Bayer HealthCare

Study Synopsis

This file is posted on the Bayer HealthCare Clinical Trials Registry and Results website and is provided for patients and healthcare professionals to increase the transparency of Bayer's clinical research.

This document is not intended to replace the advice of a healthcare professional and should not be considered as a recommendation. Patients should always seek medical advice before making any decisions on their treatment. Healthcare Professionals should always refer to the specific labeling information approved for the patient's country or region. Data on this website should not be considered as prescribing advice.

The study listed may include approved and non-approved formulations or treatment regimens. Data may differ from published or presented data and are a reflection of the limited information provided here. The results from a single trial need to be considered in the context of the totality of the available clinical research results for a drug. The results from a single study may not reflect the overall results for a drug.

2. Study synopsis

Title of the study:	Clinical effect and cost effectiveness of Ca antagonist in combination with AII receptor antagonist in patient with essential hypertension (PMS study) (Study 11518)
Investigator(s):	H Kimura[a], T Hiraoka[b], F Tomita[c], T Nagakura[d]
Study center(s):	[a]: Shinjuku Oak Tower Clinic, Tokyo [b]: Hiraoka Medical Clinic, Hiroshima [c]: Tomita Medical Clinic Internal/Cardiovascular Medicine, Hokkaido [d]: Yoga Allergy Clinic, Tokyo
Publications (references):	None
Period of study:	28 Mar 2004 to 23 Apr 2005 (first subject's first visit to last subject's last visit)
Clinical phase:	Phase IV
Objectives:	To investigate cost-effectiveness (incremental cost effectiveness) of Adalat® CR and Norvasc® in combination therapy with Diovan® for the treatment of patients with moderate to severe essential hypertension.
Methodology (design of study):	This was a randomized, double-blind, multi-centre, group-comparative study. After ≥2 weeks of pretreatment period with no anti-hypertensive medication, eligible subjects were randomized to either of Adalat® group or Norvasc® treatment group. The double-blind treatment period included four steps: Drug I, Drug II, Drug III and Drug IV. The study medication was started with Drug I. If the blood pressure after 4 weeks reached the target blood pressure according to Guidelines for the Management of Hypertension, the study medication was to remain unchanged. If the target blood pressure was not achieved, the treatment was to shift to Drug II. Likewise, when blood pressure after 8 weeks and 12 weeks reached the target blood

pressure, the same study medication was to be continued, and if not, the medication was to shift to the one in the next step. The double-blind treatment period was 16 weeks in total.

1) Drug I (Low dose of Ca antagonist)
   Adalat group: Adalat® CR 20 mg
   Norvasc group: Norvasc® 2.5 mg
2) Drug II (Low dose of Ca antagonist + Low dose of AII receptor antagonist)
   Adalat group: Adalat® CR 20 mg + Diovan® 40 mg
   Norvasc group: Norvasc® 2.5 mg + Diovan® 40 mg
3) Drug III (High dose of Ca antagonist + Low dose of AII receptor antagonist)
   Adalat group: Adalat® CR 40 mg + Diovan® 40 mg
   Norvasc group: Norvasc® 5 mg + Diovan® 40 mg
4) Drug IV (High dose of Ca antagonist + High dose of AII receptor antagonist)
   Adalat group: Adalat® CR 40 mg + Diovan® 80 mg
   Norvasc group: Norvasc® 5 mg + Diovan® 80 mg

Number of subjects: A total of 514 subjects were randomized in this study at 2 treatment groups: Adalat CR group with 250 subjects; Norvasc group with 264 subjects. Of these, 513 subjects received at least 1 dose of study medication and were valid for safety analysis. One subject in the Norvasc group did not take any study medication, and was excluded from all the analyses.

Table 2-1: Subject number by treatment

	Adalat CR	Norvasc	Total
Randomized	250 (100.0%)	264 (100.0%)	514 (100.0%)
Valid for Safety analysis	250 (100.0%)	263 (99.6%)	513 (99.8%)
Valid for FAS	245 (98.0%)	260 (98.5%)	505 (98.2%)

Diagnosis and main criteria for inclusion: Diagnosis: Essential hypertension

1) For the enrollment
   (1) Male and female
   (2) 20 years $\leq$ Age < 80 years
   (3) Outpatient
   (4) Untreated patients or patients with previous treatment by anti-hypertensive agents whose blood pressure at sitting position at the time of the entry (Visit 1) is:
   - SBP $\geq$160 mmHg or DBP $\geq$100 mmHg for untreated patients
   - SBP $\geq$150 mmHg or DBP $\geq$95 mmHg for patients

	with previous treatment by anti-hypertensive agents (5) Patients who have provided written informed consent. 2) For the randomization Patients whose blood pressure in sitting position at randomization (Visit 2) after 2 weeks (14 days) and longer of pretreatment period is: - SBP $\geq$160 mmHg or DBP $\geq$100 mmHg
Test product, dose and mode of administration, batch number:	Adalat® CR 20 mg Tablet (Batch No.: 3595F) Adalat® CR 40 mg Tablet (Batch No.: 3601F) The subject took 1 capsule of the study drugs (Drugs I to IV), once a day after breakfast, for the double-blind treatment period.
Duration of treatment:	Pretreatment period with no medication: 2 weeks and longer Double-blind treatment period: 16 weeks
Reference therapy, dose and mode of administration, batch number:	Norvasc® 2.5 mg Tablet (Batch No.: 305032C) Norvasc® 5 mg Tablet (Batch No.: 3051173, 3051183) Diovan® 40 mg Tablet (Batch No.: 30420, 30450) Diovan® 80 mg Tablet (Batch No.: 32690)
Criteria of evaluation:	Cost Effectiveness Variables: • Mean treatment cost[*1] for 16-week of double blind treatment period (primary variable) • Achievement rate to target blood pressure[*2] at the end of double blind treatment period (primary variable) Incremental cost effectiveness was investigated by comparing these primary variables between the two treatment groups. • Treatment cost per subject to achieve the target blood pressure (secondary variable): = Total costs for the double blind treatment period[*1] / Number of patients who achieve target blood pressure[*2] at the end of double blind treatment period. [*1] Including treatment costs for the drug-related AEs (with causal relationship to the study drug). The sponsor calculated the cost based on the tariff of health insurance scores. [*2] Target blood pressure: For subjects aged under 60 years: SBP <130 mmHg and DBP <85 mmHg For subjects aged 60 years and over: SBP <140 mmHg and DBP <90 mmHg

	Efficacy Variables: • The change in blood pressure (SBP and DBP) from the baseline (end of pretreatment period). • Achievement rate for each age group to target blood pressure level. Safety Variables: • Incidence of treatment-emergent drug-related adverse events • Incidence of all treatment-emergent adverse events • Vital sign • Standard 12-lead ECG • Laboratory tests
Statistical methods:	Disposition of subjects The number of the subjects randomized, valid for each analysis set and excluded from the analysis were summarized with relative frequencies by treatment group. The number of the subjects who discontinued the study after randomization was presented with their specific reasons by treatment group. Demographic and other baseline characteristics With the population of subjects valid for full analysis set, demographic data, baseline characteristics and disposition of study drugs (Drugs I to IV) were summarized by treatment group, using descriptive statistics, according to the type and nature of data. Especially for clinically important variables which might influence the efficacy outcome, the treatment group was compared by Student's t-test with respect to continuous data, and by chi-squared test or Wilcoxon rank-sum test with respect to categorical data with the significance level of 0.05. Cost effectiveness The study aimed to demonstrate both the superiority of Adalat® CR to Norvasc® in mean treatment cost, and the non-inferiority of Adalat® CR to Norvasc® in achievement rate to target blood pressure level with non-inferiority margin of -10%. The analyses were based on full analysis set. For the mean treatment cost and the achievement rate to target blood pressure level, point estimates of difference between the two treatment groups (Adalat combination therapy - Norvasc combination therapy) as well as their two-sided 95% confidence intervals were computed. Weighed difference between treatment

groups and its confidence interval in achievement rate were constructed using Mantel-Haenszel weights with strata defined by the age group (younger than 60 years, 60 or elder than 60 years). Treatment cost per subject to achieve the target blood pressure was also calculated for each treatment group.

A cost-effectiveness acceptability curve was also generated.

Efficacy assessment

Efficacy endpoints were change from the baseline in clinic sitting SBP and DBP, and achievement rate to target blood pressure level. Change from baseline in blood pressure was compared between the treatment groups by the analysis of covariance (ANCOVA) with baseline value as covariate and treatment group as main effect. The least-squares (LS) means and standard errors for each treatment group given by the ANCOVA model were also presented as well as treatment differences of LS means and their 95% confidence intervals. Achievement rates were compared between the treatment groups using Cochran-Mantel-Haenszel test with stratification according to the age group (younger than 60 years, 60 or elder than 60 years). These analyses were based on the full analysis set.

All statistical tests were two-sided with significance level of 0.05. No adjustment for multiplicity of statistical tests was planned. The LOCF principle was applied in order to impute missing data at some time points during the double-blind treatment period.

Safety assessment

Safety profile of adverse events and laboratory data were summarized by treatment group in a descriptive manner. All treatment emergent adverse events were presented by treatment group with preferred term in the MedDRA dictionary. Laboratory values and vital signs were summarized by descriptive statistics, and changes in laboratory values before and after the administration and the incidence of abnormal values were evaluated with the reference to the normal ranges.

Summary and conclusions:

Summary of efficacy:

Overall achievement rate in the target SBP was 69.8% for the Adalat CR group, and 48.5% for the Norvasc group. In the target DBP, that was 75.1% for the Adalat CR group, and 50.0% for the Norvasc group. Statistically significant difference between treatment groups was noted both in SBP and in DBP (Cochran-Mantel-Haenszel test; $p<0.001$). The adjusted difference in achievement rate of SBP (Adalat CR group - Norvasc group) was 21.3% (95%CI: 12.9%, 29.6%), and that of DBP was 24.9% (95%CI: 17.2%, 32.7%). Overall achievement rate in the target SBP as well as in the target DBP was 61.2% for the Adalat CR group, and 34.6% for the Norvasc group. Statistically significant difference between treatment groups was noted (Cochran-Mantel-Haenszel test; $p<0.001$). The adjusted difference in achievement rate was 26.5% (95%CI: 18.3%, 34.7%). Lower limit of 95% confidence interval was greater than 0% in each case.

Table 2-2: Achievement rates (Full Analysis Set)

			Adalat CR	Norvasc
Systolic Blood Pressure (SBP)	Age Group	<60	91 / 141 (64.5%)	64 / 151 (42.4%)
		60-	80 / 104 (76.9%)	62 / 109 (56.9%)
	Overall		171 / 245 (69.8%)	126 / 260 (48.5%)
	Adjusted Difference in Rates (95% CI) [a]		21.3% (12.9%, 29.6%)	
Diastolic Blood Pressure (DBP)	Age Group	<60	89 / 141 (63.1%)	55 / 151 (36.4%)
		60-	95 / 104 (91.3%)	75 / 109 (68.8%)
	Overall		184 / 245 (75.1%)	130 / 260 (50.0%)
	Adjusted Difference in Rates (95% CI) [a]		24.9% (17.2%, 32.7%)	
Both SBP and DBP	Age Group	<60	74 / 141 (52.5%)	37 / 151 (24.5%)
		60-	76 / 104 (73.1%)	53 / 109 (48.6%)
	Overall		150 / 245 (61.2%)	90 / 260 (34.6%)
	Adjusted Difference in Rates (95% CI) [a]		26.5% (18.3%, 34.7%)	

a 95% confidence interval of difference in rates (Adalat CR group – Norvasc group) adjusted by age group was calculated by using Mantel-Haenszel weight.

The treatment costs were JPY 25,955 for the Adalat CR group and JPY 29,739 for the Norvasc group. Statistical significance in the treatment cost was determined with the Wilcoxon rank sum test, which is considered to be apparently more appropriate method to analyze the current data.

Table 2-3: Confidence interval for difference in treatment cost (Full Analysis Set)

Adalat CR (N=245)	Norvasc (N=260)	Difference	95% Confidence Interval	
			Lower	Upper
25,955	29,739	-3,784	-8,297	728

unit: JPY

Table 2-4: Treatment costs - Wilcoxon rank sum test (Full Analysis Set)

Median		Wilcoxon Rank Sum test
Adalat CR (N=245)	Norvasc (N=260)	P-value
26,978	28,118	<0.001

unit: JPY

The difference of LS means of changes from baseline in SBP (Adalat CR group - Norvasc group) was -6.7 (95%CI: -8.9, -4.6), and that in DBP was -5.1 (95%CI: -6.7, -3.6). For both SBP and DBP, changes from baseline in the Adalat CR group were significantly greater than those in the Norvasc group (ANCOVA; $p<0.001$).

Table 2-5: Changes from baseline in blood pressure (Full Analysis Set)

		Adalat CR (N=245)	Norvasc (N=260)
Systolic Blood Pressure (SBP)	LS Mean (SE)	-33.8 (0.8)	-27.1 (0.8)
	Difference (95%CI)	-6.7 (-8.9, -4.6)	
Diastolic Blood Pressure (DBP)	LS Mean (SE)	-20.6 (0.6)	-15.5 (0.5)
	Difference (95%CI)	-5.1 (-6.7, -3.6)	

Visit: End of Treatment

Values were obtained using ANCOVA model including treatment group as a main effect and baseline value as a covariate.

Summary of safety:

Of the 514 subjects randomized to the study, 513 subjects received at least 1 dose of the study drugs and were valid for safety analysis. Two hundred fifty-one subjects (48.9%) of the 513 subjects valid for safety analysis experienced at least one adverse event: 130 subjects (52.0%) in the Adalat CR group and 121 (46.0%) in the Norvasc group. The most common adverse events were nasopharyngitis (18.8% of Adalat CR group, 16.7% of Norvasc group), upper respiratory tract inflammation (8.8% of Adalat CR group, 7.6% of Norvasc group) and headache (4.4% of Adalat CR group, 3.0% of Norvasc group). Drug-related adverse events were noted in 31 subjects (12.4%) in the Adalat CR group and 20 (7.6%) in the Norvasc group. The drug-related adverse events occurring in at least 2% of any treatment group were headache (2.4%), peripheral oedema (2.0%) and pollakiuria

(2.0%) in the Adalat CR group. Adverse events leading to discontinuation of the study medication were noted in 11 subjects (4.4%) in the Adalat CR group and 8 (3.0%) in the Norvasc group. Serious adverse events were noted in 3 subjects (1.2%) in the Adalat CR group and 4 (1.5%) in the Norvasc group. No death was reported during the study. Most adverse events were mild in severity.

For laboratory variables, most changes from baseline were very similar between the two groups. The incidence of laboratory abnormalities was also similar between the two groups.

It can be concluded that the safety profile of the Adalat CR group is similar to that of the Norvasc group.

Conclusions:

The Adalat CR combination therapy is dominant to the Norvasc combination therapy for the management of essential hypertension in a Japanese population.