CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 20-818

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

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Applicant: Ciba-Geigy Corporation
Name of Drug: Diovan HCT (Valsartan /HCTZ)
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1. INTRODUCTION

This review discusses the results of study 301, which was a multi-center, randomized, double-blind, placebo controlled, multifactorial, parallel trial comparing the combination therapy of valsartan/HCTZ (Val/HCTZ), to placebo and its component monotherapies, valsartan and HCTZ. After a two to four weeks of placebo run-in/washout of concomitant antihypertensive medications period, patients were randomized into one of 9 treatment groups for an 8-week double-blind treatment period. The treatment groups were placebo, valsartan 80, valsartan 160 mg, HCTZ 12.5 mg, HCTZ 25 mg and their combinations with valsartan doses.

The primary efficacy variable is the change from baseline in sitting diastolic blood pressure (SiDBP).

2. REVIEWER'S COMMENTS

2.1. Efficacy Assessment

This reviewer has checked the sponsor's results , using the submitted data, by conducting the ANOVA model described in the protocol. Based on the sponsor's results, this reviewer has constructed Tables 1 and 2 to summarize the results of this study for the sitting diastolic (SiDBP) and systolic BP (SiSBP), respectively.

To test for the significance of effect of at least one combination (out of the four combinations that were studied) versus its components, this reviewer has applied a test due to Hung , Chi, and Lipicky (**Biometrics** , 1993), using the sponsor's results for the primary endpoint. The result of this test showed a **p-value<0.0001**. Therefore, at least one of the combinations is effective.

The sponsor stated that the significance level does not need adjustment and on the basis of the results of the primary endpoint shown in Table 1 below one would declare that all combinations of valsartan 80 and 160 mg with HCTZ 12.5 and 25 mg have resulted in significant reductions in SiDBP compared to that of placebo and both of their components ($p \leq 0.0099$). However, the sponsor did not provide a convincing reason for not adjusting the level of significance and, since multiple testing are being carried out, this reviewer definitely believes that there should be an adjustment for this level, as described below.

Table 1 Results of the pairwise comparisons for the SiDBP. Each cell contains baseline value, number of randomized patients (in parenthesis), least square mean of change from baseline , p-value for the comparison versus placebo. p-value for the comparison versus the HCTZ component (bold), and p-value for the comparison versus the valsartan component(underlined).

	Placebo	Vals 80 mg	Vals 160 mg
Placebo	101.5(93) -4.12	101.5(99) -8.63 0.001	101.5(97) -9.42 0.001
HCTZ 12.5 mg	101.1(99) -7.16 0.0133	101.0(96) -11.83 0.001 **0.001** 0.0099	100.9(96) -13.51 0.001 **0.001** 0.001
HCTZ 25 mg	100.8(100) -9.28 0.001	100.4(91) -15.28 0.001 **0.001** 0.001	101.4(94) -15.31 0.001 **0.001** 0.001

Table 2 Results of the pairwise comparisons for the SiSBP. Each cell contains baseline value, number of randomized patients (in parenthesis), least square mean of change from baseline , p-value for the comparison versus placebo. p-value for the comparison versus the HCTZ component (bold), and p-value for the comparison versus the valsartan component(underlined).

	Placebo	Vals 80 mg	Vals 160 mg
Placebo	152.8(93) -1.93	153.7(99) -8.82 0.001	153.3(97) -12.13 0.001
HCTZ 12.5 mg	153.7(99) -7.32 0.0078	153.0(96) -16.53 0.001 **0.001** 0.001	154.6(96) -17.77 0.001 **0.001** 0.0053
HCTZ 25 mg	151.9(100) -12.74 0.001	152.0(91) -21.16 0.001 **0.001** 0.001	155.8(94) -22.47 0.001 **0.001** 0.001

A number of studies, and including this particular study, have shown that the monotherapies of valsartan 80 mg, 160 mg , HCTZ 12.5 mg and HCTZ 25 mg, have resulted in significant reductions in SiDBP compared to placebo Since the interest in this study lies upon testing for the efficacy of the combinations of valsartan with HCTZ, these combinations should be tested under an overall originally specified significance level α .

To show the efficacy of a combination therapy, one has to show that it causes a significant reduction in BP compared to placebo and both of its components. This means that, for each combination three pairwise comparisons have to be carried out, using an appropriate multiple comparison procedure and in this case Hochberg's MC procedure is recommended.

The following are the four combinations of valsartan with HCTZ that are studied in study 301 and one needs to test for their efficacy under the specified level of significance α.

Val 80/HCTZ 12.5 mg, Val 80/HCTZ 25 mg, Val 160/HCTZ 12.5 mg, and Val 160/HCTZ 25 mg

Using Bonferroni's approach for dividing the α level among the above four combinations (four hypotheses) and with an overall α= 0.05 level of significance, each one of these combinations should be tested under a level of significance α^*=0.05/4=0.0125. Knowing that each combination has three mutiple comparisons, the following results are found by applying Hochberg's MC procedure.

1. For the combination Val 80/HCTZ 12.5 mg, the ordered p-values for the comparisons versus placebo and both of its components are

0.0099, 0.001, 0.001.

Thus, according to Hochberg's procedure, and since 0.0099<0.0125, all comparisons are significant and the conclusion is that this combination has caused a significantly greater reduction in SiDBP compared to that of placebo and both of its components.

2. Since each one of the three multiple comparisons has resulted in a p-value =0.001 for the remaining combinations of valsartan with HCTZ, the same conclusion will apply for these combinations as stated above for the combination Val 80/HCTZ 12.5 mg.

Therefore, the conclusion that one may obtain from the results of study 301 is that, when one applies a multiple comparison procedure (e.g. Hochberg's MC procedure), all four combinations of valsartan 80 and 160 mg with HCTZ 12.5 and 25 mg have resulted in significant reductions in SiDBP compared to placebo and both of their components ($p \leq 0.0099$)

2.2. Dose Response Surface

The sponsor has fitted the following quadratic dose response surface.

$$Change = a + bx + cy + dx^2 + exy + fy^2 + \epsilon,$$

where

x=Valsartan dose, y=HCTZ dose, a, b, c,d, e, and f are constants which are to be estimated, and ϵ= Error term. Change refers to the change from baseline in SiDBP.

It is known that the regression part of this model represents a two-dimensional surface with the property that the values of the "change' increase with the increase of x and y, if this change is considered as positive, until it reaches a stationary point at some value (x_0,y_0), after which the values of this change start to decrease (or increase) indefinitely. Consequently, this quadratic surface will under-estimates (or over-estimates) changes for (x,y) values beyond (x_0,y_0) and that it will not reach a plateau at any point in the X-Y region, which means that it may not be an appropriate model for describing a dose response. Thus, it is necessary to explore another model for a dose response that would be a non-decreasing function for all positive values of x and y and such that it reaches a plateau at some point in the X-Y plane.

This reviewer has investigated a number of dose response models for the combination therapy under study. The following E_{MAX} model seems appropriate for describing the dose response behavior of the combination of valsartan and HCTZ. This model was fitted to the changes from baseline in SiDBP for the data of study 301.

$$change = \frac{a_1 . x}{(b_1 + x)} + \frac{a_2 . y}{(b_2 + y)} + \frac{c}{(1 + xy)} + \epsilon$$

where c = Placebo effect,
$a_1 = E1_{MAX} - c$,
$b_1 = EC1_{50}$,
$a_2 = E2_{MAX} - c$,
$b_2 = EC2_{50}$,
ϵ = error term, such that

$E1_{MAX}$ = Maximum change in SiDBP that the valsartan component produces,
$EC1_{50}$ = Valsartan dose level that produces 50% of the total of the maximum change in SiDBP due to this component plus placebo effect,
$E2_{MAX}$ = Maximum change in SiDBP that the HCTZ component produces, and
$EC2_{50}$ = HCTZ dose level that produces 50% of the total of the maximum change in SiDBP due to this component plus placebo effect.

By examining the nature of this model, one sees that it is a non-decreasing function with respect to both the valsartan and the HCTZ components. This is one of the charcteristics that has to be met by a dose response model.

According to this model, the maximum change from baseline in SiDBP that can be achieved by a combination therapy of valsartan with HCTZ is: $MAX=a_1 + a_2$. (Mathematically, the maximum is the limit for the change as both x and y $\rightarrow \infty$)

The estimated parameters are $c=2.29$, $a_1=10.85$, $b_1=50.29$, $a_2=13.50$, and $b_2=19.44$. The RMSE for this model is 1.084 and MAX=24.35

The graph of the estimated dose response is shown in Figure1. The true mean changes from baseline in SiDBP, their point estimates, and their 95% confidence limits using this model are shown in Table 3.

Table 3. True mean changes from baseline in SiDBP (undelined), their point estimates (bold) and their (lower, upper) 95% confidence limits using an E_{MAX} model for study 301. Values are listed without the negative sign.

		HCTZ(mg)		
		0	12.5	25
Vals(mg)	0	3.96 **2.29** (2.22, 2.36)	7.55 **7.57** (7.50, 7.65)	9.06 **9.88** (9.81, 9.96)
	80	8.29 **8.95** (8.88, 9.02)	12.06 **11.95** (11.88, 12.02)	14.81 **14.26** (14.19, 14.33)
	160	10.37 **10.55** (10.47, 10.62)	13.45 **13.54** (13.47, 13.61)	16.12 **15.85** (15.78, 15.92)

By comparing the true mean changes from baseline in SiDBP (underlined) with their point estimates (bold) shown in Table 3 for the above E_{MAX} dose response model, one can see that this model has a good fit for the data of the change from baseline in SiDBP of study 301. This model, with a RMSE=1.084, has favorable properties in that it is non-decreasing with the increase of both valsartan and HCTZ dose levels, it reaches a plateau at some dose level of the combination, and that one would expect a maximum of 24.35 mmHg in mean change from baseline in SiDBP for some combination of valsartan with HCTZ that is beyond the studied range of doses.

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This review consists of 6 pages and one figure.
Concur:
Dr. Mahjoob 10/09/97
Dr. Chi 10/21/97

cc: Orig. NDA 20-818
HFD-110/Dr. Chen
HFD-110/Dr. Lipicky
HFD-110/Ms. Bongiovanni
HFD-344/Dr. Barton
HFD-710/Dr. Chi
HFD-710/Dr. Mahjoob
HFD-710/Dr. Nuri
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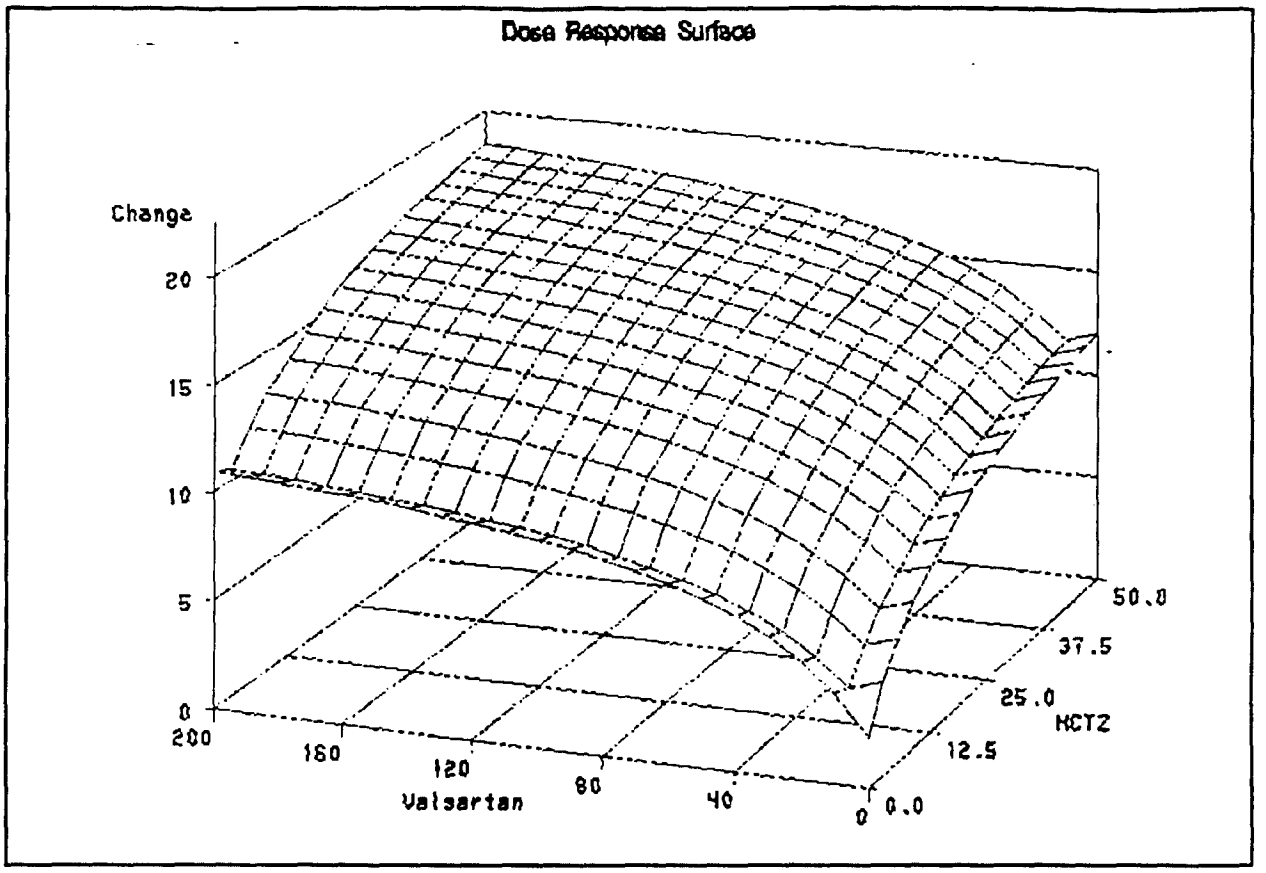

Figure 1. Dose response surface based on an E_{max} model for the change from baseline in SiDBP in study 301