Drug product:	Atacand®	**SYNOPSIS**	
Drug substance(s):	Candesartan cilexetil		
Document No.:	CV.000-250-346		
Edition No.:	1.0		
Study code:	DC-AHS-0006		
Date:	29-Aug-08		

A double-blind, randomised, dose ranging, multi-centre, phase IIIb study to evaluate the efficacy and safety of high doses of candesartan cilexetil (Atacand®) on the reduction of proteinuria in the treatment of subjects with hypertension and moderate to severe proteinuria.

Study dates: First subject enrolled: 31-Mar-03
Last subject enrolled: 16-May-06
Last subject out: 29-Dec-06
Clean file: 23-Apr-07

Phase of development: Therapeutic confirmatory (IIIb)

Objectives

Primary Objective:

The primary objective of the study was to assess the effect of high doses of candesartan cilexetil (≥16 mg) on proteinuria, in subjects with hypertension and primary glomerular disease or diabetic nephropathy (proteinuria ≥ 1g/24 hours).

Secondary Objectives:

The secondary objectives of the study were to:

- Assess the effects of high dose candesartan cilexetil on renal function as measured by serum creatinine and 24-hour creatinine clearance.
- Assess the effects of high dose candesartan cilexetil on blood pressure in subjects with hypertension and nephropathy.
- Assess the safety of high dose candesartan cilexetil in subjects with hypertension and nephropathy.

- Assess whether there is a correlation between the increased dose of candesartan cilexetil and reduction in level of serum aldosterone concentration.

- Assess the correlation between the changes in serum aldosterone levels and reduction in urine protein excretion.

Study design

This was a 38-week, double-blind, double-dummy, randomised study, performed at 29 sites across Canada. Subjects were to undergo an 8-week enrolment period during which time treatment with Angiotensin Converting Enzyme Inhibitors (ACE inhibitors) and Angiotensin Receptor Blockers (ARBs) were discontinued and after which open label candesartan cilexetil 16 mg once daily was initiated.

At the end of the enrolment period, eligible subjects were stratified according to the degree of proteinuria (1-3 g/24 hr and >3 g/24 hr) and randomised to receive a maximum dose of candesartan cilexetil 16 mg, 64 mg or 128 mg once daily. The dose titration period occurred over a period of six (6) weeks, during which time the subjects were seen every two (2) weeks for forced titration of their study medication.

Once the maximum dose was achieved, subjects were followed for 6 months with clinic visits every 4 weeks.

Target subject population and sample size

Male and female subjects, 18 to 80 years of age with stable hypertension and primary glomerular disease or diabetic nephropathy were enrolled. All subjects must have had a minimum 6-month history of nephropathy with stable proteinuria (≥ 1.0 g/day on more than 1 occasion in the 6 months prior to Visit 1).

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

The investigational product was supplied as:
Candesartan cilexetil 16 mg tablets and placebo to match.
Candesartan cilexetil 32 mg tablets and placebo to match.

Subjects were randomized to take a maximum oral dose of 16 mg, 64 mg, or 128 mg once daily.

Duration of treatment

Subjects began the study with an eight (8) week enrolment period where they received open label treatment with candesartan cilexetil 16 mg, once daily, by oral administration, during the last seven (7) weeks of this period.
Subjects were then randomised to a 30-week double-blind treatment period where they were to receive a maximum dose of candesartan cilexetil of 16 mg, 64 mg or 128 mg once daily.

Criteria for evaluation (main variables)

Efficacy

Primary variable:

The primary endpoint for the study was the 24-hour urine protein level, recognized as a measure of nephropathy.

Secondary variables:

The secondary variables for the study were as follows:

- Serum creatinine and 24-hour creatinine clearance.
- Blood pressure (seated, diastolic and systolic)
- Serum aldosterone concentration.
- Serum aldosterone levels as a function of reduction in urine protein excretion.

Safety

Standard safety assessments included adverse events and clinical laboratory data (haematology, hepatic and renal clinical chemistry, and urinalysis) vital signs, and physical examination.

Statistical methods

The statistical analysis of the primary variable, amount of protein in 24h urine, creatinine clearance and the reduction of blood pressure was performed using an analysis of co-variance with confidence intervals (CI) for the difference between the candesartan cilexetil treatments groups (16, 64 and 128 mg) via a Mixed Model with centre, treatment by centre and severity of disease at baseline as cofactors.

Subject age, time of symptom onset and other potential co-variates was analysed in an exploratory way.

Adverse events were tabulated per treatment group and analysed using categorical methods. The intention to treat (ITT) approach was used for the baseline characteristics and efficacy portions of the study. The safety group of subjects, defined as that group of subjects that are randomised and take at least one dose of medication, was used in the safety portion of the analysis. Groups of subjects assigned to their actual treatment received were also analysed as part of a modified ITT.
All other statistical tests were two-sided, and 95% CIs were constructed. Any other comparison was declared significant if $p<0.05$.

The sample size was calculated based on a pilot group of 10 subjects with renal deficiency. The subjects received increasing doses of candesartan cilexetil from 0 to 96 mg and their urinary protein excretion levels were analysed.

Subject population

400 male and female subjects, 18 to 80 years of age with stable hypertension and primary glomerular disease or diabetic nephropathy were enroled in the study. All subjects must have had a minimum 6-month history of nephropathy with stable proteinuria (≥ 1.0 g/day on more than 1 occasion in the 6 months prior to Visit 1). Of these 400 subjects, 346 entered the 8 week run-in period and were treated with 16 mg candesartan. 269 of these subjects were subsequently randomised to active treatment. The full disposition of all subjects is listed below in tables S1a and S1b.

Tables S1a and S1b Subject population and disposition

Table S1a Baseline Characteristics (Demographic and Categorical) at Enrolment (visit 1). ITT patients.

	Atacand 16 mg (N=90)		**Atacand 64 mg (N=90)**		**Atacand 128 mg (N=89)**	
	n	%	n	%	N	%
Sex						
Male	72	80.0	70	77.8	72	80.9
Female	18	20.0	20	22.2	17	19.1
Race						
Caucasian	75	83.3	82	91.1	67	75.3
Black	3	3.3	2	2.2	5	5.6
Oriental	9	10.0	5	5.6	11	12.4
Other	3	3.3	1	1.1	6	6.7
Previous use of CV medication						

Table S1a Baseline Characteristics (Demographic and Categorical) at Enrolment (visit 1). ITT patients.

	Atacand 16 mg (N=90)		Atacand 64 mg (N=90)		Atacand 128 mg (N=89)	
	n	%	n	%	N	%
ACEs	44	49.4	35	42.2	34	41.0
ACEs + ARBs	23	25.8	15	18.1	16	19.3
ARBs	20	22.5	33	39.8	31	37.3
CCB + ACEs	2	2.2			1	1.2
Non-DiPyr-CCB					1	1.2
Disease Diagnosis						
Primary glomerular disease	27	30.0	34	37.8	29	32.6
Hypertensive nephrosclerosis	13	14.4	9	10.0	12	13.5
Diabetic nephropathy	50	55.6	47	52.2	48	53.9
Age Range						
<45	17	18.9	19	21.1	22	24.7
45 - 69	63	70.0	60	66.7	58	65.2
>69	10	11.1	11	12.2	9	10.1
Degree of Proteinuria at Randomisation [1]						
<=3g	52	57.8	52	57.8	50	56.2
>3g	38	42.2	38	42.2	39	43.8
Time from Onset of Disease						
0 to 5 years	60	66.7	61	67.8	53	59.6
>5 years	30	33.3	29	32.2	36	40.4

[1] Proteinuria at Randomisation is the highest of day 1 or day 2 value of the 24-hour urine collection.

Table S1b Baseline Characteristics (Numerical) at Enrolment (visit 1) characteristics. ITT patients

		Atacand 16 mg (n=90)	Atacand 64 mg (n=90)	Atacand 128 mg (n=89)
Age (years)	N	90	90	89
	Mean (SD)	56.5 (12.2)	54.8 (12.4)	54.6 (12.6)
	Min-Max	28-77	22-80	22-78
Weight (kg)	N	90	90	89

Table S1b Baseline Characteristics (Numerical) at Enrolment (visit 1) characteristics. ITT patients

		Atacand 16 mg (n=90)	Atacand 64 mg (n=90)	Atacand 128 mg (n=89)
	Mean (SD)	92.6 (20.6)	89.2 (19.4)	93.2 (19.9)
	Min-Max	54-150	55-152	51-160
Height (cm)	N	90	90	89
	Mean (SD)	170.7 (7.8)	168.5 (8.7)	170.3 (9.6)
	Min-Max	150-185	145-193	143-191
Body Mass Index (kg/m²)	N	90	90	89
	Mean (SD)	31.7 (6.2)	31.4 (6.4)	32.2 (6.5)
	Median	30.7	31.0	30.8
	Min-Max	21.1-51.6	20.9-48.7	19.7-58.0
Pulse (beats/min), Sitting	N	89	89	89
	Mean (SD)	71.7 (10.0)	69.4 (10.4)	69.6 (11.0)
	Min-Max	46-102	46-96	46-108
Systolic BP (mmHg), Sitting	N	90	90	89
	Mean (SD)	142.0 (19.5)	136.2 (15.7)	141.2 (18.3)
	Min-Max	94-192	110-191	105-184
Diastolic BP (mmHg), Sitting	N	90	90	89
	Mean (SD)	79.9 (10.1)	77.8 (8.3)	82.9 (10.3)
	Min-Max	53-98	55-94	60-115

Efficacy results

Primary Variable

The mean reduction in urine protein for patients (intention-to-treat) on 128 mg of candesartan as compared to 16 mg was 33.05% ($p < 0.0001$, 95% CI [-45.70, -17.44]). Furthermore, the mean reduction in per protocol population treated with 128 mg compared to 16 mg was 44.34% ($p<0.0001$, 95% CI [-58.01, -26.25]). The mean difference between 16 and 64mg was -16.91% ($p=0.0492$, n.s. adjusted for 2 comparisons). All data for the primary results, by treatment group is summarised in table S1d below.

Table S1d **Statistics on 24-h proteinuria (g/day), log transformed, %-change from randomisation to final visit by treatment group, p-values and 95% confidence intervals. ITT population based on LVCF data for all patients.**

		Baseline			On therapy		Change from baseline			Treatment vs. 16mg		
Treatment	**Visit**	**N**	**GM[1]**	**SEM**	**GM[1]**	**SEM**	**GMPC[2] (%)**	**SEM**	**95%CI**	**GMPC[2] (%)**	**P-value[4]**	**95%CI[3]**
Atacand 64 mg	Visit 14	88	2.83	0.06	2.20	0.08	-22.23	6.17	[-27.43, -4.52]	-16.91	0.0492	[-32.74, 2.65]
Atacand 128 mg	Visit 14	83	2.85	0.07	1.79	0.11	-36.95	7.05	[-42.24, -22.11]	-33.05	0.0000	[-45.70, -17.44]

[1]Geometric mean. [2]Geometric mean percentage change. [3]Adjusted for multiple comparisons. Standard Error Mean in log scale. [4] Compared to 0.025 for statistical adjustment. Linear random effects model adjusted for centre and baseline proteinuria

Safety results

The study collected data on all adverse events and clinical laboratory assessments. Overall, the study did not identify any significant safety concerns and no deaths were reported. The incidence of serious adverse events was similar between the three treatment groups.

The breakdown of all adverse events, by treatment group, is listed below in tables S2a and S2b.

Table S2a Summary of Treatment Emergent Adverse Events, Open Label Phase[a] Safety set.

	N (%) of subjects who had an adverse event in each category[b]							
	Atacand 16 mg (n=90)		Atacand 64 mg (n=90)		Atacand 128 mg (n=89)		Non-randomised (n=76)	
Category of adverse event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any adverse events	50	(55.6%)	57	(63.3%)	53	(59.6%)	35	(46.1%)
Serious adverse events	4	(4.4%)	2	(2.2%)	2	(2.2%)	2	(2.6%)
Serious adverse events leading to death	0		0		0		0	
Serious adverse events not leading to death	4	(4.4%)	2	(2.2%)	2	(2.2%)	2	(2.6%)
Discontinuations of study treatment due to adverse events	2	(2.2%)	0		1	(1.1%)	11	(14.5%)
Other significant adverse events (OAEs)[c]	0		0		2	(2.2%)	1	(1.3%)
				Total number of adverse events				
Any adverse events	114		110		138		89	
Serious adverse events	6		2		2		3	
Serious adverse events not leading to death	6		2		2		3	

[a] Includes all events starting before the date of first dose of titration period.
[b] Subjects with multiple events in the same category are counted only once in that category. Subject with events in more than 1 category are counted once in each of those categories.

Table 2Sb Summary of Treatment Emergent Adverse Events, Titration and Maintenance Phase [a]. Safety set.

	N (%) of subjects who had an adverse event in each category[b]					
	Atacand 16 mg (n=90)		Atacand 64 mg (n=90)		Atacand 128 mg (n=89)	
Category of adverse event	**n**	**(%)**	**n**	**(%)**	**n**	**(%)**
Any adverse events	80	(88.9%)	82	(91.1%)	81	(91.0%)
Serious adverse events	6	(6.7%)	10	(11.1%)	8	(9.0%)
Serious adverse events leading to death	0		0		0	
Serious adverse events not leading to death	6	(6.7%)	10	(11.1%)	8	(9.0%)
Discontinuations of study treatment due to adverse events	11	(12.2%)	5	(5.6%)	8	(9.0%)
Other significant adverse events (OAEs)[c]	1	(1.1%)	2	(2.2%)	4	(4.5%)
Total number of adverse events						
Any adverse events	335		334		373	
Serious adverse events	9		14		9	
Serious adverse events not leading to death	9		14		9	

[a] Includes all events starting on or after the date of first dose of titration period.
[b] Subjects with multiple events in the same category are counted only once in that category. Subject with events in more than 1 category are counted once in each of those categories.

Tables S3a and S3b outline the number and percentage of subjects with the most commonly reported adverse events, sorted by decreasing order of frequency as summarised over all treatment groups (safety analysis set) for both the open label and randomised phases. There were no clinically significant differences between the three treatment groups for any of the adverse events.

Table S3a Most Frequent Treatment Emergent Adverse Events by Preferred Term. Open Label Phase , Safety set.

	Atacand 16 mg (n=90)		Atacand 64 mg (n=90)		Atacand 128 mg (n=90)		Non-randomized (n=76)	
Preferred Term	n	(%)	n	(%)	n	(%)	n	(%)
Headache	10	(11.1%)	5	(5.6%)	4	(4.5%)	3	(3.9%)
Nasopharyngitis	6	(6.7%)	11	(12.2%)	1	(1.1%)	5	(6.6%)
Dizziness	4	(4.4%)	6	(6.7%)	5	(5.6%)	5	(6.6%)
Fatigue	4	(4.4%)	4	(4.4%)	6	(6.7%)	0	
Oedema peripheral	4	(4.4%)	5	(5.6%)	4	(4.5%)	4	(5.3%)
Back pain	3	(3.3%)	3	(3.3%)	2	(2.2%)	5	(6.6%)
Diarrhoea	2	(2.2%)	3	(3.3%)	3	(3.4%)	4	(5.3%)
Cough	2	(2.2%)	0		5	(5.6%)	1	(1.3%)

Table S3b Most Frequent Treatment Emergent Adverse Events by Preferred Term, Titration and Maintenance Phase, Safety set

	Atacand 16 mg (n=90)		Atacand 64 mg (n=90)		Atacand 128 mg (n=90)	
Preferred Term	n	(%)	n	(%)	n	(%)
Oedema peripheral	20	(22.2%)	17	(18.9%)	11	(12.4%)
Nasopharyngitis	8	(8.9%)	19	(21.1%)	13	(14.6%)
Fatigue	9	(10.0%)	11	(12.2%)	11	(12.4%)
Dizziness	9	(10.0%)	6	(6.7%)	13	(14.6%)
Headache	10	(11.1%)	9	(10.0%)	9	(10.1%)
Back pain	9	(10.0%)	8	(8.9%)	10	(11.2%)
Cough	10	(11.1%)	5	(5.6%)	8	(9.0%)
Influenza	7	(7.8%)	9	(10.0%)	5	(5.6%)
Diarrhoea	4	(4.4%)	4	(4.4%)	8	(9.0%)
Arthralgia	7	(7.8%)	5	(5.6%)	3	(3.4%)
Hyperkalaemia	4	(4.4%)	4	(4.4%)	7	(7.9%)
Pain in extremity	3	(3.3%)	5	(5.6%)	6	(6.7%)
Muscle spasms	4	(4.4%)	7	(7.8%)	3	(3.4%)
Nausea	2	(2.2%)	4	(4.4%)	8	(9.0%)
Dyspnoea	5	(5.6%)	7	(7.8%)	1	(1.1%)

Table S3b Most Frequent Treatment Emergent Adverse Events by Preferred Term, Titration and Maintenance Phase, Safety set

	Atacand 16 mg (n=90)		Atacand 64 mg (n=90)		Atacand 128 mg (n=90)	
Preferred Term	n	(%)	n	(%)	n	(%)
Upper respiratory tract infection	6	(6.7%)	3	(3.3%)	3	(3.4%)
Insomnia	2	(2.2%)	2	(2.2%)	6	(6.7%)
Hypertension	6	(6.7%)	1	(1.1%)	2	(2.2%)
Hypotension	1	(1.1%)	5	(5.6%)	2	(2.2%)