Sponsor

Novartis

Generic Drug Name

LCI699

Therapeutic Area of Trial

Primary Hyperaldosteronism

Approved Indication

none

Study Number

CLCI699A2206

Title

A pilot, single-blind, forced-titration study to assess the hemodynamic and hormonal effects, safety and tolerability of the aldosterone synthase inhibitor LCI699 in patients with primary hyperaldosteronism

Phase of Development

Phase I

Study Start/End Dates

11 Jun 2008 (first subject dosed)
20 May 2009 (last subject dosed)

Study Design/Methodology

This pilot study in patients with primary hyperaldosteronism (PH) used a single-blind, forced-titration design to explore the pharmacodynamics (blood pressure, electrolyte and hormonal changes) and safety and tolerability of LCI699

Centres

Single-center study in France

Publication

None

Objectives

Primary objective

To assess the effects of LCI699 on mean 24-hour systolic blood pressure (SBP) as measured by ambulatory blood pressure monitoring (ABPM)

Secondary objectives

To investigate the safety and tolerability of LCI699

To explore the effects of LCI699 on plasma and urine hormone levels and electrolytes

To assess the effects of LCI699 on mean 24-hour diastolic blood pressure (DBP)

To assess the effects of LCI699 on mean diurnal (day and night) SBP and DBP

To assess the pharmacokinetics of LCI699 following bid dosing

Test Product, Doses, and Mode of Administration

LCI699 0.5 mg oral capsules given twice a day (morning and evening). Final doses of 1 and 2 mg/day.

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

N/A

Criteria for Evaluation

Pharmacodynamic assessments

Ambulatory BP measurement (ABPM) on Days -2/-1 and Days 27/28
Analysis of plasma and urine for hormones and electrolytes were assessed weekly
Cortisol stimulation test was performed on Days -15 and 30

Pharmacokinetic assessments

LCI699 was measured in plasma on Day 1 and 29
PK parameters: AUC_{τ}, C_{max}, t_{max}, $t_{½}$ were determined

Safety and tolerability assessments

Body height, weight, and temperature were measured weekly.
Office and Home Blood pressure (OBP and HBP, respectively) and heart rate (HR) and ECGs were measured weekly.
Hematology; Blood chemistry; Urinalysis were measured weekly.
Adverse events recording were performed throughout the study.

Statistical Methods

PK and PD as well as concomitant medication (anti-hypertensive and potassium supplements) data were summarized using descriptive statistics. A paired t-test was performed on ABPM comparing the Day 28 and Baseline (Day =2/-1) measurements. A linear mixed effects model with time as the fixed effect and patient as the random effect was used to analyze the HBP and OBP data. Various contrasts were set up to compare the HBP/OBP measurements between different days within the mixed effects model framework. The relationship between change in ABPM/HBP/OBP and aldosterone levels were explored using graphical and/or regression methods.

Study Population: Inclusion/Exclusion Criteria and Demographics

Male or female patients with established diagnosis of primary hyperaldosteronism (PH), BMI of 18-34 kg/m^2 and between 18 and 70 years of age are eligible for the study. Female patients were of non-child bearing potential (either post-menopausal or surgically sterile). Patients documented as having PH within the last 3 years, either with or without an aldosterone producing adenoma (APA). PH was defined by an aldosterone/renin ratio (ARR) ≥ 64 pmol/mU measured at 2 separate times and an elevated aldosterone concentration (plasma ≥ 500 pmol/L or urinary ≥63 nmol/day) after 2-6 week washout of drugs interfering with the renin/ angiotensin / aldosterone system (RAAS). Patients were hypertensive at screening (systolic and/or diastolic office blood pressure (OBP)> 140/90 mmHg **or** on current antihypertensive treatment) and had an estimated creatinine clearance ≥ 60 ml/min). Morning plasma cortisol (~8-9:00) was > 200 nmol/l at screening and 60 min post-ACTH plasma cortisol > 500 nmol/l at baseline (Day -15). Patients with persistent hypokalemia (< 3.0 mmol/l despite oral administration of 6 g/day of KCl) at baseline (Day-15) were excluded. All subjects provided written informed consent prior study entry

Number of Subjects

	Novartis product	Comparator
Planned N	12	N/A
Randomised n	18	N/A
Intent-to-treat population (ITT) n (%)	14	N/A
Completed n (%)	14	N/A
Withdrawn n (%)	4	N/A
Withdrawn due to adverse events n (%)	0	N/A
Withdrawn due to lack of efficacy n (%)	0	N/A
Withdrawn for other reasons n (%)	4	N/A

Demographic and Background Characteristics

N (Safety)	18	
N (PD, PK)	14	
Females : males	1 : 17	
Mean age, years (SD)	50.3 (7.25)	
Mean weight, kg (SD)	85.3 (10.5)	
Race White n (%) Hispanic n (%)	 17 (94.4) 1 (5.6)	

Primary Objective Result(s)

ABPM results*

	Baseline Days -2/-1	Treatment Days 27/28	Change	p-value
SBP				
24 hr	145.0 ± 9.4	140.8 ± 9.3	-4.2 ± 6.7	0.044

* mean ± SD

Secondary Objective Results

ABPM results*

	Baseline Days -2/-1	Treatment Days 27/28	Change	p-value
SBP				
Day-time	149.3 ± 10.1	145.0 ± 9.4	-4.2 ± 6.4	0.036
Night-time	135.3 ± 9.27	131.4 ± 10.52	-3.8 ± 9.62	0.178
DBP				
24 hr	89.3 ± 6.9	87.2 ± 6.9	-2.1 ± 4.1	0.085
Day-time	92.5 ± 6.8	90.9 ± 7.1	-1.6 ± 4.2	0.192
Night-time	82.2 ± 7.5	79.0 ± 7.5	-3.2 ± 6.2	0.092

* mean ± SD

Office blood pressure*

	Placebo		LCI699	Placebo
	Day -15	Day 1	Day 29	Day 36
Mean supine				
SBP	145.5 ± 16.2	145.0 ± 10.7	135.5 ± 11.3	141.3 ± 13.5
DBP	90.1 ± 7.9	91.2 ± 8.6	86.3 ± 8.6	88.4 ± 11.6

Plasma and urine hormones values*

	Placebo		LCI699	Placebo
	Day -15	Day 1	Day 29	Day 36
Plasma				
Aldosterone	151.8	194.7	46.6	144.7
(pg/mL)	(113.1, 203.8)	(133.5, 283.9)	(33.2, 65.4)	(108.6, 192.8)
Potassium	3.46	3.29	3.86	3.40
(mmol/L)	(3.16, 3.78)	(3.13, 3.46)	(3.65, 4.08)	(3.20, 3.61)
Sodium	141.8	140.6	139.8	140.8
(mmol/L)	(140.9, 142.8)	(139.6, 141.6)	(139.0, 140.7)	(139.6, 142.0)
Renin	10.6	11.5	15.0	12.5
(pg/mL)	(8.4, 13.5)	(8.3, 15.8)	(11.5, 19.5)	(9.5, 16.4)
Cortisol	294.92	282.73	265.57	283.31
(nmol/L)	(247.50, 351.43)	(242.90, 329.08)	(221.58, 318.29)	(247.78, 323.93)
24 hr urine				
Aldosterone	30.18	33.80	3.83	24.91
(µg/24 hr)	(21.37, 42.62)	(24.10, 47.39)	(2.56, 5.73)	(17.92, 34.62)
Potassium	124.4	135.1	83.0	89.5
(mmol/24 hr)	(99.9, 155.0)	(111.4, 163.9)	(69.4, 99.2)	(77.0, 104.1)
Sodium	170.3	140.1	154.2	89.5
(mmol/24 hr)	(132.2, 219.4)	(118.5, 165.6)	(121.5, 195.7)	(77.0,104.1)

Cortisol (nmol/24 hr)	87.02 (59.80, 126.61)	84.88 (65.55, 109.90)	45.63 (32.98, 63.13)	74.66 (57.34, 97.22)

Hormone levels during ACTH-stimulation test*

Day	Time	Cortisol (ng/mL)
Day -15	Pre-ACTH	220.39 (185.00,262.56)
	0.5 hr Post-ACTH	572.57 (513.25,638.75)
	1 hr Post-ACTH	651.21 (584.69,725.29)
Day 30	Pre-ACTH	270.98 (232.20,316.25)
	0.5 hr Post-ACTH	346.98 (309.39,389.13)
	1 hr Post-ACTH	375.69 (332.14,424.94)

Safety Results

Adverse Events by System Organ Class

	Placebo Run-in N=18 n (%)	LCI6699 N=14 n (%)	Placebo Washout N=14 n (%)
Patients with AE(s)*	4 (22.2)	5 (35.7)	0 (0.0)
System organ class			
General disorders and administration site conditions	3 (16.7)	0 (0.0)	0 (0.0)
Vascular disorders	1 (5.6)	1 (7.1)	0 (0.0)
Cardiac disorders	1 (5.6)	0 (0.0)	0 (0.0)
Eye disorders	0 (0.0)	1 (7.1)	0 (0.0)
Gastrointestinal disorders	0 (0.0)	1 (7.1)	0 (0.0)
Infections and infestations	0 (0.0)	1 (7.1)	0 (0.0)
Nervous system disorders	0 (0.0)	1 (7.1)	0 (0.0)

Safety analysis set

*A patient was counted in only once per treatment phase.

All adverse events - n (%) of subjects (all patients)

	Placebo Run-in N=18 n (%)	LCI699 N=14 n (%)	Placebo Washout N=14 n (%)
Patients with AE(s)	4 (22.2)	5 (35.7)	0 (0.0)
Preferred term			
Hypertension	1 (5.6)	1 (7.1)	0 (0.0)
Non-cardiac chest pain	1 (5.6)	0 (0.0)	0 (0.0)
Atrial fibrillation	1 (5.6)	0 (0.0)	0 (0.0)
Diarrhoea	0 (0.0)	1 (7.1)	0 (0.0)
Fatigue	1 (5.6)	0 (0.0)	0 (0.0)
Headache	0 (0.0)	1 (7.1)	0 (0.0)
Myodesopsia	0 (0.0)	1 (7.1)	0 (0.0)
Edema peripheral	1 (5.6)	0 (0.0)	0 (0.0)
Rhinitis	0 (0.0)	1 (7.1)	0 (0.0)

Safety analysis set

Serious Adverse Events and Deaths

One patient experienced a SAE, atrial fibrillation, in the placebo run-in period. He had recovered by later that day. No other serious adverse events, nor severe adverse events, or deaths were reported during the study.

Other Relevant Findings

None

Date of Clinical Trial Report

26 Apr 2010

CSR content final

Date Inclusion on Novartis Clinical Trial Results Database

20 May 2010

Date posted to the CTRD

Date of Latest Update

20 May 2010

Date of most recent update (ie, template was modified to include publication information)