CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-532

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
(Addendum)

NDA #: 21-532

SERIAL #: N000

DRUG NAME: Benicar HCT (omelsartan/HCTZ)

INDICATION: Hypertension

SPONSOR: Sankyo Pharma Development

DOCUMENT REVIEWED:

1. Study report in 866-318.PDF (CDER REC'D Date: August 5, 2002)
2. SAS database in EDR

STATISTICAL REVIEWER: H.M. James Hung, Ph.D. (HFD-710)

MEDICAL REVIEWER: Salma Koessel, M.D. (HFD-110)

PROJECT MANAGER: Edward Fromm (HFD-110)

STATISTICAL KEY WORDS: AVE test, Additive, Response surface, ANOVA, LOCF, Least square mean

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JHung/301-594-5436/DB1/CS-866_HCTZ1.doc/5-28-2003

Figure 2 (on page 7) of my review dated 1/31/03 should be titled "Response surface of mean sitting SBP reduction from baseline", that is, it is for SBP, not for DBP. The response surface of mean sitting DBP reduction from baseline is in the following figure (Figure 2a). This change does not affect any conclusion.

Figure 2a. Response surface of mean sitting DBP reduction from baseline

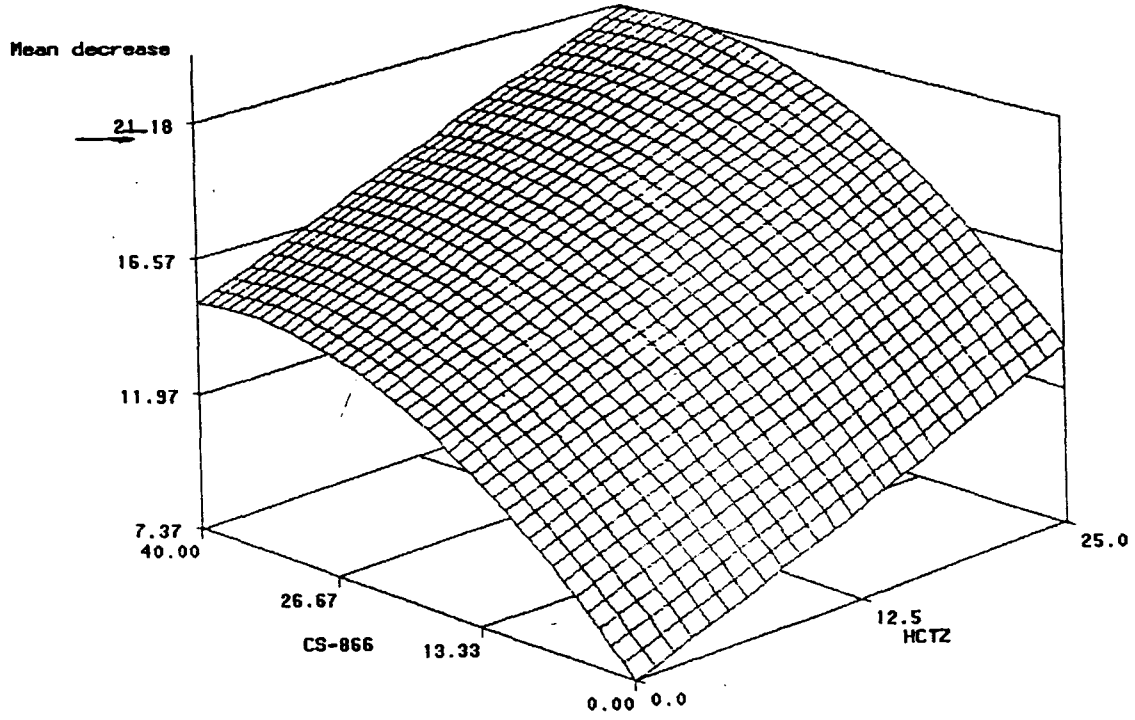

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TABLE OF CONTENTS

1. SUMMARY

All six non-zero dose combinations (i.e., CS-866 10 mg/HCTZ 12.5 mg, CS-866 10 mg/HCTZ 25 mg, CS-866 20 mg/HCTZ 12.5 mg, CS-866 20 mg/HCTZ 25 mg, CS-866 40 mg/HCTZ 12.5 mg, CS-866 40 mg/HCTZ 25 mg) are more effective than placebo (p-value < 0.0001 for each) on sitting DBP reduction.

For sitting DBP reduction, the effect of each of the six non-zero dose combination appears to be (at least numerically) greater than the sum of its component effects and hence statistically significantly greater than its component effects (ANOVA gives p-value < 0.0001 for each, AVE test gives a p-value < 0.0001).

Response surface analysis suggests that the reduction of sitting DBP significantly ($p < 0.0001$) increases as the dose of HCTZ increases or the dose of CS-866 increases. The increase in sitting DBP reduction seems to start leveling off at some point in the study dose range of CS-866, as the data suggest a curvature in the response surface with a significant quadratic term ($p = 0.0033$) of CS-866 dose.

Similar conclusions can be drawn for reduction of other blood pressures.

2. INTRODUCTION

This review pertains to the multi-level factorial design study 866-318 the sponsor submitted for evaluating the effectiveness of the combination of olmesartan and hydrochlorothiazide (HCTZ).

3. OVERVIEW OF STUDY 866-318

Study 866-318 is a 48-sites, randomized, placebo-controlled, parallel-group, factorial-design study to assess the efficacy and the safety of CS-866 (olmesartan) in combination with HCTZ in patients with essential hypertension.

After a 4-week placebo run-in period, eligible patients were assigned randomly to 1 of the 12 treatment groups (dose of CS-866/HCTZ in mg): 0/0 (placebo), 0/12.5, 0/25, 10/0, 10/12.5, 10/25, 20/0, 20/12.5, 20/25, 40/0, 40/12.5, and 40/25. The qualification criteria were: (1) daily average sitting DBP ≥ 100 mm Hg and ≤ 115 mm Hg at both the Week 3 and Week 4 placebo run-in visits, (2) a difference of ≤ 7 mm Hg between the daily average sitting DBP at the Week 3 and Week 4 placebo run-in visits, (3) at least 4 full intervening calendar days between the Week 3 and Week 4 placebo run-in visits, and (4) at lest 80% compliance with the study drug regimen during the placebo run-in period. Patients were instructed to take their daily dose of study medication in the morning at breakfast time except on the day of a study visit. On a visit day, the blood pressures were to be obtained before 12:00 noon and within 20 to 28 hours after the previous dose of study medication. Patients were to take study medication after all blood pressures measurements were recorded and all applicable tests were performed. Evaluation for

efficacy was performed on Day 1, at Weeks 1, 4, and 8. No antihypertensive medication other than the study medication was permitted during the placebo run-in period or double-blind period.

The primary efficacy variable was the mean change from baseline in sitting DBP at Week 8. Secondary efficacy variables were the mean change from baseline in sitting SBP at Week 8 and the mean change from baseline in standing DBP and SBP at Week 8. LOCF was used to impute the missing Week 8 measurement. Baseline blood pressure (DBP and SBP) is defined as the average of the sitting blood pressure values at Weeks 3 and 4 of the placebo run-in period.

3.1. Statistical Analysis Plan

The following criteria for efficacy were defined: (1) to determine whether at least one dose combination is more effective than its component doses for sitting DBP at Week 8, (2) to evaluate which combinations are more effective in reducing blood pressure compared to the respective placebo treatments, and (3) to determine the responder rate. A responder was defined as a patient whose mean sitting DBP at one of the double blind visits (Weeks 1, 4, or 8) was < 90 mm Hg or the decrease in mean sitting DBP from baseline was ≥10 mm Hg.
The first step of the efficacy evaluation was use of the AVE test (Hung et al, 1993, Biometrics) to test whether at least one dose combination is more effective than the respective component doses. Once the AVE test reaches significance, the next step was to find dose combinations with better therapeutic effect.

Response surface method with a quadratic regression model was to be used to obtain dose-response information. Nonsignificant regression coefficient terms were to be deleted from the full model to obtain a reduced model. Regression diagnostic procedures to identify influential measurements and residual plotting to identify poorly fitted observations were to be performed to ascertain that the inference based on the final model was appropriate. The final response surface derived from the quadratic model was to be estimated. The response difference between combined doses and the maximum of the respective component and the placebo-placebo combination was to be computed. Confidence surface approach of Hung (1992, Statistics in Medicine) was to be used to compute a lower bound of difference to indicate effective dose combinations and those more effective components.

The sample size was approximately 40 patients per dose combination group to ensure that the power of the AVE test against the following alternative is about 95%.

		CS-866			
		0	10	20	40
HCTZ	0	0.0	5.5	6.0	7.0
	12.5	3.0	8.5	9.0	10.0
	25	5.0	10.5	11.0	12.0

Thus, the sample size planing is based on the assumption that the effects of the two drugs are additive in any dose combination.

3.2. Sponsor's Efficacy Results

Of the 863 patients screened, 502 patients were randomized and 500 comprised the ITT population defined as those patients who were randomized to double-blind treatment, received at least one dose of double-blind study medication and had at least one post baseline cuff blood pressure measurement. There appeared to be no imbalance in any of the baseline or demographic characteristics between treatment groups in the ITT population. The absence of the two patients from the ITT population had essentially no effect on any of the demographic or baseline variables.

Table 1. Baseline mean sitting DBP ± sd (in mm Hg)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	103±3	104±4	103±2	103±2
	12.5mg	103±3	104±4	103±3	104±3
	25 mg	104±4	104±3	104±3	103±3

Table 2. Mean change from baseline in sitting DBP ± se (in mm Hg) at Week 8 LOCF, followed by sample size

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-7.7±1.2; 42	-13.1±1.3; 39	-12.7±1.3; 41	-14.4±1.3; 45
	12.5mg	-9.1±1.2; 45	-15.3±1.4; 35	-15.4±1.4; 42	-18.0±1.5; 42
	25 mg	-12.9±1.3; 43	-18.4±1.2; 38	-18.9±1.1; 46	-21.9±1.5; 39

The AVE test yielded a p-value < 0.01, confirming that at least one dose combination was more effective than its components. The Week 8 sitting DBP without imputing missing data with LOCF gave a similar result.

Response surface analysis indicated that as the dose of CS-866 and HCTZ increased there was a progressive increase in the magnitude of sitting DBP reduction. Using the response surface, based on the lack of overlap of the 95% confidence intervals, each of the three CS-866/HCTZ combinations containing 25 mg HCTZ was statistically significantly more effective than its respective components. The 20 mg CS-866/12.5 mg HCTZ and 40 mg CS-866/12.5 mg HCTZ combinations were statistically significantly more effective than the HCTZ but not the CS-866 component. Each of the six CS-866/HCTZ non-zero dose combination was statistically significantly more effective than placebo. Statistically significant differences were observed at the higher doses of HCTZ and CS-866 monotherapies as compared to placebo, but not at the lowest dose of HCTZ (12.5 mg) or CS-866 (10 mg).

Without imputing missing data by LOCF, the Week 8 mean changes from baseline in sitting DBP were numerically very similar to the Week 8 LOCF mean changes from baseline.

4. REVIEWER'S EVALUATION

4.1. Sitting DBP – primary efficacy endpoint

The sponsor's results in Table 2 are confirmed by the reviewer's analyses and the mean decreases from baseline in sitting DBP are displayed in Figure 1 (on next page). All six non-zero dose combinations were more effective than placebo (each $p < 0.0001$).

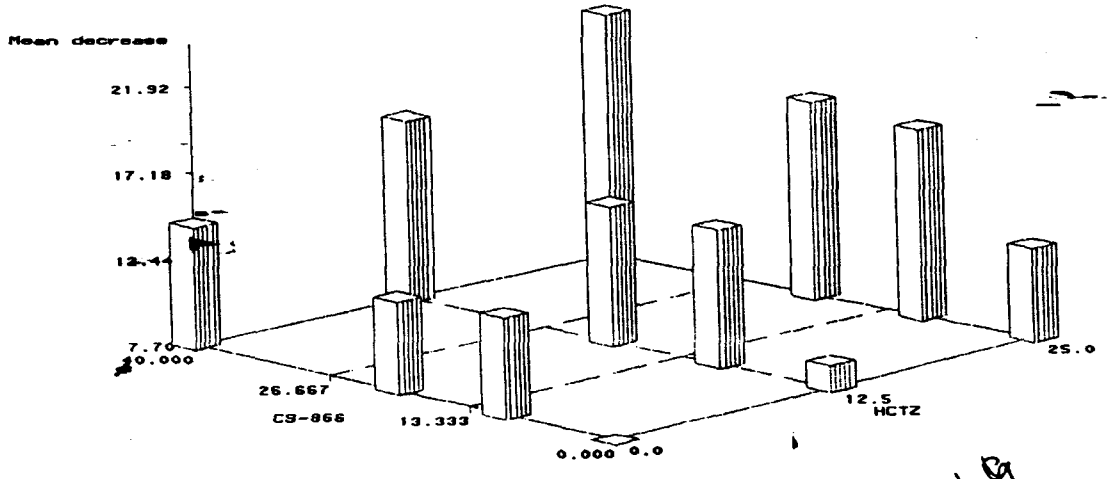
Ordinarily, factorial design was used if the effects of the two drugs were expected to be additive, that is, the effects of the dose combinations are the sum of their respective component effects. To check if the expectation holds, the potential interaction of CS-866 and HCTZ is estimated at each non-zero dose combination as shown in Table 3.

Table 3. Level of potential interaction of CS-866 and HCTZ on sitting DBP

		CS-866		
		10 mg	20 mg	40 mg
HCTZ	12.5mg	0.8	1.3	2.2
	25 mg	0.1	1.0	2.3

The degree of interaction at each non-zero dose combination is estimated as placebo-subtracted effect of the non-zero dose combination minus the sum of the placebo-subtracted effects of the components. For instance, the potential interaction of CS-866 10 mg and HCTZ 12.5 mg is calculated as (15.3 – 7.7) – (13.1-7.7) – (9.1-7.7) = 0.8 mm Hg. Table 3 suggests that the effect of each non-zero dose combination of CS-866 and HCTZ is numerically greater than the sum of its component effects, indicating better than additivity. This is often referred to as 'superadditivity'. The degree of superadditivity seems to increase as the dose of CS-866 increases, though there was no evidence of statistically significant superadditivity ($p = 0.97$).

Figure 1. Mean decrease from baseline in sitting DBP

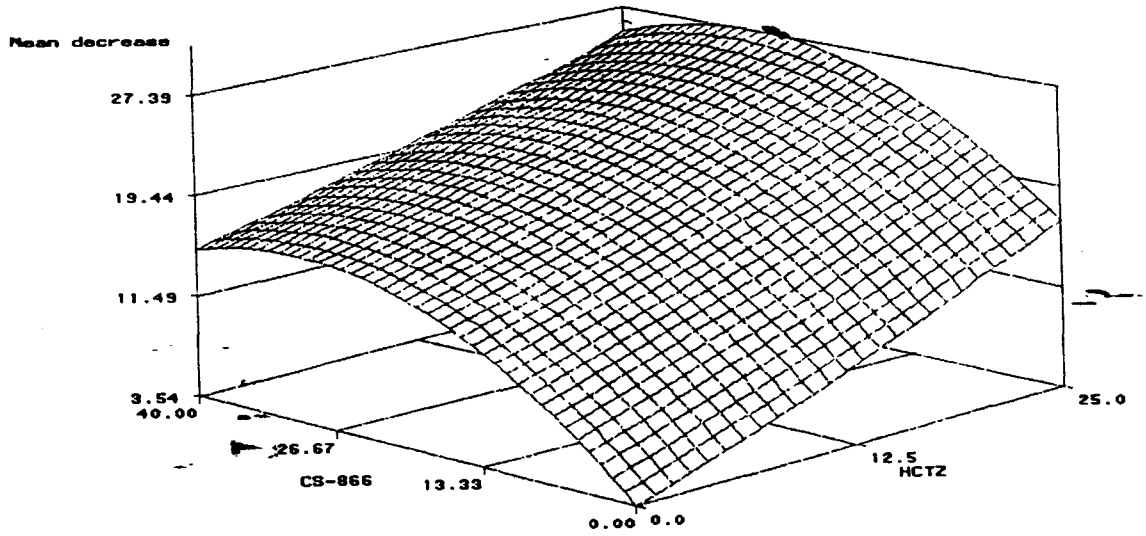


The sponsor performed the AVE test of Hung et al (1993, Biometrics) that deals with equal cell sample size cases. Because of unequal cell sample sizes, the AVE test of Hung (2000, Statistics in Medicine, page 2079-2087) should be used. This test gives a $p < 0.0001$, indicating that some non-zero dose combinations are more effective than their respective components.

The superadditivity at each non-zero dose combination also makes the classical ANOVA using the additive model slightly underestimate the effect of each non-zero dose combination relative to its components, particularly in the two non-zero dose combinations containing CS-866 40 mg. Nonetheless, the classical ANOVA leads me to conclude that on sitting DBP reduction the combination therapy of CS-866 and HCTZ is more effective than CS-866 monotherapy and HCTZ monotherapy at each of the dose combinations ($p < 0.0001$ for CS-866/HCTZ compared to CS-866 alone and HCTZ alone).

Response surface analysis suggests that the reduction of sitting DBP significantly ($p < 0.0001$) increases as the dose of HCTZ increases or the dose of CS-866 increases. In addition, the increase in sitting DBP reduction seems to start leveling off at some point in the study dose range of CS-866, as the data suggest a curvature in the response surface with a significant quadratic term ($p = 0.0033$) of CS-866 dose. The response surface of mean sitting DBP decrease from baseline is displayed in Figure 2.

Figure 2. Response Surface of mean sitting DBP reduction from baseline



4.2. Secondary efficacy endpoints

The results of sitting SBP, standing DBP and SBP are summarized in the following tables. Numerically, all six non-zero dose combinations had a greater reduction than their respective components and than placebo.

Table 4. Mean change from baseline in sitting SBP ± se (in mm Hg) at Week 8 LOCF, followed by sample size

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-3.4±1.9; 42	-10.4±1.8; 39	-15.2±2.5; 41	-16.4±2.1; 45
	12.5mg	-8.2±2.1; 45	-20.3±2.2; 35	-20.4±2.6; 42	-19.4±2.6; 42
	25 mg	-17.6±2.0; 43	-22.9±2.3; 38	-25.7±1.9; 46	-27.9±2.5; 39

Table 5. Mean change from baseline in standing DBP ± se (in mm Hg) at Week 8 LOCF, followed by sample size

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-6.3±1.3; 42	-10.0±1.1; 39	-11.0±1.3; 41	-12.6±1.2; 45
	12.5mg	-8.6±1.2; 45	-13.2±1.4; 35	-15.8±1.3; 42	-15.6±1.6; 42
	25 mg	-9.6±1.2; 43	-16.6±1.0; 38	-15.8±1.1; 46	-20.3±1.6; 39

Table 6. Mean change from baseline in standing SBP ± se (in mm Hg) at Week 8 LOCF, followed by sample size

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-4.8±1.6; 42	-11.9±1.7; 39	-11.8±2.2; 41	-16.4±2.1; 45
	12.5mg	-9.7±2.1; 45	-19.6±2.5; 35	-20.4±2.7; 42	-18.9±2.4; 42
	25 mg	-14.7±2.1; 43	-21.5±2.2; 38	-24.4±2.1; 46	-29.0±2.3; 39

The magnitude of potential interaction of the two drugs at each of the six nonzero dose combinations is estimated in Tables 7-9. For standing DBP, the effect of each of the six dose combinations was numerically greater than the sum of the respective component effects. The same conclusion as for sitting DBP applied to standing DBP. The AVE test gave a $p < 0.0001$. The response surface for the standing DBP reduction was similar to that for sitting DBP.

For sitting SBP, there appeared to be a pattern of negative interactions seen at four non-zero dose combinations as shown in Table 7; that is, the effect of each of these four dose combinations was numerically less than the sum of the component effects. However, such apparent negative interactions did not show a systematic pattern in standing SBP. The AVE test gave a $p < 0.0001$ for SBPs. The surfaces for the reductions of SBPs were also similar to that for sitting DBP.

Table 7. Level of potential interaction of CS-866 and HCTZ on sitting SBP

		CS-866		
		10 mg	20 mg	40 mg
HCTZ	12.5mg	5.1	0.4	-1.8
	25 mg	-1.7	-3.7	-2.7

Table 8. Level of potential interaction of CS-866 and HCTZ on standing DBP

		CS-866		
		10 mg	20 mg	40 mg
HCTZ	12.5mg	0.9	2.5	0.7
	25 mg	3.3	1.5	4.4

Table 9. Level of potential interaction of CS-866 and HCTZ on standing SBP

		CS-866		
		10 mg	20 mg	40 mg
HCTZ	12.5mg	2.8	3.7	-2.4
	25 mg	-0.3	2.7	2.7

4.3. Subgroup results

As summarized in Tables 10-15, the results of the age, gender and race subgroups are generally consistent with those of the overall study results, except the subgroups of age ≥ 65 years, blacks, Hispanics that were small.

Table 10. Mean change from baseline in sitting DBP (in mm Hg) at Week 8 LOCF (males/females)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-8/ -7	-12/-15	-13/-13	-14/-15
	12.5mg	-6/-12	-16/-15	-16/-15	-17/-19
	25 mg	-11/-15	-19/-18	-17/-21	-22/-22

Table 11. Mean change from baseline in sitting DBP (in mm Hg) at Week 8 LOCF (< 65 yrs / ≥65 yrs)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-8/ -8	-12/-24	-13/-14	-14/-14
	12.5mg	-9/ -9	-16/-14	-16/-10	-18/-19
	25 mg	-12/-18	-18/-19	-19/-19	-22/-22

Table 12. Mean change from baseline in sitting DBP (in mm Hg) at Week 8 LOCF (whites/blacks/hispanics)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-8/ 0/-12	-14/ -6/-15	-13/-10/-14	-14/ -9/-18
	12.5mg	-9/-14/-10	-16/ -8/-15	-15/-17/-13	-21/ -6/-14
	25 mg	-12/-12/-16	-18/-17/-24	-18/-24/-16	-23/-19/-13

asians and others are not included because of no data in some of the cells

Table 13. Mean change from baseline in sitting SBP (in mm Hg) at Week 8 LOCF (males/females)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-4/ -3	-13/-7	-17/-13	-14/-20
	12.5mg	-6/-11	-21/-19	-19/-23	-17/-22
	25 mg	-14/-21	-21/-25	-25/-26	-27/-29

Table 14. Mean change from baseline in sitting SBP (in mm Hg) at Week 8 LOCF (< 65 yrs / ≥65 yrs)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-4/ -1	-10/-16	-14/-20	-16/-19
	12.5mg	-9/ -7	-21/-19	-22/-10	-20/-17
	25 mg	-17/-18	-23/-19	-24/-32	-29/-20

Table 15. Mean change from baseline in sitting SBP (in mm Hg) at Week 8 LOCF (whites/blacks/hispanics)

		CS-866			
		0 mg	10 mg	20 mg	40 mg
HCTZ	0 mg	-2/ -5/-15	-11/ -11/-9	-18/ -6/-10	-16/-17/-16
	12.5mg	-7/-23/-7	-20/-23/-21	-19/ -9/-30	-23/ -5/-11
	25 mg	-14/-23/-21	-22/-21/-36	-26/-26/-29	-29/-21/-22

asians and others are not included because of no data in some of the cells

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5. CONCLUSIONS

All six non-zero dose combinations (i.e., CS-866 10 mg/HCTZ 12.5 mg, CS-866 10 mg/HCTZ 25 mg, CS-866 20 mg/HCTZ 12.5 mg, CS-866 20 mg/HCTZ 25 mg, CS-866 40 mg/HCTZ 12.5 mg, CS-866 40 mg/HCTZ 25 mg) are more effective than placebo (p-value < 0.0001 for each) on sitting DBP reduction.

The effect of each of the six non-zero dose combination appears to be greater than the sum of its component effects and hence greater than its component effects (ANOVA gives p-value < 0.0001 for each, AVE test gives a p-value < 0.0001) on sitting DBP reduction.

Response surface analysis suggests that the reduction of sitting DBP significantly ($p < 0.0001$) increases as the dose of HCTZ increases or the dose of CS-866 increases. The increase in sitting DBP reduction seems to start leveling off at some point in the study dose range of CS-866, as the data suggest a curvature in the response surface with a significant quadratic term ($p = 0.0033$) of CS-866 dose.

Similar conclusions can be drawn for reduction of other blood pressures.

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