CENTER FOR DRUG EVALUATION AND RESEARCH

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21-438

Statistical Review(s)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
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FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

MEDICAL DIVISION: Cardio-Renal Drug Products (HFD-110)

BIOMETRICS DIVISION: Division of Biometrics I (HFD-710)

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DRUG NAME: Propranolol Extended Release Capsules

INDICATION: Treatment of hypertension.

SPONSOR: Reliant Pharmaceuticals, LLC

DOCUMENT REVIEWED:

1. Cover letter (CDER REC'D Date: February 5, 2002) including CD-ROM & SAS data base
2. Cover letter (CDER REC'D Date: February 21, 2002) including CD-ROM, doc file for review's aids, SAS data sets, and SAS codes for the primary and secondary efficacy results

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TABLE OF CONTENTS

3. EXECUTIVE SUMMARY OF STATISTICAL FINDINGS

3.1 Conclusion and Recommendations

This clinical study demonstrated that — , administered once nightly at bedtime in a dose of 120 mg, 160 mg, and 640 mg is an effective anti-hypertensive agent in controlling morning blood pressure and in maintaining lowered trough blood pressure in the evening. The morning sitting diastolic blood pressure decreased from baseline to endpoint for the placebo and all four — dose groups. Statistically significant differences in the magnitude of the decrease between the placebo group and the 120 mg, 160 mg, and 640 mg — groups were observed for the primary analysis in both Intent-to-Treat (ITT) and Efficacy Evaluable populations. The effects of these doses are hardly distinguishable.

3.2 Overview of the Clinical Program and Studies Reviewed

This clinical program is a research and development of new drug — (propranolol hydrochloride) Extended Release 80 mg, 120 mg, — Capsules which is designed by the sponsor, Reliant Pharmaceuticals, LLC, to provide reduction in blood pressure and heart rate 24 hours, including optimal protection in the early morning hours, when patients are most vulnerable to cardiovascular events. — is a new, administered once nightly between 9:30 and 10:30 PM (bedtime) in formulation of propranolol hydrochloride (HCl). — is an oral capsule formulation containing spherical beads allowing both an immediate and delayed release of propranolol HCl.

The clinical program includes 6 clinical studies: 5 Phase I (pharmacokinetic/bioavailability) studies and one Phase III study. The study selected for the statistical review is the Phase III study: Study 3003, a randomized, double-blind, parallel, placebo-controlled, multi-center trial to study the efficacy, safety and steady state kinetics of — 80 mg, 120 mg, 160 mg, and 640 mg in the patients with essential hypertension. A total of 434 subjects were randomized in the 41 investigational centers in the United States.

The major statistical issue in this NDA submission is the statistical analysis method used for the primary and secondary efficacy analyses. The sponsor used the two-way ANCOVA model with treatment and center as the two factors and baseline value as the covaraite for the efficacy analyses. It is not appropriate to this completely randomized trial because all subjects were completely randomized by 5 treatment groups only and were not randomized by the centers. This reviewer will prove (in Appendix) that one can obtain biased estimates for the treatment effects which may lead to biased analysis results if one uses the two-way ANCOVA model for this completely randomized trial. This reviewer reanalyzed data using the one-way ANCOVA model with the treatment as the only one factor and baseline value as the covariate. The result of this reviewer's analyses demonstrated a statistically significant treatment effect.

3.3 Principal Findings

Both morning and evening sitting diastolic blood pressures decreased from baseline to endpoint for the placebo and all four — groups. Statistically significant differences in the

magnitude of the reduction between the placebo group and the 120 mg, 160 mg, and 640 mg — groups were observed for the primary analysis in both ITT and the Efficacy Evaluable populations. A trend in favor of the 80 mg — was observed in both populations.

A decrease from baseline to endpoint was observed for both morning and evening sitting systolic blood pressures in all treatment groups. Statistically significant differences in the magnitude of the decrease between the placebo group and —) groups were observed for evening sitting systolic blood pressure at the 80 mg and 640 mg — doses. Decreases from baseline and endpoint were also observed for morning and evening pulse rate, morning and evening BPRP in all treatment groups and statistically significant differences were observed for the decreases between the placebo group and the — groups.

The primary and secondary efficacy results in subgroups by age, gender, ethnic origin, and duration of hypertension were similar to those of ITT population.

4. STATISTICAL REVIEW AND EVALUATION OF EVIDENCE

4.1 Introduction and Background

Systemic hypertension is a well-recognized risk factor for coronary artery disease and sudden cardiac death. Patients with hypertensive cardiovascular disease are most at risk of heart attacks and stroke between the hours of 6 AM and noon because of the natural spike in blood pressure and heart rate which occurs upon awakening, resulting in heightened morning-time risk of angina, myocardial infarction, and stroke. The new drug — (80, 120, — extended-release capsules) is designed by the sponsor to provide reduction in blood pressure and heart rate 24 hours, including optimal protection in the early morning hours, when patients are most vulnerable to cardiovascular events.

The sponsor has conducted 6 clinical studies, including 5 Phase I studies and one Phase III study. This statistical review pertains to the efficacy results of the Phase III study for 80 mg, 120 mg, 160 mg, and 640 mg of — administered once bedtime in subjects with essential hypertension. Most efficacy results reported in this submission have been confirmed by this reviewer's analyses. Both the results of the sponsor's and the reviewer's analyses will be presented in the following sections.

4.2 Data Analyzed and Sources

The data sets analyzed were submitted by the sponsor on January 9, 2002. Some of the data sets were resubmitted by the sponsor on February 20, 2002 to replace the damaged data sets. All data sets analyzed are electronic documents and are located in the Electronic Document Room (EDR) of CDER of FDA under the Letter Date "9-JAN-2002" and "20-FEB-2002", respectively. The main data set for the efficacy analysis is "DVSCFB" which describes the Vital Signs Change from Baseline.

4.3 Statistical Evaluation of Evidence on Efficacy

4.3.1 Sponsor's Results and Conclusions

Table 1 summarizes the results of the efficacy analysis for the primary efficacy parameter: the morning sitting diastolic blood pressure for both the ITT and Efficacy Evaluable populations. The overall comparison revealed that a statistically significant difference existed among the treatment groups for the adjusted mean change from baseline to endpoint (p=0.018) and from baseline to week 8 (p=0.027) in the ITT population and for the adjusted mean change from baseline to endpoint (p=0.028) in the Efficacy Evaluable population.

Table 1. Adjusted Mean Change in DBP (AM) – 2-way ANCOVA

Mean Sitting Diastolic Blood Pressure (AM)	Placebo (N=84)	80 mg (N=88)	120 mg (N=84)	160 mg (N=84)	640 mg (N=87)	Overall[a] p-value
Intent-to-Treat Population						
Change from Baseline to Endpoint						
N	84	88	84	84	87	
Adjusted Mean Change[b]	-7.0	-10.1	-11.0	-10.4	-10.7	0.018
95% Confidence Interval[b]	(-8.9, -5.1)	(-12.0, -8.2)	(-12.9, -9.1)	(-12.4, -8.5)	(-12.6, -8.8)	
p-value[c]	NA	0.064	0.009	0.035	0.020	
Change from Baseline to Week 8						
N	72	78	77	79	79	
Adjusted Mean Change	-7.7	-11.4	-11.8	-10.7	-11.2	0.027
95% Confidence Interval	(-9.7, -5.7)	(-13.4, -9.5)	(-13.7, -9.8)	(-12.6, -8.7)	(-13.2, -9.3)	
p-value	NA	0.025	0.013	0.104	0.037	
Efficacy Evaluable Population						
Change from Baseline to Endpoint						
N	83	87	83	82	85	
Adjusted Mean Change	-7.3	-10.2	-11.0	-10.5	-11.0	0.028
95% Confidence Interval	(-9.2, -5.3)	(-12.1, -8.3)	(-13.0, -9.0)	(-12.5, -8.5)	(-13.0, -9.0)	
p-value	NA	0.084	0.019	0.056	0.018	

Sponsor's results confirmed by reviewer's analyses. NA = not applicable

[a] Overall p-value is calculated from ANCOVA for the comparison among treatments.

[b] Adjusted mean change and 95% confidence interval are calculated from ANCOVA on change from Baseline (Week 0) to Endpoint/Week 8 with factors treatment, center, and Baseline values as a covariate.

[c] P-value is calculated from Dunnett's test for comparison between treatment arm and place arm.

In both ITT and Efficacy Evaluable population, the adjusted mean change indicated a decrease in morning sitting diastolic blood pressure from baseline measurement to endpoint measurement and from baseline measurement to week 8 measurement for the placebo and 4 — dose groups. For the ITT population, comparison of the placebo group with the — dose groups using the Dunnett's test revealed a statistically significant difference in morning sitting diastolic blood pressure from baseline to endpoint for the subjects treated with 120 mg — (p=0.009), 160 mg — (p=0.035), and 640 mg — (p=0.020). For those subjects who completed the week 8

assessment, a statistically significant difference was observed in the comparison of the placebo group with 80 mg — (p=0.025), 120 mg — (p=0.013), and 640 mg — (p=0.037) by the Dunnett's test, respectively. For the Efficacy Evaluable population, comparison of the placebo group with the — treatment groups using the Dunnett's test revealed a statistically significant difference in morning sitting diastolic blood pressure from baseline to endpoint for the subjects treated with 120 mg — (p=0.019) and 640 mg — (p=0.018), respectively.

Table 2 and 3 summarize the results of the efficacy analyses in the secondary efficacy parameters for the ITT population from baseline measurement to endpoint and week 8 measurement, respectively. In both tables, the adjusted mean change indicated a decrease in all secondary efficacy parameters from baseline measurement to endpoint measurement and from baseline measurement to week 8 measurement for the placebo and 4 treatment groups.

The overall comparison among placebo group and treatment groups for the ITT population from baseline to endpoint for the following secondary efficacy parameters demonstrated statistically significant improvement: evening sitting diastolic blood pressure (p=0.001), evening sitting systolic blood pressure (p=0.046), morning and evening sitting pulse rate (p<0.0001 for both), morning and evening sitting blood pressure-rate product (p<0.0001 for both). There was no statistically significant difference in morning sitting systolic blood pressure among the treatment groups.

There was a similar result for those subjects who completed the week 8 assessment. The overall comparison among the treatment groups also revealed that a statistically significant difference existed among the treatment groups for evening sitting diastolic blood pressure (p=0.001), evening sitting systolic blood pressure (p=0.043), morning and evening sitting pulse rate (p<0.0001 for both), morning and evening sitting blood pressure-rate product (p<0.0001 for both). There was no statistically significant difference in morning sitting systolic blood pressure among the treatment groups.

The sponsor drew the following efficacy conclusions. The results of the current study demonstrate that — administered once nightly at bedtime in a dose of 80 mg to 640 mg is an effective antihypertensive agent in controlling morning blood pressure and in maintaining lowered trough blood pressure in the evening. Morning sitting diastolic blood pressure decreased from baseline to endpoint for the placebo and all four — groups. Statistically significant differences in the magnitude of the decrease between the placebo group and the 120 mg, 160 mg, and 640 mg — groups were observed for the primary analysis in both the ITT and Efficacy Evaluable populations. Statistical trends were observed for the 80 mg — dose group in both populations.

This reviewer questioned the sponsor's results because of the inappropriate statistical analysis methods. The sponsor used a two-way ANCOVA for this completely randomized trial with treatment and center as factors and baseline value as the covariate. This reviewer reanalyzed the data by the one-way ANCOVA for the efficacy analyses with treatment as the only one factor and baseline value as the covariate. This reviewer obtained different results. The detailed discussion will be included in the following sections.

Table 2. Secondary Efficacy Analysis for ITT Population – 2-way ANCOVA

Change from Baseline to Endpoint	Placebo (N=84)	80 mg (N=88)	120 mg (N=84)	160 mg (N=84)	640 mg (N=87)	Overall[a] p-value
Mean Sitting DBP – PM						
N	75	79	78	82	80	
Adjusted Mean Change[b]	-7.8	-11.4	-13.3	-11.2	-12.2	0.001
95% Confidence Interval[b]	(-9.7, -5.8)	(-13.2, -9.5)	(-15.2, -11.4)	(-13.0, -9.3)	(-14.1, -10.3)	
p-value[c]	NA	0.026	0.0002	0.035	0.003	
Mean Sitting SBP – AM						
N	84	88	84	84	87	
Adjusted Mean Change	-8.2	-12.0	-12.4	-12.2	-12.1	0.345
95% Confidence Interval	(-11.6, -4.8)	(-15.3, -8.6)	(-15.9, -9.0)	(-15.6, -8.7)	(-15.5, -8.7)	
p-value	NA	0.311	0.227	0.277	0.289	
Mean Sitting SBP - PM						
N	75	79	78	82	80	
Adjusted Mean Change	-7.6	-14.0	-13.0	-11.3	-13.5	0.046
95% Confidence Interval	(-11.0, -4.2)	(-17.3, -10.7)	(-16.4, -9.7)	(-14.5, -8.0)	(-16.8, -10.2)	
p-value	NA	0.023	0.070	0.314	0.041	
Mean Sitting Pulse Rate - AM						
N	84	88	84	84	87	
Adjusted Mean Change	-2.0	-6.1	-7.0	-8.8	-10.4	<.0001
95% Confidence Interval	(-3.6, -0.3)	(-7.7, -4.5)	(-8.6, -5.3)	(-10.5, -7.2)	(-12.0, -8.7)	
p-value	NA	0.001	<0.0001	<0.0001	<0.0001	
Mean Sitting Pulse Rate - PM						
N	75	79	78	82	80	
Adjusted Mean Change	-3.5	-6.7	-8.3	-10.3	-11.3	<.0001
95% Confidence Interval	(-5.2, -1.7)	(-8.4, -5.1)	(-10.0, -6.6)	(-12.0, -8.6)	(-13.0, -9.6)	
p-value	NA	0.022	0.0002	<0.0001	<0.0001	
Mean Sitting BPRP – AM						
N	84	88	84	84	87	
Adjusted Mean Change	-904.7	-1770.6	-1971.0	-2159.5	-2388.3	<.0001
95% Confidence Interval	(-1239.2, -570.3)	(-2097.3, -1443.9)	(-2305.5, -1636.6)	(-2497.1, -1821.9)	(-2720.4, -2056.2)	
p-value	NA	0.0008	<0.0001	<0.0001	<0.0001	
Mean Sitting BPRP - PM						
N	75	79	78	82	80	
Adjusted Mean Change	-1087.7	-2008.8	-2202.2	-2336.3	-2605.0	<.0001
95% Confidence Interval	(-1448.5, -762.9)	(-2359.4, -1658.2)	(-2554.2, -1850.2)	(-2681.8, -1990.7)	(-2956.0, -2253.9)	
p-value	NA	0.0009	<0.0001	<0.0001	<0.0001	

Sponsor's results confirmed by reviewer's analyses. DBP = diastolic blood pressure, SBP = systolic blood pressure, BPRP = systolic blood pressure-pulse rate product, NA = not applicable

[a] Overall p-value is calculated from ANCOVA for the comparison among treatments.

[b] Adjusted mean change and 95% confidence interval are calculated from ANCOVA on change from Baseline (Week 0) to Endpoint/Week 8 with factors treatment, center, and Baseline values as a covariate.

[c] P-value is calculated from Dunnett's test for comparison between treatment arm and place arm.

Table 3. Secondary Efficacy Analysis for ITT Population – 2-way ANCOVA

Change from Baseline to Week 8	Placebo (N=84)	80 mg (N=88)	120 mg (N=84)	160 mg (N=84)	640 mg (N=87)	Overall[a] p-value
Mean Sitting DBP – PM						
N	69	72	73	73	75	
Adjusted Mean Change[b]	-8.1	-10.6	-13.6	-11.1	-12.5	0.001
95% Confidence Interval[b]	(-10.1, -6.0)	(-12.6, -8.6)	(-15.6, -11.6)	(-13.1, -9.1)	(-14.5, -10.5)	
p-value[c]	NA	0.222	0.0004	0.100	0.005	
Mean Sitting SBP – AM						
N	72	78	77	79	79	
Adjusted Mean Change	-8.5	-13.3	-13.6	-12.8	-12.5	0.221
95% Confidence Interval	(-12.1, -4.8)	(-16.8, -9.9)	(-17.1, -10.2)	(-16.3, -9.3)	(-15.9, -9.0)	
p-value	NA	0.148	0.114	0.228	0.288	
Mean Sitting SBP - PM						
N	69	72	73	73	75	
Adjusted Mean Change	-7.5	-13.6	-13.7	-10.7	-13.7	0.043
95% Confidence Interval	(-11.1, -4.0)	(-17.1, -10.4)	(-17.1, -10.2)	(-14.2, -7.2)	(-17.2, -10.3)	
p-value	NA	0.049	0.042	0.489	0.036	
Mean Sitting Pulse Rate - AM						
N	72	78	77	79	79	
Adjusted Mean Change	-1.7	-6.6	-7.0	-8.5	-10.9	<.0001
95% Confidence Interval	(-3.5, -0.04)	(-8.3, -4.9)	(-8.7, -5.4)	(-10.2, -6.8)	(-12.6, -9.2)	
p-value	NA	0.0003	<0.0001	<0.0001	<0.0001	
Mean Sitting Pulse Rate - PM						
N	69	72	73	73	75	
Adjusted Mean Change	-3.6	-6.2	-8.3	-9.9	-11.3	<.0001
95% Confidence Interval	(-5.4, -1.8)	(-8.0, -4.5)	(-10.0, -6.6)	(-11.7, -8.2)	(-13.0, -9.6)	
p-value	NA	0.100	0.0005	<0.0001	<0.0001	
Mean Sitting BPRP – AM						
N	72	78	77	79	79	
Adjusted Mean Change	-876.9	-1940.9	-2068.4	-2163.0	-2503.7	<.0001
95% Confidence Interval	(-1227.6, -526.2)	(-2276.7, -1605.1)	(-2403.8, -1733.0)	(-2500.5, -1825.5)	(-2840.2, -2167.3)	
p-value	NA	<0.0001	<0.0001	<0.0001	<0.0001	
Mean Sitting BPRP - PM						
N	69	72	73	73	75	
Adjusted Mean Change	-1119.5	-1915.8	-2247.1	-2241.2	-2630.8	<.0001
95% Confidence Interval	(-1486.4, -752.5)	(-2275.8, -1555.7)	(-2598.0, -1896.3)	(-2598.7, -1883.7)	(-2982.0, -2279.5)	
p-value	NA	0.006	<0.0001	<0.0001	<0.0001	

Sponsor's results confirmed by reviewer's analyses. DBP = diastolic blood pressure, SBP = systolic blood pressure, BPRP = systolic blood pressure-pulse rate product, NA = not applicable

[a] Overall p-value is calculated from ANCOVA for the comparison among treatments.

[b] Adjusted mean change and 95% confidence interval are calculated from ANCOVA on change from Baseline (Week 0) to Endpoint/Week 8 with factors treatment, center, and Baseline values as a covariate.

[c] P-value is calculated from Dunnett's test for comparison between treatment arm and place arm.

4.3.2 Statistical Methodologies

The primary efficacy variable was the mean change from baseline to week 8 in morning sitting diastolic blood pressure. An endpoint analysis using the last observation carried forward (LOCF) method to impute missing week 8 values was used to evaluate this change. A secondary analysis for only observed week 8 values was performed to confirm the result of LOCF analysis.

The sponsor performed the analysis of covariance (ANCOVA) method with treatment and center as the two factors and the baseline mean as a covariate to conduct the primary and secondary efficacy analyses. Type III sums of squares were used as the error term for hypothesis testing. Each of the 4 — dose groups were compared to placebo with respect to the adjusted mean change from baseline. A modified Dunnett's test that compares least square means calculated from the ANCOVA was implemented via SAS PROC GLM. This test maintained the overall significance level at 0.05 and adjusted for any differences between the dose groups due to baseline values and centers. The 95% confidence interval on the calculated least square mean difference between each — dose group and placebo in change from baseline was also reported. The interaction between treatment and center was assessed graphically, using box plots. Assumptions of ANOVA and ANCOVA were examined graphically and with diagnostic tests.

This statistical reviewer questioned the sponsor's analysis method of two-way ANOVA/ANCOVA. Because this clinical study was a completely randomized design in which all subjects were completely randomized by the treatment groups only: placebo and four — doses groups. For this classical completely randomized design, the one-way ANOVA/ANCOVA is the appropriate analysis model. Detailed discussion will be included in the following sections on Statistical and Technical Issues and Appendix.

Within each treatment group, the hypothesis of no mean change from baseline to endpoint was tested using a paired t-test. Background and demographic characteristics were presented by treatment group and center. Continuous variables were summarized by sample size, mean, median, standard deviation, minimum, and maximum; treatment groups were compared using two-way ANOVA with treatment and center as factors. Discrete variables were summarized by frequencies and percentages; treatment groups were compared using the Cochran-Mantel-Haenszel test with center as the stratification variable.

A total of 41 centers enrolled subjects for this study. Data from centers where total subject enrollment is < 5 were combined, based on geographical location, to form 'pseudo' centers that contained roughly similar numbers of subjects as the centers that had larger subject enrollment. The effect of 'center' was tested to determine the influence/homogeneity of center.

Adjustments in the efficacy analysis for the baseline covariate were made. The demographic characteristics of age, ethnic origin, gender, and duration of hypertension were used as covariates in a stepwise-up regression modeling technique for only the primary efficacy variable. The model always included factors for treatment, center and baseline value. For the covariate factors age, race, gender, and the interaction of each with treatment, both entry and stay-in levels for the

model were p=0.05. Plots of the residuals from each stepwise model were examined for violations of the assumptions of ANOVA.

A sample size of 420 randomized subjects (84 per treatment group) was determined based on 80% power to detect an expected treatment difference of 4 mm Hg between the — groups and the placebo group with a common standard deviation of 6.8 mm Hg for a 2-sided significance level of 0.0125, and allowing for a dropout rate of 20%.

4.3.3 Detailed Review of Individual Studies

The clinical study is a randomized, double-blind, parallel, placebo-controlled, multi-center trial of oral — 80 mg, 120 mg, 160 mg, and 640 mg once daily between 9:30 and 10:30 PM (bedtime) with placebo in subjects with hypertension. All subjects were evaluated during a 2- to 3-week single-blind placebo run-in phase (Visits S1 to S3) after obtaining an informed consent. Following the single-blind placebo run-in phase, all qualified subjects were randomized at visit R1 into 1 of the 5 double-blind treatment groups including the placebo. The following Figure provides a summary of the study design.

Figure 1. Schematic Design Diagram

Period	Pre-randomization Phase (Place Run-in Phase)				Treatment Phase				End of Down Titration
Week Visit	Screen S1	1 S2	2 S3		0 R1	2 R2	4 R3	8 R4	10 R5
Time					AM PM	AM	AM PM	AM PM	AM

The study objectives are to assess the efficacy, safety, and pharmacokinetics of — treatment. The primary objective is to assess the efficacy of — treatment in subjects with essential hypertension by evaluating the mean change from baseline to week 8 in morning sitting diastolic blood pressure. The secondary objectives are: (1) to assess the safety of — by recording adverse events (AEs), electrocardiogram (ECG), and laboratory measurements; (2) to determine the effect of treatment on the change from baseline to week 8 in mean sitting systolic blood pressure, pulse rate, and mean sitting blood pressure-rate product (mean sitting systolic blood pressure multiplied by the pulse rate) measured in the morning and evening, and mean sitting diastolic blood pressure measured in the evening; and (3) to evaluate the dose-blood level relationship and the pharmacokinetics of trough total propranolol plasma samples collected from a subgroup of subjects at week 4 and 8 in each — dose group.

The Intent-to-Treat population consisted of subjects who had at least one post-baseline blood pressure measurement obtained. This population was used in all efficacy analyses. The safety population included all randomized subjects who received at least one dose of study medication. The pharmacokinetic population included only those subjects from the pharmacokinetic subgroup who had at least one plasma trough propranolol level.

The following table summarizes the subject populations by the treatment group.

Table 4. Subject Populations

Population	Placebo N (%)	80 mg N (%)	120 mg N (%)	160 mg N (%)	640 mg N (%)
Randomized	88 (100.0)	89 (100.0)	85 (100.0)	85 (100.0)	87 (100.0)
Intent-to-Treat	84 (95.45)	88 (98.88)	84 (98.82)	84 (98.82)	87 (100.0)
Efficacy	83 (94.32)	87 (97.75)	83 (97.65)	82 (96.47)	85 (97.70)
Safety	88 (100.0)	89 (100.0)	85 (100.0)	85 (100.0)	87 (100.0)
Pharmacokinetic	22 (25.00)	18 (20.22)	20 (23.53)	21 (24.71)	23 (26.44)

4.3.4 Statistical Reviewer's Findings

This statistical reviewer performed a different analysis model than the sponsor's model to conduct the primary and secondary efficacy analyses. The statistical reviewer's results and findings are summarized as follows.

Table 5 summarizes the results of the efficacy analysis for the primary efficacy parameter. The overall comparison revealed that a statistically significant difference existed among the treatment groups for the adjusted mean change from baseline to endpoint (p=0.017) and from baseline to week 8 (p=0.024) in the ITT and for the adjusted mean change from baseline to endpoint (p=0.025) in the Efficacy Evaluable populations.

In both ITT and Efficacy Evaluable population, the adjusted mean change indicated a decrease in morning sitting diastolic blood pressure from baseline measurement to endpoint measurement and from baseline measurement to week 8 measurement for the placebo and 4 treatment groups. For the ITT population, comparison of the placebo group with the [redacted] treatment groups using the Dunnett's test revealed a statistically significant difference in morning sitting diastolic blood pressure from baseline to endpoint for the subjects treated with 120 mg [redacted] (p=0.010), 160 mg [redacted] (p=0.034), and 640 mg [redacted] (p=0.016). For those subjects who completed the week 8 assessment, a statistically significant difference was observed in the comparison of the placebo group with 80 mg [redacted] (p=0.031), 120 mg [redacted] (p=0.015), and 640 mg [redacted] (p=0.019), respectively. For the Efficacy Evaluable population, comparison of the placebo group with the [redacted] treatment groups using the Dunnett's test revealed a statistically significant difference in morning sitting diastolic blood pressure from baseline to endpoint for the subjects treated with 120 mg [redacted] (p=0.022), 160 mg [redacted] (p=0.048), and 640 mg [redacted] (p=0.013), respectively.

According to the reviewer's findings for the primary efficacy analysis, [redacted] 160 mg of the mean change from baseline to endpoint for the Efficacy Evaluable population was statistically significant in the reviewer's results. But it was not statistically significant in the sponsor's findings.

Table 5. Adjusted Mean Change in DBP (AM) – one-way ANCOVA

Mean Sitting Diastolic Blood Pressure (AM)	Placebo (N=84)	80 mg (N=88)	120 mg (N=84)	160 mg (N=84)	640 mg (N=87)	Overall[a] p-value
Intent-to-Treat Population						
Change from Baseline to Endpoint						
N	84	88	84	84	87	
Adjusted Mean Change[b]	-6.9	-9.9	-10.9	-10.3	-10.7	0.017
95% Confidence Interval[b]	(-8.7, -5.0)	(-11.7, -8.1)	(-12.7, -9.0)	(-12.2, -8.5)	(-12.5, -8.8)	
p-value[c]	NA	0.073	0.010	0.034	0.016	
Change from Baseline to Week 8						
N	72	78	77	79	79	
Adjusted Mean Change	-7.3	-10.9	-11.3	-10.5	-11.1	0.024
95% Confidence Interval	(-9.2, -5.3)	(-12.8, -9.0)	(-13.2, -9.4)	(-12.4, -8.6)	(-13.0, -9.3)	
p-value	NA	0.031	0.015	0.066	0.019	
Efficacy Population						
Change from Baseline to Endpoint						
N	83	87	83	82	85	
Adjusted Mean Change	-7.0	-9.9	-10.7	-10.3	-10.9	0.025
95% Confidence Interval	(-8.9, -5.1)	(-11.8, -8.1)	(-12.5, -8.8)	(-12.2, -8.4)	(-12.7, -9.0)	
p-value	NA	0.087	0.022	0.048	0.013	

Reviewer's analyses. NA = not applicable

[a] Overall p-value is calculated from ANCOVA for the comparison among treatments.

[b] Adjusted mean change and 95% confidence interval are calculated from ANCOVA on change from Baseline (Week 0) to Endpoint/Week 8 with factors treatment, center, and Baseline values as a covariate.

[c] P-value is calculated from Dunnett's test for comparison between treatment arm and place arm.

Table 6 and 7 summarize the reviewer's results of the efficacy analysis in the secondary efficacy parameters for the ITT population from baseline measurement to endpoint and week 8 measurement, respectively. In both tables, the adjusted mean change indicated a decrease in all secondary efficacy parameters from baseline measurement to endpoint measurement and from baseline measurement to week 8 measurement for the placebo and 4 — › dose groups.

The differences between the reviewer's and sponsor's results are that the overall comparison among placebo group and treatment groups for the ITT population from baseline to week 8 for evening sitting systolic blood pressure is statistically significant in the sponsor's results (p=0.043) but not statistically significant in the reviewer's results (p=0.068), the comparison between placebo and — treatment for the mean change of evening sitting systolic blood pressure from baseline to week 8: 80 mg — and 120 mg — are statistically significant in the sponsor's results (p=0.049 and 0.042, respectively) but not statistically significant in the reviewer's results (p=0.092 and 0.064, respectively), and the comparison between placebo and — › treatment for the mean change of evening sitting diastolic blood pressure from baseline to endpoint 80 mg — is statistically significant in the sponsor's results (p=0.026) but not statistically significant in the reviewer's results (p=0.050).

Table 6. Secondary Efficacy Analysis for ITT Population – one-way ANCOVA

Change from Baseline to Endpoint	Placebo (N=84)	80 mg (N=88)	120 mg (N=84)	160 mg (N=84)	640 mg (N=87)	Overall[a] p-value
Mean Sitting DBP – PM						
N	75	79	78	82	80	
Adjusted Mean Change[b]	-7.6	-10.8	-13.1	-10.9	-12.3	0.001
95% Confidence Interval[b]	(-9.4, -5.7)	(-12.7, -9.0)	(-14.9, -11.2)	(-12.7, -9.1)	(-14.1, -10.5)	
p-value[c]	NA	0.050	0.0002	0.040	0.002	
Mean Sitting SBP – AM						
N	84	88	84	84	87	
Adjusted Mean Change	-7.6	-11.1	-11.9	-11.5	-11.8	0.326
95% Confidence Interval	(-10.9, -4.3)	(-14.3, -7.9)	(-15.2, -8.6)	(-14.8, -8.2)	(-15.0, -8.5)	
p-value	NA	0.363	0.206	0.295	0.226	
Mean Sitting SBP - PM						
N	75	79	78	82	80	
Adjusted Mean Change	-7.7	-13.8	-12.9	-11.1	-13.7	0.046
95% Confidence Interval	(-10.9, -4.5)	(-16.9, -10.6)	(-16.1, -9.7)	(-14.2, -8.0)	(-16.8, -10.6)	
p-value	NA	0.030	0.079	0.361	0.031	
Mean Sitting Pulse Rate - AM						
N	84	88	84	84	87	
Adjusted Mean Change	-1.5	-5.6	-6.4	-8.3	-9.8	<.0001
95% Confidence Interval	(-3.1, -0.2)	(-7.3, -4.0)	(-8.1, -4.7)	(-10.0, -6.6)	(-11.4, -8.1)	
p-value	NA	0.002	0.0002	<0.0001	<0.0001	
Mean Sitting Pulse Rate - PM						
N	75	79	78	82	80	
Adjusted Mean Change	-2.7	-6.3	-7.5	-9.4	-10.4	<.0001
95% Confidence Interval	(-4.5, -0.9)	(-8.0, -4.5)	(-9.3, -5.7)	(-11.1, -7.7)	(-12.1, -8.6)	
p-value	NA	0.019	0.001	<0.0001	<0.0001	
Mean Sitting BPRP – AM						
N	84	88	84	84	87	
Adjusted Mean Change	-786.6	-1643.9	-1849.4	-2033.5	-2279.9	<.0001
95% Confidence Interval	(-1115.9, -457.2)	(-1965.7, -1322.2)	(-2178.8, -1520.1)	(-2362.9, -1704.2)	(-2603.5, -1956.3)	
p-value	NA	0.001	<0.0001	<0.0001	<0.0001	
Mean Sitting BPRP - PM						
N	75	79	78	82	80	
Adjusted Mean Change	-977.4	-1929.3	-2068.4	-2188.1	-2477.5	<.0001
95% Confidence Interval	(-1334.0, -620.9)	(-2276.5, -1582.1)	(-2418.1, -1718.8)	(-2528.9, -1847.4)	(-2822.6, -2132.5)	
p-value	NA	0.001	<0.0001	<0.0001	<0.0001	

Reviewer's analyses. DBP = diastolic blood pressure, SBP = systolic blood pressure, BPRP = systolic blood pressure-pulse rate product, NA = not applicable

[a] Overall p-value is calculated from ANCOVA for the comparison among treatments.

[b] Adjusted mean change and 95% confidence interval are calculated from ANCOVA on change from Baseline (Week 0) to Endpoint/Week 8 with factors treatment, center, and Baseline values as a covariate.

[c] P-value is calculated from Dunnett's test for comparison between treatment arm and place arm.

Table 7. Secondary Efficacy Analysis for ITT Population – one-way ANCOVA

Change from Baseline to Week 8	Placebo (N=84)	80 mg (N=88)	120 mg (N=84)	160 mg (N=84)	640 mg (N=87)	Overall[a] p-value
Mean Sitting DBP – PM						
N	69	72	73	73	75	
Adjusted Mean Change[b]	-7.9	-10.1	-13.3	-11.1	-12.6	0.001
95% Confidence Interval[b]	(-9.8, -5.9)	(-12.1, -8.2)	(-15.2, -11.4)	(-13.0, -9.2)	(-14.5, -10.7)	
p-value[c]	NA	0.289	0.0004	0.068	0.002	
Mean Sitting SBP – AM						
N	72	78	77	79	79	
Adjusted Mean Change	-7.7	-12.2	-12.8	-12.2	-12.0	0.220
95% Confidence Interval	(-11.1, -4.2)	(-15.5, -8.9)	(-16.2, -9.5)	(-15.5, -8.9)	(-15.3, -8.7)	
p-value	NA	0.191	0.115	0.196	0.219	
Mean Sitting SBP – PM						
N	69	72	73	73	75	
Adjusted Mean Change	-7.9	-13.1	-13.4	-10.9	-13.8	0.068
95% Confidence Interval	(-11.2, -4.5)	(-16.4, -9.8)	(-16.7, -10.2)	(-14.1, -7.6)	(-17.0, -10.6)	
p-value	NA	0.092	0.064	0.516	0.040	
Mean Sitting Pulse Rate - AM						
N	72	78	77	79	79	
Adjusted Mean Change	-1.2	-6.2	-6.6	-8.0	-10.4	<.0001
95% Confidence Interval	(-2.9, -0.6)	(-7.9, -4.5)	(-8.3, -4.9)	(-9.7, -6.3)	(-12.1, -8.7)	
p-value	NA	0.0002	<0.0001	<0.0001	<0.0001	
Mean Sitting Pulse Rate - PM						
N	69	72	73	73	75	
Adjusted Mean Change	-3.0	-5.9	-7.7	-9.4	-10.7	<.0001
95% Confidence Interval	(-4.8, -1.1)	(-7.7, -4.1)	(-9.5, -5.9)	(-11.2, -7.6)	(-12.5, -9.0)	
p-value	NA	0.082	0.001	<0.0001	<0.0001	
Mean Sitting BPRP – AM						
N	72	78	77	79	79	
Adjusted Mean Change	-743.0	-1803.1	-1930.9	-2041.9	-2394.9	<.0001
95% Confidence Interval	(-1084.8, -401.2)	(-2131.4, -1474.7)	(-2261.4, -1600.3)	(-2368.1, -1715.7)	(-2721.2, -2068.6)	
p-value	NA	<0.0001	<0.0001	<0.0001	<0.0001	
Mean Sitting BPRP - PM						
N	69	72	73	73	75	
Adjusted Mean Change	-1038.5	-1828.2	-2131.4	-2164.7	-2542.3	<.0001
95% Confidence Interval	(-1395.5, -681.6)	(-2177.1, -1479.2)	(-2478.2, -1784.6)	(-2511.2, -1818.2)	(-2884.3, -2200.3)	
p-value	NA	0.007	<0.0001	<0.0001	<0.0001	

Reviewer's analyses. DBP = diastolic blood pressure, SBP = systolic blood pressure, BPRP = systolic blood pressure-pulse rate product, NA = not applicable

[a] Overall p-value is calculated from ANCOVA for the comparison among treatments.

[b] Adjusted mean change and 95% confidence interval are calculated from ANCOVA on change from Baseline (Week 0) to Endpoint/Week 8 with factors treatment, center, and Baseline values as a covariate.

[c] P-value is calculated from Dunnett's test for comparison between treatment arm and place arm.

4.4 Findings in Special/Subgroup Population

The subgroup analyses were performed for the mean change from baseline to endpoint for both morning and evening sitting diastolic blood pressures by age, gender, ethnic origin, and duration of hypertension. Table 8 summarizes the change from baseline to endpoint for morning and evening sitting diastolic blood pressure by age. A decrease in both morning and evening sitting diastolic blood pressure from baseline to endpoint was observed in all treatment groups.

Table 8. Mean Change from Baseline to Endpoint for DBP (AM and PM) by Age

Age Group (years)	Placebo	80 mg	120 mg	160 mg	640 mg
AM Sitting DBP					
18 – 64					
N	74	70	73	66	68
Mean Change	-6.76	-10.06	-11.08	-11.37	-10.14
≥ 65					
N	10	18	11	18	19
Mean Change	-8.20	-8.89	-9.21	-7.22	-11.86
PM Sitting DBP					
18 - 64					
N	65	66	69	65	65
Mean Change	-7.69	-10.56	-12.59	-11.30	-11.63
≥ 65					
N	10	13	9	17	15
Mean Change	-6.73	-12.62	-18.07	-9.88	-13.58

Reviewer's results.

Table 9 summarizes the change from baseline to endpoint for morning and evening sitting diastolic blood pressure by gender. A decrease in both morning and evening sitting diastolic blood pressure from baseline to endpoint was observed in all treatment groups.

Table 9. Mean Change from Baseline to Endpoint for DBP (AM and PM) by Gender

Gender	Placebo	80 mg	120 mg	160 mg	640 mg
AM Sitting DBP					
Female					
N	36	38	38	33	39
Mean Change	-9.93	-9.46	-14.44	-11.60	-11.07
Male					
N	48	50	46	51	48
Mean Change	-4.68	-10.10	-7.86	-9.76	-10.06
PM Sitting DBP					
Female					
N	36	33	37	32	36
Mean Change	-7.81	-12.73	-15.23	-12.39	-10.86
Male					
N	39	46	41	50	44
Mean Change	-7.33	-9.58	-11.41	-10.12	-12.92

Sponsor's results confirmed by reviewer's analyses.

Table 10 summarizes the change from baseline to endpoint for morning and evening sitting diastolic blood pressure by ethnic origin. A decrease in both morning and evening sitting diastolic blood pressure from baseline to endpoint was observed in all treatment groups except the 120 — in the other ethnic origin category.

Table 10. Mean Change from Baseline to Endpoint for DBP (AM & PM) by Ethnic Origin

Ethnic Origin	Placebo	80 mg	120 mg	160 mg	640 mg
AM Sitting DBP					
Asian					
N	0	1	1	2	0
Mean Change	-	-17.33	-25.00	-7.00	-
Black					
N	12	18	15	12	16
Mean Change	-11.67	-9.15	-11.33	-11.67	-6.83
Caucasian					
N	61	52	54	54	58
Mean Change	-6.62	-9.81	-10.95	-11.40	-11.67
Hispanic					
N	11	16	13	16	12
Mean Change	-3.45	-10.33	-9.79	-6.92	-9.28
Other					
N	0	1	1	0	1
Mean Change	-	-6.67	3.33	-	-17.33
PM Sitting DBP					
Asian					
N	0	1	1	2	0
Mean Change	-	-15.33	-4.67	-7.00	-
Black					
N	11	16	14	12	15
Mean Change	-7.94	-11.27	-10.71	-7.94	-5.91
Caucasian					
N	54	46	49	52	53
Mean Change	-6.98	-10.80	-14.53	-12.10	-12.67
Hispanic					
N	10	15	13	16	11
Mean Change	-10.33	-10.33	-11.18	-10.25	-16.48
Other					
N	0	1	1	0	1
Mean Change	-	-13.33	-19.33	-	-18.00

Sponsor's results confirmed by reviewer's analyses.

Table 11 summarizes the change from baseline to endpoint for morning and evening sitting diastolic blood pressure by duration of hypertension. A decrease in both morning and evening sitting diastolic blood pressure from baseline to endpoint was observed in all treatment groups for subjects diagnosed with hypertension for <1 year, for ≥1 to 4 years, and for ≥5 years.

Table 11. Mean Change from Baseline to Endpoint for DBP (AM and PM) by Duration of Hypertension

Duration of Hypertension	Placebo	80 mg	120 mg	160 mg	640 mg
AM Sitting DBP					
<1 year					
N	8	9	6	4	9
Mean Change	-5.50	-10.89	-13.00	-9.50	-8.74
≥1 to 4 years					
N	26	27	26	24	25
Mean Change	-6.33	-8.80	-11.23	-9.03	-8.25
≥5 years					
N	48	51	51	55	52
Mean Change	-7.28	-10.08	-10.31	-11.07	-12.19
PM Sitting DBP					
<1 year					
N	8	7	6	4	6
Mean Change	-3.08	-8.62	-13.17	-15.17	-15.39
≥1 to 4 years					
N	24	24	23	24	25
Mean Change	-9.53	-9.86	-13.61	-8.99	-12.01
≥5 years					
N	41	47	48	53	48
Mean Change	-7.17	-11.78	-13.11	-11.50	-11.58

Sponsor's results confirmed by reviewer's analyses.

4.5 Statistical and Technical Issues

Last Observation Carried Forward Analysis

The primary and confirmatory analyses were performed on the primary and secondary efficacy variables. The analysis examined the change from baseline to endpoint for each variable. In the primary analysis, the endpoint was defined as week 8 or if the subject discontinued the double-blind treatment phase prior to week 8, the last post-treatment measurement was used (LOCF). In the confirmatory analysis, missing data at week 8 was not imputed and the analysis was based on only the subjects who completed week 8 measurements. The sponsor compared the two analysis results and found that the results of the LOCF analysis were similar to the confirmatory analysis.

Subjects Excluded from Efficacy Analyses

A total of 7 subjects were excluded from the Efficacy Evaluable population. Three of the 7 subjects were excluded from the Efficacy Evaluable analyses because the study blind labels were damaged and could have possibly led to unblinding of the subject's treatment. The other four subjects who were randomized at one site were excluded because the source documentation was insufficient to verify the data entered on the CRF.

Assessment of Treatment Center Interaction

Subjects were enrolled from 41 centers for this study. There were 14 centers with less than 5 subjects and these centers were pooled to form 4 'pseudo' centers. The effect of 'center' on the efficacy analysis was tested to determine the influence/homogeneity of center and was performed on data from 31 centers. The sponsor used a 2-way ANCOVA model with treatment and center as the factors and baseline value as the covariate and assessed the interaction effect between treatment and center by using box plots. No consistent evidence of a treatment by center interaction was observed.

Assessment of Assumptions of Analysis of Covariance

The assessment of assumptions of ANOVA and ANCOVA efficacy analyses has been performed. No evidence of violation of assumptions of ANOVA and ANCOVA for ITT analyses of any efficacy parameter was found.

Method of Analysis of Covariance

The major statistical issue in this submission is that an inappropriate statistical analysis method, the two-way ANOVA/ANCOVA, was applied by the sponsor for this completely randomized trial. The sponsor clearly described this study as a one-way classification design where the subjects were completely randomized by 5 treatment groups only: placebo and 4 — dose groups and was not randomized by study centers. The sponsor also verified that the randomization scheme was balanced for the 5 treatment groups. Therefore, the one-way ANOVA/ANCOVA is the only appropriate analysis method to apply for this study where the treatment is the only one factor without/with a covariate. This reviewer proved (Appendix 4.9) that if one uses a two-way ANOVA/ANCOVA for this study, one will get biased estimates for the treatment effects and biased analysis results which will mislead our conclusions. The center can be one of demographic characteristics in the stepwise-up regression modeling analysis and subgroup analyses. But the center can not be a second factor in ANOVA/ANCOVA model because the trial was not randomized by the centers. The detailed statistical technical discussion can be found in the Appendix 4.9.

4.6 Statistical Evaluation of Collective Evidence

Table 5-7 clearly summarized the statistical results of primary and secondary efficacy analyses and provided the evidence to support the conclusions. The modified Dunnett's test was used to adjust the multiple comparisons between the placebo and — dose groups. The overall p-value and the p-values of multiple comparisons adjusted by the Dunnett's test were use for the statistical hypothesis tests. The adjusted mean change for each primary and secondary efficacy parameter and 95% confidence interval were calculated from the one-way ANCOVA on the mean change adjusted by the endpoint/week 8, treatment, and baseline value.

4.7 Conclusion and Recommendations

This reviewer agrees with the sponsor's efficacy conclusions. But this is only one efficacy study. The primary endpoint does not have a very small p-value. It might not be enough to represent for a wide-ranging population.

The results of the study demonstrated that — administered once nightly at bedtime in a dose of 120 mg, 160 mg, and 640 mg is an effective anti-hypertensive agent in controlling morning blood pressure and in maintaining lowered trough blood pressure in the evening.

Both morning and evening sitting diastolic blood pressures decreased from baseline to endpoint for the placebo and all four — groups. Statistically significant differences in the magnitude of the decrease between the placebo group and the 120 mg, 160 mg, and 640 mg — groups were observed for the primary analysis in both ITT population and the Efficacy Evaluable population. Statistical trends were observed for the 80 mg — group in both populations.

A decrease from baseline to endpoint was observed for both morning and evening sitting systolic blood pressures in all treatment groups. Statistically significant differences in the magnitude of the decrease between the placebo group and — groups were observed for evening sitting systolic blood pressure at the 80 mg and 640 mg — doses. Decreases from baseline and endpoint were also observed for morning and evening pulse rate and morning and evening BPRP in all treatment groups and statistically significant differences were observed for the decreases between the placebo group and the — groups. The effects of the 120mg, 160 mg, and 640 mg — are hardly distinguishable.

4.8 Appendix of Individual Studies Reviewed

This is the only one study to be reviewed. There is no another study to be included in this report.

4.9 Appendix of Technical Discussion on Statistical Issues

In this appendix, we will technically discuss the statistical issue that the estimate of treatment effect and statistical analysis will be biased when one applies the two-way ANOVA/ANCOVA model to a completely randomized trial. Without loss of generality, we restrict our discussion on the ANOVA model only. For the ANCOVA model, we have similar results.

In general, for analysis of variance in a two-way layout, the statistically additive model will be

$$y_{ij} = \mu + \alpha_i + \beta_j + \varepsilon_{ij}, \qquad i = 1,\Lambda\ ,a; \qquad j = 1,\Lambda\ ,b$$

with

$$\sum_{i=1}^{a} \alpha_i = 0, \qquad \sum_{j=1}^{b} \beta_j = 0, \qquad \text{and} \qquad \varepsilon_{ij} \sim IND(0,\sigma^2),$$

where α_i is the effect of the ith treatment, β_j is the effect of the jth block, and ε_{ij} is the observed error with mean zero, equal variance and no correlation. Let

$$\bar{y}_{\bullet\bullet} = \frac{1}{ab}\sum_{i,j} y_{ij}, \qquad \bar{y}_{i\bullet} = \frac{1}{b}\sum_{j=1}^{b} y_{ij}, \qquad \bar{y}_{\bullet j} = \frac{1}{a}\sum_{i=1}^{a} y_{ij}.$$

Then, we have estimates of the ith treatment and jth block effects as follows, respectively.

$$\hat{\alpha}_i = \bar{y}_{i\bullet} - \bar{y}_{\bullet\bullet}, \qquad \hat{\beta}_j = \bar{y}_{\bullet j} - \bar{y}_{\bullet\bullet}$$

We can easily check that $\hat{\alpha}_i$ and $\hat{\beta}_j$ are the unbiased estimates of the treatment and block effects, respectively.

When one uses this two-way layout model for a completely randomized trial where the subjects are randomized by treatments only, some treatment(s) will not be balanced in blocks because the subjects are not randomized by blocks. In another words, for a two-way layout, the *i*th treatment will be applied into all *b* blocks for each *i*. Therefore, all treatments will be balanced in blocks for a two-way layout. In a completely randomized trial, the *i*th treatment will not be applied into all *b* blocks and will be applied into $b_i'(\neq b)$ blocks only for some *i*. Thus,

$$\bar{y}_{i\bullet} = \frac{1}{b_i'}\sum_{j=1}^{b_i'} y_{ij}, \qquad \text{for some } i$$

and then

$$E[\bar{y}_{i\bullet}] \neq \mu + \alpha_i.$$

Therefore, $\hat{\alpha}_i$ will be a biased estimate of the *i*th treatment effect and the statistical analysis based on the two-way ANOVA model will also be biased.

4.10 Appendix of Bibliography and/or References

1. Dunn, Olive J. and Clark, Virginia A. (1974). Applied Statistics: Analysis of Variance and Regression. New York: John Wiley & Sons.

2. Kempthorne, Oscar (1952). The Design and Analysis of Experiments. New York: John Wiley & Sons.

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