

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER: NDA 21-162

STATISTICAL REVIEW(S)

Statistical Review and Evaluation

NDA: 21,162

Applicant: Boehringer Ingelheim

Drug Name: Telmisartan/hydrochlorothiazide combination

Indication: Hypertension

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This NDA submission is to study the effect of combination of telmisartan (T) and hydrochlorothiazide (H or HCTZ) in treating patients with mild to moderate hypertension. The pivotal study in this submission is Study 502.204 and it is the focus of this review.

1. Outline of Study 502.204

Design

This randomized **trial** used a factorial design to study the anti-hypertensive effect of once daily dose of telmisartan (0, 20, 40, 80, 160 mg) and hydrochlorothiazide (0, 6.25, 12.5, 25 mg). The **objective** of this study was to identify a fixed dose of T/H (telmisartan/hydrochlorothiazide) combination that is more effective in lowering blood pressure of mild to moderate hypertension than the single agents alone.

In this trial, after a single blind placebo run-in period, male and female patients between 18 and 80 years of age (with 95-114 mmHg supine diastolic bp and 140 -200 mmHg supine systolic bp) were randomized, stratified by race, into 20 treatment groups to receive either T/H combination therapies or T or H single therapies or placebo for 8 weeks (double blind period). No antihypertensive medications other than the study drugs were permitted during the trial. Changes in trough supine and standing blood pressure were assessed at 2, 4 and 8 weeks. A total of 818 patients from 49 clinical centers were involved in the study.

The **primary efficacy endpoint** in this trial was mean change from baseline in last trough supine diastolic blood pressure. The secondary efficacy endpoints included supine systolic blood pressure, and standing diastolic and systolic blood pressure. As mentioned in the protocol, the focus of the analysis of efficacy outcome was on the six key treatment groups (placebo, H12.5, T40, T80, T40/H12.5, and T80/H12.5).

The planned primary **analyses** were the Global AVE test and the Min test, aiming to determine if either or both of the combination therapies in the six key treatment groups (placebo, T40, T80, H12.5, T40/H12.5, and T80/H12.5) were more effective than their individual components. In the analysis, the AVE test was performed first. Once the

global null was rejected, the effective combination was identified by comparing each combination treatment with its component therapies with the Min test.

The following table gives the planned sample sizes for each treatment group. According to the sponsor, at one-sided 0.05 level of significance, assuming a common standard deviation of 9 mmHg, with the planned sample size, the trial had 86% power to detect a 4mmHg average minimum gain of the two combinations over their components, 73% power for non-black, and 45% power for black. Other planned analyses include by-race subgroup analysis, response surface analysis and analysis of responders.

Table 1.1 Planned sample size allocation

	T0	T20	T40	T80	T160
T0	75	20	75	75	30
H6.25	20	20	20	20	30
H12.5	75	20	75	75	30
H25	20	20	20	30	30

Result

The treatment groups appeared to be comparable with respect to major demographic and baseline factors (Table 1.2).

Table 1.2 Demographic and baseline factors

	placebo	T40	T80	H12.5	T40/H12	T80/H12
N	74	75	77	75	70	74
Median Age (year)	55	51	50	53	56	53
<65 (n, %)	62, 83.8	61, 81.3	69, 89.6	61, 81.3	52, 74.3	60, 81.1
Race (non-black, n, %)	56, 75.7	55, 73.3	55, 71.4	55, 73.3	54, 77.1	52, 70.3
Gender /male (%)	45 (60.8)	44 (58.7)	46 (59.7)	53 (70.7)	39 (55.7)	48 (64.4)
Median year of HP	6.0	6.0	6.0	6.0	8.5	7.5
Body mass index	29.2	30.8	28.1	30.2	29.4	29.5
non smoker (n, %)	36, 48.6	44, 58.7	37, 48.1	35, 46.7	32, 45.7	41, 55.4
# of non-drinker (n, %)	35, 47.3	34, 45.3	37, 48.1	40, 53.3	36, 51.4	35, 47.3
Supine dia/mean (mmHg)	100.3	101.4	100.3	100.7	100.9	101.1
Supine sys/mean (mmHg)	153.7	153.8	153.1	153.4	157.2	156.2
Stand dias/mean (mmHg)	100.9	101.8	101.1	100.7	102.2	101.1
Stand syst/mean (mmHg)	151.0	150.3	149.6	152.1	153.7	151.5
Supine heart rate (bmp)	71.9	70.5	71.8	71.4	70.8	69.8

The sponsor's analysis based on the Global AVE test indicated that at least one of the combination therapies was superior to its individual monotherapies ($p < 0.05$) in lowering supine diastolic blood pressure (DBP). Further test (the Min test) indicated that the combination therapy T80/H12.5 was significantly superior to its component monotherapies ($p < 0.01$). The combination therapy T40/H12.5 was only superior to H12.5 but not T40. All combination therapies and their individual monotherapies were superior to placebo. A similar result was found for the trough supine systolic blood

pressure (SBP) and standing DBP and SBP. For systolic blood pressures, both combinations, T40/H12.5 and T80/H12.5 were superior to their components. The results of the sponsor's analysis are summarized in the following table.

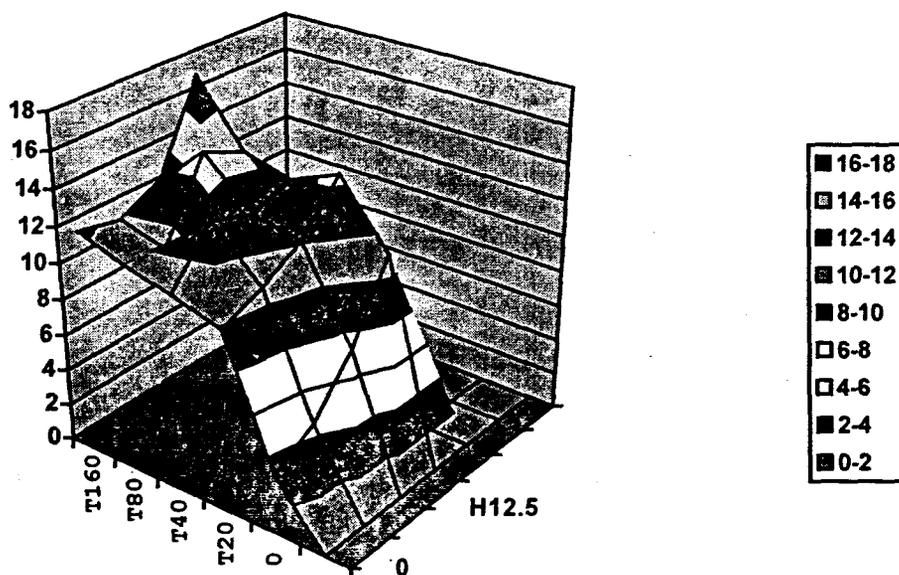
Table 1.3 Mean reduction in blood pressure (mmHg)

	placebo	T40	T80	H12.5	T40/H12	T80/H12
n	74	75	77	75	70	74
Supine diastolic	3.8	10.7	11.5	7.3	12.6	14.9*
Supine systolic	2.9	12.2	15.4	6.9	18.8	23.9
Standing diastolic	2.6	9.0	9.7	5.6	12.1	13.1
Standing systolic	1.5	10.4	15.2	7.4	17.8	22.1

* Bold font: Superior to component monotherapies at 0.05 level

The following graph shows mean reductions in supine diastolic blood pressure in all twenty treatment groups. From the graph, it appears that the magnitude of reduction in blood pressure increased as the dose of telmisartan or HCTZ increased. Such a trend seemed to flatten out at the high dose of telmisartan. The result of sponsor's response surface analysis supports this observation. Based on this response surface analysis, there were significant linear effects for both telmisartan and HCTZ with respect to supine DBP and SBP. For changes in supine DBP and SBP, the quadratic term was not significant for HCTZ but it was nominally significant for telmisartan.

Figure 1.1 Mean reduction in trough supine diastolic blood pressure



The following table summarizes the percentages of patients achieving control in supine diastolic (trough supine DBP < 90 mmHg) and adequate response in supine systolic (reduction no less than 10 mmHg from baseline in trough supine SBP) blood pressure. The percentages of patients with controlled supine systolic blood pressure for the combination therapies were significantly larger than those for their monotherapies.

Table 1.4 Percentage of patients with controlled blood pressure at trough

	placebo	T40	T80	H12.5	T40/H12	T80/H12
n	74	75	77	75	70	74
Supine diastolic	21%	49%	55%	38%	56%	64%
Supine systolic	29%	60%*	66%*	36%	81%*	85%

* Bold font: significantly superior (Mantel-Haenszel test)

Several subgroup analyses were done by the sponsor. The mean reductions in blood pressure are summarized in the following table by race, gender and age.

Table 1.3 Mean reduction in blood pressure (mmHg)

	Placebo	T40	T80	H12.5	T40/H12	T80/H12
Black						
N	18	20	22	19	16	22
Supine diastolic	3.4	6.7	4.6	5.2	10.0	13.3
Supine systolic	0.1	2.0	7.8	9.2	14.3	21.5
Standing diastolic	0.1	4.2	4.8	4.2	8.1	11.8
Standing systolic	0.7	2.0	9.4	11.5	15.0	17.1
White						
N	50	40	51	45	46	43
Supine diastolic	3.8	13.5	14.9	8.1	13.3	16.4
Supine systolic	4.1	16.5	19.9	5.7	19.9	26.5
Standing diastolic	3.2	11.8	12.3	5.6	13.3	14.6
Standing systolic	1.9	13.0	19.2	6.0	18.4	25.4
Male						
N	45	44	46	52	39	47
Supine diastolic	4.4	10.7	11.3	7.7	9.7	15.4
Supine systolic	4.8	12.7	15.6	6.5	16.5	23.9
Standing diastolic	3.6	8.9	10.1	5.9	10.9	13.6
Standing systolic	3.9	10.5	16.4	6.3	17.2	23.2
Female						
N	28	31	31	21	31	26
Supine diastolic	2.8	10.6	11.8	6.5	16.2	14
Supine systolic	-0.1	11.6	15.0	7.9	21.8	23.9
Standing diastolic	1.1	9.1	9.1	4.8	13.5	12.3
Standing systolic	-2.5	10.3	13.2	10.1	18.6	20.1
<65						
N	62	61	69	60	52	59
Supine diastolic	3.6	11.2	11.2	6.8	10.9	14.6
Supine systolic	2.8	14.1	15.3	5.8	17.2	23.5
Standing diastolic	2.2	10.3	9.3	5.1	10.8	13.0
Standing systolic	2.0	12.3	14.3	6.9	17.0	21.6
>= 65						
n	11	14	8	13	18	14
Supine diastolic	5.2	8.4	14.3	9.7	17.3	16.0
Supine systolic	-3.7	4.0	16.3	12.4	23.7	25.3
Standing diastolic	5.0	3.5	12.9	5.8	15.7	13.7
Standing systolic	-1.8	2.2	22.2	9.7	20.1	24.0

For black patient population, the Global AVE test indicated that at least one combination therapy was significantly superior to its individual monotherapies with respect to trough supine DBP ($p < 0.01$). The combination therapy of T80/H12.5 was significantly superior to T80 alone and H12.5 alone. However, the increases in the magnitude of the reduction in supine DBP for both of the monotherapies over that for placebo were not statistically significant ($p > 0.05$). There seems to be some evidence of a synergistic effect associated the combination dose T80/H12.5. The combination therapy of T80/H12.5 was also superior to its monotherapies with respect to supine SBP.

For non-black patients, the Global AVE test indicated that neither of combination therapies was superior to its individual monotherapies for supine DBP. Both of the combination therapies significantly reduced supine DBP more than the HCTZ 12.5mg alone. However, the combination therapies were not statistically superior to the corresponding telmisartan monotherapy, apparently due to the large responses for T40 and T80. The Global AVE test indicated that at least one combination therapy was superior to its monotherapies with respect to supine SBP. Further MIN test showed the superiority of both T40/H12.5 and T80/H12.5 to their corresponding monotherapies for supine SBP.

Reviewer's analysis and comments

This reviewer compared the blood pressure reductions of the six key dosing groups. The Global AVE test indicated that at least one combination was significantly superior to its individual components for supine DBP ($p = 0.0148$). Using MIN test, the superior combination was identified as T80/H12.5 ($p = 0.0081$). There was a numerically larger reduction in supine DBP associated with the combination T40/H12.5 as compared to its two monotherapy components. However, the difference was not statistically significant ($p = 0.0865$). The Global AVE and MIN tests indicated the superiority of the combinations of T80/H12.5 and T40/H12.5 to their individual components for supine SBP, standing DBP and SBP. The results of the analyses are summarized in Table 2.1. No telmisartan-by-HCTZ interaction was found with respect to supine DBP, standing DBP and standing SBP. A moderate telmisartan-by-HCTZ interaction was found for supine SBP ($p = 0.0847$). However, such an interaction appeared to be synergistic based on the observed effects for T80/H12.5, T80 and H12.5.

Table 2.1 Mean reduction in blood pressure (mmHg)

	placebo	T40	T80	H12.5	T40/H12	T80/H12
n	73	75	77	73	70	73
Supine diastolic	3.8	10.7	11.5	7.3	12.6	14.9*
Supine systolic	2.9	12.2	15.4	6.9	18.8	23.9
Standing diastolic	2.6	9.0	9.7	5.6	12.1	13.1
Standing systolic	1.5	10.4	15.2	7.4	17.8	22.1

*Bold: statistically significantly superior to component monotherapies

