CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

22-107

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 #:	22107
DRUG NAME:	Aliskiren (150 mg and 300 mg)
INDICATION:	Mild to moderate essential hypertension
APPLICANT:	Novartis
DATE OF RECEIPT:	March 19, 2007
REVIEW PRIORITY:	Standard
BIOMETRICS DIVISION:	Division of Biometrics I
STATISTICAL REVIEWER:	Steve Bai, Ph.D. (HFD-710)
SECONDARY REVIEWER:	James Hung, Ph.D. (HFD-710)
MEDICAL DIVISION:	Division of Cardio-Renal Drug Product (HFD-110)
CLINICAL TEAM:	Xiao Shen, M.D. (HFD-110)
PROJECT MANAGER:	Nguyen Quynh (HFD-110)

KEY WORDS: Aliskiren, Hypertension,

Table of Contents

List of Tables

List of Figures

1 EXECUTIVE SUMMARY

1.1 Conclusions and Recommendations

Based on Study SPP100A-2204, the one-daily oral treatment with Aliskiren in dose of 300 mg lowers blood pressure more effectively than placebo in patients with essential hypertension over 8-week treatment period. In addition, the combinations of Aliskiren and HCTZ in 150/25 mg, 300/12.5 mg and 300/25 mg doses were also found to be significantly superior to the component monotherapies in reducing msDBP. This reviewer concurred with the sponsor's findings which are: a) at least one Aliskiren monotherapy dose was superior to placebo in reducing msDBP and b) at least one combination was significantly superior overall to both component monotherapies in reducing msDBP.

1.2 Brief Overview of Clinical Studies

The study SPP100A-2204 was a randomized, double-blinded, placebo and active-controlled, multifactorial, multicenter, parallel-group study of Aliskiren monotherapy compared to placebo and combination therapy of Aliskiren with HCTZ compared to the component to the component monotherapies in patients with uncomplicated essential hypertension. The study enrolled 3190 patients in 19 countries who were randomized to 15 double-blind study treatments, i.e. Aliskiren or HCTZ each at three different doses, Aliskiren/HCTZ at eight different dose combinations or placebo. The primary efficacy assessment was the office measurement of cuff blood pressure at trough, i.e. change from baseline (visit 3) in msDBP.

This study has the following two primary objectives: 1. Confirm the efficacy of Aliskiren 75 mg, 150 mg and 300 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from Baseline to study end when compared to placebo. 2. Demonstrate the efficacy of the combination of Aliskiren and HCTZ 75/6.25 mg, 75/12.5 mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from Baseline to study end when compared to the component monotherapies.

1.3 Statistical Issues and Findings

The efficacy analyses were based upon the intent-to-treat population, which included all randomized patients who had a baseline and at least one post baseline efficacy measurement. There are two separate primary objectives for this study. For the development of Aliskiren monotherapy alone, the primary efficacy assessment is the effects of the Aliskiren doses compared to placebo. For the development of the Aliskiren plus HCTZ combination, the primary efficacy assessment is the overall effect of the combination treatment compared to both Aliskiren and HCTZ monotherapy treatments. To assess the efficacy of the Aliskiren plus HCTZ combination, the Aliskiren monotherapy also needs to demonstrate efficacy over placebo. No statistical adjustments were needed for these two assessments for the two developments in the same study. That is, the overall 0.05 significant level was used for each assessment.

Sponsor concluded Aliskiren monotherapy resulted in a statistically significant reduction in msSBP, with significant pairwise comparisons showing that the 150 mg and 300 mg doses were superior to placebo. Furthermore, these treatment effects achieved statistical significance in favor of the combinations over both monotherapies for Aliskiren/HCTZ 75/6.25, 75/25, 150/25, and all combinations with Aliskiren 300 mg. However, the sponsor did not plan multiplicity adjustments between the two objectives. The reviewer applied number of known multiplicity procedures and concluded the following statistically significant differences among the following pairs of treatments: Aliskiren 300 to placebo, Aliskiren 150/HCTZ 25 mg, Aliskiren 300/HCTZ 12.5 mg, and Aliskiren 300/HCTZ 25 mg to their each respective monotherapies.

In all studies, secondary analyses including change from baseline in msSBP, percent responder, percent control, and etc. were provided to support the primary analysis. No adjustments were made for multiple comparisons for these numerous secondary analyses and therefore, the analyses of the secondary endpoints cannot be interpreted statistically.

2 INTRODUCTION

2.1 Overview

Study SPP100A 2204 was an 8-week, double-blind, multicenter, randomized, multifactorial, placebo-controlled, parallel-group study to evaluate the efficacy and safety of Aliskiren administered alone and in combination with hydrochlorothiazide in patients with essential hypertension. The study enrolled 3190 patients in 19 countries who were randomized to 15 double-blind study treatments, i.e. Aliskiren or HCTZ each at three different doses, Aliskiren/HCTZ at eight different dose combinations or placebo. The primary efficacy assessment was the office measurement of cuff blood pressure at trough, i.e. change from baseline (visit 3) in msDBP. The mean age of the randomized population was 54.6 years (SD = 11.63 years). Across the treatment groups, 78.9% of patients were younger than 65 years of age, while only 3.6% were 75 years or older. In the randomized population, the vast majority of patients were Caucasian (85.4%). Patients were randomized equally to each of the treatment arms.

There are two separate primary objectives for this study, the assessments of the efficacy of Aliskiren monotherapy and the combination treatment. No statistical adjustments were planned for these two assessments for the two developments in the same study. That is, the overall 0.05 significant level was used for each assessment. However, Dunnett's procedure was used to adjust for the multiple comparisons of the Aliskiren doses versus placebo within the monotherapy assessment. For a given combination dose, the null hypotheses tested were that the combination dose was at most as good as one of its respective monotherapy doses versus that the combination was better than each monotherapy. The statistical test for each of the pairwise comparisons was made at a two-sided significance level of 0.05. Ninety-five percent confidence intervals were provided to quantify add-on effects for combination doses.

2.2 Data Sources

The sponsor's SAS datasets were stored in the directory of \\Cdsesub1\nonectd\N22107\N_000\2007-03-19\crt\datasets\2204\derived of the center's electronic document room.

3 STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

The study description in this section is based on the sponsor's study report, any discrepancy between the study report and the study protocol will be discussed in the section of statistical reviewer's findings and comments.

3.1.1 STUDY OBJECTIVES OF 2204

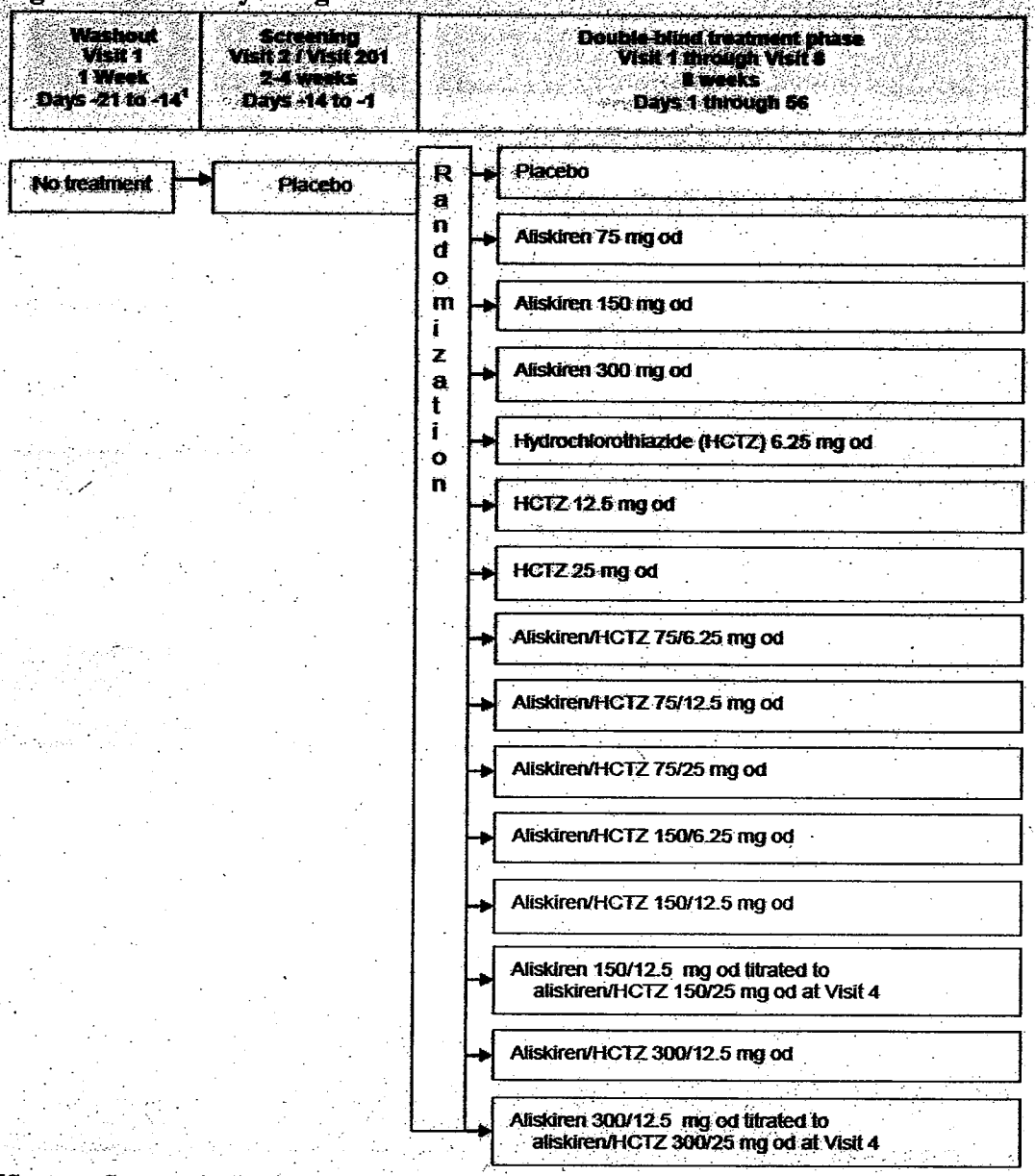
The primary objectives of this study were to:

- Confirm the efficacy of Aliskiren 75 mg, 150 mg and 300 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from Baseline to study end when compared to placebo.
- Demonstrate the efficacy of the combination of Aliskiren and HCTZ 75/6.25 mg, 75/12.5 mg, 75/25 mg, 150/6.25 mg, 150/12.5 mg, 150/25 mg, 300/12.5 mg and 300/25 mg in patients with essential hypertension by testing the hypothesis of superior reduction in msDBP from Baseline to study end when compared to the component monotherapies.

3.1.2 STUDY DESIGN

This study was a randomized, double-blind, placebo- and active-controlled, multi-factorial, multicenter, parallel-group study of Aliskiren monotherapy compared to placebo, and combination therapy of Aliskiren with HCTZ compared to the component monotherapies in patients with uncomplicated essential hypertension (msDBP $\geq$ 95 mm Hg and $<$ 110 mm Hg). The study consisted of three periods: Washout period, Single blinded screening period, and Double-blind treatment period, see Figure 1 for details of the study design.

Figure 1 Study Design



[Source: Sponsor's Study Report Figure 3-1]

3.1.3 Efficacy Measures

The primary efficacy assessment was the office measurement of cuff blood pressure at trough. The mean blood pressure was defined as the average of available readings of blood pressure from one visit.

- Primary efficacy variable: Change from Baseline (Visit 3) in msDBP.
- Secondary efficacy variables: Change from Baseline in msSBP.

- Other efficacy variables: Percent responder (msDBP < 90 mm Hg and/or at least 10 mm Hg reduction from Baseline), percent controlled (msDBP < 90 mm Hg and msSBP < 140 mm Hg); change from Baseline in standing diastolic and standing systolic BP.

3.1.4 STATISTICAL ANALYSIS PLAN

There are two separate primary objectives for this study. The primary efficacy assessments are the effects of the Aliskiren doses compared to placebo and the overall effect of the combination treatment compared to both Aliskiren and HCTZ monotherapy treatments. To assess the efficacy of the Aliskiren plus HCTZ combination, the Aliskiren monotherapy also needs to demonstrate efficacy over placebo. No statistical adjustments were needed for these two assessments for the two developments in the same study. That is, the overall 0.05 significant level was used for each assessment. The two-way analysis of covariance model with treatment and region as two factors, and the Baseline as a covariate using all 15 treatment groups, was performed for both the Aliskiren monotherapy and Aliskiren combination analyses.

To maintain an overall two-sided significance level at 5% for the statistical test, Dunnett's procedure was used to adjust for the multiple comparisons of the Aliskiren doses versus placebo. This test was primary for the assessment of Aliskiren monotherapy versus placebo; Aliskiren monotherapy treatment was considered superior to placebo (e.g., at least one of Aliskiren dose was better than placebo) if this test was statistically significant.

The test for each term (i.e., Aliskiren and HCTZ) was performed at a two-sided significance level of 0.05. These were considered primary to assess the overall contribution of the two monotherapy components. The pattern of the interaction was further examined using least-squares means. If a critical negative interaction is observed, the AVE test by Hung (2000) was planned to assess the overall assessment of combinations versus their respective monotherapies. Otherwise, it was considered that both monotherapy treatments contribute to the effect for the combination treatment if both tests for Aliskiren and HCTZ terms were statistically significant.

This global assessment for the contribution of both monotherapy treatments across all the doses was considered primary. If both monotherapy treatments demonstrated a statistically significant contribution to the overall effect of the combination treatment, it indicated that the overall efficacy of the combination treatment was significantly better than both monotherapy treatments.

If the overall assessment was positive, the following analysis was used to quantify the add-on effects for a given combination dose due to the respective monotherapy doses. The primary efficacy variable at Endpoint was analyzed using a two-way ANCOVA model with treatment and region (randomization strata) as two factors, and the Baseline as a covariate. All pairwise treatment comparisons were made based on this model. No inference was made for the pairwise comparisons between the combination dose and its respective monotherapy dose if the global test was not statistically significant. The statistical test for each of the pairwise comparisons was made at a two-sided significance level of 0.05.

3.1.5 PATIENT DISPOSITION, DEMOGRAPHIC AND BASELINE CHARACTERISTICS

A total of 3190 patients enrolled in the single-blind, placebo run-in period: 2763 (86.6%) patients completed and 427 (13.4%) discontinued this period. A total of 2776 single-blind patients were randomized into the double-blind period: 2762 of the 2763 completed, single-blind patients, and 14 patients randomized in error. All 2776 patients were included in the Randomized population; however, the 14 patients with erroneous randomization were not treated, and did not provide any post-Baseline, double-blind study data. Overall, 92.1% of the randomized patients completed the double-blind treatment period. The total discontinuation rate was 7.3%, and was highest in the placebo group (11.3%). The most common reasons for discontinuation in the Randomized population were AE (2.3%) and unsatisfactory therapeutic effect (2.0%). Patient disposition is shown Table 1.

Table 1 Patient disposition for each treatment group during the double-blind period

	Disposition			Population		
Dose group (mg)	Rand*	Complete†	Discontinue†	ITT†	PP†	SAF†
Total	2776	2558 (92.1)	204 (7.3)	2752 (99.1)	2398 (86.4)	2762 (99.5)
Monotherapy						
Placebo	195	171 (87.7)	22 (11.3)	192 (98.5)	160 (82.1)	193 (99.0)
Aliskiren 75	184	169 (91.8)	15 (8.2)	183 (99.5)	157 (85.3)	184 (100)
Aliskiren 150	185	169 (91.4)	16 (8.6)	183 (98.9)	158 (85.4)	185 (100)
Aliskiren 300	183	164 (89.6)	17 (9.3)	180 (98.4)	152 (83.1)	181 (98.9)
HCTZ 6.25	194	181 (93.3)	13 (6.7)	194 (100)	166 (85.6)	194 (100)
HCTZ 12.5	188	178 (94.7)	10 (5.3)	188 (100)	173 (92.0)	188 (100)
HCTZ 25	176	159 (90.3)	14 (8.0)	173 (98.3)	146 (83.0)	173 (98.3)
Combination therapy						
Aliskiren 75/HCTZ 6.25	188	179 (95.2)	9 (4.8)	187 (99.5)	170 (90.4)	188 (100)
Aliskiren 75/HCTZ 12.5	193	175 (90.7)	15 (7.8)	189 (97.9)	166 (86.0)	190 (98.4)
Aliskiren 75/HCTZ 25	186	173 (93.0)	13 (7.0)	186 (100)	160 (86.0)	186 (100)
Aliskiren 150/HCTZ 6.25	176	157 (89.2)	17 (9.7)	173 (98.3)	146 (83.0)	174 (98.9)
Aliskiren 150/HCTZ 12.5	186	177 (95.2)	7 (3.8)	184 (98.9)	167 (89.8)	184 (98.9)
Aliskiren 150/HCTZ 25	188	170 (90.4)	18 (9.6)	187 (99.5)	159 (84.6)	188 (100)
Aliskiren 300/HCTZ 12.5	181	170 (93.9)	11 (6.1)	180 (99.4)	159 (87.8)	181 (100)
Aliskiren 300/HCTZ 25	173	166 (96.0)	7 (4.0)	173 (100)	159 (91.9)	173 (100)

[Source: Sponsor's study report Table 7-1]

Baseline demographic and background characteristics for all randomized patients are summarized in Table 2. The treatment groups were generally comparable with respect to the demographics and Baseline characteristics, and reflected the intended target population. The mean age of the randomized population was 54.6 years (SD = 11.63 years), while the median age was 55.0 years. Across the treatment groups, 78.9% of patients were younger than 65 years of age, while only 3.6% were 75 years or older. In the randomized population, a slightly more than half the patients were male (54.8%). The vast majority of patients were Caucasian (85.4%).

Baseline summary statistics for average of the three sitting and three standing blood pressures at Visit 3 are summarized in Table 3. The randomized study population had an msDBP of 99.2 mm Hg (SD = 3.57 mm Hg) and an msSBP of 153.6 mm Hg (SD=12.17 mm Hg). The total

randomized population had a mean standing DBP of 99.7 mm Hg (SD=5.81 mm Hg) and a mean standing SBP of 153.1 mm Hg (SD=13.50 mm Hg).

Table 2 Patient background characteristics by treatment group

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 183	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 176
Sex-n (%)	Male	109 (55.9)	103 (56.0)	112 (60.5)	99 (54.1)	109 (56.2)	103 (54.8)	92 (52.3)
	Female	86 (44.1)	81 (44.0)	73 (39.5)	84 (45.9)	85 (43.8)	85 (45.2)	84 (47.7)
Age (years)	n	195	184	185	183	194	188	176
	Mean (SD)	54.4 (11.80)	55.0 (11.81)	53.5 (12.34)	54.2 (12.19)	55.2 (12.77)	55.4 (11.99)	55.1 (11.98)
Age group –n (%)	< 65	157 (80.5)	138 (75.0)	150 (81.1)	144 (78.7)	140 (72.2)	138 (73.4)	139 (79.0)
	≥ 65	38 (19.5)	46 (25.0)	35 (18.9)	39 (21.3)	54 (27.8)	50 (26.6)	37 (21.0)
	≥ 75	10 (5.1)	5 (2.7)	8 (4.3)	10 (5.5)	9 (4.6)	7 (3.7)	6 (3.4)
Hypertension duration (years)	n	187	178	178	177	187	183	170
	Mean (SD)	7.1 (7.24)	7.9 (7.37)	7.3 (7.36)	7.7 (7.23)	7.4 (7.23)	7.9 (8.20)	8.4 (8.58)
Treatment-naive † –n (%)		8 (4.1)	6 (3.3)	7 (3.8)	6 (3.3)	7 (3.6)	5 (2.7)	6 (3.4)

	Combination therapy	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 193	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 176	ALI150 / HCTZ12.5 N = 186	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2776
Sex-n (%)	Male	108 (57.4)	101 (52.3)	101 (54.3)	96 (54.5)	98 (52.7)	104 (55.3)	89 (49.2)	98 (56.6)	1522 (54.8)
	Female	80 (42.6)	92 (47.7)	85 (45.7)	80 (45.5)	88 (47.3)	84 (44.7)	92 (50.8)	75 (43.4)	1254 (45.2)
Age (years)	n	188	193	186	176	186	188	181	173	2776
	Mean (SD)	55.1 (10.63)	54.4 (10.11)	54.7 (12.17)	53.9 (11.12)	54.7 (11.35)	53.7 (11.58)	55.5 (11.67)	54.8 (10.86)	54.6 (11.63)
Age group –n (%)	< 65	153 (81.4)	166 (86.0)	147 (79.0)	148 (84.1)	148 (79.6)	151 (80.3)	133 (73.5)	138 (79.8)	2190 (78.9)
	≥ 65	35 (18.6)	27 (14.0)	39 (21.0)	28 (15.9)	38 (20.4)	37 (19.7)	48 (26.5)	35 (20.2)	586 (21.1)
	≥ 75	6 (3.2)	3 (1.6)	9 (4.8)	5 (2.8)	6 (3.2)	7 (3.7)	6 (3.3)	2 (1.2)	99 (3.6)
Hypertension duration (years)	n	182	192	183	171	181	185	174	167	2695
	Mean (SD)	6.5 (5.84)	7.8 (8.19)	8.3 (7.43)	7.0 (6.55)	7.8 (7.59)	7.4 (7.10)	7.9 (7.76)	8.4 (7.37)	7.6 (7.43)
Treatment-naive † –n (%)		6 (3.2)	1 (0.5)	3 (1.6)	5 (2.8)	5 (2.7)	3 (1.6)	7 (3.9)	6 (3.5)	81 (2.9)

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 183	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 176
Race–n (%)	Caucasian	164 (84.1)	153 (83.2)	157 (84.9)	155 (84.7)	161 (83.0)	160 (85.1)	155 (88.1)
	Black	7 (3.6)	9 (4.9)	11 (5.9)	7 (3.8)	13 (6.7)	9 (4.8)	9 (5.1)
	Asian	5 (2.6)	6 (3.3)	4 (2.2)	3 (1.6)	5 (2.6)	3 (1.6)	4 (2.3)
	Nat. American	3 (1.5)	4 (2.2)	3 (1.6)	5 (2.7)	6 (3.1)	4 (2.1)	2 (1.1)
	Pacific Islander	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)	1 (0.5)	1 (0.5)	0 (0.0)
	Other	16 (8.2)	11 (6.0)	9 (4.9)	13 (7.1)	8 (4.1)	11 (5.9)	6 (3.4)
Ethnicity–n (%)	Hispanic/Latin	55 (28.2)	47 (25.5)	55 (29.7)	55 (30.1)	54 (27.8)	50 (26.6)	45 (25.6)
	Chinese	5 (2.6)	5 (2.7)	4 (2.2)	3 (1.6)	2 (1.0)	3 (1.6)	3 (1.7)
	Indian-subcon.	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Japanese	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)
	Other	135 (69.2)	131 (71.2)	126 (68.1)	125 (68.3)	136 (70.1)	135 (71.8)	128 (72.7)

	Combination therapy	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 193	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 176	ALI150 / HCTZ12.5 N = 186	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2776
Race–n (%)	Caucasian	165 (87.8)	165 (85.5)	165 (88.7)	149 (84.7)	158 (84.9)	163 (86.7)	153 (84.5)	149 (86.1)	2372 (85.4)
	Black	5 (2.7)	12 (6.2)	5 (2.7)	8 (4.5)	10 (5.4)	5 (2.7)	10 (5.5)	7 (4.0)	127 (4.6)
	Asian	7 (3.7)	4 (2.1)	4 (2.2)	5 (2.8)	5 (2.7)	4 (2.1)	5 (2.8)	5 (2.9)	69 (2.5)
	Nat. American	3 (1.6)	3 (1.6)	3 (1.6)	4 (2.3)	3 (1.6)	3 (1.6)	3 (1.7)	1 (0.6)	50 (1.8)
	Pacific Islander	1 (0.5)	1 (0.5)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)	7 (0.3)
	Other	7 (3.7)	8 (4.1)	9 (4.8)	10 (5.7)	10 (5.4)	12 (6.4)	10 (5.5)	11 (6.4)	151 (5.4)
Ethnicity–n (%)	Hispanic/Latin	46 (24.5)	45 (23.3)	53 (28.5)	55 (31.3)	52 (28.0)	50 (26.6)	50 (27.6)	49 (28.3)	761 (27.4)
	Chinese	4 (2.1)	4 (2.1)	4 (2.2)	4 (2.3)	4 (2.2)	4 (2.1)	4 (2.2)	3 (1.7)	56 (2.0)
	Indian-subcon.	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	3 (0.1)
	Japanese	2 (1.1)	0 (0.0)	0 (0.0)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.6)	5 (0.2)
	Other	136 (72.3)	144 (74.6)	129 (69.4)	116 (65.9)	130 (69.9)	134 (71.3)	127 (70.2)	119 (68.8)	1951 (70.3)

[Source: Sponsor's study report Table 7-3]

Table 3 Summary of Baseline values for mean sitting diastolic and systolic blood pressure

	Monotherapy	Placebo N = 195	ALI75 N = 184	ALI150 N = 185	ALI300 N = 182	HCTZ6.25 N = 194	HCTZ12.5 N = 188	HCTZ25 N = 174
msDBP (mm Hg)	n	195	184	185	182	194	188	174
	Mean (SD)	99.3 (3.68)	99.4 (3.79)	99.8 (3.03)	99.3 (3.25)	99.3 (3.56)	99.1 (3.45)	99.1 (3.37)
	Median	98.7	98.5	98.0	98.7	98.7	98.7	98.7
	Minimum	90.0	90.7	93.3	88.0	92.7	93.3	86.7
	Maximum	109.3	109.3	109.3	109.3	109.3	109.0	109.3
msSBP (mm Hg)	n	195	184	185	182	194	188	174
	Mean (SD)	152.7 (11.61)	153.2 (12.66)	153.4 (12.64)	154.4 (10.88)	153.4 (12.64)	153.4 (11.60)	154.5 (12.11)
	Median	151.3	153.3	152.0	153.3	153.2	153.0	155.5
	Minimum	123.3	126.7	120.7	129.3	123.3	116.0	118.3
	Maximum	180.7	177.3	178.7	178.7	179.0	178.7	179.3

	Combination therapy	ALI75 / HCTZ6.25 N = 188	ALI75 / HCTZ12.5 N = 193	ALI75 / HCTZ25 N = 186	ALI150 / HCTZ6.25 N = 176	ALI150 / HCTZ12.5 N = 186	ALI150 / HCTZ25 N = 188	ALI300 / HCTZ12.5 N = 181	ALI300 / HCTZ25 N = 173	Total N =2776
msDBP (mm Hg)	n	188	192	186	175	185	188	181	173	2770
	Mean (SD)	98.9 (3.55)	100.0 (3.76)	99.0 (3.70)	99.0 (3.75)	99.1 (3.48)	98.4 (3.97)	99.5 (3.64)	99.3 (3.35)	99.2 (3.57)
	Median	98.5	99.3	98.2	98.3	98.3	98.0	98.7	98.7	98.7
	Minimum	84.0	93.3	88.7	82.7	92.7	76.7	92.0	91.7	76.7
	Maximum	108.7	110.7	109.7	108.7	109.3	109.3	109.3	109.3	110.7
msSBP (mm Hg)	n	188	192	186	175	185	188	181	173	2770
	Mean (SD)	154.5 (12.05)	154.0 (12.34)	152.9 (12.66)	153.3 (12.16)	154.1 (12.58)	153.2 (12.41)	153.2 (11.58)	154.6 (12.66)	153.6 (12.17)
	Median	153.3	154.7	153.3	152.0	154.7	153.3	153.3	155.0	153.3
	Minimum	129.3	118.7	128.0	120.0	122.0	110.0	118.7	129.3	110.0
	Maximum	179.3	178.7	178.7	179.3	197.7	176.0	177.3	178.3	197.7

[Source: Sponsor's study report Table 7-4]

3.1.6 SPONSOR'S PRIMARY EFFICACY RESULTS

The primary efficacy variable was the change from Baseline in msDBP at Endpoint.

Aliskiren monotherapy: Aliskiren monotherapy was more effective than placebo in reducing msDBP at Endpoint ($p = 0.0002$ based on the overall test using Dunnett's multiple comparisons procedure). The least squares mean (LSM) reductions in msDBP at Endpoint for placebo, Aliskiren 75, 150, and 300 mg were 6.93, 8.68, 8.94, and 10.26 mm Hg, respectively. Pairwise comparisons found that all 3 doses of Aliskiren were statistically superior to placebo based on the nominal p-values. However, the adjusted p-values using the Dunnett's procedure found that the 150 mg and 300 mg doses were significantly superior to placebo, but the 75 mg dose was not ($p = 0.0890$).

Combination therapy: The overall test showed that both Aliskiren and HCTZ had statistically significant contributions to the reductions in msDBP from Baseline at Endpoint ($p < 0.0001$), see Table 4.

Table 4 ANCOVA in overall effect for change from baseline msDBP at endpoint

Analysis of variance

Source	DF	Sum of Square	Mean Square	F	P-value
Aliskiren	3	4751.9521	1583.9840	24.3	<.0001*
HCTZ	3	4699.7127	1566.5709	24.1	<.0001*
Baseline	1	30.1389	30.1389	0.46	0.4963
Error	2744	178615.735	65.0932		
Corrected Total	2751	189385.337			

[Source: Sponsor's study report]

Most individual combination doses were statistically superior to their component monotherapies (exceptions: aliskiren/HCTZ 150/6.25 mg to both components; Aliskiren/HCTZ 75/12.5 mg to HCTZ 12.5 mg), see Table 5.

Table 5 Change from Baseline in mean sitting diastolic blood pressure at endpoint

Treatment		Least square mean difference in change from Baseline (standard error)	Nominal p-value
Aliskiren 75 mg	vs. placebo	-1.75 (0.83)	0.0344*
Aliskiren 150 mg	vs. placebo	-2.01 (0.83)	0.0152*
Aliskiren 300 mg	vs. placebo	-3.33 (0.83)	<0.0001*
Aliskiren 75 mg/HCTZ 6.25 mg	vs. aliskiren 75 mg	-2.08 (0.83)	0.0126*
	vs. HCTZ 6.25 mg	-1.69 (0.82)	0.0394*
Aliskiren 75 mg/HCTZ 12.5 mg	vs. aliskiren 75 mg	-2.46 (0.83)	0.0031*
	vs. HCTZ 12.5 mg	-1.03 (0.83)	0.2124
Aliskiren 75 mg/HCTZ 25 mg	vs. aliskiren 75 mg	-2.77 (0.83)	0.0009*
	vs. HCTZ 25 mg	-2.09 (0.85)	0.0136*
Aliskiren 150 mg/HCTZ 6.25 mg	vs. aliskiren 150 mg	-1.41 (0.85)	0.0962
	vs. HCTZ 6.25 mg	-1.29 (0.84)	0.1249
Aliskiren 150 mg/HCTZ 12.5 mg	vs. aliskiren 150 mg	-2.96 (0.84)	0.0004*
	vs. HCTZ 12.5 mg	1.79 (0.83)	0.0314*
Aliskiren 150 mg/HCTZ 25 mg	vs. aliskiren 150 mg	-3.70 (0.83)	<0.0001*
	vs. HCTZ 25 mg	-3.28 (0.85)	0.0001*
Aliskiren 300 mg/HCTZ 12.5 mg	vs. aliskiren 300 mg	-3.61 (0.84)	<0.0001*
	vs. HCTZ 12.5 mg	-3.76 (0.84)	<0.0001*
Aliskiren 300 mg/HCTZ 25 mg	vs. aliskiren 300 mg	-4.00 (0.85)	<0.0001*
	vs. HCTZ 25 mg	-4.90 (0.86)	<0.0001*

[Source: Sponsor's study report Table 9-1]

3.1.7 Reviewer's Analysis

This study had two objectives regarding to the efficacies of Aliskiren monotherapy and Combination therapy. However, the sponsor did not plan multiplicity adjustments between the two objectives. Furthermore, Dunnett's multiple comparisons procedure was only used to compare the monotherapies with placebo. There were no any types of multiplicity adjustments procedure planned when compare the combination therapies to their respective monotherapies. Hence, any individual combination does which were statistically superior to their component monotherapies need to be further examined.

There are 8 combination doses and 3 monotherapies are included in the current submission. Hence, there should be total 19 pairwise comparisons need to tested. However, in order to show if a combination is more effective than its' two monotherapy components, we only need to show that the larger p-value of each pair of p-values obtained from comparing each combination with its components was used. This decision was justified because a combination was considered better than its components only if both p-values from comparing the combination to its components were both statistically significant, and if the larger of the 2 p-values was smaller than the significance level, the smaller p-value was also smaller than the significance level as well. Therefore, it was justified to select the larger p-value from the pair and use the resulting 8 p-values plus 3 p-values based on monotherapies vs. placebo to go through a multiple comparison procedure rather than using all 19 p-values. There are number of different

adjustment methods can be used in this study, such as Holm, Hochberg, Hommel and even Bonferroni. These adjustment methods all produced same four significant comparisons, which are Aliskiren 300 to placebo, Aliskiren 150/HCTZ 25 mg, Aliskiren 300/HCTZ 12.5 mg, and Aliskiren 300/HCTZ 25 mg to their each respective monotherapies.

Table 6 Adjusted P-values based on Holm's method

	Aliskiren vs. Placebo			Aliskiren /HCTZ Combinations vs. Components							
	75	150	300	75 /6.25	75 /12.5	75 /25	150 /6.25	150 /12.5	150 /25	300 /12.5	300 /25
Nominal P-values	.0344	.0152	.0001	.0394	.2124	.0136	.1249	.0314	.0001	.0001	.0001
Adjusted P-values	.1570	.0952	[redacted]	.157	.2498	.0952	.2498	.157	[redacted]	[redacted]	[redacted]

[Source: FDA reviewer's analysis]

In spite of these minor discrepancies, this reviewer still concurs with the sponsor's findings which are: a) at least one Aliskiren monotherapy dose was superior to placebo in reducing msDBP and b) at least one combination was significantly superior overall to both component monotherapies in reducing msDBP.

3.2 Evaluation of Safety

Please read Dr. Xiao's review for safety assessment.

4 FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Age, Gender and Ethnic group

The results for the primary endpoint, MSDBP, in subgroups defined by age, sex, and race are listed in the following tables.

Table 7 Mean change from baseline in MSDBP by age

	<65 years		>=65 years	
Treatment group	N	Raw mean	N	Raw mean
Aliskiren/HCTZ 300/25 mg	138	-14.39	35	-14.15
Aliskiren/HCTZ 300/12.5 mg	133	-14.24	47	-13.15
Aliskiren/HCTZ 150/25 mg	150	-12.56	37	-13.65
Aliskiren 300 mg	142	-10.90	38	-8.65
Aliskiren 150 mg	148	-9.10	35	-9.23
HCTZ 25 mg	137	-8.88	36	-11.47
HCTZ 12.5 mg	138	-9.88	50	-10.95

[Source: FDA analysis]

Table 8 Mean change from baseline in trough MSDBP by sex

Treatment group	Males		Females	
	N	Raw mean	N	Raw mean
Aliskiren/HCTZ 300/25 mg	98	-13.19	75	-15.84
Aliskiren/HCTZ 300/12.5 mg	89	-13.21	91	-14.69
Aliskiren/HCTZ 150/25 mg	104	-12.16	83	-13.55
Aliskiren 300 mg	99	-9.07	81	-12.07
Aliskiren 150 mg	111	-8.24	72	-10.49
HCTZ 25 mg	90	-8.43	83	-10.50
HCTZ 12.5 mg	103	-8.95	85	-11.64

[Source: FDA analysis]

Table 9 Mean change from baseline in trough MSDBP by race

Treatment Group	Caucasian		Black		Oriental		Other	
	N	Raw mean	N	Raw mean	N	Raw mean	N	Raw mean
Aliskiren/HCTZ 300/25 mg	149	-13.89	7	-10.57	5	-20.00	12	-19.75
Aliskiren/HCTZ 300/12.5 mg	152	-13.78	10	-15.33	5	-13.60	13	-15.02
Aliskiren/HCTZ 150/25 mg	162	-13.06	5	-9.33	4	-14.83	16	-10.40
Aliskiren 300 mg	154	-10.23	6	-7.77	3	-12.22	17	-12.75
Aliskiren 150 mg	155	-9.12	11	-6.60	4	-7.75	13	-11.74
HCTZ 25 mg	153	-9.44	9	-5.59	4	-14.75	7	-10.86
HCTZ 12.5 mg	160	-10.16	9	-9.04	3	-9.55	16	-10.98

[Source: FDA analysis]

Numerically, the three subgroup analyses for the differences between each of three significant combination doses with their corresponding monotherapies appear to be consisting with the primary efficacy analysis findings.

4.2 Other Subgroup Populations

No other subgroups were analyzed.

5 SUMMARY AND CONCLUSIONS

5.1 Statistical Issues and Collective Evidence

The primary objectives of that at least one Aliskiren monotherapy dose was superior to placebo in reducing mean sitting diastolic pressure (msDBP) at endpoint and at least one pair of monotherapy treatments (Aliskiren and HCTZ) contribute to the overall effect in blood pressure reduction of the combination treatment were both shown to be statistically significant.

The sponsor's pre-specified Dunnett's procedure found that the 150 mg and 300 mg doses were significantly superior to placebo in reducing msDBP. The overall test comparing the combination of Aliskiren and HCTZ with the component monotherapies found that both monotherapies contributed significantly to the msDBP reductions of the combination (p-values < 0.0001). Furthermore, the treatment effects achieved statistical significance in favor of the combinations over both monotherapies for Aliskiren/HCTZ 75/6.25, 75/25, 150/25, and all combinations with Aliskiren 300 mg based on pairwise analyses. However, there were no pre-specified multiplicity adjustments for the pairwise comparisons within and between each of the two primary objectives. The reviewer applied number of known adjustment methods and produced four significant comparisons, which are Aliskiren 300 to placebo, Aliskiren 150/HCTZ 25 mg, Aliskiren 300/HCTZ 12.5 mg, and Aliskiren 300/HCTZ 25 mg to their each respective monotherapies.

5.2 Conclusions and Recommendations

The results of this study show that once-daily oral treatment with Aliskiren lowers blood pressure (msDBP) more effectively than placebo in patients with essential hypertension. Dose of 300 mg was significantly superior to placebo in reducing msDBP. Combinations of Aliskiren and HCTZ were found to be significantly superior to the component monotherapies in reducing msDBP.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Steven Bai
10/4/2007 01:50:45 PM
BIOMETRICS

James Hung
10/4/2007 02:45:59 PM
BIOMETRICS