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Statistical Review(s)

STATISTICAL REVIEW AND EVALUATION

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

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STATISTICAL REVIEW AND EVALUATION

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Executive Summary and Statistical Findings

1.1 Conclusions

Losartan plus hydrochlorothiazide combination therapy group had a significantly higher percentage of patients who achieved goal blood pressure (sitting diastolic blood pressure <90 mmHg) at Week 4 compared to Losartan monotherapy group. Large number of imputed data by LOCF method raised a concern about the integrity of the primary analysis. However, the reviewer's sensitivity analyses on primary endpoint with smaller number of imputed data supported the robustness of the primary analysis. The number of patients who achieved the goal at Week 6 and other supportive analyses also confirmed that Losartan plus hydrochlorothiazide combination therapy had a significantly better antihypertensive effect than Lorsartan monotherapy.

1.2 Overview of the Studies Reviewed

This NDA contains one clinical efficacy study (protocol 232). This is a randomized, double-blinded, safety and efficacy study of Lorsartan plus hydrochlorothiazide (Los/HCTZ) versus Losartan (Los) as first-line therapy in patients with severe hypertension. It is the first trial to establish that Los/HCTZ combination therapy, used as a first-line agent, confers greater antihypertensive efficacy than Los monotherapy titrated as clinically indicated, and is safe and generally well tolerated.

Patients with a confirmed means sitting diastolic blood pressure (SiDBP) ≥110 mmHg were randomized in 2:1 fashion to either Los 50 mg/HCTZ 12.5 mg or Los 50mg. These patients were titrated (Los 50 mg/HCTZ 12.5 mg → Los 50 mg/HCTZ 12.5 mg (sham titration) → Los 100 mg/HCTZ 25 mg, or Los 50 mg → Los 100 mg → Los 150 mg) as needed every 2 weeks to achieve a goal mean trough SiDBP <90 mmHg, for a total of 6 weeks on double-blind therapy.

1.3 Principal Findings

The primary endpoint was the proportion of patients whose mean trough SiDBP achieved the goal level (<90 mmHg) at Week 4. The proportions of achievers were compared between the two treatment groups using Confidence Intervals (CI) constructed using the Wilson's score method. P-values were computed using the likelihood-ratio χ^2 statistic.

The percentage of patients achieving goal SiDBP at Week 4 was significantly higher in the Los/HCTZ combination therapy group compared with the Los monotherapy group (17.8% vs. 9.4%, p=0.007).

As a secondary efficacy endpoint, the proportion of patients whose mean trough SiDBP achieved the goal at Week 6 was analyzed with the same analytical methods used for the primary analysis. The analysis on the secondary endpoint generally showed the consistent results as those seen at Week 4. The percentage of patients achieving goal BP at Week 6 was significantly higher in the Los/HCTZ combination therapy group compared with that in the Los monotherapy group (30.5% vs. 12.5%, p<0.001). The following table summarizes the results of the primary and the secondary analyses.

Table 1: Number of Patients Who Achieved Goal SiDBP at Week 4 and Week 6 *(Source: Reviewer's analysis)*

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% CI)	p-value
	n	(%)	N	(%)		
Week 4[1]	70	(17.8)	18	(9.4)	8.4 (2.39, 13.73)	0.0055
Week 6[2]	120	(30.5)	24	(12.5)	18.0 (11.08, 24.20)	<0.0001

[1] time point for primary efficacy analysis
[2] time point for secondary efficacy analysis
CI= Confidence interval

Additional analyses were performed for the change from baseline in SiDBP and the difference in proportions of responders (means trough SiDBP <90 mmHg or a decrease from baseline in means SiDBP ≥10 mmHg). These analyses also showed better antihypertensive efficacy of Los/HCTZ combination therapy compared to that of Los monotherapy.

For the primary analysis, large number of data (28%) were imputed by LOCF method due to up-titration or missing Week 4 measurement window and the high missing numbers raised a concern about the integrity of the results from the analysis. Since the majority of imputed data due to missing the Week 4 window were off the window only by 1 or 2 days, sensitivity analyses using wider window were performed by this reviewer. By allowing a wider range, up to 57 more Week 4 visit data were included in the sensitivity analyses. The sensitivity analyses gave similar results as the primary analysis. (reference table 9 on page12)

Subgroup analyses showed that Los/HCTZ combination therapy had better antihypertensive effect compared to Los monotherapy across most of the subgroups except Europe and < 40 years of age groups, which showed an opposite trend. However, the sample sizes of these subgroups were too small to draw any conclusion.

2. Statistical Review and Evaluation of Evidence

2.1 Introduction

Hypertension is one of the most common adult diseases in the United States, affecting ~50,000,000 people, as well as ~20% of the world's population. Patients with severe essential hypertension (systolic blood pressure ≥180 mmHg or diastolic blood pressure ≥110 mmHg) are identified as patients at high risk for cardiovascular morbidity and mortality. Normalization of blood pressure (<140/90 mmHg) is effective in reducing this risk. A treatment using a combination agent as initial therapy in the management of hypertension is suggested for high-risk patients in treatment guidelines, and is becoming more common in clinical practice. This is due in part to the potential for improved efficacy, response rate, and low incidence of side effects with low-dose combination therapy when compared with higher doses of monotherapy.

Losartan (Los) is the first nonpeptide, highly selective angiotensin-II receptor antagonist to be introduced. Losartan (Losartan potassium) has been demonstrated to have a potent antihypertensive effect and an excellent side effect profile.

Hydrochlorothiazide (HCTZ) is a thiazide diuretic and antihypertensive. The mechanism of the antihypertensive effect of thiazides is unknown. Thiazides do not usually affect normal blood pressure.

Merck Research Laboratories performed a meta-analysis on antihypertensive efficacy data consisting of reductions from baseline in mean sitting diastolic blood pressure (SiDBP) and response rates from variety of initial monotherapy treatments compared with Los 50 mg/HCTZ 12.5 mg in patients with severe hypertension. Although the number of patients in each treatment group was generally small, the mean change in SiDBP was greater in patients initially treated with Los 50 mg/HCTZ 12.5 mg. This analysis suggests that antihypertensive monotherapy is generally not as effective as Los/HCTZ combination therapy in reducing diastolic blood pressure (DBP) below 90 mmHg in patients with DBP ≥110 mmHg.

This NDA submission contains a clinical study (protocol 232) that was conducted to provide data in support of an indication for the first-line use of Los 50 mg/HCTZ 12.5 mg in patients with severe essential hypertension.

2.2 Background and Study Design

Study 232 was a randomized, double blind, Los-controlled, multinational study to determine the antihypertensive efficacy and safety of regimens of Los/HCTZ

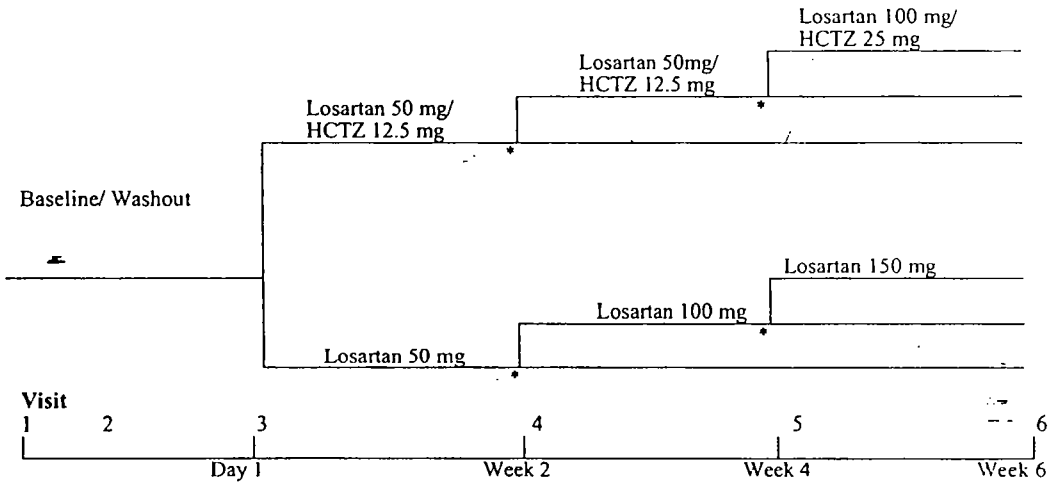
combination therapy versus Los monotherapy in patients with severe hypertension (confirmed mean SiDBP ≥110 mmHg).

Patients who met all entrance criteria were randomized in a 2:1 fashion to either Los 50 mg/HCTZ 12.5 mg or Los 50 mg, once daily. Double-blind treatment period continued for up to 6 weeks with patients returning every 2 weeks for evaluation and possible titration.

At week 2 visit, patients who did not achieve the goal of SiDBP <90 mmHg were titrated (Losartan 50 mg → Losartan 100 mg or Losartan 50 mg/HCTZ12.5 mg→ Losartan 50 mg/HCTZ12.5 mg (sham titration)). Patients in the combination therapy group with a mean SiDBP ≥110 mmHg were titrated to Losartan 100 mg/HCTZ25 mg.

Again, at week 4, patients who did not achieve the goal were titrated (Losartan 50 mg → Losartan 100 mg; Losartan 100 mg → Losartan 150 mg or Losartan 50 mg/HCTZ 12.5 mg → Losartan 100 mg/HCTZ 25 mg, if not previously titrated). All patients should return for a final visit at Week 6. Figure 1 describes the design of the study.

Figure 1: Design of Study



* Titrate if SiDBP >90 mmHg; patients with a SiDBP ≥110 mmHg in the Los/HCTZ combination therapy group were titrated to Los 100 mg/HCTZ 25 mg at Week 2.

2.3 Data Analyzed and Sources

Data used for review is from the electronic submission received on 09/24/02. The network path is "\\CDSESUB1\N20387\S_027\2002-09-24" in the EDR. The following volumes were reviewed: 1, 2, and 3.

2.4 Study Objectives

Primary Objective

- To compare the antihypertensive efficacy of Los 50 mg/HCTZ 12.5 mg versus Los 50 mg titrated as needed to Los 100 mg in lowering mean trough SiDBP to goal (<90 mmHg) after 4 weeks of first-line double-blind therapy in patients with severe hypertension (confirmed mean SiDBP ≥110 mmHg).

Secondary Objectives

- To assess the safety and tolerability of Los/HCTZ combination therapy and Los monotherapy regimens according to the incidence of overall adverse experiences and drug-related adverse experiences (with particular attention to a predefined set of antihypertensive-related adverse experiences) at first dose, 2, 4, and 6 weeks.
- To assess the efficacy of Los/HCTZ combination therapy and Los monotherapy regimens in reducing mean trough SiDBP according to the proportion of patients achieving goal mean trough SiDBP (<90 mmHg) after Week 6.
- To assess the efficacy of Los/HCTZ combination therapy and Los monotherapy regimens according to the change from baseline in mean trough SiDBP and the proportion of patients responding to therapy (mean trough SiDBP <90 mmHg or a decrease in mean SiDBP ≥10 mmHg from baseline, if the mean trough SiDBP ≥90 mmHg) at Week 4 and Week 6.

2.5 Efficacy Endpoints

Primary

The endpoint was the proportion of patients whose mean SiDBP achieves the goal level (<90 mmHg) at Week 4.

Secondary

The endpoint was the proportion of patients whose mean SiDBP achieves the goal level (<90 mmHg) at Week 6.

2.6 Sample Size Considerations

The incidence of patients in the Los monotherapy group achieving goal SiDBP was assumed to be 9% for the sample size calculation. Using a 2:1 randomization scheme with 340 patients in the Los/HCTZ combination therapy group and 170 patients treated with Los monotherapy (titrated as needed), there was at least 95% power to detect an 13% point difference between treatment group with respect to the proportion of patients achieving goal SiDBP at Week 4. This power was based upon a two-sided χ^2 test performed at a two-sided 5% level of significance.

Reviewer's Comments:

1. 393 patients and 192 patients were randomized and treated with Los/HCTZ combination therapy and Los monotherapy, respectively.

2.7 Stratification

No stratification was used in this study.

2.8 Interim Analysis

No interim analysis for efficacy was planned for this study.

2.9 Efficacy Analysis Methods

Both Intention-to-Treat (ITT) and Per-Protocol (PP) populations were analyzed. The ITT population consisted of all randomized patients who had at least one SiDBP or SiSBP reading at Visit 1 for previously untreated hypertensive patients and Visit 2 for previously treated hypertensive patients. The PP population for efficacy included the subgroup of the ITT population who were not protocol violators. Conclusions on efficacy were based on analyses of the ITT population. Patients with missing data had their values carried forward from their previous visit. If there was no blood pressure measurement within the window defined for the Week 4 analysis, then the last available measurement taken after randomization was carried forward. If blood pressure measurements were missing prior to Week 4 then this patient was treated as "non-achievement" for Week 6 analysis.

Efficacy variables were compared between the two treatment groups using Confidence Intervals (CI) constructed using the Wilson's score method. P-values were computed using the likelihood-ratio χ^2 statistic. Changes from baseline in mean trough SiDBP and SiSBP between the treatment groups at Weeks 4 and 6 were analyzed using a linear mixed model with "site" as the random effects term. Subgroup analyses for the primary and secondary hypotheses were performed using a logistic regression model. Treatment-by-covariate interaction was tested. Probabilities of achieving goal, within each subgroup, along with the CI for the difference, within each subgroup were presented. The 95% CI for the difference in rates of achieving goal BP was computed using the Wilson's score method.

2.10 Sponsor's Results and Statistical Reviewer's Findings/Comments

Two patient populations were considered for the efficacy analyses: the intention-to-treat (ITT), and the per-protocol (PP) populations. The efficacy analyses using

the PP population were considered supportive of the analyses using the ITT population.

2.10.1 Baseline Characteristics

The baseline demographic characteristics including age, gender, race, and duration of hypertension were examined for the balance between the two treatment groups. Overall, there was well-balanced enrollment between treatment groups, with the exception of a gender imbalance in the Los monotherapy group. In the Los monotherapy group, 60.9% of the patients were male and 39.1% of the patients were female. The gender was balanced in the Los/HCTZ treated group. The following table shows the baseline demographics of the patient population by treatment groups.

Table 2: Baseline Characteristics by Treatment Group
(Source: Sponsor's analysis)

	Los/HCTZ (N=393)	Los (N=192)	Total (N=585)
	N (%)	N (%)	N (%)
Gender			
Female	189 (48.1)	75 (39.1)	264 (45.1)
Male	204 (51.9)	117 (60.9)	321 (54.9)
Race			
White	183 (46.6)	91 (47.4)	274 (46.8)
Black	86 (21.9)	38 (19.8)	124 (21.2)
Asian	38 (9.7)	20 (10.4)	58 (9.9)
Hispanic	47 (12.0)	23 (12.0)	70 (12.0)
Other	39 (9.9)	20 (10.4)	59 (10.1)
Age			
39 and Under	48 (12.2)	19 (9.9)	67 (11.5)
40 to 59	239 (60.8)	121 (63.0)	360 (61.5)
60 to 79	104 (26.5)	51 (26.6)	155 (26.5)
80 and Over	2 (0.5)	1 (0.5)	3 (0.5)
Mean	52.5	53.1	52.7
SD	10.7	10.9	10.7
Median	52.0	53.0	53.0
Range	22 to 87	24 to 84	22 to 87
Duration of Hypertension			
<1 year	22 (5.6)	11 (5.7)	33 (5.6)
1 to 5 years	127 (32.3)	55 (28.6)	182 (31.1)
6 to 10 years	81 (20.6)	48 (25.0)	129 (22.1)
>10 years	161 (41.0)	78 (40.6)	239 (40.9)
Mean	10.4	11.0	10.6
SD	8.7	9.2	8.9
Median	8.0	9.0	8.0
Range	0 to 39	0 to 43	0 to 43

SD = Standard deviation

Reviewer's Comments:

1. Baseline SiSBP and SiDBP were examined by the reviewer, and the baselines were well balanced between the two treatment groups. The means of baseline SiDBP of the Los/HCTZ and the Los treated groups were 113.4 mmHg and 113.3 mmHg, respectively. The means of baseline SiSBP for the Los/HCTZ and the Los treated groups were 171.0 mmHg and 170.5 mmHg, respectively. The following table presents mean trough SiDBP and SiSBP at baseline.

Table 3: Baseline SiSBP and SiDBP
(Source: Reviewer's analysis)

	Los/HCTZ (N=393)	Los (N=192)	Total (N=585)
SiDBP			
Mean	113.4	113.3	113.4
SD	3.96	3.65	3.86
SiSBP			
Mean	171.0	170.5	170.9
SD	16.47	16.0	16.31

SD = Standard Deviation

2.10.2 Primary Efficacy Analyses

The primary hypothesis was that in patients with severe hypertension, Los 50 mg/HCTZ 12.5 mg will be more effective in lowering mean trough SiDBP than Los 50 mg titrated as needed to Los 100 mg, as assessed by the proportion of patients achieving goal blood pressure (mean trough SiDBP <90 mmHg) at Week 4. This was assessed through the proportion of patients achieving goal blood pressure, which was <90 mmHg.

The relative day (reldays) ranges were used for defining Week 2, 4, and 6 visit. Relday 1 is defined as the date that the patient was randomized to study therapy. The table below displays the relative day ranges.

Table 4: Relative Day Ranges Used for Efficacy Analyses

Time Point	**Day Range/Definition**
Baseline	Last BP measurement prior to randomization
First dose	First BP measurement with Relday >0
Week 2	15 ± 3 reldays
Week 4	29 ± 3 reldays
Week 6	43 ± 3 reldays

Among 393 patients in the Los/HCTZ treated group, 77 patients (19.6%) achieved goal blood pressure (mean trough SiDBP <90 mmHg), and 19 out of 192 patients (9.9%) in the Los treated group achieved goal blood pressure. The difference of the proportions of achievers between the groups was statistically significant with p-value=0.002, and 95% C.I. of (3.5, 15.2). The following table shows the results of the primary analysis.

Table 5: Primary Analysis of ITT Population
(Source: Sponsor's analysis confirmed by the reviewer's analysis)

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	77	19.6	19	9.9	9.7 (3.5, 15.2)	0.002

In order to evaluate the robustness of the results from the primary analysis, per-protocol population was analyzed as a supportive analysis.

Total of 504 patients (Los/HCTZ: 328, Los: 176) were included in the PP analysis. The percentage of per-protocol patients achieving goal BP (mean trough SiDBP <90 mmHg) at Week 4 was significantly higher in the Los/HCTZ combination therapy group compared with the Los monotherapy group (19.5% vs. 10.2%, p=0.005). The results of this PP population were similar to that of the primary analysis using ITT population. The following table presents the results of the PP analysis.

Table 6: Number of Patients Who Achieved Goal SiDBP at Week 4 (PP Population) *(Source: Sponsor's analysis confirmed by the reviewer's analysis)*

	Los/HCTZ (N=328)		Los (N=176)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	64	19.5	18	10.2	9.3 (2.6, 15.2)	0.005

Reviewer's Comments:

1. Any agent that could have affected blood pressure was not permitted during the study. However there were patients who had concomitant therapy for hypertension before Week 4 measurements. Among these patients, four patients in the Los/HCTZ group (patient 1093, 1033, 1400, and 1422) and one patient in the Los group (patient 1688) reached the goal (<90mmHg), and were categorized as achievers at Week 4. Since these five patients received

treatments for hypertension other than Los or Los/HCTZ, these patients were categorized as not having achieved the goal in this reviewer's analysis as a part of the reviewer's robustness analysis.

2. There were patients whose BP measurements were carried forward from an earlier visit due to titration (Los 100 mg → Los 150 mg, or Los 50 mg/HCTZ 12.5 mg → Los 100 mg/ HCTZ 25 mg) at Week 4. In some cases, patients had the up-titration on the same day that the blood pressure was measured, and these patients' BP measurements were also imputed by Last Observation Carried Forward (LOCF) method. However, the BP at Week 4 of these patients was a valid measurement since the BP was taken before a start of the titration. Among patients in this category, four patients were not correctly categorized. Patient 1337, 1656, and 1097 of the Los/HCTZ group reached the goal at Week 2, but not at Week 4. Therefore, these patients were treated as not having achieved goal based on Week 4 SiDBP in this reviewer's analysis although these patients were categorized as achievers based on Week 2 SiDBP in the sponsor's analysis. Patient 1226 of the Los/HCTZ group was an opposite case. This patient was categorized as having achieved goal based on Week 4 SiDBP in this reviewer's analysis, although this patient was not categorized as the achiever in the sponsor's analysis.

3. Patient 1093, and 1613 in the Los/HCTZ treatment group were titrated at Week 2 although their SiDBPs were well below 90 (77 and 79, respectively). However, the SiDBP for both of the patients treated with higher dosage of treatment (Los 100 mg/HCTZ 25 mg) for 2 weeks were 93, which was higher than the goal. These patients were categorized by the sponsor as having achieved the goal based on Week 2 measurements due to the up-titration. But, the patients were treated as not having achieved the goal by this reviewer because not only these patients were treated inappropriately but also the sponsor stated in the report that "any patients who titrated to Los 100mg/HCTZ 25mg at Week 2 were considered non-responders".

4. After taking account of the patients described above, 70 patients from the Los/HCTZ combination therapy group and 18 patients from the Los monotherapy group were categorized as having achieved the BP goal in the reviewer's analysis. The following table summarizes this reviewer's primary analysis.

Table 7: Number of Patients Who Achieved Goal SiDBP at Week 4
(Source: Reviewer's analysis)

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	70	17.8	18	9.4	8.4 (2.39, 13.73)	0.0055* 0.0074#

* p-value from likelihood ratio χ^2
# p-value from Fisher's exact test

As the above table shows, the difference in percentages of achievers between the two treatments was 8.4, which was slightly lower than the one of the sponsor. However, it still suggested that patients who received Los/HCTZ combination therapy were more likely to achieve the BP goal (SiDBP <90 mmHg). Also, p-value and 95% C.I. showed that the difference between the two treatments was statistically significant.

5. There were high numbers of data imputed by LOCF method. There were two reasons why an observation was likely to be imputed. One was that no BP measurement for a patient was captured within Week 4 window (relday 26 – relday 32). The other reason was that a patient could have BP measurements while on a higher dose level (Los 150 mg, or Los 100mg/HCTZ 25mg) at Week 4. The following table shows the fraction of patients whose BP measurements were imputed by LOCF in the primary analysis.

Table 8: SiDBP Carried Forward at Week 4

	Los/HCTZ N=129 (32.8%)		Los N=36 (18.8%)	
	N	%	N	%
Missing	64	49.6	34	94.4
Up-Titration	65	50.4	2	5.6

As shown above, 32.8% of patients in the Los/HCTZ group and 18.8% of patients in the Los group had their BP measurements carried forward. Among 129 patients of the Los/HCTZ group, 65 patients were up-titrated to Los 100 mg/HCTZ 25 mg before Week 4 measurements, and 64 patients were taken BP outside of the Week 4 window, or dropped out of the study early. Among 36 patients in the Los treated group, 2 patients were up-titrated to Los 150 mg before Week 4 measurements, and 34 patients were taken BP outside of the Week 4 window, or dropped out of the study early. As stated in the section 2.2, Background and Study Design, patients in the Los/HCTZ combination therapy group with SiDBP ≥110 mmHg (not ≥90 mmHg) were supposed to be titrated to Los 100mg/HCTZ 25mg at Week 2. Among the 65 patients whose BP were imputed due to up-titration before Week 4, 13 patients had their

SiDBP <110 mmHg at Week 2, and should not have been titrated per protocol. The two patients in "Up-Titration" category of the Los treatment group are the patients who were up-titrated to Los 150 mg before Week 4 window. These two patients were up-titrated to Los 100 mg, and then up-titrated again to Los 150 mg before Week 4. If a patient was up-titrated before Week 4, and BP was not taken at Week 4 window, this patient was included in "missing" category.

6. As seen in Table 8, 165 patients out of total of 585 patients (28%) in the study had their primary endpoint imputed because either it was missing or titrated. This high percentage of missing values raises a concern about the integrity of the results from the analysis.

7. Since the majority of patients who missed the Week 4 window missed BP measurement only by 1-2 days outside of the pre-defined window, day 29 ± 3, this reviewer performed a sensitivity analysis using a wider range of the Week 4 window. By allowing day 29 ± 5 as the Week 4 window, 43 more patients would have Week 4 visit data. Among the 43 patients, 3 patients (2 from the Los/HCTZ treated group, 1 from the Los treated group) were categorized into the achiever group with the Week 4 visit measurement. The table below summarizes the sensitivity analysis.

Table 9: Number of Patients Who Achieved Goal When Wider Range of Window Was Used *(Source: Reviewer's analysis)*

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	72	18.3	19	9.9	8.4 (2.28, 13.81)	0.0064* 0.0083#

* p-value from likelihood ratio χ^2
# p-value from Fisher's exact test

As the above table shows, the sensitivity analysis gives an identical estimated treatment difference and similar p-values as the primary analysis. By allowing ±9 days of range, 14 more patients would have Week 4 visit measurement, but none had achieved the BP goal at Week 4. Therefore, the result of this analysis changes little.

8. The number of patients who prematurely discontinued from the study was 53 (9.1%) which was relatively small compared to the number of patients with imputed BP values. The following table summarizes the reasons for discontinuation.

Table 10: Number of Patients Who Prematurely Discontinued from the Study *(Source: Sponsor's table)*

	Los/HCTZ N (%)	Los N (%)	Total
Clinical AE	7 (21.9)	7 (33.3)	14
Lack of Efficacy	8 (25.0)	8 (38.1)	16
Lost to Follow-up	5 (15.6)	0 (0)	5
Patient Moved	1 (3.1)	0 (0)	1
Withdrew Consent	7 (21.9)	4 (19.1)	11
Protocol Deviation	2 (6.3)	2 (9.5)	4
Other	2 (6.3)	0 (0)	2
Total	32	21	53

2.10.3 Secondary Efficacy Analyses

The secondary hypothesis of this study was that in patients with severe hypertension (confirmed mean SiDBP ≥110 mmHg), Los 50 mg/HCTZ 12.5 mg will be more effective in lowering mean trough SiDBP than Los 50 mg titrated as needed to Los 100 mg, as assessed by the proportion of patients achieving goal blood pressure (mean trough SiDBP <90 mmHg) at Week 6.

At Week 6, 122 out of 393 patients (31%) in the Los/HCTZ treated group and 24 among 192 patients (12.5%) in the Los treated group achieved goal mean trough SiDBP. Chi-squared test showed that the difference of proportions of achievers between the two treatment groups was statistically significant. The test result is summarized in the table below.

Table 11: Number of Patients Who Achieved Goal SiDBP at Week 6 (ITT) *(Source: Sponsor's Analysis confirmed by the reviewer's analysis)*

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 6	122	31.0	24	12.5	18.5 (11.6, 24.7)	<0.001

Per-protocol population was analyzed using the same analytical method to evaluate the robustness of ITT analysis.

Total of 457 patients (Los/HCTZ: 301, Los: 156) were included in the PP analysis. The percentage of per-protocol patients achieving goal BP at Week 6 was significantly higher in the Los/HCTZ combination therapy group when compared with the Los monotherapy group (32.6% vs. 12.8%, p<0.001). The following table shows the results of the analysis.

Table 12: Number of Patients Who Achieved Goal SiDBP at Week 6 (PP)
(Source: Sponsor's analysis confirmed by the reviewer's analysis)

	Los/HCTZ (N=301)		Los (N=156)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 6	98	32.6	20	12.8	19.7 (11.8, 26.7)	<0.001

Reviewer's Comments:

1. 208 of 393 patients in the Los/HCTZ treated group were titrated to Los 100 mg/HCTZ 25 mg, and 147 of 192 patients in the Los treated group were titrated to Los 150 mg at or before Week 4. At Week 6, the dosages the patients received were not homogeneous among the patients in the same treatment group.

2. Two patients (# 1400 and #1422) who had the concomitant therapy for hypertension were included in the achiever group in sponsor's analysis. These two patients were treated as not having achieved the goal in this reviewer's analysis. The result of this reviewer's analysis also showed that differences between the two groups were statistically significant; see Table 13

Table 13: Number of Patients Who Achieved Goal SiDBP at Week 6 (ITT)
(Source: Reviewer's Analysis)

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 6	120	30.5	24	12.5	18.0 (11.08, 24.20)	<0.0001* <0.0001#

*p-value from likelihood ratio χ^2
#p-value from Fisher's exact test

One secondary objective was comparing Los/HCTZ with Los according to the change from baseline in mean trough SiDBP. Mixed models with adjusting for variation due to "site" were used. When Week 4 or Week 6 measurements were missing for a patient, that patient was not included in the analysis. The mean reduction in SiDBP from baseline to Week 4 was significantly higher in the Los/HCTZ combination therapy group compared with the Los monotherapy group (-13.6 ± 9.8 mmHg vs. −10.5 ± 8.6 mmHg, p<0.001). The mean reduction in SiDBP from baseline to Week 6 was also significantly higher in the Los/HCTZ combination therapy group compared with the Los monotherapy group (-17.8 ± 9.2 mmHg vs. −11.9 ± 9.5 mmHg, p<0.001). The following table summarizes the results from the analyses.

Table 14: Changes from Baseline in Mean SiDBP at Week 4 and Week 6
(Source: Sponsor's analysis confirmed by the reviewer's analysis)

	Los/HCTZ			Los			p-value
	N	Mean change	SD	N	Mean change	SD	
Week 4	392	-13.6	9.8	192	-10.5	8.6	<0.001
Week 6	368	-17.8	9.2	178	-11.9	9.5	<0.001

- SD= Standard Deviation

Reviewer's Comments:

1. Although it was originally planned to include baseline SiDBP as covariate in the model, the baseline was not included due to its insignificance. Instead, "site" was included as a random effect in this mixed model since "site" had a significant effect. There was no significant site by treatment interaction (p=0.8).

Another secondary objective of this study was to compare Los/HCTZ to Los with the proportion of patients responding to therapy (mean trough SiDBP <90 mmHg or a decrease in mean trough SiDBP ≥10 mmHg from baseline, if the mean trough SiDBP ≥90 mmHg) at Week 4 and Week 6.

The proportions of patients responding to the therapy were analyzed with the same method used for the primary analysis. The percentages of patients responding to therapy at Week 4 and Week 6 were significantly higher in the Los/HCTZ combination therapy group compared with the Los monotherapy group (67.2% vs. 55.7%, 78.6% vs. 54.7% for Week 4 and Week 6, respectively). The following table summarizes results from the analysis.

Table 15: Analysis on Responders of Therapy (ITT)
(Source: Sponsor's analysis confirmed by the reviewer's analysis)

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	264	67.2	107	55.7	11.4 (3.1,19.8)	0.007
Week 6	309	78.6	105	54.7	23.9 (15.8,31.9)	<0.001

As a supportive analysis, an analysis on the percentage of patients who achieved goal SiSBP (mean trough SiSBP <140 mmHg) at Week 4 and Week 6 after removing those patients who entered the study with a SiSBP <140 mmHg was performed.

Total of 573 (Los/HCTZ;388, Los;185) patients were included in the analysis of SiSBP. The proportion of patients achieving SiSBP goal at Week 4 was significantly higher in the Los/HCTZ combination therapy group when compared with the Los monotherapy group (25.5% vs. 12.4%, p=0.001)

The percentage of patients achieving SiSBP goal at Week 6 was also significantly higher in the Los/HCTZ combination therapy when compared with the Los monotherapy group (37.4% vs. 14.1%, p<0.001). The following table shows the results of analysis on SiSBP at Week 4 and Week 6.

Table 16: Number of Patients Who Achieved Goal SiSBP at Week 4 and 6
(Source: Sponsor's analysis confirmed by the reviewer's analysis)

	Los/HCTZ (N=388)		Los (N=185)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	99	25.5	23	12.4	13.1 (6.2, 19.2)	<0.001
Week 6	145	37.4	26	14.1	23.3 (15.9, 29.8)	<0.001

Another supportive analysis was performed for the proportions of patients who achieved both goal SiSBP and SiDBP at Week 4 and Week 6 after removing those patients who had entered the study with a SiSBP <140 mmHg. A patient was classified as achieving goal BP with a mean trough SiDBP was <90 mmHg and a mean trough SiSBP was <140 mmHg at the same time period.

The percentage of patients achieving goal BP (systolic and diastolic) at Week 4 was significantly higher in the Los/HCTZ combination therapy group when compared with the Los monotherapy group (12.6% vs. 4.3%, p<0.001).

The percentage of patients achieving goal BP (systolic and diastolic) at Week 6 was also significantly higher in the Los/HCTZ treatment group when compared with the Los treatment group (21.4% vs. 4.9%, p<0.001). The following table presents the results of the analysis.

Table 17: Number of Patients Who Achieved Goal SBP and DBP at Week 4 and Week 6 *(Source: Sponsor's analysis confirmed by the reviewer's analysis)*

	Los/HCTZ (N=388)		Los (N=185)		Estimated Difference (95% C.I.)	p-value
	N	%	N	%		
Week 4	49	12.6	8	4.3	8.3 (3.4,12.5)	<0.001
Week 6	83	21.4	9	4.9	16.5 (10.9,21.4)	<0.001

2.10.4 Efficacy Findings in Special/Subgroup Populations

Subgroups of gender, age, race, and region were analyzed to explore the consistency of achieving goal mean trough SiDBP (<90 mmHg). The following table presents the primary endpoint (achieving goal SiDBP at Week 4) by their subgroup categories. There were no significant treatment-by-baseline characteristic interaction, indicating that achieving goal BP at Week 4 was generally similar across the subgroups within a baseline characteristic.

Table 18: Subgroup Analysis- Patients Who Achieved Goal at Week 4
(Source: Sponsor's analysis)

	Los/HCTZ N=393		Los N=192		Estimated Difference (95% CI)
	n/N	%	N/N	%	
Gender					
Female	43/189	22.8	7/75	9.3	13.4 (3.2, 21.4)
Male	34/204	16.7	12/117	10.3	6.4 (-1.8, 13.6)
Age					
< 40	8/48	16.7	4/19	21.1	-4.4 (-28.1, 13.6)
40 to 59	40/239	16.7	8/121	6.6	10.1 (2.9, 16.3)
60 to 64	11/49	22.5	4/22	18.2	4.3 (-18.1, 21.5)
65 to 74	17/52	32.7	2/26	7.7	25.0 (5.1, 39.6)
≥75	1/5	20.0	1/4	25.0	-5.0 (52.8, 42.1)
Race					
Asian	11/38	29.0	2/21	9.5	19.4 (-3.4, 36.7)
Black	11/86	12.8	3/38	7.9	4.9 (-9.1, 15.0)
Caucasian	35/184	19.0	10/91	11.0	8.0 (-1.5, 16.0)
Hispanic	8/47	17.0	2/23	8.7	8.3 (-11.5, 22.9)
Other	12/38	31.6	2/19	10.5	21.1 (-3.3, 38.7)
Region					
Africa	0/6	0.0	0/4	0.0	
Asia	11/36	30.6	0/18	0.0	30.6 (8.9, 46.9)
Europe	3/30	10.0	5/16	31.3	-21.3 (-46.5, 1.9)
North America	37/216	17.1	8/102	7.8	9.3 (1.1, 16.1)
South America	26/105	24.8	6/52	11.5	13.2 (-0.3,24.2)

n/N= the number of patients in the subgroup who achieved the goal / number of patients in the subgroup.
CI = Confidence interval

Reviewer's Comments:

1. This reviewer performed subgroup analysis by correcting for patients who were not correctly categorized to the achiever or non-achiever group as mentioned in the first three Reviewer's Comments in section 2.10.2. The following table summarizes the results of this reviewer's subgroup analysis.

Table 19: Subgroup Analysis by Reviewer- Number of Patients Who Achieved Goal at Week 4 *(Source: Reviewer's analysis)*

	Los/HCTZ N=393		Los N=192		Estimated Difference (95% CI)
	n/N	%	n/N	%	
Gender					
Female	40/189	21.2	7/75	9.3	11.8 (1.68, 19.77)
Male	30/204	14.7	11/117	9.4	5.3 (-2.57, 12.16)
Age					
< 40	8/48	16.7	4/19	21.1	-4.4 (-28.1, 13.6)
40 to 59	39/239	16.3	8/121	6.6	9.7 (2.50, 15.83)
60 to 64	9/49	18.4	3/22	13.6	4.7 (-16.68, 20.47)
65 to 74	13/52	25.0	2/26	7.7	17.3 (-1.82, 31.64)
≥75	1/5	20.0	1/4	25.0	-5.0 (52.8, 42.1)
Race					
Asian	10/38	26.3	2/21	9.5	16.8 (-5.67, 33.92)
Black	11/86	12.8	3/38	7.9	4.9 (-9.1, 15.0)
Caucasian	31/184	16.9	9/91	9.9	7.0 (-2.20, 14.58)
Hispanic	7/47	14.9	2/23	8.7	6.2 (-13.39, 20.45)
Other	11/38	29.0	2/19	10.5	18.4 (-5.62, 35.96)
Region					
Africa	0/6	0.0	0/4	0.0	
Asia	10/36	27.8	0/18	0.0	27.8 (6.53, 43.99)
Europe	3/30	10.0	4/16	25.0	-15.0 (-40.36, 6.53)
North America	34/216	15.7	8/102	7.8	7.9 (-0.19, 14.55)
South America	23/105	21.9	6/52	11.5	10.4 (-2.96, 21.12)

n/N= the number of patients in the subgroup who achieved the goal / number of patients in the subgroup.
CI = Confidence interval

2. The subgroup analyses showed a positive trend of the treatment difference in favor of combination therapy across the subgroups except patients in Europe and <40 years of age. The patients in the above two groups showed a reverse trend. However the sample sizes were too small to draw any conclusion.

3. Statistical Evaluation of Collective Evidence

This NDA contains only one clinical efficacy study (protocol 232).

The primary efficacy evaluation in this trial was the proportion of patients achieving goal mean trough SiDBP <90 mmHg after 4 weeks of therapy with either Los 50 mg/HCTZ 12.5 mg, or Los 50 mg titrated as needed to Los 100 mg. At Week 4, significantly more patients treated with Los/HCTZ combination therapy reached goal blood pressure than those treated with Los monotherapy

(17.8% vs. 9.4%, p=0.0074). PP analysis confirmed results of the primary analysis.

Patients were subsequently titrated as needed to Los 100 mg/HCTZ 25 mg or Los 150 mg in the combination and monotherapy groups, respectively. After 6 weeks, significantly more patients treated with Los/HCTZ combination therapy reached goal blood pressure compared to those treated with Los monotherapy (30.5% vs. 12.5%, p<0.0001). The per-protocol analysis confirmed these results. The following table summarizes the primary and the secondary analysis.

Table 20:Number of Patients Who Achieved Goal at Week 4 and Week 6
(Source: Reviewer's analysis)

	Los/HCTZ (N=393)		Los (N=192)		Estimated Difference (95% CI)	p-value
	N	(%)	n	(%)		
Week 4[1]	70	(17.8)	18	(9.4)	8.4 (2.39, 13.73)	0.0055
Week 6[2]	120	(30.5)	24	(12.5)	18.0 (11.08, 24.20)	<0.0001

[1] time point for primary efficacy analysis
[2] time point for secondary efficacy analysis
CI= Confidence interval

For the primary analysis, large number of data (28%) were imputed by LOCF method due to up-titration or missing Week 4 measurement window, and the high missing numbers raised a concern about the integrity of the results from the analysis. Since the majority of imputed data due to missing the Week 4 window were off the window only by 1 or 2 days, sensitivity analyses using wider window were performed by this reviewer. By allowing a wider range, up to 57 more Week 4 visit data were included in the sensitivity analyses. This sensitivity analysis gave similar results as the primary analysis

An additional analysis was performed to examine change from baseline in SiDBP. At Week 4, Los/HCTZ combination therapy resulted in a significant decrease in SiDBP from baseline compared with Los monotherapy (-13.6 ± 9.8 mmHg vs. – 10.5 ± 8.6 mmHg, p<0.001). At Week 6, the difference in efficacy between Los/HCTZ combination therapy and Los monotherapy as measured by decrease in SiDBP from baseline widened still further (-17.8 ± 9.2 mmHg vs. –11.9 ± 9.5 mmHg, p<0.001).

The difference between treatment groups in patients identified as responders (mean trough SiDBP <90 mmHg or a decrease from baseline in mean SiDBP ≥10 mmHg) was also examined. At Week 4, significantly more patients treated with Los/HCTZ combination therapy responded than those treated with Los monotherapy (67.2% vs. 55.7%, p=0.007). The response rate of those patients treated with Los/HCTZ combination therapy continued to increase at the Week 6

time point relative to the patients receiving Los monotherapy (78.6% vs. 54.7%, p<0.001).

Subgroup analyses showed that Los/HCTZ combination therapy had better antihypertensive effect compared to Los monotherapy across most of the subgroups except Europe and <40 years of age groups, which showed a reverse trend. However, the sample sizes of these subgroups were too small to draw any conclusion.

4. Conclusions

There was a statistically significant greater proportion of patients who achieved goal BP (SiDBP <90 mmHg) at Week 4 in Los/HCTZ combination therapy group compared to Los monotherapy group. Large number of imputed data by LOCF method at Week 4 raised concerns about the integrity of the primary analyses. However, sensitivity analyses performed by this reviewer on primary endpoint with smaller number of imputed data gave similar results as the primary analyses. The number of patients who achieved goal BP at Week 6 also showed that Los/HCTZ combination therapy had a significantly better antihypertensive effect compared to Los monotherapy.

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