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*APPLICATION NUMBER:*

**21-532**

# MEDICAL REVIEW

CLINICAL REVIEW

# *Cover Sheet For Medical Review Of NDA 21-532*

# BenicarHCT™ Tablets

# In

# The Treatment of Essential Hypertension

# A Review

# Of

# Efficacy

**Date: February 2003**
**Sponsor: Sankyo Pharma Inc.**
**Reviewer: Salma N. Lemtouni, MD, MPH, Medical Officer**
**HFD-110, Division of Cardio-Renal Drug Products**

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# Clinical Review for NDA 21532

## *Executive Summary*

## I. Recommendations

### A. Recommendation on Approvability

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

An extension to the CS-866-318 study is being conducted, titled "A Long Term, Open-Label Study of CS-866 and Hydrochlorothiazide in Patients with Essential Hypertension" and its objective is to assess the long-term safety of the combination of CS-866 and HCTZ.

## II. Summary of Clinical Findings

### A. Brief Overview of Clinical Program

CS-866 HCT™ is the sponsor's chosen name for the CS-866 and HCTZ combination (referred to in this review as CS-866/HCTZ). This is a fixed combination of a subtype $A_1$ angiotensin II receptor antagonist and a diuretic that acts through natriuresis and volume depletion. Both drugs are approved and marketed.

CS-866-318 (referred to as the pivotal or controlled study as well) is a randomized, factorial, double-blind, placebo-controlled trial, and it is the main study of this drug combination program because it is the only study that investigated the efficacy and safety of the combination in a controlled fashion (see C. Detailed Review of Trials by Indication for detail). Other studies that the sponsor included in the submission, and referred to as supportive studies, investigated the combination in an open-label fashion (see A. Other Relevant Materials for detail).

In the controlled trial, 502 patients were randomized to one of twelve drug combination categories including one placebo/placebo, three CS-866 only categories, 2 HCTZ only categories and six CS-866/HCTZ dose combination categories.

**B. Efficacy**

The CS-866/HCTZ combination is shown to be more efficacious than any of its components given alone especially the combinations containing 25mg of HCTZ which were found to be statistically significantly more efficacious than their CS-866 or HCTZ component doses given alone. These findings were those of a randomized, double blind, factorial clinical trial. The sponsor's recommendation is to approve three dose combinations, 20/12.5, 40/12.5 and 40/25 for the treatment of essential hypertension in patients whose blood pressure was not controlled by CS-866 or HCTZ alone. The primary endpoint in this study was sitting diastolic blood pressure, but the combination has shown an effect in sitting systolic blood pressure as well. These findings confirm and are supported by the effectiveness of other similar already approved and marketed combinations.

**C. Safety**

Please see review by Dr. Maryann Gordon

**D. Dosing**

Both of Olmesartan medoxomil (CS-866 or Benicar™) and HCTZ are approved therapies. CS-866 is approved for essential hypertension in a recommended starting dose of 20mg once daily when used as a mono-therapy which may be increased to 40mg once daily if further reduction of BP is needed.

Hydrochlorothiazide mono-therapy has been approved as a natriuretic and/or anti-hypertensive in doses ranging from 6.5 to 50mg. It has also been approved in a number of combination therapies with angiotensine converting enzyme inhibitors, angiotensine II receptor antagonists, selective and non-selective beta adrenergic receptor antagonists or other. The most relevant combinations here are those with angiotensine II receptor antagonists. In most of these combinations the dose range of HCTZ was also 12.5 and 25mg.

The decisions for dosing and administration of the CS-866/HCTZ combination were based on a combination of findings from studies conducted in the CS-866 development program, the labeled dose of Benicar, the labeled starting dose of HCTZ, and the experience with other approved and marketed combination products that are similar. The CS-866 findings that were critical for this issue are summarized in the review of NDA #21,286.

It is noteworthy to keep in mind that any dose combination that might end up approved as a result of this NDA is a dose that has been investigated in a population that is not very representative of other hypertensive sub-populations.

The recommended dosing and/or regimen that would be efficacious but not toxic in patients with renal and/or hepatic insufficiency is to be clinically determined.

## E. Special Populations

No study in the program was powered to study the effects of the study drug combination separately in females, blacks or elderly patients. Therefore, no conclusions can be drawn from this research program regarding minorities.

The sub-populations that are in dire need of other treatment modalities including patients with concomitant morbidities were not studied here either. Therefore, the generalizability of these findings to other populations remains to be confirmed.

No studies evaluating efficacy and safety of the combination have been conducted in patients with impaired renal and/or hepatic functions. However, the sponsor intends to rely on pharmakokinetic research in recommending a dose in hepatically impaired patients.

[redacted] out no investigation in the pediatric population has been started (see IX. Use in Special Populations: C. Evaluation of Pediatric Program).

The CS-866 component of the combination has not yet been investigated in pregnant women.

## *Clinical Review*

## I. Introduction and Background

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

The proposed indication for the fixed dose of CS-866/HCTZ is the treatment of essential hypertension. The sponsor recommended three dose combinations and these are 20/12.5, 40/12.5 and 40/25. These combinations are not indicated for initial therapy, but they are recommended in patients whose blood pressure is inadequately controlled by CS-866 or HCTZ alone.

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

There are numerous (at least six) angiotensine II receptor antagonists and hydrochlorothiazide combination products approved and marketed for the treatment of hypertension.

### C. Important Milestones in Product Development

The development program for CS-866 plus HCTZ was managed under the same IND as for the mono-therapy, with the main protocol CS-866-318 filed in April of 2000. The CS-866 component of the combination was approved as a mono-therapy for essential hypertension under NDA 21, 286, and is currently marketed as tablets of three different strengths, 5, 20 and 40 mg.

### D. Other Relevant Information

Per the sponsor, the combination has not been marketed anywhere in the world.

### E. Important Issues with Pharmacologically Related Agents

N/A

## III. Human Pharmacokinetics and Pharmacodynamics (See review by Dr. Nhi Nguyen)

A Bio-equivalency study for the 20/12.5mg combination was conducted, the report was submitted for review and review completed.

# IV. Description of Clinical Data and Sources

## A. Overall Data

### 1. Study type and design

There was only one study, the CS-866-318 that assessed the efficacy and safety of the CS-866 and HCTZ combination in a randomized double blind controlled fashion. In the other studies that investigated this combination, HCTZ was given in an open label fashion and, often, it was added only to patients who did not respond initially to CS-866.

### 2. Demographics

The table bellow shows the distribution of subjects by decade age categories, gender, race and duration of hypertension.

**Table 1 Demographics in the controlled study**

| | CS-866 (mg) | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | 0 | | | 10 | | | 20 | | | 40 | | |
| HCTZ | Placebo N=42 | 12.5 N=45 | 25 N=43 | 0 N=39 | 12.5 N=35 | 25 N=39 | 0 N=41 | 12.5 N=44 | 25 N=47 | 0 N=45 | 12.5 N=42 | 25 N=40 |
| Age (%) | | | | | | | | | | | | |
| 20-30 | 0 | 2.2 | 0 | 2.6 | 0 | 0 | 0 | 0 | 8.5 | 2.2 | 2.4 | 2.5 |
| 31-40 | 14.3 | 8.9 | 9.3 | 25.6 | 14.3 | 12.8 | 7.3 | 11.4 | 14.9 | 13.3 | 11.9 | 12.5 |
| 41-50 | 16.7 | 26.7 | 25.6 | 20.5 | 25.7 | 25.6 | 24.4 | 31.8 | 25.5 | 11.1 | 23.8 | 35 |
| 51-60 | 40.5 | 31.1 | 39.5 | 33.3 | 34.3 | 30.8 | 46.3 | 29.5 | 12.8 | 48.9 | 38.1 | 25 |
| 61-64 | 16.7 | 15.6 | 4.7 | 10.3 | 11.4 | 15.4 | 7.3 | 18.2 | 14.9 | 13.3 | 11.9 | 12.5 |
| 65-74 | 9.5 | 13.3 | 16.3 | 5.1 | 14.3 | 12.8 | 12.2 | 9.1 | 21.3 | 8.9 | 9.5 | 7.5 |
| >=75 | 2.4 | 2.2 | 4.7 | 2.6 | 0 | 2.6 | 2.4 | 0 | 2.1 | 2.2 | 2.4 | 5 |
| Mean (y) | 54 | 54.1 | 54.7 | 49.9 | 52.4 | 54.4 | 54.1 | 52.3 | 51.9 | 54.4 | 52 | 52 |
| Male (%) | 64.3 | 55.6 | 48.8 | 61.5 | 51.4 | 48.7 | 51.2 | 65.9 | 55.3 | 62.2 | 50 | 50 |
| Female (%) | 35.7 | 44.4 | 51.2 | 38.5 | 48.6 | 51.3 | 48.8 | 34.1 | 44.7 | 37.8 | 50 | 50 |
| White (%) | 81 | 80 | 58.1 | 76.9 | 77.1 | 82.1 | 68.3 | 72.7 | 72.3 | 75.6 | 66.7 | 80 |
| Black (%) | 7.1 | 8.9 | 27.9 | 10.3 | 5.7 | 10.3 | 19.5 | 9.1 | 12.8 | 8.9 | 14.3 | 10 |
| Other (%) | 11.9 | 11.1 | 14 | 12.8 | 17.1 | 7.7 | 12.2 | 18.2 | 14.9 | 15.6 | 19 | 10 |

| Duration of HTN (%) | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| <6 mon | 9.5 | 2.2 | 4.7 | 5.1 | 2.9 | 12.8 | 4.9 | 11.4 | 8.5 | 6.7 | 11.9 | 0 |
| 6-12 mon | 14.3 | 6.7 | 2.3 | 10.3 | 8.6 | 0 | 2.4 | 6.8 | 0 | 4.4 | 9.5 | 7.5 |
| 12-24 mon | 7.1 | 6.7 | 4.7 | 7.7 | 8.6 | 7.7 | 0 | 6.8 | 6.4 | 4.4 | 0 | 5 |
| >24 mon | 69 | 84.4 | 88.4 | 76.9 | 80 | 79.5 | 92.7 | 75 | 85.1 | 84.4 | 78.6 | 87.5 |

As the table above shows, the majority of patients are relatively young, between the ages of 40 and 65. Within this age range, study-drug-dose-combination categories vary in distribution between the age categories. One variation that stands out is that of the 20/25 dose combination category which seems to be bimodal with two peaks, a younger and an older peak. Except for the 40/25 dose combination category, patients 75 or older constitute less than 5% of each category.

## B. Tables Listing the Clinical Trials

**Table 2 Table Controlled and open-label clinical trials of effectiveness**

| | Revi-ew | Design | Durat-ion | Dose(CS-866) x (HCTZ) | N | Percentage | | |
|---|---|---|---|---|---|---|---|---|
| | | | | | | Female | > 65 y | Black |
| Controlled clinical trials | | | | | | | | |
| CS-866-318 | Page 18 | R,DB,PC,II | 8 wk | (10,20, 40) x (12.5 or 25) | 502 | 46.15 | 12.96 | 10.53 |
| Open-label clinical trials | | | | | | | | |
| CS-866-321 Long term extension to 866-318 | Page 29 | HCTZ given as OL | 40 weeks | 20 x (12.5 or 25) | 340 | 44.41 | 12.35 | 13.24 |
| CS-866-305: | Page 29 | HCTZ given as OL | 10 months | (2.5, 5, 10, 20 or 40) x (12.5 or 25) | 195 | 35.86 | 12.63 | 13.13 |
| CS-866-306 | Page 30 | HCTZ given as OL | 4 months | 40 x (12.5 or 25) | 98 | 44.12 | 10.78 | 22.55 |
| CS-866-419 treat to target with mono-therapy or after adding HCTZ and amlodipine | Page 30 | HCTZ given as OL | 16 weeks | 40 x (12.5 or 25) | 123 | 29.27 | 11.38 | 18.70 |

| | | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| SE-866/10 Long term safety of the combination | Page 31 | HCTZ given as OL | 40 weeks | (5, 10 or 20) x (12.5 or 25) | 170 | 60.00 | 32.94 | 0 |
| SE-866/10-01: A long term safety extension to study 10 | Page 31 | HCTZ given as OL | 52 weeks | (5, 10 or 20) x (12.5 or 25) | 133 | 58.96 | 35.07 | 0 |
| SE-866/17 | Page 32 | HCTZ given as OL | 12 weeks | (10 or 20) x (12.5 or 25) | 164 | 50.00 | 14.63 | 0 |
| SE-866-19 Has losartan added | Page 31 | HCTZ given as OL | 24 weeks | (10 or 20) x 25 | 54 | 46.43 | 30.36 | 0 |

### C. Postmarketing Experience

There is no postmarketing experience for this drug combination. Other AIIRA/HCTZ combination drugs have been marketed and some of their post-marketing experience may be used to hypothesize about this combination's future post-marketing experience.

The CS-866 has been marketed as a mono-therapy for use in essential hypertension.

### D. Literature Review

The sponsor's review encompassed similar combination product inserts (such as Atacand HCT, Avalide, Diovan HCT ,Hyzaar, Macardis and Microzide), FDA proposed guidelines for anti-hypertensive drugs, and publications on statistical methodology by Hung et al. And Stewart et al.

The reviewer studied the labels of all approved AIIRA/HCTZ combinations.

## V. Clinical Review Methods

### A. How the Review was Conducted

The CS-866-318 was selected for review because it was the only study in the program that investigated the combination CS-866 and HCTZ in a controlled design. Other studies that investigated the combination in an open label fashion are referred to as needed.

The original protocol of the pivotal study was reviewed in great detail. Its study documents including CRFs and data submitted as SAS export files were evaluated as needed. The sponsor's data summary and result reports were also evaluated and referred to as needed.

v) Published and unpublished findings of meta-analyses assessing the short-term acute effect of assigning hypertensive patients to placebo alone are in support of the benignity of this procedure.

2. Arguments in disfavor:

There is no data supporting the remote effect of being randomized to placebo in anti-hypertensive trials, and this would be almost impossible to tease out from the effect of being off treatment for other reasons.

### E. Evaluation of Financial Disclosure

A signed financial disclosure was provided along with the submission of other material of the NDA.

## VI. Integrated Review of Efficacy

### A. Brief Statement of Conclusions

1. Dr. Hung's analyses can be summarized as follows:
   - Each of the six non-zero combinations was statistically significantly more effective than placebo.
   - The AVE test of Hung (2000, statistics in Medicine, page 2079-2087) was statistically significant indicating that some non-zero combinations are more effective than their respective components.
   - Each of the three CS-866/25mg HCTZ combinations was more effective than its components in a statistically significant way.
   - The 20/12.5 and 40/12.5 combinations were statistically significantly more effective than their HCTZ but not CS-866 component.
   - The BP reducing effect of the combination leveled off in both the 12.5 and 25mg HCTZ doses across the 10-20mg CS-866 dose range.
   - A level of synergism was detected and the degree of this seemed to increase as the dose of CS-866 increased, but it was not statistically significant.

2. Review of statistical findings in the light of the quality of the data submitted

Per efficacy and safety reviews, it could be concluded that [redacted] 40/25 could be beneficial in the treatment of hypertension in relatively healthy and young populations.

3. Review of the sponsor's recommendations in the light of the agency's findings

The sponsor is seeking approval of three combination doses: 20/12.5, 40/12.5 and 40/25 the former two of which were found not to be significantly better than their CS-866 components (Dr. Hung's analysis). It is important to remember that the sponsor gave more weight to the results of the studies in which HCTZ was given as an open label treatment while all of the Agency's efficacy evaluation review was based on the pivotal controlled study.

The sponsor is also recommending that the combination is not to be considered as an initial therapy but to be given to patients whose BP fails to be controlled by either CS-866 or HCTZ.

4. Questions raised by sponsor's recommendations and agency's findings

[redacted]

ii) Would adding 12.5 mg of HCTZ be of significant benefit in this study population?

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

Reviewing the CS-866-318 trial data and Dr. Hung's statistical findings, the following arguments are called on in support of the efficacy of CS-866/HCTZ in the treatment of a essential hypertension in a relatively healthy hypertensive population.

1. Biological plausibility

The need to combine drugs to lower BP by acting on different BP control pathways is well proven. And the combination of a subtype A1 angiotensin II receptor antagonist with HCTZ has been shown, by similar combination products that have already been approved and marketed, to be more effective than either angiotensin II receptor antagonist or HCTZ given alone.

2. Dose Response

Response surface analysis using a quadratic regression model suggests that the reduction of seDBP (the primary efficacy endpoint) increases as either dose of the combination components increases.

3. Consistency of findings

The reproducibility of the results in this program across dose categories, in both systolic and diastolic, when BP is measured in different body positions, at different study visits, and in males and females is very supportive of the validity of this study findings. These findings are also consistent with those of preceding programs that led to approval of similar combinations.

4. Statistical significance

The AVE test yielded a p-value < 0.01 confirming that at least one dose combination is more effective than its components. Each of the CS-866/HCT combination containing 25 mg dose HCTZ, was statistically significantly more effective than its component therapies.

## C. Detailed Review of Trials by Indication

1. Description of the Pivotal Study CS-866-318

*1) Title:*
"A Randomized, Placebo-Controlled, Factorial-Design Study of CS-866 and Hydroclhlorthiazide in Patients with Essential Hypertension"

*2) Source documents:*
Study report: NDA 21-532, volume 1.115 to 1.305; electronic documents clinstat\anti-hypertensive\866-318a, 318b, 318c and 318d.pdf

*3) Investigators:*
Study conducted in 48 centers in the US.

*4) Study dates:*
This study was conducted from May 1, 2000 to December 25, 2000.

*5) Study Design:*
This study description was based upon a protocol dated 3 March 2000. There was only one amendment written before the start of the study and this concerned a correction to a typo in the exclusionary value of the number of neutrophils.

This was a randomized, double-blind, placebo-controlled, factorial study CS-866 (0, 10, 20 and 40 mg) x HCTZ (0, 12.5 and 25 mg) in subjects with moderate hypertension (100 < seDBP < 115 mm Hg). After a 4-week placebo run-in, subjects were to be randomized into the double-blind period if their seDBP on weeks 3 and 4 averaged between 100 and 115 mm Hg and the difference in seDBP at the two visits was less than 7 mm Hg. Five hundred and two patients with essential hypertension were randomized to a once-daily fixed combination of CS-866 and HCTZ for 8 weeks. The twelve dose combination categories were made up of one placebo-CS-866/placebo-HCTZ (0,0), three non-placebo-CS-866/placebo-HCTZ [(10, 0), (20, 0), (40, 0)]; two placebo-CS-866/non-placebo-HCTZ [(0,12.5), (0,25)]; and six non-placebo-CS-866 /non-placebo- HCTZ [(10, 12.5), (20, 12.5), (40, 12.5), (10, 25), (20, 25), (40, 25)].

Males and females 18 year of age or over, who were relatively healthy and non obese were to be included. Subjects were to have a diagnosis of moderate uncomplicated essential hypertension with no evidence of end organ damage.

Other Subjects that were to be excluded were those with cardiovascular disease and/or clinically significant cardiac conduction defects; those with renal, pulmonary, hepatic, GI, endocrine, metabolic hematologic, neurologic or psychiatric diseases or an oncologic matter; and those with abnormal laboratory values prior to randomization. Patients requiring cardiovascular, CNS or adrenergic agents, subjects with history of drug or alcohol abuse within 3 years of enrollment, subjects who were allergic to any angiotensin II antagonist or thiazide diuretics, and subjects participating in another study or had previously taken CS-866 were also to be excluded.

Patients were to take one placebo tablet per day, but no antihypertensive therapy for the duration of the run-in placebo period. Active CS-866 tablets, active HCTZ capsules and identical looking placebo tablets and capsules were dispensed to patients who were randomized. All concomitant medications that patients were taking when they were randomized were to remain at a stable dose unless it was medically indicated.

To be removed from the study were patients whose daily average seDBP and/or seSBP exceeded 120 or 200 mm Hg respectively, patients who became pregnant during the study, patients who withdrew their consent and patients in whom the investigator judged it was in their best interest to discontinue.

By the protocol, all patients who were removed or withdrawn from the study for whatever reason were to complete an Exit Visit prior to been placed on alternative therapy. Patients who withdrew from the study before Week 8 and received randomized study medication one day before the early termination visit, vital signs data for that visit were to be carried forward instead of the vital signs recorded in the last scheduled visit.

Patients were assigned randomly to blocks of 12 and in a ratio of 1:1:1:1:1:1:1:1:1:1:1:1. After the 8-week visit, patients were to go into an open-label phase study.

*6) Study Procedures*

Trough BP was to be measured before intake of the daily study drug dose, and two successive readings at least one minute apart at each visit were to be taken after sitting for five minutes for sitting BP and standing for three minutes for standing BP. There was no indication, nor were there plans, to assess the effect of the study drug on peak blood pressures. Follow-up visits were scheduled to capture trough measurements.

**Table 3 Study Procedure Summary:**

| Event | Screening | Placebo Run-In Week | | | | Day | Week | | |
|---|---|---|---|---|---|---|---|---|---|
| Visits/Weeks | | 1 | 2 | 3 | 4 | 1 | 1 | 4 | 8 |
| Informed Consent | • | | | | | | | | |
| Medical History | • | | | | | | | | |
| Physical Examination | • | | | | | • | | | • |
| Vital Sings | • | • | • | • | • | • | • | • | • |
| 12-Lead ECG | • | | | | | • | | | • |
| Laboratory Tests | | | | | | | | | |
| Hematology | • | | | | | • | • | • | • |
| Blood Chemistry | • | | | | | • | • | • | • |
| Urinalysis | • | | | | | • | • | • | • |
| Pregnancy test | • | | | | | • | | | |
| Adverse Events | • | • | • | • | • | • | • | • | • |
| Compliance | • | • | • | • | • | • | • | • | • |

*7) Study drug administration/formulation*

Ten, 20 and 40 mg CS-866 and identical appearing placebo tablets, and 12.5mg HCTZ and identical appearing placebo capsules were planned to be used. Each patient was to be given one tablet and two capsules.

*8) Primary objectives/endpoints*

The primary objective of the study was first to test the hypothesis that there existed at least one dose combination of CS-866 and HCTZ that would reduce BP more than each of its component doses, and second to assess the safety and tolerability of the combination. The primary endpoint focused on mean change from baseline in trough seDBP at week 8 or LOCF.

*9) Secondary objectives/endpoints*

The second objective is to evaluate which component doses were more effective in reducing BP compared to the respective placebo. Secondary efficacy endpoints included mean changes at week 8 or LOCF in seSBP, standing DBP and standing SBP.

*10) Safety Endpoints (See Safety Review by Dr. Maryann Gordon)*

Safety endpoints included adverse events observed by investigators or reported by patients; changes on 12-lead ECG, changes in blood chemistry, hematology and urinalysis and changes in lipid profiles.

*11) Statistical Methods (See Statistical Review by Dr. Hsien Ming Hung)*

The AVE test (Hung et al. 1993, Biometrics) was to be used to test that at least one dose combination is more effective than its respective component doses. A response surface method with a quadratic regression model were to be used to quantify dose response.

Two efficacy populations were defined: 1. Modified ITT population (all patients who were randomized, received study medication and had at least one post-baseline measurement) and 2. as per protocol population (only patients without major protocol violations who either completed 8 weeks of randomized treatment or discontinued prematurely as a result of uncontrolled BP will be included). The sponsor did not power for study/analysis of sub-populations.

*12) Results*

**Table 4 Number and proportion of patients in each stage of the study.**

| | N |
|---|---|
| Screened N1 | 863 |
| Enrolled N2<br>Not randomized N3<br>N3/N2 (%) | 750<br>246<br>(33) |
| Randomized N4<br>Discontinued N5<br>N5/N4 (%) | 502<br>51<br>(10) |
| ITT population N6<br>Completed N7<br>N7/N6 (%) | 500<br>451<br>90.2 |

Two patients were randomized who did not figure in the ITT total.

01/8273 This patient requested to withdraw and failed to return for an exit visit Should have been a screening failure based on body weight, but she was randomized, remained on 20 mg CS-866/25 mg HCTZ for an undetermined duration, but had no post baseline BP measurements.

21/8669 This patient was randomized to and remained on 40 mg CS-866/25 mg HCTZ for three days, was seen at an unscheduled visit for hypotension but her BP was not determined until three days later.

**Table 5 Reasons for pre-randomization exclusion**

| Total N=112 | | | |
|---|---|---|---|
| Did not qualify | 69 | Lost to follow-up | 6 |
| Subject request | 20 | BP high in investigator's opinion | 10 |
| Non controlled BP | 3 | Other | 4 |

**Table 6 Discontinuation per study drug combination category**

Number of randomized, discontinued, and patients that remained in the study (N randomized/N discontinued/N remained) per study drug combination category

| Dose | Placebo | CS-866 10 | CS-866 20 | CS-866 40 |
|---|---|---|---|---|
| HCTZ 0 | 42/5/38 | 39/5/34 | 41/6/35 | 45/2/43 |
| HCTZ 12.5 | 45/7/38 | 35/2/33 | 44/8/36 | 42/5/37 |
| HCTZ 25 | 43/1/42 | 39/2/37 | 47/4/43 | 40/4/36 |

Discontinuation rate ranged from 2% to 18% with the following drug combination categories seeing 10% or more withdrawal rates: 20/12.5 (18%), 0/12.5 (16%), 20/0 (15%), 10/0 (13%), 0/0 and 40/12.5 (12%) and 40/25 (10%). As can be seen here, four of the seven groups with high discontinuation rates were randomized to a placebo containing combination regimen and the other three were randomized to active component combinations. This leads one to assume that lack of efficacy has something to do with the majority of withdrawals. Of the three groups receiving combinations with active components, one was randomized to 20/12.5 and the other two were randomized to 40/12.5 and 40/25. It could not be concluded whether symptomatic lack of efficacy or symptoms of hypotension were to blame for discontinuations secondary to adverse events in three out of eight patients in the 20/12.5 and one of four patient in the 40/12.5 dose combination categories.

The reasons for discontinuation among the 20/12.5 group were listed as:

- Lack of efficacy in one patient (by investigator)
- Patients request secondary to AEs:
  - headache and/or dizziness in three patients
  - hypotension in a one
  - intermittent flashing and irritation in one
- Loss to follow-up in one patient
- Patient request unrelated to AEs in one patient

The reasons for discontinuation in the 40/12.5 group were listed as:

- Adverse events:
  - headache, lightheadedness and frequent urination and/or dizziness or in two
  - patients request unrelated to AEs in three patients

Reasons for discontinuation in the 40/25 group were listed as:

- Adverse events:
  - Hypotension in one and suspicion of hypotension in a second (patient passed out)
- Patients request in the remaining two

Interesting enough that all three-dose combinations that the sponsor recommends for approval were amongst the categories with the highest rates of discontinuation, with the 20/12.5 combination at the high end. If we assumed that the adverse events that led to three withdrawals in this category were symptoms of lack of efficacy and accounted for all cases of lack of efficacy in the analyses, this would lead to different results in the responder rate for this drug combination dose.

**Table 7 Reasons for discontinuation per study drug combination category**

| | CS-866 0 mg | | | CS-866 10 mg | | | CS-866 20 mg | | | CS-866 40 | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCTZ<br>N | 0<br>42 | 12.5<br>45 | 25<br>43 | 0<br>39 | 12.5<br>35 | 25<br>39 | 0<br>41 | 12.5<br>44 | 25<br>47 | 0<br>45 | 12.5<br>42 | 25<br>40 | Total |
| AE | 0 | 1 | 0 | 1 | 0 | 1 | 1 | 3 | 1 | 0 | 2 | 2 | 12 |
| Subject request | 4 | 2 | 1 | 1 | 0 | 1 | 0 | 3 | 2 | 0 | 3 | 2 | 18 |
| BP>limit | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 1 |
| Lost to follow-up | 0 | 1 | 0 | 1 | 2 | 0 | 0 | 1 | 1 | 1 | 0 | 0 | [redacted] |
| BP high (investigator) | 1 | 0 | 0 | 0 | 0 | 0 | 2 | 1 | 0 | 1 | 0 | 0 | 5 |
| Concomitant meds | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Compliance | 0 | 0 | 0 | 1 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 2 |
| Administrative | 0 | 0 | 0 | 0 | 0 | 0 | 1 | 0 | 0 | 0 | 0 | 0 | 1 |
| Unqualified | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 | 0 |
| Total | 5 | 5 | 1 | 4 | 2 | 2 | 5 | 8 | 4 | 2 | 5 | 4 | 46 |

**Table 8 Protocol violation**

| Site-Subject | CS-866/HCTZ | Reason for Discontinuation | Site-Subject | CS-866/HCTZ | Reason for Discontinuation |
|---|---|---|---|---|---|
| 22-8745 | 0/12.5 | Intake of non-study anti-hypertensive | 31-8145 | 0/12.5 | Beta-blocker intake |
| 24-8158 | 20/0 | Concurrent participation in two sites | 36-8357 | 10/0 | Weight outside margin + use of concomitant medication |

**Table 9 Demographics**

| | CS-866 0 mg | | | CS-866 10 mg | | | CS-866 20 mg | | | CS-866 40 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCTZ | 0 | 12.5 | 25 | 0 | 12.5 | 25 | 0 | 12.5 | 25 | 0 | 12.5 | 25 |
| N | 42 | 45 | 43 | 39 | 35 | 39 | 41 | 44 | 47 | 45 | 42 | 40 |
| Male (%) | 64 | 56 | 51 | 62 | 51 | 49 | 51 | 66 | 57 | 62 | 50 | 51 |
| Female (%) | 36 | 44 | 49 | 38 | 49 | 51 | 49 | 34 | 43 | 38 | 50 | 49 |
| White (%) | 81 | 80 | 58 | 77 | 77 | 82 | 68 | 73 | 74 | 76 | 67 | 80 |
| Black (%) | 7 | 09 | 28 | 10 | 6 | 10 | 19 | 9 | 13 | 9 | 14 | 10 |
| Other (%) | 12 | 12 | 14 | 13 | 17 | 8 | 13 | 17 | 13 | 15 | 19 | 10 |
| Age (~~mean~~) | 54 | 54 | 55 | 50 | 52 | 54 | 54 | 53 | 52 | 57 | 52 | 52 |
| >=65 (%) | 9 | 13 | 21 | 8 | 9 | 15 | 12 | 7 | 21 | 9 | 12 | 12 |

Two issues can be raised from data presented in this table:

1. The sponsor did not make a great effort to include special populations. One factor that might have led to the disproportion of numbers in blacks and seniors especially, is the exclusion of patients with co-morbidities and/or hypertension related end organ damage. Also, given the study small sample size, it would not have been informative had these minorities been enrolled in equal proportions.

2. There is a disproportion in demographic characteristics between the randomized categories. This could be explained by the too-small sample size for randomization to accomplish its balancing effect. Even though the numbers are not balanced in the 12 randomized categories, the differences are not statistically significant

**Table 10 Baseline vital signs**

| | CS-866 0 mg | | | CS-866 10 mg | | | CS-866 20 mg | | | CS-866 40 | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| HCTZ | 0 | 12.5 | 25 | 0 | 12.5 | 25 | 0 | 12.5 | 25 | 0 | 12.5 | 25 |
| N | 42 | 45 | 43 | 39 | 35 | 39 | 41 | 44 | 47 | 45 | 42 | 40 |
| Se DBP (mean) | 103 | 103 | 104 | 104 | 104 | 104 | 103 | 103 | 104 | 103 | 103 | 103 |
| SD | 3 | 3 | 4 | 4 | 4 | 3 | 2 | 3 | 4 | 2 | 3 | 3 |
| SeSBP (mean) | 152 | 153 | 156 | 154 | 157 | 154 | 155 | 152 | 155 | 153 | 152 | 154 |
| SD | 13 | 13 | 12 | 12 | 15 | 13 | 10 | 15 | 14 | 12 | 13 | 13 |
| SHR (mean) | 75 | 74 | 73 | 76 | 74 | 75 | 75 | 74 | 73 | 78 | 75 | 76 |
| SD | 8 | 8 | 8 | 8 | 7 | 8 | 8 | 8 | 8 | 8 | 7 | 8 |

Baseline vital signs expressed in means are not different between the six active dose combination categories and their comparator categories.

**Table 11 Mean change from baseline in sitting DBP ± se (in mm Hg) at Week 8 LOCF**

| | | CS-866 | | | |
|---|---|---|---|---|---|
| | | 0 mg | 10 mg | 20 mg | 40 mg |
| HCTZ | 0 mg | -7.7±1.2; 42 | -13.1±1.3; 39 | -12.7±1.3; 41 | -14.4±1.3; 45 |
| | 12.5mg | -9.1±1.2; 45 | -15.3±1.4; 35 | -15.4±1.4; 42 | -18.0±1.5; 42 |
| | 25 mg | -12.9±1.3; 43 | -18.4±1.2; 38 | -18.9±1.1; 46 | -21.9±1.5; 39 |

Table taken from Dr. Hung's review

**Table 12 Mean change from baseline in sitting SBP ± se (in mm Hg) at Week 8 LOCF**

| | | CS-866 | | | |
|---|---|---|---|---|---|
| | | 0 mg | 10 mg | 20 mg | 40 mg |
| HCTZ | 0 mg | -3.4±1.9; 42 | -10.4±1.8; 39 | -15.2±2.5; 41 | -16.4±2.1; 45 |
| | 12.5mg | -8.2±2.1; 45 | -20.3±2.2; 35 | -20.4±2.6; 42 | -19.4±2.6; 42 |
| | 25 mg | -17.6±2.0; 43 | -22.9±2.3; 38 | -25.7±1.9; 46 | -27.9±2.5; 39 |

Table taken from Dr. Hung's review

As can be seen from the above tables, compared to baseline, blood pressure means including systolic and diastolic scaled down in all randomized categories including placebo. Compared to their respective components, all active dose combinations produced a sizable reducing effect on both sitting systolic and diastolic blood pressures. The 40/25 combination seems to be most effective for it produced a change ($\Delta \approx 22$ mm Hg) in seDBP at least 3 mm Hg greater than did the second most effective combinations, (10/25, 20/25 and 40/12.5 which produced similar levels of BP reduction ( $\Delta \approx 18.5$ mm Hg)) . The superiority of the 40/25 is also seen with SBP. The 10/12.5 and 20/12.5 combination doses produced similar lowering effects on both seDBP ($\Delta \approx$ 15.5 mm Hg) and seSBP ($\Delta \approx 20$ mm Hg) in this study.

Statistically speaking, all combination doses were significantly more effective than placebo. Most of the combination doses produced an effect equivalent to or higher than the sum effect of their respective components. Only the combination doses with 25mg HCTZ were significantly more effective than both respective components. The 20/12.5 and 40/12.5 combination doses were significantly more effective than the HCTZ component only (Dr. Hung's findings).

*13) Detail on statistical findings of the CS-866-318 study (see review by Dr. Hsien Ming Hung)*

2. Description of other studies (see XI. AppendixB. Individual More Detailed Study Reviews (If performed)

**D. Efficacy Conclusions**

Efficacy substantiation of the CS-866/HCTZ combination rests solely on the CS-866-318 study evaluation because this is the only study in the program in which

the combination was assessed in a randomized, double blind and controlled manner. Arguments in favor of this substantiation are three: 1. Similar combinations have been approved for the same condition. 2. Acceptable study design and conduct. 3. The statistical significance of the demonstrated efficacy

## VII. Integrated Review of Safety (See review by Dr. Maryann Gordon)

## VIII. Dosing, Regimen, and Administration Issues

The efficacy review of the CS-318-866 study leads to a certain level of confidence that any CS-866/25mg HCTZ dose combination will be effective in reducing blood pressure in populations similar to the one involved in this study .

The sponsor recommends approval for three dose combinations, 20/12.5, 40/12.5 and 40/25 and Dr. Hung's analyses showed that two of the recommended combinations (20/12.5 and 40/12.5) were not statistically significantly different from their CS-866 components.

As mentioned earlier, the sponsor included findings from other studies in its decision making.

The sponsor recommends that the combination should not be considered as an initial therapy. It should be a resource for patients whose BP was not controlled by either CS-866 or HCTZ alone. Since he 20/12.5 and 40/12.5 combination doses were statistically significantly more effective than the HCTZ component but not the CS-866 component, if they were to be approved, what therapeutic claim should these two combination doses have?

## IX. Use in Special Populations

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

Differences in gender distribution ranged between 12 to 32% favoring males. These differences were not statistically significant and no significant differences were seen with regard to baseline vital signs.

Three things to be said here.

1. Randomization was unable to balance gender and/or other characteristics in all 12-drug combination categories.
2. The sponsor did not make an effort to recruit as many females as males.

3. The study is not powered to conduct analyses by gender and/or other characteristics.

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

1. Age

It is important to highlight here that the study sub-selected only patients who have not developed hypertension-related complications and/or other concomitant diseases which led to an age selection of younger patients. Only 11.7% of study population was 65 and less than 2.4% was 75 years of age or older. The numbers are too small for any kind of analysis by age categories.

It is noteworthy to keep in mind that blood pressure components in hypertension, systolic vs. diastolic matter with regard to hypertension complications depending on whether patients were elderly or not. Baseline systolic and diastolic BP showed different trends with age (non portrayed results) in patients 65 and older compared to the majority of patients who are younger.

It is also important to keep in mind this sub-selection of younger and healthier patients in the review of labeling and indication.

2. Race (non-Black vs. Black)

The sponsor did not size their study or make an effort to recruit and study the effect of the drug combination in blacks and as a result no attempts of conducting meaningful analyses were made. The proportion of blacks in dose combination categories ranged from 5.7 to 28% (see Table 1 Demographics in the controlled study.)

C. [redacted]

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

No studies involving the combination of CS-866 and HCTZ were conducted in any special population.

Patients with concomitant cardiovascular diseases were excluded from the study and no conclusion can be drawn from these findings with regard to the safety and/or efficacy of the study drug combination in these populations.

The drug accumulated in patients with renal failure, especially patients with severe renal insufficiency, data concerning safety and tolerability in these patients are not available, and here again, no conclusions can be drawn about the safety or efficacy of the study drug combination in this population.

Patients with hepatic insufficiency exhibited Increases in AUC and Cmax and it is not clear how this would translate clinically

## X. Conclusions and Recommendations

### A. Conclusions

The hypothesis that has been tested in the pivotal study is been verified in all three 10, 20 and 40mg CS-866 plus 25mg HCTZ dose combinations (see VI. Integrated Review of Efficacy)

In light of the sponsor's recommendations about dose approvability, only the 40/25 dose combination is verified to be effective from Dr. Hung's findings.

Based on the information presented and the analyses done, 40/25 is approvable (given it showed no major safety issues).

### B. Recommendations

Given that the 40/25 combination dose is acceptable per Dr. Maryann Gordon's safety review, it is an approvable dose combination for the treatment of essential hypertension in patients with no concomitant diseases including hypertension end-organ damage.

To make available a dose range that allows the primary care provider and patient to aim for individual anti-hypertensive therapy adjustment, the following is recommended:

# XI. Appendix

## A. Other Relevant Materials

## ~~B.~~ Individual More Detailed Study Reviews (If performed)

1. Summary of all other studies

In the following studies, all dosages of CS-866 and HCTZ were given once daily, and HCTZ was always given in an open-label fashion either as background, as an adjunct to randomized treatment (which could be CS-866 or placebo or other BP medication) or as a supplement to further control BP. In all these studies, the evaluation of efficacy was conducted a-posteriori. Most of these studies compared patients taking the combination to a comparator group defined as patients taking CS-866 alone, HCTZ alone, Placebo, losartan alone, losartan + HCTZ or CS-866 + HCTZ + amlodipine (still awaiting response from the sponsor regarding the rational for the choice of comparative groups and their specific numbers in each dose combination category).

The following table is to detail exposure to each drug combination dose in the open-label studies (data is promised by sponsor to arrive this week).

**Table 13 Drug exposure in the open-label studies**

| | CS-866 mg | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Duration | 2.5 | | 5 | | 10 | | 20 | | 40 | |
| HCTZ mg | 12.5 | 25 | 12.5 | 25 | 12.5 | 25 | 12.5 | 25 | 12.5 | 25 |
| 0-4 Weeks | 12 | 7 | 34 | 8 | 29 | 3 | 49 | 6 | 140 | 36 |
| 4-6 Weeks | 8 | 3 | 4 | 2 | 1 | 0 | 18 | 2 | 52 | 30 |
| 6-8 Weeks | 4 | 1 | 6 | 2 | 2 | 3 | 11 | 8 | 9 | 10 |
| 8-12 Weeks | 8 | 1 | 6 | 3 | 6 | 1 | 20 | 19 | 29 | 28 |
| 3-6 Months | 1 | 4 | 10 | 4 | 7 | 7 | 276 | 24 | 10 | 10 |
| 6-9 Months | 5 | 9 | 6 | 10 | 10 | 5 | 7 | 13 | 4 | 3 |
| 9-12 Months | 13 | 4 | 26 | 10 | 24 | 12 | 23 | 4 | 15 | 3 |
| 12-15 Months | 0 | 0 | 2 | 0 | 5 | 1 | 3 | 1 | 0 | 0 |
| 15-18 Months | 0 | 0 | 2 | 3 | 1 | 3 | 0 | 0 | 0 | 0 |
| 18-21 Months | 0 | 0 | 1 | 13 | 1 | 8 | 2 | 6 | 0 | 0 |
| 21-24 Months | 0 | 0 | 18 | 3 | 15 | 3 | 12 | 0 | 0 | 0 |
| Total Subject Years | 17 | 11 | 71 | 49 | 66 | 41 | 149 | 35 | 38 | 19 |

*1) CS-866-321*
(July 2000 to April 2001)

- Title: A Long Term, Open-Label Study of CS-866 and Hydrochlorothiazide in Patients with Essential Hypertension"

This study was a 4-month extension of the pivotal study, was conducted in 43 US sites, and all patients( 451) who completed the CS-866-318 study were eligible.

Objectives: to assess the long-term safety of the CS-866/HCTZ combination in patients with essential hypertension.

Dose: CS-866 20mg x (12.5 or 25mg) Upward titrated to 25mg HCTZ was done when BP was uncontrolled (seDBP ≥ 95 mm Hg at two consecutive visits or ≥ 105 mm Hg at any one visit.)

Population: Three hundred forty male and female patients, 75% of all eligible people were enrolled, received the CS-866/HCTZ combination and were followed up to 4 months. No comparator group was used in this study.

*2) CS-866-305*
(August 1997 to February 1999)

A Randomized, Placebo-Controlled, Parallel-Group Study of CS-866 with long-term Safety Evaluation in Patients with Essential Hypertension

This study was conducted in 54-center in the US and enrolled 476 patients with moderate to severe essential hypertension (100 mm Hg ≤ seDBP ≤ 115 mm Hg) who were relatively healthy and not overweight. After a placebo run-in period, patients were randomized into six blocks of five CS-866 doses (2.5, 5, 10, 20 and 40mg) and a placebo arm. After 8 weeks of randomized therapy if DBP was not controlled HCTZ was supplemented.

Objectives: The only objective involving the CS-866/HCTZ combination was the evaluation of safety with and without HCTZ in the short and the long term periods respectively.

Dose: CS-866 (2.5, 5, 10, 20 or 40mg) x HCTZ (12.5 or 25mg)

Population: One hundred ninety five, 41% of all patients, whose DBP was not controlled (≥95 mm Hg at any tow consecutive visits or ≥105 mm Hg at any one visit) were given HCTZ. These were compared to a group of 281 patients and were followed for up to 10 months.

*3) CS-866-306*
(September 1997 to August 1998)

A Randomized, Placebo-Controlled, Dose-Titration Study of CS-866 with Long-Term Safety Evaluation in Patients with Essential Hypertension

This study was conducted in 50 sites in the US, and enrolled four hundred and two relatively healthy male and female patients with mild to moderate hypertension (100 mm Hg < seDBP < 115 mm Hg).

Objectives: The evaluation of the safety of the CS-866/ HCTZ combination was a secondary objective of the study.

Dose: CS-866 40mg x HCTZ (12.5 or 25mg)

Population: Ninety eight, 24% of the patients initially enrolled and whose DBP was not controlled, seDBP ≥ 95 mm Hg at two consecutive visits or ≥ 105 mm Hg at any visit, were given HCTZ and followed for four months.

*4) CS-866-419*
(July 2000 to September 2001)

Title: A Study to Assess the Percentage of Patients with Mild to Moderate Hypertension Initially Treated with CS-866 who Achieved Target Blood Pressure Control Using a Medication Treatment Algorithm of Three Anti-hypertensive Agents

This study was conducted in the US, and it was a non-comparative, multi-center study consisting of six 4-week treatment periods following a screening and a placebo run-in period. A total of 370 patients with mild to moderate diastolic hypertension, 90 mm Hg ≤ seDBP ≤ 109 mm Hg, were enrolled.

Objectives: To assess the percentage of patients who reach target BP with either CS-866 alone, CS-866 plus HCTZ or CS-866 plus HCTZ and amlodipine. Another secondary objective was to evaluate the effect of the study drug on the QOL.

Dose: CS-866 40mg x HCTZ (12.5 or 25mg) x Amlodipine (5 or 10mg)

Starting with 20mg CS-866 and adjusting the therapy at 4-week intervals following a stepwise algorithm until target BP is achieved. The algorithm consisted of upward titration of CS-866 to 40mg; addition of 12.5mg HCTZ; upward titration to 25mg of HCTZ; addition of 5 mg amlodipine and upward titration of amlodipine to 10mg.

Population: One hundred and twenty three patients, 33% of all patients enrolled in the initial phase of the study who did not reach target blood pressure on 40 mg CS-866 alone were added HCTZ 12.5 mg or 25mg if needed. These were compared to a group of 75 patients. The average follow-up of patients taking the CS-866/HCTZ combination ranged between 4 weeks to 16 weeks.

*5) SE-866/10*
(9/1997-7/1999)

Title: A multi-Center Double-Blind Long Term, Safety, Efficacy and Tolerability Study of the Oral Antiangiontensin II-Antagonist CS-866 in Patients with Mild to Moderate Essential Hypertension

This study was to be conducted in ≅ 40 sites in the EU and it randomized 559 patients.

Objectives: No objective involved the CS-866/HCTZ combination.

Dose: CS-866 (5, 10 or 20mg) x HCTZ (12.5 or 25mg)

Population: One hundred seventy, 30% of all initially enrolled, patients whose BP was not controlled with CS-866, dBP > 90 mm Hg ended up receiving a combination therapy, were compared to a group of 391 patients and followed up for a total of 40 weeks.

*6) SE-866/10-01*
(October/1998 to July/2000)

Title: A mutlti-Centre, Double-Blind, Long Term Safety, Tolerability and Efficacy Study of the Oral Angiotensin II-Antagonist CS-866 in patients with Mild to Moderate Essential Hypertension

This was an extension of the SE-866/10 study. It was conducted in 42 investigational sites in the EU and enrolled 462 patients who completed the SE-866-10 study and relatively responded to the study drug.

Objectives: No objective involved the CS-866/HCTZ combination.

Dose: CS-866 (5, 10 or 20mg) x HCTZ (12.5 or 25mg)

Population: One hundred thirty three male and female patients, 29% of all patients who entered the previous study on CS-866 mono-therapy and whose dBP > 90 mm Hg were given 12.5mg HCTZ and titrated up to 25mg if their seDBP remained > 90 mm Hg. This population was compared to a group of 320 patients and was followed up for 50 weeks.

*7) SE-866/17*
(February1998 to April 1999)

Title: A comparison of the Efficacy and Safety of the Oral Angiotensin II-Antagonist CS-866 with that of Atenolol in patient with Moderate to Severe Hypertension under Persistent Treatment of Hydrochorothiazide

This was a multi-center, randomized, double-blind, dose titration study. A four-week open 25mg HCTZ run-in phase and a 12-week double blind active CS-866 or atenolol treatment phase under continuous treatment with HCTZ were to be completed. Three hundred twenty eight patients

with severe hypertension, 105 mm Hg ≤ seDBP ≤ 120 mm Hg, were randomized to either 10mg of CS-866 or 50mg of atenolol which were titrated up to 20mg or 100mg respectively if dBP did not meet a cutoff criteria..

Objectives: None of the objectives of this study was to evaluate the effect of the combination of CS-866 and HCTZ

Dose: 25mg HCTZ x [CS-866 (10 or 20mg) or Atenolol]

Population: One hundred sixty four patients, 50% of all the study population received a combination of CS-866 and HCTZ. These patients were compared to a group of 164 other patients and followed up to 12 weeks.

*8) SE-866/19*
(March 1998 to August 1999)

Title: A Multi-Centre, Double-Blind, Efficacy, Tolerability and Safety Study of the Oral Angiotensin II-Antagonist CS-866 Versus Losartan in Patients with Mild to Moderate Essential Hypertension

This double dummy parallel and dose titration study was conducted in 25 centers the EU. A total of 294 patients with mild to moderate hypertension (dBP 95-114 mm Hg) were enrolled.

Objectives: The only objective involving the CS-866/HCTZ combination is the comparison between the losartan and CS-866 groups of the proportion of patients needing HCTZ to control their BP.

Dose: CS-866 (10 or 20mg) x HCTZ (12.5 or 25 mg)

Population: Fifty four male and female patients, 18% of all patients and 36% of those randomized to CS-866 only, who participated in the initial 12 weeks of treatment with either CS-866 or losartan and who failed to have their BP controlled were added 12.5mg HCTZ which was titrated up to 25mg if needed. These patients were compared to a group of 240 patients and followed up to 24 weeks.

2. Conclusion concerning the open-label studies of CS-866/HCTZ

All these studies gave HCTZ in a non-randomized, open-label design and explored the efficacy of the CS-866/HCTZ combination after the studies were conducted and completed. In some of these studies, patients were titrated up to a higher dose of CS-866, and were given 12.5mg HCTZ only if they did not respond to their CS-866 dose, and then were titrated up to 25mg HCTZ if the addition of 12.5mg did not control BP. As a result, all these studies were not designed to evaluate the efficacy of the combination, and any exploratory efficacy findings would be

weighed down by selection, unblinding, detection and other biases that would render the interpretability of any such results very difficult.

# MEDICAL REVIEW OF SAFETY

NDA#21,532
Drug Name: olmesartan medoxomil/hydrochlorothiazide (Benicar HCT™)
Sponsor: Sankyo Pharma
Date received: August, 2002
Medical Reviewer: Maryann Gordon, M.D.

Table of contents

**Summary of safety**

There were 1243 hypertensive subjects who received olmesartan medoxomil/hydrochlorothiazide in one of nine Phase II-III clinical trials. Tested doses ranged from 2.5 mg olmesartan/12.5 HCTZ to 40 mg olmesartan/25 mg HCTZ. The most commonly used dose was 20 mg olmesartan// 12.5 HCTZ.

Of the 9 clinical trials, only 1 (866-318) randomized subjects to the combination. This placebo controlled, multifactorial, efficacy trial was 8 weeks in duration. There were no deaths among the randomized patients. Of the 9 dropouts for adverse events, 7 occurred in the combination groups. Of these 7, 6 dropouts were attributed to dizziness, hypotension, syncope. (The 7th dropout resulted from tachycardia).

The table below shows the number of patients reporting any adverse event in study 866-318.

Number and (percent) of patients reporting at least 1 adverse event

| Dose of study drug (olmesartan medoxomil/hydrochlorothiazide | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 22 (52.4) | 17 (43.6) | 21 (51.2) | 19 (42.2) | 20 (44.4) | 16 (45.7) | 22 (50.0) | 23 (54.8) | 19 (44.2) | 22 (56.4) | 21 (44.7) | 20 (50.0) |

Events were reported similarly across treatment groups.

Dizziness was the only adverse event that appears to be linked to use of the combination. The table below shows the number of patients reporting dizziness in the trials.

**Dizziness:** no. and (percent) of patients

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 1 (2.4) | 0 | 1 (2.4) | 0 | 3 (6.7) | 1 (2.9) | 3 (6.8) | 4 (9.5) | 4 (9.3) | 5 (12.8) | 4 (8.5) | 6 (15.0) |

The highest combination dose (40/25) was associated with the highest incidence rate (15.0%) of dizziness. Headache and upper respiratory tract infection were commonly reported but with less convincing association with study drug.

Other adverse events (commonly associated with angiotensin receptor blocker/HCT) reported in this study included minor drop in hemoglobin/hematocrit, increase in BUN/serum creatinine, and hyperuricemia. There were sporadic reports of elevation of liver function tests and 1 report of a mild elevation of bilirubin.

Safety data from long term use of the combination (up to 1 year), although not derived from randomized trials, did not change conclusions drawn from study 866-318.

Overall, this is a small safety data base. There was only 1 completed study that randomized patients to the combination rather than allow HCT as add on. However, it is adequate considering that both monotherapies and other similar combinations are being marketed with no unusual safety issues.

**1.0 Overall Clinical Program**

The olmesartan medoxomil/hydrochlorothiazide (referred to in this document as the combination) program contains both completed and ongoing clinical safety and efficacy studies as well as clinical pharmacology studies.

The primary safety profile of the combination is obtained from 9 clinical trials with a total of 1243 hypertensive patients receiving the combination. Duration of treatment was up to 2 years. Olmesartan medoxomil (monotherapy) was approved for use in hypertension April 25, 2002.

The indication currently being pursued for the combination is hypertension (htn). There are no other INDs associated with this drug.

1.1 Studies with healthy volunteers

Completed studies
- 1 dose tolerance (SE-866CMB/01)
- 3 bioavailability/bioequivalence studies (866-126, 866-127, 866-134);

| Protocol no | Design and type+ | No. of subjects Olme/other | Dose (olmesartan/HCT); duration |
|---|---|---|---|
| SE-866CMB/01 | Randomized, open, crossover, PK | 24 | 20/25mg 7 days |
| 866-126 | Randomized, open, crossover, BE | 33 | 20/12.5mg single dose |
| 866-127 | Randomized, open, crossover, BE, DP | 18 | 10/12.5mg 20/12.5mg 40/12.5 single dose |
| 866-134 | Randomized, open, crossover, BE | 0/30 | 12.5 HCT only single dose |

+PK=pharmacokinetics, BA=bioavailability, BE=bioequivalence, DP=dose proportionality

1.2 Studies with patients

Completed controlled studies
- 7 efficacy/safety (866-318, 866-305, 866-306, SE-866/10, SE-866/10-01, SE-866/17, SE-866/19)

Ongoing controlled studies
- 3 efficacy/safety (SE-866CMB/02, SE-866CMB/03, 866-428);

Completed uncontrolled studies
- 2 safety (866-321, 866-419)

Ongoing uncontrolled studies
- 3 efficacy/safety (146-005, 146-006, 146-009)

The sponsor collected safety data from both US and European trials obtained on or before Jan 1, 2002. Data from studies that were ongoing as of Jan 1, 2002 are limited to serious adverse events that were reported to the sponsor by that date, and all deaths reported by June 15, 2002.

1.3 Safety review organization

The sponsor organized the safety review according to 3 groups:

-data from placebo-controlled study (study 866-318),

-data from long-term studies with duration of one year or less (866-305, 866-306, 866-318/321, 866-419, SE-86610, SE-866/19) and 1 study with patients treated for more than 1 year (866-10-01),
-data from a severe hypertension study(SE-866/17).

In addition, adverse events in all hypertensive patients who received the combination were analyzed across all studies.

The following 9 studies comprise the core safety program for the combination:

| Protocol no | Design and type+ | Type of subject | No. of subjects Olme/other/pl+ | Dose (olmesartan/HCT); duration |
|---|---|---|---|---|
| **Placebo controlled** | | | | |
| 866-318 | Randomized, DB, placebo controlled, parallel groups. Multifactorial design | Essential htn (mean sitting DBP≥100 and ≤115 mmHg | 247/255/42 | 10-40 mg/12.5-25 mg 8 weeks |
| **Long term** | | | | |

| Protocol no | Design and type+ | Type of subject | No. of subjects Olme/other/pl+ | Dose (olmesartan/HCT); duration |
|---|---|---|---|---|
| 866-321 | Long term, open label extension of 318 | Completed 866-318 | 206 | 20 mg/12.5-25 mg 4 months |
| 866-305^ | Randomized, DB, placebo controlled, parallel groups with HTC added on as needed | Essential htn (mean sitting DBP≥100 and ≤115 mmHg | 526 total | 2.5-40 mg or placebo for 2 months plus 8 months with HCT 12.5-25 mg added on if needed |
| 866-306^ | Randomized, DB, placebo controlled, parallel groups with HTC added on as needed | Essential htn (mean sitting DBP≥100 and ≤115 mmHg | 457 total | 5-20 mg or placebo for 8 weeks; open label 20-40m plus HCT 12.5-25 mg if needed for 4 months |
| SE-866/10^ | Randomized, DB, placebo controlled, parallel groups | Essential htn (mean sitting DBP≥100 and ≤114 mmHg | 619 total | 5-20 mg or placebo for 12 weeks; 12.5-25 mg HCT added if needed for 40 weeks |
| SE-866/10-1 | Randomized, DB, placebo controlled, parallel groups, long term extension of SE-866/10 | Completed study SE-866/10 and had mean sitting DBP ≤90 | 462 total | 5-20 mg and hct 12.5-25 mg as needed for 52 weeks |
| SE-866/17^ | Randomized, DB, atenolol controlled, parallel groups, | Moderate to severe htn (mean sitting DBP≥100 and ≤120 mmHg while taking HCT 25 mg | 328 total | 10-20mg/25mg or atenolol +HCT for 8 weeks |
| 866-419 | Open, dose titration | Mild to moderate htn (DBP≥90 and ≤109 mmHg) | 201 total | 20-40mg/12.5-25 hct added as needed. Amlodipine added as needed |
| SE-866/19^ | Randomized, DB, losartan controlled, parallel groups | Essential htn (mean sitting DBP≥100 and ≤114 mmHg | 316 total | 10-20mg/12.5-25 mg added if needed |

Pl=placebo
^study reviewed in NDA monotherapy

Ongoing clinical trials
The ongoing trials are shown in the table below.

| Protocol no | Design and type | Type of subject | No. of subjects Olme/other/pl | Dose (olmesartan/HCT); duration |
|---|---|---|---|---|
| SE-866 CMB/02 | Randomized, DB, PC, factorial | Mild to moderate htn | 1490 total | 10-40mg/15.5-25 mg for 12 weeks followed by 40 week prolongation phase |
| SE-866 CMB/03 | Randomized, DB, PC, add on | Mild to moderate htn | 367 total | 20 mg for 4 weeks followed by 20/0 mg, 20/12.5 or 20/25 mg for 8 weeks |
| SE-866 CMB/04 | Randomized, DB, active controlled | Moderate to severe htn | 16 | 2.5-40 single dose cross over |
| 866-428 | Randomized, DB, PC, add on | Essential htn and left ventricular hypertrophy (ECHO) | 100 total | 20 mg for 52 weeks with dose increased to 40 mg and then 10 mg amlodipine and then 25 mg hct and then 1 mg terazosin |

Japanese studies

| | | | | |
|---|---|---|---|---|
| 146-005 | Open label, | severe htn (mean sitting DBP≥110 mmHg | 29 total | 10-40 mg Up to 8 weeks |
| 146-006 | Open label | Mild to moderate htn | 49 | 10-40 mg 52 weeks |
| 146-009 | Open label | Renally impaired htn | 25 | 10-40 mg Up to 8 weeks |

1.4 Safety update

The safety update includes data from 5 ongoing studies (described above) reported between January 2, 2002 and September 1, 2002.

1.5 Numbers of study patients

The numbers of patients who received placebo, hct monotherapy, olmesartan monotherapy, the combination and/or the combination with amlodipine are shown below. In all but one study (866-318), patients were not randomized to the combination (i.e., hct was add-on therapy).

Number of patients

| Placebo | Hct alone | Olme alone | combination | Olme+htc+ amlodipine | Total olme^ |
|---|---|---|---|---|---|
| 342 | 188 | 1888 | 1243 | 49 | 2389 |

^each patient is counted only once

A total of 1243 patients received at least one dose of the combination.

1.6 Number of patients by dose

The doses of the combination that were tested in 1243 patients ranged from 2.5/12.5 to 40/25. The table

below shows the number of patients who received each dose of study drug.

TABLE 2
NUMBER OF PATIENTS EXPOSED TO CS-866
ALL STUDIES IN PATIENTS[1]

| | CS-866 DOSE [2] | | | | | | |
|---|---|---|---|---|---|---|---|
| | PLACEBO | 2.5 mg | 5 mg | 10 mg | 20 mg | 40 mg | TOTAL CS-866[3][4] |
| HCTZ PLACEBO | 342 | 91 | 603 | 536 | 999 | 464 | 1888 |
| HCTZ 12.5 mg[2] | 145 | 51 | 115 | 136 | 489 | 301 | 1043 |
| HCTZ 25 mg[2] | 113 | 29 | 58 | 249 | 194 | 160 | 638 |
| HCTZ 25 mg + AMLODIPINE 5 mg[2] | | | | | | 49 | 49 |
| HCTZ 25 mg + AMLODIPINE 10 mg[2] | | | | | | 22 | 22 |
| TOTAL CS-866 ALONE | | | | | | | 1888 |
| TOTAL CS-866 + HCTZ | | | | | | | 1243 |
| TOTAL CS-866 + HCTZ + AMLODIPINE | | | | | | | 49 |
| GRAND TOTAL CS-866 | | | | | | | 2389 |

[1] DATA ARE FROM STUDIES 305, 306, 318/321, 419, 10, 10-1, 17 AND 19.
[2] A PATIENT IS COUNTED ONCE IN EACH TREATMENT RECEIVED.
[3] EACH PATIENT IS COUNTED ONLY ONCE IN EACH ROW.
[4] EXCLUSIVE OF PLACEBO.

A total of 1888 patients received only olmesartan (doses 2.5mg-40 mg), 1243 patients received the combination (doses 2.5-40 mg/12.5-25mg), and an additional 49 patients received olmesartan hct amlodipine triple combination (40m/12.5-25mg/5-10). Only a small number of subjects received the combination doses 2.5/12.5 or 2.5/25 (51 and 29 patients, respectively). The doses that were given to the highest number of patients include 20/12.5 and 20/25 (489 and 794 patients, respectively).

1.7 Duration of exposure

Of the 1243 patients who received olmesartan HCT in the clinical program, 316 were treated for more than 6 months, and 112 were treated for more than 1 year[1].

The number of patients who received up to 52 weeks of treatment with study drug is shown below by dose.

[1] See page 27 ISS

TABLE 23
DURATION OF EXPOSURE
LONG-TERM COHORT -- FIRST YEAR[1]
FREQUENCY OF PATIENTS

| DURATION IN FIRST YEAR | CS-866 10 mg[2] PLACEBO | CS-866 10 mg[2] HCTZ 12.5 mg | CS-866 10 mg[2] HCTZ 25 mg | CS-866 20 mg [2] PLACEBO | CS-866 20 mg [2] HCTZ 12.5 mg | CS-866 20 mg [2] HCTZ 25 mg | CS-866 40 mg [2] PLACEBO | CS-866 40 mg [2] HCTZ 12.5 mg | CS-866 40 mg [2] HCTZ 25 mg |
|---|---|---|---|---|---|---|---|---|---|
| 1 DAY TO 12 WKS | 247 | 75 | 46 | 531 | 155 | 102 | 379* | 272 | 152 |
| > 12 WKS TO 26 WKS | 133 | 8 | 9 | 300 | 285 | 26 | 39 | 10 | 2 |
| > 26 WKS TO 52 WKS | 57 | 47 | 26 | 60 | 45 | 20 | 19 | 19 | 6 |
| > 52 WKS | 99 | 0 | 0 | 108 | 0 | 0 | 27 | 0 | 0 |
| TOTAL PATIENTS | 536 | 130 | 81 | 999 | 485 | 148 | 464 | 301 | 160 |

Of the subjects who received the combination for at least 26 weeks, 47 were taking the lowest dose (10/12.5), and 6 were taking the highest (40/25). At the time of the NDA preparation, no subject had received the combination for more than 1 year.

**2.0 Placebo controlled trial (866-318)**
(This was the only completed, placebo-controlled trial in which patients were randomized to the combination.)

Study design: randomized, placebo controlled, parallel group, multifactorial study in which hypertensive patients were randomized to once daily placebo, olmesartan (10, 20 or 40 mg), hct (12.5 or 25 mg), or the combination (10/12.5, 20/ 12.5, 40/12.5, 10/25, 20/25, 40/25 mg). Group sample sizes ranged from 35-47 subjects. Duration of treatment was 8 weeks.

Subject disposition: a total of 502 subjects were randomized and received at least 1 dose of study drug. The table below shows the number randomized and number dropped out for any reason and the number who dropped out because of an adverse event, by treatment group.

| Olme/hct mg dose group | Randomized/dropped out for any reason | Dropped out for AE |
|---|---|---|
| 0/0 | 42/5 (11.9%) | 0 |
| 10/0 | 39/5 (12.8%) | 1^ |
| 20/0 | 41/6 (14.6%) | 1 |
| 40/0 | 45/2 (4.4%) | 0 |
| 0/12.5 | 45/7 (15.6) | 1 |
| 10/12.5 | 35/2 (5.7%) | 0 |
| 20/12.5 | 44/8 (18.2%) | 2 |
| 40/12.5 | 42/5 (11.9%) | 2 |
| 0/25 | 43/1 (2.3%) | 0 |
| 10/25 | 39/2 (5.1%) | 0 |
| 20/25 | 47/4 (8.5%) | 1 |
| 40/25 | 40/4 (10%) | 2 |

^dropped out for lab abnormality

The drop out rate for placebo was 11.9% The drug group with the highest rate was 20/12.5 (18.2%). Overall, the percents of dropout for the combination groups were not dissimilar to the monotherapy groups. Only a small number dropped out for adverse events in any of the treatment groups.

Deaths and serious adverse events: none of the patients who were randomized to treatment died. There were 2 deaths reported for pre randomized patients: one occurred during the placebo run-in phase (died secondary to ruptured aortic aneurysm) and one occurred in a patient who had insufficient blood pressure for inclusion criterion (died secondary to ruptured cerebral aneurysm).

Discontinuations for adverse events: there were 10 patients who withdrew from study drug because of an adverse event. These are shown in the table below, by dose and reason.

| Randomized dose | event |
|---|---|
| 10/0 | Abnormal liver enzymes |
| 20/0 | Abnormal ECG: J point elevation V2-V5 |
| 0/12.5 | Increased palpitations |
| 20/12.5 | dizziness |
| 20/12.5 | Hypotension, dizziness |
| 40/12.5 | Dizziness, frequent urination, headaches lightheaded |
| 40/12.5 | Dizziness |
| 20/25 | tachycardia |
| 40/25 | hypotension |
| 40/25 | syncope, dizziness |

Dizziness (plus hypotension and syncope which may be the same event) was reported by and led to discontinuation in 6 patients, all on the combination. There was one discontinuation resulting from abnormal liver enzymes in a monotherapy patient.

Serious events-randomized patients only: there was only 1 report of serious adverse event. Patient # 38/8507 randomized to placebo, reported angina and underwent catheterization. There was no evidence of coronary artery disease.

Routine adverse events: the table below shows the number and percent of patients who reported at least one adverse event, by treatment group.

Number and (percent) of patients reporting at least 1 adverse event

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 22 (52.4) | 17 (43.6) | 21 (51.2) | 19 (42.2) | 20 (44.4) | 16 (45.7) | 22 (50.0) | 23 (54.8) | 19 (44.2) | 22 (56.4) | 21 (44.7) | 20 (50.0) |

The incidence rate of reporting adverse events is similar across treatment groups.

The tables below show the number and percent of adverse events that were reported by > 2 patients in one or more of the combination groups and had a higher incidence rate than did the placebo group.

**Headache**: no. and (percent) of patients

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 3 (7.1) | 2 (5.1) | 6 (14.6) | 3 (6.7) | 2 (4.4) | 3 (8.6) | 5 (11.4) | 2 (4.8) | 2 (4.7) | 1 (2.6) | 2 (4.3) | 0 |

Headache was a commonly reported event with a high placebo incidence rate (7.1%). Of the combination groups only 10/12.5 and 20/12.5 dose groups had somewhat higher rates (8.6% and 11.4%).

**Upper respiratory tract infection**: no. and (percent) of patients

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 0 | 2 (5.1) | 2 (4.9) | 4 (8.9) | 2 (4.4) | 0 | 4 (9.1) | 4 (9.5) | 4 (9.3) | 3 (7.7) | 4 (8.5) | 1 (2.5) |

URIs were reported more often in the combination group compared to placebo. There was no dose response.

**Dizziness:** no. and (percent) of patients

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 1 (2.4) | 0 | 1 (2.4) | 0 | 3 (6.7) | 1 (2.9) | 3 (6.8) | 4 (9.5) | 4 (9.3) | 5 (12.8) | 4 (8.5) | 6 (15.0) |

Dizziness seems likely to be related to combination use with the highest dose (40/25) associated with the highest incidence rate (15.0%). There were 3 drop outs for dizziness (1 in the 20/12.5 group and 2 in the 40/12.5 group).

Laboratory values[2]

There was one patient (10/0 group) who dropped out because of abnormal labs values (elevated LFTs).

**Hematology**

The table below shows the mean changes from baseline at week 8 for hematology parameters.

TABLE 74
CHANGE FROM BASELINE OF LABORATORY TEST VALUES[1] - HEMATOLOGY
PLACEBO-CONTROLLED COHORT[2]
HEMOGLOBIN (g/dL)

| | CS-866 PLACEBO | | | CS-866 10 mg | | | CS-866 20 mg | | | CS-866 40 mg | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | HCTZ | | | HCTZ | | | HCTZ | | | HCTZ | | |
| | 0 mg | 12.5 mg | 25 mg | 0 mg | 12.5 mg | 25 mg | 0 mg | 12.5 mg | 25 mg | 0 mg | 12.5 mg | 25 mg |
| CHANGE FROM BASELINE AT WEEK 8 | | | | | | | | | | | | |
| N | 36 | 38 | 41 | 33 | 31 | 35 | 35 | 35 | 42 | 42 | 37 | 36 |
| MEAN | 0.0 | 0.1 | 0.2 | -0.1 | -0.3 | -0.4 | -0.2 | -0.2 | -0.4 | -0.3 | -0.2 | -0.5 |
| MEDIAN | 0.2 | 0.0 | 0.1 | -0.1 | -0.3 | -0.4 | -0.1 | -0.3 | -0.4 | -0.3 | -0.4 | -0.7 |
| S.D | | | | | | | | | | | | |
| MINIMUM | | | | | | | | | | | | |
| MAXIMUM | | | | | | | | | | | | |
| P-VALUE[5] | | | | | | | | | | | | |

[1]ONLY PATIENTS WITH BOTH BASELINE AND WEEK 8 VALUES ARE INCLUDED.
[2]DATA ARE FROM STUDY 318. VALUES WERE NORMALIZED BASED ON ORIGINAL NORMAL RANGES AND THEN CONVERTED TO VALUES BASED ON COVANCE CENTRAL LABORATORY NORMAL RANGES.
[3]ANOVA FOR MEAN CHANGE FROM BASELINE COMPARING TOTAL PLACEBO ALONE, TOTAL HCTZ ALONE, TOTAL CS-866 ALONE, TOTAL CS-866 + HCTZ GROUPS WITH TREATMENT AS A FACTOR (CONTINUOUS VARIABLES ONLY).
[4]BASELINE = DAY 1 (PRE-RANDOMIZATION LABORATORY SPECIMEN).
[5]PAIRED T-TEST TO DETERMINE SIGNIFICANT CHANGE FROM BASELINE WITHIN TOTAL PLACEBO ALONE, TOTAL HCTZ ALONE, TOTAL CS-866 ALONE, TOTAL CS-866 + HCTZ GROUPS (CONTINUOUS VARIABLES ONLY).

As seen with angiotensin receptor blockers, there was a consistent, albeit small decrease in hemoglobin in the combination and olmesartan monotherapy groups compared to placebo and hct monotherapy groups.

[2] All tables in this section are from table 45 in the clinstat report, protocol 318

One patient (008219, black female) in the combination group had a drop in hemoglobin from 9.3 g/dl at baseline to 8.6 g/dl. The patient remained on study drug.

**Chemistry**

*Potassium*

There was 1 combination patient (0.4%) with a potassium value above 5.7 mEg/L at endpoint compared to no patients either taking placebo or hct monotherapy. There were fewer combination patients with a potassium value below 3.4 mEq/L at endpoint compared to hct monotherapy patients (2.1% vs 4.5%, respectively).

*BUN*

Table below shows the number and (percent) of patients with BUN values that went from ≤ 24 at baseline to > 24 mg/dl at week 8.

BUN: no. and (percent) of patients

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **0/0** | **10/0** | **20/0** | **40/0** | **0/12.5** | **10/12.5** | **20/12.5** | **40/12.5** | **0/25** | **10/25** | **20/25** | **40/25** |
| 3 (7.3) | 1 (2.6) | 0 | 0 | 1 (2.2) | 0 | 2 (4.7) | 2 (9.5) | 0 | 1 (2.6) | 4 (8.9) | 8 (20.0) |

The 40/12.5, 20/25 and 40/25 dose groups had higher incidence rates of subjects with elevated values (9.5%, 8.9%, and 20%, respectively) compared to placebo (7.3%).

*Creatinine*

~~Table below~~ shows the number and (percent) of patients with creatinine values that went from ≤ 1.2 (male) or ≤ 1.1 (female) at baseline to >1.2 (male) or 1.1 (females) mg/dl at week 8.

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **0/0** | **10/0** | **20/0** | **40/0** | **0/12.5** | **10/12.5** | **20/12.5** | **40/12.5** | **0/25** | **10/25** | **20/25** | **40/25** |
| 0 | 1 (2.6) | 0 | 0 | 0 | 0 | 1 (2.3) | 1 (2.4) | 0 | 0 | 1 (2.2) | 6 (15.0) |

The incidence rate for the 40/25 group (15%) was much higher than the other dose groups.

There were 6 subjects[3] who had increases in both BUN and creatinine. Of these 6, 5 received the higher dose hct (25 mg). Most changes were minor and subjects continued taking study drug. One subject had chronic elevation of BUN and creatinine, proteinuria and hematuria, and another had elevated values at baseline.

*Uric acid*

The table below shows the number and (percent) of patients with uric acid values that went from ≤ 7.5 at baseline to >7.5 mg/dl at week 8.

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **0/0** | **10/0** | **20/0** | **40/0** | **0/12.5** | **10/12.5** | **20/12.5** | **40/12.5** | **0/25** | **10/25** | **20/25** | **40/25** |
| 0 | 5 (12.8) | 2 (4.9) | 1 (2.3) | 5 (11.1) | 5 (14.7) | 6 (14.0) | 3 (7.1) | 9 (20.9) | 5 (12.8) | 9 (20.0) | 12 (30.0) |

As expected, the treatment groups with the 25 mg dose of HCT tended to have the highest incidence rate of increases in uric acid. The percent of patients reporting hyperuricemia as an adverse event was highest in the combination group (4.0%). The incidence rates of reported hyperuricemia were 2.4% for the placebo group and 2.3% for hct alone group.

[3] data from sponsor letter dated 10-24-02

*Liver function tests*

One patient (32/8199) dropped out because of elevated liver function tests. The patient's values for AST, ALT, and GGt were all elevated at baseline and the patient admitted to heavy alcohol intake. His lab values are shown below.

| Normal Range | ALT (U/L) 6-43 U/L | AST (U/L) 11-36 U/L | GGT (U/L) 10-61 U/L | CK (U/L) 18-198 U/L |
|---|---|---|---|---|
| Screening | 100 H | 64 H | 270 HT | 440 H |
| Screening R | 96 H | 74 H | 273 HT | nd |
| Study Day 1 | 103 H | 82 H | 294 HT | 630 H |
| Week 1 | 111 H* | 100 H* | 340 HT* | 521 H* |
| Week 4 | 108 H* | 87 H* | 317 HP* | 518 H* |
| Early Termination | 120 H | 84 H | 298 HT | 624 H |

Abbreviations: R, repeat test; H, high; T, telephone alert; nd, not done; P, panic alert
* indicates value is clinically significant as assessed by the investigator.

Follow-up?

The table below shows the number and (percent) of patients with ALT values that went from ≤ 43 (male) or 34 (female) at baseline to >43 (male) or >34 UL (female) at week 8.

ALT

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 3 (7.3) | 2 (5.1) | 1 (2.4) | 6 (13.6) | 4 (8.9) | 3 (8.8) | 2 (4.7) | 3 (7.1) | 2 (4.7) | 2 (5.1) | 0 | 5 (12.5) |

Number and (percent) of patients with AST values that went from ≤ 36 (male) or 34 (female) at baseline to >36 (male) or >34 UL (female) at week 8.

AST

| Dose of study drug | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 0/0 | 10/0 | 20/0 | 40/0 | 0/12.5 | 10/12.5 | 20/12.5 | 40/12.5 | 0/25 | 10/25 | 20/25 | 40/25 |
| 3 (7.3) | 0 | 1 (2.4) | 2 (4.5) | 2 (4.4) | 0 | 6 (14.0) | 0 | 2 (4.7) | 3 (7.7) | 2 (4.4) | 4 (10) |

There are sporadic increases in ALT/AST in most of the treatment groups. There does not appear to be a relationship between abnormal liver enzymes and the combination

*Bilirubin*

There was a report of 1 patient (20/25 group) whose bilirubin went from ≤ 1.2 at baseline to > 1.2 –1.5 mg/dl at 8 weeks.

### 3.0 Demographics-All study patients

The mean age, the percent of each gender, treatment group shows below the percent of each race, and the mean weight for all patients[4].

TABLE 3
DEMOGRAPHICS
ALL PATIENTS[1]
BY INITIAL TREATMENT

| | PLACEBO | | PLACEBO +HCTZ | | CS-866 ALONE | | CS-866 +HCTZ | |
|---|---|---|---|---|---|---|---|---|
| AGE (yr) | | | | | | | | |
| N | 342 | | 88 | | 1787 | | 411 | |
| MEAN | 55.8 | | 54.4 | | 55.8 | | 53.7 | |
| MEDIAN | 56.0 | | 55.0 | | 55.0 | | 53.0 | |
| S.D. | 11.28 | | 10.61 | | 11.59 | | 11.01 | |
| MINIMUM | 23.0 | | 26.0 | | 22.0 | | 24.0 | |
| MAXIMUM | 88.0 | | 83.0 | | 92.0 | | 91.0 | |
| <50 | 96 | | 26 | | 551 | | 138 | |
| 50-64 | 173 | | 46 | | 850 | | 205 | |
| 65-74 | 55 | | 13 | | 258 | | 58 | |
| >=75 | 18 | | 3 | | 128 | | 10 | |
| GENDER N(%) | | | | | | | | |
| MALE | 209 | (61.1%) | 46 | (52.3%) | 947 | (53.0%) | 215 | (52.3%) |
| FEMALE | 133 | (38.9%) | 42 | (47.7%) | 840 | (47.0%) | 196 | (47.7%) |
| RACE N(%) | | | | | | | | |
| CAUCASIAN | 287 | (83.9%) | 61 | (69.3%) | 1480 | (82.8%) | 349 | (84.9%) |
| BLACK | 24 | (7.0%) | 16 | (18.2%) | 146 | (8.2%) | 28 | (6.3%) |
| ASIAN | 1 | (0.3%) | 1 | (1.1%) | 18 | (1.0%) | 7 | (1.7%) |
| HISPANIC | 27 | (7.9%) | 9 | (10.2%) | 137 | (7.7%) | 24 | (5.8%) |
| OTHER | 3 | (0.9%) | 1 | (1.1%) | 6 | (0.3%) | 5 | (1.2%) |
| WEIGHT (kg) | | | | | | | | |
| N | 341 | | 87 | | 1586 | | 411 | |
| MEAN | 86.4 | | 87.6 | | 84.1 | | 85.5 | |
| MEDIAN | 85.5 | | 85.5 | | 82.3 | | 85.0 | |
| S.D. | 17.25 | | 16.62 | | 16.62 | | 16.22 | |
| MINIMUM | 47.7 | | 57.3 | | 40.0 | | 46.8 | |
| MAXIMUM | 134.1 | | 128.6 | | 185.0 | | 137.7 | |

The mean age was around 55 years, more than half were male, most were white, and the mean weight was around 85 kg. Only 6.3% of patients in the combination group were black.

Treatment group shows below the mean height and mean duration of hypertension.

APPEARS THIS WAY ON ORIGINAL

[4] includes patients in studies 305, 306, 318/321, 419, 10/10-1, 17 and 19

TABLE 3
DEMOGRAPHICS
ALL PATIENTS[1]
BY INITIAL TREATMENT

| | PLACEBO | PLACEBO +HCTZ | CS-866 ALONE | CS-866 +HCTZ |
|---|---|---|---|---|
| HEIGHT (cm) | | | | |
| N | 342 | 88 | 1783 | 411 |
| MEAN | 171.6 | 170.0 | 170.0 | 169.9 |
| MEDIAN | 172.0 | 170.2 | 170.2 | 170.2 |
| S.D. | 9.90 | 10.99 | 9.97 | 10.03 |
| MINIMUM | 142.2 | 149.9 | 127.0 | 137.2 |
| MAXIMUM | 200.7 | 190.5 | 200.7 | 195.6 |
| HYPERTENSION HISTORY (yr) | | | | |
| N | 342 | 88 | 1785 | 409 |
| MEAN | 9.8 | 9.4 | 9.0 | 8.1 |
| MEDIAN | 7.0 | 6.2 | 6.2 | 5.4 |
| S.D. | 9.16 | 8.46 | 8.54 | 8.09 |
| MINIMUM | | | | |
| MAXIMUM | | | | |

Mean height was about 170 cm and patients had a mean duration of hypertension of about 9 years.

## 4.0 Patient disposition

The number and (percent) of patients who discontinued study drug are shown below by reason and drug group.

TABLE 5
REASONS FOR DISCONTINUATION
ALL STUDIES IN PATIENTS[1]

| | PLACEBO ALONE | HCTZ ALONE | CS-866 ALONE | CS-866 + HCTZ |
|---|---|---|---|---|
| REASON FOR DISCONTINUATION | N (%) | N (%) | N (%) | N (%) |
| TOTAL PATIENTS | 342 (100.0%) | 188 (100.0%) | 1888 (100.0%) | 1243 (100.0%) |
| ADVERSE EVENT | 7 (2.0%) | 8 (4.3%) | 66 (3.5%) | 25 (2.0%) |
| SUBJECT REQUEST | 25 (7.3%) | 8 (4.3%) | 70 (3.7%) | 46 (3.7%) |
| PROTOCOL VIOLATION | 1 (0.3%) | 2 (1.1%) | 11 (0.6%) | 7 (0.6%) |
| INVESTIGATOR JUDGEMENT | 3 (0.9%) | 3 (1.6%) | 14 (0.7%) | 10 (0.8%) |
| DID NOT MEET ENTRY CRITERIA | 1 (0.3%) | 0 (0.0%) | 2 (0.1%) | 0 (0.0%) |
| UNCONTROLLED BLOOD PRESSURE AS DEFINED IN THE PROTOCOL | 6 (1.8%) | 17 (9.0%) | 10 (0.5%) | 27 (2.2%) |
| LOST TO FOLLOWUP | 3 (0.9%) | 1 (0.5%) | 14 (0.7%) | 10 (0.8%) |
| NON-COMPLIANCE | 2 (0.6%) | 1 (0.5%) | 13 (0.7%) | 12 (1.0%) |
| CONCOMITANT MEDICATION | 0 (0.0%) | 0 (0.0%) | 4 (0.2%) | 1 (0.1%) |
| TERMINATION OF STUDY BY SPONSOR | 1 (0.3%) | 0 (0.0%) | 3 (0.2%) | 0 (0.0%) |
| LACK OF EFFICACY | 12 (3.5%) | 8 (4.3%) | 10 (0.5%) | 16 (1.3%) |
| OTHER REASON | 5 (1.5%) | 1 (0.5%) | 18 (1.0%) | 21 (1.7%) |
| TOTAL NUMBER OF PATIENTS DISCONTINUED | 66 (19.3%) | 49 (26.1%) | 235 (12.4%) | 175 (14.1%) |

[1]DATA FROM STUDIES 305, 306, 318, 321, 419, 10, 10-1, 17 AND 19.

Patients who received hct monotherapy were discontinued (for any reason) more often (26.1%) than any of the other treatment groups. There was a slightly higher rate of discontinuation for the combination (14.1%) compared to olmesartan alone (12.4%), but lower compared to the placebo rate (19.3%).

AVG duration of exposure

The most often cited reasons for discontinuation in the combination group were adverse event and subject request (2.0% and 3.7%, respectively). These incidence rates were not dissimilar to those reported for the other treatment groups.

**5.0 Serious safety**

5.1 Deaths

There were 7 reports of deaths: 2 were placebo patients, 1 received hct alone, 3 received olmesartan alone, and 1 received the combination.

| Study (patient) no. | Dose mg/day | Cause of death |
|---|---|---|
| SE-866/10 (000398) | 20 olmesartan/~ 11 months | Illeus, anemia in 70 yr chronically ill female |
| SE-866/19 (000153) | 20/12.5 combo/~ 3 months | CVA in 73 year old male |
| SE-866/19 (000293) | 10 olmesartan/~ 3 weeks | Esophageal carcinoma in 68 year old male |
| SE-866/19 (000093) | 20/25 combo/ 11 days after study ended | Left ventricular failure in 61 year old female |
| SE-866/10-01 (000066) | 25 hct/150 days | Sudden death in 68 year old female |
| SE-866/10-01 (000427) | 5 olmesartan/262 days | CVA in 81 year old female |
| SE-866/10-01 (000505) | Placebo/210 days | Sudden death in 67 year old male |
| SE-866/10-01 (000793) | Placebo/221 days | Traumatic injury and intestinal ischemia in a 90 year old male |

The youngest patient in this group of reported deaths was 67 years. There were 2 reports of cerebral vascular accidents, 1 report of cancer, 1 report of illeus and anemia in a chronically ill patient, 1 report of heart failure, 2reports of sudden death, and 1 report of traumatic injury. There is no indication that the use of study drug resulted in a death of any of these patients.

5.2 Discontinuations resulting from an adverse event

In the first year cohort group[5], 21 (2.0%) of the combination patients discontinued for an adverse event compared to 55 (2.9%) of olmesartan alone and 5 (2.7%) hct alone. The table below shows the number and percent of discontinuations for a selected[6] adverse event by drug group.



[5] long-term studies with a duration of one year or less
[6] reported by at least 2 patients in at least 1 drug group

TABLE 8.4.5.3.2a
TREATMENT EMERGENT ADVERSE EVENTS THAT RESULTED IN DISCONTINUATION OF MORE THAN ONE TOTAL CS-866 PLUS HCTZ TREATED PATIENT
LONG-TERM COHORT -- FIRST YEAR

| BODY SYSTEM AE PREFERRED TERM | TOTAL PLACEBO ALONE (N = 342) N | (%) | TOTAL HCTZ ALONE (N = 185) N | (%) | TOTAL CS-866 ALONE (N = 1888) N | (%) | TOTAL CS-866 + HCTZ (N = 1063) N | (%) |
|---|---|---|---|---|---|---|---|---|
| NO AE | 338 | (99.1%) | 180 | (97.3%) | 1833 | (97.1%) | 1042 | (98.0%) |
| AT LEAST ONE AE | 3 | (0.9%) | 5 | (2.7%) | 55 | (2.9%) | 21 | (2.0%) |
| CENTR & PERIPH NERVOUS SYSTEM DISORDERS | | | | | | | | |
| TOTAL | 0 | (0.0%) | 0 | (0.0%) | 11 | (0.6%) | 5 | (0.5%) |
| DIZZINESS | 0 | (0.0%) | 0 | (0.0%) | 7 | (0.4%) | 4 | (0.4%) |
| CARDIOVASCULAR DISORDERS, GENERAL | | | | | | | | |
| TOTAL | 0 | (0.0%) | 0 | (0.0%) | 4 | (0.2%) | 3 | (0.3%) |
| HYPOTENSION | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 2 | (0.2%) |
| LIVER AND BILIARY SYSTEM DISORDERS | | | | | | | | |
| TOTAL | 0 | (0.0%) | 1 | (0.5%) | 2 | (0.1%) | 3 | (0.3%) |
| GAMMA-GT INCREASED | 0 | (0.0%) | 1 | (0.5%) | 1 | (0.1%) | 3 | (0.3%) |
| SGPT INCREASED | 0 | (0.0%) | 1 | (0.5%) | 1 | (0.1%) | 3 | (0.3%) |
| SGOT INCREASED | 0 | (0.0%) | 1 | (0.5%) | 1 | (0.1%) | 2 | (0.2%) |
| METABOLIC AND NUTRITIONAL DISORDERS | | | | | | | | |
| TOTAL | 0 | (0.0%) | 1 | (0.5%) | 3 | (0.2%) | 3 | (0.3%) |
| HYPERURICAEMIA | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 2 | (0.2%) |

SOURCE: TABLE 34

The above events reported more often in the combination group compared to placebo include dizziness (0.4%), hypotension (0.2%), liver function tests increased (0.3%), and hyperuricemia (0.2%). Liver function test increased was also reported more often in the olmesartan alone group (0.5%) compared to placebo. Overall, drop out rates for an adverse event are low in all treatment groups.

In the second year cohort[7] group, 2.2% of the combination patients who discontinued for an adverse event compared to 2.1% of olmesartan alone and 7.1% of hct alone. The table below shows the number and percent of discontinuations for selected[8] adverse events by drug group.



[7] long-term studies with a duration of more than one year
[8] reported by at least 2 patients in at least 1 drug group

TABLE 8.4.5.3.2b
TREATMENT EMERGENT ADVERSE EVENTS THAT RESULTED IN DISCONTINUATION
OF ONE OR MORE TOTAL CS-866 PLUS HCTZ TREATED PATIENT
LONG-TERM COHORT -- SECOND YEAR

| BODY SYSTEM AE PREFERRED TERM | TOTAL PLACEBO ALONE (N = 27) | | TOTAL HCTZ ALONE (N = 28) | | TOTAL CS-866 ALONE (N = 289) | | TOTAL CS-866 + HCTZ (N = 134) | |
|---|---|---|---|---|---|---|---|---|
| | N | (%) | N | (%) | N | (%) | N | (%) |
| NO AE | 23 | (85.2%) | 26 | (92.9%) | 283 | (97.9%) | 131 | (97.8%) |
| AT LEAST ONE AE | 4 | (14.8%) | 2 | (7.1%) | 6 | (2.1%) | 3 | (2.2%) |
| BODY AS A WHOLE - GENERAL DISORDERS TOTAL | 1 | (3.7%) | 1 | (3.6%) | 0 | (0.0%) | 1 | (0.7%) |
| SYNCOPE | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| CARDIOVASCULAR DISORDERS, GENERAL TOTAL | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| CARDIAC FAILURE LEFT | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| HYPERTENSION AGGRAVATED | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| MYO ENDO PERICARDIAL & VALVE DISORDERS TOTAL | 1 | (3.7%) | 0 | (0.0%) | 1 | (0.3%) | 1 | (0.7%) |
| MYOCARDIAL INFARCTION | 1 | (3.7%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| RESPIRATORY SYSTEM DISORDERS TOTAL | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| BRONCHITIS | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |
| LARYNGITIS | 0 | (0.0%) | 0 | (0.0%) | 0 | (0.0%) | 1 | (0.7%) |

SOURCE: TABLE 49

There was no individual adverse event that resulted in discontinuation of more than 1 combination patient.

For all trials combined, the table below shows the adverse events resulting in discontinuation for at least 2 combination patients.