CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-401

STATISTICAL REVIEW(S)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	22-401 / S_000
Drug Name:	TWYNSTA® (telmisartan/amlodipine) Tablets
Indication(s):	.Treatment of Hypertension
Applicant:	Boehringer Ingelheim
Date(s):	Date of Document: December 18, 2008 PDUFA Due Date: October 18, 2009
Review Priority:	Standard
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Keywords:	Twynsta, Hypertension, Factorial Design

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

.The study showed that the combination therapy of telmisartan plus amlodipine is more effective than either telmisartan or amlodipine in lowering seated trough cuff DBP in patients with Stage I or II hypertension, as well as in patients with moderate or severe hypertension. The study also seems to support the combination therapy for use as an initial therapy indication in patients with higher blood pressure baselines.

1.2 Brief Overview of Clinical Studies

This sNDA includes one pivotal study (1235.1) to support the safety and efficacy of TWYNSTA in the treatment of patients with Stage I or II hypertension and moderate or severe hypertension. This sNDA also seeks an initial therapy indication.

The primary objective of the study was to demonstrate that for both active therapies of telmisartan and amlodipine there existed an overall dose response, thereby showing that combinations of telmisartan and amlodipine were more effective in reducing diastolic blood pressure than each of the respective monotherapies. The primary efficacy variable was the change from baseline in the in-clinic seated trough cuff diastolic blood pressure (DBP) after eight weeks of treatment.

1.3 Statistical Issues and Findings

The study showed that the combination therapy of telmisartan plus amlodipine is effective in lowering seated trough cuff DBP in patients with Stage I or II hypertension, as well as in patients with moderate or severe hypertension. The four key combination therapies of T40+A5, T40+A10, T80+A5, and T80+A10 had a statistically significantly greater reduction in diastolic blood pressure than each of the respective monotherapies ($p<0.0001$). The study also suggests that the probability of achieving a systolic or diastolic goal was higher with the combination than with either monotherapies in patients with relatively higher blood pressure baseline (DBP $\geq$ 100 mmHg or SBP $\geq$150mmHg).

2. INTRODUCTION

2.1 Overview

The telmisartan/amlodipine fixed-dose combination is an angiotensin II receptor blocker (ARB) and a dihydropyridine (DHP) calcium channel block (CCB) combination product developed for the treatment of hypertension in patients not adequately controlled with antihypertensive monotherapy and as initial therapy in patients likely to need multiple drugs to achieve their BP goals. The telmisartan/amlodipine FDC comprises of 2

approved drugs, telmisartan (T), approved under New Drug Application (NDA) 020850 and marketed under the trade name Micardis®, and amlodipine (A), approved under NDA 019787 and marketed under the trade name Norvasc®. This NDA applies for the commercial use of the telmisartan /amlodipine FDC in the strengths of 40/5mg, 40/10mg, 80/5mg, and 80/10mg.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of "**\\FDSWA150\NONECTD\N22401\N_000\2008-12-18"** of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

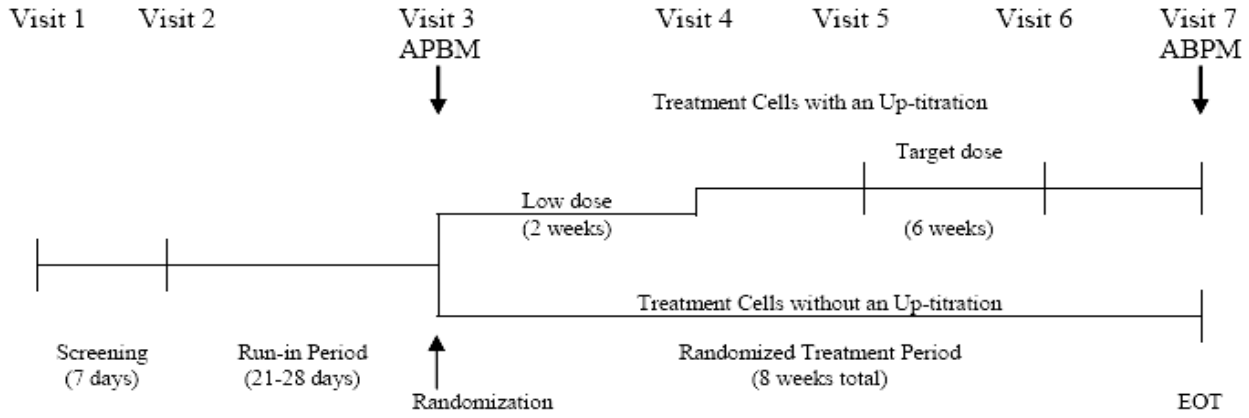
3.1.1 STUDY 1235.1

3.1.1.1 Study Objectives

The primary objective was to demonstrate that for both active therapies of telmisartan and amlodipine there existed an overall dose response, thereby showing that combinations of telmisartan and amlodipine were more effective in reducing diastolic blood pressure than each of the respective monotherapies in patients with Stage I or II hypertension. The second primary objective was to demonstrate the effectiveness of combination therapy in patients with moderate or severe hypertension at baseline (seated DBP $\geq$ 100 mmHg).

3.1.1.2 Study Design

Study 1235.1 is a Phase III, randomised, double-blind, double-dummy, placebo-controlled, international, multi-center, parallel group, 4x4 factorial design trial. 1280 subjects with Stage I or II hypertension from worldwide were enrolled into the study. This study consisted of three periods including 16 treatment groups as shown below in Figure 1:



EOT – End of Trial

Treatment Cells with an Up-titration: A10, T20A10, T40A10, T80A10

Low Dose:	Target Dose:
A5	A10
T20A5	T20A10
T40A5	T40A10
T80A5	T80A10

Treatment Cells without an Up-titration: Placebo, A2.5, A5, T20, T40, T80, T20A2.5, T40A2.5, T80A2.5, T20A5, T40A5, T80A5

Figure 1 Study Design

(Source: Sponsor's figure 9.1:1)

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary variable was the change from baseline in the in-clinic seated trough cuff diastolic blood pressure (DBP) after eight weeks of treatment.

(2) Secondary Efficacy Endpoints

- Change from baseline in the in-clinic seated trough cuff systolic blood pressure (SBP)
- Percentage of patients who responded to treatment based on in-clinic mean seated trough cuff BP measurements at the end of the eight week active treatment period defined as:

  DBP Control: Mean seated DBP <90 mmHg at trough
  DBP Response: Mean seated DBP <90 mmHg at trough and/or a reduction from baseline of ≥10 mmHg
  SBP Response: Mean seated SBP <140 mmHg at trough and/or a

reduction from baseline of ≥10 mmHg

- Changes from baseline in the in-clinic standing trough cuff DBP and SBP after eight weeks of treatment
- Changes from baseline in DBP and SBP hourly means over the 24-hour dosing interval as measured by ABPM after eight weeks of treatment (sub-study only)
- Changes from baseline in the 24-hour ABPM mean (relative to dose time) for DBP and SBP after eight weeks of treatment (sub-study only)

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Table 1 summarizes patient disposition, demographic and baseline characteristics. In the study, 50.4% were male, 79.4% Caucasian, 16.2% black, and 4.4% Asian. The overall mean age was 53.1 years, 14.0% patients were ≥65 years old.

Table 1 Demographic and Baseline Characteristics (All Randomized Patients)

Telmisartan **(mg)**			Amlodipine **(mg)**				
			A0	A2.5	A5	A10	Total
All randomized patients		T0	46	50	140	129	365
		T20	42	44	46	44	176
		T40	130	47	143	129	449
		T80	135	48	146	142	471
		Total	353	189	475	444	1461
Moderate/server patients		T0	35	38	102	87	262
		T20	33	34	35	30	132
		T40	101	30	110	100	341
		T80	92	37	109	105	343
		Total	261	139	356	322	1078
Sex, n (%)	**Men** 737 (50.4)	T0	29 (63.0)	27 (54.0)	72 (51.4)	65 (50.4)	193 (52.9)
		T20	26 (61.9)	26 (59.1)	21 (45.7)	26 (59.1)	99 (56.3)
		T40	66 (50.8)	26 (55.3)	71 (49.7)	62 (48.1)	225(50.1)
		T80	60 (44.4)	22 (45.8)	74 (50.7)	64 (45.1)	220(46.7)
		Total	181(51.3)	101(53.40	238(50.10	217(48.9)	737(50.4)
	Women 724 (49.6)	T0	17 (37.0)	23 (46.0)	68 (48.6)	64 (49.6)	172(47.1)
		T20	16 (38.1)	18 (40.9)	25 (54.3)	18 (40.9)	77 (43.8)
		T40	64 (49.2)	21 (44.7)	72 (50.3)	67 (51.9)	224(49.9)
		T80	75 (55.6)	26 (54.2)	72 (49.3)	78 (54.9)	251(53..3)
		Total	172(48.7)	88(46.6)	237(49.9)	227(51.1)	724(49.6)
Age, (years)		T0	52.5 (12.3)	55.3 (10.4)	53.1 (10.6)	53.4 (10.7)	53.4 (10.8)
		T20	53.6 (10.4)	54.0 (10.8)	54.4 (10.2)	51.0 (11.2)	53.3 (10.7)

mean (SD)		T40	52.0 (11.0)	50.7 (10.2)	52.3 (11.9)	53.3 (11.3)	52.3 (11.3)
53.1(11.1)		T80	53.1 (11.3)	54.8 (9.7)	52.7 (11.9)	53.9 (11.6)	53.4 (11.4)
		Total	52.7 (11.2)	53.7 (10.3)	52.9 (11.3)	53.3 (11.2)	53.1 (11.1)
Race, n (%)	**Caucasian** 1160 (79.4)	T0	40 (87.0)	41 (82.0)	108(77.1)	102(79.1)	291(79.7)
		T20	34 (81.0)	36 (81.8)	38(82.6)	39 (88.6)	147(83.5)
		T40	104(80.0)	37 (78.7)	110(76.9)	105(81.4)	356(79.3)
		T80	105(77.8)	37 (77.1)	110(75.3)	114(80.3)	366(77.7)
		Total	283(80.2)	151(79.9)	366(77.1)	360(81.1)	1160(79.4)
	Black 237 (16.2)	T0	5 (10.9)	6 (12.0)	24 (17.1)	23 (17.8)	58 (15.9)
		T20	7 (16.7)	5 (11.4)	6 (13.0)	4 (9.1)	22(12.5)
		T40	18 (13.8)	8 (17.0)	26 (18.2)	18 (14.0)	70(15.6)
		T80	24 (17.8)	7 (14.6)	31 (21.2)	25 (17.6)	87 (18.5)
		Total	54 (15.3)	26 (13.8)	87 (18.3)	70 (15.8)	237(16.2)
	Asian 64 (4.4)	T0	1 (2.2)	3 (6.0)	8 (5.7)	4 (3.1)	16 (4.4)
		T20	1 (2.4)	3 (6.8)	2 (4.3)	1 (2.3)	7 (4.0)
		T40	8 (6.2)	2 (4.3)	7 (4.9)	6 (4.7)	23 (5.1)
		T80	6 (4.4)	4 (8.3)	5 (3.4)	3 (2.1)	18 (3.8)
		Total	16 (4.5)	12 (6.3)	22 (4.6)	14 (3.2)	64 (4.4)

(Source: Sponsor's Tables 15.1.4.1:1, 15.1.4.1:2, 15.1.4.1:3, 15.1.4.1:4, 15.1.4.1:5)

3.1.1.5 Sponsor's Primary Efficacy Results

1. Statistical method

The primary objective of this trial was to demonstrate that treatment with combination therapy of telmisartan and amlodipine was more effective in reducing DBP than each of the respective monotherapies in patients with Stage I or II hypertension. It was pre-specified that the primary objective was tested by first showing that there was an overall significant (α=0.05) effect among both the dosages of telmisartan and among the dosages of amlodipine, and second by showing a lack of any significant (α=0.10) telmisartan-by-amlodipine interaction. The second primary objective was to demonstrate the effectiveness of combination therapy in patients with moderate or severe hypertension at baseline (seated DBP $\geq$ 100 mmHg). The second primary objective was tested only if the primary objective was achieved.

An analysis of covariance (ANCOVA) was used for the primary endpoint. A statistical model includes the main effects of treatment with telmisartan (TELM), treatment with amlodipine (AMLO), and country/region with baseline DBP as a covariate. The TELM-by-AMLO interaction was also included in the model and evaluated with significance of α=0.10. If the TELM-by-AMLO interaction was significant at α=0.10, then patients treated with placebo would be excluded from the analysis. The results of this analysis were to be used to evaluate the influence on the treatment-by-treatment interaction due to

the placebo treatment group and to evaluate any treatment-by-treatment interaction over the range of active treatments.

In the event of not being able to rule out a possible treatment-by-treatment interaction, the effects of treatment with each of the four key treatment combinations involving telmisartan 40 or 80 mg and amlodipine 5 or 10 mg was to be compared to the respective monotherapies using the full ANCOVA that included all sixteen treatment cells. Least square means were used to quantify treatment effects with the mean squared error (MSE) used to evaluate differences between treatment with combination therapy and its individual components. Such comparisons were to use the Hochberg procedure to account for multiple testing.

2. Results

Stage I or II hypertensives at baseline

The analysis results showed that there was a significant difference among the four dosage levels of telmisartan irrespective of amlodipine dose (T0: -12.5 mmHg, T20: -16.8 mmHg, T40: -16.6 mmHg, and T80: -17.2 mmHg; $p<0.0001$; Table 2) and among the four dosage levels of amlodipine irrespective of telmisartan dose (A0: -12.2 mmHg, A2.5: -15.3 mmHg, A5: -16.2 mmHg, and A10:-19.3 mmHg; $p<0.0001$, Table 2). When involving all treatment groups there was, as anticipated, a significant TELM-by-AMLO interaction ($p=0.0317$). However, when excluding patients treated with placebo there was no significant TELM-by-AMLO interaction effect ($p=0.1777$).

The four key treatment combination including telmisartan 40 or 80 mg and amlodipine 5 or 10 mg on the changes from baseline in in-clinic seated trough cuff DBP were compared to the respective individual monotherapies, and it showed that each of the four key treatment combinations reduced in-clinic seated trough cuff DBP to a significantly greater degree than each of the respective individual monotherapies ($p<0.0090$) (Tables 3)

Table 2 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP (FAS−TC)

Model*		A0	A2.5	A5	A10	Total
T0	N	46	48	137	124	355
	Adj Mean (SE)	-6.2(1.19)	-10.6(1.17)	-13.4(0.69)	-17.1(0.73)	-12.5(0.45)
T20	N	42	44	45	40	171
	Adj Mean (SE)	-13.8(1.25)	-18.3(1.22)	-15.9(1.20)	-19.3(1.28)	-16.8(0.63)
T40	N	129	47	141	123	440
	Adj Mean (SE)	-13.4(0.71)	-16.9(1.18)	-16.5(0.68)	-20.2(0.73)	-16.6(0.41)
T80	N	132	46	143	136	457
	Adj Mean (SE)	-14.0(0.71)	-15.7(1.19)	-18.2(0.68)	-20.1(0.70)	-17.2(0.40)
			Telm x Amlo interaction effect**: p=0.0317			
					Telm effect*:	p<0.0001
Total	N	349	185	466	423	
	Adj Mean (SE)	-12.2(0.46)	-15.3(0.60)	-16.2(0.40)	-19.3(0.42)	Amlo effect*: p<0.0001

* Estimates from main effects model including dosage of telmisartan, dosage of amlodipine, and country/region with baseline value as a covariate
** Model that also includes a term for the Telm x Amlo interaction
SE - Standard Error

(Source: Sponsor's Table 15.2.1.1.1: 2)

Table 3 Comparison of key combination therapies to individual components on change from baseline (LOCF) in in-clinic seated trough cuff DBP (mmHg) (FAS-TC)

		A0	A5	A10
T0	N	46	137	124
	Adj mean† (SE)	-6.2 (1.19)	-13.4 (0.69)	-17.1 (0.73)
T40	N	129	141	123
	Adj mean† (SE)	-13.4 (0.71)	-16.5 (0.68)	-20.2 (0.73)
	Diff versus T			
	Adj mean† (SE)		-3.1 (0.98)	-6.8 (1.01)
	95% CI		(-5.0, -1.2)	(-8.8, -4.8)
	p-value		0.0016	<0.0001
	Diff versus A			
	Adj mean† (SE)		-3.1 (0.97)	-3.1 (1.02)
	95% CI		(-5.0, -1.2)	(-5.1, -1.1)
	p-value		0.0013	0.0023
T80	N	132	143	136
	Adj mean† (SE)	-14.0 (0.71)	-18.2 (0.68)	-20.1 (0.70)
	Diff versus T			
	Adj mean† (SE)		-4.2 (0.97)	-6.1 (0.98)
	95% CI		(-6.1, -2.3)	(-8.0, -4.1)
	p-value		<0.0001	<0.0001
	Diff versus A			
	Adj mean† (SE)		-4.9 (0.96)	-3.0 (1.00)
	95% CI		(-6.7, -3.0)	(-5.0, -1.1)
	p-value		<0.0001	0.0024

† Adjusted for country/region (POOLCTR) effect and baseline value
SE – Standard Error

(Source: Sponsor's Table `11.4.1.1.2: 1`)

Moderate or severe hypertensives at baseline

A similar result was found in patients with moderate or severe hypertension at baseline (DBP ≥ 100mmHg). There was a significant difference among the four dosage levels of telmisartan (T0: -12.7 mmHg, T20: -17.3 mmHg, T40: -17.3 mmHg, and T80: -18.0 mmHg; p<0.0001, Table 4) and among the four dosage levels of amlodipine (A0: -12.5 mmHg, A2.5: -16.4 mmHg, A5: -16.7 mmHg, and A10: -19.7 mmHg; p<0.0001, Table 4). When involving all treatment groups there was, as anticipated, a significant TELM-by-AMLO interaction (p=0.0461). However, when excluding patients treated with placebo there was no significant TELM-by-AMLO interaction effect (p=0.2299). Each of the four key treatment combinations was found to reduce in-clinic seated trough cuff DBP to a significantly greater degree than each of the respective individual monotherapies (Table 5)

Table 4 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP (FAS−TC−MS)

Model*		A0	A2.5	A5	A10	Total
T0	N	35	37	101	83	256
	Adj Mean (SE)	-5.8(1.39)	-11.7(1.35)	-13.3(0.82)	-17.6(0.90)	-12.7(0.54)
T20	N	33	34	34	28	129
	Adj Mean (SE)	-14.4(1.43)	-18.9(1.41)	-15.9(1.41)	-19.7(1.55)	-17.3(0.73)
T40	N	100	30	108	96	334
	Adj Mean (SE)	-14.2(0.83)	-18.8(1.50)	-17.2(0.79)	-20.1(0.84)	-17.3(0.48)
T80	N	89	36	106	100	331
	Adj Mean (SE)	-14.1(0.87)	-16.6(1.37)	-19.1(0.80)	-21.0(0.83)	-18.0(0.48)
			Telm x Amlo interaction effect**: p=0.0461		Telm effect*:	p<0.0001
Total	N	257	137	349	307	
	Adj Mean (SE)	-12.5(0.54)	-16.4(0.71)	-16.7(0.47)	-19.7(0.50)	Amlo effect*: p<0.0001

* Estimates from main effects model including dosage of telmisartan, dosage of amlodipine, and country/region with baseline value as a covariate
** Model that also includes a term for the Telm x Amlo interaction
SE - Standard Error

(Source: Sponsor's Table 11.4.1.1.2.1)

Table 5 Comparison of key combination therapies to individual components on change from baseline (LOCF) in in-clinic seated trough cuff DBP (FAS-TC-MS)

		A0	A5	A10
T0	N	35	101	83
	Adj mean† (SE)	-5.8 (1.39)	-13.3 (0.82)	-17.6 (0.90)
T40	N	100	108	96
	Adj mean† (SE)	-14.2 (0.83)	-17.2 (0.79)	-20.1 (0.84)
	Diff versus T			
	Adj mean† (SE)		-3.0 (1.14)	-5.9 (1.17)
	95% CI		(-5.2, -0.7)	(-8.2, -3.6)
	p-value		0.0090	<0.0001
	Diff versus A			
	Adj mean† (SE)		-3.9 (1.14)	-2.5 (1.23)
	95% CI		(-6.1, -1.7)	(-4.9, -0.0)
	p-value		0.0006	0.0459
T80	N	89	106	100
	Adj mean† (SE)	-14.1 (0.87)	-19.1 (0.80)	-21.0 (0.83)
	Diff versus T			
	Adj mean† (SE)		-5.0 (1.18)	-6.8 (1.20)
	95% CI		(-7.3, -2.7)	(-9.2, -4.5)
	p-value		<0.0001	<0.0001
	Diff versus A			
	Adj mean† (SE)		-5.8 (1.14)	-3.3 (1.22)
	95% CI		(-8.1, -3.6)	(-5.7, -0.9)
	p-value		<0.0001	0.0065

† Adjusted for country/region (POOLCTR) effect and baseline value
SE – Standard Error

(Source: Sponsor's Table 11.4.1.1.2.2)

3.1.1.6 Sponsor's Secondary Efficacy Results

1. In-clinic seated trough cuff systolic blood pressure (SBP)

Stage I or II hypertensives at baseline

For In-clinic seated trough cuff SBP, it showed that there was a statistically significant difference among the mean changes of the four dosage levels of telmisartan (T0: -13.3 mmHg, T20: -19.9 mmHg, T40: -20.3 mmHg, and T80: -20.4 mmHg; p<0.0001; Table 6) and among the mean changes of the four dosage levels of amlodipine (A0: -12.0 mmHg, A2.5: -17.4 mmHg, A5: -20.2 mmHg, and A10: -24.3 mmHg; p<0.0001; Table 6). When involving all treatment groups there was, as anticipated, a significant TELM-by-AMLO interaction (p=0.0950). However, when excluding patients treated with placebo there was no significant TELM-by-AMLO interaction effect (p=0.4970). Each of the four key treatment combinations reduced in-clinic seated trough cuff SBP to a significantly greater degree than each of the respective individual monotherapies (Table 7).

Table 6 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough SBP (FAS−TC)

Model*		A0	A2.5	A5	A10	Total
T0	N	46	48	137	124	355
	Adj Mean (SE)	-2.5(1.82)	-11.4(1.79)	-15.4(1.06)	-20.7(1.11)	-13.3(0.69)
T20	N	42	44	45	40	171
	Adj Mean (SE)	-15.1(1.91)	-18.8(1.87)	-21.0(1.85)	-24.4(1.96)	-19.9(0.96)
T40	N	129	47	141	123	440
	Adj Mean (SE)	-14.6(1.09)	-21.9(1.81)	-21.8(1.05)	-24.7(1.12)	-20.3(0.62)
T80	N	132	46	143	136	457
	Adj Mean (SE)	-14.3(1.08)	-17.4(1.82)	-22.1(1.04)	-26.4(1.07)	-20.4(0.61)
			Telm x Amlo interaction effect**: p=0.0950		Telm effect*:	p<0.0001
Total	N	349	185	466	423	
	Adj Mean (SE)	-12.0(0.70)	-17.4(0.92)	-20.2(0.61)	-24.3(0.64)	Amlo effect*: p<0.0001

* Estimates from main effects model including dosage of telmisartan, dosage of amlodipine, and country/region with baseline value as a covariate
** Model that also includes a term for the Telm x Amlo interaction
SE - Standard Error

(Source: sponsor's Table 15.2.2.1.1: 2)

Table 7 Comparison of treatment effects on the change from baseline in in−clinic seated trough SBP (LOCF) for combination therapy versus the individual components (FAS−TC)

		A0	A2.5	A5	A10
T0	N	46	48	137	124
	Adj* mean (SE)	-2.5 (1.82)	-11.4 (1.79)	-15.4 (1.06)	-20.7 (1.11)
T20	N	42	44	45	40
	Adj* mean (SE)	-15.1 (1.91)	-18.8 (1.87)	-21.0 (1.85)	-24.4 (1.96)
	Diff versus T				
	Adj* mean (SE)		-3.7 (2.67)	-5.8 (2.65)	-9.3 (2.73)
	95% CI		(-8.9, 1.5)	(-11.1, -0.6)	(-14.7, -4.0)
	p-value		0.1641	0.0276	0.0006
	Diff versus A				
	Adj* mean (SE)		-7.4 (2.57)	-5.6 (2.12)	-3.8 (2.24)
	95% CI		(-12.5, -2.4)	(-9.7, -1.4)	(-8.2, 0.6)
	p-value		0.0039	0.0090	0.0930
T40	N	129	47	141	123
	Adj* mean (SE)	-14.6 (1.09)	-21.9 (1.81)	-21.8 (1.05)	-24.7 (1.12)
	Diff versus T				
	Adj* mean (SE)		-7.4 (2.10)	-7.2 (1.50)	-10.1 (1.55)
	95% CI		(-11.5, -3.2)	(-10.2, -4.3)	(-13.2, -7.1)
	p-value		0.0005	<0.0001	<0.0001
	Diff versus A				
	Adj* mean (SE)		-10.6 (2.54)	-6.4 (1.48)	-4.0 (1.57)
	95% CI		(-15.5, -5.6)	(-9.3, -3.5)	(-7.1, -0.9)
	p-value		<0.0001	<0.0001	0.0108
T80	N	132	46	143	136
	Adj* mean (SE)	-14.3 (1.08)	-17.4 (1.82)	-22.1 (1.04)	-26.4 (1.07)
	Diff versus T				
	Adj* mean (SE)		-3.2 (2.11)	-7.8 (1.49)	-12.1 (1.51)
	95% CI		(-7.3, 1.0)	(-10.8, -4.9)	(-15.1, -9.2)
	p-value		0.1343	<0.0001	<0.0001
	Diff versus A				
	Adj* mean (SE)		-6.1 (2.55)	-6.7 (1.47)	-5.7 (1.53)
	95% CI		(-11.1, -1.1)	(-9.6, -3.8)	(-8.7, -2.7)
	p-value		0.0175	<0.0001	0.0002

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Table 15.2.2.1.1: 3)

Moderate or severe hypertensives at baseline

It has showed that there was a significant difference among the mean changes of the four dosage levels of telmisartan (T0: -13.3 mmHg, T20: -20.5 mmHg, T40: -21.0 mmHg, and T80: -20.8 mmHg; p<0.0001; Table 8) and among the mean changes of the four dosage levels of amlodipine (A0: -12.7 mmHg, A2.5: -17.9 mmHg, A5: -20.4 mmHg, and A10: -

24.7 mmHg; p<0.0001; Table 15.2.2.1.2: 2). As well, when involving all treatment groups no significant TELM-by-AMLO interaction effect was found (p=0.1026). Each of the four key treatment combinations reduced in-clinic seated trough cuff SBP to a significantly greater degree than each of the respective individual monotherapies (Table 9).

Table 8 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough SBP (FAS−TC−MS)

Model*		A0	A2.5	A5	A10	Total
T0	N	35	37	101	83	256
	Adj Mean (SE)	-1.9(2.07)	-12.4(2.02)	-14.8(1.23)	-21.0(1.35)	-13.3(0.80)
T20	N	33	34	34	28	129
	Adj Mean (SE)	-15.6(2.14)	-19.0(2.11)	-22.1(2.11)	-25.2(2.32)	-20.5(1.09)
T40	N	100	30	108	96	334
	Adj Mean (SE)	-15.4(1.23)	-23.2(2.24)	-22.2(1.18)	-25.3(1.26)	-21.0(0.71)
T80	N	89	36	106	100	331
	Adj Mean (SE)	-15.4(1.30)	-17.4(2.04)	-22.5(1.20)	-26.5(1.23)	-20.8(0.71)
			Telm x Amlo interaction effect**: p=0.1026			
					Telm effect*:	p<0.0001
Total	N	257	137	349	307	
	Adj Mean (SE)	-12.7(0.80)	-17.9(1.06)	-20.4(0.70)	-24.7(0.74)	Amlo effect*: p<0.0001

* Estimates from main effects model including dosage of telmisartan, dosage of amlodipine, and country/region with baseline value as a covariate
** Model that also includes a term for the Telm x Amlo interaction
SE - Standard Error

(Source: Sponsor's Table 15.2.2.1.2: 2)

Table 9 Comparison of treatment effects on the change from baseline in in−clinic seated trough SBP (LOCF) for combination therapy versus the individual components (FAS−TC−MS)

		A0	A2.5	A5	A10
T0	N	35	37	101	83
	Adj* mean (SE)	-1.9 (2.07)	-12.4 (2.02)	-14.8 (1.23)	-21.0 (1.35)
T20	N	33	34	34	28
	Adj* mean (SE)	-15.6 (2.14)	-19.0 (2.11)	-22.1 (2.11)	-25.2 (2.32)
	Diff versus T				
	Adj* mean (SE)		-3.4 (3.01)	-6.6 (3.00)	-9.7 (3.15)
	95% CI		(-9.4, 2.5)	(-12.4, -0.7)	(-15.9, -3.5)
	p-value		0.2523	0.0286	0.0021
	Diff versus A				
	Adj* mean (SE)		-6.6 (2.91)	-7.3 (2.43)	-4.2 (2.68)
	95% CI		(-12.3, -0.9)	(-12.1, -2.6)	(-9.5, 1.0)
	p-value		0.0231	0.0025	0.1165
T40	N	100	30	108	96
	Adj* mean (SE)	-15.4 (1.23)	-23.2 (2.24)	-22.2 (1.18)	-25.3 (1.26)
	Diff versus T				
	Adj* mean (SE)		-7.8 (2.55)	-6.8 (1.70)	-9.9 (1.75)
	95% CI		(-12.8, -2.8)	(-10.1, -3.5)	(-13.4, -6.5)
	p-value		0.0021	<0.0001	<0.0001
	Diff versus A				
	Adj* mean (SE)		-10.8 (3.01)	-7.4 (1.69)	-4.3 (1.83)
	95% CI		(-16.7, -4.9)	(-10.8, -4.1)	(-7.9, -0.7)
	p-value		0.0003	<0.0001	0.0194
T80	N	89	36	106	100
	Adj* mean (SE)	-15.4 (1.30)	-17.4 (2.04)	-22.5 (1.20)	-26.5 (1.23)
	Diff versus T				
	Adj* mean (SE)		-2.0 (2.41)	-7.0 (1.76)	-11.1 (1.78)
	95% CI		(-6.7, 2.7)	(-10.5, -3.6)	(-14.6, -7.6)
	p-value		0.4071	<0.0001	<0.0001
	Diff versus A				
	Adj* mean (SE)		-5.0 (2.86)	-7.7 (1.70)	-5.5 (1.82)
	95% CI		(-10.6, 0.6)	(-11.0, -4.3)	(-9.0, -1.9)
	p-value		0.0792	<0.0001	0.0026

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Table 15.2.2.1.2: 3)

2. Blood pressure control and response

Stage I or II hypertensives at baseline

Comparing the effects of the four key combination therapies of T40+A5, T40+A10, T80+A5, and T80+A10 to the respective individual monotherapies, with the exception of T40+A10 vs. A10 for DBP control and DBP response, and T80+A10 vs. A10 for DBP response and SBP response, each of the four key combination therapies were found to have response rates that were significantly ($p \leq 0.05$) greater than the respective individual

monotherapies (Table 10).

Table 10 Analysis of in−clinic blood pressure control and response (FAS−TC)

	DBP control	DBP response	SBP response	SBP response 3	BP control
T40	69 (53.5)	90 (69.80	89 (69.0)	82 (63.60	55(42.6)
T40/A5	101 (71.6)	114 (80.90	129 (91.5)	125 (88.7)	83 (58.9)
T40/A10	101 (82.1)	113 (91.9)	119 (96.7)	113 (91.90	93 (75.6)
T80	80 (60.6)	103 (78.0)	90 (68.20	86 (65.20	55 (41.7)
T80/A5	107 (74.8)	127 (88.80	125 (87.4)	120 (83.90	94 (65.7)
T80/A10	116 (85.3)	124 (91.2)	129 (94.90	123 (90.4)	104 (76.5)
A5	72 (52.60	93 (67.9)	107 (78.10	100 (73.0)	58 (42.3)
A10	91 (73.4)	106 (85.5)	110 (88.70	102 (82.3)	78 (62.9)
Comparison	P-values				
T40/A5 vs. T40	0.0017	0.0313	<.0001	<.0001	0.0075
T40/A5 vs. A5	0.0013	0.0134	0.0021	0.0010	0.0062
T40/A10 vs. T40	<.0001	<.0001	<.0001	<.0001	<.0001
T40/A10 vs. A10	0.0941	0.1117	0.0199	0.0240	0.0284
T80/A5 vs. T80	0.0096	0.0152	0.0001	0.0003	<.0001
T80/A5 vs. A5	0.0001	<.0001	0.0349	0.0222	<.0001
T80/A10 vs. T80	<.0001	0.0033	<.0001	<.0001	<.0001
T80/A10 vs. A10	0.0167	0.1553	0.073	0.0521	0.0157

```
DBP control: DBP < 90 mmHg
DBP response: DBP < 90 mmHg or >= 10 mmHg reduction in DBP
SBP response: SBP < 140 mmHg or >= 10 mmHg reduction in SBP
SBP response 3: SBP < 140 mmHg or >= 15 mmHg reduction in SBP
BP Control: SBP < 140 mmHg and DBP < 90 mmHg
```

(Source: Sponsor's Table 15.2.2.4.1:1 & statdoc 6.5.1.1, 6.5.1.2, 6.5.1.3, 6.5.1.5, 6.5.1.7)

Moderate or severe hypertensives at baseline

Similarly, in the patients with moderate or severe hypertensive at baseline, the combination therapies were found to have response rates that were statistically significantly ($p \leq 0.05$) greater than the respective individual monotherapies. See Table 11.

Table 11 Analysis of in−clinic blood pressure control and response (FAS−TC--MS)

	DBP control	DBP response	SBP response	SBP response 3	BP control

T40	48 (48.0)	69 (69.0)	69 (69.0)	62 (62.0)	41 (41.0)
T40/A5	75 (69.4)	88 (81.5)	96 (88.9)	92 (85.2)	58 (53.7)
T40/A10	74 (77.1)	86 (89.6)	93 (96.9)	87 (90.6)	68 (70.8)
T80	44 (49.4)	67 (75.3)	66 (74.2)	62 (69.7)	32 (36.0)
T80/A5	73 (68.90)	93 (87.7)	90 (84.9)	85 (80.2)	62 (58.5)
T80/A10	85 (85.0)	93 (93.0)	95 (95.0)	81 (91.0)	77 (77.0)
A5	43 (42.6)	64 (63.4)	77 (76.2)	71 (70.3)	33 (32.7)
A10	54 (65.1)	69 (83.1)	71 (85.5)	64 (77.1)	43 (51.8)
Comparison	P-values				
T40/A5 vs. T40	0.0021	0.0469	0.0007	0.0002	0.0758
T40/A5 vs. A5	0.0001	0.0030	0.0099	0.0043	0.0016
T40/A10 vs. T40	<.0001	0.0007	<.0001	<.0001	<.0001
T40/A10 vs. A10	0.0810	0.2096	0.0102	0.0096	0.0069
T80/A5 vs. T80	0.0051	0.0259	0.0546	0.0622	0.0012
T80/A5 vs. A5	0.0002	<.0001	0.0694	0.0459	0.0001
T80/A10 vs. T80	<.0001	0.0010	0.0002	0.0003	<.0001
T80/A10 vs. A10	0.0018	0.0390	0.0309	0.0086	0.003

DBP control: DBP < 90 mmHg
DBP response: DBP < 90 mmHg or >= 10 mmHg reduction in DBP
SBP response: SBP < 140 mmHg or >= 10 mmHg reduction in SBP
SBP response 3: SBP < 140 mmHg or >= 15 mmHg reduction in SBP
BP Control: SBP < 140 mmHg and DBP < 90 mmHg

(Source: Sponsor's Table 15.2.2.4.1:1 & statdoc 6.5.2.1, 6.5.2.2, 6.5.2.3, 6.5.2.5, 6.5.2.7)

3. Reviewer's analyses and results

This reviewer confirmed the sponsor's analyses and concurred with their results.

This reviewer assessed the additivity of the two component drugs. The assessment suggests that there seems to be a systematic pattern of negative interaction existing across all cells (difference values are negative, Table 12), implying that the combination drug effect is less than the sum of the component effects (observed mean change < expected mean change, Table 12). The assessment was consistent to the sponsor's result that a statistically significant interaction (α=0.10) was detected in the analysis of ANOCOVA. In this case, pair-wise comparisons of the combination treatment groups versus their component treatment groups with multiplicity adjustment are crucial. The Hochberg procedure was used to adjust multiplicity in the analysis.

Table 12 Descriptive Assessment of Additivity (ITT)

in−clinic seated trough DBP	Telmisartan	Amlodipine		
		0	A5	A10
Observed raw mean change	0	-5.9	-13.0	-16.5
	T40	-13.1	-16.0	-19.6
	T80	-13.6	-17.8	-19.6
Observed placebo-subtracted mean change	0	-	-7.1	-10.6
	T40	-7.2	-10.1	-13.7
	T80	-7.7	-11.9	-13.7
Sum of placebo-subtracted mean change of monotherapies (expected change if treatments are additive)	T40		-14.3	-17.8
	T80		-14.8	-18.3
Observed placebo-subtracted mean change for combinations	T40		-10.1	-13.7
	T80		-11.9	-13.7
Difference (expected -observed) for assessing additivity	T40		-4.2	-4.1
	T80		-2.9	-4.6

(Source: Reviewer's analysis)

3.1.1.7 Conclusions

The analysis of primary efficacy endpoint shows that the four key combination therapies of telmisartan plus amlodipine are more effective than either respective monotherapy in lowering in-clinic seated trough cuff DBP in patients with Stage I or II hypertension, as well as in patients with moderate or severe hypertension.

3.2 Evaluation of Initial Therapy Indication

Graphs of the probability of achieving a blood pressure control (defined by < 140 or < 130 mmHg systolic, < 90 or < 80 mmHg diastolic) are currently used to illustrate advantage of a combination drug over its component drugs and to support the combination therapy for use as an initial therapy. Each graph contains regression curves for the probability of reaching a blood pressure target (defined by < 140 or < 130 mmHg systolic, < 90 or < 80 mmHg diastolic) after treatment as a function of baseline blood pressure for the treatment groups. The curves are often based on logistic regression modeling.

3.2.1 Probability of reaching a blood pressure (SBP and DBP) control

A logistic regression analysis was used to estimate the probability of reaching a systolic BP or diastolic BP target at Week 8 based on baseline BP. A probability curve based on logistic regression modeling was generated for each of the following treatment group: the highest dose combination, its monotherapy doses, and placebo. After extensive analyses of the data, it was decided to remove some of the extreme values at either or both end of the baseline blood pressure range because only a few numbers of subjects are available and not all treatment groups have comparable baseline blood pressures at both ends. There were total of four subjects with baseline SBP >165 mmHg in the placebo group

and four subjects with baseline SBP > 175 mmHg in the amlodipine group excluded from the plots of probability of achieving SBP <140 mmHg (Figure 2) and probability of achieving DBP <130 mmHg (Figure 4). There were also total of twenty-four subjects with baseline DBP <95 mmHg or DBP>110 mmHg excluded from the plots of probability of achieving DBP <90 mmHg (Figure 3) and probability of achieving DBP <80 mmHg (Figure 5). In general, the graphs showed that for most levels of baseline BP, the probability of achieving a systolic or diastolic goal was higher with the combination than with either monotherapy with a possible exception of lower-end BP baselines (SBP ≤ 150 mmHg or DBP ≤ 100 mmHg). It appears that patients with lower BP baselines do not appear to be benefited or less benefited from the combination drug relative to amlodipine 10 mg.

Figure 2 Probability of achieving SBP control (<140 mmHg) by baseline SBP

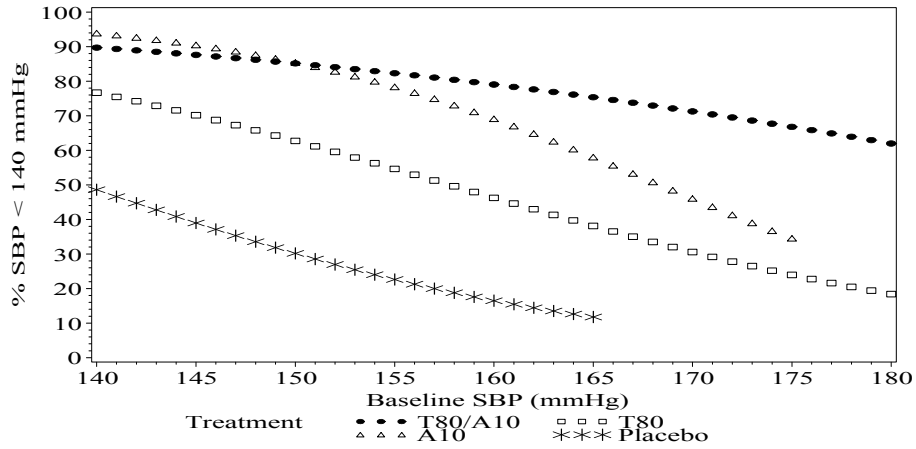


Figure 3 Probability of achieving DBP control (<90 mmHg) by baseline DBP

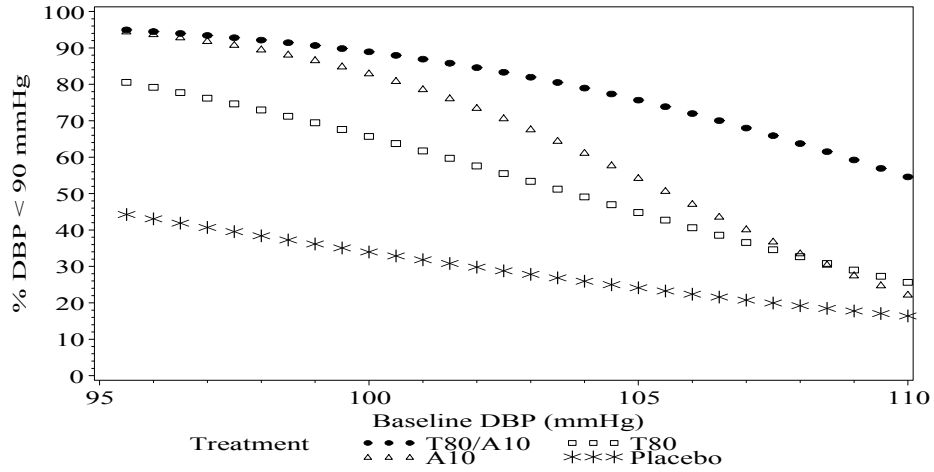


Figure 4 Probability of achieving SBP control (<130 mmHg) by baseline SBP

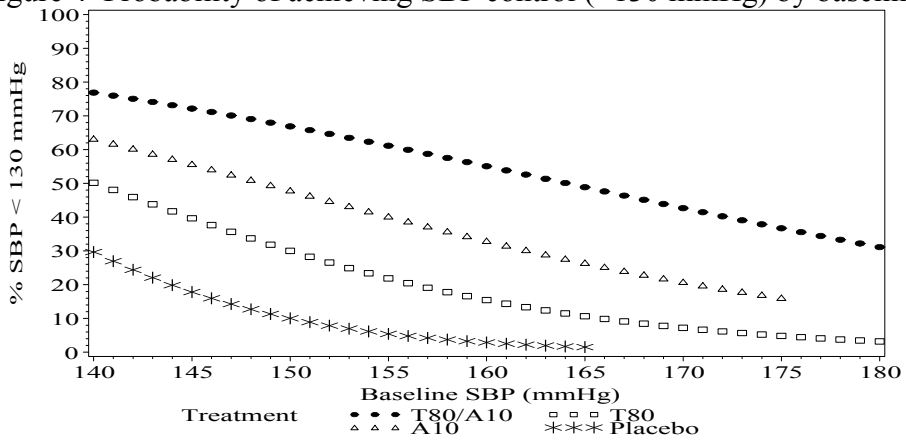
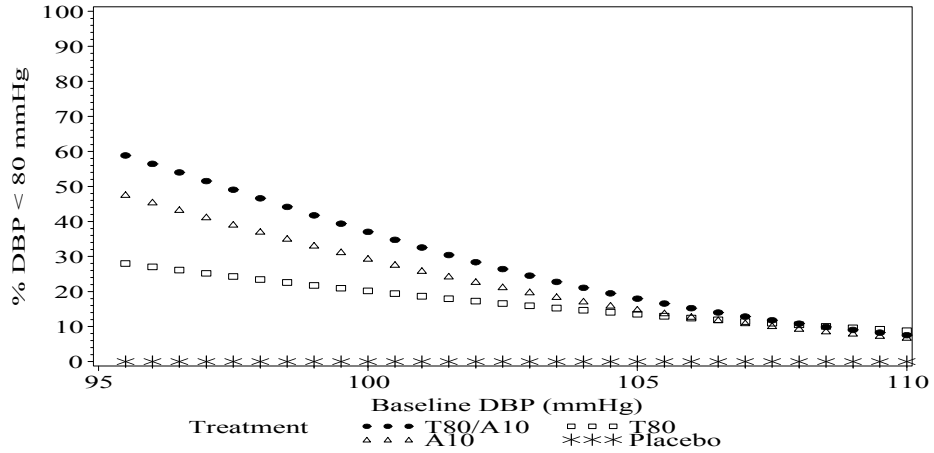


Figure 5 Probability of achieving DBP control (<80 mmHg) by baseline DBP



(Source: Sponsor's Figures 2.1:4, 2.2:4, 2.3:4, 2.4:4)

3.2.2 Model diagnostics- Sponsor's analysis

3.2.2.1 Goodness-of-fit in logistic regression modeling

The Hosmer-Lemeshow test was used to assess goodness-of-fit of the model. A statistically insignificant p-value for the goodness-of-fit tests indicates that the overall fit may be reasonable for the logistic regression model (Table 13).

Table 13 Logistic regression model overall goodness-of-fit by Hosmer-Lemeshow test at Week 8 endpoint

BP Control Goal	Treatment	Chi-Square	DF	Pr>Chi-Square
DBP < 90 mmHg	Placebo	7.1476	6	0.3074
	T80	8.1595	8	0.4180
	A10	8.3833	7	0.3000

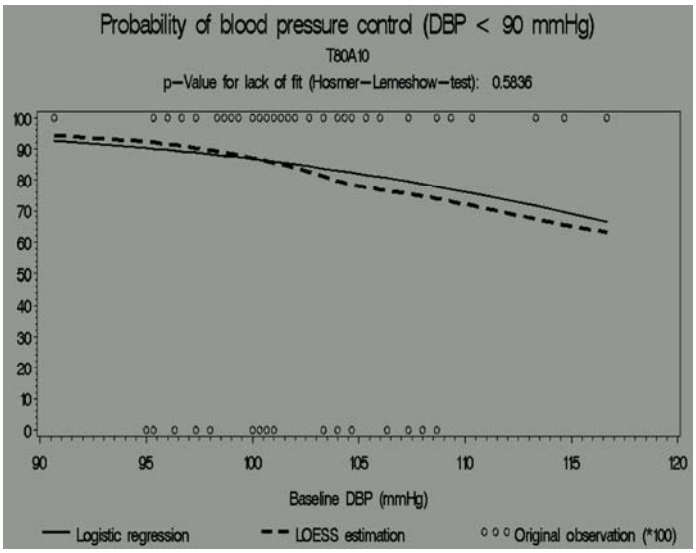
	T80 + A10	4.6940	6	0.5836
SBP < 140 mmHg	Placebo	7.4474	6	0.2814
	T80	9.8640	8	0.2747
	A10	3.7140	8	0.8820
	T80 + A10	6.1177	8	0.6341
DBP < 80 mmHg	Placebo	4.6940	6	0.5836
	T80	12.9030	8	0.1152
	A10	12.0532	7	0.0988
	T80 + A10	2.9724	6	0.8123
SBP < 130 mmHg	Placebo	9.1569	6	0.1649
	T80	13.5066	8	0.0956
	A10	10.0378	8	0.2624
	T80 + A10	5.5013	8	0.7029

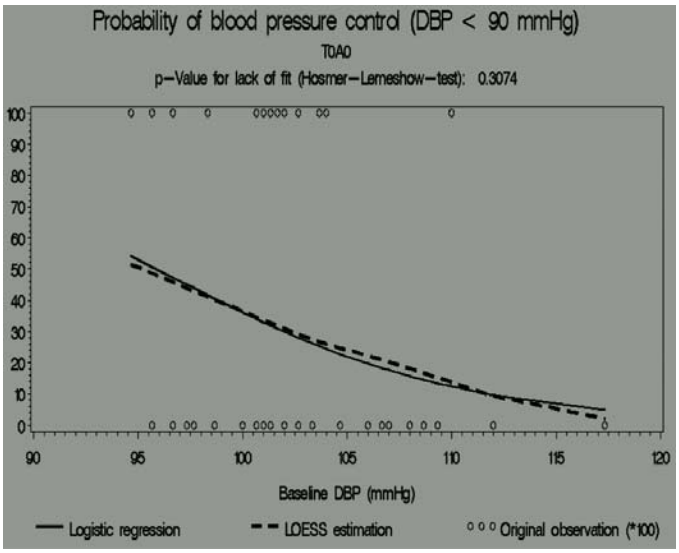
(Source: Sponsor's attachments 1b, 2b, 3b & 4b)

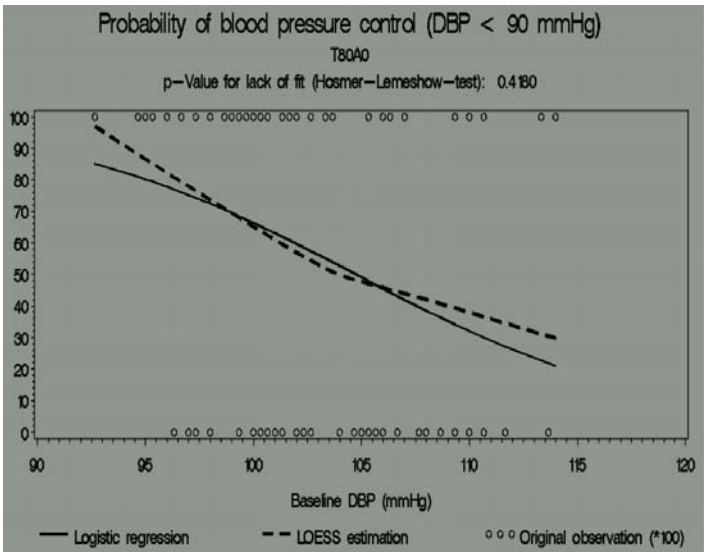
3.2.2.2 Comparison of logistic regression model with LOESS fitting

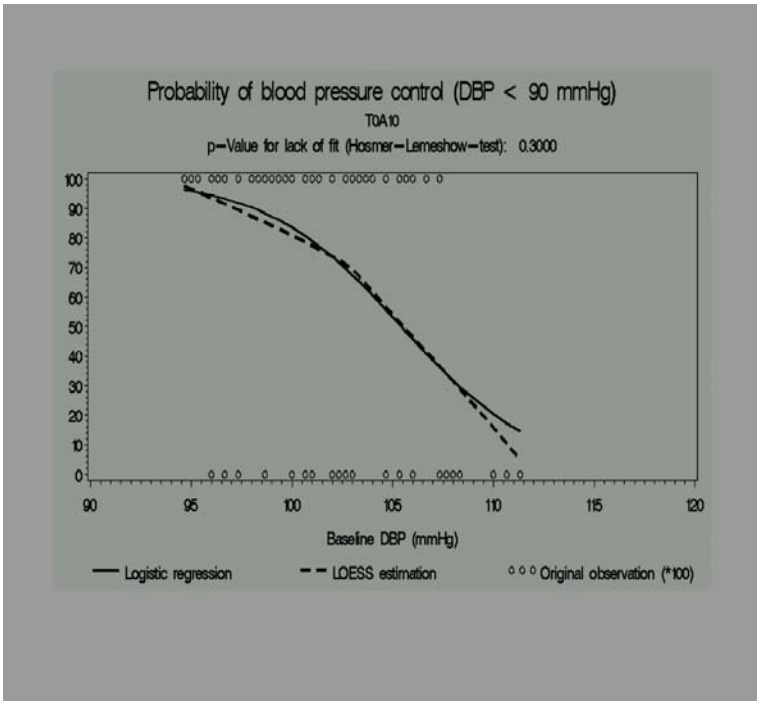
The non-parametric local regression (LOESS) was used with a smoothing factor of 1. It means that all observations are included in the estimation of the regression curve at each individual point, applying the standard weighting function. The non-parametric LOESS curves are very close to the curves resulting from the parametric logistic curves (Figure 6).

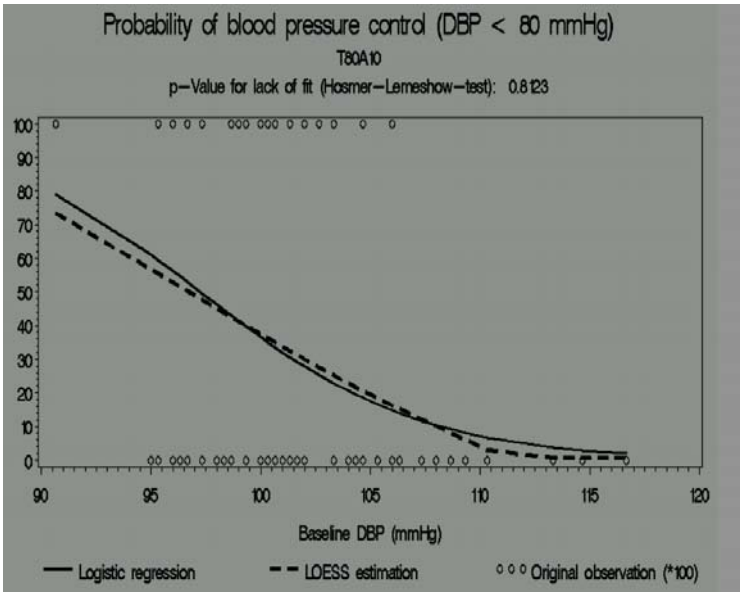
Figure 6 Non-parametric LOESS Curves (Sources: Sponsor's attachments 1a, 2a, 3a & 4a)

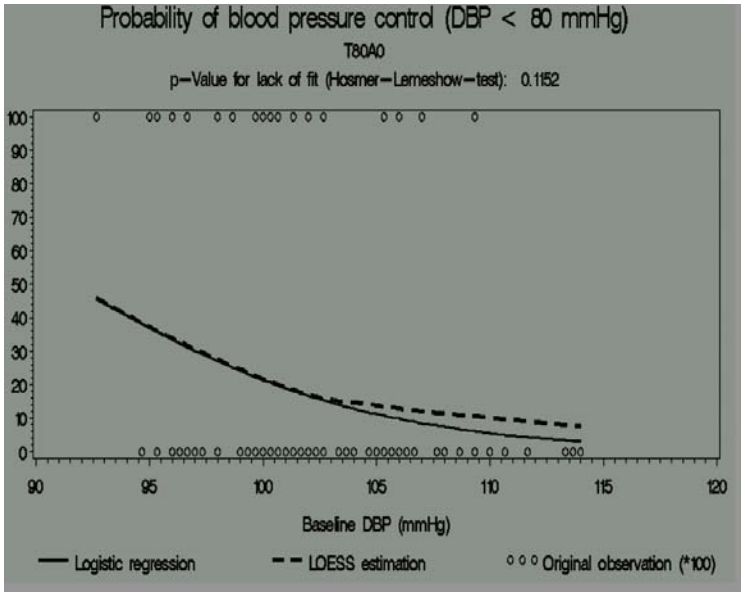


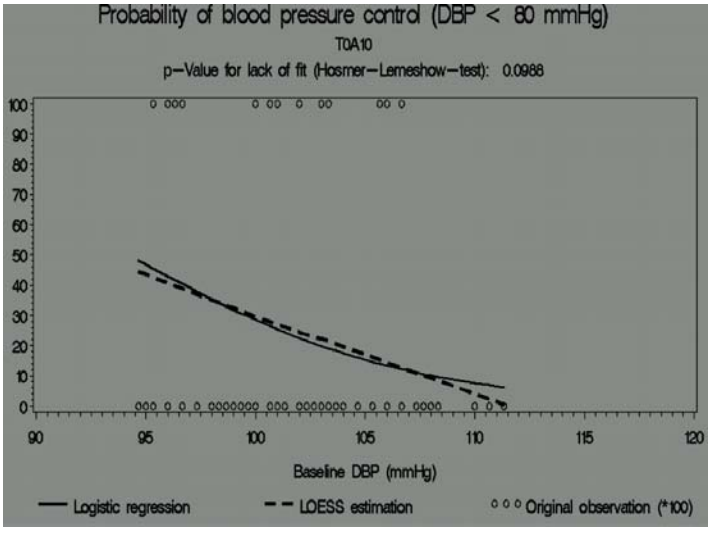


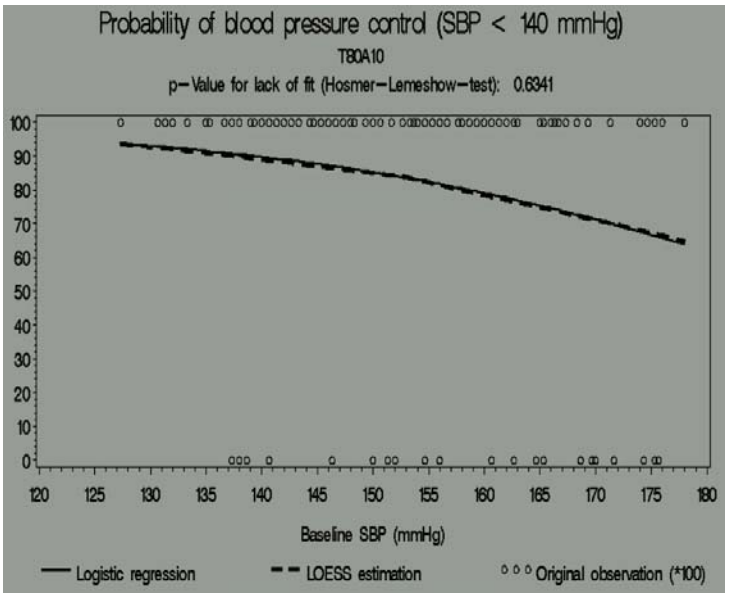

Probability of blood pressure control (DBP < 90 mmHg)
T80A0
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.4180
Baseline DBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

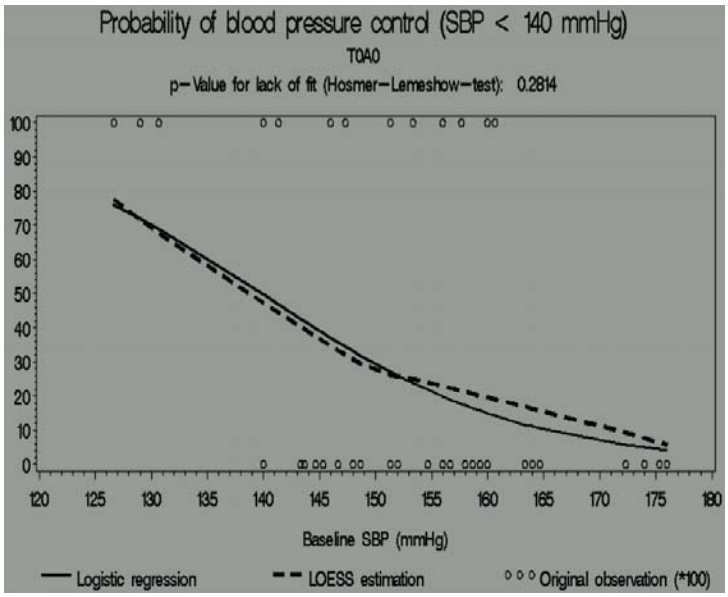

Probability of blood pressure control (DBP < 90 mmHg)
T0A10
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.3000
Baseline DBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

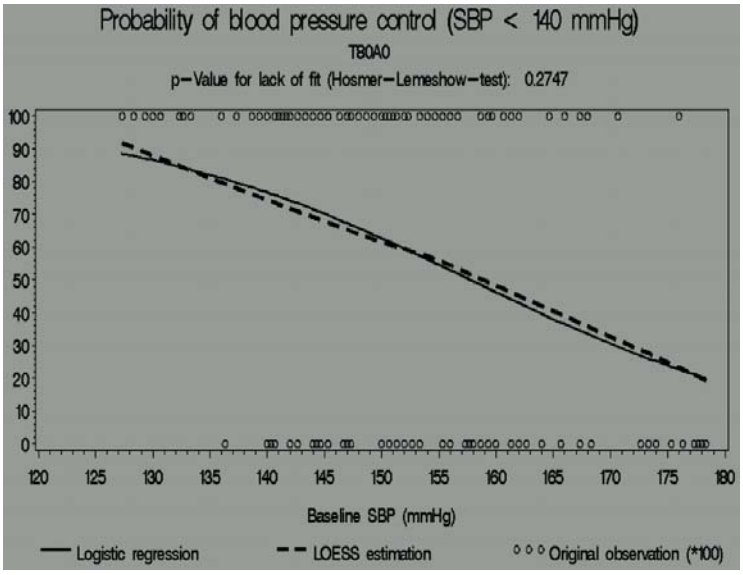

Probability of blood pressure control (DBP < 80 mmHg)
T80A10
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.8123
Baseline DBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

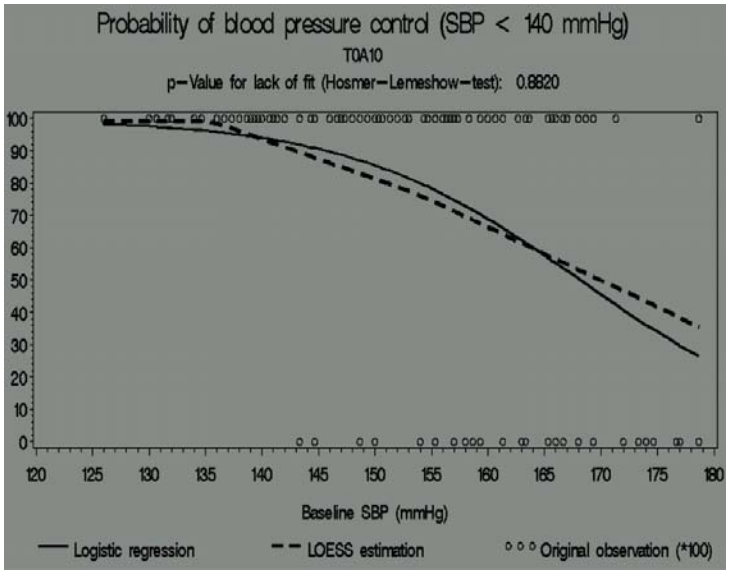

Probability of blood pressure control (DBP < 80 mmHg)
T80A0
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.1152
Baseline DBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

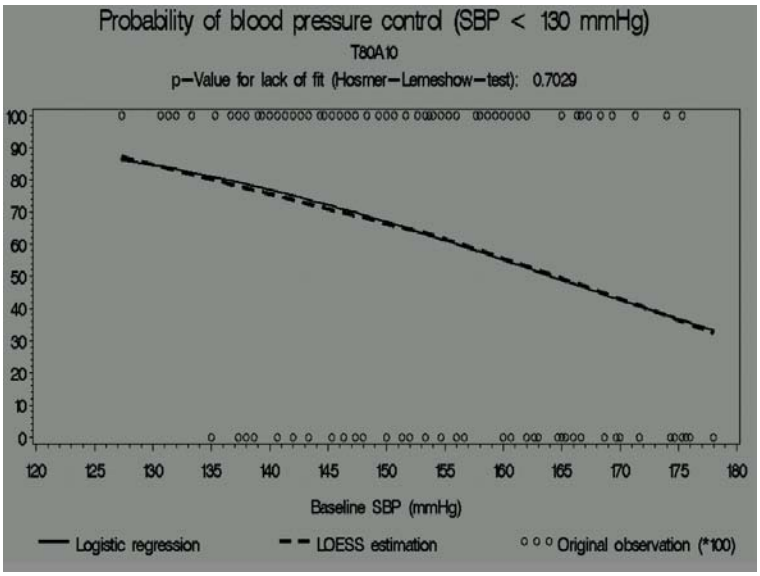

Probability of blood pressure control (DBP < 80 mmHg)
T0A10
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.0988
Baseline DBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

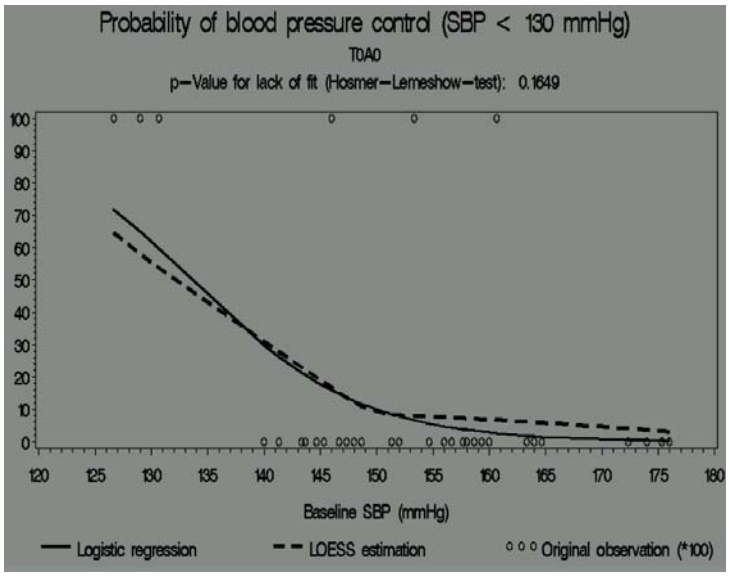

Probability of blood pressure control (SBP < 140 mmHg)
T80A10
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.6341
Baseline SBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

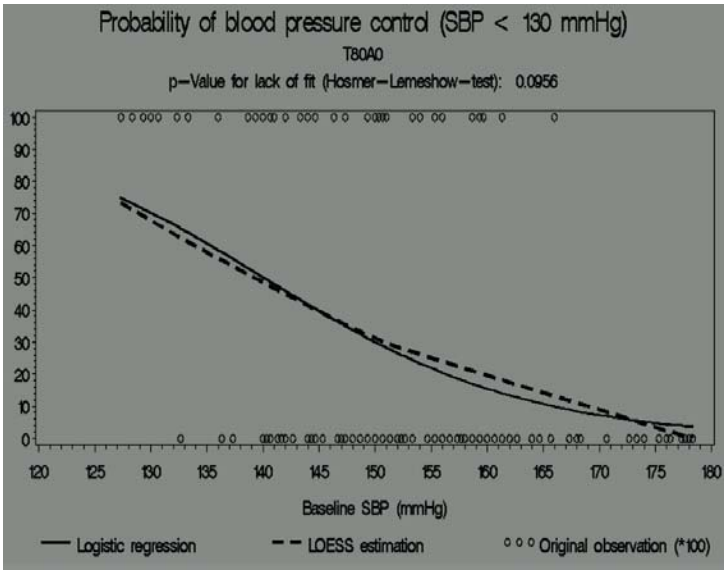

Probability of blood pressure control (SBP < 140 mmHg)
T0A0
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.2814
Baseline SBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

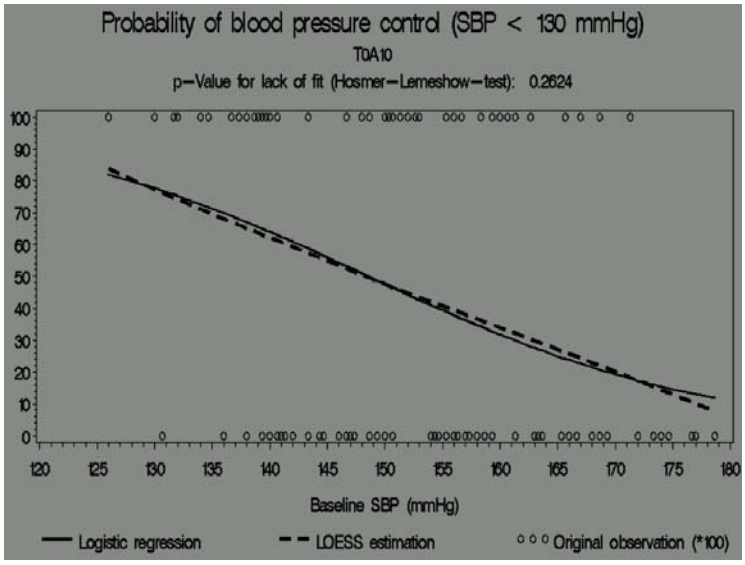

Probability of blood pressure control (SBP < 140 mmHg)
T80A0
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.2747
Baseline SBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)


Probability of blood pressure control (SBP < 140 mmHg)
T0A10
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.8820
Baseline SBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)


Probability of blood pressure control (SBP < 130 mmHg)
T80A10
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.7029
Baseline SBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)


Probability of blood pressure control (SBP < 130 mmHg)
T0A0
p-Value for lack of fit (Hosmer-Lemeshow-test): 0.1649
Baseline SBP (mmHg)
Logistic regression
LOESS estimation
Original observation (*100)

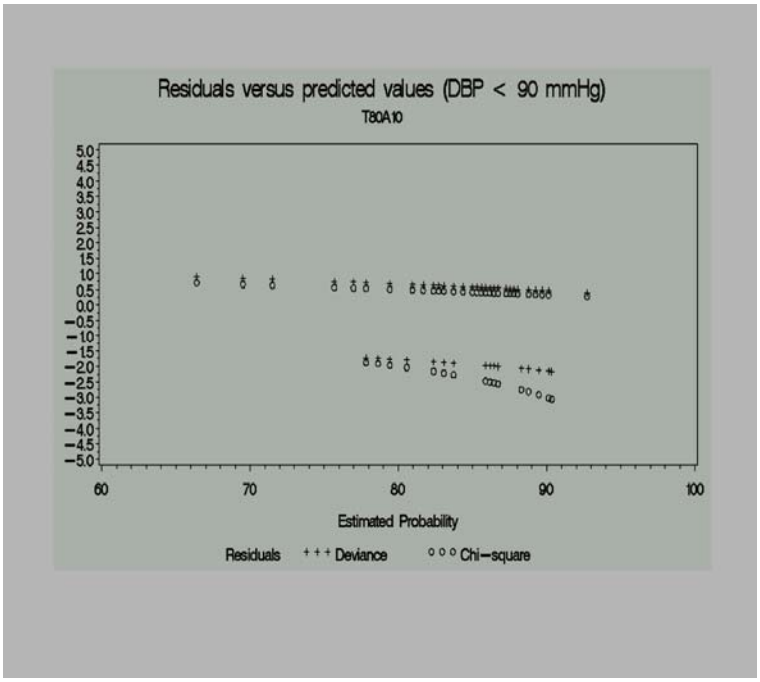


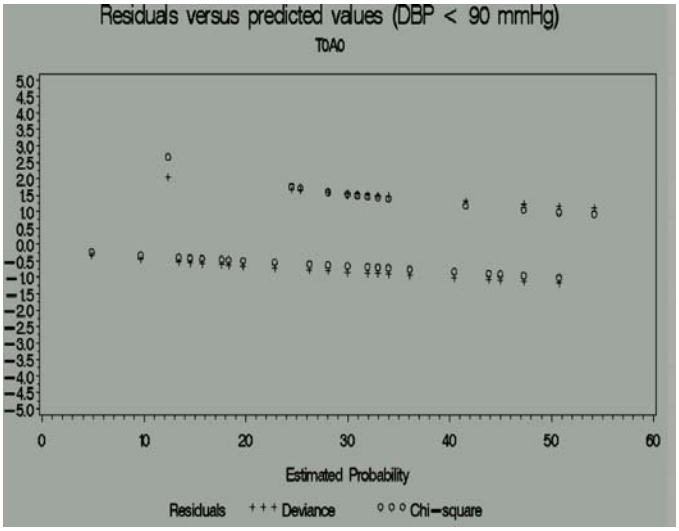


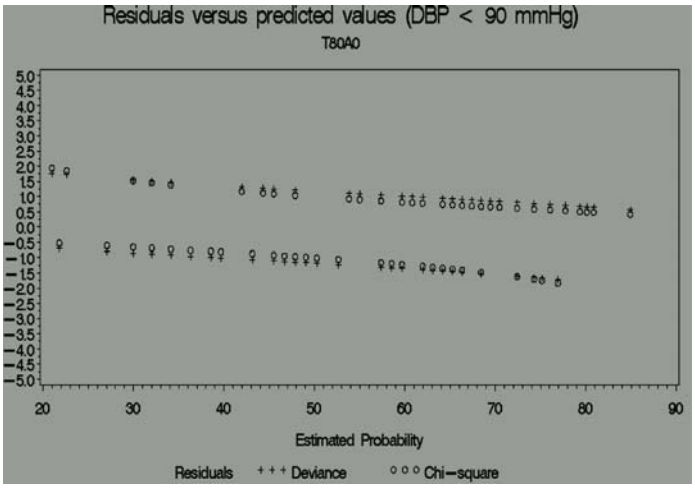
3.2.2.3 Residual analysis

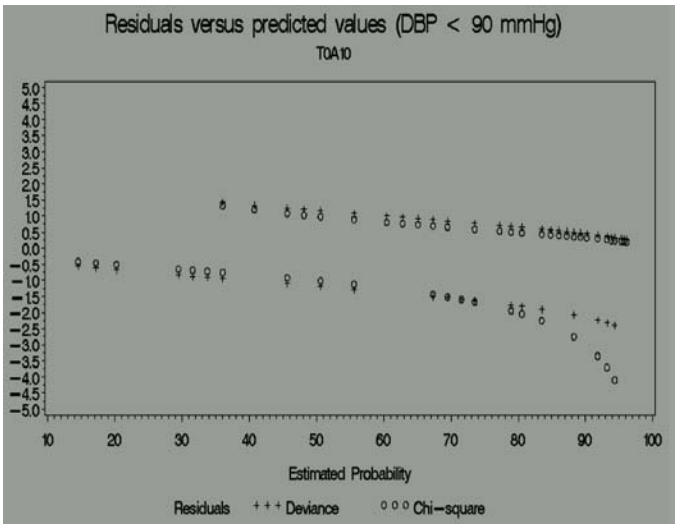
Figure 7 displays chi-square and deviance residuals for the estimated probabilities of achieving BP control at Week 8 endpoint obtained from the logistic regression model for T80/A10, T80, A10 and placebo. Both types of residuals appeared to be relatively small; the standardized residuals were generally within ±3 and only very few outliers were found (residual>4).

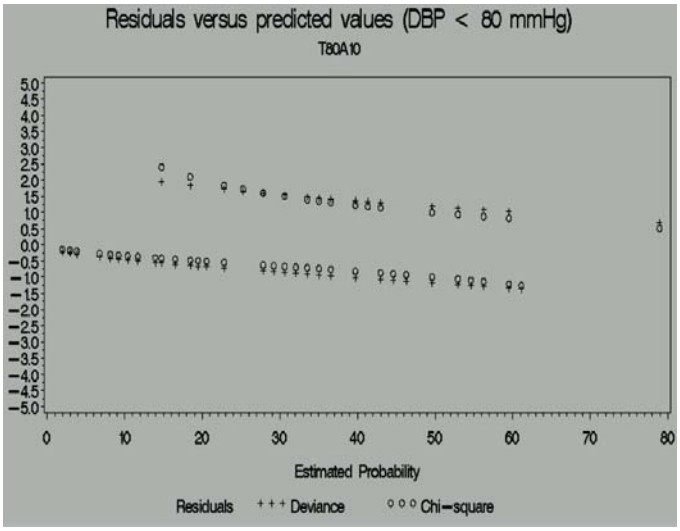
Figure 7 Residual Plots
(Sources: Sponsor's attachments 1a, 2a, 3a & 4a)

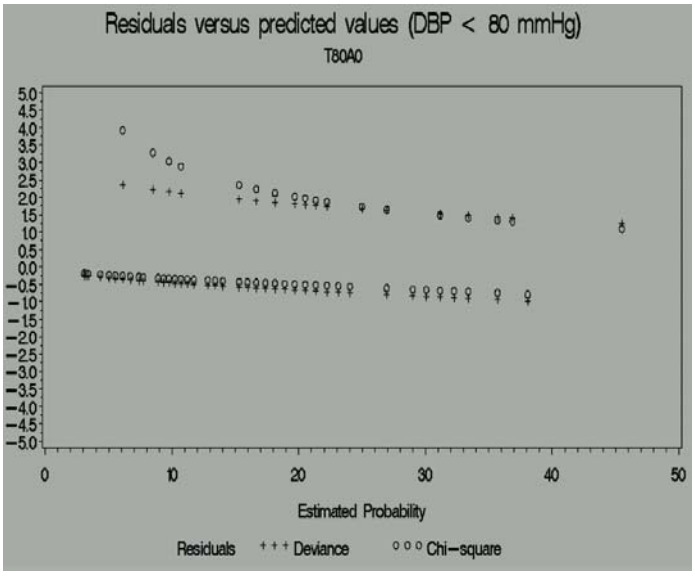


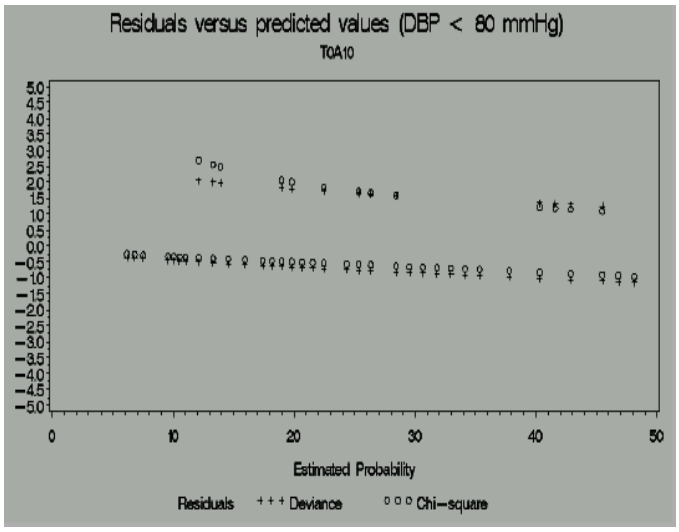


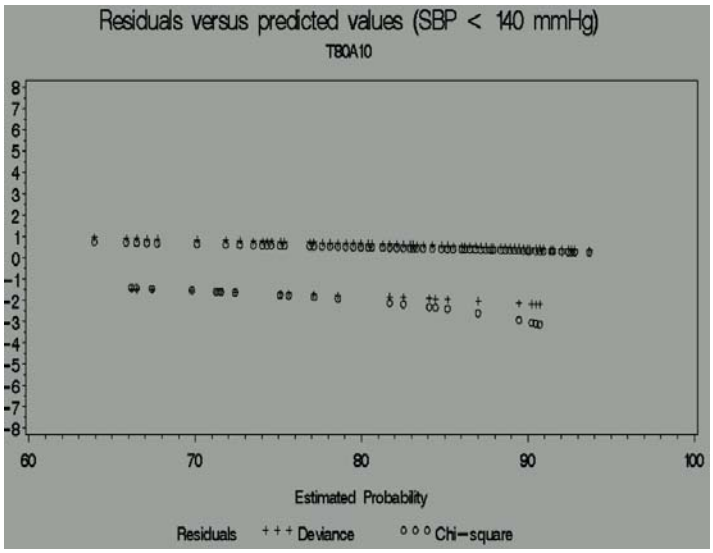

Residuals versus predicted values (DBP < 90 mmHg)
T80A0
Estimated Probability
Residuals +++ Deviance ooo Chi-square

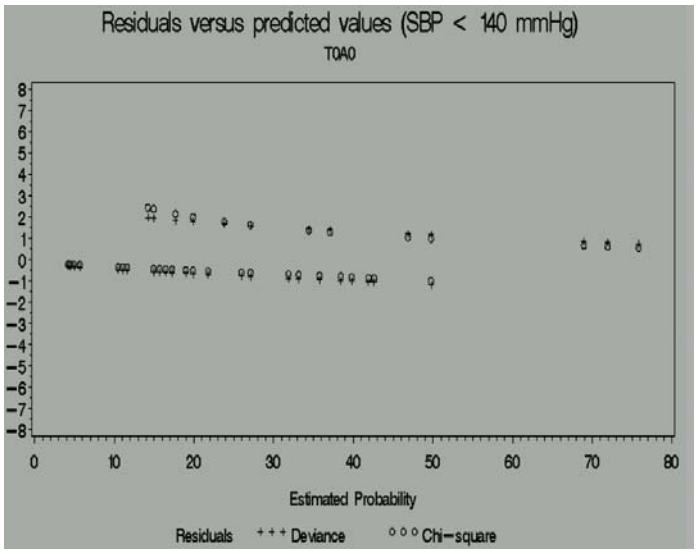

Residuals versus predicted values (DBP < 90 mmHg)
T0A10
Estimated Probability
Residuals +++ Deviance ooo Chi-square

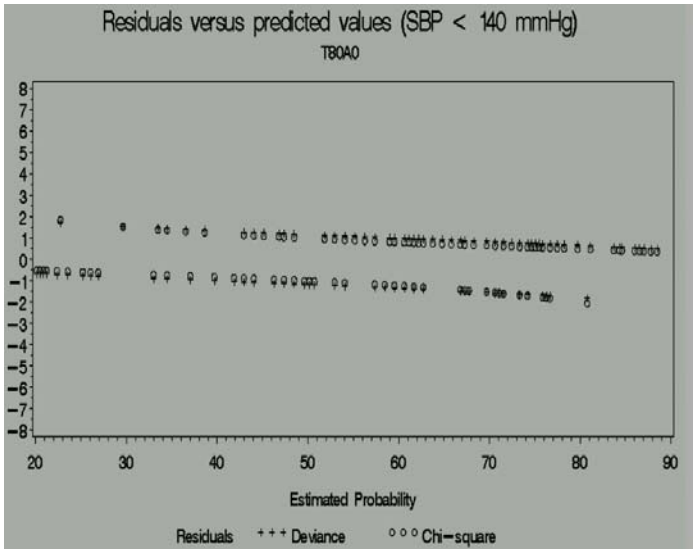

Residuals versus predicted values (DBP < 80 mmHg)
T80A10
Estimated Probability
Residuals +++ Deviance ooo Chi-square

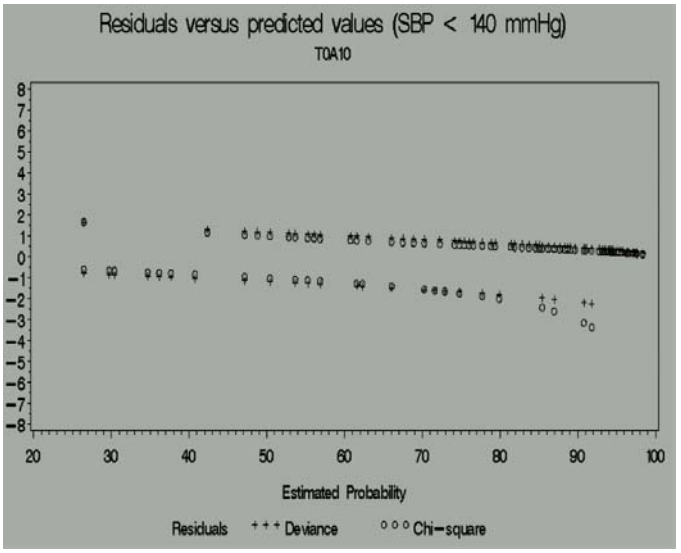

Residuals versus predicted values (DBP < 80 mmHg)
T80A0
Estimated Probability
Residuals +++ Deviance ooo Chi-square

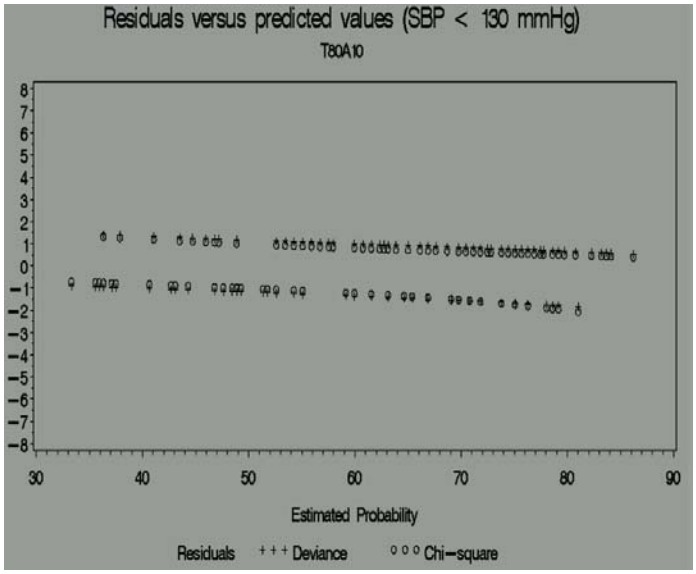

Residuals versus predicted values (DBP < 80 mmHg)
T0A10
Estimated Probability
Residuals +++ Deviance ooo Chi-square

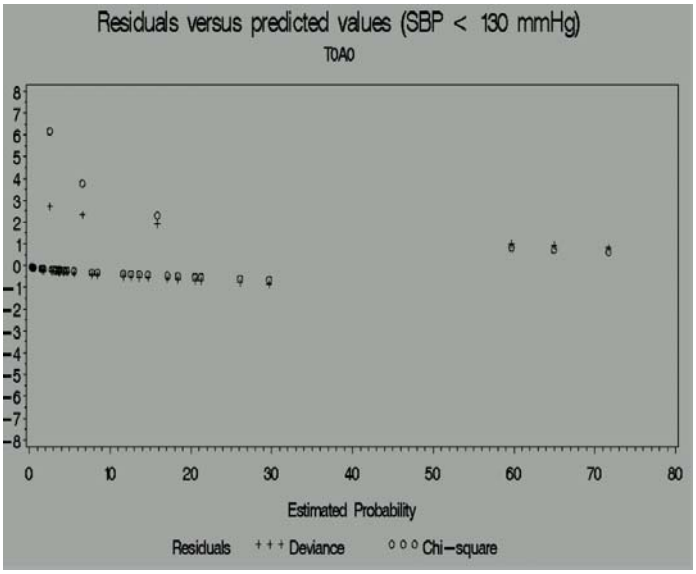

Residuals versus predicted values (SBP < 140 mmHg)
T80A10
Estimated Probability
Residuals +++ Deviance ooo Chi-square

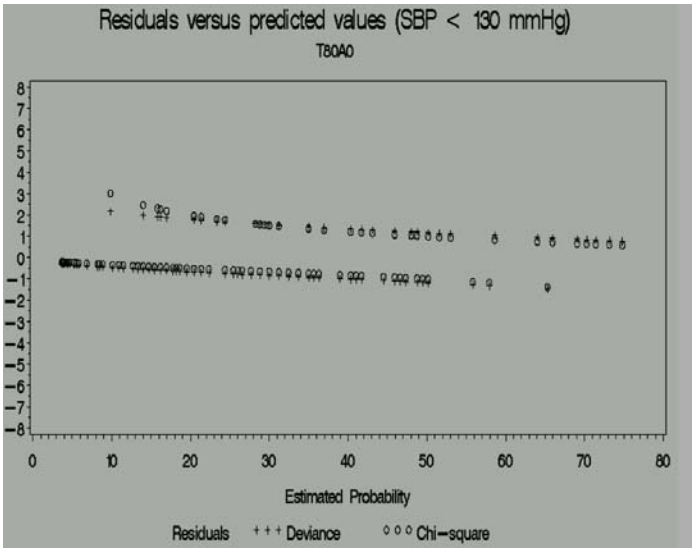

Residuals versus predicted values (SBP < 140 mmHg)
T0A0
Estimated Probability
Residuals +++ Deviance ooo Chi-square

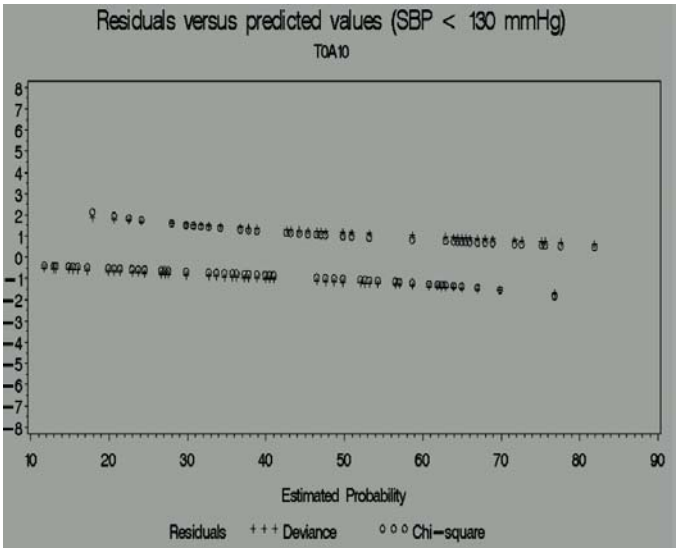

Residuals versus predicted values (SBP < 140 mmHg)
T80A0
Estimated Probability
Residuals +++ Deviance ooo Chi-square


Residuals versus predicted values (SBP < 140 mmHg)
T0A10
Estimated Probability
Residuals +++ Deviance ooo Chi-square


Residuals versus predicted values (SBP < 130 mmHg)
T80A10
Estimated Probability
Residuals +++ Deviance ooo Chi-square


Residuals versus predicted values (SBP < 130 mmHg)
T0A0
Estimated Probability
Residuals +++ Deviance ooo Chi-square





3.2.2.4 Conclusion in modeling and diagnostics

Overall, the results of model diagnostics indicate a sufficient fit of the logistic regression models to the study data based on:

- non-statistically significant Hosmer-Lemeshow tests.
- the non-parametric LOESS curves that are very close to the curves resulting from the parametric model.
- both types of residuals appeared to be relatively small, the standardized values of the residuals are generally within ±3.

3.2.3 Conclusions

The graphs provide reasonable logistic model fit to the study data and can provide support for use of the combination therapy as an initial therapy. However, it may be worth noting that the combination drug is probably not needed for patients with lower baseline BP (e.g., SBP<150 mmHg or DBP <100 mmHg).

3.3 Evaluation of Safety

Please refer to Dr. Blank's review for safety assessment.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Subgroup analysis was performed by age (Tables 14-15), gender (Tables 16-17) and race (Tables18-19) for change from baseline to Week 8 in the in-clinic seated trough cuff diastolic blood pressure (DBP). It appears that the treatment effect is larger in the older, male and black patients. However the sample size is relatively small in these subgroups, thus the results may not be reliable.

Table 14 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating age group effects (FAS−TC)

		Age group	
		<65 years	>=65 years
Placebo	N	40	6
	Adj Mean* (SE)	-6.8(1.3)	-1.8(3.3)
T40	N	111	18
	Adj Mean* (SE)	-12.8(0.8)	-16.6(1.9)
T40+A5	N	120	21
	Adj Mean* (SE)	-16.3(0.7)	-17.5(1.8)
T40+A10	N	106	17
	Adj Mean* (SE)	-19.9(0.8)	-21.6(2.0)
T80	N	112	20
	Adj Mean* (SE)	-13.8(0.8)	-15.3(1.8)
T80+A5	N	121	22
	Adj Mean* (SE)	-17.6(0.7)	-21.2(1.7)
T80+A10	N	114	22
	Adj Mean* (SE)	-19.6(0.8)	-22.7(1.7)
A5	N	117	20
	Adj Mean* (SE)	-12.9(0.8)	-15.5(1.8)
A10	N	106	18
	Adj Mean* (SE)	-16.5(0.8)	-20.1(1.9)
Treatment-by age group interaction:		p=0.9257	

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.2.2.1:1)

Table 15 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating age group effects (FAS−TC-MS)

		Age group	
		<65 years	>=65 years
Placebo	N	30	5
	Adj Mean* (SE)	-6.3(1.5)	-2.4(3.7)
T40	N	87	13
	Adj Mean* (SE)	-13.7(0.9)	-17.3(2.3)
T40+A5	N	93	15
	Adj Mean* (SE)	-17.2(0.9)	-17.1(2.1)
T40+A10	N	85	11
	Adj Mean* (SE)	-19.9(0.9)	-21.7(2.5)
T80	N	79	10
	Adj Mean* (SE)	-13.5(0.9)	-18.6(2.6)
T80+A5	N	88	18
	Adj Mean* (SE)	-18.2(0.9)	-23.5(1.9)
T80+A10	N	87	13
	Adj Mean* (SE)	-20.8(0.9)	-22.0(2.3)
A5	N	88	13
	Adj Mean* (SE)	-13.1(0.9)	-14.4(2.3)
A10	N	71	12
	Adj Mean* (SE)	-16.9(1.0)	-21.7(2.4)
Treatment-by age group interaction:		p=0.8768	

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.2.2.2:1)

Table 16 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating gender effects (FAS−TC)

		Gender	
		Male	Female
Placebo	N	29	17
	Adj Mean* (SE)	-3.8(1.5)	-10.0(1.9)
T40	N	65	64
	Adj Mean* (SE)	-12.2(1.0)	-14.5(1.0)

T40+A5	N	70	71
	Adj Mean* (SE)	-15.0(1.0)	-17.9(1.0)
T40+A10	N	60	63
	Adj Mean* (SE)	-19.8(1.0)	-20.5(1.0)
T80	N	57	75
	Adj Mean* (SE)	-13.1(1.1)	-14.7(0.9)
T80+A5	N	71	72
	Adj Mean* (SE)	-17.7(1.0)	-18.7(0.9)
T80+A10	N	62	74
	Adj Mean* (SE)	-19.5(1.0)	-20.5(0.9)
A5	N	70	67
	Adj Mean* (SE)	-11.5(1.0)	-15.3(1.0)
A10	N	63	61
	Adj Mean* (SE)	-15.7(1.0)	-18.4(1.0)
Treatment-by gender interaction:		p=0.2794	

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.2.2.1:2)

Table 17 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating gender effects (FAS−TC-MS)

		Gender	
		Male	Female
Placebo	N	25	10
	Adj Mean* (SE)	-4.6(1.6)	-8.6(2.6)
T40	N	57	43
	Adj Mean* (SE)	-13.3(1.1)	-15.4(1.2)
T40+A5	N	53	55
	Adj Mean* (SE)	-15.9(1.1)	-18.4(1.1)
T40+A10	N	49	47
	Adj Mean* (SE)	-19.7(1.2)	-20.4(1.2)
T80	N	34	55
	Adj Mean* (SE)	-12.7(1.4)	-15.0(1.1)

T80+A5	N	59	47
	Adj Mean* (SE)	-18.3(1.1)	-20.1(1.2)
T80+A10	N	50	50
	Adj Mean* (SE)	-20.3(1.2)	-21.5(1.2)
A5	N	56	45
	Adj Mean* (SE)	-11.2(1.1)	-15.8(1.2)
A10	N	41	42
	Adj Mean* (SE)	-16.1(1.3)	-19.1(1.3)
Treatment-by gender interaction:		p=0.7873	

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.2.2.2:2)

Table 18 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating race effects (FAS−TC)

		Race		
		Caucasian	Black	Asian
Placebo	N	40	5	1
	Adj Mean* (SE)	-6.8(1.3)	-2.7(3.6)	3.3(8.1)
T40	N	103	18	8
	Adj Mean* (SE)	-13.6(0.8)	-10.5(1.9)	-17.1(2.9)
T40+A5	N	108	26	7
	Adj Mean* (SE)	-17.0(0.8)	-13.7(1.6)	-19.3(3.1)
T40+A10	N	101	18	4
	Adj Mean* (SE)	-20.3(0.8)	-20.8(1.9)	-16.1(4.1)
T80	N	102	24	6
	Adj Mean* (SE)	-14.2(0.8)	-13.6(1.7)	-14.4(3.3)
T80+A5	N	108	30	5
	Adj Mean* (SE)	-18.6(0.8)	-16.7(1.5)	-20.6(3.6)
T80+A10	N	109	24	3
	Adj Mean* (SE)	-20.6(0.8)	-17.2(1.7)	-25.4(4.7)

A5	N	105	24	8
	Adj Mean* (SE)	-13.1(0.8)	-13.7(1.7)	-16.2(2.9)
A10	N	100	21	3
	Adj Mean* (SE)	-16.9(0.8)	-17.5(1.8)	-20.0(4.7)
Treatment-by	race interaction:	p=0.7952		

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.2.2.1:3)

Table 19 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating race effects (FAS−TC-MS)

		Race		
		Caucasian	Black	Asian
Placebo	N	30	4	1
	Adj Mean* (SE)	-6.7(1.5)	-1.2(4.1)	1.8(8.2)
T40	N	79	15	6
	Adj Mean* (SE)	-14.4(0.9)	-11.7(2.1)	-19.1(3.4)
T40+A5	N	87	17	4
	Adj Mean* (SE)	-17.7(0.9)	-14.1(2.0)	-19.6(4.2)
T40+A10	N	78	14	4
	Adj Mean* (SE)	-20.4(0.9)	-19.8(2.2)	-16.4(4.2)
T80	N	64	20	5
	Adj Mean* (SE)	-14.4(1.0)	-13.2(1.8)	-15.8(3.7)
T80+A5	N	78	24	4
	Adj Mean* (SE)	-20.0(0.9)	-16.1(1.7)	-22.3(4.1)
T80+A10	N	81	16	3
	Adj Mean* (SE)	-21.1(0.9)	-19.8(2.1)	-26.1(4.8)

A5	N	77	16	8
	Adj Mean* (SE)	-13.1(0.9)	-13.1(2.1)	-16.5(3.0)
A10	N	64	17	2
	Adj Mean* (SE)	-17.2(1.0)	-18.6(2.0)	-25.0(5.8)
Treatment-by race interaction:		p=0.8829		

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.2.2.2:3)

4.2 Efficacy by Country/Region

The interaction effect of treatment by country/region was also examined among the four key treatment combinations. It appears that the efficacy of twynsta is consistent across country/regions with exception of Argentina and Mexico in both patients with stage I or II and patients with moderate or severe hypertension. In Argentina and Mexico, the placebo effect was substantial large and thus the treatment effect was much smaller than other country/regions (Tables 20-21).

Table 20 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating any treatment−by−country/region interaction (FAS−TC)

		Country/Region (POOLCTR)							
		Argentina	Brazil	Mexico	S. Africa	US-1	US-2	US-3	US-4
Placebo	N	3	3	5	6	8	9	8	4
	Adj Mean* (SE)	-13.3(4.6)	2.3(4.6)	-14.2(3.6)	-5.2(3.3)	-4.1(2.8)	-3.5(2.7)	-3.3(2.8)	-9.1(4.0)
T40	N	9	7	17	18	21	23	21	13
	Adj Mean* (SE)	-12.8(2.7)	-11.7(3.0)	-14.0(1.9)	-12.3(1.9)	-12.1(1.7)	-15.2(1.7)	-10.6(1.7)	-14.9(2.2)
T40+A5	N	7	9	17	19	23	25	24	17
	Adj Mean* (SE)	-20.5(3.0)	-20.0(2.7)	-16.0(1.9)	-18.6(1.8)	-16.1(1.7)	-16.0(1.6)	-13.0(1.6)	-13.1(1.9)
T40+A10	N	6	8	14	17	19	22	22	15
	Adj Mean* (SE)	-26.2(3.3)	-23.3(2.8)	-20.8(2.1)	-20.4(1.9)	-20.4(1.8)	-19.6(1.7)	-16.0(1.7)	-17.8(2.1)
T80	N	8	9	18	20	19	21	25	12
	Adj Mean* (SE)	-16.1(2.8)	-18.1(2.7)	-14.5(1.9)	-14.6(1.8)	-12.1(1.8)	-11.3(1.7)	-12.7(1.6)	-14.6(2.3)

T80+A5	N	7	8	15	22	24	28	22	17
	Adj Mean* (SE)	-23.3(3.0)	-18.6(2.8)	-15.3(2.1)	-18.9(1.7)	-20.5(1.6)	-17.2(1.5)	-14.0(1.7)	-17.6(1.9)
T80+A10	N	7	9	14	22	20	24	22	18
	Adj Mean* (SE)	-21.9(3.0)	-20.7(2.7)	-19.5(2.1)	-22.2(1.7)	-18.3(1.8)	-17.6(1.6)	-19.2(1.7)	-20.2(1.9)
A5	N	7	8	15	22	22	21	23	19
	Adj Mean* (SE)	-15.1(3.0)	-18.6(2.8)	-12.8(2.1)	-16.6(1.7)	-15.7(1.7)	-11.6(1.7)	-8.7(1.7)	-8.8(1.8)
A10	N	8	9	15	15	21	19	20	17
	Adj Mean* (SE)	-14.3(2.8)	-20.9(2.7)	-20.6(2.1)	-16.9(2.1)	-17.1(1.7)	-15.8(1.8)	-13.9(1.8)	-15.0(1.9)

Treatment-by-country/region interaction: p=0.0720

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

(Source: Sponsor's Table 15.2.1.1.1:5)

Table 21 Analysis of change from baseline to end of study (LOCF) in in−clinic seated trough DBP evaluating any treatment−by−country/region interaction (FAS−TC−MS)

		Country/Region (POOLCTR)							
		Argentina	Brazil	Mexico	S. Africa	US-1	US-2	US-3	US-4
Placebo	N	3	3	2	6	5	6	7	3
	Adj Mean* (SE)	-13.5(4.7)	2.0(4.7)	-19.3(5.8)	-5.7(3.3)	-3.2(3.6)	-3.9(3.3)	-2.1(3.1)	-9.2(4.7)
T40	N	7	5	12	15	16	17	16	12
	Adj Mean* (SE)	-13.1(3.1)	-10.1(3.6)	-14.3(2.4)	-15.4(2.1)	-12.8(2.0)	-14.7(2.0)	-11.7(2.0)	-16.2(2.3)
T40+A5	N	6	8	14	16	16	20	14	14
	Adj Mean* (SE)	-21.7(3.3)	-20.2(2.9)	-17.8(2.2)	-19.0(2.0)	-15.8(2.0)	-15.8(1.8)	-14.3(2.2)	-14.7(2.2)
T40+A10	N	6	6	10	16	11	19	15	13
	Adj Mean* (SE)	-26.6(3.3)	-23.6(3.3)	-22.4(2.6)	-20.5(2.0)	-21.2(2.5)	-20.0(1.9)	-13.8(2.1)	-16.6(2.3)
T80	N	8	7	10	16	13	11	17	7
	Adj Mean* (SE)	-16.5(2.9)	-18.0(3.1)	-15.7(2.6)	-15.9(2.0)	-11.0(2.3)	-12.2(2.5)	-11.8(2.0)	-12.7(3.1)

T80+A5	N	6	7	9	21	14	24	14	11
	Adj Mean* (SE)	-25.7(3.3)	-18.2(3.1)	-16.2(2.7)	-19.4(1.8)	-22.7(2.2)	-18.3(1.7)	-13.4(2.2)	-19.6(2.5)
A5	N	5	7	11	22	17	9	15	15
	Adj Mean* (SE)	-15.3(3.6)	-17.5(3.1)	-14.0(2.5)	-17.0(1.7)	-15.1(2.0)	-10.2(2.7)	-7.5(2.1)	-8.6(2.1)
A10	N	4	8	8	13	11	11	16	12
	Adj Mean* (SE)	-14.8(4.1)	-21.9(2.9)	-23.1(2.9)	-17.4(2.3)	-19.5(2.5)	-16.3(2.5)	-12.6(2.0)	-15.3(2.3)

Treatment-by-country/region interaction: p=0.1949

* Adjusted for country/region (POOLCTR) effect and baseline value
SE - Standard Error

Source: Sponsor's Table 15.2.1.1.3:5)

4.3 Other Subgroup Populations

No other subgroup analyses were performed.

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The study showed that the combination therapy of telmisartan plus amlodipine is effective in lowering seated trough cuff DBP in patients with Stage I or II hypertension, as well as in patients with moderate or severe hypertension. The four key combination therapies of T40+A5, T40+A10, T80+A5, and T80+A10 had a statistically significant greater reduction in diastolic blood pressure than each of the respective monotherapies ($p<0.0001$). The study also suggests that the combination therapy has a higher probability of reaching a blood pressure goal compared to telmisartan, or amlodipine monotherapy.

5.2 Conclusions and Recommendations

The study showed that the combination therapy of telmisartan plus amlodipine is more effective than either telmisartan or amlodipine in lowering seated trough cuff DBP in patients with Stage I or II hypertension, as well as in patients with moderate or severe hypertension. The study also seems to support the combination therapy for use as an initial therapy indication in patients with higher blood pressure baselines.

Linked Applications	Submission Type/Number	Sponsor Name	Drug Name / Subject
NDA 22401	ORIG 1	BOEHRINGER INGELHEIM PHARMACEUTICALS INC	TELMISARTAN/AMLODIPINE FIXED DOSE COM TB

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/s/

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08/31/2009

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08/31/2009