Clinical Study Synopsis

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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:	12313	NCT00750113
Study Phase:	IV	
Official Study Title:	A Multicenter Study Evaluating the Efficacy of Nifedipine GITS - Telmisartan Combination in Blood Pressure Control and Beyond: comparison of two treatment strategies (TALENT).	
Therapeutic Area:	CV Risk Management; Indication: essential hypertension	
Test Product		
Name of Test Product:	Nifedipine Gastro- Intestinal Therapeutic System (GITS)/ BAY a1040 Adalat®	
Name of Active Ingredient:	Nifedipine	
Dose and Mode of Administration:	This is a three arm study. Each subject was treated for at least 16 weeks, with an additional (optional extension) open label 8 week treatment foreseen: - Combination therapy: 16 weeks with nifedipine GITS 20mg and telmisartan 80mg combination - Nifedipine monotherapy: 8 weeks with nifedipine GITS 20mg and telmisartan 80mg matching placebo, followed by 8 weeks with nifedipine GITS 20mg and telmisartan 80mg combination - Telmisartan monotherapy: 8 weeks with telmisartan 80mg and nifedipine GITS 20mg matching placebo, followed by 8 weeks with nifedipine GITS 20mg and telmisartan 80mg combination	
Reference Therapy/Placebo		
Reference Therapy:	Matching placebo for the second study drug in the monotherapy arms.	
Dose and Mode of Administration:	Combined with active medication for monotherapy: nifedipine GITS 20mg matching placebo tablets and telmisartan 80mg matching placebo tablets, both for oral administration once daily in the morning. Uptitration of nifedipine GITS to 30 mg od was foreseen.	
Duration of Treatment:	Two treatment periods of 8 weeks (16 weeks in total); extension treatment period of a further 8 weeks optional	
Studied period:	**Date of first subjects' first visit:**	03 October 2007
	Date of last subjects' last visit:	17 August 2009
Study Center(s):	34 investigational sites in 2 countries: 26 in Italy and 8 in Spain	
Methodology:	Multicenter, randomized, double-blind, three-arm active control, two treatment periods with an optional extension	

Indication/ Main Inclusion Criteria:	Men and women, from 18 to 75 years of age, diagnosed with hypertension (office systolic BP >135mmHg), untreated or poorly controlled but stable anti-hypertensive regimen for ≥4 weeks. In addition, each of the two criteria required: Presence of type 2 diabetes mellitus or target organ damage (echocardiographic or electrocardiographic left ventricular hypertrophy or microalbuminuria) Presence of a metabolic syndrome, ie at least two of the following: (a) Impaired glucose tolerance (fasting plasma glucose 110 – 125mg/dL); (b) Raised serum triglycerides (≥150mg/dL) or concomitant use of statins for this indication; (c) Low HDL cholesterol (<40mg/dL in men, <50mg/dL in women); (d) Waist circumference >102cm in men, >88cm in women.
Study Objectives:	**Overall:** Please see primary and secondary objectives. **Primary:** To evaluate the efficacy in blood pressure (BP) control when anti-hypertensive therapy was initiated with a combination of low dose nifedipine GITS and telmisartan compared to a regimen starting with monotherapy before adding the other drug. **Secondary:** To assess the effect of treatment on the metabolic and inflammation markers as indicators of cardiovascular risk.
Evaluation Criteria:	**Efficacy (Primary):** 24-hour mean systolic blood pressure (SBP) on ambulatory blood pressure monitoring (ABPM) at 16 weeks of treatment compared to baseline [time frame: at 16 weeks of treatment compared to baseline] **Efficacy (Secondary):** Office blood pressure (BP), response rate (≥10mmHg decrease of office DBP and SBP, ≥ 20mmHg decrease of office SBP), control rate (≤130/80, ≤140/90), 24-hour mean diastolic blood pressure (DBP) [time frame: 8, 16 and 24 weeks of treatment] ABPM: % patients achieving BP < 125/80mmHg, morning BP increase/surge, 24h mean DBP, day average BP, night average BP, BP variability, pulse pressure, through to peak ratio, smoothness index dipping or non dipping [time frame: 8, 16 and 24 weeks] Microalbuminuria in subgroup (any reduction) [time frame: 8, 16 and 24 weeks] Metabolic parameters: fasting blood glucose, total cholesterol, low-density lipoprotein (LDL) cholesterol, high-density lipoprotein (HDL) cholesterol, triglycerides [time frame: 8, 16 and 24 weeks] Inflammatory markers: soluble receptors for advanced glycation end products (sRAGE), eotaxin-3, C-reactive protein (CRP) [time frame: 8, 16 and 24 weeks]

	Safety: Safety variables included adverse events, vital signs and routine laboratory blood tests.
	Pharmacokinetics: Not applicable **Other:** Not applicable
Statistical Methods:	**Efficacy (Primary):** The primary efficacy analysis was performed in subjects valid for per protocol (PPS). The intent-to-treat analysis performed on the full analysis set (FAS) was supportive. In the efficacy analyses, centers were clustered by country. The decision on center pooling was made before unblinding. Statistical analyses were adjusted to these clusters of centers. For the evaluation of the primary efficacy endpoint, mean 24-hour systolic BP from ABPM at Week 16, analysis of covariance (ANCOVA) was used, including treatment and center main effects and baseline (Week 0) systolic BP as a covariate. Two-sided 95% confidence intervals (CIs) for the difference in least-square (adjusted) means between each of the monotherapy arms and the combination arm were calculated. If these confidence intervals both lied above -5 mmHg (combination – monotherapy) then non-inferiority of the monotherapy arms against the combination arm could be concluded. All statistical tests were performed with a type I two sided error rate of α=5%. **Efficacy (Secondary):** All other efficacy comparison at Weeks 8, 16 and 24 were descriptive only. **Safety:** The incidence of treatment-emergent adverse events (TEAEs) was tabulated by treatment group. Adverse events were considered treatment-emergent if they had started or worsened after first application of study medication up to 7 days after end of treatment with study medication. Further tables were prepared for serious and/or drug-related treatment-emergent adverse events. Evaluation of laboratory data included descriptive analysis of continuous laboratory parameters and incidence rates of treatment-emergent laboratory abnormalities by treatment group. **Pharmacokinetics - if applicable:** Not applicable. **Other - if applicable:** Not applicable.
Number of Subjects:	Of 405 subjects randomized, 201 were randomized to combination therapy, 103 to nifedipine monotherapy and 101 to telmisartan monotherapy.

Study Results

Results Summary — Subject Disposition and Baseline

A total of 477 subjects were screened; 72 subjects could not be randomized because they did not fulfill the inclusion/exclusion criteria. Thus, 405 subjects were randomized.

In the groups randomized to combination therapy, nifedipine monotherapy and telmisartan monotherapy (201, 103 and 101 subjects, respectively) entered the double-blind treatment phase and received at least one dose of study drug. The majority of subjects completed the double-blind treatment phase (87.6%, 91.3%, 84.2%). Consent withdrawn was the most frequent reason for not completing the double-blind phase.

A total of 132, 71 and 55 subjects entered the open-label phase; most of these (90.9%, 97.2%, 98.2%) also completed the open-label phase.

Results Summary — Efficacy

Primary efficacy

The primary efficacy analysis on the PPS (N=327) demonstrated that a treatment regimen of starting with nifedipine monotherapy or telmisartan monotherapy is not inferior to nifedipine + telmisartan combination therapy in the reduction of 24 hour mean systolic BP (Table 1). Change from baseline at Week 16 was -10.7 mmHg for combination therapy, -10.4 mmHg for nifedipine, and -11.6 mmHg for telmisartan. The difference in least squared (LS) mean change from baseline was -0.33 mmHg (CI: -2.89, +2.22) for combination vs nifedipine and +1.19 mmHg (CI: -1.52, +3.90) for combination vs telmisartan. The primary efficacy analysis yielded consistent results for the subgroups of age, gender, baseline BMI, and diabetic status at baseline.

Table 1: Analysis of change of 24-hour mean systolic blood pressure (mmHg) at Week 16 and non-inferiority test (PPS)

	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
Baseline	Mean (SD)	136.8(11.7)	137.2(12.5)	136.2(11.6)
Week 16	Mean (SD)	126.0(11.7)	126.8(13.0)	124.7(9.12)
Change from baseline at Week 16	Mean (SD)	-10.7(10.9)	-10.4(14.4)	-11.6(8.85)
LS mean change from baseline	LS Mean (SE)	-11.89(0.86)	-11.56(1.14)	-13.08(1.22)
	Difference in LS mean [a]		-0.33	1.19
	95% CI		(-2.89,2.22)	(-1.52,3.90)

a: LS mean change from baseline of combination - LS mean change from baseline of monotherapy
SD: standard deviation, LS: least squared, SE: standard error, CI: confidence interval.

Sensitivity analysis performed on the FAS (N=380) supported the results of the primary endpoint. Change from baseline at Week 16 was -10.0mmHg for combination therapy (N=187), -10.2mmHg for nifedipine (N=99), and -9.9mmHg for telmisartan (N=94). The difference in LS mean change from baseline was -0.03mmHg (CI: -2.53, +2.46) for combination vs nifedipine and -0.23mmHg (CI: -2.77, +2.31) for combination vs telmisartan.

Secondary efficacy

Descriptive results on office BP are summarized in Table 2. The first five variables express the response rates as number and percent of subject who meet the respective criterion. The last two variables show the change from baseline in office BP. Office BP showed no difference between the treatment groups at Week 8, 16 and 24.

Table 2: Secondary efficacy variables: office blood pressure at Week 8, Week 16 and Week 24 (PPS)

	Visit	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
≥10 mmHg decrease of office SBP	W8	n(%)	97(59.1%)	50(56.2%)	47(63.5%)
	W16		106(64.6%)	67(75.3%)	56(75.7%)
	W24		109(66.5%)	60(67.4%)	60(81.1%)
≥20 mmHg decrease of office SBP	W8	n(%)	44(26.8%)	21(23.6%)	25(33.8%)
	W16		69(42.1%)	44(49.4%)	35(47.3%)
	W24		71(43.3%)	39(43.8%)	32(43.2%)
≥10 mmHg decrease of office DBP	W8	n(%)	63(38.4%)	23(25.8%)	28(37.8%)
	W16		75(45.7%)	45(50.6%)	37(50.0%)
	W24		85(51.8%)	42(47.2%)	42(56.8%)
≤130/80 mmHg of office BP	Baseline	n(%)	3(1.8%)	1(1.1%)	0(0.0%)
	W8		36(22.0%)	6(6.7%)	11(14.9%)
	W16		50(30.5%)	31(34.8%)	19(25.7%)
	W24		45(27.4%)	25(28.1%)	19(25.7%)
≤140/90 mmHg of office BP	Baseline	n(%)	32(19.5%)	14(15.7%)	12(16.2%)
	W8		77(47.0%)	38(42.7%)	34(45.9%)
	W16		96(58.5%)	59(66.3%)	50(67.6%)
	W24		113(68.9%)	55(61.8%)	51(68.9%)
Office SBP	Baseline	Mean(SD)	151.1(11.8)	151.3(11.9)	151.7(11.8)
	Change at W8		-11.8(14.3)	-10.3(13.1)	-11.6(14.7)
	Change at W16		-15.5(14.9)	-17.1(15.1)	-16.5(11.3)
	Change at W24		-16.0(14.5)	-15.1(14.3)	-17.2(12.7)
Office DBP	Baseline	Mean(SD)	90.9(9.37)	90.8(7.66)	92.0(8.95)
	Change at W8		-7.4(9.18)	-5.3(9.67)	-6.8(9.45)
	Change at W16		-8.5(9.27)	-8.7(10.9)	-8.7(8.25)
	Change at W24		-9.0(8.88)	-8.0(11.3)	-10.3(9.11)

SBP: systolic blood pressure, DBP: diastolic blood pressure, BP: blood pressure, W: Week, SD: standard deviation.

Descriptive results on ambulatory blood pressure monitoring (ABPM) are summarized in Table 3. Compared to baseline, there were similarly significant blood pressure reductions and controls in all three groups after 16 weeks and 24 weeks. During the earlier period (8 weeks), however, distinct differences in blood pressure control between treatment groups were noticed.

The greater BP effect of the combination was also visible by the results provided by calculation of the rate of BP control and the smoothness index.

Table 3: Secondary efficacy variables: ABPM blood pressure at Week 8, Week 16 and Week 24 (PPS)

	Visit	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
24-hour mean SBP (mmHg)	Baseline	Mean(SD)	136.8(11.7)	137.2(12.5)	136.2(11.6)
	Change at W8		-9.4(9.83)	-5.1(11.2)	-6.3(11.7)
	Change at W16		-10.7(10.9)	-10.4(14.4)	-11.6(8.85)
	Change at W24		-10.4(11.6)	-10.3(13.3)	-12.3(9.33)
24-hour mean DBP (mmHg)	Baseline	Mean(SD)	81.7(9.33)	81.3(9.14)	82.6(10.7)
	Change at W8		-5.6(5.95)	-2.6(7.18)	-4.3(6.94)
	Change at W16		-6.4(7.26)	-6.2(8.49)	-7.4(5.94)
	Change at W24		-6.5(7.62)	-6.7(8.67)	-7.9(5.99)
<125/80 mmHg ABPM BP	Baseline	n(%)	24(14.6%)	14(15.7%)	8(10.8%)
	W8		68(42.0%)	24(27.3%)	21(28.4%)
	W16		76(46.3%)	37(41.6%)	29(39.2%)
	W24		80(48.8%)	41(46.1%)	35(47.3%)
Day average SBP (mmHg)	Baseline	Mean(SD)	140.6(12.3)	141.3(13.5)	140.1(12.9)
	Change at W8		-9.9(11.6)	-4.5(13.4)	-6.0(13.2)
	Change at W16		-11.1(12.5)	-11.0(17.0)	-11.8(10.2)
	Change at W24		-11.5(13.2)	-11.0(15.4)	-12.4(11.1)
Day average DBP (mmHg)	Baseline	Mean(SD)	85.2(10.3)	85.3(10.2)	86.0(11.8)
	Change at W8		-5.9(6.81)	-2.3(8.48)	-4.1(8.77)
	Change at W16		-6.7(8.51)	-6.8(10.3)	-7.4(7.43)
	Change at W24		-7.2(8.80)	-7.4(10.2)	-7.8(7.38)
Night average SBP (mmHg)	Baseline	Mean(SD)	126.7(14.4)	127.9(14.7)	125.2(13.0)
	Change at W8		-8.3(11.1)	-6.5(12.1)	-6.2(12.6)
	Change at W16		-9.9(12.0)	-9.9(14.5)	-10.2(12.4)
	Change at W24		-8.3(13.1)	-9.6(14.2)	-11.1(10.9)
Night average DBP (mmHg)	Baseline	Mean(SD)	73.1(9.94)	72.8(9.93)	74.3(11.7)
	Change at W8		-4.9(7.76)	-3.3(8.25)	-4.4(7.84)
	Change at W16		-5.7(8.01)	-5.6(8.90)	-7.0(9.25)
	Change at W24		-5.4(8.52)	-5.8(8.91)	-7.3(8.07)

Table 3: Secondary efficacy variables: ABPM blood pressure at Week 8, Week 16 and Week 24 (PPS)

	Visit	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
SBP variability	Baseline	Mean(SD)	14.4(3.39)	14.4(3.00)	14.3(3.35)
	Change at W8		-1.0(3.61)	-0.3(4.01)	-0.2(3.06)
	Change at W16		-1.6(3.35)	-1.2(3.69)	-0.8(4.08)
	Change at W24		-1.9(3.80)	-1.0(3.73)	-0.6(3.77)
DBP variability	Baseline	Mean(SD)	11.1(2.49)	11.4(2.10)	11.3(2.80)
	Change at W8		-0.6(2.48)	-0.1(2.16)	-0.5(2.36)
	Change at W16		-0.8(2.57)	-0.6(2.58)	-0.4(2.79)
	Change at W24		-0.9(2.53)	-0.6(2.54)	-0.5(2.54)
Morning SBP increase (mmHg)	Baseline	Mean(SD)	26.5(11.9)	23.2(12.7)	27.1(10.4)
	Change at W8		-2.5(14.7)	-0.3(14.9)	1.8(10.9)
	Change at W16		-2.5(15.6)	0.1(15.5)	-1.7(14.3)
	Change at W24		-3.1(15.0)	-0.2(16.8)	-3.7(12.1)
SBP trough to peak ratio	W8	Mean	0.7	0.6	0.7
	W16		0.8	0.6	0.8
	W24		0.7	0.5	0.9
DBP trough to peak ratio	W8	Mean	0.7	0.6	0.7
	W16		0.8	0.6	0.8
	W24		0.7	0.5	0.9
SBP smoothness index	W8	Mean(SD)	0.8(0.87)	0.4(0.93)	0.5(1.03)
	W16		0.9(1.00)	0.9(1.23)	0.9(0.80)
	W24		0.9(1.02)	0.8(1.06)	1.0(0.86)
DBP smoothness index	W8	Mean(SD)	0.7(0.73)	0.3(0.85)	0.5(0.77)
	W16		0.8(0.88)	0.7(1.04)	0.8(0.65)
	W24		0.8(0.96)	0.8(0.95)	0.8(0.66)
SBP dipping	Baseline	n(%)	87(53.0%)	43(48.3%)	39(52.7%)
	W8		78(48.1%)	49(55.7%)	38(51.4%)
	W16		84(51.2%)	47(52.8%)	31(41.9%)
	W24		70(42.7%)	39(43.8%)	33(44.6%)
DBP dipping	Baseline	n(%)	112(68.3%)	63(70.8%)	45(60.8%)
	W8		112(69.1%)	66(75.0%)	54(73.0%)
	W16		114(69.5%)	66(74.2%)	47(63.5%)
	W24		106(64.6%)	61(68.5%)	48(64.9%)

ABPM: ambulatory blood pressure monitoring, W: Week, SD: standard deviation,
SBP: systolic blood pressure, DBP: diastolic blood pressure, BP: blood pressure.

Descriptive results on renal function parameters are summarized in Table 4.

GFR was computed using the Modification of Diet in Renal Disease (MDRD) formula. Baseline GFR showed high, normal values; the values were similar between the groups. The GFR slightly increased from the baseline in all groups at all post-baseline visits and remained similar between the groups.

At baseline, the telmisartan group had a higher percentage in the 30-300 and >300mg/dL categories than the other treatment groups. The percentage of subjects in the <30mg/dL category increased compared to the baseline in all three groups at all post-baseline visits; the greatest change was observed in the telmisartan group.

Table 4: Secondary efficacy variables: Renal function at Week 8, Week 16 and Week 24 (PPS)

	Visit	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
GFR (mL/min)	Baseline	Mean(SD)	95.2(26.6)	92.6(25.8)	92.0(24.6)
	Change at W8		1.4(30.8)	5.4(30.7)	2.2(16.4)
	Change at W16		0.0(18.3)	2.9(16.4)	2.0(14.4)
	Change at W24		2.7(35.3)	2.4(19.4)	1.3(15.5)
Microalbuminuria (mg/dL)	Baseline	<30	74(66.1%)	39(68.4%)	30(55.6%)
		30-300	38(33.9%)	18(31.6%)	23(42.6%)
		>300	0(0.0%)	0(0.0%)	1(1.9%)
	W8	<30	82(73.9%)	38(71.7%)	30(62.5%)
		30-300	28(25.2%)	15(28.3%)	17(35.4%)
		>300	1(0.9%)	0(0.0%)	1(2.1%)
	W16	<30	91(72.8%)	47(72.3%)	41(67.2%)
		30-300	34(27.2%)	18(27.7%)	20(32.8%)
		>300	0(0.0%)	0(0.0%)	0(0.0%)
	W24	<30	89(70.1%)	53(75.7%)	44(69.8%)
		30-300	38(29.9%)	17(24.3%)	19(30.2%)
		>300	0(0.0%)	0(0.0%)	0(0.0%)

GFR: glomerular filtration rate; W: Week, SD: standard deviation.

Descriptive results on metabolic parameters are summarized in Table 5. Analysis on fasting blood glucose (FBG) showed a reduction at Week 8 in the telmisartan monotherapy group while there was no change in the other two groups. The magnitude of change from baseline in telmisartan group gradually decreased after the subjects had taken nifedipine + telmisartan combination. There was no difference in change from baseline between treatment groups at Week 24. Total cholesterol and low density lipoprotein (LDL) showed a great reduction in nifedipine monotherapy group, which was maintained until the end of study, while no reduction was observed in the telmisartan monotherapy group and a slight decrease in the combination group. High density lipoprotein (HDL) showed a slight decrease from baseline in the combination group and a slight increase in the monotherapy groups. However, the magnitude of change was negligible. Triglycerides showed a decrease from baseline in telmisartan group but no change or slight increase in the nifedipine monotherapy group and the nifedipine + telmisartan group.

Table 5: Secondary efficacy variables: Metabolic parameters at Week 8, Week 16 and Week 24 (PPS)

	Visit	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
FBG (mg/dL)	Baseline	Mean(SD)	122.9(40.2)	121.4(43.7)	124.8(48.3)
	Change at W8		0.6(43.2)	2.6(29.6)	-9.9(41.7)
	Change at W16		-4.6(36.6)	-4.5(33.3)	-7.2(34.3)
	Change at W24		-5.4(36.6)	-6.9(30.5)	-4.5(33.3)
Total cholesterol (mg/dL)	Baseline	Mean(SD)	196.6(40.6)	196.3(44.3)	192.2(40.0)
	Change at W8		-4.1(34.9)	-5.9(34.8)	-1.3(28.1)
	Change at W16		-1.1(34.1)	-5.1(34.0)	-1.0(28.6)
	Change at W24		-5.2(37.5)	-6.6(42.3)	2.0(32.4)
HDL cholesterol (mg/dL)	Baseline	Mean(SD)	48.2(12.9)	46.5(10.6)	48.0(12.1)
	Change at W8		-1.9(8.02)	1.9(13.3)	0.7(7.37)
	Change at W16		-1.5(7.73)	0.3(8.43)	1.1(8.09)
	Change at W24		-1.7(8.30)	0.9(7.83)	1.7(9.78)
LDL cholesterol (mg/dL)	Baseline	Mean(SD)	120.4(34.4)	120.9(41.5)	115.3(36.5)
	Change at W8		-3.1(32.6)	-9.9(32.9)	-1.7(32.3)
	Change at W16		-2.4(29.8)	-8.3(30.3)	1.0(30.0)
	Change at W24		-4.1(32.0)	-9.5(37.0)	2.2(33.6)
Triglycerides (mg/dL)	Baseline	Mean(SD)	148.9(112)	153.6(91.2)	158.8(89.6)
	Change at W8		4.4(76.7)	0.6(68.6)	-15.0(59.0)
	Change at W16		5.1(98.0)	-0.6(74.1)	-19.4(52.9)
	Change at W24		3.8(70.5)	6.0(129)	-13.8(68.2)

FBG: fasting blood glucose, HDL: high density lipoprotein; LDL: low density lipoprotein, W: Week, SD: standard deviation.

Descriptive results on inflammation markers are summarized in Table 6. There was no notable change from baseline in any treatment group.

Table 6: Secondary efficacy variables: Inflammation markers at Week 8, Week 16 and Week 24 (PPS)

	Visit	Statistics	Nifedipine GITS 20mg+ Telmisartan 80mg (N=164)	Nifedipine GITS 20mg (N=89)	Telmisartan 80mg (N=74)
sRAGE (pg/mL)	Baseline	Mean(SD)	217.4(180)	173.0(103)	207.6(163)
	Change at W8		-2.6(42.8)	-0.4(34.7)	0.7(39.5)
	Change at W16		-2.5(48.8)	-0.3(35.2)	1.7(37.7)
	Change at W24		-1.7(48.3)	-0.2(36.6)	7.4(35.2)
Eotaxin-3 (pg/mL)	Baseline	Mean(SD)	49.4(66.1)	47.9(35.0)	48.1(29.0)
	Change at W8		0.3(26.1)	0.6(12.7)	0.7(16.8)
	Change at W16		-0.5(31.9)	0.1(12.6)	3.0(22.3)
	Change at W24		-0.9(34.4)	1.8(25.8)	2.6(27.5)
CRP (mg/L)	Baseline	Mean(SD)	0.4(0.35)	0.5(0.32)	0.4(0.35)
	Change at W8		0.0(0.08)	0.0(0.21)	0.2(1.76)
	Change at W16		0.0(0.09)	-0.0(0.17)	-0.0(0.11)
	Change at W24		0.0(0.10)	-0.0(0.16)	-0.0(0.11)

sRAGE: soluble receptor for advanced glycation end-products, CRP: C-reactive protein, W: Week, SD: standard deviation.

Results Summary — Safety

Extent of exposure

Mean duration of treatment was 140.8 days in subjects receiving nifedipine + telmisartan, 145.1 days in subjects receiving nifedipine and 133.2 days in those receiving telmisartan. More than 75% of subjects took study drug for at least 16 weeks: 83.6% nifedipine + telmisartan, 85.4% nifedipine, and 77.2% telmisartan.

Adverse events

In the combination therapy group, the nifedipine monotherapy group and the telmisartan monotherapy group, 39.3%, 44.7% and 43.6% of subjects had TEAEs (Table 7). Treatment-emergent serious adverse events were reported for 1.5% of subjects (combination), 2.9% (nifedipine monotherapy), and 2.0% (telmisartan monotherapy) of subjects. The serious adverse events under combination therapy were syncope (drug-related), presyncope (not related), and hypoacusis (not related). Under nifedipine monotherapy, these included angioedema and urticaria (drug-related), malignant lip neoplasm (not related), and ischaemic cerebral infarction (not related). Under telmisartan monotherapy, the serious adverse events included nephrectomy (not related), and renal colic (not related). There were no deaths.

Table 7: Incidence rates of adverse events (SAF)

	Nifedipine GITS 20mg + Telmisartan 80mg (N=201)	Nifedipine GITS 20mg (N=103)	Telmisartan 80mg (N=101)
Adverse events [a]	98 (48.8%)	52 (50.5%)	52 (51.5%)
Treatment-emergent adverse events [a]	79 (39.3%)	46 (44.7%)	44 (43.6%)
Drug-related treatment-emergent adverse events [a]	36 (17.9%)	14 (13.6%)	14 (13.9%)
Serious adverse events	3 (1.5%)	3 (2.9%)	2 (2.0%)
Treatment-emergent serious adverse events	3 (1.5%)	3 (2.9%)	2 (2.0%)
Drug-related treatment-emergent serious adverse events	1 (0.5%)	1 (1.0%)	0 (0.0%)
Premature termination due to adverse events [a]	10 (5.0%)	4 (3.9%)	4 (4.0%)
Serious adverse events with outcome death	0 (0.0%)	0 (0.0%)	0 (0.0%)

a: Including serious adverse events, Treatment emergent: adverse events that occurred or worsened on or after the first dose date up to 7 days after the last dose.

There were some individual cases of renal TEAEs such as microalbuminuria and renal impairment but none were considered drug-related. In the combination therapy group, the cardiovascular TEAE considered drug-related with an incidence of at least 1% were palpitations (1.5%, 1.0%, 1.0%) and hypotension (1.0%, 1.0%, 2.0%). Furthermore, in the nifedipine monotherapy group, these were supraventricular systoles (0.0%, 1.0%, 0.0%) and tachycardia (0.5%, 1.0%, 2.0%).

Laboratory and ECG

There were no notable differences among the treatment groups with respect to blood urea nitrogen, urea or any other biochemistry, hematology and urinalysis parameters. There were no medically important laboratory abnormalities in any treatment group.

In the combination therapy group, the nifedipine and telmisartan monotherapy groups, the percentages of subjects with an abnormal ECG finding was 23.5%, 16.5%, and 23.8%, respectively, at the screening visit. The percentages with abnormal ECG at the end of double-blind treatment were 20.3%, 16.5% and 16.7% , which may be explained by the pre-existing differences.

Results Summary — Pharmacokinetics

Not applicable

Results Summary — Other

Not applicable

Conclusion(s)

The primary efficacy analysis demonstrated that a treatment regimen of starting with nifedipine GITS 20 mg monotherapy or telmisartan 80mg monotherapy is not inferior to starting with combination therapy in the reduction of 24-hour mean systolic blood pressure at 16 weeks.

Compared to baseline, the ABPM systolic and diastolic blood pressure was slightly more reduced in the nifedipine/ telmisartan combination group compared to the monotherapy groups at week 8. The reduction at week 16 and 24 was comparable between the groups. The office systolic BP was similar between the treatment groups throughout the study. The reduction of office diastolic BP was slightly greater in the nifedipine/ telmisartan group compared to the monotherapy groups at Week 8. The office diastolic BP was similar between the treatment groups at week 16 and 24. It is therefore concluded that combination treatment with nifedipine GITS and telmisartan according to all the three therapeutic strategies evaluated was effective and led to the same outcome, though combination from the outset permitted a swifter initial blood pressure reduction.

The greater BP effect of the combination was also visible by the results provided by calculation of the rate of BP control and the smoothness index.

The results on secondary endpoints (lipid profile, microalbuminuria, glomerular filtration rate, etc) were as described in the report.

There were no negative effects on lipid parameters or other secondary parameters.

The reported side effects of the drug treatment in all groups were very low. The tolerability and safety profiles were similar for all three treatment groups. The safety profile obtained in this study is consistent with that presented in the nifedipine monotherapy and telmisartan monotherapy given in their current labels.

Publication(s):	- Mancia G, Parati G, Bilo G, Choi J, Kilama MO, Ruilope LM; TALENT investigators. Blood pressure control by the nifedipine GITS-telmisartan combination in patients at high cardiovascular risk: the TALENT study. J Hypertens. 2011 Mar;29(3):600-9. Erratum in J Hypertens. 2011 May;29(5):1022.
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