Clinical Study Synopsis

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Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer HealthCare AG	
Study Number:	14511	NCT00993109
Study Phase:	IV	
Official Study Title:	Randomized, open-label, parallel design comparator study of effect of Nifedipine GITS/OROS (Adalat®) 30 mg in combination with Valsartan (Diovan®) 80 mg compared to Valsartan (Diovan®) 160 mg monotherapy in patients whose blood pressure is not well controlled by Valsartan 80 mg alone	
Therapeutic Area:	CV Risk Management	
Test Product		
Name of Test Product:	Nifedipine GITS/OROS (Adalat®, BAY A-1040) + Diovan® (Valsartan)	
Name of Active Ingredient:	Nifedipine + Valsartan	
Dose and Mode of Administration:	Nifedipine 30 mg + Valsartan 80 mg, once a day (Group A) Oral	
Reference Therapy/Placebo		
Reference Therapy:	Valsartan	
Dose and Mode of Administration:	160 mg, once a day (Group B) Oral	
Duration of Treatment:	12 weeks	
Studied period:	Date of first subjects' first visit:	04 FEB 2010
	Date of last subjects' last visit:	27 MAY 2011
Premature Study Suspension / Termination:	NA	
Substantial Study Protocol Amendments:	The original protocol was amended 3 times. Amendment 1 included the following modifications: • Clarification of inclusion criterion. For subjects who were switched from prior therapy to valsartan 80 mg and subsequently were treated with 4 weeks of valsartan 80 mg	

	monotherapy, the following clarification was added, "provided the hypertension is still not well controlled." • Clarification of exclusion criterion for severe hypertension, definition changed from "systolic blood pressure (SBP) / diastolic blood pressure (DBP) = 180/110 mmHg" to "DBP ≥ 110 mmHg and/or SBP ≥ 180 mmHg." • The maximum number of subjects enrolled at each study site was increased from 26 to 32. The purpose of Amendment 2 was to correct a minor error in the exclusion criterion stating that proteinuria was to be determined only by urine test strips. Proteinuria was specified in the protocol to be determined by urine test strips in the exclusion criteria. However, proteinuria could also be determined by urinalysis conducted at the Screening visit. Therefore, "determined by urine test strips" was deleted, as this was not the sole test used to determine proteinuria. The purpose of Amendment 3 was to revise the inclusion criterion to enable subjects previously treated with agiotensin receptor blockers (ARBs) other than the study drug valsartan to be included, and to make administrative changes.
Study Centre(s):	Sixteen investigational sites treated patients in 2 countries: China and Korea.
Methodology:	This was a multicenter, prospective, randomized, open-label, parallel design, 2-arm comparator study. This study consisted of a screening visit, followed by randomization and administration of either nifedipine GITS/OROS 30 mg in combination with valsartan 80 mg or valsartan 160 mg for 12 weeks of treatment. Each study center was to recruit a minimum of 10 and a maximum of 32 subjects.
Indication/ Main Inclusion Criteria:	Adult men and women, aged 18 to 75 years, with essential hypertension not well controlled by current low-dose (80 mg) valsartan monotherapy for at least 4 weeks. Subjects on prior treatment with monotherapy diuretic, angiotensin converting enzyme inhibitor (ACE-I), beta-blocker, or an angiotensin receptor blocker (ARB) other than valsartan and switched to the current low-dose valsartan 80 mg monotherapy for at least 4 weeks were also eligible, provided the hypertension was still not well controlled. Office SBP (sitting) > 140 mmHg (sitting for ≥ 5 minutes, no cigarettes and/or coffee/tea for ≥ 30 minutes before blood pressure measurement).
Study Objectives:	The objective of this study was to compare the efficacy of nifedipine GITS/OROS 30 mg in combination with valsartan 80 mg versus that of up-titrated valsartan 160 mg monotherapy in subjects whose blood pressure had not been well controlled by valsartan 80 mg alone.
Evaluation Criteria:	<u>Efficacy (Primary):</u> The primary efficacy endpoints were the change from baseline in mean SBP and DBP at Week 12 (last observation carried forward [LOCF]). Blood pressure was measured twice at each visit. The mean of the 2 measurements was used as the reference value for inclusion in this study and assessment of efficacy. During the screening visit, blood pressure was measured for both arms (twice per arm). The arm with the higher value was selected as the reference arm for all subsequent recordings.

	Efficacy (Secondary): The secondary efficacy variables were as follows: • Response rate (≥ 10 mmHg decrease of mean office SBP and ≥ 5 mmHg decrease of mean office DBP) at 8 and 12 weeks of treatment • Control rate (mean SBP ≤ 140 mmHg and mean DBP ≤ 90 mmHg) at 8 and 12 weeks of treatment • Change in mean pulse pressure (difference between SBP and DBP) at 12 weeks of treatment Safety: Safety variables included adverse event (AEs), vital signs, laboratory tests, and 12-lead electrocardiogram (ECG). All safety analyses were based on the Safety Analysis Set. All laboratory tests were performed locally at each center. Different units used by the local laboratories were converted to the International System of Units (SI unit) for the summaries.
	Other: Other efficacy variables were as follows: • Urinary (micro)albumin excretion (UAE) in subjects with microalbuminuria (any reduction at 12 weeks of treatment compared to baseline)
Statistical Methods:	All statistical hypothesis tests were 2-sided and conducted at the 5% significance level if not mentioned otherwise. All variables were summarized descriptively by treatment group and visit (if appropriate). Continuous variables were summarized in terms of the mean, standard deviation (SD), minimum, lower quartile (Q1), median, upper quartile (Q3), and maximum. Categorical data were summarized in terms of frequency tables (counts and percentages). Efficacy (Primary): The primary efficacy endpoints, the change from baseline in mean SBP and DBP at Week 12 (LOCF), were analyzed using the analysis of covariance (ANCOVA) model with treatment and center as factors and baseline blood pressure as a covariate. For the purpose of the summaries and analyses, the 'Baseline' value was defined as the latest non-missing value prior to the start of randomized treatment (ie, Visit 2 value if available; otherwise, the Visit 1 value). Efficacy (Secondary): Control rates and response rates at Week 8 and Week 12 were compared using the Cochran-Mantel-Haenszel test with center as a stratification factor. The change from baseline to Week 12 (LOCF) in mean pulse pressure was analyzed using ANCOVA with treatment and center as factors and baseline mean pulse pressure as a covariate.

	Safety: Summary tables for safety variables were provided by treatment group and overall, based on the Safety Analysis Set. Other: For subjects who had microalbuminuria at baseline, the number of subjects with a reduction in UAE from baseline to Week 12 (LOCF) was summarized by treatment group.
Number of Subjects:	A total of 151 subjects per treatment group, or 302 subjects in total were required for the analysis. Allowing for 15% invalidity, 356 subjects were to be randomized to the 2 treatment groups. A total of 360 subjects were randomized to treatment; 359 subjects were included in the Full Analysis Set, 313 were included in the Per Protocol Set, and 359 were included in the Safety Analysis Set (177 subjects in nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 182 subjects in the valsartan 160 mg group).

Study Results

Results Summary — Subject Disposition and Baseline

A total of 360 subjects were randomized to treatment, including 178 subjects in nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 182 subjects in the valsartan 160 mg group. The Full Analysis Set was the primary population for the analysis of efficacy data. Only 1 of the 360 randomized subjects was excluded from Full Analysis Set (did not take any study medication after randomization). The Safety Analysis Set was identical to the Full Analysis Set. Of the 359 subjects in the Full Analysis Set, 46 subjects had at least 1 major protocol deviation and were excluded from the Per Protocol Set; the remaining 313 subjects comprised the Per Protocol Set.
The 2 treatment groups were comparable with respect to baseline demographics and characteristics. The mean age of the nifedipine GITS/OROS 30 mg + valsartan 80 mg group was 56.3 years (range: 33 to 75 years), 50.8% of subjects were male, and all subjects were Asian. In the valsartan 160 mg group, mean age was 55.5 years (range: 27 to 74 years), 53.8% of subjects were male, and all subjects were Asian. There were 42.9% and 48.4% of subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg and valsartan 160 mg groups, respectively, whose BMI was less than 25 kg/m^2. The mean (standard deviation [SD]) baseline SBP values were 151.8 (8.0) and 151.8 (8.5) mmHg and the mean (SD) baseline DBP values were 94.3 (6.8) and 93.9 (7.4) mmHg in the nifedipine GITS/OROS 30 mg + valsartan 80 mg and valsartan 160 mg groups, respectively.

Results Summary — Efficacy

Primary efficacy variables

Change from baseline in mean SBP at Week 12 (LOCF)

In the Full Analysis Set after 12 weeks of treatment, mean SBP decreased 18.3 mmHg and 16.5 mmHg in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and valsartan 160 mg group, respectively. The difference in LS means between the 2 treatment groups was -1.9 mmHg (95% CI [-4.1, 0.4]; p=0.0998). This difference was not statistically significant.

Change from baseline in mean DBP at Week 12 (LOCF)

In the Full Analysis Set after 12 weeks of treatment, mean DBP decreased 9.8 mmHg and 7.4 mmHg in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and valsartan 160 mg group, respectively. The difference in LS means between the 2 treatment groups was -2.4 mmHg (95% CI [-3.8,-1.0]; p=0.0011).

Change from baseline in mean SBP and DBP at Week 12 (Per Protocol Set)

In the Per Protocol Set analysis, mean SBP decreased 19.2 mmHg and 16.8 mmHg in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and valsartan 160 mg group, respectively. The difference in LS means between the 2 treatment groups was -2.4 mmHg (95% CI [-4.7,-0.2]; p=0.0342). Mean DBP decreased 10.3 mmHg and 7.2 mmHg in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and valsartan 160 mg group, respectively. The difference in LS means between the 2 treatment groups was -3.1 mmHg (95% CI [-4.6,-1.7]; p<0.0001).

Secondary efficacy variables

Control rate (Calculated dropouts as uncontrolled)

In the Full Analysis Set after 8 weeks, 65.3% of subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 50.8% of subjects in the valsartan 160 mg group had controlled blood pressure. At Week 12, the blood pressure control rates were 69.3% and 54.1% for the 2 treatment groups, respectively. The blood pressure control rates were significantly higher both after 8 weeks (p=0.0041) and 12 weeks (p=0.0022) of treatment.

Response rate (Calculated dropouts as non-responders)

In the Full Analysis Set at Week 8, the response rate was 64.8% in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group as compared with 44.8% in the valsartan 160 mg group. At Week 12, the response rates were 65.3% and 53.6% for the 2 treatment groups, respectively. The blood pressure response rate in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group was significantly higher than the blood pressure response rate in the valsartan 160 mg group at 8 weeks (p<0.0001) and 12 weeks (p=0.0209).

Mean pulse pressure

In the Full Analysis Set at Week 12, mean pulse pressure decreased 8.5 mmHg in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 9.0 mmHg in the valsartan 160 mg group. The difference in LS means between the 2 treatment groups was not statistically significant (0.5 mmHg; 95% CI [-1.2,2.3]; p=0.5365).

Other efficacy variables

UAE in subjects with microalbuminuria at baseline

After 12 weeks of treatment (LOCF), the percentage of subjects with reductions in UAE from baseline was 75.0% (21/28 subjects) in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group compared with 80.0% (16/20 subjects) in the valsartan 160 mg group. The number of subjects with microalbuminuria at baseline in both treatment groups was too small to draw meaningful conclusions regarding these data.

Summary of mean SBP and DBP over time

The reduction in SBP and DBP was numerically greater in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group compared with the valsartan 160 mg group. This effect was observed as early as Week 4.

Control rate and response rate over time

A higher proportion of subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group achieved blood pressure control and response as compared with the valsartan 160 mg group. This effect was observed as early as Week 4.

Results Summary — Safety

The incidence of treatment-emergent adverse events (TEAEs) was similar between treatment groups. TEAEs were reported by 65/177 (36.7%) subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 58/182 (31.9%) subjects in the valsartan 160 mg

group. The most frequent TEAE reported in both treatment groups overall was upper respiratory tract infection (3.4% and 3.8% of subjects, respectively).

Most of the subjects in both treatment groups had TEAEs assessed by the investigator as mild in intensity. Seven (4.0%) subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 9 (4.9%) subjects in the valsartan 160 mg group experienced TEAEs assessed as moderate. None of the TEAEs in either treatment group was assessed as severe in intensity. At least 1 TEAE was assessed by the investigator as study drug-related in 8 subjects (4.5% and 4.4% for nifedipine GITS/OROS 30 mg + valsartan 80 mg and valsartan 160 mg, respectively) in each treatment group.

No deaths occurred during the study. Treatment-emergent serious adverse events (SAEs) were reported in 2 (1.1%) subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group (scrub typhus in 1 subject and multiple fractures, muscle injury, and road traffic accident in the other subject) and 1 (0.5%) subject in the valsartan 160 mg group (medical device complication). None of the SAEs was assessed as study drug-related. Eleven subjects discontinued study treatment due to a TEAE, including 7 (4.0%) subjects in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group and 4 (2.2%) subjects in the valsartan 160 mg group; of these 11 subjects, 4 and 3 in the 2 groups, respectively, discontinued treatment due to a study drug-related TEAE.

There were no clinically meaningful changes from baseline in serum chemistry, hematology, or urinalysis analytes for either treatment group or between treatments. Shifts in serum chemistry, hematology, or urinalysis analytes from normal at baseline to abnormal (high or low) post-baseline were infrequent and comparable in both treatment groups (≤ 5% difference between treatments), with the exception of hemoglobin, LDH, creatine kinase, and triglycerides, all of which showed a higher percentage of subjects with a shift from normal to high in the valsartan 160 mg group than in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group.

The median change from baseline in UAE at the last visit in the total population was small in both the nifedipine GITS/OROS 30 mg + valsartan 80 mg group (-0.02 mg/g creatine) and the valsartan 160 mg group (0 mg/g creatine).

There were no clinically relevant changes from baseline in vital signs or ECGs in either treatment group.

Conclusion(s)

- Combination therapy with nifedipine GITS/OROS 30 mg + valsartan 80 mg group showed a larger reduction in both co-primary endpoints than monotherapy with valsartan 160 mg: for SBP the difference between the 2 treatment groups was 1.9 mmHg (p=0.0998) and for DBP the difference between the 2 treatment groups was 2.4 mmHg (p=0.0011) in the Full Analysis Set, although the difference for SBP was not statistically significant.
- In the Per Protocol Set, the difference between the 2 treatment groups with regard to the reduction from baseline in SBP (a difference of 2.4 mmHg; p=0.0342) and the reduction from baseline in DBP (a difference of 3.1 mmHg; p<0.0001) was statistically significant in favor of the combination of nifedipine GITS/OROS 30 mg + valsartan 80 mg.
- The blood pressure control and response rates were higher in the nifedipine GITS/OROS 30 mg + valsartan 80 mg group than in the valsartan 160 mg group; this effect was observed as early as Week 4 and was maintained consistently through the end of the study.
- The safety profiles of combination therapy with nifedipine GITS/OROS 30 mg + valsartan 80 mg and monotherapy with valsartan 160 mg were similar, without any major clinical concerns.
- Although 1 of the 2 co-primary end points (the decrease in SBP from baseline to Week 12 [LOCF] in the Full Analysis Set) did not fulfill initial assumptions, comprehensive evaluation of the data implied that combination treatment with

	nifedipine GITS/OROS 30 mg + valsartan 80 mg resulted in a better blood pressure-lowering effect than monotherapy with valsartan 160 mg.
Publication(s):	none
Date Created or Date Last Updated:	29 March 2012

Product Identification Information

US Trade Name(s)	Adalat GITS is not marketed in USA
All Trade names (worldwide)	Adalat, Adalat GITS, Adalat OROS, Adalat CR, Adalat XL, Adalat LA, OSMO- Adalat, Adalat CRONO, CHRONADALATE
Generic names	Nifedipine
Company code(s)	BAY a1040
Chemical description	Nifedipine: Dimethyl 2,6-dimethyl-4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate
Aliases	