38.5)	5 (38.5)	6 (46.2)	25 (39.7)
Asian	2 (16.7)	1 (8.3)	1 (7.7)	0	1 (7.7)	5 (7.9)
Ethnicity - n (%)						
Hispanic/Latino	0	0	1 (7.7)	2 (15.4)	1 (7.7)	4 (6.3)
Chinese	0	0	0	0	0	0
Indian (Indian subcontinent)	0	0	0	0	0	0
Japanese	0	0	1 (7.7)	0	0	1 (1.6)
Mixed Ethnicity	1 (8.3)	1 (8.3)	2 (15.4)	2 (15.4)	3 (23.1)	9 (14.3)
Other	8 (66.7)	5 (41.7)	3 (23.1)	4 (30.8)	6 (46.2)	26 (41.3)
None Specified	3 (25.0)	6 (50.0)	6 (46.2)	5 (38.5)	3 (23.1)	23 (36.5)
Baseline height (cm)						
n	12	12	13	13	13	63
Mean	168.8	171.3	172.8	170.6	172.0	171.1
SD	9.51	11.41	7.62	12.35	10.32	10.12
Median	170.3	167.8	170.2	169.6	176.3	170.2
Minimum	157.5	154.9	162.5	154.7	152.4	152.4
Maximum	182.9	188.0	188.2	192.8	184.2	192.8
Baseline weight (kg)						
n	12	12	13	13	13	63
Mean	88.7	99.9	97.3	89.7	101.8	95.5
SD	17.67	22.91	14.35	16.60	20.10	18.67
Median	86.0	100.2	93.8	89.8	102.3	93.8
Minimum	56.9	61.4	79.5	54.4	78.5	54.4
Maximum	121.8	137.5	125.0	111.6	141.9	141.9
Baseline BMI (kg/m^2)						
n	12	12	13	13	13	63

NOVARTIS

Demographic variable	LCI699 0.5mg QD N=12	LCI699 1.0mg QD N=12	LCI699 1.0mg BID N=13	LCI699 2.0mg QD N=13	Placebo N=13	Overall Total N=63
Mean	31.19	33.63	32.73	30.70	34.45	32.54
SD	6.563	4.853	5.399	4.158	6.196	5.505
Median	30.98	35.21	30.08	30.02	33.81	31.97
Minimum	22.94	25.58	26.58	22.64	24.51	22.64
Maximum	49.10	39.96	42.83	38.49	44.24	49.10
Baseline waist circumference (cm) (males)						
n	8	7	10	8	9	42
Mean	106.1	113.5	106.0	105.1	110.6	108.1
SD	14.69	16.53	7.75	7.40	16.33	12.70
Median	105.0	109.0	104.5	106.0	110.0	107.0
Minimum	81.3	88.0	94.2	93.0	88.0	81.3
Maximum	133.0	136.5	122.0	118.0	139.0	139.0
Baseline waist circumference (cm) (females)						
n	4	5	3	5	4	21
Mean	96.9	102.4	114.5	95.5	107.5	102.4
SD	24.12	10.81	12.38	17.46	14.39	16.22
Median	89.8	105.0	110.0	101.0	103.5	104.0
Minimum	78.0	83.8	105.0	66.5	95.0	66.5
Maximum	130.0	112.0	128.5	113.0	128.0	130.0

Primary Outcome Result(s)

LCI699 MTD under alternative definitions (20 percent failure rate, 60 minutes post-ACTH injection)

Cortisol cut point (nmol/L)	No. of visits	MTD (mg) QD						
		Mean	SD	Median	Min	Max	90% PI	
400	1	2.85	0.68	2.75	1.19	5.63	1.92	4.09
450	1	1.58	0.36	1.55	0.71	3.00	1.08	2.25
500	1	0.94	0.22	0.93	0.41	1.79	0.63	1.33
400	2	1.87	0.40	1.83	0.84	3.83	1.29	2.58
450	2	1.05	0.23	1.04	0.42	2.00	0.71	1.47
500	2	0.60	0.15	0.58	0.18	1.10	0.39	0.86
400	4	1.30	0.29	1.25	0.65	2.70	0.88	1.81
450	4	0.72	0.17	0.70	0.29	1.69	0.46	1.03
500	4	0.37	0.12	0.36	0.07	0.93	0.20	0.58

90% PI = 90% prediction interval, taken as the 5th and 95th percentiles of the simulated MTDs.

Secondary Outcome Result(s)

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

Visit	Treatment group	n	Mean	SE	95% CI
Day 7	LCI699 0.5mg QD	11	690.00	32.288	(625.27, 754.73)
	LCI699 1.0mg QD	12	669.40	30.903	(607.44, 731.35)

	LCI699 1.0mg BID	12	625.06	30.965	(562.98, 687.14)	
	LCI699 2.0mg QD	13	562.04	30.325	(501.24, 622.84)	
	Placebo	12	799.06	31.161	(736.59, 861.54)	
	Pairwise comparisons vs Placebo		**Difference of means**	**SE**	**95% CI**	**Two-sided P-value**
	LCI699 0.5mg QD - Placebo		-109.06	44.703	(-198.69, -19.44)	0.018
	LCI699 1.0mg QD - Placebo		-129.67	44.031	(-217.95, -41.39)	0.005
	LCI699 1.0mg BID - Placebo		-174.00	43.689	(-261.59, -86.41)	<.001
	LCI699 2.0mg QD - Placebo		-237.02	44.098	(-325.43, -148.61)	<.001
Visit	**Treatment group**	**n**	**Mean**	**SE**	**95% CI**	
Day 28	LCI699 0.5mg QD	10	634.87	32.181	(570.20, 699.54)	
	LCI699 1.0mg QD	11	573.41	30.642	(511.83, 634.98)	
	LCI699 1.0mg BID	12	554.79	29.466	(495.58, 614.01)	
	LCI699 2.0mg QD	10	539.09	32.826	(473.12, 605.06)	
	Placebo	12	804.86	29.786	(745.00, 864.71)	
	Pairwise comparisons vs Placebo		**Difference of means**	**SE**	**95% CI**	**Two-sided P-value**
	LCI699 0.5mg QD - Placebo		-169.99	44.081	(-258.57, -81.41)	<.001
	LCI699 1.0mg QD - Placebo		-231.45	42.848	(-317.55, -145.34)	<.001
	LCI699 1.0mg BID - Placebo		-250.06	41.535	(-333.53, -166.60)	<.001
	LCI699 2.0mg QD - Placebo		-265.77	45.116	(-356.43, -175.10)	<.001

NOVARTIS

Visit	Treatment group	n	Mean	SE	95% CI	
Day 30 (T)	LCI699 0.5mg QD	10	662.99	31.412	(599.72, 726.26)	
	LCI699 1.0mg QD	10	628.28	31.382	(565.07, 691.48)	
	LCI699 1.0mg BID	12	559.16	28.672	(501.41, 616.90)	
	LCI699 2.0mg QD	8	560.98	35.212	(490.06, 631.90)	
	Placebo	11	811.39	30.203	(750.56, 872.22)	
	Pairwise comparisons vs Placebo		**Difference of means**	**SE**	**95% CI**	**Two-sided P-value**
	LCI699 0.5mg QD - Placebo		-148.40	43.849	(-236.71, -60.08)	0.001
	LCI699 1.0mg QD - Placebo		-183.11	43.785	(-271.30, -94.92)	<.001
	LCI699 1.0mg BID - Placebo		-252.23	41.388	(-335.59, -168.87)	<.001
	LCI699 2.0mg QD - Placebo		-250.41	46.771	(-344.61, -156.21)	<.001
Visit	**Treatment group**	**n**	**Mean**	**SE**	**95% CI**	
Day 42	LCI699 0.5mg QD	8	647.51	45.593	(555.36, 739.65)	
	LCI699 1.0mg QD	8	626.08	45.441	(534.24, 717.92)	
	LCI699 1.0mg BID	12	539.68	37.146	(464.61, 614.76)	
	LCI699 2.0mg QD	7	479.91	48.865	(381.15, 578.67)	
	Placebo	11	812.91	39.096	(733.90, 891.93)	
	Pairwise comparisons vs Placebo		**Difference of means**	**SE**	**95% CI**	**Two-sided P-value**
	LCI699 0.5mg QD - Placebo		-165.41	60.436	(-287.55, -43.26)	0.009
	LCI699 1.0mg QD - Placebo		-186.84	60.116	(-308.34, -65.34)	0.003
	LCI699 1.0mg BID - Placebo		-273.23	53.690	(-381.74, -164.72)	<.001
	LCI699 2.0mg QD - Placebo		-333.00	63.068	(-460.47, -205.54)	<.001

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

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

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

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

LCI699 Plasma Pharmacokinetic Parameter Summary Statistics (Geometric Mean, CV percent) Following the Last Dose of Study Medication (Day 42)

Treatment group	N	Cmax (ng/mL)	Tmax* (hr)	AUC_{0-8} (ng*hr/mL)	$AUC_{0-\tau}$ (ng*hr/mL)	t1/2 (hr)
LCI699 0.5mg QD	10**	1.42 (36%)	2.21 (1.0-4.0)	6.60 (42%)	9.23 (50%)	4.67 (37%)
LCI699 1.0mg QD	7**	2.94 (35%)	1.00 (1.0-4.0)	14.1 (30%)	18.8 (51%)	3.79 (43%)
LCI699 1.0mg BID	12**	4.62 (35%)	1.00 (0.5-4.0)	24.1 (39%)	30.6 (41%)	5.52 (33%)
LCI699 2.0mg QD	4	8.86 (21%)	1.00 (1.0-3.)	46.4 (13%)	68.9 (19%)	4.90 (17%)

* Median (Range)

** N is reduced by 1 for the AUC and t/2 parameters

NOVARTIS

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

	LCI699 0.5mg QD N=12 n/N (%)	LCI699 1.0mg QD N=12 n/N (%)	LCI699 1.0mg BID N=13 n/N (%)	LCI699 2.0mg QD N=13 n/N (%)	Placebo N=13 n/N (%)
SBP Response (<140mmHg or reduction from baseline >=20mmHg)	7/12 (58.3)	6/12 (50.0)	9/13 (69.2)	10/13 (76.9)	8/13 (61.5)
DBP Response (<90mmHg or reduction from baseline >=10mmHg)	7/12 (58.3)	8/12 (66.7)	13/13 (100.0)	10/13 (76.9)	8/13 (61.5)
SBP Control (<140mmHg for non-diabetics and <130mHg for diabetics)	6/12 (50.0)	5/12 (41.7)	8/13 (61.5)	10/13 (76.9)	7/13 (53.8)
DBP Control (<90mmHg for non-diabetics and <80mHg for diabetics)	7/12 (58.3)	8/12 (66.7)	10/13 (76.9)	10/13 (76.9)	6/13 (46.2)
Both SBP and DBP Control	5/12 (41.7)	5/12 (41.7)	7/13 (53.8)	9/13 (69.2)	5/13 (38.5)

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

NOVARTIS

Safety Results

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

System Organ Class	LCI699 0.5mg QD N=12 n (%)	LCI699 1.0mg QD N=12 n (%)	LCI699 1.0mg BID N=13 n (%)	LCI699 2.0mg QD N=13 n (%)	LCI699 Total N=50 n (%)	Placebo N=13 n (%)
Total AEs for any primary system organ class	6 (50.0)	9 (75.0)	10 (76.9)	10 (76.9)	35 (70.0)	10 (76.9)
Nervous system disorders	3 (25.0)	4 (33.3)	6 (46.2)	2 (15.4)	15 (30.0)	4 (30.8)
Gastrointestinal disorders	2 (16.7)	3 (25.0)	6 (46.2)	1 (7.7)	12 (24.0)	4 (30.8)
Investigations	2 (16.7)	1 (8.3)	3 (23.1)	5 (38.5)	11 (22.0)	0
Infections and infestations	0	1 (8.3)	3 (23.1)	4 (30.8)	8 (16.0)	1 (7.7)
General disorders and site administration conditions	1 (8.3)	4 (33.3)	2 (15.4)	0	7 (14.0)	1 (7.7)
Musculoskeletal and connective tissue disorders	1 (8.3)	3 (25.0)	2 (15.4)	1 (7.7)	7 (14.0)	1 (7.7)
Metabolism and nutrition disorders	1 (8.3)	1 (8.3)	1 (7.7)	0	3 (6.0)	2 (15.4)
Psychiatric disorders	1 (8.3)	1 (8.3)	0	0	2 (4.0)	1 (7.7)

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

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

Serious Adverse Events and Deaths

No serious adverse events or deaths occurred during the study.

Conclusion:

- The estimated Maximally Tolerated Dose (MTD) in hypertensive patients, with respect to Adrenocorticotropic Hormone (ACTH) cortisol stimulation is 1.30mg QD (0.88mg QD – 1.81mg QD, 90% prediction interval), based on no more than 20% of patients achieving ACTH-stimulated cortisol response of <400nmol/L.
- The study further demonstrated that the aldosterone synthase inhibitor, LCI699, produced clinically meaningful decreases in both Systolic Blood Pressure (SBP) and Diastolic Blood Pressure (DBP) compared to placebo. However, the magnitude of the response should be interpreted with caution due to the limited sample size and the discontinuation of the LCI699 2.0mg QD treatment group.
- Other than ACTH-stimulated cortisol suppression, no safety results from the present study would preclude further evaluation of doses up to 2.0mg daily.

Date of Clinical Trial Report

February 5, 2010