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# APPROVAL PACKAGE FOR:

# APPLICATION NUMBER

# 20-387/S-013, 015 & 027

# Medical Review(s)

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# Memorandum

DATE: 8.01.03

FROM: Douglas C. Throckmorton, M.D., Director
Division of Cardio-Renal Drug Products (DCRDP), HFD-110

SUBJECT: NDA 20-387/S-027
NAME OF DRUG: Hyzaar (Losartan hydrochloride/ HCTZ)
SPONSOR: Merck and Company

DOCUMENTS USED FOR MEMO:

1. Medical Review, including draft labeling, by Mehul Desai, M.D., including draft labeling, dated 5.5.03.
2. Secondary Medical Review, by Norman Stockbridge, M.D., Ph.D., dated 5.9.03.
3. Statistical Review by Jasmine Choi, Ph.D., dated 4.4.03.
4. Clinical Pharmacology and Biopharmaceutics Review by Elena Mishina, dated xxx.
5. NDA 20-387/S-027, including supplemental materials.

CONCLUSIONS

This memorandum constitutes the Divisional memorandum for the approvability of losartan/HCTZ as first line therapy for the treatment of individuals with severe hypertension (HTN), where the risks of delayed therapy outweigh the risks of initiating therapy with two antihypertensives as initial therapy. There are no outstanding issues with the exception of agreement on the labeling to reflect this claim.

BACKGROUND

This supplements represents a precedent-setting foray into the use of combination antihypertensives as initial therapy. The sponsors has conducted a single trial, essentially a safety trial, to support their contention that two things are true:

- It is safe to initiate therapy with the combination of losartan and HCTZ in the setting of severe hypertension (arbitrarily but not unreasonable defined as repeated measures of ≥110 diastolic), given the findings of the study, and
- It is beneficial to initiate therapy with the combination of losartan and HCTZ in the setting of severe hypertension, given the severity of the hypertension and the perceived risk to the patients if BP is not reduced quickly.

## What Did The Trial Find?

Drs. Choi and Desai have reviewed the trial. Both conclude that in a population with substantially elevated BP, off all antihypertensives, the combination of losartan and HCTZ lowered BP more than losartan alone (administered once per day at top labeled dose). This translated into a larger fraction of patients on the combination achieving 'goal' BP, and in fact demonstrated that the use of the monotherapy was 'futile' if the notion was achieving goal in this population (of note, it was only marginally less futile to use both drugs....). The difference in blood pressure

lowering effects was not huge in the trial (a mean effect of around 3-4 mmHg diastolic more for the combination). Dr. Choi found that the directionality of the antihypertensive effect was similar in the three usual demographics of interest: age, gender and race. There were, however, very few patients >65, so the confidence intervals around the two point estimates for change in BP are particularly uncertain in this regard.

As regards safety, the trial was, of course, underpowered to look at the rare adverse events associated with the use of HCTZ (*e.g.*, pancreatitis). For the anticipated acute safety concerns from these drugs (syncope, hypotension, renal injury), there were few of these events reported. It would be interesting to review the available combination trials to see how frequently these events were described in the trials conducted to date. One possibility is that the concern has been over-stated in the labeling--- that is, that the risk of these events in the hypertensive population, especially with the low doses of HCTZ used initially, combined with certain classes of drugs (*e.g.*, ACE-inhibitors, ARBs) is really quite low. Alternatively, the clinical trials may select a 'well' population of hypertensives, such that the low frequency of events in the trial tells us little about their occurrence in the real world. In a population like the one in the study, then, the acute safety of the combination was not distinguishable from the monotherapy. Whether this would be the case in the larger population of patients with extremely high BP is less certain.

**What Does The Trial Mean?**

As Dr. Stockbridge points out in his review, the study provides reassurance that the initiation of combination therapy does not result in a substantial increase in adverse events like syncope, hypotension or renal failure. He and Dr. Desai also agree that a small fraction (around 10%) of individuals came under control (as defined in the protocol) with the use of losartan. If multiple meds are needed, and starting two drugs initially is well tolerated, Norman argues that 'the sooner the better' is a sufficient argument for approval in this population. Dr. Desai disagrees, arguing that the benefit seen with the combination (around 20% attaining BP goal compared with around 10% for the monotherapy over 8 weeks) is not an apparent benefit. His concern about changing... 'the practice of traditional titration of anti-hypertensive medications without adequate justification', however, misses what I think is the point of the trial.

What he meant, perhaps, is that no formal risk-benefit analysis was conducted in support of the initial use. This is true. The sponsor's submission simply misses what I believe is the critical, and unperformed, analysis. The calculus is also more complicated that Dr. Stockbridge says. Simply saying that you can't get there with one drug, so you might as well start with two drugs if they are well-tolerated glosses over two uncertainties: the benefits of getting BP reduced in 4 rather than 8 or 12 weeks, and the risks of HCTZ to the (small) population of patients who would never have needed it (10% or so in this study).

As regards the benefits of 'early' BP control, the sponsor has made general statements about the utility of getting early BP control: fewer doctor's office visits, increased compliance, convenience, and more rapid reduction in BP. No data exist to corroborate their assertions save to say that uncontrolled BP over a 6-month period is associated with increases in adverse clinical outcomes. In trials of mild-to-moderate HTN it is not even apparent that a clear risk can be described for patients who go untreated for periods of up to 8 weeks! It is, however, clear that severely hypertensive individuals carry a higher risk of events, and it seems likely that, for them, the treatment benefit would be seen earlier.

As for the risks of receiving HCTZ for the 10% of the population who would have needed only monotherapy, again we simply lack any estimate of the risk. The point is not simply that the risk of the combination of rare adverse events (*e.g.*, pancreatitis) and the potential metabolic effects of diuretic use (certainly quite low given the doses of HCTZ used here) is likely appreciably rare and difficult to estimate. Rather, the point is that no estimate was forwarded by the sponsor, such that the regulatory decision must be made without it.

There is an additional irony here, related to the class of antihypertensive studied. ACE inhibitors and ARBs (like losartan) are weak antihypertensives (by which I mean peak reductions in BP at top labeled doses). This is reflected in the poor job that both the monotherapy and the combination did in getting control in the study population. It is quite likely that a calcium-channel blocker would have had better success in achieving control with monotherapy (that is, it would have failed the 'futility' test as monotherapy). One way of looking at these data, then, is to ask the following: Why start one weak antihypertensive when two weak antihypertensives won't even be likely to work?

In the end, however, I side with Norman for this population, for this drug combination, and agree that the benefits, even if not well characterized, are sufficient to outweigh the uncertainty over the risks of combination therapy. In

particular, I am swayed by the data on the outcomes associated with severe hypertension (*e.g.*, the early VA Cooperative study), where intervention to achieve BP control had a large impact on stroke in a very short period of time. Absent firm data, severe hypertension has an urgency that allows us to accept less firm estimates of risk. This is not the same as mild-to-moderate hypertension, where the time-course of effects seems quite different (recognizing the imprecision of the word 'seems'). Here, given that individuals started on a combination are likely to remain on that combination (including, potentially, a drug they didn't need), a trial of the sort conducted in this supplement, and the poorly-characterized risk/benefit calculus conducted here would not be sufficient to warrant a claim as initial therapy.

This supplement, then, is approvable pending resolution of labeling issues. In particular, it is essential to retain the caution against the initial use of this product in less severe hypertension, and to limit the indication to those patients with severe enough hypertension that the physician believes that the need for more rapid control outweighs the risks of initiating (and continuing) therapy with two drugs.

Dr. Mishina has also recommended that language regarding the kinetics of losartan and HCTZ in patients with renal insufficiency be included in labeling. There is an apparent inconsistency that needs to be resolved with the sponsor, as the current label states the end-stage renal disease does not affect losartan metabolism, even though less significant renal impairment clearly does lead to increased serum concentrations and decreased renal clearance of both the parent and active metabolite.

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Doug Throckmorton
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MEDICAL OFFICER

# DIVISION OF CARDIO-RENAL DRUG PRODUCTS

*Secondary Review*

**NDA:** 20-387

**Sponsor:** Merck

**Submission:** S-027 (24 September 2002): a request to approve the combination of losartan plus HCTZ as first-line treatment of severe essential hypertension.

**Review date:** May 9, 2003

**Reviewer:** N. Stockbridge, M.D., Ph.D., HFD-110

The sponsor presents the results of two clinical studies in support of this efficacy supplement. These trials, ably reviewed by Dr. Desai, are summarized briefly here.

Study 232 was a randomized, double-blind, parallel comparison of antihypertensive effects of losartan alone and losartan plus HCTZ. The 585 subjects had to have a baseline seated diastolic pressure >110 mmHg and seated systolic pressure <220 mmHg. Losartan alone was started at 50 mg and then titrated to 100 mg at 2 weeks and 150 mg at 4 weeks, if needed to meet blood pressure goals. Losartan plus HCTZ was started at 50/12.5 mg and titrated to 100/25 at 4 weeks, as needed. The primary end point was at 4 weeks, so the principal comparison is between losartan 50 or 100 mg and losartan plus HCTZ 50/12.5 mg.

The end point was fraction of subjects meeting criteria of seated diastolic pressure <90 mmHg. The 90-mmHg cutoff is somewhat arbitrary and the fraction of subjects meeting this threshold is very much a function of the initial distribution of diastolic pressures. The trial did distinguish treatments on the basis of the sponsor's primary end point, but perhaps more importantly, it established that there is a readily identifiable population needing more than one drug to treat their hypertension.

Study 228 was a randomized, double-blind, parallel comparison of antihypertensive effects of placebo, and losartan plus HCTZ 50/12.5 and 100/25 mg. The 446 subjects had to have seated diastolic pressure >105 mmHg, although about 30% had diastolic pressure >110 mmHg. The primary end point was change in seated diastolic pressure at 8 weeks, and the two groups demonstrated placebo-subtracted effects of -7 (low dose) and -9 mmHg (high dose).

Dr. Desai correctly observes that the development program did not establish the clinical benefit (i.e., reduction in morbidity and mortality) associated with losartan plus HCTZ as initial therapy compared with a 'stepped care regimen', in which one gets to combination therapy only after demonstrating that a single drug is inadequate. However, if one has a high likelihood of needing two drugs, then the real issue is how to get to optimal treatment soonest. Too rapid uptitration or addition of multiple agents might result in tolerance problems, requiring more visits and delaying stable therapy. The two studies provide some reassurance in this regard. Study 232 completed as many subjects begun on the combination as begun on losartan alone (92% and 89%, respectively). Study 228 completed as many on the combination at 100/25 mg (93%) as

on 50/12.5 mg (96%). Adverse events were similar in active treatment groups of both studies.

Thus the two studies show that the combination can be started safely together. In a population clearly in need of multiple drugs, the benefit of earlier attainment of blood pressure goals is self-evident. Losartan plus HCTZ should be approved as first-line treatment in hypertensive patients far from treatment goals.

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Norman Stockbridge
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MEDICAL OFFICER

CLINICAL REVIEW

# Supplemental NDA 20-387
# Hyzaar

**Mehul Desai, M.D.**
**Medical Officer, Division of Cardio-Renal Drug Products**

# *Table of Contents*

# Clinical Review for NDA 20-387

## *Executive Summary*

## I. Recommendations

### A. Recommendation on Approvability

In this supplemental new drug application (sNDA), the sponsor seeks approval of Hyzaar for use in patients with "severe" hypertension as defined by a mean sitting diastolic blood pressure (SiDBP) greater than 110 mm Hg. The patient population studied by the sponsor most closely resembled Stage 3 hypertension according to JNC VI guidelines.

Through a controlled clinical trial (protocol P232), the sponsor showed that in patients with a SiDBP > 110 mm Hg, the combination of Losartan 50 mg + Hydrochlorothiazide 12.5 mg (aka Hyzaar 50/12.5) was more effective in reducing SiDBP than monotherapy with Losartan 50 mg titrated to maximal labeled doses of 100 mg. In a separate study (P228) involving patients with both Stage 2 and Stage 3 hypertension, the sponsor showed that Hyzaar was more effective than placebo.

The premise in submitting this sNDA is that patients with this magnitude of blood pressure elevation are so far from goal that more than one drug will be necessary to treat them. This premise shifts away from the traditional titration approach to labeling of starting with low doses of one drug, maximizing therapy, followed by adding a second drug. In this application the sponsor presumes that their strategy of starting 2 drugs at one time is superior to the stepped-care approach. However, this application does not provide evidence that starting 2 drugs simultaneously reduces morbidity or mortality compared to starting one drug, titrating it to maximal doses followed by adding a second drug. No conclusions can be drawn regarding the harm in waiting 6 weeks to add a second drug. The simplified conclusion of this supplemental NDA was that control of blood pressure is better with 2 drugs compared to one. This was a predictable outcome of the study (it should be obvious that 2 drugs are better than 1). If the Agency decides to approve this sNDA, it could indirectly affect the traditional titration approach to treatment of hypertension. Changing the approach to treatment of hypertension without showing that it leads to improved long-term compliance, improved outcomes, or increased safety does not seem optimal.

The studies supporting this sNDA for use of Hyzaar as a first line agent in patients with "severe" hypertension are **NOT** a sufficient basis of approval.

**B. Recommendation on Phase 4 Studies and/or Risk Management Steps**

N/A

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

The FDA first approved Hyzaar in 1995 labeled for the treatment of hypertension. In March 2000, the Sponsor requested a meeting to discuss plans for a supplemental NDA to support the use of Hyzaar as a first-line treatment for patients with severe hypertension.

In support of this indication, the sponsor completed 2 clinical trials. The first of these studies, P232, was an active control study of patients with SiDBP > 110 mm Hg and was the pivotal study. In this study, the sponsor showed that Hyzaar (50/12.5) was superior to Losartan 50 mg titrated to 100 mg in terms of percentage of patients achieving a SiDBP of < 90 mm Hg at the end of a 4 week study period. The side effect profile was not markedly different between the two groups.

The second study (P228), was a non-pivotal, placebo controlled trial comparing the efficacy of Hyzaar (100/25) and Hyzaar (50/12.5) to placebo. It is important to note that more than 2/3 of the patients in P228 had SiDBP < 110 mm Hg at baseline. The results of this study showed Hyzaar 100/25 lowered blood pressure marginally better than did Hyzaar 50/12.5 and that both doses were superior to placebo in terms of blood pressure reduction.

### B. Efficacy

Pivotal study, P232, was a randomized, double blind safety and efficacy study of Hyzaar versus Losartan in patients with SiDBP > 110 mm Hg. The study was 6 weeks in duration and enrolled a total of 585 patients (Hyzaar: Losartan :: 2:1). There was approximately a 10% discontinuation rate that was similar in both study arms. The primary endpoint was the percentage of patients achieving a SiDBP < 90 mm Hg at 4 weeks. In the Hyzaar group, 19.6% of patients achieved this goal blood pressure while in the Losartan group 9.9% achieved this goal despite dose titration from 50 mg to 100 mg. This was a statistically significant difference with a p value of 0.002. The mean SiDBP lowering in the Hyzaar and Losartan groups were 13.6 $\pm$ 9.8 mm Hg vs. 10.5 $\pm$ 8.6 mm Hg respectively ($p < 0.001$). It is worth noting that females appeared to respond more favorably to Hyzaar than did males. There was a greater percentage of females at baseline in the Hyzaar arm relative to the Losartan monotherapy arm.

Study P228 was a double blind, randomized, parallel, placebo-controlled efficacy study of Hyzaar 100/25 and Hyzaar 50/12.5 in patients with essential hypertension. The study enrolled a total of 446 patients with both stage 2 and 3 hypertension and was 8 weeks in duration. The percentage of patients who completed the study were 92.5%, 95.7%, and 73% on Hyzaar 100/25, Hyzaar 50/12.5, and placebo groups respectively. The primary endpoint in the study was the mean change in SiDBP from baseline at week 8. The mean changes in SiDBP were $-17.7 \pm 7.3$ mm Hg, $-15.4 \pm 7.5$ mm Hg, and $-8.4 \pm 7.9$ mm Hg in the Hyzaar 100/25, Hyzaar 50/12.5, and placebo groups respectively. The mean changes in both active treatment arms were statistically significantly different from placebo with a p value $< 0.001$. The mean changes in the Hyzaar 100/25 group were also statistically significantly greater than in the Hyzaar 50/12.5 arm with a p value = 0.006. It is worth noting that 70.6% of patients in this study had Baseline SiDBP between 105-109 while 29.4% had baseline SiDBP between 110-115.

C. **Safety**

No new safety concerns were raised in either of the 2 studies referenced in this sNDA. The adverse event findings were consistent with those reported in the label in the 2002 PDR. There were no notable differences in the frequency of pre-specified adverse events of hypotension, dizziness, and worsening renal function in the Hyzaar group relative to the Losartan group or Hyzaar groups relative to placebo. There were no reports of death in either study.

D. **Dosing**

N/A

E. **Special Populations**

In study P232 females appeared to have a more favorable response than did men in terms of achieving goal SiDBP. It is worth noting the differences in baseline characteristics with respect to sex. The male to female ratio in the overall study population was approximately 1.2 to 1. However in the Hyzaar arm this ratio was approximately 1.1 to 1 while in the Losartan arm this ratio was 1.5 to 1.

In study P228, the male to female ratio in the overall study was approximately 1.6 to 1 and ranged from 1.5 – 1.7 to 1 among the 3 treatment arms.

Both studies in support of this sNDA studied an ethnically diverse group. The three ethnic groups that represented the majority of study patients were Whites, Blacks, and Hispanics. In the pivotal study, the results seen among the

different ethnic subgroups were consistently in the same direction showing a favorable effect of Hyzaar versus Losartan monotherapy.

## *Clinical Review*

## I. Introduction and Background

### A. Drug Established and Proposed Trade Name, Drug Class, Sponsor's Proposed Indication(s), Dose, Regimens, Age Groups

1. **Established Trade Name:** Hyzaar
2. **Drug Class:** Anti-hypertensive
3. **Proposed Indication:** Severe Hypertension (DBP $\geq$ 110)
4. **Dose:** Hyzaar 50/12.5 (Losartan 50mg / Hydrochlorothiazide 12.5mg), Hyzaar 100/25 (Losartan 100mg / Hydrochlorothiazide 25mg)
5. **Regimen:** Oral tablet for once a day use
6. **Age groups:** Adults

### B. State of Armamentarium for Indication(s)

N/A

### C. Important Milestones in Product Development

The FDA first approved Hyzaar in 1995 labeled for the treatment of hypertension. In March of 2000, the Sponsor requested a meeting to discuss plans for a supplemental NDA to support the use of Hyzaar as a first-line treatment for patients with severe hypertension. At a meeting between the FDA and Sponsor in May 2000, it was agreed that it may be appropriate to indicate Hyzaar for first-line treatment of severe hypertension if it could be demonstrated that monotherapy with losartan is ineffective and that initial therapy with Hyzaar provided a safe and effective alternative. This represented a change from the FDA's traditional titration approach to labeling for hypertension. Additionally, distinction about treatment based on severity of blood pressure would be a change in the way the Agency labeled anti-hypertensive drugs.

The Agency stressed to the sponsor the importance of faster titration throughout monotherapy in the proposed protocol. Initiating titration at 2 weeks would be better than initiating at 4 weeks (to potentially decrease the time where patients would be unresponsive to drug). It was also deemed reasonable to use higher than approved doses of losartan monotherapy to fully support the notion that monotherapy is futile in these patients.

### D. Other Relevant Information

N/A

E. **Important Issues with Pharmacologically Related Agents**
N/A

## II. Clinically Relevant Findings From Chemistry, Animal Pharmacology and Toxicology, Microbiology, Biopharmaceutics, Statistics and/or Other Consultant Reviews

N/A

## III. Human Pharmacokinetics and Pharmacodynamics

A. **Pharmacokinetics**
N/A

B. **Pharmacodynamics**
N/A

## IV. Description of Clinical Data and Sources

A. **Overall Data**

1. NDA20-387, SE1-027 with a correspondence date of 9/24/02 (both hard copy and electronic).
2. IND 33,383 Serial Numbers: 880, 896, 847, 968, 993.
3. Response to Dr. Choi's questions from January 21st, 2003.
4. Response to FDA questions from January 24, 2003 teleconference.
5. Response to FDA request from January 31, 2003 email.

### B. Tables Listing the Clinical Trials

**Table 1: List of studies in support of sNDA 20-387 on Hyzaar**

| Studies supporting labeling changes | Titles of Studies | Referenced IND/Serial # |
|---|---|---|
| Protocol 232 | "A Randomized, Double Blind Safety and Efficacy Study of Losartan Plus Hydrochlorothiazide versus Losartan as First-line Therapy after 6 weeks in Patients With Severe Hypertension" | IND 33,383 (serial = 880) |
| Protocol 228 | "A Double Blind, Randomized, Parallel, Placebo-Controlled, Efficacy Study of Losartan 100mg-Hydrochlorothiazide 25mg versus Losartan 50mg – Hydrochlorothiazide 12.5mg in patients with essential hypertension" | IND 33, 383 (serial = 847) |

### C. Postmarketing Experience

N/A

### D. Literature Review

N/A

## V. Clinical Review Methods

### A. How the Review was Conducted

The Sponsor submitted 2 clinical trials (P232 and P228) to support the proposed labeling changes. The two trials were reviewed separately. The pivotal study, P232, was reviewed first followed by a review of the supportive study, P228. The efficacy analysis from both trials was reviewed first followed by the safety analysis.

### B. Overview of Materials Consulted in Review

The protocols and protocol amendments from IND 33,383 were reviewed prior to initiating the efficacy review.

### C. Overview of Methods Used to Evaluate Data Quality and Integrity

A DSI audit was not requested for this application at the time of filing and there are no plans to conduct one at the present time.

**D. Were Trials Conducted in Accordance with Accepted Ethical Standards**

Per the sponsor, both of the submitted studies were "conducted in conformance with applicable country or local requirements regarding ethical committee review, informed consent, and other statutes or regulations regarding the protection of the rights and welfare of human subjects participating in biomedical research."

**E. Evaluation of Financial Disclosure**

FDA forms 3454 and 3455 were completed and signed by the Sponsor.
As shown in the table below 15 of the 838 Investigators/Sub-investigators had "Significant payments of other sorts or Equity Interest" in the sponsor (Merck).
An analysis of the impact of financial conflict of interest on the primary endpoint is shown in Table1 in the Appendix.

**Table 2: Details of financial disclosure of investigators/sub-investigators[a]**

| Investigator Category | Total Number |
|---|---|
| Grand Total Number of Investigators/Subinvestigators per Protocol and Site | 838 |
| Total Number of Investigators/ Subinvestigators Who Are Certified Regarding an Absence of Financial Arrangements per Protocol and Site | 786 |
| Total Number of Investigators/Subinvestigators Not Providing Information and Not Certified per Protocol and Site | 37 |
| Total Number of Investigators/Subinvestigators Not Certified Due to "Significant Payments of Other Sorts" or Equity Interest per Protocol and Site | 15 |
| Total Number of Investigators/ Subinvestigators Receiving Payments based on Outcome of study per protocol and per site | 0 |
| Total Number of Investigators/ Subinvestigators with Proprietary Interest in the Test Product or Company per Protocol and Site | 0 |

[a]Data from Table A-3, in the "Financial Information" section of the electronic submission of 9/2002

# VI. Integrated Review of Efficacy

## A. Brief Statement of Conclusions

The sponsor seeks approval of Hyzaar as a first line agent in the treatment of "severe" hypertension. Pivotal study P232 supports this claim by showing that Hyzaar 50/12.5 was superior to Losartan 50 mg titrated as needed to 100 mg. The patient population studied had a mean SiDBP of $\geq$ 110 mm Hg with a mean SiSBP $\leq$ 220 mm Hg at the time of randomization (after an adequate washout of existing anti-hypertensives). Hyzaar was superior in terms of the primary

endpoint of percentage of patients achieving a pre-defined goal of mean SiDBP < 90 mm Hg after 4 weeks of treatment had elapsed. Randomization achieved balance in the 2 groups except with regard to gender. There were slightly more females in the Hyzaar group versus Losartan monotherapy. Interestingly, it was the female group that responded better to Hyzaar rather Losartan monotherapy.

Study P228, a non-pivotal placebo controlled study, supports the findings of study P232. The major difference of study P228 compared to study P232 was in the population studied: more than two-thirds of the patients in P228 could be classified according to JNC VI criteria as having Stage 2 hypertension. Patients in P232 were JNC VI classified as having primarily Stage 3 hypertension.

**B. General Approach to Review of the Efficacy of the Drug**

Study P232 was the pivotal study while P228 was a supportive study. Both were reviewed in similar detail. While P232 was an active control study that showed superiority of Hyzaar relative to Losartan, study P228 was a placebo controlled dose ranging study showing efficacy of Hyzaar relative to placebo in moderate to severe hypertensives. Both studies were evaluated independently starting with efficacy and concluding with safety.

**C. Detailed Review of Trials by Indication**

1. **Protocol 232: "A Randomized, Double Blind Safety and Efficacy Study of Losartan Plus Hydrochlorothiazide versus Losartan as First-line Therapy after 6 weeks in Patients With Severe Hypertension."**

   a. **Summary of major amendments to the study protocol (Original Protocol date was 8/15/00)**

   The Protocol Amendment of 11/9/00 provided a clarification of the titration scheme. The original protocol inaccurately described the titration scheme at week 4 for patients whom at Week 2 were not titrated. The amendment stated that at the end of 4 weeks, patients previously on Dose Level 1 (the lowest dose in Los/HCTZ arm) with a mean trough SiDBP $\geq$ 90 mm Hg would be titrated to Dose Level 3. In other words patients with inadequate blood pressure control at week 4 in the combination arm wouldn't be sham titrated to Los50/HCTZ12.5 (Dose level 2) but instead would be titrated to Los100/HCTZ25 (Dose level 3). Those with mean trough SiDBP < 90 mm Hg would remain on Dose Level 1.

   b. **Study Design**

A randomized, double-blind, active control (Losartan), multinational study in patients with "severe" hypertension receiving no other anti-hypertensive therapy.

**Definition of "Severe" Hypertension**

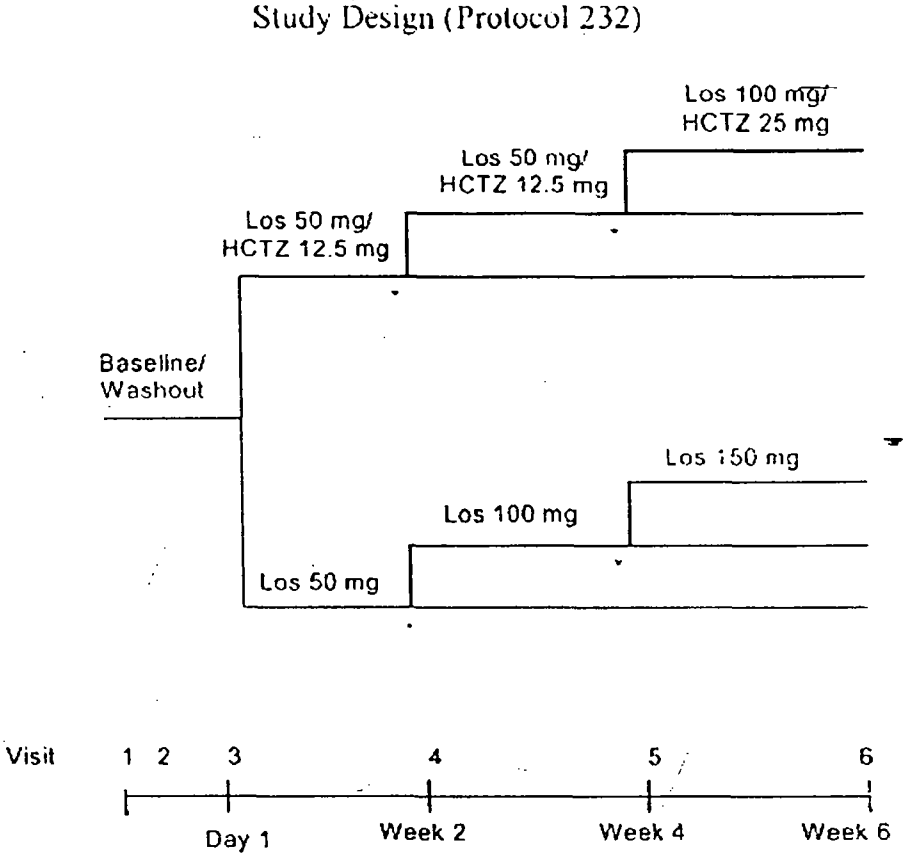
Severe hypertension was defined as a mean SiDBP $\geq$ 110 mg Hg (with a SBP $\leq$ 220 mm Hg). Patients on existing anti-hypertensive therapy were also eligible if they have a mean trough SiDBP $\geq$ 95 mm Hg at the initial screening visit. These patients were washed off their existing anti-hypertensive and had their BP re-evaluated. Upon follow-up, if they had a mean SiDBP $\geq$ 110 mm Hg they were eligible.

**Study duration and number enrolled**

The randomized, double blind portion of this study was 6 weeks in duration. Approximately 510 patients were expected to be randomized. The patients were randomized 2:1 to receive either Los/HCTZ or Los alone.

The design scheme is shown in Figure 1 below. The length of the washout period ranged from between 24 hours up to 3 weeks post screening visit.

**Figure 1: Schematic of study design for protocol 232.**




* Titrate if SiDBP >90 mm Hg; patients with a SiDBP ≥110 mm Hg in the combination therapy arm were titrated to Los 100 mg/HCTZ 25 mg at Week 2. The primary endpoint was at Week 4.

There were two time points at which patients could be titrated in this study: Week 2 and Week 4. At week 2, patients in the Los/HCTZ arm were sham titrated to Los25/HCTZ12.5 (dose level 2) as shown in the Figure above unless they had a mean SiDBP ≥ 110 mm Hg in which case they were titrated to Los100/HCTZ25 (dose level 3). In the case of Losartan, the titration scheme was titration to Los 100mg (dose level 2) at week 2 if mean SiDBP > 90 mm Hg. If at week 4 SiDBP was again > 90 mm Hg, patients were titrated to 150mg (dose level 3).

c. **Blinding/Randomization**

The Los/HCTZ combination and its corresponding placebo were identical (with respect to color, shape, markings, etc.)at all doses studied. They were tear-drop shaped. Similarly Los and its

corresponding placebo were identical (with respect to color, shape, markings, etc.) at all doses studied and were both round in shape. However, the Los/HCTZ and Los were not identical. Because of this, a double-dummy technique was used. As a result, all patients took 4 tablets a day.

Drug disclosure information was provided in a sealed envelope, which were to remain sealed except in the case of an emergency. There were no instances of unblinding (accidental or otherwise) during the study.

Block randomization with each study site given 6 numbers uniquely assigned to that site.

d **Primary and Secondary endpoints**

The primary efficacy measurement was blood pressure reduction as assessed by conventional mercury sphygmomanometer.

**Primary**

To compare the anti-hypertensive efficacy of losartan 50 mg + HCTZ 12.5 mg once a day versus losartan 50 mg once a day titrated as needed to losartan 100 mg once a day in lowering mean trough SiDBP to a goal of < 90 mm Hg after 4 weeks of first-line double-blind therapy in patients with severe hypertension.

**Secondary**

To assess the safety and tolerability of Los/HCTZ versus Los according to the incidence of overall adverse experiences and drug-related adverse experiences at first dose, 2, 4, and 6 weeks.

To assess the efficacy of combination therapy and monotherapy regimens in reducing mean trough SiDBP according to the proportion of patients achieving goal mean trough SiDBP after 6 weeks.

To assess the efficacy of Los/HCTZ versus Los according to the change from baseline in mean trough SiDBP and the proportion of patients responding to therapy (mean trough SiDBP < 90 mm Hg or a decrease in mean trough SiDBP ≥ 10 mm Hg if mean trough SiDBP ≥ 90 mm Hg at 4 and 6 weeks.

e. **Inclusion/Exclusion Criteria**

**Inclusion Criteria**

i. Male or female with severe hypertension over the legal age of consent.

ii. Taking no more than 3 anti-hypertensive medications prior to study entrance (Visit 1; Screening).

iii. Patients met the following blood pressure criteria:

For previously treated patients:
Mean trough SiDBP≥ 95 mm Hg, mean trough SiSBP ≤220 mm Hg at screening; mean SiDBP ≥110 mm Hg, mean trough SiSBP ≤220 mm Hg after washout and at randomization.

For previously untreated patients:
Mean SiDBP ≥110 mm Hg, mean SiSBP ≤220 mm Hg at screening and randomization.

**Exclusion Criteria**

i. A history of secondary hypertension of any etiology, such as unilateral or bilateral renal disease, renal artery stenosis, coarctation of the aorta, or pheochromocytoma.

ii. A history of malignant hypertension, or any current evidence of impending or active malignant hypertension, including headache, papilledema, and chest pain.

iii. A history of cerebrovascular accident (stroke), transient ischemic attacks, or audible carotid bruits.

iv. A documented history of myocardial infarction or angina pectoris in the 6 months prior to study start.

v. A history of clinically significant atrioventricular (AV) conduction disturbance without a permanent pacemaker, i.e., second or third-degree AV block. Sick-sinus syndrome or clinically significant bradycardia (resting heart rate <45 beats/minute) without a pacemaker.

vi. A history of unexplained syncope within the 2 years prior to study start, or a known syncopal disorder.

vii. A history of atrial fibrillation.

viii. A history of congestive heart failure or a known left ventricular ejection fraction ?40%. i) Hemodynamically significant obstructive valvular disease or cardiomyopathy.

ix. A prior known sensitivity reaction to Los, or HCTZ or other sulfonamide-derived drugs. Patients with a history of angioedema were excluded from the study.

x. Use of other drugs with hemodynamic effects.

**xi.** Use of psychotropic medication with possible hemodynamic effects.

**xii.** Use of lithium.

**xiii.** A regular user (daily) of nonsteroidal anti-inflammatory drugs (NSAIDs) or high-dose aspirin. (NOTE: Aspirin taken prophylactically as a cardioprotective agent up to 325 mg/day was permitted. Acetaminophen was the preferred agent for pain relief. Intermittent use of an NSAID was permitted; however, NSAIDs were not be taken within 3 days of a scheduled clinic visit.)

**xiv.** A concomitant user of oral steroids or adrenocorticotrophic hormone (ACTH).

**xv.** Use of replacement hormones (thyroid, testosterone, estrogen) whose regimen had not been stable for ? 3 months. q) Evidence of significant hepatic dysfunction as indicated by history or laboratory evaluation.

**xvi.** A serum creatinine ? 1.5 mg/dL and a creatinine clearance <60 cc/min calculated from the Cockcroft and Gault equation.

**xvii.** Proteinuria >2+.

**xviii.** AST/SGOT and/or ALT/SGPT greater than twice the upper limit of normal.

**xix.** A clinically significant laboratory value outside of the established normal range including but not limited to any of the following parameters: hematocrit, hemoglobin, or platelet count.

**xx.** A white blood cell count <3000/$mm^3$.

**xxi.** A serum potassium <3.5 or >5.5 mEq/L.

**xxii.** Hematuria (>20/hpf) of unknown etiology. Prior to patient entry, any hematuria was evaluated, the etiology established/documented and treatment rendered as appropriate.

**xxiii.** Known to have been HIV or hepatitis B positive, although no screening was required.

**xxiv.** A history of clinically important malabsorption or gastrointestinal resection or cirrhosis of the liver.

**xxv.** Pregnant or lactating patient. (NOTE: Females of childbearing age who were not surgically sterilized and who were using effective contraception [e.g., double-barrier protection, intrauterine device, hormonal contraceptives, abstinence, surgical sterilization, patient or partner was sterile]) could enter only if an exclusionary pregnancy test was done prior to entering the study.

**xxvi.** Pregnancy tests were repeated at Weeks 4 and 6 of the study. In the event of a positive test, the patient was to be discontinued immediately and the medical monitor was to be notified.)

**xxvii.** A fasting serum glucose level >240 mg/dL at baseline. (NOTE: Patients with diabetes mellitus were permitted to enter the study, provided they were clinically stable on a consistent dose of an oral hypoglycemic agent or insulin during the baseline period and no hypoglycemic episodes had occurred.)

**xxviii.** A concurrent severe disease (e.g., neoplasm) that could preclude participation or survival.

**xxix.** A known bleeding or platelet disorder.

**xxx.** Was currently abusing alcohol or drugs or had a well-documented history (within the 2 years prior to study start) of alcohol or drug abuse.

**xxxi.** Mentally or legally incapacitated.

**xxxii.** Participation in another investigational drug trial (i.e., informed consent obtained) within 28 days of starting the baseline period.

**xxxiii.** Presence of a single functioning kidney.

**xxxiv.** An arm circumference >41 cm.

### f. Efficacy and Safety endpoints measured

The following table summarizes the timepoints at which clinical data was collected in this study.

**Table 3: Study flow chart**[a]

| | Screening | Screening 24 hrs to 3 wks | Randomization | Treatment Weeks | | |
|---|---|---|---|---|---|---|
| | | | | 2 | 4 | 6 |
| **Clinic Visit I.D.:** | 1 | 2 | 3 | 4 | 5 | 6 |
| Obtained informed consent | X | | | | | |
| Reviewed inclusion/exclusion Criteria | X | X | X | | | |
| Medical history | X | | | | | |
| Complete physical examination | X | | | | | X |
| Sitting and standing blood pressure And heart rate | X | X | X | X | X | X |
| Adverse experience assessment | | X | X | X | X | X |
| Complete laboratory test | X | | | | | X |
| Abbreviated laboratory test | | | | | X | |
| Serum pregnancy test | X | | | | X | X |
| 12-lead electrocardiogram | X | | | | | X |
| Discontinued or tapered off all Anti-hypertensive medications | X | | | | | |
| Dispensed medication | | | X | X | X | |
| Ambulatory blood pressure Monitoring[b] | | | X | | | |

[a]Data from P232 study report Table 3

[b]Ambulatory blood pressure monitoring was performed in a subset of patients for approximately 26 hours post (1 hour pre-dose to 1 hour post-dose the following day)

## g. Statistical Considerations

### i. Power

The proportion of patients achieving BP control as defined by a mean SiDBP < 90 mm Hg was expected to be 9% in the monotherapy group (Losartan only) for purposes of power calculations. There was 95% power to detect a 13% (e.g. 9% vs. 22%) difference in the proportion of patients achieving goal BP at the end of 4 weeks given a total of 340 patients in the combination arm (Los + HCTZ) and 170 patients in the single therapy arm (Los only). This was based on an ? level of 5%.

### ii. Multiplicity

There was only 1 primary treatment comparison, and consequently no correction for multiplicity was necessary. There was no formal multiplicity correction for the secondary comparisons.

### iii. Statistical Methods

All randomized patients with at least 1 follow-up visit were included in the analysis. With respect to the calculation of mean changes in SiDBP, patients with missing data had their SiDBP value carried forward from their previous visit.

The following summarizes which blood pressure results were used to determine whether a patient achieved goal or was a "responder" (in the event the patient did not show up within the pre-specified time window):

**Week 2:** The last SiDBP before titration, observed between day 12 to day 18 relative to start of the study was used. If no observations were trapped within this window then the last measurement in the window (day 1 to day 18) was carried forward and used for the analysis.

**Week 4:** The last SiDBP before titration observed between day 26 and 32 relative to the start of the study was used. If no observations were trapped within this window then the last measurement in the window (day 1 to day 25) was carried forward and used for the analysis.

**Week 6:** The last SiDBP from day 40 to 46 relative to the start of the study was used. If no observations were trapped within this window then the last measurement in the window (day 26 to day 39) was carried forward and used for the analysis.

Comparison of treatment groups with respect to the proportion of patients achieving goal SiDBP was based on the chi-square test. Comparison of the treatment groups with respect to mean changes in SiDBP was based on an analysis of covariance model with pretreatment SiDBP as a covariate.

**iv. Interim Analysis**

No interim analysis was planned in this study.

**v. Safety Analysis**

The safety of the two treatment regimens was compared by comparison of the incidence of clinical adverse events and lab adverse events.

h. **Efficacy Outcomes**

**i.** Disposition of subjects

**Table 4: Patient accounting**[a]

| | Los/HCTZ | Los | Total |
|---|---|---|---|
| TOTAL PATIENTS | 393 | 192 | 585 |
| Male (age range—years) | 204 (26 to 75) | 117 (29 to 76) | 321 (26 to 76) |
| Female (age range—years) | 189 (22 to 87) | 75 (24 to 84) | 264 (22 to 87) |
| COMPLETED TRIAL | 361 (91.9%) | 171 (89.1%) | 532 (90.9%) |
| DISCONTINUED TRIAL | 32 (8.1%) | 21 (10.9%) | 53 (9.1%) |
| Clinical adverse experience | 7 (1.8%) | 7 (3.6%) | 14 (2.4%) |
| Laboratory adverse Experience | 0 | 0 | 0 |
| Lack of efficacy | 8 (2.0%) | 8 (4.2%) | 16 (2.7%) |
| Lost to follow-up | 5 (1.3%) | 0 | 5 (0.9%) |
| Patient moved | 1 (0.3%) | 0 | 1 (0.2%) |
| Withdrew consent | 7 (1.8%) | 4 (2.1%) | 11 (1.9%) |
| Protocol deviation | 2 (0.5%) | 2 (1.0%) | 4 (0.7%) |
| Other[b] | 2 (0.5%) | 0 | 2 (0.3%) |

[a] Data from P232 Study report Table 5.
[b] Includes miscellaneous reasons such as patient incarceration and patient's decision.

There were 284 patients who were screened but not randomized. The top 3 reasons for not randomizing these patients were 1) They did not meet blood pressure criteria (67%) 2) They had a serum creatinine $\geq$ 1.5 mg/dL (10%) 3) They had a clinically significant lab value outside of the normal range (7 %).

ii. Protocol deviations

Protocol violators were pre-defined in the Data Analysis Plan and were identified prior to unblinding of the database. There were no patients whose treatment was prematurely unblinded during the course of the study. Protocol violators fell into 1 of 4 general categories as follows:

- Patients who did not meet blood pressure entry criteria
- Patients who were non-compliant with the study medication
- Patients who discontinued the study
- Incorrectly titrated patients

iii. Patient demographics and baseline characteristics

The next 5 tables (Tables 5–9) summarize baseline characteristics by treatment group with respect to age, gender, race, duration of hypertension, risk factors for cardiovascular disease, concomitant and prior medical therapy, and baseline blood pressure.

As shown in Table 5, a relatively greater percentage of patients randomized to the Losartan/HCTZ group were female whereas a relatively greater percentage of patients randomized to Los were male. The mean age of all patients was 53. A majority of the subjects in both treatment arms had a duration of hypertension greater than 6 years.

**Table 5: Baseline patient characteristics by treatment group[a]**

| | Los/HCTZ (N=393) | | Los (N=192) | | Total (N=585) | |
|---|---|---|---|---|---|---|
| | n | (%) | N | (%) | n | (%) |
| **Gender** | | | | | | |
| Male | 204 | (51.9) | 117 | (60.9) | 321 | (54.9) |
| Female | 189 | (48.1) | 75 | (39.1) | 264 | (45.1) |
| **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 | |
| **Race** | | | | | | |
| Asian | 38 | (9.7) | 20 | (10.4) | 58 | (9.9) |
| Black | 86 | (21.9) | 38 | (19.8) | 124 | (21.2) |
| European | 1 | (0.3) | 0 | (0.0) | 1 | (0.2) |
| Hispanic | 47 | (12.0) | 23 | (12.0) | 70 | (12.0) |
| Multi-Racial | 38 | (9.7) | 19 | (9.9) | 57 | (9.7) |
| Polynesian | 0 | (0.0) | 1 | (0.5) | 1 | (0.2) |
| White | 183 | (46.6) | 91 | (47.4) | 274 | (46.8) |
| **Duration of Hypertension[b]** | | | | | | |
| <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 | |

[a] Data from P232 study report Table 9

[b] Two subjects did not have documentation of their duration of hypertension and thus were not included this analysis.

As shown in Table 6 below, both treatment arms were similar with respect to secondary diagnoses that were risk factors for coronary artery disease.

**Table 6: Listing of specific secondary diagnoses (risk factors for coronary artery disease) in the patient population occurring with an incidence of 5% or greater.** [a]

| | Los/HCTZ (N = 393) | | Los (N = 192) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| **Cardiovascular System** | 141 | (35.9) | 77 | (40.1) |
| Left Ventricular hypertrophy | 38 | (9.7) | 21 | (10.9) |
| Sinus Bradycardia | 14 | (3.6) | 11 | (5.7) |
| **Endocrine System** | 61 | (15.5) | 38 | (19.8) |
| Diabetes Mellitus | 33 | (8.4) | 17 | (8.9) |
| Type 2 DM | 12 | (3.1) | 10 | (5.2) |
| **Metabolism and Nutrition** | 142 | (36.1) | 60 | (31.2) |
| Hypercholesterolemia | 51 | (13.0) | 23 | (12.0) |
| Hyperlipidemia | 23 | (5.9) | 14 | (7.3) |
| Obesity | 59 | (15.0) | 20 | (10.4) |

[a] Modified from P232 study report Table 10.

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**Table 7: Number (%) of patients with specific prior therapies by drug category (drugs/drug classes with an incidence of ≥ 5% are reported only)[a]**

| Class | Drug | Los/HCTZ[b] (N=393) n | (%) | Los[b] (N=192) n | (%) |
|---|---|---|---|---|---|
| Patients with one or more prior Therapies | | 350 | (89.1) | 170 | (88.5) |
| Patients with no prior therapy | | 43 | (10.9) | 22 | (11.5) |
| Alimentary Tract and Metabolism | Antacid, Drug for Treatment of Peptic Ulcer and Flatulence | 16 | (4.1) | 13 | (6.8) |
| | Drug Used in Diabetes | 31 | (7.9) | 21 | (10.9) |
| | [c]Glyburide | 10 | (2.5) | 11 | (5.7) |
| | Vitamin | 32 | (8.1) | 14 | (7.3) |
| Cardiovascular System | Agent Acting on the Renin-Angiotensin System | 178 | (45.3) | 101 | (52.6) |
| | Captopril | 31 | (7.9) | 21 | (10.9) |
| | Enalapril maleate | 33 | (8.4) | 22 | (11.5) |
| | Lisinopril | 15 | (3.8) | 13 | (6.8) |
| | Antihypertensive | 14 | (3.6) | 11 | (5.7) |
| | Beta Blocking Agent | 90 | (22.9) | 43 | (22.4) |
| | Atenolol | 59 | (15.0) | 22 | (11.5) |
| | Calcium Channel Blocker | 113 | (28.8) | 58 | (30.2) |
| | Amlodipine | 22 | (5.6) | 14 | (7.3) |
| | Nifedipine | 38 | (9.7) | 18 | (9.4) |
| | Diuretic | 107 | (27.2) | 51 | (26.6) |
| | Hydrochlorothiazide | 76 | (19.3) | 30 | (15.6) |
| | Serum Lipid Reducing Agent | 29 | (7.4) | 15 | (7.8) |
| Genitourinary System and Sex Hormones | Sex Hormone and Modulator of the Genital System | 22 | (5.6) | 9 | (4.7) |
| Musculoskeletal System | Anti-Inflammatory and Antirheumatic Product | 46 | (11.7) | 11 | (5.7) |
| | Ibuprofen | 20 | (5.1) | 6 | (3.1) |
| Nervous System | Analgesic | 81 | (20.6) | 50 | (26.0) |
| | Acetaminophen | 30 | (7.6) | 19 | (9.9) |
| | Aspirin | 38 | (9.7) | 28 | (14.6) |

[a]Data from P232, Table 12

[b]Although a patient may have had 2 or more prior therapies, the patient is counted only once within a category. The same patient may appear in different categories. All drug classes are listed in which an overall 5% incidence was seen.

[c]Shaded area represents use of prior therapy 2x more common in one group compared to another

**Table 8: Number (%) of patients with specific concomitant therapies by drug category (Therapies used with an incidence of ≥ 5% only)[a]**

| Class | Name | Los/HCTZ[b] (N=393) n | (%) | Los[b] (N=192) n | (%) |
|---|---|---|---|---|---|
| Patients with one or more Concomitant therapies | | 230 | (58.5) | 119 | (62.0) |
| Patients with no Concomitant therapy | | 163 | (41.5) | 73 | (38.0) |
| Alimentary Tract and Metabolism | Antacid, Drug for Treatment of Peptic Ulcer and Flatulence | 17 | (4.3) | 15 | (7.8) |
| | Drug Used in Diabetes | 31 | (7.9) | 21 | (10.9) |
| | [c]Glyburide | 11 | (2.8) | 11 | (5.7) |
| | Vitamin | 31 | (7.9) | 16 | (8.3) |
| Cardiovascular System | Serum Lipid Reducing Agent | 28 | (7.1) | 15 | (7.8) |
| General Anti-Infectives For Systemic Use | Antibiotic for Systemic Use | 35 | (8.9) | 16 | (8.3) |
| Genitourinary System and Sex Hormones | Sex Hormone and Modulator of the Genital System | 21 | (5.3) | 9 | (4.7) |
| Musculoskeletal System | [c]Anti-Inflammatory and Antirheumatic Product | 43 | (10.9) | 10 | (5.2) |
| | Ibuprofen | 20 | (5.1) | 6 | (3.1) |
| Nervous System | Analgesic | 96 | (24.4) | 55 | (28.6) |
| | Acetaminophen | 48 | (12.2) | 29 | (15.1) |
| | Aspirin | 36 | (9.2) | 25 | (13.0) |
| Various | All Other Therapeutic Products, Including Homeopathic and Herbal Preparations and Composition Unspecified | 14 | (3.6) | 11 | (5.7) |

[a]Data from P252, Table 13

[b]Although a patient may have had 2 or more prior therapies, the patient is counted only once within a category. The same patient may appear in different categories. All drug classes are listed in which an overall 5% incidence was seen.

[c]Shaded area represents use of prior therapy 2x more common in one group compared to another

As shown in Table 9 below, 8 subjects were in violation of inclusion criteria having a mean SiDBP of < 110 mm Hg. 7 of these subjects were on Los/HCTZ while 1 was on Los. A graphical distribution of the baseline mean SiDBP are shown in Figures 1 and 2 of the Appendix of this review. The pattern of SiDBP at baseline were positively skewed and similar in both treatment arms.

**Table 9: Summary of Baseline mean SiDBP at randomization (just prior to dosing)[a]**

| | Los/HCTZ (n = 393) | | Los (n = 193) | |
|---|---|---|---|---|
| | N | (%) | n | (%) |
| SiDBP ≥ 120 mm Hg | 25 | (6.4) | 16 | (8.3) |
| SiDBP ≥ 110 < 120 mm Hg | 361 | (91.9) | 176 | (91.2) |
| SiDBP < 110 mm Hg[b] | 7 | (1.8) | 1 | (0.5) |
| Mean SiDBP (mm Hg) | 113.4 | | 113.4 | |
| Standard deviation | 4.0 | | 3.7 | |

[a]Reviewer's analysis from electronic data set provided by sponsor
[b]All 8 subjects with a mean SiDBP < 110 mm Hg (7 on Los/HCTZ and 1 on Los alone) had a mean SiDBP of 109.

iv. Primary efficacy analyses (Intention to treat population)

The results of the primary endpoint are summarized in the table below. The primary endpoint was the percentage of patients achieving a SiDBP < 90 mm Hg at the end of 4 weeks of treatment.

**Table 10: Results of primary efficacy endpoint (% of patients with SiDBP < 90 mmHg) at the end of 4 weeks of treatment[a]**

| | Los/HCTZ (n = 393) | | Los (n = 192) | | Estimated Difference (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | | |
| Week 4 | 77 | (19.6) | 19 | (9.9) | 9.7 (3.5, 15.2) | 0.002 |

[a]Data from P232 Table 14

v. Secondary efficacy analyses

**Table 11: Results of secondary efficacy endpoint (% of patients with SiDBP < 90 mm Hg at the end of 6 weeks of treatment [a.b]**

| | Los/HCTZ (n = 393) | | Los (n = 192) | | Estimated Difference (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | n | (%) | n | (%) | | |
| Week 6 | 122 | (31.0) | 24 | (12.5) | 18.5(11.6, 24.7) | <0.001 |

[a] Data from P232, Table 14.
[b] This analysis was based on the intention to treat population

**Table 12: Number (percent) of Titrated patients[a]**

| | Losartan/HCTZ (n = 393) 100/25 mg | | Losartan(n = 192) 100 mg | | 150 mg | |
|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) |
| Week 2 | 75 | (19.1) | 166 | (86.5) | 0 | (0) |
| Week 4 | 208 | (52.9) | 4 | (2.1) | 147 | (76.6) |

[a] Data from Table 3 of "Response to FDA questions from January 24, 2003 tele-conference

**Table 13: Number (%) of patients who achieved goal SiDBP or a reduction in mean SiDBP from baseline of > 10 mm Hg at weeks 4 and 6 [a,b].**

| | Los/HCTZ (n = 393) | | Los (n = 192) | | Estimated Difference (95% CI) | 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 |

[a] This analysis was based on the intention to treat population.
[b] Data from P232 study report Table 17.

**Table 14: Mean SiSBP/SiDBP at 4 and 6 weeks[a]**

| | Los/HCTZ[b] | | Los[c] | |
|---|---|---|---|---|
| | Mean SiSBP/SiDBP (mm Hg) | SD | Mean SiSBP/SiDBP change (mm Hg) | SD |
| Baseline | 171.0/113.4 | 16.5/4.0 | 170.5/113.3 | 16/3.6 |
| Week 4 | 153.0/99.7 | 19.9/10.8 | 158.1/102.8 | 18.6/9.8 |
| Week 6 | 145.8/95.4 | 18.1/9.9 | 156.2/101.3 | 18.8/10.6 |

[a] Data from P232 Tables 18 and 19
[b] N = 392 at week 4 and 368 at week 6
[c] N = 192 at week 4 and 178 at week 6

**Table 15: Change from baseline in mean SiDBP at 4 and 6 weeks[a]**

| | Los/HCTZ[b] | | Los[c] | | p-value |
|---|---|---|---|---|---|
| | Mean change (mm Hg) | SD | Mean change (mm Hg) | SD | |
| Week 4 – Baseline | -13.6 | 9.8 | -10.5 | 8.6 | <0.001 |
| Week 6 – Baseline | -17.8 | 9.2 | -11.9 | 9.5 | <0.001 |

[a] Data from P232 Table 18
[b] N = 392 at week 4 and 368 at week 6
[c] N = 192 at week 4 and 178 at week 6

vi. Subgroup analyses of efficacy

Table 16 below shows the subgroup analysis as relates to the primary efficacy endpoint.

Females appeared to benefit to a greater extent than did males when treated with Hyzaar. It is important to note that at baseline 48% of patients were females in Los/HCTZ arm versus 39% females in the Los arm.

Patients less than 40 years of age and those > 75 years of age benefited the least with Los/HCTZ relative to Los alone. However in these groups the N's were small and 95% CI were broad. The majority of the patients studied were Caucasian. However, in all races studied there was a greater achievement of goal SiDBP on Los/HCTZ versus Los alone although the 95% CI was broad and occasionally crossed 0 in some of the groups.

**Table 16: Subgroup analysis- Number (%) of patients who achieved goal sitting diastolic blood pressure at week 4[a].**

| | Los/HCTZ N=393 n/N[b] | (%) | Los N=192 n/N | (%) | Estimated Difference (95% CI) |
|---|---|---|---|---|---|
| **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) | ¼ | (25.0) | -5.0 (52.8, 42.1) |
| **Race** | | | | | |
| Asian[c] | 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[d] | 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) |

[a] Data from P232 Table 15

[b] n/N = the number of patients in the subgroup who achieved goal SiDBP (<90 mm Hg)/number of patients in the subgroup

[c] The racial category of Asian represents those patients listed as either Asian or Polynesian in the demographic analysis

[d] The racial category of Caucasian represents those patients listed as either White or European in the demographic analysis

The results of subgroup analysis at the 6 week timepoint was not markedly different compared to the 4 week results.

2. Protocol 228: "A double-blind, randomized, parallel, placebo-controlled, efficacy study of losartan potassium 100mg – hydrochlorothiazide 25mg versus losartan potassium 50 mg – hydrochlorothiazide 12.5mg in patients with essential hypertension."

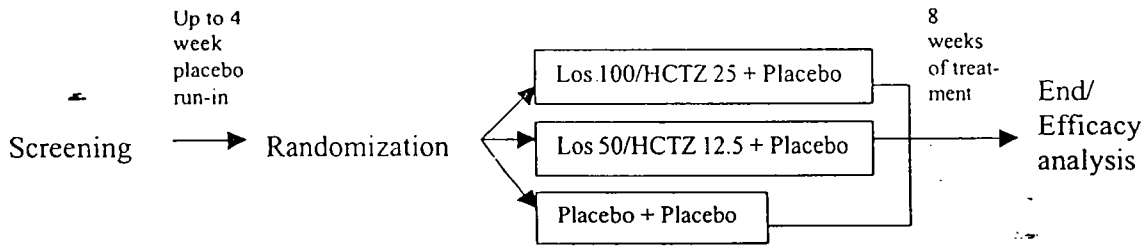
   a. Major amendments to the protocol

      An amendment to the original protocol was made in 12/2000. The primary purpose of the amendment was to modify several inclusion/exclusion criteria in order to boost enrollment. These amendments did not substantially affect the population enrolled and eventually randomized.

   b. Study Design

      This was a multi-centered, prospective, double-blind, double-dummy, randomized, parallel group, placebo-controlled study performed to compare the efficacy of Los 100 mg/HCTZ 25 mg and Los 50 mg/HCTZ 12.5 mg in the treatment of men and women over 21 years of age with moderate-to-severe essential hypertension defined as a mean trough SiDBP between 105 and 115 mm Hg at randomization.

      The scheme below summarizes the key elements of the study design.




      Patients eligible for randomization were stratified according to baseline SiDBP into 2 groups: 1) mean trough SiDBP ranging from 105-109 mm Hg 2) mean trough SiDBP ranging from 110 to 115 mm Hg.

      Patients were randomized in a 2:2:1 ratio to the Los 100-mg/HCTZ 25-mg arm, Los 50-mg/HCTZ 12.5-mg arm, and placebo arm, respectively.

   c. Blinding and Randomization

i. Blinding was accomplished using double-dummy placebo tablets (one matching the Los 100-mg/HCTZ 25-mg tablet and one matching the Los 50-mg/HCTZ 12.5-mg tablet).

ii. Within each study center, patients were randomized to treatment using computer-generated allocation schedules and assigned an allocation number (AN). Patients were randomized in a 2:2:1 ratio to the Los 100-mg/HCTZ 25-mg, Los 50-mg/HCTZ 12.5-mg, or placebo groups, respectively. Randomization was stratified according to mean trough SiDBP at the randomization visit. The two strata were as follows:

(1) mean trough SiDBP ranged from 105 to 109 mm Hg
(2) mean trough SiDBP ranged from 110 to 115 mm Hg

d. Primary and Secondary endpoints

i. Primary

To compare the anti-hypertensive efficacy of Los 100 mg/HCTZ 25 mg once a day versus Los 50 mg/HCTZ 12.5 mg once a day in patients with essential hypertension, as measured by change from baseline in the mean trough SiDBP.

ii. Secondary

(1) To evaluate the dose-dependent reduction in trough SiDBP for Los 50 mg/HCTZ 12.5 mg and Los 100 mg/HCTZ 25 mg versus placebo at 8 weeks.

(2) To compare the anti-hypertensive efficacy of Los 100 mg/HCTZ 25 mg versus Los 50 mg/HCTZ 12.5 mg in patients with essential hypertension, as measured by change from baseline in mean trough sitting systolic blood pressure (SiSBP).

(3) To compare the anti-hypertensive efficacy of Los 100 mg/HCTZ 25 mg and Los 50 mg/HCTZ 12.5 mg versus placebo in patients with essential hypertension, as measured by change from baseline in mean trough SiSBP.

(4) To compare the safety and tolerability of Los 100 mg/HCTZ 25 mg versus Los 50 mg/HCTZ 12.5 mg in patients with essential hypertension as measured by the overall incidence of adverse experiences and drug-related adverse experiences.

(5) To compare the safety and tolerability of Los 100 mg/HCTZ 25 mg and Los 50 mg/HCTZ 12.5 mg versus placebo in patients with essential hypertension as measured by the overall incidence of adverse experiences and drug-related adverse experiences.

(6) To compare the anti-hypertensive efficacy of Los 100 mg/HCTZ 25 mg versus Los 50 mg/HCTZ 12.5 mg in patients with essential hypertension as measured by the percentage of patients who respond to therapy (where response to therapy is defined as achieving a mean trough SiDBP <90 mm Hg or at least a 10-mm Hg decrease from baseline in mean trough SiDBP if mean trough SiDBP ≥ 90 mm Hg) at Week 8.

e. Inclusion / Exclusion Criteria

Inclusion:

i. Patient was not taking more than 2 anti-hypertensive medications.

ii. Patient was at least 21 years of age.

iii. Patient had a mean trough SiSBP ≤ 220 mm Hg.

iv. Patient had a mean trough SiDBP at Visit 1 of ≤115 mm Hg.

v. Patient had a mean trough SiDBP at Visits 2 and 3 between 105 to 115 mm Hg.

Exclusion:

i. Patient had secondary hypertension of any etiology, such as renal artery stenosis, coarctation of the aorta or pheochromocytoma, and hypertension induced by oral contraceptives.

ii. Patient had a history of malignant hypertension.

iii. Patient had any clinically significant renal disease including a single functioning kidney or a known history of anuria. Patient had any severe renal impairment, as manifested by serum creatinine more than 1.5 mg/dL and creatinine clearance <40 cc/mm (calculated using

Cockcroft and Gault formula), or proteinuria >2+ by urine dipstick.

iv. Patient had any known sensitivity or intolerance to an angiotensin II receptor antagonist or HCTZ or any other sulfonamide-derived drugs.

v. Patient had a history of angioedema.

vi. Patient was a pregnant woman or a woman of childbearing potential who was sexually active and did not use an appropriate method of birth control (double barrier or oral contraceptives).

vii. Patient had unstable diabetes mellitus. A patient with diabetes mellitus could have entered the study, provided he or she was clinically stable and on a consistent dose of an oral hypoglycemic agent and/or insulin during the placebo baseline period and no hypoglycemic episodes had occurred. Patients needed to have a baseline fasting glucose of <240 mg/dL.

viii. Patient was using concomitant therapy with any anti-hypertensive medications, including those used for indications other than hypertension (e.g., diuretics for any reason, nitroglycerin for angina pectoris, ROGAINE™ (Minoxidil 2%, Pharmacia & Upjohn) for hair loss, INDERAL™ (Propranolol HCl, Wyeth-Ayerst Laboratories) for migraine, HYTRIN™ (Terazosin HCl, Abbott Laboratories) for benign prostatic hyperplasia, VIAGRA™ (Sildenafil citrate, Pfizer US Pharmaceutical Group) for erectile dysfunction, VASOTEC™3 for congestive heart failure, or any agent that could cause a change in blood pressure). Intermittent use of VIAGRA™ was permitted except within 72 hours of clinic visits for mean trough blood pressure measurements. Patients who were unwilling to discontinue these medications or patients in whom the investigator felt it was clinically inappropriate to discontinue these medications were excluded from the study.

ix. Patient was using concomitant therapy with allopurinol, probenecid, colchicine, or sulfinpyrazone.

x. Patient was using concomitant therapy with lithium.

A patient who was on antidepressants such as PROZAC™ (Fluoxetine HCl, Eli Lilly and Co.), ZOLOFT™ (Sertraline HCl, Roerig), or ELAVIL™ (Amitriptyline HCl, Zeneca Pharmaceuticals) was permitted to enter the study provided he/she was on a stable dose prior to screening and were anticipated to continue on that dose throughout the study.

**xi.** Patient was using concomitant therapy with oral steroids or ACTH.

**xii.** Patient was using concomitant therapy with daily use of NSAIDs, COX-II inhibitor or high-dose aspirin. Aspirin taken prophylactically as a cardioprotective agent at 325 mg or less daily was permitted. Acetaminophen was the preferred agent for pain relief. Intermittent use of NSAIDs and COX-II inhibitors was permitted except within 72 hours of clinic visits for mean trough SiDBP measurements.

**xiii.** Patient was using concomitant therapy with cold and/or flu medications containing ephedrine. Intermittent use of therapies containing ephedrine was permitted except within 72 hours of clinic visits for mean trough SiDBP measurements.

**xiv.** Patient had unstable angina occurring within 6 months prior to randomization.

**xv.** Patient had experienced a myocardial infarction, percutaneous coronary intervention, coronary artery bypass surgery, congestive heart failure, transient ischemic attacks, or CVA within 6 months prior to randomization.

**xvi.** Patient exhibited clinically significant AV conduction disturbance, i.e., second or third degree AV block, sick sinus syndrome, or clinically significant bradycardia (resting heart rate <45 beats/minute) without a permanent pacemaker.

**xvii.** Patient exhibited atrial flutter, atrial fibrillation, or an accessory bypass tract (e.g., Stokes-Adams syndrome or Wolff-Parkinson-White syndrome).

**xviii.** Patient exhibited potentially life-threatening ventricular arrhythmias, decompensated valvular disease, presence of

hemodynamically significant obstructive valvular disease, or cardiomyopathy.

**xix.** Patient's serum potassium was <3.5 or >5.5 mEq/L.

**xx.** Patient exhibited severe hepatic impairment as manifested by AST (SGOT) > twice the upper limit of normal or ALT (SGPT) > twice the upper limit of normal.

**xxi.** Patient had hematuria >20 RBCs/hpf or of unknown etiology. Prior to patient entry, any hematuria was evaluated, the etiology was established and documented, and appropriate treatment rendered.

**xxii.** Patient had any clinically significant laboratory value that in the investigator's judgment could have been clinically significant to the outcome of this study. This included, but was not limited to, hematocrit, hemoglobin, or platelet count.

**xxiii.** Patient had a history of clinically important gastrointestinal resection, malabsorption, or cirrhosis of the liver.

**xxiv.** Patient had any concurrent severe disease that, in the investigator's judgment, could have precluded participation or survival. This included, but was not limited to, recent or current alcoholism, drug abuse (within 2 years prior to study start), mental (e.g., unstable depression) or legal incapacitation, or any disease that could have reasonably been expected to be fatal or life-threatening during the course of the study (e.g., malignancy within 5 years prior to study start, HIV/AIDS).

**xxv.** Patient used any investigational drug or participated in any drug study during or within 30 days prior to the screening visit.

**xxvi.** Patient was unable to be taken off of all current antihypertensive medication and placed on placebo for up to 12 weeks.

**xxvii.** Patient was unwilling or unable to give consent or to follow the protocol procedures.

**xxviii.** Patient's arm circumference was >41 cm.

xxix. Patient was not compliant at the end of the placebo period (<80% or >120% compliant). To calculate compliance for each study bottle, the actual number of tablets taken was divided by the number of tablets the patient was expected to take for that number of days and multiplied by 100. This number was the percent compliance.

f. Efficacy / Safety assessments

Blood pressure was measured using a mercury sphygmomanometer in the non-dominant arm at every office visit after 5 minutes of rest in the sitting position. Individual blood pressure readings were recorded in even numbers and read to the nearest 2-mm Hg mark on the manometer. Mean blood pressure readings were obtained by taking 3 consecutive sitting blood pressure readings 1 to 3 minutes apart. Individual clinic SiDBP readings were required to be within ±5 mm Hg of the mean of 3 readings. If not, consecutive readings were taken until this criterion was met.

Assessments were obtained at the same time of day, between 6 AM and 10 AM, for each individual patient throughout the study. The morning dose of medication was to be taken between 6 AM and 10 AM. To allow for trough blood pressure readings, the patients were instructed not to take the study medication on the day of the office visit until instructed to do so by study personnel.

**Table 17: Schedule of clinical observations and laboratory measurements.**

| | Placebo Baseline Washout Phase | | Double-Blind (Active Treatment Phase) | | |
|---|---|---|---|---|---|
| | Visit 1 | Visit 2 | Visit 3 | Visit 4 | Visit 5 |
| Procedure | Week –4 | Week-2 | Day 1 | Week 4 | Week 8 |
| Obtained informed consent | X | | | | |
| Reviewed inclusion/exclusion criteria | X | | X | | |
| Obtained medical history | X | | | | |
| Completed physical examination | X | | | | X |
| Obtained mean trough sitting blood pressure measurements and heart rate | X | X | X | X | X |
| Obtained laboratory safety tests | X | | X | | X |
| Obtained serum pregnancy test | X | | | | X |
| Obtained 12-lead ECG | X | | | | X |
| Discontinued or began tapering off all Anti-hypertensive medications | X | | | | |
| Dispensed placebo medication | X | | | | |
| Randomized patient | | | X | | |
| Dispensed active study medication | | | X | | |
| Studied medication count | | X | X | X | X |
| Collected study medication bottles | | | X | | X |
| Adverse experience evaluation | | X | X | X | X |

Data from P228 study report, Table 1

g. Statistical Considerations

i. Power: Given a sample size of 150 patients in each active treatment group and 75 patients in the placebo group, this study had 90% power to detect a difference between Los/HCTZ 50/12.5 and Los/HCTZ 100/25 of 3.0 mm Hg in the change from baseline in mean trough SiDBP as statistically significant at an alpha level of 0.05, assuming a standard deviation of 8 mm Hg.

ii. Multiplicity: No correction for multiplicity was needed as there was only one primary endpoint being tested.

iii. Statistical Methods: The primary statistical method that was used to analyze efficacy was the "all patients treated approach." This method will include in the analysis all patients who received the test drug and have a valid mean trough SiDBP measurement at baseline and at least one valid measurement after baseline. This was considered the modified intent to treat population (mITT). A last observation carried forward was used in the analyses of the mITT population.

An ANCOVA was used to compare the treatments of the mean change from baseline to Week 8 in trough SiDBP. The ANCOVA

model included terms for treatment, investigator, the interaction of treatment and investigator, baseline mean trough SiDBP as a covariate, and the interaction of treatment and baseline mean trough SiDBP.

iv. Interim Analysis: No interim analyses was planned for this study.

v. Safety Analysis: The safety of the 3 treatments were compared through pair-wise comparisons of the overall incidence of adverse experiences (regardless of relatedness and drug-related adverse experiences.)

h. Efficacy Outcomes

i. A total of 446 patients were enrolled and randomized to begin the study. The male to female ratio was approximately 1.6:1. There was a greater than 90% completion rate in both active arms of the study. However, there was a 4-5 fold greater discontinuance rate in the placebo arm relative to either active arm. Adverse events were much more common in the placebo group relative to either active treatment group as shown in Table 18 below.

**Table 18: Patient Accounting[a]**

| | Los/HCTZ | | | |
|---|---|---|---|---|
| | 100 mg/25 mg | 50 mg/12.5 mg | **Placebo** | **Total** |
| **Total Patients** | 173 | 184 | 89 | 446 |
| Female (age range in years) | 64 (32 to 89) | 75 (31 to 71) | 35 (29 to 68) | 174 (29 to 89) |
| Male (age range in years) | 109 (29 to 79) | 109 (25 to 76) | 54 (33 to 76) | 272 (25 to 79) |
| | N (%) | N (%) | N (%) | N (%) |
| **Patients completed the study** | 160 (92.5) | 176 (95.7) | 65 (73.0) | 401 (89.9) |
| **Patients discontinued from the study** | 13 (7.5) | 8 (4.3) | 24 (27.0) | 45 (10.1) |
| Clinical adverse experience | 6 (3.5) | 3 (1.6) | 9 (10.1) | 18 (4.0) |
| Patient was discontinued due to lack of test drug efficacy | 1 (0.6) | 1 (0.5) | 8 (9.0) | 10 (2.2) |
| Patient withdrew consent | 2 (1.2) | 1 (0.5) | 4(4.5) | 7(1.6) |
| Patient lost to follow-up | 3 (1.7) | 2 (1.1) | 1 (1.1) | 6 (1.3) |
| Patient moved or relocated | 0 (0.0) | 1 (0.5) | 1 (1.1) | 2 (0.4) |
| Laboratory adverse experience | 1 (0.6) | 0 (0.0) | 0 (0.0) | 1 (0.2) |
| Deviation from protocol | 0 (0.0) | 0 (0.0) | 1 (1.1) | 1 (0.2) |

[a]Data from P228 study report, Table 7

ii. Protocol deviations

The protocol deviations are listed in the Table 19 below.

The major protocol deviation of note as stated in footnote b of the table was that through site monitoring and auditing, it was found

that 13 randomized patients enrolled from Site 007 (Dr. Colton) were considered to be unreliable due to invalid documentation and lack of support for existing data. The data from this site were excluded in both the mITT analyses and per protocol populations. Inclusion of the results from this site did not modify the conclusions of the study.

**Table 19: Number of patients who were excluded because of protocol violations at week 8[a].**

| | Los/HCTZ 100 mg/25 mg | Los/HCTZ 50 mg/12.5 mg | Placebo | Total |
|---|---|---|---|---|
| Total Patients used in the Modified Intent-to-Treat analyses | 166 | 180 | 84 | 430[b] |
| **Excluded Patients** | 29 (17.5%) | 31 (17.2%) | 30 (35.7%) | 90 (20.9%) |
| **Reason Excluded** | | | | |
| No assessment done within the per-protocol visit window | 16 (9.6%) | 24 (13.3%) | 24 (28.6%) | 64 (14.9%) |
| Prohibited concomitant therapy (allopurinol, probenecid, etc.) | 5 (3.0%) | 2 (1.1%) | 1 (1.2%) | 8 (1.9%) |
| Prohibited concomitant therapy taken within 2 days of clinic visit | 3 (1.8%) | 3 (1.7%) | 1 (1.2%) | 7 (1.6%) |
| Mean trough sitting diastolic blood pressure (SiDBP) at Visit 3 <105 or >115 mm Hg | 2 (1.2%) | 0 (0.0%) | 3 (3.6%) | 5 (1.2%) |
| Study drug compliance < 80% or > 120% | 1 (0.6%) | 0 (0.0%) | 3 (3.6%) | 4 (0.9%) |
| Missed study medication for 2 consecutive days prior to Visit 4 or 5 | 2 (1.2%) | 0 (0.0%) | 1 (1.2%) | 3 (0.7%) |
| Fewer than 20 hours between last dose and blood pressure (BP) Measurements | 1 (0.6%) | 2 (1.1%) | 0 (0.0%) | 3 (0.7%) |
| Non-study anti-hypertensive therapy taken during the 2 days prior to a Clinic visit or for more than 2 days | 0 (0.0%) | 0 (0.0%) | 1 (1.2%) | 1 (0.2%) |
| Mean trough SiDBP at Visit 2 >115 mm Hg | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) | 0 (0.0%) |

[a] Taken from P228 study report Table 9

[b] Total # of randomized patients was 446. From these 13 were excluded in the mITT population because one site (Dr. Colton) had an unreliable assessment of vital signs. 3 were excluded from the mITT population because they did not have a post baseline assessment of the primary efficacy parameter (SiDBP).

iii. Patient demographics and baseline characteristics

As seen in the table below the male to female ratio in both treatment arms and placebo was approximately 3:2. The majority of patients in all 3 groups were between the ages of 36 to 64. Whites and Blacks were the 2 most common races studied. The majority of patients had hypertension for at least 5 years with a baseline SiDBP between 105-109 mm Hg.

**Table 20: Patient demographics[a]**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | n | (%) | n | (%) | n | (%) |
| **Gender** | | | | | | | | |
| Female | 64 | (37.0) | 75 | (40.8) | 35 | (39.3) | 174 | (39.0) |
| Male | 109 | (63.0) | 109 | (59.2) | 54 | (60.7) | 272 | (61.0) |
| **Age (Years)** | | | | | | | | |
| <36 | 10 | (5.8) | 7 | (3.8) | 2 | (2.2) | 19 | (4.3) |
| 36 to 45 | 27 | (15.6) | 28 | (15.2) | 17 | (19.1) | 72 | (16.1) |
| 46 to 55 | 71 | (41.0) | 74 | (40.2) | 38 | (42.7) | 183 | (41.0) |
| 56 to 64 | 50 | (28.9) | 57 | (31.0) | 22 | (24.7) | 129 | (28.9) |
| 65 to 74 | 13 | (7.5) | 16 | (8.7) | 9 | (10.1) | 38 | (8.5) |
| 75 and over | 2 | (1.2) | 2 | (1.1) | 1 | (1.1) | 5 | (1.1) |
| Mean age | | 52.3 | | 53.2 | | 52.8 | | 52.8 |
| SD | | 9.8 | | 9.27 | | 9.42 | | 9.53 |
| Median age | | 52. | | 54 | | 52 | | 53 |
| Age range | | 29 to 89 | | 25 to 76 | | 29 to 76 | | 25 to 89 |
| **Race** | | | | | | | | |
| Asian | 6 | (3.5) | 5 | (2.7) | 2 | (2.2) | 13 | (2.9) |
| Black | 44 | (25.4) | 41 | (22.3) | 19 | (21.3) | 104 | (23.3) |
| Hispanic American | 16 | (9.2) | 20 | (10.9) | 9 | (10.1) | 45 | (10.1) |
| Indian (subcontinent) | 1 | (0.6) | 0 | (0.0) | 0 | (0.0) | 1 | (0.2) |
| Multi-racial population | 1 | (0.6) | 1 | (0.5) | 0 | (0.0) | 2 | (0.4) |
| Native American | 0 | (0.0) | 0 | (0.0) | 1 | (1.1) | 1 | (0.2) |
| White | 105 | (60.7) | 117 | (63.6) | 58 | (65.2) | 280 | (62.8) |
| **Duration of hypertension** | | | | | | | | |
| < 1 year | 20 | (11.6) | 17 | (9.2) | 7 | (7.9) | 44 | (9.9) |
| 1 to <5 years | 51 | (29.5) | 56 | (30.4) | 26 | (29.2) | 133 | (29.8) |
| 5 to <10 years | 35 | (20.2) | 40 | (21.7) | 23 | (25.8) | 98 | (22.0) |
| > 10 years | 67 | (38.7) | 71 | (38.6) | 33 | (37.1) | 171 | (30.3) |
| **Baseline SiDBP** | | | | | | | | |
| 105-109 | 123 | (71.1) | 131 | (71.2) | 61 | (68.5) | 315 | (70.6) |
| 110-115 | 50 | (28.9) | 53 | (28.8) | 28 | (31.5) | 131 | (29.4) |

[a] Data from P228 study report Table 11 and Appendix 4.11 Table 3.

Table 21: Listing of specific secondary diagnoses in the patient population[a]

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | n | (%) | n | (%) | n | (%) |
| **Cardiovascular System** | | | | | | | | |
| Left axis deviation | 12 | (6.9) | 13 | (7.1) | 6 | (6.7) | 31 | (7.0) |
| Left ventricular hypertrophy | 20 | (11.6) | 18 | (9.8) | 11 | (12.4) | 49 | (11.0) |
| Sinus bradycardia | 7 | (4.0) | 12 | (6.5) | 4 | (4.5) | 23 | (5.2) |
| Systolic murmur | 11 | (6.4) | 10 | (5.4) | 3 | (3.4) | 24 | (5.4) |
| T-wave abnormality | 8 | (4.6) | 8 | (4.3) | 8 | (9.0) | 24 | (5.4) |
| **Endocrine System and Metabolism** | | | | | | | | |
| Hyperthyroidism | 5 | (2.9) | 10 | (5.4) | 3 | (3.4) | 18 | (4.0) |
| Type 2 Diabetes mellitus | 8 | (4.6) | 6 | (3.3) | 5 | (5.6) | 19 | (4.3) |
| Hypercholesterolemia | 20 | (11.6) | 23 | (12.5) | 14 | (15.7) | 57 | (12.8) |
| Hyperlipidemia | 14 | (8.1) | 14 | (7.6) | 3 | (3.4) | 31 | (7.0) |
| Obesity | 13 | (7.5) | 16 | (8.7) | 6 | (6.7) | 35 | (7.8) |

[a]Data from P228 study report Table 12

As shown in the Table 22 below, the majority of patients enrolled were on agents acting on the renin-angiotensin system, followed by calcium channel blockers, diuretics and beta blockers.

**Table 22: Listing of prior anti-hypertensive use by drug category[a, b]**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | n | (%) | n | (%) | n | (%) |
| Agent acting on the Renin Angiotensin System | 68 | (39.3) | 71 | (38.6) | 43 | (48.3) | 182 | (40.8) |
| Beta Blocking Agent | 18 | (10.4) | 27 | (14.7) | 12 | (13.5) | 57 | (12.8) |
| Calcium Channel Blocker | 36 | (20.8) | 28 | (15.2) | 18 | (20.2) | 82 | (18.4) |
| Diuretic | 29 | (16.8) | 26 | (14.1) | 14 | (15.7) | 69 | (15.5) |
| Other Anti-hypertensive | 8 | (4.6) | 9 | (4.9) | 2 | (2.2) | 19 | (4.3) |

[a]Data from P228 Table 13

[b]Although a patient may have had 2 or more prior therapies, the patient is counted only once within a category. The same patient may appear in different categories.

**Table 23: Listing of prior therapies other than anti-hypertensives (incidence ≥ 5% in any one treatment/placebo group) for which the incidence of use was at least 2 fold different relative to any other group.[a]**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | n | (%) | n | (%) | n | (%) |
| Acetaminophen | 13 | (7.5) | 19 | (10.3) | 4 | (4.5) | 36 | (8.1) |
| Drug used in Diabetes | 13 | (7.5) | 5 | (2.7) | 8 | (9.0) | 26 | (5.8) |
| Calcium | 3 | (1.7) | 4 | (2.2) | 5 | (5.6) | 12 | (2.7) |
| Psycholeptic | 4 | (2.3) | 6 | (3.3) | 5 | (5.6) | 15 | (3.4) |
| Conjuated estrogen | 4 | (2.3) | 9 | (4.9) | 10 | (11.2) | 23 | (5.2) |
| Ascorbic Acid | 8 | (4.6) | 11 | (6.0) | 2 | (2.2) | 21 | (4.7) |
| Vitamin E | 11 | (6.4) | 18 | (9.8) | 4 | (4.5) | 33 | (7.4) |

[a]Data from P228 Table 14

**Table 24: Listing of concomitant therapies (incidence ≥ 5% in any one treatment/placebo group) for which the incidence of use was at least 2 fold different relative to any other group.[a]**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | n | (%) | n | (%) | n | (%) |
| Antacid, Drug for treatment of peptic ulcer and flatulence | 11 | (6.4) | 10 | (5.4) | 10 | (11.2) | 31 | (7.0) |
| Drug used in Diabetes | 13 | (7.5) | 6 | (3.3) | 9 | (10.1) | 28 | (6.3) |
| Calcium | 3 | (1.7) | 4 | (2.2) | 5 | (5.6) | 12 | (2.7) |
| Psycholeptic | 2 | (1.2) | 6 | (3.3) | 5 | (5.6) | 13 | (2.9) |
| Conjuated estrogen | 4 | (2.3) | 9 | (4.9) | 10 | (11.2) | 23 | (5.2) |
| Ascorbic Acid | 7 | (4.0) | 11 | (6.0) | 2 | (2.2) | 20 | (4.5) |
| Vitamin E | 10 | (5.8) | 18 | (9.8) | 4 | (4.5) | 32 | (7.2) |

[a]Data from P228 Table 15

**iv.** Primary efficacy analysis (modified intention to treat population)

The results of the primary endpoint are shown in Table 25. Los 100/ HCTZ 25 showed greater SiDBP lowering than did Los 50/ HCTZ 12.5. Both doses showed a statistically significant greater SiDBP lowering than did placebo. In the placebo group there was

a 8.4 mm Hg lowering of blood pressure relative to baseline that was highly statistically significant.

**Table 25: Mean change in the Sitting diastolic blood pressure (SiDBP) from baseline at week 8 (primary efficacy endpoint)[a].**

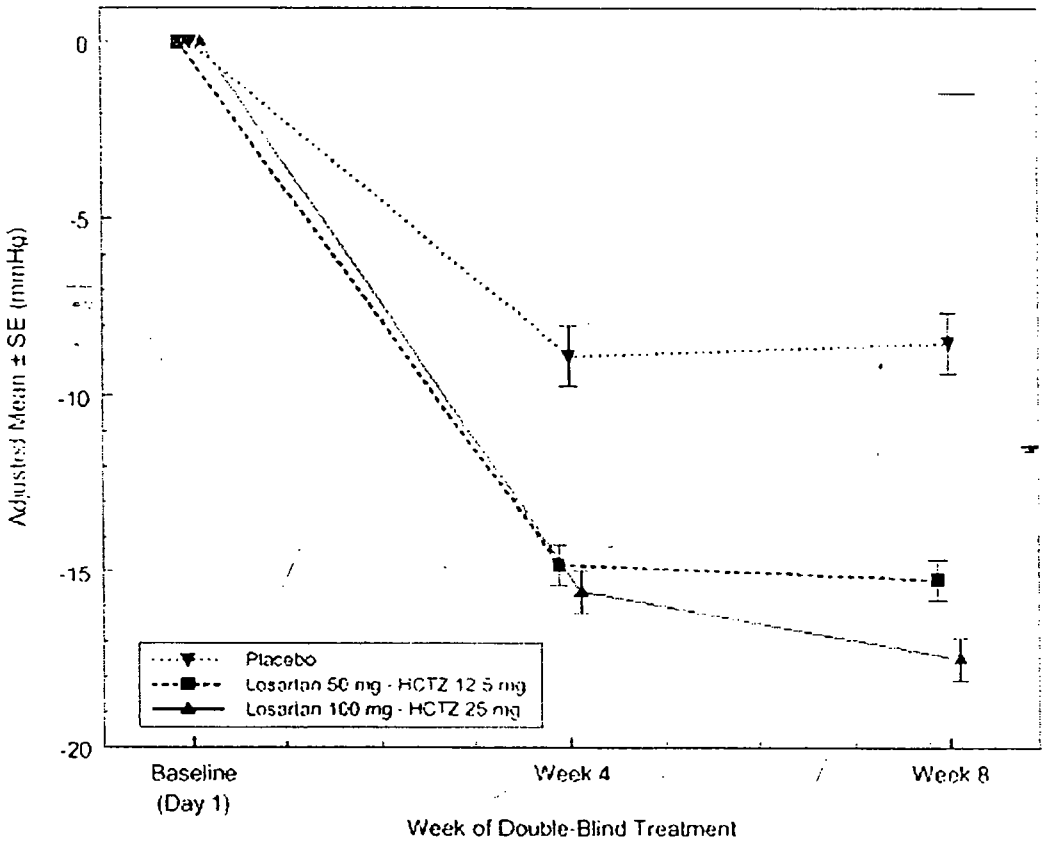
| | Los 100 mg/HCTZ 25 mg (n = 166)[b] | | | Los 50 mg/HCTZ 12.5 mg (n = 180)[b] | | | Placebo (n = 84)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Week 8 | Change | Baseline | Week 8 | Change | Baseline | Week 8 | Change |
| Mean (mm Hg) | 107.9 | 90.2 | -17.7 | 108.0 | 92.6 | -15.4 | 108.2 | 99.8 | -8.4 |
| SD (mm Hg) | 2.78 | 8.05 | 7.31 | 2.78 | 7.80 | 7.53 | 3.32 | 8.98 | 7.85 |
| P-value | | | <0.001 | | | <0.001 | | | <0.001 |
| 95% CI | | | (-18.7,-16.3) | | | (-16.4,-14.1) | | | (-10.1, -6.9) |

| Between-group Comparisons | Diff (SE) | 95% CI | p-Value | Model p-Values [a] | |
|---|---|---|---|---|---|
| 100/25 mg vs. 50/12.5 mg | -2.2 (0.82) | ( -3.8, -0.6) | 0.006 | Treatment: | <0.001 |
| 100/25 mg vs PBO | -9.0 (1.02) | (-11.0, -7.0) | <0.001 | Dose Response: Linear: | <0.001 |
| 50/12.5 mg vs. PBO | -6.7 (1.01) | (-8.7, -4.8) | <0.001 | Quadratic: | 0.003 |

[a] Data from P228 Table 18

[b] Represents modified intent to treat population (mITT)

Figure 2: Changes from baseline in the mean trough SiDBP[a]




[a]Data from P228 Figure 1.

v. Secondary efficacy analyses (mITT)

Table 26: Mean change in the Sitting systolic blood pressure (SiSBP) from baseline at week 8 (secondary efficacy endpoint)[a].

| | Los 100 mg/HCTZ 25 mg (n = 166)[b] | | | Los 50 mg/HCTZ 12.5 mg (n = 180)[b] | | | Placebo (n = 84)[b] | | |
|---|---|---|---|---|---|---|---|---|---|
| | Baseline | Week 8 | Change | Baseline | Week 8 | Change | Baseline | Week 8 | Change |
| Mean (mm Hg) | 159.9 | 138.1 | -21.8 | 160.5 | 141.9 | -18.6 | 161.1 | 156.4 | -4.7 |
| SD (mm Hg) | 13.59 | 14.17 | 13.95 | 13.74 | 15.07 | 13.78 | 13.89 | 18.14 | 13.85 |
| P-value | | | <0.001 | | | <0.001 | | | 0.001 |
| 95% CI | | | (-23.8, -19.8) | | | (-20.3, -16.4) | | | (-7.4, -1.9) |

| Between-group Comparisons | Diff (SE) | 95% CI | p-Value | Model p-Values[c] | |
|---|---|---|---|---|---|
| 100/25 mg vs. 50/12.5 mg | -3.4 (1.38) | (-6.2, -0.7) | 0.013 | Treatment: | <0.001 |
| 100/25 mg vs. PBO | -17.1 (1.72) | (-20.5, -13.7) | <0.001 | Dose Response: Linear: | <0.001 |
| 50/12.5 mg vs. PBO | -13.7 (1.70) | (-17.0, -10.3) | <0.001 | Quadratic | <0.001 |

[a]Data from P228 study report Table 19
[b]Represents modified intent to treat population (mITT)

As seen in Table 27 below, both doses of Los/HCTZ were superior to placebo in terms of percentage of patients who "responded" to therapy. However there was only a trend towards response when Los 100/HCTZ 25 was compared to Los 50/HCTZ 12.5.

**Table 27: Percentage of patients who responded to therapy at week 8 as measured by SiDBP[a].**

| | Anti-hypertensive Response Category Responders,n(%) | | | | Responders Categories | 95% CI for |
|---|---|---|---|---|---|---|
| | I[b] | II[c] | III[d] | Total[e] | I + II, n (%) | % Responders |
| Los 100 mg/HCTZ 25 mg | 78 (47.0) | 66 (39.8) | 22 (13.3) | 166 | 144(86.7) | (80.7,91.1) |
| Los 50 mg/HCTZ 12.5 mg | 65 (36.1) | 77 (42.8) | 38 (21.1) | 180 | 142(78.9) | (72.4,84.2) |
| Placebo | 10 (11.9) | 32 (38.1) | 42 (50.0) | 84 | 42(50.0) | (39.5,60.5) |

| Between-Group Comparisons | Odds Ratio | 95% CI | p-Value |
|---|---|---|---|
| 100/25 mg vs. 50/12.5 mg | 1.75 | (0.99, 3.11) | 0.056 |
| 100/25 mg vs. PBO | 6.55 | (3.52, 12.17) | <0.001 |
| 50/12.5 mg vs. PBO | 3.74 | (2.14, 6.53) | <0.001 |

[a]Data from P228 Table 20
[b]I = patients with mean trough SiDBP < 90 mm Hg
[c]II = patients with mean trough SiDBP ≥ 90 mm Hg, reduction ≥ 10 mm Hg
[d]III = neither I nor II.

vi. Subgroup analyses (by SiDBP strata 105 to 109 mm Hg versus 110 to 115 mm Hg).

As seen in Table 28 below, both doses of the Los/HCTZ combination were superior to placebo in terms of lowering SiDBP in both strata. The effect of blood pressure lowering was greater with the higher dose of the combination than with the lower dose. This effect was more pronounced in the lower blood pressure strata (SiDBP 105 to 109 mm Hg) versus the higher blood pressure strata (SiDBP 110 to 115 mm Hg).

**Table 28: Change in SiDBP at week 8 stratified by baseline SiDBP (mITT population)[a]**

| | Los/HCTZ | | | | | | Placebo (n = 56) | | |
|---|---|---|---|---|---|---|---|---|---|
| | 100 mg/25 mg (n = 115) | | | 50 mg/12.5 mg (n = 129) | | | | | |
| | Baseline | Week 8 | Change | Baseline | Week 8 | Change | Baseline | Week 8 | Change |
| **SiDBP: 105 to 109 mm Hg** | | | | | | | | | |
| N[b] | 115 | 115 | | 129 | 129 | | 56 | 56 | |
| Mean (mm Hg) | 106.3 | 88.2 | -18.1 | 106.5 | 91.3 | -15.2 | 106.8 | 97.4 | -9.3 |
| SD (mm Hg) | 1.22 | 7.19 | 7.10 | 1.22 | 7.04 | 7.07 | 1.35 | 7.99 | 7.83 |
| P-value[†] | | | <0.001 | | | <0.001 | | | <0.001 |
| 95% CI[‡] | | | (-19.3,-16.5) | | | (-16.3,-13.6) | | | (-11.2, -7.2) |
| **SiDBP: 110 to 115 mm Hg** | | | | | | | | | |
| N[b] | 49 | 49 | | 51 | 51 | | 25 | 25 | |
| Mean (mm Hg) | 111.7 | 94.9 | -16.8 | 111.8 | 95.8 | -16.1 | 112.0 | 106.4 | -5.6 |
| SD (mm Hg) | 1.38 | 8.20 | 7.77 | 1.67 | 8.72 | 8.62 | 1.55 | 7.30 | 7.07 |
| P-value[†] | | | <0.001 | | | <0.001 | | | <0.001 |
| 95% CI[‡] | | | (-18.9,-14.6) | | | (-18.1,-13.9) | | | (-9.0, -3.0) |

[a]Data from P228, Table 22

[b]Modified intent to treat population (mITT population)

## C. Efficacy Conclusions

The sponsor is seeking the claim that Hyzaar is safe and effective in patients with "severe hypertension." By JNC VI criteria the patients in the pivotal study were classified as having Stage 3 hypertension. The sponsor has completed and referenced 2 adequate and well controlled studies: P232 and P228 in support of this claim.

Study P232 was an active control study involving 585 patients performed over a 6 week period. The study showed that Hyzaar 50/12.5 is superior to Losartan monotherapy (50 mg titrated to the maximum labeled dose of 100 mg as needed) in terms of the percentage of patients achieving a goal SiDBP of< 90 mm Hg. In the Hyzaar group 19.6% of patients achieved goal while in the Losartan group 9.9% achieved goal. The baseline characteristics in study P232 were overall similar except with regard to sex. There were proportionately a greater number of women in the Hyzaar arm of the study than in the Losartan monotherapy arm. It is of interest to note that women responded more favorably to treatment than did men.

Study P228 was a placebo controlled dose ranging study comparing the anti-hypertensive effects of Hyzaar 100/25, Hyzaar 50/12.5, and placebo over an 8 week period in a total of 446 patients. This study involved patients primarily with Stage 2 hypertension according to JNC VI criteria and therefore may not

have as much applicability to the claim the sponsor is seeking. However the study showed that both doses of Hyzaar were superior to placebo. The study also showed that the additional blood pressure reduction seen with increasing the Hyzaar dose from 50/12.5 to 100/25 is small.

## VII. Integrated Review of Safety

### A. Brief Statement of Conclusions

This sNDA was primarily aimed at showing efficacy of Hyzaar in severe hypertensives with a secondary objective assessing safety. Hyzaar is on the market and is used relatively commonly as an anti-hypertensive. Safety information was collected over a 6 week and 8 week period in study P232 and P228 respectively. The adverse event profiles in these 2 studies were consistent with what is reported in the existing labeling of Hyzaar. With regards to pre-specified adverse events of hypotension, dizziness, and worsening renal function, there were no concerning signals.

### B. Description of Patient Exposure

Study P232 was a 6 week study. The mean exposure in each study arm was 41.4 and 40.1 days respectively. Study P228 was a 8 week study. The mean number of days spent on Los100/HCTZ25 and Los50/HCTZ12.5 were 54.1 and 55.6 days respectively.

**Table 29: Exposure to study drug by treatment group[c]**

| | Los/HCTZ (N = 393) | Los (N = 192) |
|---|---|---|
| Mean (days) | 41.4 | 40.1 |
| Median (days) | 42 | 42 |
| SD [a] (days) | 8.1 | 9.6 |
| % drug exposure [b] | 95.9 | 95.5 |

[a] SD = standard deviation

[b] Number of days on active therapy/number of days in the study.

[c] Data from P232 study report Table 35

## C. Methods and Specific Findings of Safety Review

Protocol 232

In the safety analysis of P232, non-serious adverse events were collected for up to 24 hours after the last dose of study drug. Serious adverse events were collected for up to 14 days after the last dose of study drug.

If dose information was missing in a particular interval (e.g. 2 weeks, 4 weeks, 6 weeks), information was carried forward from the immediate past dose level records. If a patient discontinued before Week 2, the patient was not counted at Week 4 and Week 6. Similarly if a patient was discontinued between Week 2 and Week 4, the patient was not counted at Week 6.

**Table 30: Number (%) of patients with specific clinical adverse experiences (incidence ≥ 1%) occurring at least 2 times more often in the Los/HCTZ group relative to the Los group[a].**

| | Los/HCTZ (n = 393) | | Los (n = 192) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Abdominal pain | 5 | (1.3) | 1 | (0.5) |
| Flushing | 4 | (1.0) | 1 | (0.5) |
| Pain (unspecified) | 4 | (1.0) | 1 | (0.5) |
| Constipation | 4 | (1.0) | 1 | (0.5) |
| Diarrhea | 9 | (2.3) | 2 | (1.0) |
| Pharyngitis | 4 | (1.0) | 0 | (0.0) |
| Muscular weakness | 4 | (1.0) | 0 | (0.0) |
| Anxiety | 5 | (1.3) | 1 | (0.5) |

[a]Data from P232 study report Table 38

Serious adverse events occurred in 4 and 7 patients receiving Los/HCTZ and Los respectively. Some individuals had more than one serious adverse events. Table 31 displays a listing of serious adverse events occurring in the Los/HCTZ more often than in the Los group. There were no deaths reported in either group during the study period.

**Table 31: Number (%) of patients with specific *serious* clinical adverse experiences (incidence ≥ 0%) occurring at least 2 times more often in the Los/HCTZ group relative to the Los group[a,b].**

| | Los/HCTZ (n = 393) | | Los (n = 192) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Cerebrovascular accident | 1 | (0.3) | 0 | (0.0) |
| Coronary artery disease | 1 | (0.3) | 0 | (0.0) |
| Uncontrolled hypertension | 1 | (0.3) | 0 | (0.0) |
| Ophthalmic inflmmation | 1 | (0.3) | 0 | (0.0) |
| Vitreous detachment | 1 | (0.3) | 0 | (0.0) |
| Cholelithiasis | 1 | (0.3) | 0 | (0.0) |

[a]Data from P232 study report Table 39

[b]Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

**Table 32: Number (%) of patients with specific clinical adverse experiences resulting in discontinuation by body system during treatment phase[a]**

| | Los/HCTZ (n = 393) | | Los (n = 192) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| Patients with 1 or more adverse experiences resulting in discontinuation | 1 | (0.3) | 2 | (1.0) |
| Blood pressure increased | 0 | (0) | 1 | (0.5) |
| Uncontrolled hypertension | 1 | (0.3) | 0 | 0(0) |
| Ectopic pregnancy | 0 | (0) | 1 | (0.5) |

[a]Data from P232 study report Table 43

**Table 33: Number (%) of patients with specific laboratory adverse clinical experiences (incidence ≥ 0%) occurring at least 2 times more often in the Los/HCTZ group relative to the Los group[a,b].**

| | Los/HCTZ (n = 393) | | Los (n = 192) | |
|---|---|---|---|---|
| | N | (%) | N | (%) |
| BUN increased | 2/385 | (0.5) | 0/185 | (0) |
| $Cr_{CL}$ decreased[c] | 1/384 | (0.3) | 0/184 | (0) |
| Hypercalcemia | 1/385 | (0.3) | 0/185 | (0) |
| Hypokalemia | 4/385 | (1.0) | 1/185 | (0.5) |
| Total serum protein increased | 1/385 | (0.3) | 0/185 | (0) |
| Uric Acid increased | 4/385 | (1.0) | 0/185 | (0) |
| Hematuria | 1/382 | (0.3) | 0/184 | (0) |
| Proteinuria | 2/382 | (0.5) | 0/184 | (0) |

[a]Data from P232 study report Table 46

[b]Although a patient may have had 2 or more clinical adverse experiences, the patient is counted only once in a category. The same patient may appear in different categories.

[c]$Cr_{CL}$ = creatinine clearance

**Table34: Number (%) of patients with pre-specified adverse experiences (hypotension, dizziness, worsening renal function) after the first dose, Week 2, Week 4, and Week 6[a].**

| | Time frame | Los/HCTZ | | Los | |
|---|---|---|---|---|---|
| | | N/N | (%) | n/N | (%) |
| Syncope[c] | | 0/393 | 0 | 0/192 | 0 |
| Hypotension | 1st dose | 0/393 | 0 | 0/192 | 0 |
| | Week2 | 0/393 | 0 | 0/192 | 0 |
| | Week4 | 1/393 | 0.3 | 0/192 | 0 |
| | Week6 | 1/393 | 0.3 | 0/192 | 0 |
| Dizziness | 1st dose | 6/393 | 1.5 | 5/192 | 2.6 |
| | Week2 | 15/393 | 3.8 | 10/192 | 5.2 |
| | Week4 | 20/293 | 5.1 | 14/192 | 7.3 |
| | Week6 | 22/393 | 5.6 | 15/192 | 7.8 |
| Worsening of Renal function[b] | Week2 | 0/13 | 0 | 0/7 | 0 |
| | Week4 | 0/118 | 0 | 1/46 | 2.2 |
| | Week6 | 3/358 | 0.8 | 2/173 | 1.2 |

[a]Data from P232 study report Table 50

[b]Defined as an increase in serum creatinine of 0.5 mg/dL.

[c]Data from P232 study report Table 48

P228

All 446 randomized patients who received at least one dose of study medication and were included in the safety analysis.

The mean numbers of days spent on active study therapy in the Los100/ HCTZ 25 and Los 50/HCTZ 12.5 were 54.1 and 55.6 respectively.

**Table 35: Summary of clinical adverse experiences[a].**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | N | (%) | n | (%) | n | (%) |
| Number (%) of patients: | | | | | | | | |
| With one or more adverse experiences | 60 | (34.7) | 44 | (23.9) | 29 | (32.6) | 133 | (29.8) |
| With no adverse experience | 113 | (65.3) | 140 | (76.1) | 60 | (67.4) | 313 | (70.2) |
| With serious adverse experiences | 2 | (1.2) | 1 | (0.5) | 2 | (2.2) | 5 | (1.1) |
| Who died | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |
| [b]Discontinued due to adverse experiences | 6 | (3.5) | 3 | (1.6) | 9 | (10.1) | 18 | (4.0) |
| Discontinued due to serious adverse experiences | 2 | (1.2) | 0 | (0.0) | 2 | (2.2) | 4 | (0.9) |

[a]Data from P228 study report Table 26

[b]Specific reasons for discontinuation due to adverse events are described in the text below.

The reasons for discontinuation due to adverse events for each treatment arm are as follows:

Los100/HCTZ25: dizziness, diaphoresis, increased platelet count, cholecystitis, Hepatitis A, headache, bronchitis

Los50/HCTZ12.5: headache, uncontrolled hypertension

Placebo: dizziness, asthenia/fatigue, diaphoresis, facial edema, lower extremity edema, uncontrolled hypertension, hypertension, hypertensive crisis, labile hypertension, systolic hypertension, epistaxis, increased platelet count, cholecystitis, hepatitis A, muscle weakness, neck stiffness, headache, muscle spasm, anxiety, bronchitis, dyspnea, nocturia.

**Table 36: Number (%) of patients with specific clinical adverse experiences occurring with a frequency of ≥ 0.4 % in the total population studied.**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | N | (%) | n | (%) | n | (%) |
| Upper respiratory infection | 11 | (6.4) | 9 | (4.9) | 3 | (3.4) | 23 | (5.2) |
| Dizziness | 9 | (5.2) | 6 | (3.3) | 4 | (4.5) | 19 | (4.3) |
| Abdominal pain | 3 | (1.7) | 1 | (0.5) | 1 | (1.1) | 5 | (1.1) |
| Asthenia/fatigue | 2 | (1.2) | 0 | (0.0) | 2 | (2.2) | 4 | (0.9) |
| Lower extremity edema | 0 | (0.0) | 1 | (0.5) | 2 | (2.2) | 3 | (0.7) |
| Facial edema | 0 | (0.0) | 0 | (0.0) | 2 | (2.2) | 2 | (0.4) |
| Upper extremity edema | 2 | (1.2) | 0 | (0.0) | 0 | (0.0) | 2 | (0.4) |
| Nausea | 3 | (1.7) | 3 | (1.6) | 1 | (1.1) | 7 | (1.6) |
| Diarrhea | 2 | (1.2) | 2 | (1.1) | 0 | (0.0) | 4 | (0.9) |
| Sinusitis | 2 | (1.2) | 1 | (0.5) | 0 | (0.0) | 3 | (0.7) |
| Muscular weakness | 0 | (0.0) | 2 | (1.1) | 1 | (1.1) | 3 | (0.7) |
| Back pain | 2 | (1.2) | 0 | (0.0) | 0 | (0.0) | 2 | (0.4) |
| Headache | 4 | (2.3) | 11 | (6.0) | 11 | (12.4) | 26 | (5.8) |
| Somnolence | 1 | (0.6) | 0 | (0.0) | 1 | (1.1) | 2 | (0.4) |
| Bronchitis | 3 | (1.7) | 2 | (1.1) | 1 | (1.1) | 6 | (1.3) |
| Rash | 2 | (1.2) | 0 | (0.0) | 0 | (0.0) | 2 | (0.4) |
| Urinary tract infection | 2 | (1.2) | 2 | (1.1) | 1 | (1.1) | 5 | (1.1) |

The most common reported adverse events with the Los100/HCTZ25 (n = 173) were upper respiratory infection(6.4%), dizziness (5.2%), headache (2.3%), nausea (1.7%), abdominal pain (1.7%), bronchitis (1.7%), asthenia/fatigue (1.2%), upper extremity edema (1.2%), diarrhea (1.2%), sinusitis (1.2%), back pain (1.2%), rash (1.2%), urinary tract infection (1.2%).

The most common reported adverse events with Los50/HCTZ12.5 (N = 184) were headache (6%), upper respiratory infection (4.9%), dizziness (3.3%), nausea (1.6%), diarrhea (1.1%), muscular weakness (1.1%), bronchitis (1.1%), urinary tract infection (1.1%).

The most common reported adverse events with placebo (N = 89) were headache (12.4%), dizziness (4.5%), upper respiratory infection (3.4%), asthenia/fatigue (2.2%), facial edema (2.2%), lower extremity edema (2.2%).

The adverse event profile in this study was consistent with what is described in the product information label in the PDR 2002.

Adverse events of special interest

Three events listed in Table 37 were identified as adverse events of special interest. They were dizziness, syncope and hypotension that are all manifestations of hypoperfusion.

**Table 37: Number (%) of patients with adverse experiences of "special interest"[a]**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446) | |
|---|---|---|---|---|---|---|---|---|
| | n | (%) | N | (%) | n | (%) | n | (%) |
| Dizziness | 9 | (5.2) | 6 | (3.3) | 4 | (4.5) | 19 | (4.3) |
| Syncope | 0 | (0.0) | 1 | (0.5) | 0 | (0.0) | 1 | (0.2) |
| Hypotension | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) | 0 | (0.0) |

[a]Data from P228 study report Table 33

Narratives of serious clinical adverse events

There are a total of 5 subjects who had "serious" clinical adverse events that are described below. Of these 5, 2 occurred in the Los100/HCTZ25 group, 1 in the Los50/HCTZ12.5, and 2 in the placebo group.

Los100/HCTZ25

A 49 y/o white female with a history of diabetes, fibromyalgia, and bronchitis, was hospitalized for symptoms of chest discomfort, shortness of breath, and a cough for 48 hours prior to admission. These symptoms started approximately 1 month after starting therapy on Los100/HCTZ25. Her symptoms improved with an "inhaler" and antibiotics. Her Los100/HCTZ25 was discontinued and she was started on Los50/HCTZ12.5.

A 58 y/o black male was hospitalized with acute cholecystitis a little less than 2 months after starting therapy with Los100/HCTZ25. The patient underwent a successful cholecystectomy. At post discharge follow-up about a week later, the patient had an elevated ALT (119 U/L) and an elevated AST (61 U/L).

Los50/HCTZ12.5

A 33 y/o white female with a history of nephrolithiasis and elevated ALT/AST(97/50 at during placebo run-in) was started on Los50/HCTZ12.5 Eight days after starting therapy she was hospitalized with acute cholecystitis (confirmed on abdominal ultrasound). It appears as though the bout of cholecystitis resolved with medical management and she continued on the study until completion. She underwent a successful cholecystectomy after study completion.

Placebo

A 58 y/o black male with a history of diabetes mellitus developed onset of nosebleeds prior to randomization and went to the Emergency room the evening of starting blinded therapy because of recurrent nose bleeds. His blinded medication was stopped. Evaluation in the ED revealed a questionable SBP of about 300 mm Hg. A follow-up reading revealed a blood pressure of 202/113 mm Hg. His nose bleeds were treated with both a cocaine solution and nasal packing. His blood pressure was controlled with clonidine 0.1 mg and amlodipine 5 mg. He was discharged from the ED the following morning, feeling better, with relatively better BP control (190/94 mm Hg).

A 50 y/o white male was started on blinded therapy. One month after starting therapy his BP was 235/115 mm Hg (which on repeat 1 hour later was 231/114 mm Hg). His study therapy was stopped and he was discontinued from the study. He was instructed to go the hospital immediately despite any specific complaints. His hospital work-up revealed ECG changes of consistent with myocardial ischemia. These changes, however, were not confirmed on a cardiac stress test.

As shown in Table 38 below, elevations is AST/ALT occurred with both doses of the Los/HCTZ combination while there were no elevations in the placebo group were reported. Hyperglycemia was also present in 2 subjects receiving either dose of the Los/HCTZ combination while no elevations in the placebo group were reported.

**Table 38: Number (%) of patients with specific laboratory adverse experiences (incidence 0% in one or more treatment groups) by Laboratory test category during the treatment phase[a].**

| | Los/HCTZ 100 mg/25 mg (N=173) | | Los/HCTZ 50 mg/12.5 mg (N=184) | | Placebo (N=89) | | Total (N=446)[b] | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | n | (%) | n | (%) |
| **Blood Chemistry** | | | | | | | | |
| Alanine aminotransferase increased | 2/170[c] | (1.2) | 1/180 | (0.6) | 0/83 | (0.0) | 3/433 | (0.7) |
| Aspartate aminotransferase increased | 1/170 | (0.6) | 1/180 | (0.6) | 0/83 | (0.0) | 2/433 | (0.5) |
| Blood urea nitrogen increased | 0.170 | (0.0) | 2/180 | (1.1) | 0/83 | (0.0) | 2/433 | (0.5) |
| Hyperglycemia | 1/170 | (0.6) | 1/180 | (0.6) | 0/83 | (0.0) | 2/433 | (0.5) |
| Prostate-specific antigen increased | 1/1 | (100.0) | 0/0 | (0.0) | 0/0 | (0.0) | 1/1 | (100.0) |
| Serum creatinine increased | 0/170 | (0.0) | 2/180 | (1.1) | 0/83 | (0.0) | 2/433 | (0.5) |
| Uric acid increased | 0/170 | (0.0) | 1/180 | (0.6) | 0/83 | (0.0) | 1/433 | (0.2) |
| **Hematology** | | | | | | | | |
| Hematocrit decreased | 1/169 | (0.6) | 0/179 | (0.0) | 0/83 | (0.0) | 1/431 | (0.2) |
| Hemoglobin decreased | 1/169 | (0.6) | 0/179 | (0.0) | 0/83 | (0.0) | 1/431 | (0.2) |
| Lymphocytes increased | 1/170 | (0.6) | 0/179 | (0.0) | 0/83 | (0.0) | 1/432 | (0.2) |
| **Urinalysis** | | | | | | | | |
| Hematocrit | 0/168 | (0.0) | 2/179 | (1.1) | 1/83 | (1.2) | 3/430 | (0.7) |
| Proteinuria | 0/168 | (0.0) | 1/179 | (0.6) | 0/83 | (0.0) | 1/430 | (0.2) |

[a]Data from P228 study report Table 31

[b]Of the 446 randomized patients 434 had at least one lab test post randomization.

[c]One patient receiving Los100/HCTZ25 discontinued due to an increased ALT.

As seen in Table 39 below, there was a dose proportional increase in the % of patients with a change in BUN from baseline of 5 mg/dL. Additionally , patients on either dose of Hyzaar were more likely to have a labile serum potassium (changes from baseline of 0.5 mEq/L up or down) compared to placebo.

**Table 39: Number (%) of patients exceeding pre-defined limits of change[a]**

| Laboratory Test | Predefined Limit of Change | Treatment | Number[†]/ Total [‡](%) | |
|---|---|---|---|---|
| Serum Blood Urea Nitrogen (mg/dL) | Increase >5 | | | |
| | | Los 100 mg/HCTZ 25 mg | 30/170 | (17.6) |
| | | Los 50 mg/HCTZ 12.5 mg | 23/180 | (12.8) |
| | | Placebo | 3/83 | (3.6) |
| Serum Creatinine (mg/dL) | Increase >0.5 | | | |
| | | Los 100 mg/HCTZ 25 mg | 1/170 | (0.6) |
| | | Los 50 mg/HCTZ 12.5 mg | 0/180 | (0.0) |
| | | Placebo | 0/83 | (0.0) |
| Serum Potassium (mEq(K)/L) | Increase >0.5 | | | |
| | | Los 100 mg/HCTZ 25 mg | 7/170 | (4.1) |
| | | Los 50 mg/HCTZ 12.5 mg | 9/180 | (5.0) |
| | | Placebo | 1/83 | (1.2) |
| | Decrease >0.5 | | | |
| | | Los 100 mg/HCTZ 25 mg | 21/170 | (12.4) |
| | | Los 50 mg/HCTZ 12.5 mg | 13/180 | (7.2) |
| | | Placebo | 3/83 | (3.6) |

[a]Data from P228 study report Table 36

**D. Adequacy of Safety Testing**

The safety database for this sNDA was derived from a 6 week active control trial (P232) and an 8 week placebo controlled, dosing ranging trial. Both studies evaluated patients with moderate to severe hypertension. The studies appear to be adequate but because of their size and study duration can not be expected to detect rare adverse events (e.g. < 1/1000).

**E. Summary of Critical Safety Findings and Limitations of Data**

The adverse event profile from both studies was consistent with what is in the existing product label. No new concerning signals were raised from either of these studies.

In study P232, an active controlled trial, the mean exposure in the Hyzaar arm was 41.4 days while in the Losartan arm the mean exposure was 40.1 days. No concerning signals were identified in this study. The frequency of serious adverse events was too low to allow for a meaningful comparison between the two treatment arms. There were no differences between the 2 treatment arms with respect to hypotension, dizziness, or worsening of renal function (pre-specified adverse events of special interest).

In study P228, a placebo controlled dose ranging study, the mean exposures were 54.1 and 55.6 days on Los/HCTZ 100/25 and Los/HCTZ 50/12.5 respectively. In terms of the pre-specified adverse events of special interest (e.g. dizziness, hypotension, syncope) there were no dose dependant differences in the treatment arms and placebo. In terms of lab abnormalities, BUN increased by at least 5mg/dL in 17.6%, 12.8%, and 3.6% on Los/HCTZ 100/25, Los/HCTZ 50/12.5, and placebo respectively. The clinical significance of this is limited. Additionally serum potassium abnormalities (e.g. either increase or decrease by 0.5 mEq/L) were more common in either treatment arm relative to placebo. This is an expected finding as both components of Los/HCTZ can affect K physiology, albeit in different directions.

## VIII. Dosing, Regimen, and Administration Issues

N/A

## IX. Use in Special Populations

The 2 studies in this sNDA evaluated patients with "severe" hypertension. Because of the population being studied some patients may have had underlying renal dysfunction. However, this sNDA did not specifically study patients with either renal or hepatic dysfunction.

A. **Evaluation of Sponsor's Gender Effects Analyses and Adequacy of Investigation**

Subgroup analysis of study P232 revealed that women responded more favorably to Hyzaar relative to Losartan monotherapy than did men. The primary efficacy endpoint was the percentage of patients achieving a sitting DBP < 140. Among females 22.8% and 9.3% achieved this goal on Los/HCTZ and Los respectively (difference = 13.4% with a 95% CI of 3.2 to 21.4). Among males 16.7% and 10.3% achieved goal on Los/HCTZ and Los respectively (difference = 6.4% with a 95% CI of −1.8, 13.6). Therefore, although a clear trend existed among males it was not statistically significant in nominal terms. It is clear that the Los/HCTZ combination was more effective than Los monotherapy in both males and females with Stage 3 hypertension. However, it was the females that benefit to a greater extent.

B. **Evaluation of Evidence for Age, Race, or Ethnicity Effects on Safety or Efficacy**

In a subgroup analysis by age, all age subgroups responded more favorably to Los/HCTZ versus Los monotherapy. The exceptions to this were patients less than 40 years of age and patients more than 75 years of age. There were only 9 patients older than 75 years of age in this trial and conclusions in this group are limited. Among patients less than 40 years of age (11.5% of the entire study population), 16.7% achieved response on Los/HCTZ compared to 21.1% who achieved response on Los monotherapy (difference = -4.4 with a 95% CI of −28.1 to 13.6).

The main racial groups studied in P232 were Caucasians, Blacks, Hispanics, and Asians. All racial subgroups responded more favorably to the Los/HCTZ combination than Los monotherapy.

C. **Evaluation of Pediatric Program**

The Sponsor is requesting a full waiver for a pediatric program on the basis that necessary studies are impossible or highly impractical because of the number of such pediatric patients with essential severe hypertension is small.

D. **Comments on Data Available or Needed in Other Populations**

N/A

## X. Conclusions and Recommendations

A. **Conclusions**

The sponsor seeks the addition of a claim to the current Hyzaar labeling allowing use in patients with "severe" hypertension. The patients studied in the

pivotal trial P232 most closely resemble Stage 3 hypertensives according to JNC VI. In support of this claim they have completed and referenced 2 adequate and well controlled studies: P232 and P228.

Study P232, the pivotal study, was an active control study involving 585 patients over a 6 week period. The study showed that Hyzaar 50/12.5 is superior to Losartan monotherapy (50 mg titrated to the maximum labeled dose of 100 mg as needed) in terms of the percentage of patients achieving a goal SiDBP of< 90 mm Hg. In the Hyzaar group 19.6% of patients achieved goal while in the Losartan group 9.9% achieved goal. Subgroup analyses showed that women responded more favorably to Los/HCTZ than did men.

Study P228 was a placebo controlled dose ranging study comparing the anti-hypertensive effects of Hyzaar 100/25, Hyzaar 50/12.5, and placebo over an 8 week period in a total of 446 patients. This study involved patients primarily with SiDBP < 110 mm Hg and can not be used to support the indication the sponsor is seeking. The study showed that both doses of Hyzaar were superior to placebo. The study also showed that the additional blood pressure reduction seen with increasing the Hyzaar dose from 50/12.5 to 100/25 was statistically significant but clinically small.

The safety databases from these 2 studies did not add new information to what is already known about Hyzaar.

**B. Recommendations**

Although the findings were clearly positive, they were predictable. It was with little surprise that a combination of 2 drugs (Hyzaar) achieved blood pressure "control" more often than did monotherapy (Losartan). Presumably this finding would not be limited to severe hypertension but to mild and moderate hypertension as well.

At the May 2000 meeting between the FDA and the sponsor it was stated that Hyzaar could get approval for Hyzaar as a first line treatment of severe hypertension if it could be demonstrated that monotherapy with losartan is "ineffective." The definition of ineffective is a subjective one. Goal blood pressure was achieved in approximately 10% of patients with Losartan monotherapy versus approximately 20% of patients on combination therapy. It could be argued that Losartan monotherapy was not completely ineffective. Although twice as many people achieved goal on combination therapy relative to monotherapy and this difference was statistically significant, the clinical significance of this difference has not been validated with the studies provided. It is not known whether morbidity or mortality is reduced by starting combination therapy early versus monotherapy. I believe this application can not be approved because it may change the practice of traditional titration of anti-hypertensive medications without adequate justification.

## Appendix:

Results of primary endpoint excluding patients enrolled at a site where an investigator had "significant payments of other sorts or equity interest" in the sponsor. The results of the primary endpoint were not affected by exclusion of the subjects whose investigator had conflicting financial interests.

**Table 1: Results of primary efficacy endpoint (% of patients with SiDBP < 90 mmHg) at the end of 4 weeks of treatment[a]**

| | Los/HCTZ (n = 364) | | Los (n = 182) | | Estimated Difference (95% CI) | P-value |
|---|---|---|---|---|---|---|
| | N | (%) | n | (%) | | |
| Week 4 | 63 | (17.3) | 18 | (9.9) | 7.4 (1.1, 11.9) | 0.018 |

[a]Analysis provided by Dr. Jasmine Choi of FDA

Figure 1: Distribution of mean sitting diastolic blood pressure (SiDBP) at baseline (visit 3A) on Losartan (n = 193)

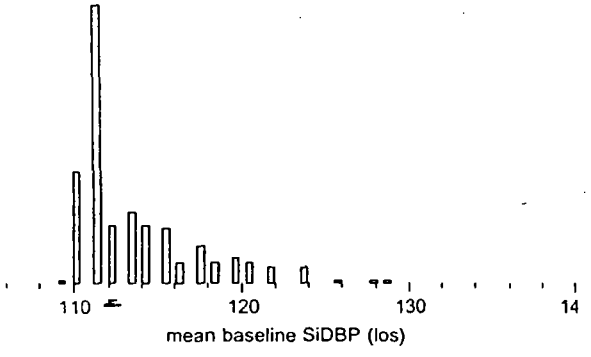
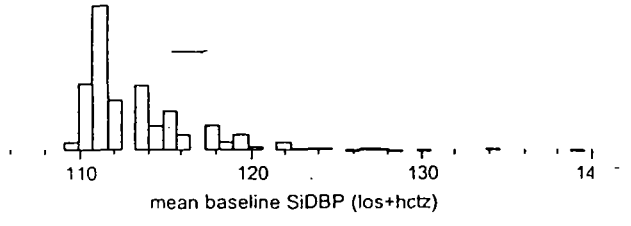
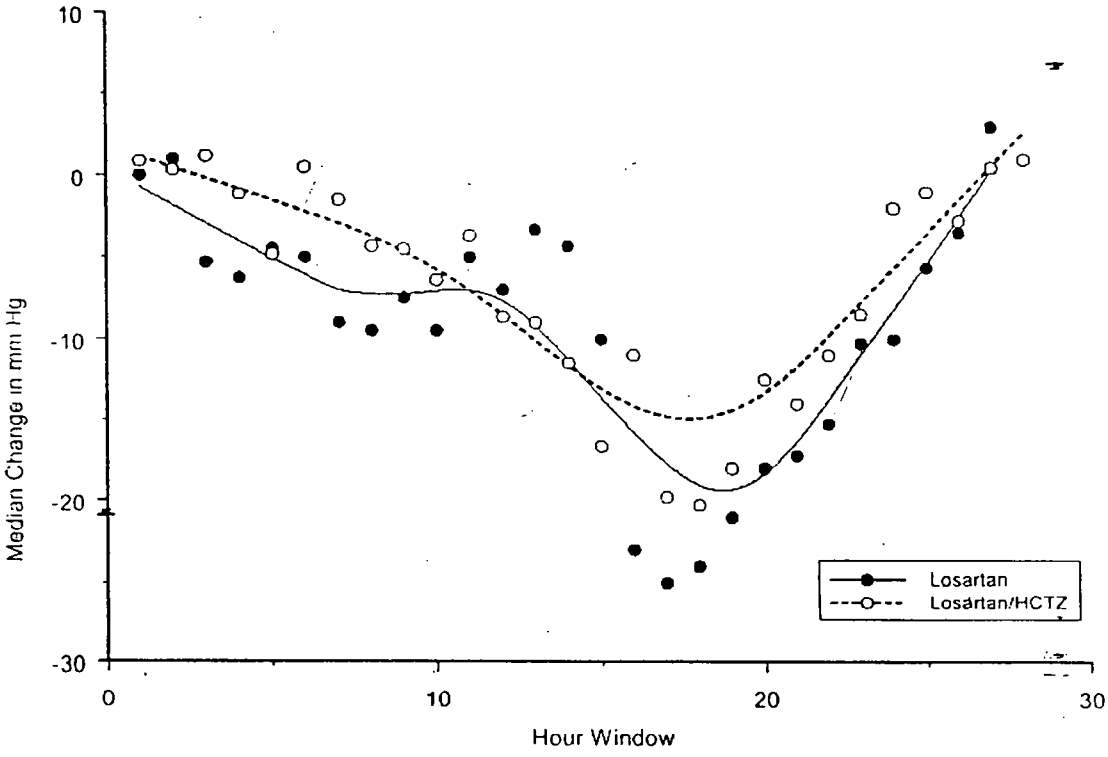



Figure 2: Distribution of mean sitting diastolic blood pressure (SiDBP) at baseline (visit 3A) on Losartan + Hydrochlorothiazide (n = 393)



A subset of patients in study protocol P232 had ambulatory blood pressure monitoring that allowed for comparison of blood pressure control during the inter-dosing interval. The results are shown in the Figure below. A total of 28 patients were in the losartan + hydrochlorothiazide arm and a total of 15 subjects were in the losartan monotherapy arm. As seen in the figure below, blood pressure control over 24 hours was generally better on Los+HCTZ relative to Los monotherapy at all time points except for a period of about 3 hours or so occurring 11 hours post dosing.

Figure 3: Lowess curves for median reduction from baseline in diastolic ambulatory blood pressure.



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/s/

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Mehul Desai
5/5/03 11:27:19 AM
MEDICAL OFFICER

There have been no safety updates since the original submission of September 24, 2002.

APPEARS THIS WAY
ON ORIGINAL