Science For A Better Life

Clinical Study Synopsis

This Clinical Study Synopsis 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 labelling information approved for the patient's country or region. Data in this document or on the related 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.

Bayer HealthCare

Clinical Trial Results Synopsis

Study Design Description		
Study Sponsor:	Bayer Healthcare AG	
Study Number:	14696	NCT01071122
Study Phase:	IV Interventional	
Official Study Title:	A prospective, open-label, active-controlled, randomized study comparing nifedipine GITS versus valsartan versus a combination of both on central blood pressure in inadequately controlled essential hypertension.	
Therapeutic Area:	CV Risk Management	
Test Product		
Name of Test Product:	Nifedipine GITS	
Name of Active Ingredient:	Nifedifine	
Dose and Mode of Administration:	30mg, 60mg once daily, oral	
Reference Therapy/Placebo		
Reference Therapy:	valsartan	
Dose and Mode of Administration:	80mg, 160mg once daily, oral	
Duration of Treatment:	8 weeks	
Studied period:	Date of first subjects' first visit:	15 Mar 2010
	Date of last subjects' last visit:	15 Feb 2012
Premature Study Suspension / Termination:	N/A	
Substantial Study Protocol Amendments:	3 times - Original protocol, dated 04 SEP2 009 - Protocol amendment 1, version 1.0, dated 11 DEC 2009	

	- Protocol amendment 2, version 3.0, dated 23 AUG 2010 grade 3 hypertension untreated or treated with diuretics and/or beta-blockers will be eligible for enrollment - Protocol amendment 3, version 4.0, dated 09 MAR 2011
Study Centre(s):	17 study centers in Korea
Methodology:	All patients performed a screening visit and were randomized two times. Period of study treatment was 8 weeks and at week 0 (baseline), all eligible patients were randomized to nifedipine 30mg or valsartan 80mg group each (1st randomization) and treated for 4 weeks (step 1). After 4 weeks, patients who did not reach the target BP of less than 140/90 mm Hg (130/80mmHg for patients with diabetes) in the two group, was randomized to one of the three randomized groups (group A: Nifedepine GITS 30 mg plus Valsartan 80mg or group B: Nifedipine GITS 60mg or group C: Valsartan 160 mg) again (2nd randomization) and treated for 4 weeks (step 2).
Indication/ Main Inclusion Criteria:	Essential hypertension • Men and women aged 20-70 years • Untreated grade 2 or grade 3 hypertension defined by mean diastolic BP ≥100 and/or mean systolic BP≥160mmHg without anti-hypertensive treatment or Treated grade 2 or grade 3 hypertension defined by mean diastolic BP≥100 and/or mean systolic BP≥160mmHg with current diuretics and/or beta-blockers use for ≥ 4 weeks • Signed written informed consent
Study Objectives:	<u>Overall:</u> The study is aimed to determine whether the combination of nifedipine GITS and valsartan is more effective in reducing central blood pressure than nifedipine GITS high dose or valsartan high dose alone in inadequately controlled essential hypertension by nifedipine GITS low dose or valsartan low dose alone. <u>Primary:</u> to evaluated the central SBP change from baseline to week 8 <u>Secondary:</u> to evaluated other efficacy variables and safety
Evaluation Criteria:	<u>Efficacy (Primary):</u> The primary efficacy parameters were changes in central systolic blood pressure (SBP) between baseline and at week 8. Blood pressure was measured three times at each visit. The mean of three measurements was used for inclusion criteria of this study and assessment of efficacy

	Efficacy (Secondary): Secondary efficacy parameters were the following: • Change in central DBP and pulse pressure at week 4 and 8 of treatment • Change in central SBP at week 4of treatment • Change in brachial SBP and DBP at week 4 and 8 of treatment • Change in brachial pulse pressure at week 4 and 8 of treatment • Change in augmentation index and augmentation pressure at week 4 and 8 of treatment • Response rate (≥10 mmHg decrease of brachial SBP and ≥5mmHg decrease of brachial DBP) at week 4 and 8 of treatment • Control rate (≤140/90 mmHg, 130/80 mmHg for diabetes, of brachial BP) at week 4 and 8 of treatment Safety: Safety variables included adverse events (AEs), laboratory safety findings, vital signs and ECGs. All safety variables were analyzed based on the Safety Analysis Set.
Statistical Methods:	Efficacy (Primary): The primary efficacy variable, central SBP change from baseline at week 8 was analyzed using analysis of covariance (ANCOVA), including treatment and center as main effects and baseline (day 0) BP, age, and previous treatment for the hypertension (untreated/treated) as covariates. The covariates, age and previous treatment for the hypertension, were selected as the prognostic factors and were planned to be included in the model to correct for the possible imbalance between the nifedipine 60mg and valsartan 160mg groups that could be introduced when the response rates were different at week 4. The pairwise comparisons between the nifedipine GITS 30 mg plus valsartan 80 mg group and the monotherapy group were performed using the Laska-Meisner Min test to control the type I error rate at 0.05. The least-squares means (LS means), the difference between LS means (combination therapy minus monotherapy), the corresponding p-values were provided (based on Type III sums of squares). Efficacy (Secondary): The continuous efficacy variables of the change in central DBP, pulse pressure, central SBP, brachial SBP and DBP, brachial pulse pressure, augmentation index and augmentation pressure at week 8 were analyzed using the same method for the primary efficacy variable. The baseline BP as covariate meant the baseline value of their response variables. The changes from baseline at week 4 and from week 4 to week 8 were also analyzed using the same method for the primary efficacy variable.

	The categorical efficacy variables of the response rate (≥10 mmHg decrease of brachial SBP and ≥5mmHg decrease of brachial DBP), control rate (<140/90 mmHg, <130/80 mmHg for diabetes, of brachial BP) at week 8 were analyzed using the Cochran-Mantel-Haenszel (CMH) statistics stratified by the clusters of centers, baseline brachial diastolic BP (< median, ≥median), age group (<= 65, >65), and previous treatment for the hypertension (untreated, treated). The categorical efficacy variables at week 4 were analyzed using the same method. Safety: The incidence of treatment-emergent adverse events will be tabulated by treatment group. Adverse events are considered to be treatment-emergent if they have started or worsened after first application of study medication up to 0(step 1) or 7(step 2) days after end of treatment with study medication. Further tables will be prepared for serious and/or drug-related treatment-emergent adverse events. Laboratory data will be presented according to their scale, i.e. sample statistics for continuous measures and frequency tables for categorical measures. Change from baseline will also be presented as frequency counts for patients outside of the normal range by visit and treatment group. Other - if applicable: The exploratory variables The BP reducing effect of Nifedipine GITS alone and valsartan alone was analyzed for all efficacy variables at week 4 and week 8 for the Exploratory analysis set. The analysis at week 8 was done by pooling low dose group and high dose group, regardless of the responses at week 4, to avoid possible bias that could be introduced when the response rates were different between the monotherapies during the first 4 weeks. The 95% confidence interval of the difference between the nifedipine GITS and valsartan groups (Nifedipine GITS – valsartan) was presented by the randomization at week 0 using the same ANCOVA model stated in efficacy variables.
Number of Subjects:	Planned: 356 subjects Analyzed: A total of 367 subjects were randomized; 198 subjects were included in the Efficacy Analysis Set, 169 subjects were included in the Per Protocol Set. For the Safety Analysis set, 363 subjects were included in the step 1, and 202 subjects were included in the step 2.

Study Results

Results Summary — Subject Disposition and Baseline

Of the 391 subjects screened for inclusion in step 1, a total of 367 subjects were randomized to treatment (1st randomization), including 184 subjects in the nifedipine GITS 30 mg group and 183 subjects in the valsartan 80 mg group. The 24 subjects were screened but not randomized (screening failure). Of the 367 subjects randomized to study treatment, 329 subjects (158 subjects in the nifedipine GITS 30 mg group; 171 subjects in the valsartan 80 mg) completed step 1 of the study and 38 subjects (26 subjects in the nifedipine GITS 30 mg group; 12 subjects in the valsartan 80 mg group) withdrew prematurely from the study.

The 203 subjects who did not reach to the target BP randomized to study treatment in step 2 (2nd randomization). The 126 subjects who reached to the target BP were not assigned randomization to study treatment in step 2 and were continued with the treatment in step 1. A total of 203 subjects randomized to study treatment(2nd randomization), including 68 subjects in the nifedipine GITS 60 mg group, 66 subjects in combination (nifedipine GITS 30 mg plus valsartan 80 mg) group, 69 subjects in the valsartan 160 mg. A total of 314 subjects (65 subjects in combination (nifedipine GITS 30 mg plus valsartan 30 mg group), 64 subjects in nifedipine GITS 60 mg group, 63 subjects in valsartan 160 mg group, 63 subjects in nifedipine GITS 30 mg group, and 62 subjects in valsartan 80 mg group) completed step 2 and 15 subjects (1 subject in combination (nifedipine GITS 30 mg plus valsartan 80 mg group; 4 subjects in nifedipine GITS 60 mg group; 6 subjects in valsartan 160 mg group; 2 subjects in nifedipine GITS 30 mg group; 2 subjects in valsartan 80 mg group) withdrew prematurely from the study.

Of the total 367 randomized subjects in step 1, 4 subjects were excluded from the Safety Analysis Set (3 subjects in nifedipine GITS 30 mg group; 1 subject in valsartan 80 mg group). Of the total 203 randomized subjects in step 2, only 1 subject was excluded from the Safety Analysis Set (1 subject in valsartan 160 mg group).

The mean age of the nifedipine GITS 30 mg plus valsartan 80 mg group was 47.74 years (range: 26 to 69 years), 72.73% of subjects were male, and 27.27% of subjects were female. In the nifedipine GITS 60 mg group, mean age was 48.01 years (range: 25 to 68 years), 77.94% of subjects were male, and 22.06% of subjects were female. In the valsartan 160 mg group, mean age was 49.88 years (range: 29 to 68 years), 70.59% of subjects were male, and 29.41% of subjects were female.

The mean (SD) BMI was 25.91 (3.20) kg/m^2 in nifedipine GITS 30 mg plus valsartan 80 mg group, 25.81 (3.36) kg/m^2 in nifedipine GITS 60 mg and 26.27 (4.34) kg/m^2 in valsartan 160 mg group, respectively.

The mean (SD) brachial SBP values was 163.62 (11.30) mm Hg in nifedipine GITS 30 mg plus valsartan 80 mg group, 165.88 (11.97) mm Hg in nifedipine GITS 60 mg and 163.23 (10.47) mm Hg in valsartan 160 mg group, respectively.

The mean (SD) brachial DBP values was 103.40 (7.91) mm Hg in nifedipine GITS 30 mg plus valsartan 80 mg group, 103.57 (9.29) mm Hg in nifedipine GITS 60 mg and 101.95 (9.56) mm Hg in valsartan 160 mg group, respectively.

Results Summary — Efficacy

Primary efficacy variables

In case of central SBP changes between baseline and week 8 as a primary efficacy variable, the mean reduction (SD) was 27.21 (14.70) mmHg in the nifedipine GITS 30 mg plus valsartan 80 mg group, 27.08 (16.48) mmHg in the nifedipine GITS 60 mg group, 14.36 (16.61) mmHg in the valsartan 160 mg group.

There was a significant decrease in the nifedipine GITS 30 mg plus valsartan 80 mg group

and nifedipine GITS 60 mg group compared with valsartan 160 mg group (p=0.0001, p<0.0001 respectively). However, there were no significant differences between the nifedipine GITS 30 mg plus valsartan 80 mg group and the nifedipine GITS 60 mg group.

Secondary efficacy variables

This trend was also observed in central DBP, central pulse pressure, peripheral BP, peripheral pulse pressure, Augmentation index, Augmentation pressure at week 8.

Results Summary — Safety

For Safety Set during step 1, 25.41% (46/181 subjects, 70 cases) of subjects experienced adverse events in the nifedipine GITS 30 mg group, 17.68% (32/181 subjects, 41 cases) in the valsartan 80 mg group. Regarding the serious adverse events, there was 2 cases (1/181 subject) in the nifedipine GITS 30 mg group, and 1 case (1/181 subjects). All of these SAEs were not related with study drugs. For the incidence of adverse drug reactions that the relationship with test drug could not be ruled out, there was 12.71% (23/181 subjects, 38 cases) in the nifedipine GITS 30 mg group, and 3.87% (7/181 subjects, 10 cases) in the valsartan 80 mg group.

For Safety Set during step 2, 10.61% (7/66 subjects, 7 cases) of subjects experienced adverse events in the nifedipine GITS 30 mg plus valsartan 80 mg group, 10.45% (7/67 subjects, 9 cases) in the nifedipine GITS 60 mg group, 16.18% (11/68 subjects, 16 cases) in the valsartan 160 mg group, 8.20% (5/61 subjects, 5 cases) in the nifedipine GITS 30 mg group, 14.06% (9/64 subjects, 9 cases) in the valsartan 80 mg group.

Regarding the serious adverse events, there was 1 cases (1/67 subjects) in the nifedipine GITS 30 mg group. All of these SAEs were not related with study drugs. For the incidence of adverse drug reactions that the relationship with test drug could not be ruled out, there was 1.52% (1/66 subjects, 1 case) in the nifedipine GITS 30 mg plus valsartan 80 mg group, 4.48% (3/67 subjects, 4 cases) in the nifedipine GITS 60 mg group, 5.80% (4/68 subjects, 5 cases) in the valsartan 160 mg group, and 1.33% (1/64 subjects, 1 case) in the valsartan 80 mg group.

Conclusion(s)

☐ For central SBP changes between baseline and week 8 as a primary efficacy variable, low dose combination of nifedipine 30 mg plus valsartan 80 mg were more effective than high dose valsartan 160 mg alone.

☐ Regarding above primary efficacy variable, high dose of nifedipine 60 mg alone was as effective as low dose combination of nifedipine 30 mg plus valsartan 80 mg and more effective than high dose valsartan 160 mg alone.

☐ This trend was also observed in central DBP, central pulse pressure, peripheral SBP/DBP, peripheral pulse pressure, Augmentation Index, Augmentation Pressure between baseline and week 8.

☐ When initially administrated, the low dose Nifedipine 30 mg showed unfavorable safety profile in comparison with low dose Valsartan 80 mg.

☐ However, administrated high dose at week 4, Nifedipine 60 mg was well tolerated and there is no difference in safety profile in comparison with Valsartan 160 mg.

Publication(s):	None
Date Created or Date Last Updated:	2 Jan 2013