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STATISTICAL REVIEW(S)



DEPARTMENT OF HEALTH AND HUMAN SERVICES
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STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

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1. EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Studies have demonstrated that both valsartan and amlodipine contribute to the overall effect in blood pressure reduction of the combination. The combinations identified to be more effective than their respective components in the reduction of both diastolic and systolic blood pressure from the four studies are: val/aml 40/5 mg, val/aml 80/2.5 mg, val/aml 80/5 mg, val/aml 160/5 mg, val/aml 160/10 mg, val/aml 320/5 mg, val/aml 320/10 mg.

1.2 Brief Overview of Clinical Studies

This sNDA includes five clinical studies (2201, 2307, 2305, 2306, 2308) to support the safety and efficacy of Exforge in the treatment of patients with essential hypertension. The full range of globally approved doses of valsartan and amlodipine was studied.

The primary objective of the studies was to demonstrate the efficacy and safety of the combination of valsartan with amlodipine for the treatment of hypertension. Study 2201 and 2307 were double-blind, randomized, parallel design trials, comparing the combinations of valsartan and amlodipine to their monotherapy components and placebo in mild to moderate hypertension. Studies 2305, 2306, and 2308 were double-blind, randomized active-controlled studies in mild to moderate and severe hypertension (Study 2308 was not reviewed since there was no statistical analysis conducted). The primary measure of efficacy used in this clinical program was the change from baseline to Week 8 in mean sitting diastolic blood pressure (MSDBP).

1.3 Statistical Issues and Findings

In each combination drug study, controlling type I error rate in comparing multiple dose combinations with their respective monotherapy components is a key issue of concern. The FDA's statistical reviewer used sensible multiplicity adjustment method to check and verify the sponsor's analysis results. Both the reviewer's results and the sponsor results seem to be consistent and support that both valsartan and amlodipine contribute to the overall effect in blood pressure reduction of the combination.

2. INTRODUCTION

2.1 Overview

The combination of an angiotensin converting enzyme (ACE/ARB) inhibitor and a dihydropyridine calcium antagonist has been shown to be more effective in lowering blood pressure, with less of the undesirable side effects, than either agent alone. Amlodipine besylate is a dihydropyridine calcium channel blocker (DHP-CCB) and Valsartan is an active angiotensin II receptor blocker (ARB). In the US, valsartan

(Diovan®) and amlodipine (Norvasc®) are currently approved in the doses of 80 to 320 mg and 2.5 to 10 mg, respectively, for the treatment of hypertension. In this new drug application, Novartis developed _____ of valsartan/amlodipine: _____ 160/5 mg; 160/10 mg; 320/5 mg; and 320/10 mg. The purpose of this submission is to gain marketing approval for the fixed combination doses of amlodipine besylate/valsartan in doses _____ 5/160 mg, 10/160 mg, 5/320 mg (U.S. only) and 10/320 mg (U.S. only).

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of
\\Cdsub1\N21990\N_000\2006-02-22 of the Center's electronic document room.

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1 STUDY A: 2201

3.1.1.1 Study Objectives

The primary objective of this trial was to assess the blood pressure lowering effects of a once daily regimen of various combinations of valsartan and amlodipine, compared to their monotherapy components and placebo, in mild to moderate hypertensive patients.

3.1.1.2 Study Design

Study 2201 is a multicenter, randomized, double-blind, placebo controlled, parallel group design. 1911 subjects from 150 centers worldwide were enrolled into the study and randomized to fifteen treatment groups. This study consisted of a single-blind placebo run-in period of two to four weeks preceded an 8-week double-blind active treatment period as shown below in Table 1.

Table 1 Study design

Washout (2 weeks)	Single-blind run-in (2-4 weeks)	Double-blind treatment (8 weeks)					
Visit 0	1	2	3	4	5	6	7*
Week -4 to -6	-2 to -4	0	1	2	4	6	8
		↓ Randomization					
		Placebo					
		Valsartan 40 mg OD					
		Valsartan 80 mg OD					
		Valsartan 160 mg OD					
		Valsartan 320 mg OD					
		Amlodipine 2.5 mg OD					
		Amlodipine 5 mg OD					
		Valsartan/Amlodipine 40/2.5 mg OD					
		Valsartan/Amlodipine 40/5 mg OD					
		Valsartan/Amlodipine 80/2.5 mg OD					
		Valsartan/Amlodipine 80/5 mg OD					
		Valsartan/Amlodipine 160/2.5 mg OD					
		Valsartan/Amlodipine 160/5 mg OD					
		Valsartan/Amlodipine 320/2.5 mg OD					
		Valsartan/Amlodipine 160/2.5mg OD		Valsartan/Amlodipine 320/5mg OD			
*At the end of the 8 week double-blind treatment phase, patients at selected centers who completed all the double-blind visits without serious adverse experiences were eligible to enroll in a one-year open-label extension.							

(Source: Sponsor's figure 3-1)

3.1.1.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary variable was change from baseline to week 8 in mean sitting diastolic blood pressure (MSDBP).

(2) Secondary Efficacy Endpoints

- Changes from baseline to Week 8 in sitting systolic blood pressure, standing diastolic and systolic blood pressures
- Sitting and standing pulse

3.1.1.4 Patient Disposition, Demographic and Baseline Characteristics

Tables 2 and 3 summarize patient disposition, demographic and baseline characteristics.

Table 2 Demographics by treatment group (randomized population)

Treatment Group	N	Age (yrs) Mean	Sex n (%)		Race n (%)			
			Male	Female	Caucasian	Black	Oriental	Other
Val/Aml 320/5 mg	127	55.3	71 (55.9)	56 (44.1)	103 (81.1)	9 (7.1)	4 (3.1)	11 (8.7)
Val/Aml 320/2.5 mg	129	55.1	75 (58.1)	54 (41.9)	103 (79.8)	13 (10.1)	3 (2.3)	10 (7.8)
Val/Aml 160/5 mg	127	54.9	58 (45.7)	69 (54.3)	104 (81.9)	12 (9.4)	1 (0.8)	10 (7.9)
Val/Aml 160/2.5 mg	127	55.1	67 (52.8)	60 (47.2)	102 (80.3)	10 (7.9)	2 (1.6)	13 (10.2)
Val/Aml 80/5 mg	128	54.2	57 (44.5)	71 (55.5)	99 (77.3)	15 (11.7)	2 (1.6)	12 (9.4)
Val/Aml 80/2.5 mg	130	54.1	79 (60.8)	51 (39.2)	100 (76.9)	17 (13.1)	3 (2.3)	10 (7.7)
Val/Aml 40/5 mg	125	53.4	71 (56.8)	54 (43.2)	102 (81.6)	12 (9.6)	1 (0.8)	10 (8.0)
Val/Aml 40/2.5 mg	129	54.5	76 (58.9)	53 (41.1)	105 (81.4)	10 (7.8)	3 (2.3)	11 (8.5)
Val 320 mg	128	56.8	67 (52.3)	61 (47.7)	100 (78.1)	16 (12.5)	0 (0.0)	12 (9.4)
Val 160 mg	128	53.0	69 (53.9)	59 (46.1)	105 (82.0)	9 (7.0)	2 (1.6)	12 (9.4)
Val 80 mg	124	53.1	56 (45.2)	68 (54.8)	95 (76.6)	19 (15.3)	2 (1.6)	8 (6.5)
Val 40 mg	127	55.0	72 (56.7)	55 (43.3)	97 (76.4)	16 (12.6)	0 (0.0)	14 (11.0)
Aml 5 mg	128	53.8	68 (53.1)	60 (46.9)	106 (82.8)	10 (7.8)	3 (2.3)	9 (7.0)
Aml 2.5 mg	126	54.4	66 (52.4)	60 (47.6)	95 (75.4)	19 (15.1)	1 (0.8)	11 (8.7)
Placebo	128	53.7	70 (54.7)	58 (45.3)	103 (80.5)	12 (9.4)	3 (2.3)	10 (7.8)
Total	1911	54.4	1022 (53.5)	889 (46.5)	1519 (79.5)	199 (10.4)	30 (1.6)	163 (8.5)

(Source: Sponsor's Table 7-4)

Table 3 Baseline mean-sitting blood pressures and pulse by treatment group (randomized population)

Treatment Group	No. of Pts	Mean Sitting Diastolic BP (mmHg)	Mean Sitting Systolic BP (mmHg)	Sitting Pulse (bpm)
		Mean (SD)	Mean (SD)	Mean (SD)
Val/Aml 320/5 mg	127	99.3 (3.75)	152.5 (12.25)	71.8 (8.95)
Val/Aml 320/2.5 mg	129	99.4 (3.71)	152.3 (12.49)	74.8 (9.77)
Val/Aml 160/5 mg	127	99.4 (3.59)	153.0 (13.07)	73.4 (10.14)
Val/Aml 160/2.5 mg	127	99.0 (3.42)	152.1 (13.29)	73.2 (9.18)
Val/Aml 80/5 mg	128	99.1 (3.32)	153.2 (12.75)	72.6 (8.94)
Val/Aml 80/2.5 mg	130	99.5 (3.88)	151.8 (13.71)	72.8 (9.06)
Val/Aml 40/5 mg	125	99.4 (3.48)	153.0 (13.68)	71.5 (9.46)
Val/Aml 40/2.5 mg	129	99.6 (3.84)	153.1 (13.21)	74.0 (9.55)
Val 320 mg	128	99.3 (3.59)	154.6 (11.41)	72.7 (9.05)
Val 160 mg	128	98.9 (3.54)	152.0 (14.19)	73.4 (9.29)
Val 80 mg	124	99.2 (3.55)	153.2 (11.63)	73.1 (8.71)
Val 40 mg	127	99.2 (3.22)	153.7 (12.56)	73.8 (10.67)
Aml 5 mg	128	99.0 (3.49)	152.6 (12.70)	72.6 (10.15)
Aml 2.5 mg	126	99.5 (3.73)	153.9 (12.86)	73.4 (9.79)
Placebo	128	99.4 (3.72)	151.6 (12.57)	72.5 (9.38)
Total	1911	99.3 (3.59)	152.8 (12.83)	73.0 (9.49)

(Source: Sponsor's Table 7-5)

3.1.1.5 Sponsor's Primary Efficacy Results

1. Global assessment of MSDBP

Global assessment of MSDBP reduction at endpoint using an ANCOVA model with valsartan, amlodipine and region as 3 factors and the baseline as a covariate showed both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment ($p < 0.0001$ for both valsartan and amlodipine). The result is showed in Table 4.

Table 4 Summary of ANCOVA Model with Interaction for Changes from Baseline to Week 8 in MSDBP (ITT)

Parameter	DF	Mean square estimate	F-value	P-value
valsartan	4	1457.69	27.32	<0.0001
amlodipine	2	2406.65	45.10	<0.0001
valsartan * amlodipine	8	82.69	1.55	0.1352
Baseline	1	177.12	3.32	0.0686
Region	13	267.13	5.01	<0.0001
Model statistics				
Mean square error	1869	53.36		
F-statistic for model			9.95	
P-value for model				<0.0001

(Source: Sponsor's Table 9.1-1A)

2. Between-treatment comparisons of MSDBP

The analysis of between-treatment comparisons showed that combination treatments were statistically significantly superior to their monotherapy components and placebo in MSDBP reduction at endpoint with the only exceptions being [val/aml 320/2.5 mg vs. val 320 mg], [val/aml 40/2.5 mg vs. aml 40 mg] and [val/aml 40/2.5 mg vs. aml 2.5 mg]. The results were showed in Table 5.

Table 5 Between-treatment comparisons of MSDBP (mmHg) at endpoint (ITT)

Comparison	LSM difference in change from baseline (SE)	95% CI in LSM difference	p-value
[Val/Aml 320/5 mg] vs [Val 320 mg]	-2.54 (0.917)	(-4.34, -0.74)	0.0057 *
[Val/Aml 320/5 mg] vs [Aml 5 mg]	-4.48 (0.920)	(-6.28, -2.68)	<.0001 *
[Val/Aml 320/5 mg] vs Placebo	-9.19 (0.920)	(-10.99, -7.39)	<.0001 *
[Val/Aml 320/2.5 mg] vs [Val 320 mg]	-0.77 (0.914)	(-2.56, 1.03)	0.4021
[Val/Aml 320/2.5 mg] vs [Aml 2.5 mg]	-4.83 (0.919)	(-6.63, -3.03)	<.0001 *
[Val/Aml 320/2.5 mg] vs Placebo	-7.41 (0.916)	(-9.21, -5.62)	<.0001 *
[Val 320 mg] vs Placebo	-6.65 (0.916)	(-8.44, -4.85)	<.0001 *
[Val/Aml 160/5 mg] vs [Val 160 mg]	-3.14 (0.921)	(-4.95, -1.34)	0.0007 *
[Val/Aml 160/5 mg] vs [Aml 5 mg]	-2.74 (0.919)	(-4.54, -0.94)	0.0029 *
[Val/Aml 160/5 mg] vs Placebo	-7.45 (0.918)	(-9.25, -5.65)	<.0001 *
[Val/Aml 160/2.5 mg] vs [Val 160 mg]	-2.23 (0.925)	(-4.04, -0.41)	0.0162 *
[Val/Aml 160/2.5 mg] vs [Aml 2.5 mg]	-3.94 (0.925)	(-5.76, -2.13)	<.0001 *
[Val/Aml 160/2.5 mg] vs Placebo	-6.53 (0.923)	(-8.34, -4.72)	<.0001 *
[Val 160 mg] vs Placebo	-4.30 (0.920)	(-6.11, -2.50)	<.0001 *
[Val/Aml 80/5 mg] vs [Val 80 mg]	-4.78 (0.928)	(-6.60, -2.96)	<.0001 *
[Val/Aml 80/5 mg] vs [Aml 5 mg]	-3.06 (0.921)	(-4.86, -1.25)	0.0009 *
[Val/Aml 80/5 mg] vs Placebo	-7.77 (0.921)	(-9.57, -5.96)	<.0001 *
[Val/Aml 80/2.5 mg] vs [Val 80 mg]	-3.62 (0.922)	(-5.42, -1.81)	<.0001 *
[Val/Aml 80/2.5 mg] vs [Aml 2.5 mg]	-4.01 (0.917)	(-5.81, -2.22)	<.0001 *
[Val/Aml 80/2.5 mg] vs Placebo	-6.60 (0.915)	(-8.39, -4.80)	<.0001 *
[Val 80 mg] vs Placebo	-2.98 (0.925)	(-4.80, -1.17)	0.0013 *
[Val/Aml 40/5 mg] vs [Val 40 mg]	-4.52 (0.925)	(-6.33, -2.70)	<.0001 *
[Val/Aml 40/5 mg] vs [Aml 5 mg]	-3.18 (0.926)	(-5.00, -1.37)	0.0006 *
[Val/Aml 40/5 mg] vs Placebo	-7.89 (0.925)	(-9.71, -6.08)	<.0001 *
[Val/Aml 40/2.5 mg] vs [Val 40 mg]	-0.72 (0.916)	(-2.51, 1.08)	0.4337
[Val/Aml 40/2.5 mg] vs [Aml 2.5 mg]	-1.51 (0.919)	(-3.31, 0.29)	0.1005
[Val/Aml 40/2.5 mg] vs Placebo	-4.09 (0.917)	(-5.89, -2.30)	<.0001 *
[Val 40 mg] vs Placebo	-3.38 (0.918)	(-5.18, -1.58)	0.0002 *
[Aml 5 mg] vs Placebo	-4.71 (0.918)	(-6.51, -2.91)	<.0001 *
[Aml 2.5 mg] vs Placebo	-2.59 (0.920)	(-4.39, -0.78)	0.0050 *

* indicates statistical significance at 0.05 level.

(Source: Sponsor's Table 9-3)

3.1.1.6 Sponsor's Secondary Efficacy Results

1.- Global assessment of MSSBP

Global assessment of MSSBP reduction at endpoint showed both monotherapy treatments contribute to the overall effect in MSSBP reduction of the combination treatment ($p < 0.0001$ for both valsartan and amlodipine). See Table 6.

Table 6 Summary of ANCOVA Model with Interaction for Changes from Baseline to Week 8 in MSSBP (ITT)

Parameter	DF	Mean square estimate	F-value	P-value
valsartan	4	2907.47	21.49	<0.0001
amlodipine	2	7877.26	58.23	<0.0001
valsartan * amlodipine	8	104.81	0.77	0.6250
Baseline	1	70411.39	520.53	<0.0001
Region	13	261.70	1.93	0.0227
Model statistics				
Mean square error	1869	135.27		
F-statistic for model			28.56	
P-value for model				<0.0001

(Source: Sponsor's table 9.1-1B)

2. Between-treatment comparisons of MSSBP

The between-treatment analysis showed that the combination treatments are statistically significantly superior to their monotherapy components and placebo in MSSBP reduction at endpoint with the only exceptions being [val/aml 320/2.5 mg vs. val 320 mg] and [val/aml 160/2.5 mg vs. val 160 mg]. The results were showed in Table 7.

Table 7 Between-treatment comparisons of MSSBP (mmHg) at endpoint (ITT)

Comparison	LSM difference in change from baseline (SE)	95% CI in LSM difference	p-value
[Val/Aml 320/5 mg] vs [Val 320 mg]	-7.07 (1.465)	(-9.94, -4.20)	<.0001 *
[Val/Aml 320/5 mg] vs [Aml 5 mg]	-7.67 (1.457)	(-10.53, -4.82)	<.0001 *
[Val/Aml 320/5 mg] vs Placebo	-16.01 (1.463)	(-18.88, -13.14)	<.0001 *
[Val/Aml 320/2.5 mg] vs [Val 320 mg]	-2.67 (1.460)	(-5.53, 0.20)	0.0678
[Val/Aml 320/2.5 mg] vs [Aml 2.5 mg]	-5.94 (1.460)	(-8.80, -3.07)	<.0001 *
[Val/Aml 320/2.5 mg] vs Placebo	-11.61 (1.458)	(-14.46, -8.75)	<.0001 *
[Val 320 mg] vs Placebo	-8.94 (1.465)	(-11.8, -6.07)	<.0001 *
[Val/Aml 160/5 mg] vs [Val 160 mg]	-4.44 (1.459)	(-7.30, -1.58)	0.0024 *
[Val/Aml 160/5 mg] vs [Aml 5 mg]	-4.43 (1.454)	(-7.28, -1.58)	0.0024 *
[Val/Aml 160/5 mg] vs Placebo	-12.76 (1.460)	(-15.62, -9.90)	<.0001 *
[Val/Aml 160/2.5 mg] vs [Val 160 mg]	-1.69 (1.466)	(-4.56, 1.19)	0.2498
[Val/Aml 160/2.5 mg] vs [Aml 2.5 mg]	-4.34 (1.469)	(-7.22, -1.46)	0.0032 *
[Val/Aml 160/2.5 mg] vs Placebo	-10.01 (1.467)	(-12.88, -7.13)	<.0001 *
[Val 160 mg] vs Placebo	-8.32 (1.462)	(-11.19, -5.46)	<.0001 *
[Val/Aml 80/5 mg] vs [Val 80 mg]	-7.81 (1.472)	(-10.69, -4.92)	<.0001 *
[Val/Aml 80/5 mg] vs [Aml 5 mg]	-5.68 (1.457)	(-8.54, -2.83)	<.0001 *
[Val/Aml 80/5 mg] vs Placebo	-14.01 (1.463)	(-16.88, -11.15)	<.0001 *
[Val/Aml 80/2.5 mg] vs [Val 80 mg]	-4.09 (1.465)	(-6.96, -1.22)	0.0053 *
[Val/Aml 80/2.5 mg] vs [Aml 2.5 mg]	-4.63 (1.459)	(-7.49, -1.77)	0.0015 *
[Val/Aml 80/2.5 mg] vs Placebo	-10.30 (1.456)	(-13.15, -7.45)	<.0001 *
[Val 80 mg] vs Placebo	-6.21 (1.472)	(-9.09, -3.32)	<.0001 *
[Val/Aml 40/5 mg] vs [Val 40 mg]	-7.86 (1.471)	(-10.74, -4.98)	<.0001 *
[Val/Aml 40/5 mg] vs [Aml 5 mg]	-4.55 (1.466)	(-7.42, -1.68)	0.0019 *
[Val/Aml 40/5 mg] vs Placebo	-12.88 (1.472)	(-15.77, -10.00)	<.0001 *
[Val/Aml 40/2.5 mg] vs [Val 40 mg]	-3.78 (1.456)	(-6.63, -0.92)	0.0095 *
[Val/Aml 40/2.5 mg] vs [Aml 2.5 mg]	-3.13 (1.460)	(-5.99, -0.27)	0.0320 *
[Val/Aml 40/2.5 mg] vs Placebo	-8.80 (1.457)	(-11.66, -5.95)	<.0001 *
[Val 40 mg] vs Placebo	-5.03 (1.462)	(-7.89, -2.16)	0.0006 *
[Aml 5 mg] vs Placebo	-8.33 (1.457)	(-11.19, -5.48)	<.0001 *
[Aml 2.5 mg] vs Placebo	-5.67 (1.466)	(-8.54, -2.80)	0.0001 *

* indicates statistical significance at 0.05 level.

(Source: Sponsor's Table 9-10)

3.1.1.7 Reviewer's Results

- 1) The assessment of additivity of two components suggests that valsartan/amlodipine combinations, especially in the higher dose combinations, seem to yield a BP (MSDBP and MSSBP) lowering effect smaller than the sum of the effects of valsartan alone and amlodipine alone (See Tables 8 and 9). Because of the suspicion of this potential negative drug by drug interaction (i.e., sub-additivity), the validity of ANOVA using an additive model is questionable and therefore the significant main effects of the two components from the ANOVA may be questionable, though they are statistically significant ($p < 0.0001$ for both valsartan and amlodipine). Pair-wise comparison of the combination treatment groups versus their monotherapy treatment groups with adequately controlling overall type I error rate then becomes important.

The sponsor did not pre-specify multiplicity adjustment method for their pair-wise comparisons. The FDA statistical reviewer chose Holm's procedure to adjust for multiplicity since this procedure is less conservative in controlling the overall type I error rate. The result showed that all combinations are more effective than their monotherapy components with the exception of val/aml 40/2.5 mg and val/aml 320/2.5 mg in the reduction of MSDBP and val/aml 40/2.5 mg, val/aml 160/2.5 mg and val/aml 320/2.5 mg in the reduction of MSSBP. See Tables 10 and 11.

Table 8 Descriptive Assessment of Additivity for MSDBP (ITT)

	Amlodipine dosage	Valsartan dosage			
		40 mg	80 mg	160 mg	320 mg
Sum of mean changes for monotherapies (expected change if treatments are additive)	2.5 mg	-6.13	-5.75	-7.14	-9.41
	5.0 mg	-8.1	-7.72	-9.11	-11.38
Observed mean change for combinations	2.5 mg	-4.14	-6.69	-6.56	-7.47
	5.0 mg	-8	-7.79	-7.55	-9.3
Difference (observed minus expected)	2.5 mg	1.99	-0.94	0.58	1.94
	5.0 mg	0.1	-0.07	1.56	2.08

(Source: Reviewer's analysis)

Table 9 Descriptive Assessment of Additivity for MSSBP (ITT)

	Amlodipine dosage	Valsartan dosage			
		40 mg	80 mg	160 mg	320 mg
Sum of mean changes for monotherapies (expected change if treatments are additive)	2.5 mg	-12.45	-13.5	-14.89	-16.85
	5.0 mg	-14.33	-15.38	-16.77	-18.73
Observed mean change for combinations	2.5 mg	-9.17	-10.16	-10.0	-11.77
	5.0 mg	-13.38	-14.5	-13.2	-16.2
Difference (observed minus expected)	2.5 mg	3.28	3.34	4.89	5.08
	5.0 mg	0.95	0.88	0.57	2.53

(Source: Reviewer's analysis)

Table 10 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations to Monotherapies for Mean Changes from Baseline to Week 8 for MSDBP (ITT)

	Amlodipine dosage	Valsartan dosage			
		40 mg	80 mg	160 mg	320 mg
Raw p-values for pair-wise comparisons of combinations to Valsartan	2.5 mg	0.4337	<0.0001*	0.0162*	0.4021
	5.0 mg	<0.0001*	<0.0001*	0.0007*	0.0057*
Raw p-values for pair-wise comparisons of combinations to Amlodipine	2.5 mg	0.1005	<0.0001*	<0.0001*	<0.0001*
	5.0 mg	0.0006*	0.0009*	0.0029*	<0.0001*
Maximum p-values	2.5 mg	0.4337	<0.0001*	0.0162*	0.4021
	5.0 mg	0.0006*	0.0009*	0.0029*	0.0057*
Holm-adjusted p-values	2.5 mg	0.8042	<0.0008*	0.0486*	0.8042
	5.0 mg	0.0042*	0.0054*	0.0145*	0.0228*

* Statistically significant at $\alpha=0.05$.

(Source: Reviewer's analysis)

Table 11 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations to Monotherapies for Mean Changes from Baseline to Week 8 for MSSBP (ITT)

	Amlodipine dosage	Valsartan dosage			
		40 mg	80 mg	160 mg	320 mg
Raw p-values for pair-wise comparisons of combinations to Valsartan	2.5 mg	0.0095*	0.0053*	0.2498	0.0678
	5.0 mg	<0.0001*	<0.0001*	0.0024*	<0.0001*
Raw p-values for pair-wise comparisons of combinations to Amlodipine	2.5 mg	0.032*	0.0015*	0.0032*	<0.0001*
	5.0 mg	0.0019*	<0.0001*	0.0024*	<0.0001*
Maximum p-values	2.5 mg	0.032*	0.0053*	0.2498	0.0678
	5.0 mg	0.0019*	<0.0001*	0.0024*	<0.0001*
Holm-adjusted p-values	2.5 mg	0.096	0.0212*	0.2498	0.1356
	5.0 mg	0.0114*	<0.0008*	0.0120*	<0.0008*

* Statistically significant at $\alpha=0.05$.

(Source: Reviewer's analysis)

3.1.1.8 Conclusions

The analysis of primary efficacy endpoint showed that both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment ($p<0.0001$ for both valsartan and amlodipine). Pair-wise comparisons with adjustment

of multiplicity showed that combination treatments were statistically significantly superior to their monotherapy components with the exceptions being val/aml 40/2.5 mg and val/aml 320/2.5 mg in MSDBP reduction; and val/aml 40/2.5 mg, val/aml 160/2.5 mg and val/aml 320/2.5 mg in MSSBP reduction.

3.1.2 STUDY B: 2307

3.1.2.1 Study Objectives

The primary objective of this trial was to assess the blood pressure lowering effects of a once daily regimen of various combinations of valsartan (160 and 320 mg) and amlodipine (10 mg), compared to their monotherapy components and placebo.

3.1.2.2 Study Design

The study was a multicenter, randomized, double-blind, placebo controlled, parallel group design. A total of 1250 subjects were enrolled into the study and randomized to six treatment groups. The study consisted of a single-blind placebo run-in period of two to four weeks preceded an 8-week double-blind active treatment period. The overall study design is shown in Table 12.

Table 12 Study design

Washout (2 weeks)	Single-blind run-in (2-4 weeks)	Double-blind treatment (8 weeks)					
Visit 0	1	2	3	4	5	6	7*
Week -6 to -4	-4 to -2	0	1	2	4	6	8
		↓ Randomization					
	Placebo	Placebo					
		Valsartan 160 mg OD					
		Valsartan 320 mg OD					
		Amlodipine 10 mg OD					
		Valsartan/Amlodipine 160/10 mg OD					
		Valsartan/Amlodipine 160/5 mg OD			Valsartan/Amlodipine 320/10 mg OD		
*At the end of the 8 week double-blind treatment phase, the first 400 patients to complete all double-blind visits, with no drug-related serious adverse experiences during the trial, were eligible to enroll in a one-year open-label extension.							

(Source: Sponsor's Figure 3-1)

3.1.2.3 Efficacy Measures

(1) Primary Efficacy Endpoint

Changes from baseline to Week 8 in mean sitting diastolic blood pressure (MSDBP).

(2) Secondary Efficacy Endpoints

- Changes from baseline to Week 8 in mean sitting systolic blood pressure (MSSBP)
- Responder rate for achieving mean sitting diastolic blood pressure (MSDBP) < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline
- Control rate for achieving mean sitting diastolic blood pressure (MSDBP) < 90 mmHg

3.1.2.4 Patient Disposition, Demographic and Baseline Characteristics

Tables 13 and 14 describe patient disposition, demographic and baseline characteristics.

Table 13 Demographics by treatment group (ITT)

Treatment Group	N	Age	Sex	Race				
		(yrs) Mean	n (%) Male	Female	n (%) Caucasian	Black	Oriental	Other
Val/Aml 320/10 mg	210	58.0	113 (53.8)	97 (46.2)	163 (77.6)	1 (0.5)	30 (14.3)	16 (7.6)
Val/Aml 160/10 mg	209	56.7	109 (52.2)	100 (47.8)	167 (79.9)	0 (0.0)	28 (13.4)	14 (6.7)
Val 320 mg	208	56.7	108 (51.9)	100 (48.1)	170 (81.7)	0 (0.0)	28 (13.5)	10 (4.8)
Val 160 mg	207	56.8	92 (44.4)	115 (55.6)	163 (78.7)	2 (1.0)	27 (13.0)	15 (7.2)
Aml 10 mg	207	55.4	114 (55.1)	93 (44.9)	164 (79.2)	1 (0.5)	29 (14.0)	13 (6.3)
Placebo	209	58.0	93 (44.5)	116 (55.5)	165 (78.9)	1 (0.5)	29 (13.9)	14 (6.7)
Total	1250	56.9	629 (50.3)	621 (49.7)	992 (79.4)	5 (0.4)	171 (13.7)	82 (6.6)

(Source: Sponsor's Table 7-4)

Table 14 Baseline mean sitting blood pressures and pulse by treatment group (ITT)

Treatment Group	Number of Patients	Mean Sitting Diastolic BP (mmHg) Mean (SD)	Mean Sitting Systolic BP (mmHg) Mean (SD)	Sitting Pulse (bpm) Mean (SD)
Val/Aml 320/10 mg	210	99.2 (3.5)	157.2 (12.0)	74.6 (9.1)
Val/Aml 160/10 mg	209	99.3 (3.6)	157.4 (11.5)	73.9 (9.1)
Val 320 mg	208	99.1 (3.6)	157.5 (11.5)	74.0 (8.9)
Val 160 mg	207	98.9 (3.3)	155.6 (11.3)	73.2 (8.5)
Aml 10 mg	207	98.8 (3.2)	156.2 (12.6)	72.7 (8.5)
Placebo	209	99.0 (3.3)	156.4 (11.5)	73.2 (8.6)
Total	1250	99.1 (3.4)	156.7 (11.7)	73.6 (8.8)

(Source: Sponsor's Table 7-5)

3.1.2.5 Sponsor's Primary Efficacy Results

I. Global assessment of MSDBP

Global assessment of MSDBP reduction at endpoint showed both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment ($p < 0.0001$ for both valsartan and amlodipine shown in Table 15).

Table 15 Summary of ANCOVA Model with Interaction for Changes from Baseline to Week 8 in MSDBP (ITT)

Parameter	DF	Mean square estimate	F-value	P-value
valsartan	2	1771.13	27.16	<0.0001
amlodipine	1	9412.89	144.34	<0.0001
valsartan * amlodipine	2	151.21	2.32	0.0988
Baseline	1	534.20	8.19	0.0043
Region	9	180.14	2.76	0.0033
Model statistics				
Mean square error	1230	65.22		
F-statistic for model			16.1	
P-value for model				<0.0001

(Source: Sponsor's analysis, Table 9.1-1a)

2. Between-treatment comparisons of MSDBP

The between-treatment analysis showed that both combination treatments were statistically significantly superior to their monotherapy components and placebo in MSDBP reduction at endpoint. The results were showed in Table 16.

Table 16 Between-treatment comparisons for change from baseline in MSDBP at endpoint (ITT)

Comparison	LSM difference in change from baseline (SE)	95% CI in LSM difference	p-value
Val/Aml 320/10 mg vs. Val 320 mg	-5.33 (0.79)	(-6.89, -3.78)	<.0001 *
Val/Aml 320/10 mg vs. Aml 10 mg	-3.01 (0.79)	(-4.57, -1.45)	0.0002 *
Val/Aml 320/10 mg vs. Placebo	-9.87 (0.79)	(-11.42, -8.32)	<.0001 *
Val/Aml 160/10 mg vs. Val 160 mg	-4.32 (0.79)	(-5.87, -2.76)	<.0001 *
Val/Aml 160/10 mg vs. Aml 10 mg	-2.01 (0.79)	(-3.57, -0.45)	0.0115 *
Val/Aml 160/10 mg vs. Placebo	-8.87 (0.79)	(-10.42, -7.32)	<.0001 *
Val 320 mg vs. Placebo	-4.53 (0.79)	(-6.08, -2.98)	<.0001 *
Val 160 mg vs. Placebo	-4.55 (0.79)	(-6.10, -3.00)	<.0001 *
Aml 10 mg vs. Placebo	-6.86 (0.79)	(-8.41, -5.30)	<.0001 *

*indicates statistical significance at 0.05 level.

(Source: Sponsor's analysis, Table 9-3)

3.1.2.6 Sponsor's Secondary Efficacy Results

1. Global assessment of MSSBP

Global assessment of MSSBP reduction at endpoint showed both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment ($p < 0.0001$ for both valsartan and amlodipine, see Table 17).

Table 17 Summary of ANCOVA Model with Interaction for Changes from Baseline to Week 8 in MSSBP (ITT)

Parameter	DF	Mean square estimate	F-value	P-value
valsartan	2	4319.81	28.58	<0.0001
amlodipine	1	25832.4	170.88	<0.0001
valsartan * amlodipine	2	364.71	2.41	0.0900
Baseline	1	38411.41	254.09	<0.0001
Region	9	1042.18	6.89	<0.0001
Model statistics				
Mean square error	1230	151.17		
F-statistic for model			34.75	
P-value for model				<0.0001

(Source: Sponsor's analysis, Table 9.1-1b)

2. Between-treatment analysis of MSSBP

The between-treatment analysis showed the combination treatments are statistically significantly superior to their monotherapy components and placebo in MSSBP reduction at endpoint. The results were showed in Table 18.

Table 18 Between-treatment comparisons for change from baseline in MSSBP at endpoint (intent-to-treat population)

Treatment comparison (A vs. B)	LSM difference in change from baseline (SE)	95% CI in LSM difference	p-value +
Val/Aml 320/10 mg vs. Val 320 mg	-8.52 (1.21)	(-10.89, -6.15)	<.0001 *
Val/Aml 320/10 mg vs. Aml 10 mg	-4.25 (1.21)	(-6.63, -1.88)	0.0005 *
Val/Aml 320/10 mg vs. Placebo	-15.49 (1.21)	(-17.85, -13.12)	<.0001 *
Val/Aml 160/10 mg vs. Val 160 mg	-7.62 (1.21)	(-10.00, -5.25)	<.0001 *
Val/Aml 160/10 mg vs. Aml 10 mg	-3.70 (1.21)	(-6.08, -1.33)	0.0022 *
Val/Aml 160/10 mg vs. Placebo	-14.94 (1.21)	(-17.30, -12.57)	<.0001 *
Val 320 mg vs. Placebo	-6.96 (1.21)	(-9.33, -4.59)	<.0001 *
Val 160 mg vs. Placebo	-7.32 (1.21)	(-9.69, -4.94)	<.0001 *
Aml 10 mg vs. Placebo	-11.23 (1.21)	(-13.61, -8.86)	<.0001 *

*indicates statistical significance at 0.05 level.

(Source: Sponsor's analysis, Table 9-10)

3. Responder and control rates

Both combination treatments were statistically significantly superior to their respective valsartan monotherapy component and placebo, but not the amlodipine component, in responder and control rates at endpoint. The results were showed in Table 19.

Table 19 Between-treatment comparisons of responder and control rates at endpoint (ITT)

Comparison	Responder rate p-value	Control rate p-value
[Val/Aml 320/10 mg] vs [Val 320 mg]	0.0001*	<0.0001*
[Val/Aml 320/10 mg] vs [Aml 10 mg]	0.8459	0.2793
[Val/Aml 320/10 mg] vs Placebo	<0.0001*	<0.0001*
[Val/Aml 160/10 mg] vs [Val 160 mg]	0.0004*	0.0074*
[Val/Aml 160/10 mg] vs [Aml 10 mg]	0.6112	0.6565
[Val/Aml 160/10 mg] vs Placebo	<0.0001*	<0.0001*
[Val 320 mg] vs Placebo	<0.0001*	<0.0001*
[Val 160 mg] vs Placebo	<0.0001*	<0.0001*
[Aml 10 mg] vs Placebo	<0.0001*	<0.0001*

(Source: Sponsor's analysis, Table 9-10)

3.1.2.7 Reviewer's Results

Similar to Study 2201, the assessment of additivity of two components suggests that valsartan/amlodipine combinations seem to yield a BP (MSDBP and MSSBP) lowering effect smaller than the sum of the effects of valsartan alone and amlodipine alone (See Tables 20 and 21). The FDA statistical reviewer checked the sponsor's pair-wise comparison results using Holm's procedure to control for type I error rate. The results showed that the two combinations, val/aml 160/10 mg and val/aml 320/10 mg, are more effective than their monotherapy (Tables 22 and 23).

Table 20 Descriptive Assessment of Additivity for MSDBP (ITT)

	Amlodipine dosage	Valsartan dosage	
		160 mg	320 mg
Sum of mean changes for monotherapies (expected change if treatments are additive)	10 mg	-11.26	-11.25
Observed mean change for combinations	10 mg	-8.98	-9.90
Difference (observed minus expected)	10 mg	2.28	1.35

(Source: Reviewer's analysis)

Table 21 Descriptive Assessment of Additivity for MSSBP (ITT)

	Amlodipine dosage	Valsartan dosage	
		160 mg	320 mg
Sum of mean changes for monotherapies (expected change if treatments are additive)	10 mg	-18.23	-18.71
Observed mean change for combinations	10 mg	-15.54	-15.92
Difference (observed minus expected)	10 mg	2.69	2.79

(Source: Reviewer's analysis)

Table 22 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations to Monotherapies for Mean Changes from Baseline to Week 8 for MSDBP (ITT)

Amlodipine dosage		Valsartan dosage	
		160 mg	320 mg
Raw p-values for pair-wise comparisons of combinations to Valsartan	10 mg	<0.0001	<0.0001
Raw p-values for pair-wise comparisons of combinations to Amlodipine	10 mg	0.0115	0.0002
Maximum p-values	10 mg	0.0115	0.0002
Holm-adjusted p-values	10 mg	0.0115	0.0004

(Source: Reviewer's analysis)

Table 23 Multiplicity-Adjusted Results for Pair-wise Comparisons of Combinations to Monotherapies for Mean Changes from Baseline to Week 8 for MSSBP (ITT)

Amlodipine dosage		Valsartan dosage	
		160 mg	320 mg
Raw p-values for pair-wise comparisons of combinations to Valsartan	10 mg	<0.0001	<0.0001
Raw p-values for pair-wise comparisons of combinations to Amlodipine	10 mg	0.0022	0.0005
Maximum p-values	10 mg	0.0022	0.0005
Holm-adjusted p-values	10 mg	0.0022	0.0010

(Source: Reviewer's analysis)

3.1.2.8 Conclusions

The analysis of primary efficacy endpoint shows that both monotherapy treatments contribute to the overall effect in blood pressure reduction of the combination treatment ($p < 0.0001$ for both valsartan and amlodipine). Pair-wise comparisons with adjustment of multiplicity showed that the two combination treatments, val/aml 320/10 mg and val/aml 160/10 mg, were statistically significantly superior to their monotherapy components in MSDBP and MSSBP reduction.

3.1.3 STUDY C: 2305

3.1.3.1 Study Objectives

The primary objective of this study was to assess the blood pressure lowering effects of the combinations of valsartan/amlodipine 160/10 mg or 160/5 mg, in patients with essential hypertension not adequately controlled on valsartan 160 mg monotherapy compared to valsartan 160 mg alone.

3.1.3.2 Study Design

This was a multicenter, randomized, double-blind, active-controlled, parallel-group study in adult patients with essential uncomplicated hypertension. A total of 1136 subjects were enrolled into the study and randomized to three treatment groups. The study consisted a single-blind valsartan run-in period for four weeks and then a double-blind active treatment for 8 weeks (Table 24).

Table 24 Study Design

Phase	Screening	Single-blind	Double-blind		
Period	Washout (1 - 4 weeks)	Valsartan Run-in (4 weeks)	Study drug treatment (8 weeks)		
Visit	1	2	3	4	5
Day	-56 to -28	-28	1	28	56
Week	-8 to -4	-4	1	5	9
			Randomization (1:1:1 ratio)		
			Valsartan 160 mg o.d.		
		Valsartan 160 mg o.d.	Valsartan/amlodipine 160/5 mg o.d.		
			Valsartan/amlodipine 160/10 mg o.d.		

(Source: Sponsor's Figure 3-1)

3.1.3.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary variable was change from baseline to week 8 in mean sitting diastolic blood pressure (MSDBP).

(2) Secondary Efficacy Endpoints

- Changes from baseline to Week 8 in sitting systolic blood pressure, standing diastolic and systolic blood pressures
- Responder rate for achieving MSDBP < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline
- Control rate for achieving MSDBP < 90 mmHg. A controlled patient was defined as a patient with a MSDBP < 90 mmHg.

3.1.3.4 Patient Disposition, Demographic and Baseline Characteristics

Tables 25 and 26 describe patient demographic and baseline characteristics.

Table 25 Demographics by treatment

Demographic Variable	Val/Aml 160/10 mg n (%)	Val/Aml 160/5 mg n (%)	Val 160 mg n (%)	Total n (%)
Number of Patients	317	322	308	947
Age (years)				
Mean (SD)	53.9 (10.8)	55.4 (10.3)	54.5 (9.9)	54.6 (10.4)
Sex				
Male	171 (53.9)	174 (54.0)	172 (55.8)	517 (54.6)
Female	146 (46.1)	148 (46.0)	136 (44.2)	430 (45.4)
Race				
Caucasian	314 (99.1)	320 (99.4)	305 (99.0)	939 (99.2)
Black	2 (0.6)	1 (0.3)	3 (1.0)	6 (0.6)
Oriental	0	1 (0.3)	0	1 (0.1)
Other	1 (0.3)	0	0	1 (0.1)
Unknown	0	0	0	0

(Source: Sponsor's Table 7-4)

Table 26 Baseline mean sitting blood pressures and pulse by treatment group (ITT)

Sitting Blood Pressure and Pulse	Val/Aml 160/10 mg Mean (SD)	Val/Aml 160/5 mg Mean (SD)	Val 160 mg Mean (SD)	Total Mean (SD)
Number of Patients	317	322	308	947
Mean Sitting Diastolic BP (mmHg)	96.5 (4.5)	96.8 (4.5)	96.2 (4.6)	96.5 (4.5)
Mean Sitting Systolic BP (mmHg)	149.1 (13.2)	149.6 (12.1)	149.8 (13.4)	149.5 (12.9)
Sitting Pulse (bpm)	72.8 (8.5)	72.9 (8.4)	72.3 (8.2)	72.7 (8.4)

(Source: Sponsor's Table 7-5)

3.1.3.5 Sponsor's Primary Efficacy Results

Both combination treatment groups were statistically significantly superior to valsartan 160 mg in MSDBP reduction at endpoint ($p < 0.0001$ using Dunnett's adjustment for multiple comparisons). Furthermore, valsartan/amlodipine 160/10 mg was statistically significantly superior to valsartan/amlodipine 160/5 mg in MSDBP reduction at endpoint ($p=0.0006$). Table 27 summarizes the results.

Table 27 Between-treatment comparisons of change from baseline MSDBP (mmHg) at endpoint (ITT)

Comparison	Between-treatment LSM difference (SE)	95% CI	P-value
Dunnett Multiple Comparison			
[Val/Aml 160/10 mg] vs. [Val 160 mg]	-4.78 (0.547)	(-5.99, -3.57)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	-2.93 (0.545)	(-4.13, -1.72)	<0.0001
Pairwise Comparison			
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	-1.85 (0.541)	(-2.91, -0.79)	0.0006

(Source: Sponsor's Table 9-2)

3.1.3.6 Sponsor's Secondary Efficacy Results

(1) Change from baseline in MSSBP at endpoint

Both combination treatment groups were statistically significantly superior to valsartan 160 mg in MSSBP reduction at endpoint ($p < 0.0001$ using Dunnett's adjustment for multiple comparisons). Furthermore, the reduction in MSSBP with valsartan/amlodipine 160/10 mg was also statistically superior ($p=0.0164$), compared to valsartan/amlodipine 160/5 mg. Table 28 summarizes the results.

Table 28 Between-treatment comparisons of change in MSSBP (mmHg) at endpoint (ITT)

Comparison	Between-treatment LSM difference (SE)	95% CI	P-value
Dunnett Multiple Comparison			
[Val/Aml 160/10 mg] vs. [Val 160 mg]	-6.04 (0.885)	(-8.00, -4.08)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	-3.94 (0.880)	(-5.89, -1.99)	<0.0001
Pairwise Comparison			
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	-2.10 (0.875)	(-3.82, -0.39)	0.0164

(Source: Sponsor's Table 9-6)

(2) Responder and control rates

Both combination treatment groups produced a greater percentage of successful responders and patients with controlled MSDBP at endpoint compared to valsartan 160 mg. Tables 29 and 30 summarize the results.

Table 29 Between-treatment comparisons of successful responders at endpoint (ITT)

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Val 160 mg]	3.76	(2.56, 5.52)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	1.74	(1.23, 2.47)	0.0018
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	2.16	(1.47, 3.18)	<0.0001

(Source: Sponsor's Table 9-8)

Table 30 Between-treatment comparisons of patients with controlled MSDBP at endpoint (ITT)

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Val 160 mg]	3.18	(2.20, 4.57)	<0.0001
[Val/Aml 160/5 mg] vs. [Val 160 mg]	1.59	(1.13, 2.24)	0.0074
[Val/Aml 160/10 mg] vs. [Val/Aml 160/5 mg]	1.99	(1.39, 2.86)	0.0002

(Source: Sponsor's Table 9-9)

3.1.3.7 Reviewer's Results

The reviewer verified the sponsor's primary and secondary efficacy analysis and concurs with their conclusion that both combination treatment groups were statistically significantly superior to valsartan 160 mg in MSDBP and MSSBP reduction at endpoint ($p < 0.0001$ using Dunnett's adjustment for multiple comparisons). However, the comparison between the two combinations should be only considered as exploratory since no multiplicity was adjusted.

3.1.3.8 Conclusions

The analysis of primary efficacy endpoint showed that both combination treatment groups were statistically significantly superior to valsartan 160 mg in MSDBP reduction at endpoint.

3.1.4 STUDY D: 2306

3.1.4.1 Study Objectives

The primary objective of this study was to assess the efficacy of the combination of valsartan/amlodipine 160/10 mg in patients with essential hypertension not adequately controlled on amlodipine 10 mg monotherapy compared to amlodipine 10 mg alone.

3.1.4.2 Study Design

This was a multi-center, randomized, double-blind, active controlled parallel group trial. A total of 944 subjects were enrolled into the study and randomized to two treatment groups. The study consisted of a single-blind amlodipine run-in period of two to four weeks preceded an 8-week double-blind active treatment period. The overall study design is shown in Table 31.

Table 31 Study design

Phase	Screening	Single-blind	Double-blind		
Period	Washout	Amlodipine Run-in	Study drug treatment		
Duration	(1 to 4 weeks)	(4 weeks)	(8 weeks)		
Visit	1	2	3	4	5
Day	-56 to -28	-28	1	28	56
Week	-8 to -4	-4	1	5	9
		Amlodipine 10 mg o.d.	Randomization		
			Amlodipine 10 mg o.d.		
			Valsartan/amlodipine 160/10 mg o.d.		

(Source: Sponsor's Figure 3-1)

3.1.4.3 Efficacy Measures

(1) Primary Efficacy Endpoint

The primary variable was change from baseline to Week 8 in MSDBP.

(2) Secondary Efficacy Endpoints

- Change from baseline in MSSBP
- Responder rate for achieving MSDBP < 90 mmHg or a ≥ 10 mmHg decrease compared to baseline
- Control rate for achieving MSDBP < 90mmHg. A controlled patient was defined as a patient with a MSDBP < 90mmHg

3.1.4.4 Patient Disposition, Demographic and Baseline Characteristics

Tables 32 and 33 describe patient demographic and baseline characteristics.

Table 32 Demographics by treatment group (ITT)

Demographic Variable	Val/Aml 160/10 mg n (%)	Aml 10 mg n (%)	Total n (%)
Number of Patients	473	471	944
Age (years)			
Mean (SD)	54.1 (12.0)	54.1 (12.2)	54.1 (12.1)
Sex			
Male	251 (53.1)	253 (53.7)	504 (53.4)
Female	222 (46.9)	218 (46.3)	440 (46.6)
Race			
Caucasian	472 (99.8)	471 (100.0)	943 (99.9)
Black	1 (0.2)	0	1 (0.1)
Oriental	0	0	0
Other	0	0	0
Unknown	0	0	0

(Source: Sponsor's Table 7-4)

Table 33 Baseline mean sitting blood pressures and pulse by treatment group (ITT)

Sitting Blood Pressure and Pulse	Val/Aml 160/10 mg Mean (SD)	Aml 10 mg Mean (SD)	Total Mean (SD)
Number of Patients	473	471	944
Mean Sitting Diastolic BP (mmHg)	94.8 (3.8)	95.3 (4.0)	95.1 (3.9)
Mean Sitting Systolic BP (mmHg)	146.0 (11.2)	147.9 (11.0)	147.0 (11.1)
Sitting Pulse (bpm)	74.2 (8.6)	74.5 (8.6)	74.4 (8.6)

(Source: Sponsor's Table 7-5)

3.1.4.5 Sponsor's Primary Efficacy Results

The analysis shows that the combination of valsartan/amlodipine 160/10 mg produced a statistically superior reduction in MSDBP at endpoint compared to amlodipine 10 mg alone, with a treatment difference of 2.1 mmHg ($p < 0.0001$). See Table 34.

Table 34 Between-treatment comparisons of MSDBP (mmHg) at endpoint (ITT)

Comparison	Between-treatment difference (SE)	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Aml 10 mg]	-2.11 (0.438)	(-2.97, -1.25)	<0.0001

(Source: Sponsor's Table 9-2)

3.1.4.6 Sponsor's Secondary Efficacy Results

(1) Change from baseline to Week 8 in MSSBP

The combination of valsartan/amlodipine 160/10 mg produced a statistically superior reduction in MSSBP compared to amlodipine 10 mg alone with a treatment difference of 2.9 mmHg ($p < 0.0001$). See Table 35.

Table 35 Between-treatment comparisons of MSSBP (mmHg) at endpoint (ITT)

Comparison	Between-treatment difference (SE)	95% CI	P-value
Val/Aml 160/10 mg vs. Aml 10 mg	-2.87 (0.665)	(-4.17, -1.56)	<0.0001

(Source: Sponsor's Table 9-5)

(2) Responder and control rates

The combination treatment of valsartan/amlodipine 160/10 mg was statistically superior to treatment with amlodipine 10 mg monotherapy in the responder rate and control rate at endpoint. Tables 36 and 37 summarize the results.

Table 36 Between-treatment comparisons of successful responders at endpoint (ITT)

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Aml 10 mg]	1.66	(1.22, 2.24)	0.0011

(Source: Sponsor's Table 9-8)

Table 37 Between-treatment comparison of patients with controlled MSDBP at endpoint (ITT)

Comparison	Odds Ratio	95% CI	P-value
[Val/Aml 160/10 mg] vs. [Aml 10 mg]	1.83	(1.36, 2.46)	< 0.0001

(Source: Sponsor's Table 9-10)

3.1.4.7 Reviewer's Results

The reviewer has verified the sponsor's primary and secondary efficacy analysis and concurs with their conclusion that the combination treatment group was statistically

significantly superior to amlodipine 10 mg in MSDBP and MSSBP reduction at endpoint ($p < 0.0001$).

3.1.4.8 Conclusion

The analysis showed that the combination treatment group of valsartan/amlodipine 160/10 mg is superior to amlodipine 10 mg in lowering MSDBP.

3.2 Evaluation of Safety

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

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

Subgroup analysis of change from baseline to Week 8 in MSDBP by age, gender and race was conducted. It is noticed that the drug shows better effect for all the doses and dose combinations in non-black population compared to black population in Study 2201. Tables 38-43 summarize the results.

Table 38 Study 2201 Subgroup Analysis of Primary Endpoint (ITT)

MSDBP	Amlodipine (mg)	Valsartan (mg)				
		0	320	160	80	40
Age (years) Mean (n) <65	0	-6.3 (108)	-12.1 (100)	-10.5 (108)	-9.1 (108)	-10.0 (104)
	5	-10.5 (104)	-16.0 (100)	-13.8 (102)	-14.0 (104)	-14.0 (104)
	2.5	-8.5 (106)	-13.6 (96)	-12.9 (97)	-12.8 (106)	-9.9 (103)
≥65	0	-7.0 (19)	-17.1 (28)	-13.1 (19)	-12.7 (15)	-9.4 (23)
	5	-13.8 (24)	-14.9 (26)	-14.7 (32)	-15.7 (19)	-16.9 (19)
	2.5	-12.2 (20)	-14.7 (32)	-13.5 (28)	-14.6 (23)	-13.3 (25)
Sex Mean (n) Male	0	-6.6 (70)	-13.0 (67)	-10.4 (69)	-8.9 (56)	-9.1 (72)
	5	-9.9 (68)	-16.1 (70)	-12.3 (58)	-13.1 (56)	-9.9 (76)
	2.5	-7.0 (66)	-14.1 (74)	-11.3 (67)	-12.0 (78)	-9.9 (76)
Female	0	-6.2 (57)	-13.3 (61)	-11.4 (58)	-10.0 (67)	-10.9 (55)
	5	-12.4 (60)	-15.2 (56)	-15.4 (69)	-15.2 (70)	-15.0 (52)
	2.5	-11.5 (60)	-13.6 (54)	-15.0 (58)	-14.8 (51)	-11.5 (52)
Race Mean (n) Non-Black	0	-7.0 (115)	-14.0 (112)	-11.3 (118)	-10.1 (105)	-10.2 (111)
	5	-11.3 (118)	-15.6 (117)	-14.1 (115)	-14.6 (111)	-14.8 (112)
	2.5	-9.4 (107)	-14.1 (115)	-13.0 (115)	-13.5 (112)	-10.8 (118)
Black	0	-1.2 (12)	-7.7 (16)	-5.4 (9)	-6.1 (18)	-6.1 (18)
	5	-8.6 (10)	-17.9 (9)	-12.9 (12)	-11.3 (15)	-10.7 (11)
	2.5	-7.6 (19)	-12.4 (13)	-13.4 (10)	-10.5 (17)	-7.7 (10)

(Source: Sponsor's analysis, Tables 9-5, 9-6, 9-7)

Table 39 Study 2307 Subgroup Analysis of Primary Endpoint (ITT)

MSDBP	Amlodipine (mg)	0	320	160
Age (years)				
Mean (n)	0	-8.9 (147)	-11.8 (151)	-11.5 (143)
	10	-14.7 (155)	-18.1 (138)	-17.8 (154)
<65				
	0	-6.6 (62)	-15.4 (56)	-15.6 (64)
	10	-15.9 (51)	-18.2 (70)	-15.7 (55)
≥65				
Sex				
Mean (n)	0	-6.9 (93)	-11.9 (108)	-11.6 (92)
	10	-14.4 (114)	-17.7 (112)	-17.4 (109)
Male				
	0	-9.3 (116)	-13.7 (99)	-13.7 (115)
	10	-15.7 (92)	-18.7 (96)	-17.0 (100)
Female				
Race				
Mean (n)	0	-8.2 (165)	-12.6 (169)	-12.6 (163)
	10	-14.4 (164)	-17.3 (162)	-16.1 (167)
Caucasian				
	0	+7.3 (1)	--	-12.4 (2)
	10	-24.6 (1)	-6.4 (1)	--
Black				
	0	-8.9 (29)	-13.8 (28)	-13.2 (27)
	10	-18.1 (28)	-21.5 (29)	-21.6 (28)
Oriental				
	0	-8.5 (14)	-12.9 (10)	-14.0 (15)
	10	-15.3 (13)	-18.3 (16)	-22.0 (14)
Other				

(Source: Sponsor's analysis, Tables 9-5, 9-6, 9-7)

Table 40 Study 2305 Change from baseline MSDBP at endpoint by treatment group and age Group (ITT)

Treatment Group	<65 years		≥ 65 years	
	N	Mean change from baseline in MSDBP (± SD)	N	Mean change from baseline in MSDBP (± SD)
Val/Aml 160/10 mg	269	-11.0 ± 6.7	47	-13.8 ± 6.5
Val/Aml 160/5 mg	261	-9.4 ± 7.4	61	-10.6 ± 8.1
Val 160 mg	264	-6.7 ± 7.3	44	-6.0 ± 8.2

(Source: Sponsor's analysis, Table 9-3)

Table 41 Study 2305 Change from baseline MSDBP at endpoint by treatment group and sex (ITT)

Treatment Group	Male		Female	
	N	Mean change from baseline in MSDBP (± SD)	N	Mean change from baseline in MSDBP (± SD)
Val/Aml 160/10 mg	170	-11.0 ± 6.9	146	-11.8 ± 6.6
Val/Aml 160/5 mg	174	-9.2 ± 7.4	148	-10.1 ± 7.7
Val 160 mg	172	-5.8 ± 7.5	136	-7.5 ± 7.2

(Source: Sponsor's analysis, Table 9-4)

Table 42 Study 2306 Change from baseline MSDBP at endpoint by treatment group and age Group (ITT)

Treatment Group	<65 years		≥ 65 years	
	N ¹	Mean change from baseline in MSDBP (± SD)	N ¹	Mean change from baseline in MSDBP (± SD)
Val/Aml 160/10 mg	378	-11.7 ± 7.9	94	-12.0 ± 8.2
Aml 10 mg	375	-10.1 ± 8.3	93	-9.6 ± 7.2

(Source: Sponsor’s analysis, Table 9-3)

Table 43 Study 2306 Change from baseline MSDBP at endpoint by treatment group and sex (ITT)

Treatment Group	Male		Female	
	N ¹	Mean change from baseline in MSDBP (± SD)	N ¹	Mean change from baseline in MSDBP (± SD)
Val/Aml 160/10 mg	250	-11.3 ± 7.8	222	-12.4 ± 8.1
Aml 10 mg	252	-9.3 ± 8.4	216	-10.8 ± 7.7

(Source: Sponsor’s analysis, Table 9-4)

5. SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

In each combination drug study, controlling type I error rate in comparing multiple dose combinations with their respective monotherapy components is the key issue needing to be of concern. The FDA’s statistical reviewer used sensible multiplicity adjustment method to check and verify the sponsor’s analysis results. Both results seem to be consistent and support that both valsartan and amlodipine contribute to the overall effect in blood pressure reduction of the combination. The combinations identified to be more effective than their components in the reduction of both diastolic and systolic blood pressure from the four studies (see Table 44) are: val/aml 40/5 mg, val/aml 80/2.5 mg, val/aml 80/5 mg, val/aml 160/5 mg, val/aml 160/10 mg, val/aml 320/5 mg, val/aml 320/10 mg.

Table 44 Effective combinations identified from the study

Amlodipine	Valsartan			
	40	80	160	320
2.5		S2201		
5	S2201	S2201	S2201, S2305*	S2201
10			S2307, S2305*, S2306*	S2307

* The combination was only compared to one monotherapy

5.2 Conclusions and Recommendations

Studies have demonstrated that both valsartan and amlodipine contribute to the overall effect in blood pressure reduction of the combination. The combinations identified to be more effective than their components in the reduction of both diastolic and systolic blood

pressure from the four studies are: val/aml 40/5 mg, val/aml 80/2.5 mg, val/aml 80/5 mg, val/aml 160/5 mg, val/aml 160/10 mg, val/aml 320/5 mg, val/aml 320/10 mg.

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