CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: NDA 20125

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-125 Drug Class: 14C
Applicant: Parke-Davis Pharmaceutical Research
Drug Name: Accuretic (Quinapril/HCTZ) Tablets
Indication: Treatment of Hypertension
Document Reviewed:

Vols. 1.1, 1.54, 1.55, 1.56, 1.63, 1.64
Efficacy data of Study 906-241 and Study 906-300 on [illegible] diskettes

This review was completed after discussion with Dr. [illegible] medical reviewer.

1. INTRODUCTION

This review pertains to two major double-blind, randomized clinical studies of the New Drug Application for the combination drug with quinapril (QNPL) and hydrochlorothiazide (HCTZ). Some statistical analyses used by the sponsor in the first study, in my opinion, may not be able to answer the question as to whether combination therapy is more effective than its component therapies alone. Data are then reanalyzed using the recently accepted methods proposed by Hung et al (1992).

2. OVERVIEW OF TWO CONTROLLED CLINICAL STUDIES

Study 906-241 (placebo-controlled)

This 31-center 4 x 4 factorial clinical trial was designed to compare the efficacy and safety of concomitant QNPL and HCTZ with each drug as monotherapy, and to evaluate the dose-response relationship of this combination therapy on blood pressure. Men, and women using reliable birth control, at least 18 years old, with hypertension and normal serum potassium were selected for the study. Sitting DBP of the outpatients who entered the double-blinded phase of the study was ≥100 and ≤115 mm Hg at each of the last two consecutive placebo baseline visits.

The primary efficacy variable is sitting DBP at trough (24±4 hours postdose). The proposed dosing interval is once per day.

Following a 2- to 4-week placebo-baseline period, a total of 460 patients were randomized to receive fixed doses of placebo, QNPL 2.5 mg, 10 mg or 40 mg, HCTZ 6.25 mg, 12.5 mg or 25 mg, or QNPL plus HCTZ at these doses (i.e. 16 parallel treatment groups in total) for a 8-week treatment period. Less than 20% of the population were from North America; others were from Europe, Scandinavia, or South Africa. Forty-one (9%) patients withdrew; of them, 15 were due to lack of efficacy (placebo and HCTZ groups had 8 in total); 14 were due to adverse events. There seems to be a trend indicating more withdrawals in the high-dose-combination groups (see Table 1), but it is not clear.

Two patients (not having valid baseline measurement or double-blind measurement) were excluded from the intent-to-treat population. Eighty six patients were excluded from evaluable patients population (24 with baseline DBP < 100 mm Hg, 23 on study drug < 26 days, 27 with no evaluable visits on or after Day 26). No evidence was found to indicate any baseline imbalance in the treat groups.

Sponsor's Results

The primary analyses are the so-called "marginal analyses" in which the average of the three HCTZ monotherapy cells were compared to the averages of the three cells of each QNPL dose with HCTZ added, and similarly the average of the three QNPL monotherapy cells were compared to the averages of the three cells of each HCTZ dose with QNPL added. Williams test procedure was exercised to determine the lowest dose of QNPL which, when added to HCTZ, was more effective than HCTZ monotherapy, and to determine the lowest dose of HCTZ which, when added to QNPL, was more effective than QNPL monotherapy. The sample size was planned for these analyses.

Table 2 presents the raw mean changes from baseline and adjusted mean changes from baseline in sitting DBP at trough for evaluable patients and intent-to-treat patients. Mean changes in other blood pressures are summarized in Table 3. The marginal analyses on adjusted mean changes (mm Hg) in sitting DBP at trough are presented as follows:

	HCTZ only	HCTZ + QNPL 2.5	HCTZ + QNPL 10	HCTZ + QNPL 40
Evaluable	8.2	10.0	11.0	13.6*
Intent-to-treat	6.5	8.7	11.5*	12.0*

* significantly different from HCTZ only

	QNPL only	QNPL + HCTZ 6.25	QNPL + HCTZ 12.5	QNPL + HCTZ 25
Evaluable	8.1	10.3	10.8	13.5#
Intent-to-treat	8.2	10.0	8.9	13.3#

significantly different from QNPL only

Same analyses were performed on sitting SBP; the results were similar to those on sitting DBP, except that all QNPL doses when added to HCTZ are significantly different from HCTZ alone. As to be commented in Section 3, these analyses may not answer the question regarding the effectiveness of the combination product relative to the components.

Dose-response relationship on sitting DBP was explored using response surface analysis. The full quadratic model including QNPL dose, HCTZ dose, the quadratic terms, and the cross-product (interaction) term was used. No evidence for a lack-of-fit was found according to Lack-of-Fit F test (p = 0.67) and residual plots. The coefficient estimates for the quadratic model on mean change in sitting DBP are provided as follows:

Parameter	Estimate	s.e.	p-value
Intercept	-4.20	1.14	0.0003
QNPL	-0.39	0.16	0.015
HCTZ	-0.34	0.18	0.064
QNPL x QNPL	0.006	0.004	0.12
HCTZ x HCTZ	0.002	0.006	0.72
QNPL x HCTZ	0.003	0.003	0.37

Based on the estimate 0.003 for the interaction QNPL x HCTZ (p = 0.37), the sponsor concluded that the effects of the two drugs are additive. As to be commented in Section 3, this point may be overstated. The maximum mean decrease in sitting DBP predicted by this model is 15.7 mm Hg with 95% confidence interval (12.7, 18.6); the maximum decrease occurs at QNPL 28 mg + HCTZ 25 mg; the 95% confidence region of this optimum dose combination does not contain either monotherapy axis, supporting the greater effectiveness of comination therapy over the monotherapies.

The QNPL x QNPL, HCTZ x HCTZ, and QNPL x HCTZ terms were not significant and then removed from the model. It resulted in a linear model fit, which was found adequate as well based on Lack-of-fit F test (p = 0.63) and residual plots. This model is presented as follows:

Parameter	Estimate	s.e.	p-value
Intercept	-5.52	0.78	0.0001
QNPL	-0.12	0.03	0.0001
HCTZ	-0.24	0.05	0.0001

Based on this model, the maximum mean decrease in sitting DBP is estimated as 16.4 mmHg with 95% confidence interval (14.2, 18.5). The maximum decrease occurred at QNPL 40 mg + HCTZ 25 mg; 95% confidence region of the optimum dose combination also does not contain either monotherapy axis.

Peak measurements of sitting DBP were taken hourly for four hours postdose at week 4. Only 293 patients had evaluable baseline, trough, and peak data. Trough and peak changes in these patients are summarized in Table 4. The sponsor reported that more than

50% of the response achieved at peak remained at trough with all but the lowest dose combination.

There were too few (0-7 per cell) elderly patients (age ≥ 65 yrs) in the study; no obvious trend in the effectiveness of QNPL, HCTZ, or the combination product was found. Nor was found for black patients (only 7%).

Study 906-303 (force-titration)

This 29-center European study is to compare the efficacy of QNPL + HCTZ with QNPL alone and HCTZ alone, given once daily in patients with moderate to severe hypertension (baseline supine DBP between 105 and 120 mm Hg inclusive).

After 2 to 4 weeks of placebo washout period, 368 patients were randomized to one of the three arms: QNPL 10 mg, HCTZ 12.5 mg, and QNPL 10 mg + HCTZ 12.5 mg for four weeks. After that, the doses were doubled for an additional four weeks, except 45 patients with supine DBP < 80 mm Hg or supine SBP < 120 mm Hg. The three treatment groups appeared to be comparable with respect to baseline characteristics and blood pressures. There were 22 dropouts, evenly distributed to the three groups. Six patients were excluded from intent-to-treat analyses (because of no baseline or double-blind blood pressure readings); 50 patients were excluded from the evaluable patient analyses of low dose; 84 patients were excluded from the evaluable patient analyses of high dose. Frequent reasons for exclusion were blood pressures taken outside the 24±4 hours postdose window, inadequate baseline DBP, duration on low dose <=19 days.

The results of the intent-to-treat analyses were very similar to those of the evaluable patient analyses and reported as follows:

LOW DOSE PHASE

	QNPL 10 mg (N=118)	QNPL 10 mg + HCTZ 12.5 mg (N=121)	HCTZ 12.5 mg (N=123)
Supine DBP			
Baseline Mean	109.5	109.7	109.2
Adj. Mean Decrease	11.8	14.4	12.2
p-value		.008	.020
Supine SBP			
Baseline Mean	173.5	169.9	170.9
Adj. Mean Decrease	13.2	17.2	11.5
p-value		.018	.0014

HIGH DOSE PHASE

	QNPL (N=118)		QNPL + HCTZ (N=121)		HCTZ (N=123)
# of patients on low dose/high dose	16/84		14/86		7/93
Supine DBP					
Baseline Mean	109.5		109.7		109.2
Adj. Mean-Decrease	16.5		18.7		16.5
p-value		.025		.023	
Supine SBP					
Baseline Mean	173.5		169.9		170.9
Adj. Mean_Decrease	18.7		24.7		19.2
p-value		<.001		<.001	

Similar results were also obtained with standing blood pressures. A greater mean decrease in supine DBP and SBP with QNPL + HCTZ compared to its components was also observed in patients with baseline > 110 mm Hg. In patients of age ≥ 65 years, the effect of QNPL 20 mg / HCTZ 25 mg is similar to that of HCTZ alone (Table 5). Only two black patients were entered into this study.

3. REVIEWER'S EVALUATIONS

Study 906-241

The hypotheses tested in the sponsor's marginal analyses do not necessarily explain that QNPL plus HCTZ is more effective than QNPL and HCTZ alone. Even if they do in some sense, the use of Williams procedure in the way as was done in their analyses has not yet been proven valid for showing that QNPL plus HCTZ is more effective than QNPL and HCTZ alone at 5% level of significance. It is understandable that the sponsor did such analyses, since statistical method is not available for entertaining this difficult problem at the time of planning this trial. The method of Hung et al (1992) is now available.

The following table is generated from Table 2 by subtracting mean decrease in sitting DBP of the placebo group from each cell.

		QNPL 0	2.5	10	40
HCTZ	0	0	4.4	5.1	8.1
	6.25	3.7	6.7	8.1	9.5
	12.5	5.0	7.2	6.0	12.7
	25	9.2	9.4	12.5	12.1

The minimum gains (i.e., greater mean decrease) of the nine active dose combination relative to their respective component doses are tabulated as follows:

		QNPL			
		0	2.5	10	40
HCTZ	0	-	-	-	-
	6.25	-	2.3	3.0	1.4
	12.5	-	2.2	0.9	4.6
	25	-	0.2	3.3	2.9

On average, combining QNPL with HCTZ at these studied doses yield an additional decrease of 2.3 mm Hg in sitting DBP. The estimated standard deviation is 8.6 and the sample size of each cell is approximately 24. Based on the AVE test of Hung et al, the additional decrease of 2.3 mm Hg is statistically significant ($p = 0.024$). Analysis of intent-to-treat patients yields the same result. Thus I conclude that QNPL plus HCTZ is more beneficial than either QNPL or HCTZ alone in lowering sitting DBP.

I question the sponsor's statement that the effects of QNPL and HCTZ are additive. The statistical hypothesis of additivity is generally difficult to establish because of insufficient sample size. In this study, the effects of QNPL/HCTZ are compared with the effects of QNPL alone plus the effects of HCTZ alone as follows:

EVALUABLE PATIENTS

		QNPL			
		0	2.5	10	40
HCTZ	0	0	4.4	5.1	8.1
	6.25	3.7	6.7 (8.1)	8.1 (8.8)	9.5 (11.8)
	12.5	5.0	7.2 (9.4)	6.0 (10.1)	12.7 (13.1)
	25	9.2	9.4 (13.6)	12.5 (14.3)	12.1 (17.3)

Number in each parenthesis is the sum of the effect of QNPL and the effect of HCTZ.

The observed effect of each active combination dose is smaller than the sum of the component effects. The data suggests negative interactions between QNPL and HCTZ.

The observed mean decreases in sitting DBP seem to level off around the high doses of HCTZ or QNPL (QNPL 40mg / HCTZ 12.5mg, QNPL 40mg / HCTZ 25 mg, and QNPL 10 mg / HCTZ 25 mg all have similar mean reductions). I also found that center factor, not included in the sponsor's analyses, explains a great portion of variability. A polynomial response surface including center effects suggests that mean decrease in sitting DBP increases (linear trend: $p < 0.0001$) as a function of both QNPL and HCTZ doses, with a possible mild indication (quadratic trend: $p \approx 0.06$) of leveling-off as the dosage of QNPL approaches the upper end. Body weight explains only some fraction of variability; including it in the response model helps little to resolve the leveling-off issue. Age or race explains little of variability.

The lowest dose of the combination that beats placebo is QNPL 2.5 mg + HCTZ 6.25 mg; the difference is about 6.7 mm Hg and statistically significant ($p<0.01$, according to evaluable patients). The observed effect of this dose combination is greater than those of its components by at least 2.3 mm Hg. With the inclusion of the highly significant center factor, ANCOVA of intent-to-treat patients also shows that this low dose combination has a significantly greater decrease than placebo by 5.0 mm Hg and a greater mean reduction than its components by at least 1.3 mm Hg. The data of this factorial trial seems to suggest that this low dose combination is also usable.

Study 906-303

My analyses confirm the sponsor's results. Based on this study, the combination QNPL 10 mg/HCTZ 12.5 mg yields a 2 to 3 mm Hg greater reduction in supine DBP than its components alone after the 4 weeks period; it is statistically significant. The same result is obtained with doses of QNPL and HCTZ doubled.

4. CONCLUSIONS (MAY BE CONVEYED TO THE SPONSOR)

In the dose region of QNPL 0 to 40 mg and HCTZ 0 to 25 mg, an increase in the dosage of either QNPL or HCTZ increases the average reduction in sitting DBP. Fall of sitting DBP seems to level off around the upper dose level of QNPL or HCTZ; the leveling off phenomenon around the upper dose level of QNPL is only and mildly indicated in response surface analyses.

Data from the factorial trial suggests negative interactions between quinapril and hydrochlorothiazide (see reviewer's arguments provided in Section 3). The sponsor's statement that their effects are additive is overstated.

Combining QNPL and HCTZ at the study doses yields, on average, a

2.3 mm Hg greater reduction in sitting DBP than either component drug alone; this additional reduction of 2.3 mm Hg is statistically significant (p=0.024). Thus overall speaking, the combination of QNPL and HCTZ is more effective than the component drugs. The forced-titration trial with a larger cell sample size shows that the combination of QNPL 10 mg and HCTZ 12.5 mg yields a 2 to 3 mm Hg greater decrease in supine DBP and a 5 to 6 mm Hg greater decrease in supine SBP than its components; both are statistically significant ($p<0.05$). Similar benefits are also obtained when the doses of QNPL and HCTZ are doubled.

The results of the factorial trial seem to suggest that the combination of quinapril 2.5 mg and hydrochlorothiazide 6.25 mg is also usable (its effect relative to placebo is 5.0 to 6.7 mm Hg). In evaluable patients this dose combination has a 2.3 mm Hg greater mean reduction of sitting DBP than its components, while in intent-to-treat patients the difference is at least 1.3 mm Hg. This combination was not studied in the forced-titration study.

In elderly patients (age ≥ 65 years), QNPL 20 mg plus HCTZ 25 mg seems to have a similar effect as HCTZ alone, based on data from approximately 60 elderly patients (Table 5).

The validity of the so-called marginal analyses used by the sponsor for showing the superiority of the combination therapy relative to its component therapies is questionable. One reason is that the hypotheses tested in the marginal analyses do not necessarily explain that QNPL plus HCTZ is more effective than QNPL or HCTZ alone. This issue has been discussed in Hung et al (1990). In addition, these analyses have not been proven valid for showing that QNPL plus HCTZ is more effective than the components alone at 5% level of significance. The methods proposed by Hung et al (1992) may be used to deal with the issue of 'A+B > A and A+B > B' in a multi-level factorial trial. These methods are used by this reviewer to reach the above conclusion.

References

Hung, H.M.J., Chi, G.Y.H. and Lipicky, R.J. (1992). Testing for the existence of a desirable dose combinations. Biometrics (to appear).

Hung, H.M.J., Ng, T.H., Chi, G.Y.H., and Lipicky, R.J. (1990). Response surface and factorial designs for combination anti-hypertensive drugs. Drug Information Journal 24, 371-378.

/S/

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This review contains 9 pages of text, followed by 5 tables.

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cc: Orig. NDA
HFD-110
HFD-110/Dr. Lipicky
HFD-110/Dr. Dern
HFD-110/Ms. Morgenstern
HFD-344/Dr. Lisook
HFD-713/Dr. Dubey [File: DRU 1.3.2 NDA]
HFD-713/Dr. Chi
HFD-713/Dr. Hung

JHung/x2814/SERB/ACCURET.*/11-20-91

Table 1. Withdrawals Due to Adverse Events (Study 906-241)

		QNPL			
		0	2.5	10	40
HCTZ	0	1	0	0	1
	6.25	0	2	0	1
	12.5	0	1	1	3
	25	0	1	1	2

Table 2. Adjusted Mean Decrease in Sitting DBP and Baseline Sitting DBP at Trough from Baseline (Study 906-241)

EVALUABLE PATIENTS

		QNPL			
		0	2.5	10	40
HCTZ	0	2.2/106	6.6/107	7.3/105	10.3/106
	6.25	5.9/106	8.9/104	10.3/105	11.7/106
	12.5	7.2/106	9.4/104	8.2/106	14.9/105
	25	11.4/105	11.6/105	14.7/105	14.3/106

INTENT-TO-TREAT PATIENTS

		QNPL			
		0	2.5	10	40
HCTZ	0	2.9/106	7.2/106	7.2/104	10.1/105
	6.25	5.2/106	7.5/104	10.7/106	12.0/106
	12.5	6.0/105	7.2/104	8.8/105	10.7/105
	25	8.5/105	11.4/105	15.1/105	13.3.104

Raw mean changes and adjusted mean changes are almost identical in intent-to-treat patients. Standard errors are very close to 1.7 and cell sample sizes are near 29.

Standard errors for adjusted mean changes in evaluable patients are very close to 1.8 and cell sample sizes are near 24.

Table 3. Raw Mean Decreases in Other Blood Pressures (mm Hg) at Trough from Baseline (Evaluable Patients, Study 906-241)

Sitting SBP

		QNPL			
		0	2.5	10	40
HCTZ	0	3.7	3.7	6.0	13.8
	6.25	3.8	8.6	14.9	14.9
	12.5	5.0	13.4	13.6	24.7
	25	11.1	15.8	20.2	20.2

Standing DBP

		QNPL			
		0	2.5	10	40
HCTZ	0	2.5	5.1	4.5	9.8
	6.25	7.2	9.2	8.8	11.7
	12.5	8.8	8.3	7.0	12.2
	25	10.4	10.2	12.9	12.1

Standing SBP

		QNPL			
		0	2.5	10	40
HCTZ	0	2.4	6.4	5.2	11.1
	6.25	5.8	10.2	13.4	17.2
	12.5	4.0	11.0	12.5	18.6
	25	11.1	14.4	21.7	17.7

Table 4. Trough/Peak Decrease in Sitting DBP (Study 906-241)

(placebo response subtracted)

		QNPL			
		0	2.5	10	40
HCTZ	0		6.3/5.4 >100%	4.7/7.9 59%	7.0/9.2 76%
	6.25	3.0/0.6 >100%	1.8/5.1 35%	6.0/7.4 81%	6.9/10.3 67%
	12.5	1.5/0.2 >100%	7.0/6.7 >100%	5.1/6.8 75%	9.0/9.6 94%
	25	6.9/4.2 >100%	6.9/8.3 83%	6.9/8.0 86%	8.4/10.3 82%

(placebo response included)

		QNPL			
		0	2.5	10	40
HCTZ	0	3.9/7.2 54%	10.2/12.6 81%	8.6/15.1 57%	10.9/16.4 66%
	6.25	6.9/7.8 88%	5.7/12.3 46%	9.9/14.6 68%	10.8/17.5 62%
	12.5	5.4/7.4 73%	11.0/13.9 79%	9.0/14.0 64%	12.9/16.8 77%
	25	10.8/11.4 95%	10.8/15.5 70%	10.8/15.2 71%	12.3/17.5 70%

Table 5. Raw Mean Decrease (mm Hg) in Supine DBP at Trough (Study 906-303)

Study Drug	Age < 65 years N	Baseline	Mean Decrease	Age ≥ 65 years N	Baseline	Mean Decrease
Low Dose Phase						
QNPL 10 mg	70	110.2	12.3	31	108.9	12.3
HCTZ 12.5 mg	69	109.8	10.1	40	109.3	16.3
QNPL + HCTZ	80	110.1	13.6	28	110.1	18.0
High Dose Phase						
QNPL 20 mg	62	110.3	17.1	29	109.1	17.5
HCTZ 25 mg	60	109.9	15.2	39	109.4	20.0
QNPL + HCTZ	70	110.3	18.9	24	110.5	20.7