Clinical Study Synopsis

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Date of study report:	30 OCT 2012
Study title:	A Multicenter, Multifactorial, Randomized, Double-Blind, Placebo-Controlled Dose-Finding Study of Nifedipine GITS and Candesartan in Combination Compared to Monotherapy in Adult Patients with Essential Hypertension
Sponsor's study number:	14725
NCT number:	NCT01303783
EudraCT number:	2009-017077-37
Sponsor:	Bayer HealthCare
Clinical phase:	Phase II
Study objectives:	Primary objective: To determine the dose-response of the various combinations of nifedipine GITS (gastrointestinal therapeutic system) and candesartan cilexetil as compared to monotherapy and placebo based on the blood pressure (BP)-lowering effects (mean seated diastolic blood pressure [MSDBP]) of a once-daily regimen in subjects with World Health Organization (WHO) classification Grades 1 and 2 essential hypertension (MSDBP ≥95 mmHg and <110 mmHg). Secondary objectives: • To confirm the best chosen dosage by tests for the response rate, the control rate, and the changes of MSDBP and mean seated systolic blood pressure (MSSBP) at week 8 from the baseline • To assess safety and tolerability of the combination product
Test drug:	Nifedipine and candesartan cilexetil (loose combination) (BAY 98-7106) Nifedipine GITS (Adalat LA, BAYA1040) Candesartan cilexetil (Atacand)
Name of active ingredient(s):	Nifedipine and candesartan cilexetil
Dose:	***Monotherapy***: Nifedipine GITS: 20 mg, 30 mg, and 60 mg Candesartan cilexetil: 4 mg, 8 mg, 16 mg, and 32 mg ***Combination therapy***: Nifedipine GITS/candesartan cilexetil: 20/4 mg (N20C4), 20/8 mg (N20C8), and 20/16 mg (N20C16) Nifedipine GITS/candesartan cilexetil: 30/8 mg (N30C8), 30/16 mg (N30C16), and 30/32 mg (N30C32) Nifedipine GITS/candesartan cilexetil: 60/16 mg (N60C16) and 60/32 mg

	(N60C32)
Route of administration:	Oral
Duration of treatment:	8 weeks (once daily [od) in the morning)
Reference drug:	Placebo
Dose:	Not applicable
Route of administration:	Oral
Duration of treatment	2-4 weeks (run-in phase); 8 weeks (od in the morning)
Background treatment	Eligible subjects may or may not have been taking antihypertensive medication prior to enrollment – these medications were to be discontinued during the planned study washout (week −6 to −4)
Indication:	Treatment of mild to moderate essential hypertension (MSDBP ≥95 mmHg and < 110 mmHg)
Diagnosis and main criteria for inclusion:	• Male and female subjects 18 years or older. Female subjects must be either post-menopausal for 1 year, surgically sterile, or using an effective contraceptive method. Hormonal contraceptive use is disallowed. • Subjects must have mild to moderate essential hypertension (Grade I and II WHO classifications) as measured by a calibrated electronic BP measuring device. (MSDBP of ≥90 mmHg and <110 mmHg at Visit 1 (placebo run-in) and MSDBP of ≥95 mmHg and <110 mmHg at Visit 2 (randomization). • Subjects must have an absolute difference in their MSDBP of <10 mmHg between Visit 1 (placebo run-in) and Visit 2 (randomization).
Study design:	This was a multifactorial, multicenter, randomized, double-blind, placebo-controlled, parallel group trial in mild-to-moderate hypertensive subjects (World Health Organization [WHO] classification Grades I and II).
Methodology:	The study consisted of 3 periods: (1) a 2 week screening/washout in order to allow subjects to taper off previous anti-hypertensives; (2) a single-blind, placebo run-in period of 2 (to 4) weeks; and (3) an 8-week double-blind placebo-controlled treatment period. Blinding was achieved by using a quadruple dummy design (each subject received 1 capsule and 3 tablets daily). Eligible subjects were randomized in an equal ratio to 1 of 16 treatment groups to receive candesartan cilexetil monotherapy od; nifedipine GITS monotherapy od; the combination of nifedipine GITS/candesartan cilexetil; or placebo. There was a forced titration period of 1 week for subjects randomized to

	the highest dose of the combination therapy. During this period, the subjects randomized to the highest dose received the combination drug with one lower dose of each of the combination drug components (N60C32 received N30C16). From the second post-randomization week through the end of treatment (Week 8), all treatment groups received their final dose of randomized medication giving a minimum of 7 weeks on each of the final doses. Safety was monitored by assessing the incidence of adverse events (AEs) and measuring vital signs (blood pressure and pulse) at each visit and by performing laboratory tests at randomization visit and at the end of treatment.
Study center(s):	A total of 131 study centers from 12 countries were involved in this study, including Argentina (16 centers), Belgium (4 centers), Canada (16 centers), Italy (7 centers), Lithuania (5 centers), Russia (2 centers), South Africa (7 centers), South Korea (17 centers), Spain (8 centers), Ukraine (12 centers), United Kingdom (14 centers), and United States of America (23 centers).
Publication(s) based on the study (references):	None at the time of report creation.
Study period:	**Study Start Date:** 28 APR 2011 **Study Completion Date:** 28 MAY 2012
Early termination:	Not applicable
Number of subjects:	**Planned:** 1200 subjects (evaluable) **Analyzed:** 1381 subjects
Criteria for evaluation	
Efficacy:	***Primary efficacy variable***: The change from baseline in MSDBP and MSSBP at Week 8 using response surface model ***Secondary efficacy variables***: • Change from baseline in MSDBP and MSSBP at Week 8 using analysis of covariance (ANCOVA) • Control rate at Week 8 • Response rate at Week 8 • Time to achieve first BP control Control rate was defined as the percentage of subjects that reached the predetermined BP target <140/90 mmHg. In addition, the percentage of subjects that reached the predetermined BP target <140/90 mmHg for subjects without diabetes or chronic renal disorder (baseline estimated

	glomerular filtration rate [GFR] <60 mL/min) and <130/80 mmHg for subjects with diabetes or chronic renal disorder was provided as well. Response rate was defined as the percentage of subjects achieving a SBP response (MSSBP of <140 mmHg or a reduction of MSSBP of >20 mmHg from baseline value), or a DBP response (i.e. MSDBP of <90 mmHg or a reduction of MSDBP of >10 mmHg from baseline value) after 8 weeks treatment.
Safety:	Incidence of AEs, vital signs, laboratory tests and peripheral oedema
Statistical methods:	The following analysis sets were used for safety and efficacy analysis: Full analysis set (FAS): The full analysis set was defined as all subjects randomized to treatment group and has taken at least 1 dose of study medication who had baseline and at least 1 valid post-baseline BP measurement. This analysis set was used for the efficacy analyses. Subjects in the FAS were analyzed as randomized. Safety analysis set (SAF): The safety analysis set was defined as all randomized subjects who took at least 1 unit of study drug. This analysis set was used for the safety analyses. Per protocol set (PPS): The per protocol set was defined as all subjects in the full analysis set who did not have any major protocol deviations that could impact efficacy assessments. Subject data were summarized and analyzed according to the actual treatment taken. All statistical hypothesis tests were 2 sided and conducted at the 5% significance level if not mentioned otherwise. All variables were analyzed descriptively with appropriate statistical methods. Categorical variables were analyzed by frequency tables and continuous variables by sample statistics (mean, standard deviation [SD], minimum, median, and maximum). The incidences of treatment-emergent adverse events (TEAEs) were summarized by treatment using the Medical Dictionary for Regulatory Activities (MedDRA) Version 15, system organ class (SOC), preferred terms. Primary efficacy variable - the change from baseline in MSDBP and MSSBP at Week 8 - was analyzed using ANCOVA, including treatment, the clusters of centers, and the diabetic status at the baseline as the fixed effects and the baseline BP along with age as the covariate. Based on the model, the means of the combination group and its components were tested using the Min test. The response rates and the control rate (BP <140/90 mmHg and BP <stratified target) at Week 8 between the combination groups and its components were tested using the logistic regression model with independent variables of treatment groups, clusters of centers, baseline value, age and diabetic status at the baseline. The generalized Min test

based on odds ratio was used for the comparisons between the combination group and its two components.

Subgroup analyses were performed for the change from baseline in MSDBP and MSSBP at Week 8 and control rate. All subgroup analyses were descriptive only. The variables included in the subgroup analyses and level of each variable were as follows:

- Age (<65, 65- <75 years, ≥75 years)
- (Pooled) Country (North America, Western EU, Asia, Other)
- Gender (Female, Male)
- (Pooled) Race (White, Black, Asian, Other)
- Hypertension category. Grade I is defined as 140-<160 mmHg in systolic BP (SBP) or 90-<100 mmHg in diastolic BP (DBP) at baseline. Grade II is defined as SBP ≥160 mmHg or DBP ≥100 mmHg at baseline. A subject who fulfilled the criteria of both Grade 1 and Grade 2 was classified as Grade 2. Grade is based on baseline SBP/DBP.
- Diabetes mellitus at baseline (Yes, No)
- Baseline BMI (<30, ≥30 kg/m^2)
- Prior antihypertensive medication (Yes, No)
- Estimated GFR (30-<60, 60-<90,.≥90 mL/min)
- SBP group (<160 mmHg, ≥160 mmHg) based on baseline SBP
- DBP group(<100 mmHg, ≥100 mmHg) based on baseline DBP
- BP target group (130/80 mmHg if diabetes or baseline estimated GFR <60 mL/min, 140/90 mmHg for all others)
- Renal impairment group (Yes if estimated GFR <60 mL/min; No if estimated GFR≥60 mL/min)

Substantial protocol changes: Protocol Version 2/Amendment 1, dated 14 DEC 2010, was globally implemented and included the following changes:

- Exclusion criterion "creatinine level >1.4 mg/dL" was revised to "estimated GFR of <50 mL/min (computed using the Cockroft-Gault formula)." For subjects whose estimated GFR was <90 mL/min at Visit 1 or Visit 2, a blood sample was to be obtained for serum creatinine and potassium level (and subsequent estimated GFR calculation) at Week 1 (Visit 3) and Week 4 (Visit 5). The range of normal potassium was changed from 3.0–5.0 mmol/L to 3.4–5.4 mmol/L to align with the normal range of the central laboratory.
- The monotherapy dose groups were expanded to include the 4 mg dose of candesartan cilexetil. The combination dose groups were expanded to

	include the nifedipine GITS/candesartan cilexetil 20/4 mg dose groups. Two combination doses (nifedipine GITS/candesartan cilexetil 20/32 mg, and nifedipine GITS/candesartan cilexetil 60/8 mg) were removed. • Clarification of certain study procedures

Subject disposition and baseline

A total of 1381 subjects were randomized equally into 16 treatment groups, with 83-90 subjects per group (candesartan cilexetil monotherapy treatment: 346 subjects, nifedipine GITS monotherapy treatment: 254 subjects, combination treatment: 693 subjects, placebo: 88 subjects). Of these 1381 subjects, 1259 subject (91.2%) completed the study and 122 subjects (8.8%) withdrew prematurely from the study. Of the total 1381 randomized subjects, 19 subjects were excluded from the FAS. Of the 1362 subjects in the FAS, 165 subjects were excluded from the PPS, and the remaining 1197 subjects (86.7% of the randomized subjects) comprised the PPS. The SAF included all the 1381 subjects randomized in this study.

All the treatment groups were comparable with respect to demographics and baseline characteristics. The overall mean (SD) age of the subjects was 54.0 (10.3) years (range from 22 to 86 years, with 85.5% of the subjects younger than 65 years and 1.8% of the subjects over 75 years), and 57.9% of subjects were male. Majority of the subjects (72.8%) were white, and 16.1% and 8.9% of the subjects were black and Asian, respectively. The mean (SD) BMI of the total subjects was 31.02 (5.70) kg/m^2, and 52.8% of the total subjects had the BMI value $\geq$30 kg/m^2. Prior to this study, 65.0% of the subjects were treated with an antihypertensive agent. According to WHO classification, 38.7% of the subjects were classified as Grade 1 hypertension and 61.3% of the subjects were classified as Grade 2 hypertension. The mean (SD) baseline SBP value was 156.5 (11.3) mmHg and the mean (SD) baseline DBP values was 99.6 (3.5) mmHg, respectively. The mean (SD) heart rate/pulse rate at baseline was 75.3 (10.8) beats/min. At baseline, 39.1% of the subjects had SBP value $\geq$160 mmHg and 41.6% of the subjects had DBP value $\geq$100 mmHg. Among all the subjects, 14.8% had diabetes mellitus. Subjects with mild to moderate renal impairment were included in this study and their distribution was well balanced among all the treatment groups. A total of 3.7% of the subjects had estimated GFR <60 mL/min and 31.0% of the subjects had estimated GFR <90 mL/min.

Efficacy evaluation

Analysis of the efficacy variables showed that both nifedipine GITS and candesartan cilexetil contributed significantly to the blood pressure reduction of the nifedipine GITS and candesartan cilexetil combination ($p < 0.0001$). Within the dose range investigated in this study (nifedipine GITS 20-60 mg and candesartan cilexetil 4-32 mg), a positive dose-response relationship was demonstrated which showed that the higher the dose of each component the larger BP reduction effects. In addition, when increasing the dose of candesartan cilexetil from 16 mg to 32 mg a signal of plateau effect was observed.

The combination treatment groups were associated with a trend of significantly greater reductions in MSDBP and MSSBP at the end of the study compared with their individual monotherapy components and placebo. Similar trend was observed in control rate as in BP reduction. Combination treatments

were statistically significantly superior to their monotherapy components and placebo in control rate at Week 8 with the exceptions of N30C8 mg and N60C32 mg numerically superior to candesartan cilexetil 8 mg and 32 mg, respectively. The median time to achieve the first BP control was shorter for the subjects with combination treatments compared to those with monotherapy component treatments.

Results of subgroup analysis were generally consistent with the results from overall analysis.

Primary efficacy variables - change from baseline in MSDBP and MSSBP at Week 8 using response surface model:

Based on the results from response surface model, both nifedipine and candesartan cilexetil contributed significantly (P <0.0001) to the BP reduction effect of the combination of nifedipine GITS and candesartan cilexetil. A positive dose-response relationship was demonstrated within the studied dose range of the combination of nifedipine GITS/candesartan cilexetil, and the larger BP reduction effects were observed at the higher dose of each component. The numerically highest estimate MSDBP and MSSBP reductions were both achieved in subjects with the highest doses combination treatment (N60C32 group, MSDBP reduction:16.2 mmHg, MSSBP reduction: 23.4 mmHg).

Secondary efficacy variables - change from baseline in MSDBP and MSSBP at Week 8 using ANCOVA:

After 8 weeks of treatment, all treatment groups showed statistically significant and clinically significant reduction from baseline in MSDBP and MSSBP. The highest MSDBP reduction from baseline reported in the N60C32 group was16.5 mmHg (95% confidence interval [CI] [−18.5, −14.5]; p <0.05), and additional MSDBP reduction was obtained compared to the monotherapy components (N60C32 vs N60: additional 4.6 mmHg reduction, 95% CI [−7.2, −1.9]; N60C32 vs C32: additional 3.7 mmHg reduction, 95% CI [−6.4, −1.1]). The highest MSSBP reduction from baseline reported in the N60C32 group was 23.8 mmHg (95% CI [−26.9, −20.7]; p <0.05), and additional MSSBP reduction was obtained compared to the monotherapy components (N60C32 vs. N60: additional 7.0 mmHg reduction, 95% CI [-11.1, -2.8]; N60C32 vs. C32: additional 7.3 mmHg reduction, 95% CI [−11.4, −3.1]).

All combinations tested in the study were statistically and clinically significant better than their monotherapy components in term of MSDBP and MSSBP reduction.

Secondary efficacy variables - control rate at Week 8:

After 8 weeks of treatment, the highest control rate was observed in the N30C32 group (65.5%), followed by the N60C32 group (61.9%). The control rates with the combination treatment were marginally significantly higher (p <0.10) than those with the monotherapy treatment of their relevant component at the same dosage, with exception of the N30C8 group vs C8 group. The highest control rate, based on stratified target at Week 8 (BP <130/80 mmHg if diabetes or renal impairment defined as baseline [estimated GFR <60 mL/min] and BP <140/90 mmHg for all other subjects), was observed in the N30C32 group (58.6%), followed by the N60C32 group (58.3%). The control rates of most subjects with combination treatment were significantly higher (p <0.05) than those with the monotherapy treatment of relevant component at the same dosage, with exception of the N30C8 group vs C8 group.

Secondary efficacy variables - response rate at Week 8:

After 8 weeks of treatment, the highest response rate was observed in the N60C16 group (91.5%), followed by the N60C32 group (90.5%). The response rates in most combination groups were significantly higher ($p < 0.05$) than their relevant component at the same dosage, with exception of the N30C8 group vs C8 group.

Secondary efficacy variables - time to achieve first BP control:

The median time to achieve the first BP control was shorter for the subjects with combination treatment compared to those with monotherapy treatment. The shortest median time to achieve first BP control was observed in the N60C16 group (12 days). The shortest median time to achieve first BP control (BP stratified target: BP <130/80 mmHg if diabetes or renal impairment defined as baseline [estimated GFR <60 mL/min] and BP < 140/90 mmHg for all other subjects) was observed in several combination treatment groups (15 days).

Subgroup analysis:

Results of subgroup analysis demonstrated no apparent patterns among all subgroups regarding the reduction of both MSDBP and MSSBP from baseline. It was shown that the treatment effect trend of the nifedipine GITS/candesartan cilexetil combination was essentially consistent within the specific subgroups. Subgroup analysis results also showed that most subjects without administration of prior antihypertensive agent, with Grade I hypertension, had lower baseline SBP/DBP level (SBP/DBP <160/100 mmHg), and subjects without diabetes and with BMI <30 kg/m^2 achieved numerically higher control rate in this study.

Safety evaluation

All 1381 subjects randomized to the double-blind treatment phase were included in the safety analysis set. The mean duration of treatment was similar in all treatment groups, with overall mean (SD) as 54.5 (10.7) days.

TEAEs were reported by 536/1381 (38.8%) subjects and the highest AE incidence was observed in the N60C32 group (52.3%). Study drug-related AEs were reported by 224 subjects (16.2%). Majority of AEs were mild or moderate. The most frequently reported AEs with primary SOC were general disorder and administration site condition.

No death occurred during the post-randomized study treatment period. One drug naive patient died during the screening period. A total of 6 SAEs were reported from 5 treatment groups and one of them in the N60C32 group was judged as related to the study drug. A total of 33 subjects discontinued study drug due to TEAEs. The TEAEs leading to discontinuation of the study drug was most commonly seen in the N60C32 group (6/86 subjects), followed by the N60C16 group (5/83 subjects) and N60 group (5/84 subjects). The incidences of vasodilatory AEs remained on expected levels, as flushing was reported by 0.5% of the subjects, headache by 6.1% of the subjects, and oedema by 11.5% of the subjects. By adding candesartan cilexetil onto nifedipine GITS, the incidences of vasodilatory AEs, headache, and oedema decreased.

Incidence of treatment-emergent peripheral oedema in placebo group was 3.4%, candesartan 4 mg group was 2.4%, candesartan 8 mg group was 5.6%, candesartan 16 mg group was 9.5%, candesartan 32 mg group was 3.4%, nifedipine 20 mg group was 11.6%, nifedipine 30 mg group was 7.1%, nifedipine 60 mg group was 11.9%, N20C4 group was 5.7%, N20C8 group was 8.0%, N20C16 group was 4.6%, N30C8 group was 10.5%, N30C16 group was 5.7%, N30C32 group was 5.7%, N60C16 group was 14.5%, and N60C32 group was 10.5%.

No notable differences were observed in laboratory parameters among the 16 treatment groups.

There were no clinically relevant changes from baseline in heart rate or weight in either treatment group. The mean (SD) heart rate/pulse rate at baseline was 75.31 (10.78) beats/min overall and the mean (SD) change from baseline at the Visit 7 was −1.04 (10.52) beats/min overall. The median change from baseline was 0 beats/min overall.

One AE in 1 subject in the N60C32 group (moderate, non-serious AE judged to be related to the study drug) was reported to be associated with heart rate increase.

The mean (SD) weight at baseline was 88.52 (18.17) kg overall and the mean (SD) change from baseline at the Visit 7 was −0.04 (2.53) kg overall. The median change from baseline was 0.00 kg overall. Three AEs were reported associated with weight increase (1 subject each in the C16 group, N30C16 group, and N60C16 group). The incidence of ECG findings on screening visit was low and remained similar among treatment groups.

In general, the combination of nifedipine GITS and candesartan cilexetil was safe and well tolerated regardless of age, race, or sex. No additional safety concern was shown compared to the monotherapy.

Overall conclusions

This multifactorial, multi-center, randomized, double-blind, placebo-controlled, parallel group dose-finding trial investigated the efficacy and safety of nifedipine GITS and candesartan cilexetil in combination compared to monotherapy in adult subjects with essential hypertension. Data support the following conclusions:

Both nifedipine GITS and candesartan cilexetil contributed significantly to the blood pressure reduction of the combination of nifedipine GITS and candesartan cilexetil.

Within the dose range investigated in this study (nifedipine GITS 20-60 mg and candesartan cilexetil 4-32 mg), a positive dose-response relationship was demonstrated which showed that the higher the dose of each component the larger BP reduction effects. In addition, a signal of plateau effect when increasing the dose of candesartan cilexetil from 16 mg to 32 mg was observed.

The combination treatment groups were associated with a trend of significantly greater reductions in MSDBP and MSSBP and higher control rate at the end of the study compared with their individual components and placebo.

The combination was generally safe and well tolerated and was associated with lower incidence of vasodilatory effects compared to nifedipine GITS monotherapy.