AstraZeneca

Clinical Study Report Synopsis

Drug Substance	Candesartan Cilexetil
Study Code	D2452L00015
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A 28-week, Randomised, Open-label, Parallel-Group, Multi-Center Study To Find the Effective Dose of Candesartan Cilexetil (Atacand) for Renoprotection in Korean Hypertensive Patients with Non-diabetic Nephropathy
ARIA (Atacand Renoprotection In NephropAthy Pt.)

Study dates: First patient enrolled: 24 December 2007
Last patient completed: 26 August 2009

Phase of development: IV

This study was performed in compliance with Good Clinical Practice, including the archiving of essential documents.

Study centre(s)

Subjects were recruited from a total of 8 centres in Korea. A total of 155 subjects were enrolled, of whom 128 were randomized.

Publications

None at the time of writing this report.

Objectives and criteria for evaluation

Table S1 summarises the variables of this study, and shows how they relate to the study objectives.

Table S1 Primary and secondary objectives and outcome variables

Objectives	Outcome variables	Type
Primary	**Primary**	
1. To determine the effective dose of candesartan cilexetil for reduction of urinary protein excretion in hypertensive patients with non-diabetic chronic kidney disease with baseline urinary protein/creatinine ratio between 500mg/g and 5000mg/g, by assessing the change in urinary protein/creatinine ratio from baseline to the end of 28-week treatment.	1. Change in urinary protein/creatinine ratio from baseline to 28 weeks	Efficacy
Secondary	**Secondary**	
2. To evaluate the effect of candesartan cilexetil at various doses (8, 16, 32mg) in the same population on Systolic and diastolic blood pressure	2. Change in systolic and diastolic BP from baseline to 28 weeks	Efficacy
3. To evaluate the effect of candesartan cilexetil at various doses (8, 16, 32mg) in the same population on Inflammatory marker (hs-CRP)	3. Change in inflammatory marker (hs-CRP) from baseline to 28 weeks	Efficacy
4. To evaluate the effect of candesartan cilexetil at various doses (8, 16, 32mg) in the same population on Estimated GFR predicted from the Modification of Diet in Renal Disease (MDRD) equation	4. Change in Estimated GFR predicted from the Modification of Diet in Renal Disease (MDRD) equation from baseline to 28 weeks	Efficacy
5. To evaluate the effect of candesartan cilexetil at various doses (8, 16, 32mg) in the same population on the incidence and severity of adverse events and laboratory data changes	5. Adverse events and laboratory data	Safety

Study design

This was a randomized, open-label, parallel-group, multi-center, phase IV study evaluating the effects of candesartan cilexetil 8mg, 16mg, and 32mg over 28 weeks on urinary protein excretion in hypertensive non-diabetic chronic kidney disease patients with baseline urinary protein/creatinine ratio between 500mg/g and 5000mg/g.

Subjects underwent a 5-week enrolment period (washout 4-week) during which treatment with Angiotensin Converting Enzyme Inhibitors (ACE inhibitors), Angiotensin Receptor Blockers (ARBs), and non-DHPD CCB were discontinued. Subjects could be prescribed with other antihypertensive (diuretics, DHPD CCB, beta blocker) to maintain the blood pressure at 130/80 mmHg.

At the end of the enrollment period, eligible subjects were randomized to receive a maximum dose of candesartan cilexetil 8mg, 16mg, and 32mg once daily. The dose titration period occurred over a period 4 weeks, during which time the subjects were seen every 2 weeks for forced titration of their study medication.

Once the maximum dose had been achieved, subjects were followed for 24 weeks with clinic visit every 8 weeks.

Target subject population and sample size

Subjects were male or female hypertensive patients, with non-diabetic chronic kidney disease, aged from 18 to 70 years, with baseline urinary protein/creatinine ratio between 500mg/g and 5000mg/g. 128 subjects from 8 centres were assigned to study treatment.

Investigational product and comparator(s): dosage, mode of administration and batch numbers

Subjects were randomized to take a maximum of candesartan cilexetil 8 mg, 16 mg, or 32 mg once daily, by mouth.

Duration of treatment

The enrollment period lasted for 5 weeks and during the last 4 weeks of this period, the subjects were washed out for ACEI, ARB, and non-DHPD calcium channel blocker. The subjects could be treated with other antihypertensive agents at the physician's discretion to maintain the standard blood pressure level (130/80mmHg). After randomization to different doses of candesartan cilexetil, patients went through 4 weeks of titration period, after which the patients received treatment at designated doses for 24 weeks.

Statistical methods

-The pairwise comparisons were done in a sequential order starting with the highest dose versus the lowest dose at a significance level of 0.05.

-If this test was significant, the intermediate dose was compared to the lowest dose at the same significance level.

-If this test was also significant, the highest dose was tested against intermediate dose.

Also, the primary variable was analysed in a one-way ANCOVA with dose as a group factor and baseline values as a covariate. Pairwise comparisons of the doses in ANCOVA were performed.

Efficacy data was evaluated based on an intention-to-treat (ITT) population. The ITT population consisted of subjects who have a baseline reading and at least one post-baseline reading for at least one urinary protein variable, and who have taken at least one dose of study treatment. The per protocol (PP) population as secondary analysis set consisted of all subjects in the ITT population who did not have a major protocol violation or deviation that would likely to affect the efficacy outcomes.

The safety population consisted of all subjects who took at least 1 dose of study medication.

Subject population

In total, 155 patients were screened and 128 patients were randomly assigned to receive candesartan 8mg, candesartan 16mg, or candesartan 32mg.

Overall, 2.5% of the candesartan 8mg group, 11.1% of the candesartan 16mg group, and 23.3% of the candesartan 32mg group discontinued the study during randomized treatment. The rate of discontinuation was higher in the candesartan 32mg group compared to the candesartan 8mg and candesartan 16mg groups. A total of 8.9% and 7.0% of patients in the candesartan 16mg and candesartan 32mg were incorrect enrollment of randomization which is main reason for early study discontinuation.

Of the 128 randomly assigned patients, 120 received study medication and were included in the safety analysis set. The ITT set comprised 119 subjects and 108 subjects were included in PP set.

Table S2 Subject population and disposition

	Cand 8mg	Cand 16mg	Cand 32mg	Total
	n	n	n	n
All enrolled subjects				155
All randomized subjects	40	45	43	128
Subjects who completed	39	40	33	112
Subjects who discontinued	1	5	10	16
Safety set	40	43	37	120
ITT set (ITT)	39	44	36	119
Per-protocol set (PP)	36	39	33	108

Summary of efficacy results

The mean reductions in PCR were as follows: -794.0mg/g for candesartan 8mg, -639.9mg/g for candesartan 16mg, and -819.0mg/g for candesartan 32mg. The candesartan 32mg showed a greater mean change in PCR at week 28 compared with candesartan 8mg; however,

superiority over candesartan 8mg was not demonstrated based on the t-test. Similar results were observed when using the ANCOVA method (least square [LS] mean change for candesartan 32mg versus candesartan 8mg of -3.6, 95% CI: -355.5, 348.2).

Treatment comparisons between other candesartan treatments groups did not performed because of this test above was not significant. There was no relation between the primary efficacy variable, reduction of urine protein/creatinine ratio, and the dose increase of candesartan cilexetil.

Table S3 Change in PCR between candesartan 8mg and candesartan 32mg (ITT set)

	Cand 8mg N=39	Cand 32mg N=36	Difference (8mg-32mg)	p-value
	Mean [SD]	Mean [SD]		
Baseline	1734.3 [1031.7]	1788.7 [934.1]		0.8119*
Week 28	940.3 [921.3]	970.0 [905.3]		
Change	-794.0 [1070.1]	-819.0 [823.6]	25.0	0.9106*
LS mean change	-770.2	-766.5	-3.6	(-355.5, 348.2)**

* unpaired t-test, ** 95% CI from one-way ANCOVA model (pairwise comparison)

No significant difference (t-test) in systolic BP was found for the comparison between the candesartan 8mg and candesartan 32mg in the ITT analysis set. The mean reductions in candesartan 8mg and candesartan 32mg were 11.7mmHg and 16.1mmHg. And the adjusted mean values were almost identical, differing only by 0.02mmHg. The results for the DBP analysis were similar.

Table S4 Change in BP between candesartan 8mg and candesartan 32mg (ITT set)

		Cand 8mg N=39	Cand 32mg N=36	Difference (8mg-32mg)	p-value
		Mean [SD]	Mean [SD]		
SBP	Change	-11.7 [14.9]	-16.1 [17.3]	4.4	0.2357*
	LS mean change	-13.6	-13.6	-0.02	(-5.78, 5.75)**
DBP	Change	-8.9 [13.3]	-13.0 [14.7]	4.1	0.2075*
	LS mean change	-9.2	-9.7	0.50	(-4.41, 5.42)**

* unpaired t-test, ** 95% CI from one-way ANCOVA model (pairwise comparison)

There was a statistically significant difference on inflammatory marker (hs-CRP) only between candesartan 8mg and candesartan 32mg. And candesartan 8mg and candesartan 32mg were similar with regard to improvement of estimated GFR.

In summary, no significant difference in urine protein/creatinine ratio was found for the comparison between the candesartan 8mg and candesartan 32mg. However, the reduction in urine protein/creatinine ratio, systolic and diastolic blood pressure from baseline to endpoint was showed within each treatment group.

Summary of safety results

A total of 44 (36.7%) out of 120 subjects (15 subjects (37.5%) on candesartan 8mg, 13 subjects (30.2%) on candesartan 16mg, and 16 (43.2%) on candesartan 32mg) reported at least 1 adverse event in safety set. Possibly related treatment-emergent AEs occurred in only 4 subjects (3.3%). 2 (1.7%) of the 120 subjects had a total 3 serious treatment-emergent adverse events. In addition, one subjects participating in this study died. And 2 subjects discontinued permanently due to AE.

Table S5 Number(%) of subjects who had at least one treatment-emergent adverse event in any category (Safety set)

	Cand 8mg N=40 n(%)	Cand 16mg N=43 n(%)	Cand 32mg N=37 n(%)
Any adverse events	15(37.5)	13(30.2)	16(43.2)
Possibly related adverse events	0	1(2.3)	3(8.1)
Serious adverse events	0	1(2.3)	1(2.7)
Possibly related serious adverse events	0	0	0
Study permanently discontinuation due to adverse events	0	0	2(5.4)
Died during the treatment period due to adverse events	0	0	1(2.7)

The incidence of possibly related AEs and AEs that led to their permanently discontinuing of study treatment was very low. And all SAEs were assessed by the investigator as having been unrelated to study medication.

Although the change in some lab data form baseline to end of treatment was significant, the difference among treatment groups were small, generally unremarkable and no significance.

Changes from baseline in pulse rate and weight at week 28 were similar in the each candesartan dose. There was essentially no change in pulse rate and weight in all treatment groups.