SYNOPSIS

A multicenter, non-comparative, phase IV study to evaluate the effect of candesartan based therapy in the percent change of proBNP level after 24 week treatment in the patients with hypertension with left ventricular hypertrophy

Study Centres

Subjects were recruited from a total of 21 centres in Korea. A total of 333 subjects were enrolled, of whom 315 were treated.

Publications

None at the time of writing this report

Study dates

First patient enrolled 15 June 2006

Last patient completed 05 June 2008

Phase of development

IV

Objectives

Primary:

The primary objective of this study was to investigate the percent change of B type natriuretic peptides (BNP) level in the subjects with hypertension and left ventricular hypertrophy treated with candesartan based therapy for 24 weeks.

Secondary:

The secondary objectives of this study were to investigate the following factors in the subjects with hypertension and left ventricular hypertrophy after 24 weeks of treatment on:

1. To evaluate LVH regression by echocardiogram parameter(LV mass, E/E', LA volume) in all patients
2. Change of systolic and diastolic blood pressure
3. Percent change of proBNP in patients treated with candesartan only
4. Percent change of proBNP in patients treated with candesartan plus felodipine
5. Change of mean ambulatory blood pressure (systolic and diastolic) in the subgroup of patients
6. Change of biomarkers related with collagen synthesis and degradation in the subgroup of patients:
    - PICP (procollagen type I carboxyterminal propeptide): synthesis marker
    - ICTP (collagen type I carboxyterminal propeptide): degradation marker
    - PICP/ICTP ratio

Study design

This was a multi-centre, non-comparative phase IV study. The study comprised the following 2 periods:

- 2 weeks screening period (week -2 to 0)
- 24 weeks treatment period (week 0 to 24)

Target subject population and sample size

Subject were male or female, aged from 18 to 75 years with essential hypertension and left ventricular hypertrophy.

The size of the study population was calculated to estimate the proBNP percent change. It was estimated that 385 evaluable subjects would be required to have 95% confidence interval for proBNP percent change with distance from mean to limit of 1.25 and standard deviation of 12.5.

Investigational product: dosage and mode of administration

Candesartan 16mg once daily in oral tablet form

Candesartan 32mg once daily in oral tablet form

Felodipine 5mg once daily in oral tablet form

Felodipine 10mg once daily in oral tablet form

Duration of treatment

Subjects were treated for 24 weeks with Candesartan 16mg once daily as initial dose. Subjects were modified investigational product dose to Candesartan 32mg, Candesartan 32mg + Felodipine 5mg, Candesartan 32mg + Felodipine 10mg, sequentially according to their blood pressures.

Endpoints

Primary endpoint:

Percentage change from baseline (week 0) in proBNP at 6 months

Secondary endpoints

The secondary endpoints are the following:

1. Change of echocardiogram parameters (LV mass, E/E', LA volume) in all patients
2. Change of systolic and diastolic blood pressure from baseline
3. Percentage change of proBNP in patients treated with candesartan only
4. Percentage change of proBNP in patients with candesartan plus felodipine
5. Percentage of mean ambulatory blood pressure (systolic and diastolic) in the subgroup of patients
6. Change of biomarkers related with collagen synthesis and degradation in the subgroup of patients;
   - PICP (procollagen type I carboxyterminal propeptide): synthesis marker
   - UCTP (collagen type I carboxyterminal propeptide): degradation marker
   - PICP/ICTP ratio

Statistical methods

The primary analysis population was intention to treat (ITT) population. This included all subjects with a baseline and at least one post-baseline efficacy evaluation.

Descriptive statistics were used to summarize the demographic, baseline characteristic data, medical history and concomitant medication for the treated subjects. No statistical tests were performed on demographic and baseline characteristic data.

The primary efficacy variable, percent change in proBNP, was analyzed according to the following procedures. Only subjects for whom both baseline and endpoint value are available were included in the analysis.

- Descriptive statistics of proBNP were summarized for baseline and endpoint.
- Descriptive statistics of percent change in proBNP were summarized.
- 95% confidence intervals of percent change in proBNP were estimated.
- Descriptive statistics of log transformed percent change in proBNP were summarized.

Secondary efficacy variables (echocardiogram parameters, SBP, DBP, ambulatory BP, and biomarkers) were analyzed with the similar method used for the primary efficacy variable.

- Descriptive statistics of secondary efficacy variables were summarized for baseline, and endpoint.
- Descriptive statistics of percent and/or absolute change in secondary efficacy variables were summarized.
- 95% confidence intervals of percent and/or absolute change in secondary efficacy variables were estimated.

Statistical tests using Wilcoxon's signed rank test (or paired t-test) for each efficacy variable were performed at a significance level of 5%.

Subject population

The subject population and disposition are presented in Table S1. A total of 333 were screened for participating in this study. Of them, 315 took part in the treatment period and took at least one dose of study medication. Two-hundred-forty-nine (249) subjects completed this study and 66 were dropped out during the treatment period. Twenty-three subjects were excluded from the ITT analysis set on the grounds of having no recorded post-dose proBNP results. The ITT set thus comprised 292 subjects and 203 subjects were included in PP set.

Table S1 Subject population and disposition

		N
All enrolled subjects		333
All treated subjects		315
N(%) of subjects who	Completed	249
	Discontinued	66
Safety analysis set		315

Full analysis set (ITT)	292
Per-protocol set (PP)	203

The demographic and background characteristics of study subjects are summarised in Table S2. There were more (74.3%) men than women, and all subjects were Oriental (Korean). The mean age was 49.9 years, and ages ranged from 19 to 78. The mean weight and height at baseline was 67.2kg and 165.4cm, respectively. Weight ranged from 38 to 100kg for all subjects. Mean waist was 86.9cm and mean BMI was 24.5kg/m^2. BMI ranged from 16.5kg/m^2 to 34.4kg/m^2.

Concomitant illnesses that were ongoing at enrolment were reported in 177(56.2%) of the 315 treated subjects. One-hundred-Seventy-Seven (56.2%) of all treated subjects before the start of the study and during the course of the study took at least one concomitant medication with study medication.

Table S2 Demographic and baseline characteristics (Safety set)

		N=315
Sex	Male	234(74.3%)
(n and % of subjects)	Femle	81(25.7%)
Age(years)	Mean (SD)	49.9(11.9)
	Range	19 to 78
Origin	Oriental	315(100.0%)
(n and % of subjects)	Other	0
Weight(kg)	Mean (SD)	67.2(10.7)
	Range	38 to 100
Height(cm)	Mean (SD)	165.4(8.3)
	Range	142 to 184
Waist(cm)*	Mean (SD)	86.9(7.8)
	Range	68 to 108
BMI(kg/m^2)	Mean (SD)	24.5(2.8)

	Range	16.5 to 34.4

* N=314

Efficacy results

The median of percent change in proBNP was -29.2% (95% CI: -35.3%, -16.7%) and the mean antilog value after log transformation of percent change in proBNP was -30.1% (95% CI: -36.7%, -22.8%). The proBNP value at endpoint was significantly lower than at baseline, and this change was clinically relevant.

The LV mass and LV mass index (the value of LV mass divided by body surface area) reduction was showed at end of study (median percent change in LV mass: -8.7%. median percent change in LV mass index: -9.0%)

And there were statistically significant reductions in systolic/diastolic BP and ambulatory systolic/diastolic BP. Both candesartan only and candesartan plus felodipine treatment groups resulted in significantly reductions of percent change in proBNP.

Candesartan affected significantly reductions in proBNP, some echocardiogram (LV mass and LV mass index), blood pressures (including ambulatory BP), and a biomarker (ICTP).

Table S3 Summary of major efficacy results (ITT analysis set)

Efficacy variables		**N**	**Mean (95% CI)**	**Median (95% CI)**	**p-value***
proBNP	Absolute change	292	-37.2 (-62.7, -11.7)	-9.5 (-11.9, -4.4)	<0.0001
	Percent change	292	-2.06 (-12.5, 8.4)	-29.2 (-35.3, -16.7)	<0.0001
	Percent change (log transformation)	292	-30.1 (-36.7, -22.8)	NA	NA
Echocardiogram parameter: LV mass [g]	Absolute change	265	-17.6 (-22.7, -12.5)	-15.9 (-19.6, -13.0)	<0.0001
	Percent change	265	-6.6 (-9.0, -4.3)	-8.7 (-11.4, -6.8)	<0.0001

Echocardiogram parameter: LV mass index [g/ m^2]	Absolute change	245	-10.9 (-14.0, -7.7)	-9.5 (-12.7, -7.0)	<0.0001
	Percent change	245	-7.2 (-9.6, -4.7)	-9.0 (-11.4, -6.8)	<0.0001
Echocardiogram parameter: E/E' ratio	Absolute change	262	-0.51 (-0.93, -0.09)	-0.2 (-0.7, 0.0)	0.0102
	Percent change	262	4.72 (-3.50, 12.95)	-1.4 (-7.2, 0.0)	0.1897
Echocardiogram parameter: LA volume [mL/m^2]	Absolute change	263	-1.07 (-1.94, -0.21)	-1.18 (-1.93, -0.41)	0.0038
	Percent change	263	0.49 (-3.76, 4.74)	-4.81 (-7.85, -2.09)	0.0606
Systolic BP	Absolute change	302	-32.8 (-34.8, -30.9)	-32.0 (-35.0, -30.0)	<0.0001
Diastolic BP	Absolute change	302	-18.9 (-20.2, -17.6)	-20.0 (-20.0, -18.0)	<0.0001

* Wilcoxon's signed rank test

Safety results

The proportions of subjects reporting at least one treatment-emergent AE was 36.5%. During treatment period, 186 AEs in 115 of 315 subjects in safety set were reported. Possibly related treatment-emergent AEs and treatment-emergent serious AEs occurred in 15 subjects (4.8%) and 8 subjects (2.5%), respectively. Only 1 adverse event (Cough) was severe and 9 subjects discontinued permanently due to AE.

There was no possibly related serious AE and death due to AE.

Table S4 **Number (%) of subjects who had at least one treatment-emergent adverse event in any category, and total number of adverse events (safety analysis set)**

	N=315	
	n(%)	events
Any adverse event	115(36.5)	186
Possibly related adverse event	15(4.8)	18
Adverse events of severe intensity	1(0.3)	1
Serious adverse event	8(2.5)	8
Possiby related SAEs	0	0
Study permanently discontinuation due to Aes	9(2.9)	10
Died during the treatment period due to AEs	0	0