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

# STATISTICAL REVIEW AND EVALUATION

## CLINICAL STUDIES

| | |
|---|---|
| **NDA/Serial Number:** | 20-757/ (b)(4)034 |
| **Drug Name:** | Avapro (Irbesartan) |
| **Indication(s):** | Hypertension in pediatric patients |
| **Applicant:** | Sanofi-Aventis c/o Bristol-Myers Squibb Company |
| **Date(s):** | July, 30 2004 |
| **Review Priority:** | Standard |
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**Keywords:** dose-response, pediatric exclusivity, sample size

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# 1. EXECUTIVE SUMMARY

## 1.1 Conclusions and Recommendations

This study failed to show a statistically significant dose-response slope. The analysis on a withdrawal effect of irbesartan showed a borderline statistically significant difference. However, the clinical significance of the observed small treatment difference needs to be assessed by the medical division. (b) (4)

## 1.2 Brief Overview of Clinical Studies

To respond to FDA's Written Request, the sponsor conducted a clinical trial to investigate the efficacy and the safety of irbesartan in pediatric patients. The study was a randomized, multi-center, double-blind, dose-response, active control study of irbesartan in children and adolescent with hypertension or high normal blood pressure. A total of 318 patients were randomized to one of 0.5/0.5 mg/kg, 0.5/1.5 mg/kg, or 1.5/4.5 mg/kg irbesartan group for 3 weeks of irbesartan treatment (Period B), then the patients were re-randomized to either placebo or irbesartan group (Period C). 302 patients were included in the primary analysis.

The primary efficacy endpoint was the change in trough seated systolic blood pressure (SeSBP) measured from baseline to the Week 3 of Period B. If the primary endpoint did not show the statistically significant dose trend, then the first secondary efficacy endpoint, which was the change in SeSBP from the end of Period B to the Week 2 of Period C, was analyzed to evaluate the withdrawal effect of irbesartan treatment.

## 1.3 Statistical Issues and Principal Findings

The primary endpoint, SeSBP changes at 3 weeks of irbesartan treatment from the baseline, was analyzed by fitting ANCOVA model using the baseline as the covariate. This analysis showed no statistically significant dose trend (p=0.118). The results of the analysis are summarized in the table below.

Table 1: Primary analysis Result
*(sponsor's results confirmed by the reviewer)*

| | 0.5/0.5 mg/kg n=108 | 0.5/1.5 mg/kg n=107 | 1.5/4.5 mg/kg n=103 |
|---|---|---|---|
| N | 101 | 101 | 100 |
| Baseline Mean (SD) | 134.3 (9.7) | 134.5 (9.9) | 135.1 (11.2) |
| Mean at 3 Week of period B | 122.8 (12.1) | 125.3 (11.7) | 121.8 (12.9) |
| LS Mean change | -11.7 (1.1) | -9.3 (1.1) | -13.2 (1.1) |
| 95% confidence interval | (-13.8, -9.6) | (-11.5, -7.2) | (-15.3, -11.0) |
| p-value for the trend test | | | 0.118 |

Because the primary analysis showed no statistically significant dose trend, the withdrawal effect of irbesartan was evaluated. The patients were re-randomized to either placebo or irbesartan group at the end of Period B. The change of SeSBP from end of Period B to end of Period C was analyzed. The following table shows the results of the analysis.

Table 2: Mean changes form End of Period B in Trough SeSBP to Week 2 of Period C *(sponsor's results confirmed by the reviewer)*

| | Placebo N=148 | Irbesartan N=150 |
|---|---|---|
| N | 141 | 145 |
| End of period B mean (SD) | 122.7 (11.9) | 124.0 (12.5) |
| LS Mean change | 2.4 (0.8) | 0.1 (0.8) |
| Est. difference between the groups | | -2.3 |
| 95% CI for estimated difference | | (-4.63, -0.01) |
| p-value | | 0.050 |

The p-value from the ANCOVA model using the baseline as the covariate was 0.05, which reached the borderline significance. However, the mean difference between the groups was only 2.3mmHg, which was far smaller than the projected mean difference of 4.2mmHg. The clinical significance of this small difference needs to be assessed by the medical division. Due to the increase of chances in false positive finding, the interpretation of a secondary endpoint is not generally appropriate when a study fails on the primary endpoint. [redacted] (b) (4)

# 2. INTRODUCTION

## 2.1 Overview

Irbesartan is for treating hypertensive adults at doses of 75 mg, 150 mg, and 300 mg administered once-daily. At the written request from the FDA, the sponsor conducted a study to evaluate the dose-response relationship of irbesartan in the treatment of hypertension in pediatric patient. This reviewer evaluated this dose-response relationship study (Study cv131154).

Study cv131154 was randomized, multi-center, double-blind, dose-ranging study of irbesartan in children (6 years – Tanner stage <3) and adolescents (Tanner stage ≥ 3 - <17 years) with hypertension or high-normal blood pressure. Patients were randomly assigned to receive one of the three doses of irbesartan (0.5 mg/kg, 0.5/1.5 mg/kg, and 1.5/4.5 mg/kg).

## 2.2 Data Sources

Data used for review is from the electronic submission received on 07/30/04. The network path is " \\CDSESUB1\N20757\N_000\2004-07-30" in the EDR.

# 3. STATISTICAL EVALUATION

## 3.1 Evaluation of Efficacy

### 3.1.1 Study Design

This study is multi-center, randomized, double-blind, dose ranging study evaluated the safety and efficacy of a range of irbesartan doses in the treatment of children (6 years – Tanner stage <3) and adolescents (Tanner stage ≥ 3 - <17 years) with hypertension or high-normal blood pressure. The study consisted of four periods. During period A, previous antihypertensive therapy and prohibited concomitant medications were withdrawn. In period B patients were randomly assigned to double-blind treatment with one of three irbesartan regimens (0.5 mg/kg, 0.5 → 1.5 mg/kg, and 1.5 mg/kg → 4.5 mg/kg). Study medication was titrated up to the assigned target dose after the first week; this dose was continued for the remaining 2 weeks of Period B. At period C, the patients were re-assigned to randomized therapy with either placebo or irbesartan at the assigned target dose last taken during period B. The blood pressure was measured at the end of Week 1 and Week 2. The patients who completed period C and the patients who met the discontinuation criteria for direct enrollment into period D, entered the open-label extension period.

### 3.1.2 Study Objectives

Primary Objective
To evaluate the dose-response relationship in change from baseline in trough seated systolic blood pressure (SeSBP) after 3 weeks of double-blind treatment (end of initial treatment Period B) with low, medium or high doses of irbesartan in children and adolescents aged 6 to 16 years.

Secondary Objectives

- To evaluate the change from the end of the initial treatment period to the end of the withdrawal period in trough SeSBP for irbesartan versus placebo

- To evaluate the dose-response relationship in change from baseline in trough seated diastolic blood pressure (SeDBP) at the end of the initial treatment period

- To evaluate the change from the end of the initial treatment period to the end of the withdrawal period in trough SeDBP for irbesartan versus placebo

- To evaluate the percentage of subjects who reach a target BP of $< 90^{th}$ percentile for both SeSBP and SeDBP at the end of the initial treatment period

- To assess the safety and tolerability of irbesartan in the pediatric population

### 3.1.3 Efficacy Endpoints

Primary

Change from baseline in trough SeSBP at Week 3 of Period B.

Secondary
The most important secondary efficacy measurement was the change in trough SeSBP from the end of Period B to end of Period C. Other efficacy measurements were the changes from original baseline at each visit in trough SeSBP and SeDBP, and the number of patients reached the target BP at each visit during the study.

### 3.1.4 Sample Size

The sample size was originally determined that a total of 189 subjects (63 per dose level) would provide 80% power to detect a significant trend across the three dose groups assuming a difference between high and low groups of 6 mmHg.

However, the planned number of sample size was increased to 270 (90 per dose level) to keep the intended children adolescent balance as per the FDA written request. This number would provide a power of 80% for detecting a significant trend across the three dose groups assuming the smaller difference of 5.0 mmHg between high and low groups. The estimated standard deviation of change from baseline in SeSBP was 12mmHg and the dropout rate was10%.

For the secondary analysis investigating the effect of a 2-week withdrawal from irbesartan by the end of period C, an additional allowance of 5% was for new losses between the end of period B and the end of period C. Thus, a total of 126 patients for irbesartan and 126 for placebo were expected in period C. For the simple two-group comparison, the planned sample size would be sufficient to provide 80% power to detect a difference of 4.2 mmHg, assuming the same standard deviation of 12 mmHg and a two-sided test at alpha level of 0.05.

*Reviewer's Comments:*

A total of 441 subjects were enrolled into the study; 318 patients were in period B; 298 patients were in period C; 294 patients were in period D. In the primary analysis, 302 patients (100/101 patients per dose level) were included, and 286 patients (141 and 145 patients in the placebo and the irbesartan group, respectively) were included in the first secondary analysis. The sample sizes of the primary and the secondary analyses were greater than planned sample sizes, and these greater sample sizes can make the p-values reach the significance level without any clinically meaningful difference between the groups.

### 3.1.5 Stratification

No stratification was used in this study.

### 3.1.6 Interim Analysis

No interim analysis for efficacy was planned for this study.

### 3.1.7 Efficacy Analysis Methods

The primary analysis was a test for linear trend across the three dose groups with respect to changes from baseline in trough SeSBP at Week 3 of Period B. The analysis was carried out using a linear contrast applied to the adjusted mean changes from an ANCOVA model having a term for treatment group and baseline value as covariate. The contrast coefficients of -5, -2, and +7 were linearly related to the final target doses of 0.5, 2.5 and 4.5 mg/kg, respectively. As the test for linear trend in changes in trough SeSBP at Week 3 of Period B was not significant ($p>0.05$), a comparison of the changes in trough SeSBP between the

two groups, the placebo and the irbesartan, from the end of Period B to Week 2 of Period C was performed. This comparison was also carried out using a similar ANCOVA model with group as a main factor and baseline value as covariate.

### 3.1.8 Baseline Characteristics

The baseline demographic characteristics including age, gender, race, weight, hypertensive status, region, and Tanner Scale were examined for the balance between the three treatment groups.

**Table 3: Baseline Characteristics by Treatment Group**
*(Source: Sponsor's analysis confirmed by the reviewer)*

| | Low Dose | Medium Dose | High Dose | Overall |
|---|---|---|---|---|
| Age (month) | | | | |
| Mean | 12.3 | 12.5 | 12.6 | 12.5 |
| SD | 2.8 | 2.9 | 2.9 | 2.8 |
| Range | 6 – 16 | 6 – 16 | 6 - 16 | 6 – 16 |
| Gender (n(%)) | | | | |
| Male | 74 (68.5) | 71 (66.4) | 69 (67.0) | 214 (67.3) |
| Female | 34 (31.5) | 36 (33.6) | 34 (33.0) | 104 (32.7) |
| Race (n(%)) | | | | |
| White | 94 (87.0) | 92 (86.0) | 89 (86.4) | 275 (86.5) |
| Black | 9 (8.3) | 11 (10.3) | 12 (11.7) | 32 (10.1) |
| Other/Unknown | 5 (4.6) | 4 (3.7) | 2 (1.9) | 11 (3.5) |
| Weight (kg) | | | | |
| Mean | 60.9 | 66.1 | 67.4 | 64.8 |
| SD | 24.0 | 24.8 | 28.3 | 25.8 |
| Range | 19.7 – 136.0 | 21.0 – 172.1 | 20.6 – 165.6 | 19.7 – 172.1 |
| Region (n(%)) | | | | |
| N. America | 27 (25.0) | 29 (27.1) | 27 (26.2) | 83 (26.1) |
| Europe | 81 (75.0) | 78 (72.9) | 76 (73.8) | 235 (73.9) |
| Hypertensive Status | | | | |
| Hypertension | 82 (75.9) | 84 (78.5) | 88 (85.4) | 254 (79.9) |
| High-normal | 22 (20.4) | 19 (17.8) | 14 (13.6) | 55 (17.3) |
| Normal | 4 (3.7) | 4 (3.7) | 1 (1.0) | 9 (2.8) |
| Tanner Scale (n(%)) | | | | |
| 6 yrs to < 3 TS | 61 (56.5) | 54 (50.5) | 44 (42.7) | 159 (50.0) |
| ≥ 3 TS to < 17 yrs. | 47 (43.5) | 53 (49.5) | 59 (57.3) | 159 (50.0) |

SD: Standard Deviation, TS: Tanner Stage

As shown above, the distributions of baseline demographic characteristics were generally similar across the irbesartan treatment groups. There were small

differences between the groups for race, weight, hypertensive status, and Tanner scale. The frequency of black patients, patients with hypertension, patients in upper Tanner Stage, and the mean weight increased slightly with the dose level. However, these differences were not statistically significant. The following table shows the baseline efficacy measures for patients randomized into period B.

Table 4: Baseline Efficacy Measures
*(Source: Sponsor's results confirmed by the reviewer)*

| | Low Dose | Medium Dose | High Dose | Overall |
|---|---|---|---|---|
| SBP (mmHg) | | | | |
| N | 108 | 107 | 103 | 318 |
| Mean | 133.9 | 134.1 | 135.0 | 134.3 |
| SD | 9.9 | 9.9 | 11.1 | 10.3 |
| Range | 107.7 – 152.7 | 115.0 – 168.3 | 110.3 – 174.3 | 107.7 – 174.3 |
| DBP (mmHg) | | | | |
| N | 108 | 107 | 103 | 318 |
| Mean | 71.9 | 70.7 | 71.4 | 71.3 |
| SD | 8.8 | 8.6 | 8.4 | 8.6 |
| Range | 51.7 – 97.7 | 53.0 – 94.0 | 51.3 – 92.7 | 51.3 – 97.7 |
| HR (beats/min) | | | | |
| N | 108 | 107 | 103 | 318 |
| Mean | 89.2 | 88.9 | 89.2 | 89.1 |
| SD | 13.8 | 13.8 | 12.6 | 13.4 |
| Range | 56.3 – 120.7 | 58.0 – 116.3 | 47.3 – 119.0 | 47.3 – 120.7 |

The mean baseline of SBP, DBP, and HR were similar across the irbesartan treatment group.

### 3.1.9 Primary Efficacy Analyses

The primary analysis was done on trough SeSBP for change from baseline to Week 3 of period B. The drop out rate was less than 10%, and the number of patients who had the BP measurements at Week 3 in period B was greater than the planned sample size. Therefore, the missing values were not imputed, and the patients without BP measurements at the Week 3 in period B were excluded in the primary analysis. The primary analysis showed no statistically significant dose trend with p=0.118. The results of the analysis are presented in the table below.

Table 5: Primary analysis Result
*(Source: Sponsor's results confirmed by the reviewer)*

| | 0.5/0.5 mg/kg n=108 | 0.5/1.5 mg/kg n=107 | 1.5/4.5 mg/kg n=103 |
|---|---|---|---|
| N | 101 | 101 | 100 |
| Baseline Mean (SD) | 134.3 (9.7) | 134.5 (9.9) | 135.1 (11.2) |
| Mean at 3 Week of period B | 122.8 (12.1) | 125.3 (11.7) | 121.8 (12.9) |
| LS Mean change | -11.7 (1.1) | -9.3 (1.1) | -13.2 (1.1) |
| 95% confidence interval | (-13.8, -9.6) | (-11.5, -7.2) | (-15.3, -11.0) |
| p-value for the trend test | | | 0.118 |

The least square (LS) mean changes from baseline were -11.7, -9.3, and -13.2 mmHg for the low, medium and high-dos irbesartan treatment groups, respectively. The LS mean change of the medium dose group was less than the one of the low dose group, and the difference between the low and the high dose group was only 1.5. The test for linear trend across these treatment groups did not demonstrate a statistically significant dose-response relationship (p=0.118).

**3.1.10 Secondary Efficacy Analyses**

Because the test for linear trend in changes in trough SeSBP at Week 3 of period B was not significant, the comparison between irbesartan and placebo with respect to changes from the end of period B to Week 2 of period C in SeSBP was performed. This analysis was done to evaluate the effect of withdrawal from irbesartan over the two-week period. As the primary analysis, ANCOVA model using the baseline as covariate was used for the comparison between the placebo and the irbesartan group. The following table summarizes the test results.

Table 6: Mean changes form End of Period B in Trough SeSBP to Week 2 of Period C *(Source: Sponsor's results confirmed by the reviewer)*

| | Placebo N=148 | Irbesartan N=150 |
|---|---|---|
| N | 141 | 145 |
| End of period B mean (SD) | 122.7 (11.9) | 124.0 (12.5) |
| LS Mean change | 2.4 (0.8) | 0.1 (0.8) |
| Est. difference between the groups | | -2.3 |
| 95% CI for estimated difference | | (-4.63, -0.01) |
| p-value | | 0.050 |

The p-value of the test barely met the significance level (p=0.05), and the sponsor claimed that the difference between the withdrawal from irbesartan and no withdrawal was statistically significant. However, the estimated difference between the two groups was only 2.3 mmHg, and the clinical significance of this small treatment difference needs to be assessed by the medical division. As stated

in section 3.1.4 Sample Size, the planned sample size of this analysis was 126 per group to detect a difference of 4.2 mmHg. This analysis was done on the total of 286 patients (141 in the placebo and 145 in the irbesartan), and this greater number of sample size made this smaller difference between the groups statistically significant. If the sample size of this analysis was as planned (126 per group), then the difference of 2.3 mmHg between the groups would not meet the significance level and therefore not be statistically significant. Furthermore, when a study fails on the primary endpoint, the interpretation of any secondary endpoint is generally not appropriate because the chance of false positive findings from such interpretation increases.

SeDBP and responder rates were analyzed as the secondary endpoints. Change of SeDBP from baseline to Week 3 of Period B and from the end of Period B to Week 2 of Period C was analyzed. The adjusted mean changes from baseline to the Week 3 of Period B were -3.8, -3.2, and -5.6 mmHg for the low, medium, and high-dose irbesartan treatment groups, respectively. The test for linear trend across these groups showed the statistically significant dose-response relationship (p=0.024). The LS mean change between the irbesartan group and the placebo group at the Week 2 of Period C was also statistically significant (p=0.0014). The following table summarizes the test results of SeDBP.

Table 7: LS Mean Change of SeDBP from the Baseline to the Week 3 of Period B and from the End of Period B to the Week 2 of Period C
*(Source: Sponsor's results confirmed by the reviewer)*

| SeDBP from the Baseline to the Week 3 of Period B | | | |
|---|---|---|---|
| | 0.5/0.5 | 0.5/1.5 | 1.5/4.5 |
| N | 101 | 101 | 100 |
| Baseline | 71.4 (8.8) | 70.9 (8.7) | 71.1 (8.4) |
| LS Mean Change | -3.8 (0.7) | -3.2 (0.7) | -5.6 (0.7) |
| 95% C.I. | (-5.2, -2.4) | (-4.6, -1.8) | (-7.0, -4.3) |
| p-value | | | 0.024 |
| SeDBP from the End of Period B to the Week 2 of Period C | | | |
| | Placebo | Irbesartan | |
| N | 141 | 145 | |
| End of Period B | 67.3 (6.9) | 66.3 (8.2) | |
| LS Mean Change | 2.0 (0.5) | -0.3 (0.5) | |
| Est. Difference | | -2.3 | |
| 95% C.I. | | (-3.75, -0.92) | |
| p-value | | 0.0014 | |

The proportions of patients reaching target BP, which was defined as less than the 90$^{th}$ percentile based on age, gender, and height, was analyzed. The proportions of the responders at Week 3 of Period B were 0.55, 0.41 and 0.51 for the low, medium, and high dose groups, respectively (Table 8). The proportions of

responder did not increase as the dose of irbesartan increased. The proportions of the responder at Week 2 of Period C also showed a similar pattern (Table 8). In terms of the overall treatment groups, there was a greater proportion of responders for the group remaining on irbesartan (0.46 compared to 0.35). The analysis results are summarized in the table below.

Table 8: Proportions of Responders at the Week 3 of Period B and the Week 2 of Period C.
*(Source: Sponsor's results confirmed by the reviewer)*

| | Any Placebo | Irbesartan 0.5/0.5 | Irbesartan 0.5/1.5 | Irbesartan 1.5/4.5 | Any Irbesartan |
|---|---|---|---|---|---|
| Week 3 of B | | | | | |
| Responders/n | - | 56/101 | 41/101 | 51/100 | 148/302 |
| Proportion | - | 0.55 | 0.41 | 0.51 | 0.49 |
| Week 2 of C | | | | | |
| Responders/n | 50/141 | 22/48 | 16/47 | 28/50 | 66/145 |
| Proportion | 0.35 | 0.46 | 0.34 | 0.56 | 0.46 |

**3.2 Findings in Special/Subgroup Populations**

The sponsor performed the subgroup analyses on age, gender, race, Tanner score and geographic region. The sponsor stated that each subgroup, with the exception of 'other' race, showed a withdrawal effect in the placebo group, consisting of greater increase of mean systolic and diastolic blood pressures from the end of period B to the end of Period C compared to the irbesartan group. However, no firm conclusion from the results of any given subgroup can be drawn. The following tables are the summary statistics of trough SeSBP for changes from baseline to Week 3 of Period B and for changes from the end of Period B to Week 2 of Period C.

Table 9: Subgroup Analysis for Change of SeSBP from Baseline to Week 3 of Period B
*(Source: Sponsor's results)*

| | 0.5/0.5 | | 0.5/1.5 | | 1.5/4.5 | |
|---|---|---|---|---|---|---|
| | n | LS mean change of SBP | n | LS mean change of SBP | N | LS mean change of SBP |
| Age | | | | | | |
| 6-12 | 47 | -8.2 (11.3) | 46 | -8.2 (10.7) | 45 | -11.3 (10.8) |
| 13-16 | 54 | -14.5 (10.0) | 55 | -10.2 (12.3) | 55 | -15.1 (13.7) |
| Gender | | | | | | |
| Male | 69 | -11.5 (10.8) | 67 | -9.9 (11.3) | 67 | -14.2 (12.8) |
| Female | 32 | -11.6 (11.7) | 34 | -8.0 (12.3) | 33 | -11.7 (11.9) |
| Race | | | | | | |
| White | 87 | -11.9 (11.3) | 88 | -9.9 (12.0) | 87 | -13.4 (12.6) |
| Black | 9 | -11.1 (10.9) | 9 | -3.0 (7.4) | 11 | -11.7 (11.9) |
| Other | 5 | -6.1 (5.9) | 4 | -9.3 (7.5) | 2 | -19.3 (21.2) |
| Tanner Score | | | | | | |
| < 3 | 56 | -9.3 (11.3) | 52 | -8.0 (10.6) | 44 | -11.6 (11.7) |
| ≥ 3 | 45 | -14.3 (10.2) | 49 | -10.7 (12.5) | 56 | -14.7 (13.1) |
| Region | | | | | | |
| U.S. | 26 | -10.2 (9.5) | 27 | -4.8 (10.1) | 26 | -11.7 (12.2) |
| Europe | 75 | -12.0 (11.6) | 74 | -10.9 (11.7) | 74 | -13.9 (12.7) |

Table 10: Subgroup Analysis for Change of SeSBP from End of Period B to Week 2 of Period B *(Source: Sponsor's results)*

| | Placebo | | Irbesartan | |
|---|---|---|---|---|
| | n | LS mean change of SBP | N | LS mean change of SBP |
| Age | | | | |
| 6-12 | 66 | 3.0 (10.0) | 64 | -1.9 (12.2) |
| 13-16 | 75 | 2.4 (11.5) | 81 | 1.2 (11.1) |
| Gender | | | | |
| Male | 91 | 3.0 (11.4) | 99 | 1.2 (11.4) |
| Female | 50 | 2.3 (9.7) | 46 | -3.2 (11.8) |
| Race | | | | |
| White | 118 | 3.0 (10.9) | 129 | -0.5 (11.7) |
| Black | 17 | 2.7 (9.8) | 14 | 1.0 (9.1) |
| Other | 6 | -2.7 (10.5) | 2 | 10.2 (23.8) |
| Tanner Score | | | | |
| < 3 | 72 | 3.0 (11.0) | 70 | -1.9 (12.2) |

| | | | | |
|---|---|---|---|---|
| ≥ 3 | 69 | 2.4 (10.7) | 75 | 1.4 (11.0) |
| Region | | | | |
| U.S. | 41 | 1.8 (9.5) | 36 | 0.4 (11.0) |
| Europe | 100 | 3.1 (11.3) | 109 | -0.4 (11.9) |

# 4. SUMMARY AND CONCLUSIONS

## 4.1 Statistical Issues and Collective Evidence

Change of seated systolic blood pressure from the baseline to Week 2 of Period B was analyzed as the primary endpoint. If the primary endpoint failed to show the linear trend, then a comparison of the changes in SeSBP between the two groups, any placebo and any irbesartan, was carried out to evaluate the effect of withdrawal from irbesartan over the two week period.

ANCOVA model using the baseline SeSBP as the covariate was used for the primary and the first secondary analysis. The analysis on SeSBP changes from the baseline to Week 2 of Period B showed no statistically significant trend (p=0.118). The following table summarizes the results from the primary analysis.

Table 11: Primary analysis Result
*(Source: Sponsor's results confirmed by the reviewer)*

| | 0.5/0.5 mg/kg n=108 | 0.5/1.5 mg/kg n=107 | 1.5/4.5 mg/kg n=103 |
|---|---|---|---|
| N | 101 | 101 | 100 |
| Baseline Mean (SD) | 134.3 (9.7) | 134.5 (9.9) | 135.1 (11.2) |
| Mean at 3 Week of period B | 122.8 (12.1) | 125.3 (11.7) | 121.8 (12.9) |
| LS Mean change | -11.7 (1.1) | -9.3 (1.1) | -13.2 (1.1) |
| 95% confidence interval | (-13.8, -9.6) | (-11.5, -7.2) | (-15.3, -11.0) |
| p-value for the trend test | | | 0.118 |

Since the first primary endpoint failed to show the statistical significance, the effect of withdrawal from irbesartan was analyzed by comparing the SeSBP changes from the end of Period B to the Week 2 of Period C between the irbesartan group and the placebo group. The following table summarizes the test result.

Table 12: Mean changes form End of Period B in Trough SeSBP to Week 2 of Period C *(Source: Sponsor's results confirmed by the reviewer)*

| | Placebo N=148 | Irbesartan N=150 |
|---|---|---|
| N | 141 | 145 |
| End of period B mean (SD) | 122.7 (11.9) | 124.0 (12.5) |
| LS Mean change | 2.4 (0.8) | 0.1 (0.8) |
| Est. difference between the groups | | -2.3 |
| 95% CI for estimated difference | | (-4.63, -0.01) |
| p-value | | 0.050 |

The p-value reached borderline significance (p=0.05). However, the observed mean difference is only 2.3mmHg, which is far smaller than the projected 4.2mmHg. Clinical significance of this smaller treatment difference in SeSBP needs to be assessed by the medical division. When a study fails on the primary endpoint, interpretation of any secondary endpoint is generally not proper because the chance of false positive findings from such interpretation increases. (b) (4)

## 4.2 Conclusions and Recommendations

This dose range study without a placebo group failed to show a statistically significant dose trend. The randomized withdrawal period showed a borderline statistically significant difference. However, the clinical significance of the observed small difference needs to be assessed by the medical division. (b) (4)

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