CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

21-532

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDA: 21-532	Submission Date(s):
	N000 August 5, 2002
	N000 (B2) March 14, 2003
Brand Name	Benicar HCT™
Generic Name	Olmesartan medoxomil-hydrochlorothiazide
	CS-866 and HCTZ
Reviewer	B. Nhi Nguyen, Pharm.D.
Team Leader	Patrick Marroum, Ph.D.
OCPB Division	One
ORM division	Cardio-renal
Sponsor	Sankyo Pharma Development
Relevant IND(s)	
Formulation; Strength(s):	20/12.5 mg, 40/12.5, 40/25 mg tablets
Indication	Hypertension

1 EXECUTIVE SUMMARY

Benicar HCT™ is a combination of olmesartan medoxomil and hydrochlorothiazide (HCTZ) proposed for the treatment of hypertension. The single drug entities are approved for the treatment of hypertension (Benicar™ in April 2002). Benicar™ (olmesartan medoxomil or CS-866) is the medoxomil ester prodrug of the angiotensin II receptor (AT_1) blocker olmesartan (RNH-6270). Hydrochlorothiazide is a thiazide diuretic.

The effectiveness is based on a randomized, double-blind, placebo-controlled, factorial design study (study 866-318) and eight supportive studies. These studies included 2,757 patients (1,230 patients received olmesartan medoxomil and hydrochlorothiazide). The doses used in the pivotal effectiveness study ranged from 10/12.5 mg to 40/12.5 mg and 10/25 mg to 40/25 mg. However, the sponsor did conduct other effectiveness studies using olmesartan medoxomil doses as low as 2.5 mg and 5 mg combined with HCTZ 12.5 mg or 25 mg. The safety is based on the integrated analysis of nine trials.

The potentially marketable drug strengths of Benicar HCT™ are 20/12.5 mg, 40/12.5 mg, and 40/25 mg tablets, however the sponsor only wants approval of three strengths: 20/12.5 mg, 40/12.5 mg and 40/25 mg . The sponsor conducted three bioequivalence (BE) studies with the combination to-be-marketed product since the monoentitites were used in the clinical trials: 20/12.5 mg, 40/12.5 mg tablets. The sponsor is only seeking a biowaiver for the 40/25 mg tablet (based on the 20/12.5 mg and 40/12.5 mg tablet data).

20/12.5

40/12.5

The to-be-marketed 20/12.5 mg and 40/12.5 mg tablets were bioequivalent to their respective single entities.

Olmesartan (RNH-6270) AUC and Cmax and HCTZ AUC were within the accepted (80, 1.25) 90 % confidence interval.

A biowaiver is granted for the to-be-marketed 40/25 mg tablet. This decision is based on the reference strengths' (20/12.5 mg and 40/12.5 mg tablets) data. The following support the biowaivers:

- Linear pharmacokinetics over the concentration range,
- Proportionately similar compositions between the 40/12.5 mg and 40/25 mg tablets,
- Comparable dissolution profiles in three media, and
- Bioequivalence of the individual formulations.

The following dissolution method and specification are recommended:

CS-866

Medium:	900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus:	USP II (paddle)
Speed:	50 rpm
Specifications:	Q not less than at 45 minutes

HCTZ

Medium:	900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus:	USP II (paddle)
Speed:	50 rpm
Specifications:	Q not less than at 15 minutes

1.1 Recommendation

NDA 21-532 is acceptable from a Clinical Pharmacology and Biopharmaceutics perspective. A biowaiver is granted for the 40/25 mg tablet. The following dissolution methods and specifications are recommended:

CS-866

Medium:	900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus:	USP II (paddle)
Speed:	50 rpm
Specifications:	Q not less than ... at 45 minutes

HCTZ

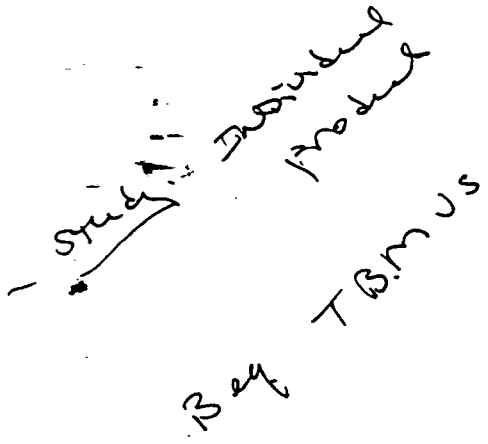
Medium:	900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus:	USP II (paddle)
Speed:	50 rpm
Specifications:	Q not less than ... at 15 minutes

There are no further labeling recommendations.

OCPB briefing held on April 10, 2003. Mehta, Sahajwalla, Ramchandani, Bhattaram and Marroum attended.

B. Nhi Nguyen, Pharm.D.
Division of Pharmaceutical Evaluation I
Primary reviewer

FT Initialed by Patrick Marroum, Ph.D.
CC: HFD-110 (Fromm, Cooper, Srinivasachar): NDA 21-532; HFD-860 (Mehta, Sahajwalla); CDER central document room



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Abbreviations

$AUC_{(0-t)}$	area under the curve from time zero to time of last quantifiable concentration
$AUC_{(0-\infty)}$	area under the curve from time zero to infinity
Cmax	maximum concentration
CS-866	olmesartan medoxomil
HCTZ	Hydrochlorothiazide
HPLC	High performance liquid chromatography
LLOQ	lower limit of quantitation
NLT	Not less than
OTC	Over the counter
RNH-6270	olmesartan (active metabolite of CS-866)
Tmax	time to Cmax
T ½	elimination half-life of drug in plasma, calculated as [ln1/ k_{el}]
k_{el}	elimination rate constant, estimated as [-(slope x 2.303)] from a log linear regression plot of the last 3 to 5 observed plasma concentrations

3 SUMMARY OF CPB FINDINGS

The sponsor wants approval of three combination strengths of olmesartan medoxomil/HCTZ (20/12.5 mg, 40/12.5 mg and 40/25 mg tablets), however there are potentially marketable drug strengths of Benicar HCT™;
The sponsor conducted bioequivalence (BE) studies with the combination to-be-marketed product: 20/12.5 mg, 40/12.5 mg and . The sponsor is only seeking a biowaiver for the 40/25 mg tablet (based on the 20/12.5 mg tablet data).

The to-be-marketed 20/12.5 mg and 40/12.5 mg tablets were bioequivalent to their respective single entities. The mg tablet was not bioequivalent.

Olmesartan (RNH-6270) AUC and Cmax and HCTZ AUC were within the accepted (80, 1.25) 90 % confidence interval.

The sponsor demonstrated bioequivalence between HCTZ 12.5 mg capsule and the overencapsulated capsule.

A biowaiver is granted for the to-be-marketed 40/25 mg tablet. This decision is based on the reference strength's (20/12.5 mg and 40/12.5 mg tablets) data. The following support the biowaiver:

- Linear pharmacokinetics over the concentration range,
- Proportionately similar compositions between the 40/12.5 mg and the 40/25 mg,
- Comparable dissolution profiles in three media, and
- Bioequivalence to the individual formulations.

The sponsor also conducted a study that found the three dosage strengths of CS-866 (10, 20, and 40 mg) to be dose proportional when given as the combination tablet of 10/12.5, 20/12.5 and 40/12.5 mg. HCTZ in the three formulations were bioequivalent.

In a drug interaction study between olmesartan , HCTZ had no effect on RNH-6270, however the bioavailability of HCTZ in the combination product was 20 % less than in the single entity.

The following dissolution method and specification are recommended:

CS-866
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than at 45 minutes

HCTZ
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than at 15 minutes

4 QUESTION BASED REVIEW

4.1 General Clinical Pharmacology

Background

Olmesartan medoxomil (CS-866) is a prodrug that is rapidly and completely hydrolyzed to its active metabolite olmesartan (RNH-6270). RNH-6270 exhibits linear pharmacokinetics following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. The absolute bioavailability of RNH-6270 is approximately 26 %. After oral administration, the peak plasma concentration of RNH-6270 is reached in 1 to 2 hours. Food does not affect the bioavailability. RNH-6270 is bound to albumin and α1-acid glycoprotein, but not to serum globulin. RNH-6270 has a terminal elimination half-life of approximately 13 hours. RNH-6270 is eliminated in urine and feces essentially unchanged. Dose adjustments are not required in mild to moderate renal or hepatic impairment.

The primary basis for effectiveness of CS-866/HCTZ comes from the U.S. study 866-318, a randomized, double-blind, placebo-controlled, parallel-group, factorial design (with and without HCTZ), multicenter study of patients with essential hypertension. Study 866-318 included 502 patients; 247 were randomized to receive olmesartan medoxomil and HCTZ, while 255 were randomized to receive either olmesartan, HCTZ or placebo. This trial had a four week placebo run-in period followed by double-blind treatment in twelve groups for eight weeks. The twelve treatment groups were (mg olmesartan medoxomil/mg HCTZ): 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, and 40/25. The effectiveness is also supported by eight more studies conducted in the US and Europe. In total, 2,757 patients (1,230 patients received olmesartan medoxomil and hydrochlorothiazide)are included in the effectiveness analysis. Olmesartan medoxomil doses as low as 2.5 and 5 mg have been studied. The safety of combination CS-866 and HCTZ is supported by the above mentioned studies, five controlled phase 3 studies submitted with the Benicar™ (olmesartan medoxomil) NDA and the clinical pharmacology studies included in this review. All of the clinical trials used the monoentitities.

4.2 Extrinsic Factors

4.2.1 Is there a food effect?

There is no food effect with the monoentities. The sponsor did not study the effect of food when taking both drugs together. In the pivotal study 866-318, patients were instructed to take their study medication in the morning with breakfast. Since food does not affect the monoentities, it is unlikely that food will affect the combination tablet, thus a study is not warranted.

4.3 General Biopharmaceutics

4.3.1 Is the market formulation bioequivalent to the formulations used in the clinical trials?

Yes, the 20/12.5 mg and 40/12.5 mg to-be-marketed tablets are bioequivalent to the single entities.

20/12.5 mg

The ratios for AUC and Cmax are within the 90 % confidence intervals (see tables).

Table 1. Study 866-126: 20/12.5 mg RNH-6270 Point Estimates and 90 % CI

	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	Cmax
C vs. A	1.04 (0.99 – 1.10)	1.04 (0.98 – 1.10)	1.08 (1.02 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.07 (1.01 – 1.13)	1.08 (1.01 – 1.15)

A = 20 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)
B = 20 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)
C = 20 mg CS-866 / 12.5 mg HCTZ tablet

Table 2. Study 866-126: 20/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
$AUC_{(0-t)}$ (ng*h/mL)	3463 ± 799	3603 ± 817	3373 ± 781
$AUC_{(0-\infty)}$ (ng*h/mL)	3561 ± 843	3695 ± 872	3459 ± 806
Cmax (ng/mL)	560 ± 123	606 ± 137	560 ± 117
Tmax (h)	2.0 (1.5 – 4.0)	2.0 (1.0 – 3.0)	1.5 (1.0 – 4.0)
T ½ (h)	21.4 ± 17.8	20.4 ± 16.3	21.6 ± 13.5
k_{el}	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02

mean ± SD or median (range)

Table 3. Study 866-126: 20/12.5 mg HCTZ Point Estimates and 90 % CI

	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	Cmax
C vs. A	1.04 (0.98 – 1.10)	1.05 (0.99 – 1.10)	1.06 (0.98 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.08 (1.02 – 1.14)	1.06 (0.98 – 1.15)

A = 20 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)
B = 20 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)
C = 20 mg CS-866 / 12.5 mg HCTZ tablet

Table 4. Study 866-126: 20/12.5 mg HCTZ PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
$AUC_{(0-t)}$ (ng*h/mL)	507 ± 136	522 ± 121	495 ± 138
$AUC_{(0-\infty)}$ (ng*h/mL)	566 ± 140	585 ± 118	547 ± 134
Cmax (ng/mL)	90 ± 30	94 ± 32	89 ± 28
Tmax (h)	2.0 (1.0 – 4.0)	1.5 (1.0 –3.0)	1.5 (1.0 – 4.0)
T ½ (h)	11.3 ± 7.2	11.0 ± 2.9	10.6 ± 2.0
k_{el}	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.01

mean ± SD or median (range)

40/12.5 mg

The ratios for AUC and Cmax are within the 90 % confidence intervals (see tables).

Table 5. Study 866-138: 40/12.5 mg RNH-6270 Point Estimates and 90 % CI

	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
C vs. A	0.97 (0.90 – 1.04)	0.98 (0.91 – 1.05)	1.03 (0.96 – 1.11)
C vs. B	0.97 (0.91 – 1.05)	0.99 (0.92 – 1.06)	1.03 (0.96 – 1.11)

A = 40 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)
B = 40 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)
C = 40 mg CS-866 / 12.5 mg HCTZ tablet

Table 6. Study 866-138: 40/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	6633 ± 1704	6362 ± 2056	6601 ± 2056
AUC $_{(0-\infty)}$ (ng*h/mL)	6759 ± 1699	6569 ± 1526	6743 ± 2091
Cmax (ng/mL)	1048 ± 289	1071 ± 270	1050 ± 331
Tmax (h)	2.0	1.5	2.0
T ½ (h)	19.3 ± 16.0	21.4 ± 21.0	19.0 ± 13.4

mean ± SD or median (range)

Table 7. Study 866-138: 40/12.5 mg HCTZ Point Estimates and 90 % CI

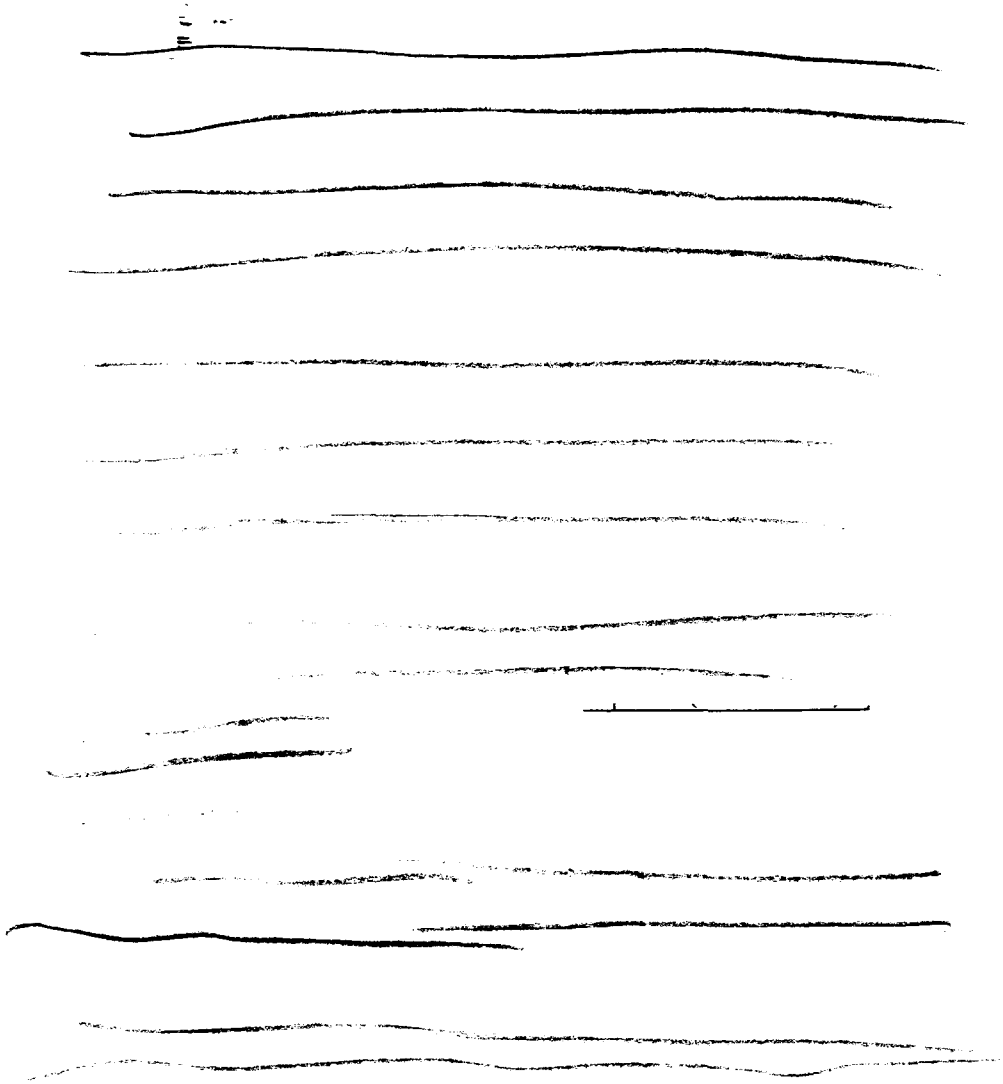
	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
C vs. A	0.95 (0.90 – 1.00)	0.96 (0.92 – 1.00)	0.97 (0.90 – 1.04)
C vs. B	0.97 (0.92 – 1.02)	0.96 (0.92 – 1.01)	1.01 (0.93 – 1.08)

A = 40 mg CS-866 tablet + 12.5 mg HCTZ capsule (US)
B = 40 mg CS-866 tablet + 12.5 mg HCTZ tablet (Europe)
C = 40 mg CS-866 / 12.5 mg HCTZ tablet

Table 8. Study 866-138: 40/12.5 mg HCTZ PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	493 ± 100	472 ± 108	489 ± 122
AUC $_{(0-\infty)}$ (ng*h/mL)	542 ± 96	522 ± 104	542 ± 121
Cmax (ng/mL)	80 ± 22	78 ± 22	80 ± 30
Tmax (h)	1.75	1.5	1.75
T ½ (h)	9.6 ± 1.8	10.0 ± 1.9	10.2 ± 1.7

mean ± SD or median (range)



4.3.1.1 What formulations were used in the trials for Benicar/HCT?

The monoentities were used in all of the clinical trials. Sankyo Co., Ltd in Tokyo, Japan manufactured the 20 mg CS-866 film-coated tablets used in the pivotal study 966-318 and the Phase 3 US study 866-321. Commercially available 12.5 mg Microzide™ (HCTZ) capsules from [redacted], were used in the pivotal study 866-318 and study 866-321. The 20 mg CS-866 film-coated tablets used in study SE-866CMB/01 conducted by Sankyo Europe GmbH in Germany were manufactured by Sankyo Pharma GmbH of Munich, Germany. The commercially available 12.5 mg HCTZ tablets used in the Sankyo Europe GmbH study were obtained from [redacted] A list of the formulations can be found in the Appendix.

Sankyo Pharma GmbH manufactured the combination product. The formulations of the combination product are listed in the table below.

Table 4.3. 1: Quantitative formulation of the Sankyo Pharma GmbH CS-866/HCTZ commercial tablets

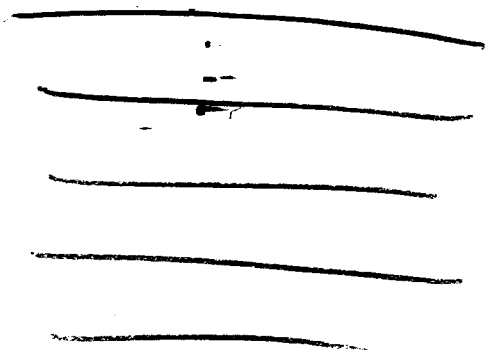
Ingredient	20/12.5 mg tablet	40/12.5 mg tablet	40/25 mg tablet
CS 866[1]	20 mg	40 mg	40 mg
Hydrochlorothiazide	12.5 mg	12.5 mg	25 mg
Microcrystalline cellulose			
Lactose			
Hydroxypropyl cellulose			
Magnesium Stearate			
Tablet Core Weight			
Coated Tablet Weight			
Tablet shape	Round	Oval	Oval
Tablet Core Dimensions	8.5 mm dia.	15 x 7 mm	15 x 7 mm

4.3.1.2 Can a waiver be granted for the 40/25 mg tablet? ?

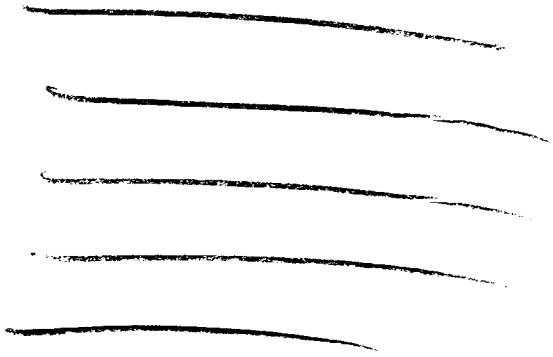
A waiver was requested and can be granted for the 40/25 mg tablet. The data that support this waiver include:

- The 20/12.5 mg to-be-marketed tablet is bioequivalent to the single entities.
- The pharmacokinetics are linear over the dosage range.
- Comparative dissolution profiles are similar in three media. F2 for CS-866 in water and pH 6.8 were 75.4. The F2 for CS-866 in pH 1.2 and for HCTZ were not calculated because of very rapid dissolution. The dissolution profiles are shown below for CS-866.

20/12.5 mg Dissolution

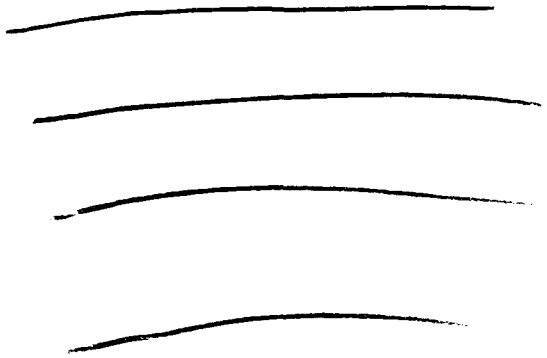


40/25 mg Dissolution

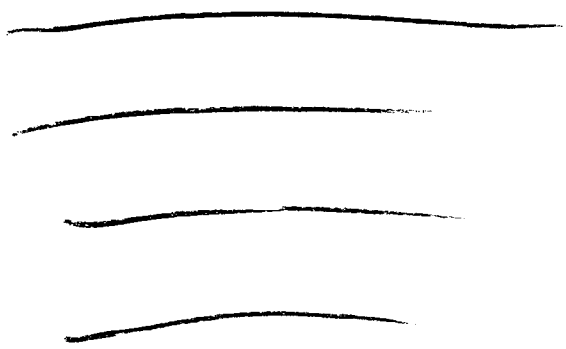


The dissolution profiles are shown below for HCTZ.

20/12.5 mg Dissolution



40/25 mg Dissolution



- The compositions of the 40/12.5 mg (reference) and the 40/25 mg are proportionally similar. The difference in HCTZ is

Ingredient	40/12.5 mg tablet	40/25 mg tablet
CS 866[1]	40 mg	40 mg
Hydrochlorothiazide	12.5 mg	25 mg
Microcrystalline cellulose		
Lactose.		
Hydroxypropyl cellulose		
Magnesium Stearate		
Tablet Core Weight		
Coated Tablet Weight		
Tablet shape	Oval	Oval
Tablet Core Dimensions	15 x 7 mm	15 x 7 mm

4.3.1.3 Are the sponsor's recommended dissolution specifications and methodology acceptable?

Sponsor's Recommended Dissolution Specifications and Methodology for CS-866

20/12.5 mg tablet

Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than — at —

40/12.5 mg and 40/25 mg tablet

Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than — at —

Sponsor's Recommended Dissolution Specifications and Methodology for HCTZ

Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than — at —

The sponsor's recommended dissolution specifications and method for olmesartan medoxomil/HCTZ are unacceptable for the following reasons:

- The sponsor's dissolution was corrected for a degradation of — Dissolution should be unaltered.
- The sponsor's Q of — is too low. A drug product that releases only — is less likely to be bioequivalent than a product that releases 100 %. Therefore we are recommending a Q of —

The recommended dissolution specifications and method for olmesartan medoxomil/HCTZ are:

CS-866

Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than —, at 45 minutes

HCTZ

Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than —, at 15 minutes

5 LABELING

5.1 Are the proposed labeling recommendations appropriate?

The labeling for the clinical pharmacology section is composed of the Benicar and hydrochlorothiazide labels. There are no further labeling recommendations.

6 APPENDIX

6.1 Proposed labeling

16 Draft Labeling Page(s) Withheld

6.2 Individual Study Reviews

6.2.1 Pharmacokinetics – Healthy Volunteers - Bioequivalence

6.2.1.1 866-126: 20 /12.5 mg BE of olmesartan tablets plus HCTZ capsules or HCTZ tablets and olmesartan/HCTZ tablets

Study: 866-126 Volume: 1.35 p. 1 – 3397

Title: A randomized, open-label, three-way crossover bioequivalence study of CS-866 tablets plus hydrochlorothiazide capsules or tablets and CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers

Principal Investigator: [redacted]
Study site: [redacted]

First patient enrolled: August 10, 2001
Last patient completed: August 28, 2001

Objectives: To determine the bioequivalence of the clinical trial supply of CS-866 20 mg tablets and HCTZ 12.5 mg capsules or tablets administered orally in combination versus oral administration of the market image single tablet formulation of CS-866/HCTZ

Study design: randomized, open-label, three-way crossover, single dose study

Duration: approximately 30 days – 88 hours in the clinic on three separate visits, 7 day washout period between visits

Population: Thirty subjects (17 males, 13 females) completed the study, however 36 subjects were planned and only 33 were enrolled.

Table 13. Study 866-126: Demographics of enrolled subjects

males/females	17/16
Age (yrs)	26.5 ± 8 (18 – 44)
Weight (kg)	71 ± 12 (52 – 96)
Height (cm)	168 ± 10 (150 – 185)
Race n (%)	12 (36 %) Caucasian 14 (42 %) Black 1 (3 %) Asian 5 (15 %) Hispanic

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different combinations of CS-866 and HCTZ at each of three different dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose. Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ

concentrations. Urine was also collected and the volume was recorded, however it was not quantified.

Other medications: Except for oral contraceptives, other medications were not allowed during the study. Any prescription drug was prohibited within 14 days of the dose and any nonprescription drug was prohibited within seven days of the dose.

Treatment: single dose of
A) 20 mg CS-866 investigational tablet + 12.5 mg HCTZ capsule
B) 20 mg CS-866 investigational tablet + 12.5 mg HCTZ tablet
C) 20 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet

Formulation: Sankyo Pharma Development supplied Study drug.

- 20 mg CS-866 investigational tablet – batch #B99T20, size
- 12.5 mg HCTZ capsule – batch #015103 – US commercial supply,
- 12.5 mg HCTZ tablet – batch #2145601 – European commercial supply,
- 20 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet – batch #3139V01004, size

Assay: RNH-6270 was determined in plasma by Concentrations of HCTZ were determined in plasma using a validated method.

Table 14. Study 866-126: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270				
HCTZ				

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

Natural-log transformed PK parameters were analyzed by ANOVA. The formulation differences (C vs. A and C vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) bioequivalence criteria.

Results: Both test formulations (A and B) were bioequivalent to the to-be-marketed formulation (C) (see tables).

Table 15. Study 866-126: 20/12.5 mg RNH-6270 Point Estimates and 90 % CI

	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	Cmax
C vs. A	1.04 (0.99 – 1.10)	1.04 (0.98 – 1.10)	1.08 (1.02 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.07 (1.01 – 1.13)	1.08 (1.01 – 1.15)

Table 16. Study 866-126: 20/12.5 mg HCTZ Point Estimates and 90 % CI

	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	Cmax
C vs. A	1.04 (0.98 – 1.10)	1.05 (0.99 – 1.10)	1.06 (0.98 – 1.15)
C vs. B	1.07 (1.01 – 1.13)	1.08 (1.02 – 1.14)	1.06 (0.98 – 1.15)

The plasma concentrations for RNH-6270 and HCTZ are shown in the figures and tables that follow. Generally, RNH-6270 and HCTZ concentrations are higher in the combination tablet, however these differences were insignificant.

Figure 1. Study 866-126: RNH-6270 Cp (mean ±SD)

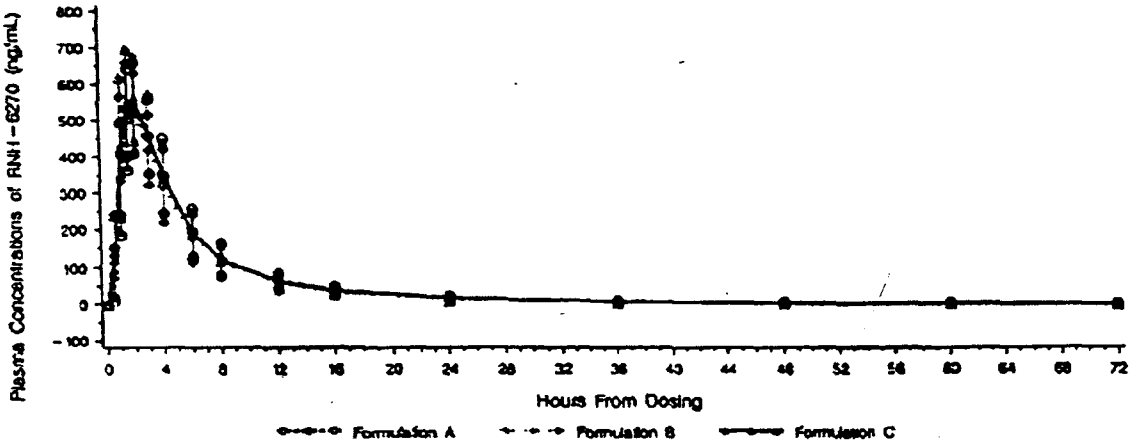


Table 17. Study 866-126: 20/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
$AUC_{(0-t)}$ (ng*h/mL)	3463 ± 799	3603 ± 817	3373 ± 781
$AUC_{(0-\infty)}$ (ng*h/mL)	3561 ± 843	3695 ± 872	3459 ± 806
Cmax (ng/mL)	560 ± 123	606 ± 137	560 ± 117
Tmax (h)	2.0 (1.5 – 4.0)	2.0 (1.0 – 3.0)	1.5 (1.0 – 4.0)
T ½ (h)	21.4 ± 17.8	20.4 ± 16.3	21.6 ± 13.5
k_{el}	0.04 ± 0.02	0.05 ± 0.02	0.04 ± 0.02

mean ± SD or median (range)

Figure 2. Study 866-126: HCTZ Cp (mean ± SD)

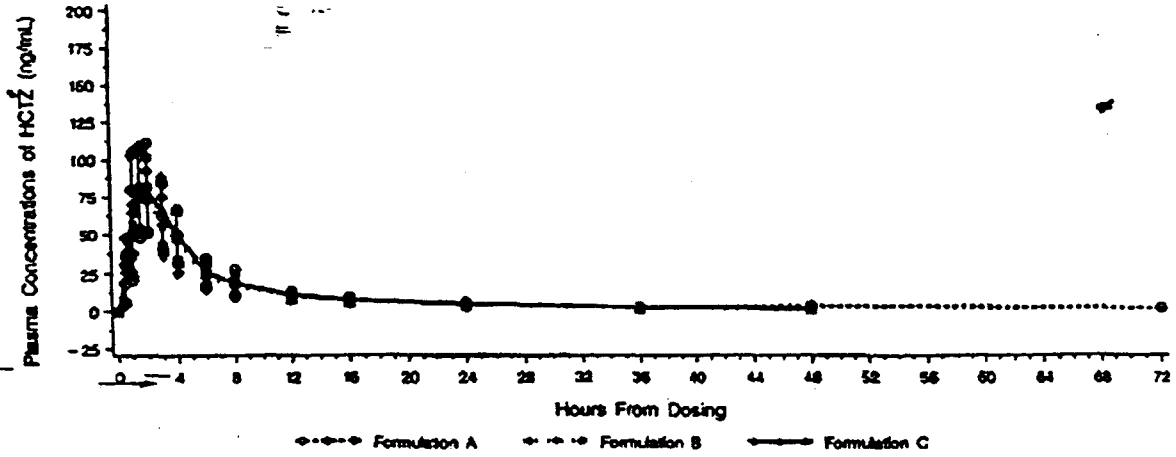


Table 18. Study 866-126: 20/12.5 mg HCTZ PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	507 ± 136	522 ± 121	495 ± 138
AUC $_{(0-\infty)}$ (ng*h/mL)	566 ± 140	585 ± 118	547 ± 134
Cmax (ng/mL)	90 ± 30	94 ± 32	89 ± 28
Tmax (h)	2.0 (1.0 – 4.0)	1.5 (1.0 –3.0)	1.5 (1.0 – 4.0)
T ½ (h)	11.3 ± 7.2	11.0 ± 2.9	10.6 ± 2.0
k_{el}	0.07 ± 0.02	0.07 ± 0.02	0.07 ± 0.01

mean ± SD or median (range)

Headache, dizziness and nausea were the most commonly reported AEs. One subject withdrew because of nausea and vomiting.

Sponsor's Conclusions: The single drug entities given together as CS-866 20 mg and HCTZ 12.5 mg tablet or 12.5 mg capsule are bioequivalent to the 20/12.5 mg to-be-marketed tablet.

Reviewer's Comments: The tablet batch size of the lot (3139v01004) used for the pivotal BE study was [redacted]. The tablet production size of the 20/12.5 mg tablet is [redacted] tablets. It is noted that the tablet batch size used in the BE study is less than the recommended [redacted] of the tablet production size (i.e., the tablet batch size should be at least [redacted] tablets).

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions.

6.2.1.2 866-139: [redacted] BE of olmesartan tablets plus HCTZ capsules or HCTZ tablets and olmesartan/HCTZ tablets

Study: 866-139 Volume: 16 – 29 (March 14, 2003) p. 1 – 1821

Title: A randomized, open-label, three-way crossover bioequivalence study of 20 mg CS-866 tablets plus [redacted] hydrochlorothiazide capsules or tablets and [redacted] CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator: [redacted]
Study site: [redacted]

First patient enrolled: November 16, 2002
Last patient completed: December 6, 2002

Objectives: To determine the bioequivalence of the clinical trial supply of CS-866 20 mg tablets and HCTZ [redacted] capsules or tablets administered orally in combination versus oral administration of the market image single tablet formulation of CS-866/HCTZ

Study design: randomized, open-label, three-way crossover, single dose study

Duration: approximately eleven days (264 hours) – 88 hours in the clinic on three separate visits, 7 day washout period between treatment sequences

Population: Thirty-two subjects completed the study. Thirty-six subjects (26 males, 10 females) were enrolled. Unlike the other clinical pharmacology studies, this study contained a higher percentage of Blacks compared to Whites.

Table 19. Study 866-139: Demographics of enrolled subjects

males/females	26 males, 10 females
Age (yrs)	30 ± 8 (18 – 45)
Weight (kg)	72.3 ± 10.3 (50.3 – 90)
Height (cm)	174.8 ± 9.5 (152 – 193)
Race n (%)	5 (14 %) Caucasian 23 (64 %) Black 2 (6 %) Asian 5 (14 %) Hispanic 1 (3 %) American Indian

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different combinations of CS-866 and HCTZ at each of three different dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose. Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study.

Treatment: single dose of
A) 20 mg CS-866 investigational tablet + [redacted] mg HCTZ capsule (US supply)
B) 20 mg CS-866 investigational tablet + [redacted] mg HCTZ tablet (European supply)
C) 20 mg CS-866/ [redacted] HCTZ to-be-marketed combination tablet

Formulation: Sankyo Pharma Development supplied Study drug.
- 20 mg CS-866 investigational tablet – batch #2234V01007, size [redacted] Sankyo Pharma GmbH
- 12.5 mg HCTZ capsule – batch #032658, commercial size. [redacted]
- [redacted] HCTZ tablet – batch #3998V01008, commercial size. [redacted]
- 20 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet – batch #3148V01002, size [redacted]

Assay: RNH-6270 was determined in plasma by [redacted] Concentrations of HCTZ were determined in plasma using a validated [redacted] method.

Table 20. Study 866-139: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270	[redacted]			
HCTZ	[redacted]			

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

Natural-log transformed PK parameters were analyzed by ANOVA. The treatment differences (C vs. A and C vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the treatment bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) to test bioequivalence.

SAS version 6.12 was used for analysis.

Results: Both test formulations (A and B) were bioequivalent to the to-be-marketed formulation (C) (see tables) for RNH-6270 concentrations. HCTZ total exposure in all treatments was bioequivalent. HCTZ peak exposure was bioequivalent between the [redacted] market tablet (Treatment C) and the 20 mg CS-866 and [redacted] HCTZ tablet European clinical supply (Treatment B). However, the point estimate (90 % CI) for the ratio of the peak exposure of

HCTZ between the to-be-marketed tablet and Treatment A (US clinical supply) was 0.85 (0.77, 0.93).

Table 21. Study 866-139: [redacted] mg RNH-6270 Point Estimates and 90 % CI

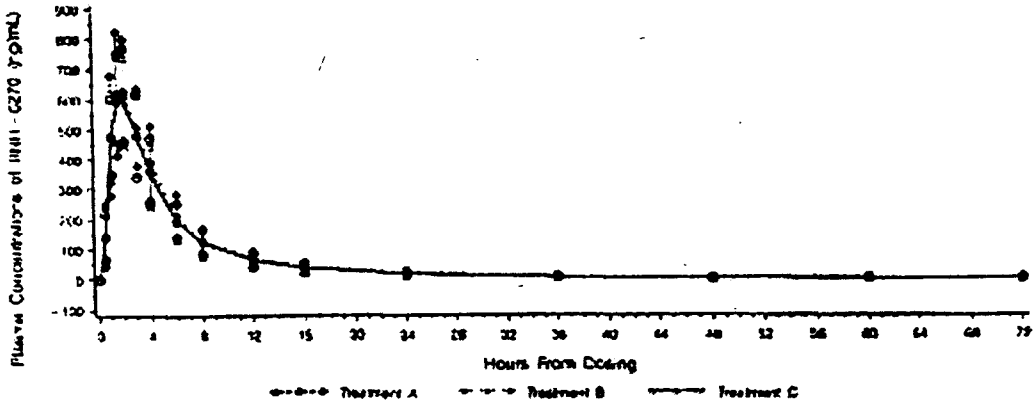
	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
C vs. A	0.99 (0.92 – 1.05)	0.98 (0.92 – 1.05)	1.01 (0.94 – 1.08)
C vs. B	0.95 (0.89 – 1.01)	0.94 (0.88 – 1.00)	0.96 (0.90 – 1.03)

Table 22. Study 866-139: [redacted] mg HCTZ Point Estimates and 90 % CI

	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
C vs. A	0.91 (0.85 – 0.96)	0.92 (0.87 – 0.97)	*0.85 (0.77 – 0.93)*
C vs. B	0.94 (0.89 – 1.00)	0.95 (0.90 – 1.01)	0.93 (0.85 – 1.02)

The plasma concentrations for RNH-6270 and HCTZ are shown in the figures and tables that follow.

Figure 3. Study 866-139: RNH-6270 Cp (mean ±SD)



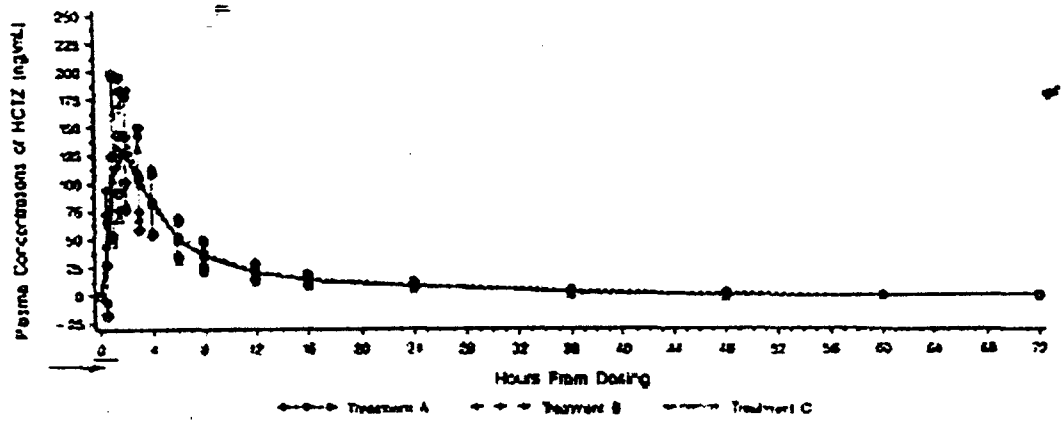
Treatment A = 20 mg CS-866 Tablet + [redacted] mg HCTZ Capsule(U.S.);
Treatment B = 20 mg CS-866 Tablet + [redacted] mg Tablet(Europe);
Treatment C = 20 mg CS-866 [redacted] Combination Tablet.
Source Data: Table 3.1

Table 23. Study 866-139: [redacted] mg RNH-6270 PK parameters

Formulation [redacted]	A (single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	3716 ± 938	3666 ± 878	3850 ± 923
AUC $_{(0-\infty)}$ (ng*h/mL)	3780 ± 957	3727 ± 900	3727 ± 900
Cmax (ng/mL)	632 ± 153	635 ± 137	635 ± 138
Tmax (h)	2.0	1.5	1.5
T ½ (h)	18.6 ± 10.7	18.5 ± 8.9	18.5 ± 8.9

mean ± SD or median

Figure 4. Study 866-139: HCTZ Cp (mean ± SD)



Treatment A = 20 mg CS-866 Tablet + [redacted] mg HCTZ Capsule(US);
Treatment B = 20 mg CS-866 Tablet + [redacted] HCTZ Tablet(Europe);
Treatment C = 20 mg CS-866/[redacted] Combination Tablet.
Source Data: Table 3.2

Table 24. Study 866-139: [redacted] ng HCTZ PK parameters

Formulation	A/(single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	1053 ± 308	969 ± 317	1019 ± 308
AUC $_{(0-\infty)}$ (ng*h/mL)	1094 ± 306	1015 ± 314	1061 ± 305
Cmax (ng/mL)	173 ± 62	148 ± 52	160 ± 61
Tmax (h)	1.5	1.8	2.0
T ½ (h)	10.5 ± 1.7	11.3 ± 2.3	10.5 ± 2.4

mean ± SD or median (range)

Headache was the most commonly reported AEs. No subject withdrew due to an AE.

Sponsor's Conclusions:

- The RNH-6270 in all treatments was bioequivalent.
- HCTZ total exposure in all treatments was bioequivalent.
- HCTZ peak exposure was bioequivalent between the [redacted] market tablet (Treatment C) and the 20 mg CS-866 and [redacted] HCTZ tablet European clinical supply (Treatment B). However, the point estimate (90 % CI) for the ratio of the peak exposure of HCTZ between the to-be-marketed tablet and Treatment A (US clinical supply) was 0.85 (0.77, 0.93). This small decrease in peak exposure is not considered clinically significant.

Reviewer's Comments: The tablet batch size of the lot (3148v01002) used for the pivotal BE study was [redacted] which is greater than [redacted] of the production batch size. This is acceptable. The tablet production size of the [redacted] mg tablet is [redacted] tablets.

Reviewer's Conclusions:

- The AUC and Cmax of RNH-6270 in the [redacted] mg / [redacted] tablet are similar to the single entities.
- The HCTZ AUC in the [redacted] mg / [redacted] tablet is similar to that in the single HCTZ tablet.
- The HCTZ Cmax in the to-be-marketed tablet was on average 15 % lower than the single HCTZ US tablet. The 90 % CI for the ratio of the peak exposure of HCTZ between the to-be-marketed tablet and the US clinical supply was (0.77, 0.93). This small decrease in peak exposure is not considered clinically significant.

6.2.1.3 866-138: 40 /12.5 mg BE of olmesartan tablets plus HCTZ capsules or HCTZ tablets and olmesartan/HCTZ tablets

Study: 866-138 Volume: 1-15 (March 14, 2003) p. 1 – 1807

Title: A randomized, open-label, three-way crossover bioequivalence study of 40 mg CS-866 tablets plus 12.5 mg hydrochlorothiazide capsules or tablets and 40/12.5 mg CS-866/hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator: [redacted]
Study site: [redacted]

First patient enrolled: December 21, 2002
Last patient completed: January 7, 2003

Objectives: To determine the bioequivalence of the clinical trial supply of CS-866 40 mg tablets and HCTZ 12.5 mg capsules or tablets administered orally in combination versus oral administration of the market image single tablet formulation of CS-866/HCTZ

Study design: randomized, open-label, three-way crossover, single dose study

Duration: approximately eleven days (264 hours) – 88 hours in the clinic on three separate visits, 7 day washout period between treatment sequences

Population: Thirty-eight subjects (26 males, 12 females) completed the study, however 42 (27 males, 15 females) were enrolled.

Table 25. Study 866-138: Demographics of enrolled subjects

males/females	27/15
Age (yrs)	28.4 ± 8 (19 – 44)
Weight (kg)	74.6 ± 11.7 (52.3 – 99.1)
Height (cm)	175.5 ± 10.6 (152 – 193)
Race n (%)	32 (76 %) Caucasian 3 (7 %) Black 2 (5 %) Asian 3 (7 %) Hispanic 2 (5 %) Other

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different combinations of CS-866 and HCTZ at each of three different dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose. Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study.

Treatment: single dose of

A) 40 mg CS-866 investigational tablet + 12.5 mg HCTZ capsule – US supply
B) 40 mg CS-866 investigational tablet + 12.5 mg HCTZ tablet – European supply
C) 40 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet

Formulation: Sankyo Pharma Development supplied Study drug.

- 40 mg CS-866 investigational tablet – batch #B00T18, size , manufactured by Sankyo Co., Ltd.
- 12.5 mg HCTZ capsule – batch #032658, commercial size,
- 12.5 mg HCTZ tablet – batch #2145601, commercial size,
- 40 mg CS-866/12.5 mg HCTZ to-be-marketed combination tablet – batch #3140V01019, size manufactured by Sankyo Pharma GmbH

Assay: RNH-6270 was determined in plasma by Concentrations of HCTZ were determined in plasma using a validated method.

Table 26. Study 866-138: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270				
HCTZ				

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

Natural-log transformed PK parameters were analyzed by ANOVA. The formulation differences (C vs. A and C vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) bioequivalence criteria.

Results: Both test formulations (A and B) were bioequivalent to the to-be-marketed formulation (C) (see tables).

Table 27. Study 866-138: 40/12.5 mg RNH-6270 Point Estimates and 90 % CI

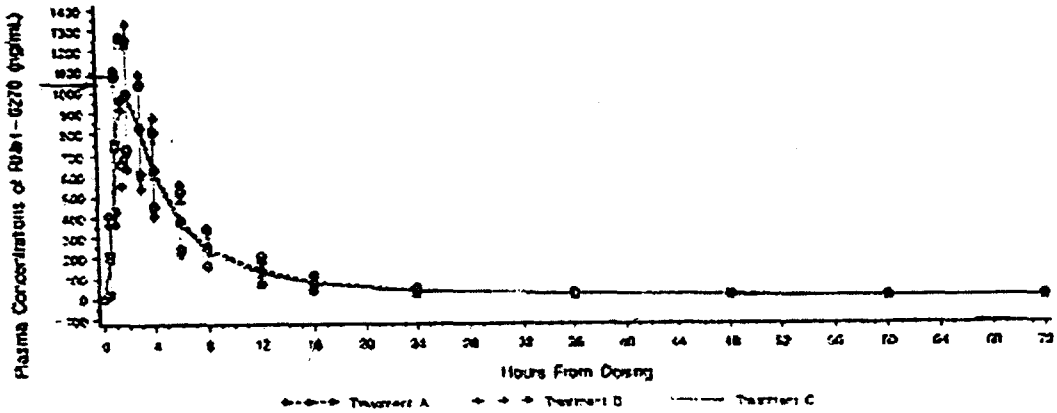
	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
C vs. A	0.97 (0.90 – 1.04)	0.98 (0.91 – 1.05)	1.03 (0.96 – 1.11)
C vs. B	0.97 (0.91 – 1.05)	0.99 (0.92 – 1.06)	1.03 (0.96 – 1.11)

Table 28. Study 866-138: 40/12.5 mg HCTZ Point Estimates and 90 % CI

	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
C vs. A	0.95 (0.90 – 1.00)	0.96 (0.92 – 1.00)	0.97 (0.90 – 1.04)
C vs. B	0.97 (0.92 – 1.02)	0.96 (0.92 – 1.01)	1.01 (0.93 – 1.08)

The plasma concentrations for RNH-6270 and HCTZ are shown in the figures and tables that follow.

Figure 5. Study 866-138: RNH-6270 Cp (mean ±SD)



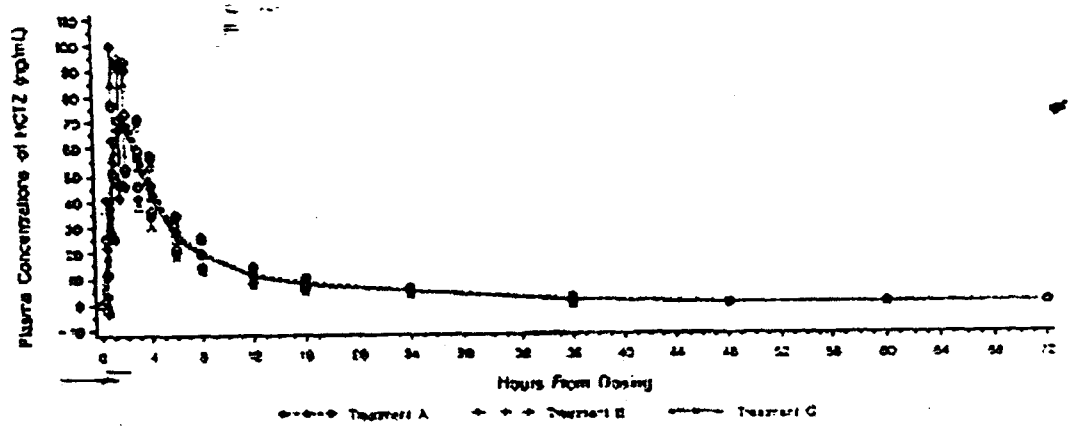
Treatment A - 40 mg CS - 266 Tablet + 12.5 mg HCTZ Capsule(U.S.).
Treatment B - 40 mg CS - 266 Tablet + 12.5 mg HCTZ Tablet(Europe).
Treatment C - 40 mg CS - 266/12.5 mg HCTZ Combination Tablet.
Source Data: Table 3.1

Table 29. Study 866-138: 40/12.5 mg RNH-6270 PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	6633 ± 1704	6362 ± 2056	6601 ± 2056
AUC $_{(0-\infty)}$ (ng*h/mL)	6759 ± 1699	6569 ± 1526	6743 ± 2091
Cmax (ng/mL)	1048 ± 289	1071 ± 270	1050 ± 331
Tmax (h)	2.0	1.5	2.0
T ½ (h)	19.3 ± 16.0	21.4 ± 21.0	19.0 ± 13.4

mean ± SD or median (range)

Figure 6. Study 866-138: HCTZ Cp (mean ±SD)



Treatment A - 40 mg CS-866 Tablet + 12.5 mg HCTZ Capsule(U.S.).
Treatment B - 40 mg CS-866 Tablet + 12.5 mg HCTZ Tablet(European).
Treatment C - 40 mg CS-866/12.5 mg HCTZ Combination Tablet
Source Data: Table 37

Table 30. Study 866-138: 40/12.5 mg HCTZ PK parameters

Formulation	A (single entity)	C (combination tablet)	B (single entity)
AUC $_{(0-t)}$ (ng*h/mL)	493 ± 100	472 ± 108	489 ± 122
AUC $_{(0-\infty)}$ (ng*h/mL)	542 ± 96	522 ± 104	542 ± 121
Cmax (ng/mL)	80 ± 22	78 ± 22	80 ± 30
Tmax (h)	1.75	1.5	1.75
T ½ (h)	9.6 ± 1.8	10.0 ± 1.9	10.2 ± 1.7

mean ± SD or median (range)

Headache and dizziness were the most commonly reported AEs.

Sponsor's Conclusions: The single entities given together as CS-866 40 mg and HCTZ 12.5 mg tablet or 12.5 mg capsule are bioequivalent to the 40/12.5 mg to-be-marketed tablet.

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions.

6.2.1.4 866-134: HCTZ 12.5 mg BE of capsule and overencapsulated capsule

Study: 866-134 Volume: 1.52 p. 1 – 1184

Title: A randomized, open-label, two-way crossover bioequivalence study of hydrochlorothiazide capsules in healthy adult volunteers

Principal investigator:
Study site:

First patient enrolled: December 14, 2001
Last patient completed: December 23, 2001

Objectives: To determine the bioequivalence of HCTZ 12.5 mg following oral administration of two different encapsulated dosage forms

Study design: randomized, open-label, two-way, crossover, single dose study

Duration: approximately 14 days – 64 hours in the clinic on two separate visits, 7 day washout period between visits

Population: Twenty-nine subjects (16 males, 13 females) completed the study, however 30 were enrolled.

Table 31. Study 866-134: Demographics of enrolled subjects

males/females	16/14
Age (yrs)	24.5 ± 6 (18 – 44)
Weight (kg)	70 ± 11 (47 – 89)
Height (cm)	171 ± 10 (152 – 188)
Race n (%)	15 (50 %) Caucasian 12 (40 %) Black 3 (10 %) Asian

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of two different HCTZ dose forms at each of two dosing periods. Subjects spent 64 hours in the clinic during each visit for a total of 128 hours during the study. A seven day washout period separated each dose.

Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study. Any prescription drug was prohibited within 14 days of the dose and any nonprescription drug was prohibited within seven days of the dose.

Treatment: single dose of
A) 12.5 mg HCTZ capsule used in study 866-126
B) 12.5 mg HCTZ overencapsulated capsule used in study 866-318 phase 3 factorial for blinding purposes

Formulation:

- 12.5 mg HCTZ tcapsule – batch #015103 – US commercial supply – reference.
- 12.5 mg HCTZ overencapsulated (with a capsule – batch #1006138/02, size test.

, was provided to the study site by also overencapsulated HCTZ capsules by using capsules.

Assay: Concentrations of HCTZ were determined in plasma using a validated method.

Table 32. Study 866-134: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
HCTZ				

Pharmacokinetics: Plasma samples for HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 post dose.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

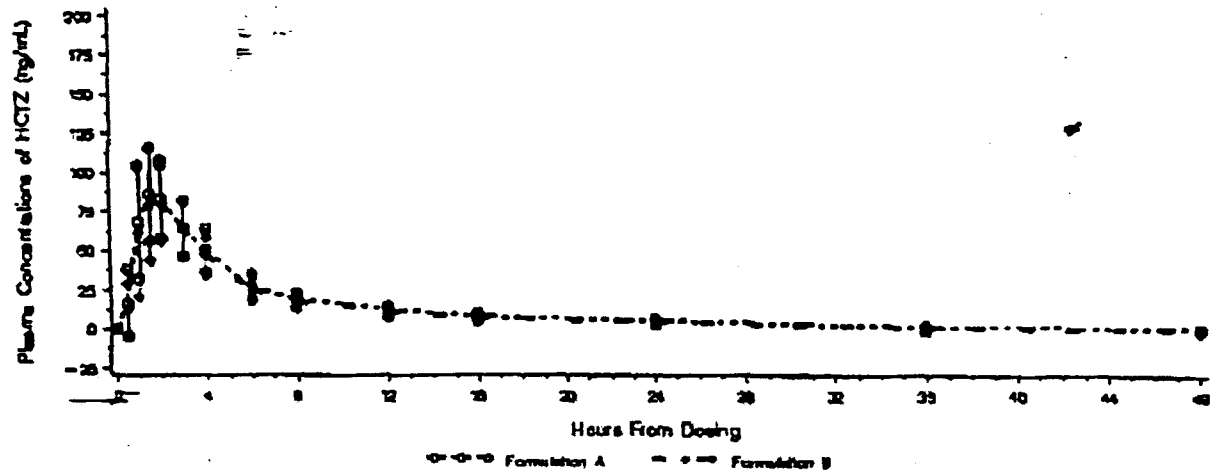
Natural-log transformed PK parameters were analyzed by ANOVA. The formulation differences (A vs. B) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) bioequivalence criteria.

Results: The two formulations of HCTZ 12.5 mg capsule are bioequivalent.

Table 33. Study 866-134: HCTZ Point Estimates and 90 % CI

	$AUC_{(0-t)}$	$AUC_{(0-\infty)}$	Cmax
A vs. B	0.98 (0.93 – 1.02)	0.98 (0.93 – 1.02)	1.01 (0.94 – 1.08)

Figure 7. Study 866-134 HCTZ Cp (mean ±SD)



Formulation A = 12.5 mg HCTZ Market–Image Capsule
Formulation B = 12.5 mg HCTZ Over–Encapsulated Market–Image Capsule

Table 34. Study 866-134: HCTZ PK parameters

Formulation	A (to-be-marketed cap)	B (overencapsulated cap)
AUC $_{(0-t)}$ (ng*h/mL)	550 ± 134	532 ± 108
AUC $_{(0-\infty)}$ (ng*h/mL)	604 ± 134	582 ± 102
Cmax (ng/mL)	96 ± 29	96 ± 27
Tmax (h)	1.5 (1.0 – 4.0)	1.5 (1.0 – 4.0)
T ½ (h)	10.1 ± 1.8	10.8 ± 2.9
k_{el}	0.07 ± 0.01	0.07 ± 0.02

mean ± SD or median (range)

Headache, reported by four subjects was the most frequently reported AE.

Sponsor's Conclusions: The two capsule formulations of HCTZ 12.5 mg are bioequivalent.

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions.

6.2.2 Pharmacokinetics – Healthy volunteers – dose proportionality

6.2.2.1 866-127: Dose proportionality: [redacted] 20/12.5 and 40/12.5 mg

Study: 866-127 Volume: 1.45 p. 1 – 2050

Title: A randomized, open-label, three-way crossover study of different strength of CS-866 - hydrochlorothiazide combination tablets in healthy adult volunteers

Principal investigator: [redacted]
Study site: [redacted]

First patient enrolled: September 7, 2001
Last patient completed: September 24, 2001

Objectives: To evaluate the comparative bioequivalence of HCTZ and the dose proportionality of CS-866 following oral administration of three different tablet formulations of CS-866/HCTZ: [redacted], 20/12.5 and 40/12.5 mg.

Study design: randomized, open-label, three-way, crossover, single dose study

Duration: approximately 28 days – 88 hours in the clinic on three separate visits, 7 day washout period between visits

Population: Eighteen subjects were enrolled and completed the study.

Table 35. Study 866-127: Demographics

males/females	9/9
Age (yrs)	31.6 ± 8 (20 – 43)
Weight (kg)	73 ± 14 (52 – 99)
Height (cm)	172 ± 10 (152 – 188)
Race n (%)	9 (50 %) Caucasian 6 (33 %) Black 1 (5 %) Asian 2 (11 %) Hispanic

mean ±SD (range)

Procedure: Subjects were randomized to receive a single dose of one of three different CS-866/HCTZ doses at each of three dosing periods. Subjects spent 88 hours in the clinic during each visit for a total of 264 hours during the study. A seven day washout period separated each dose.

Subjects fasted overnight for 12 hours and remained fasting until 4 hours post dose. Plasma was collected to quantitate RNH-6270 and HCTZ concentrations.

Other medications: Except for oral contraceptives, other medications were not allowed during the study. Any prescription drug was prohibited within 14 days of the dose and any nonprescription drug was prohibited within seven days of the dose.

Treatment: single dose of
A) CS-866/HCTZ
B) CS-866/HCTZ 20/12.5 mg to-be-marketed capsule
C) CS-866/HCTZ 40/12.5 mg to-be-marketed capsule

Formulation: Study drug was supplied by
A) CS-866/HCTZ mg to-be-marketed capsule – batch #3138V01006
B) CS-866/HCTZ 20/12.5 mg to-be-marketed capsule – batch #3139V01004
C) CS-866/HCTZ 40/12.5 mg to-be-marketed capsule – batch #3140V01005

Assay: RNH-6270 was determined in plasma by Concentrations of HCTZ were determined in plasma using a validated method.

Table 36. Study 866-127: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270				
HCTZ				

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36, 48, 60 and 72 hours post dose. Urine was collected predose and at the following time intervals post-dose: 0-4, 4-12, 12-24, 24-48 and 48-72 hours postdose, but were only analyzed if necessary.

Plasma concentrations below the LLOQ were assigned a value of zero for calculations of average concentration at a given time period.

RNH-6270 AUCs and Cmax were used to assess dose proportionality using a power model. ANCOVA was performed on the log transformed PK data with subject (random effect), period and dose as factors, and ln(dose) as covariates. Estimates of the proportionality parameter (obtained from the slope estimate for natural log-transformed dose [ln(dose)] with its confidence interval (CI) were used to quantify the degree of non-proportionality. The sponsor declared dose proportionality if all of the 90 % CI for AUCs and Cmax were within the interval (0.68, 1.32).

For HCTZ, the natural-log transformed AUCs and Cmax were analyzed by ANOVA. The formulation differences (A vs. B, A vs. C, and B vs. C) and their corresponding 90 % CI were obtained from the analyses and were exponentiated to obtain the formulation bioequivalence ratios and their corresponding 90 % CIs. The 90 % CIs were compared with (0.8, 1.25) to test bioequivalence hypotheses.

Results: The RNH-6270 in the combination tablets were dose proportional. (See table.)

Table 37. Study 866-127: RNH-6270 90 % CI for dose proportionality

AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
0.853 (0.803 – 0.904)	0.853 (0.803 – 0.902)	0.798 (0.749 – 0.847)

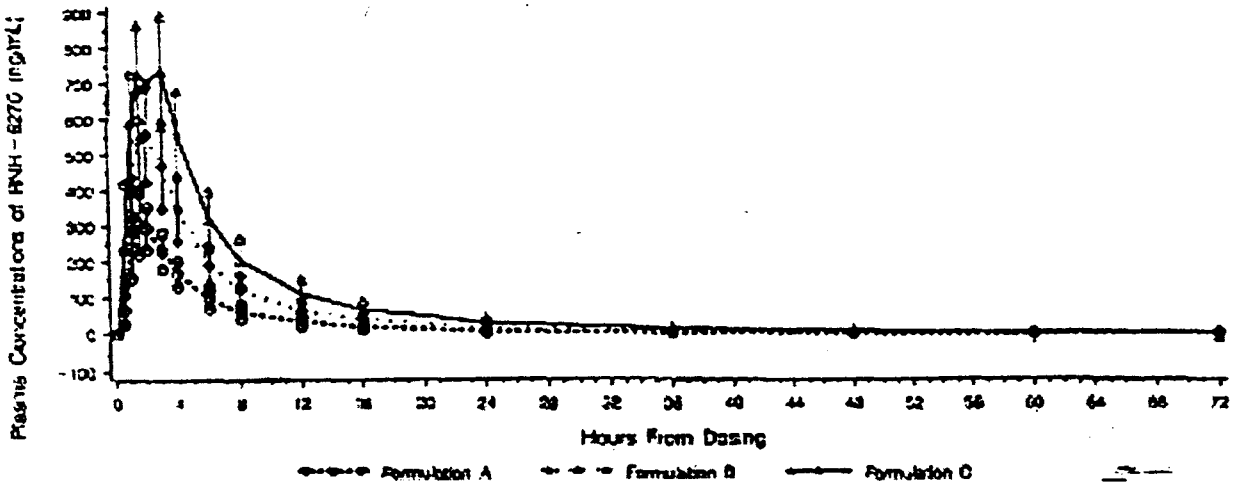
RNH-6270 PK and plasma concentrations are shown in the table and figure below.

Table 38. Study 866-127: RNH-6270 PK parameters

Formulation	A	B (20/12.5 mg)	C (40/12.5 mg)
AUC $_{(0-t)}$ (ng*h/mL)	1841 ± 468	3626 ± 955	5987 ± 1471
AUC $_{(0-\infty)}$ (ng*h/mL)	1912 ± 518	3760 ± 1046	6195 ± 1541
Cmax (ng/mL)	318 ± 76	587 ± 126	959 ± 202
Tmax (h)	1.5 (1.5 – 2.0)	2.0 (1.0 – 3.0)	2.0 (1.0 – 3.0)
T ½ (h)	28.7 ± 21.9	25.2 ± 24.1	25.3 ± 16.9
k_{el}	0.04 ± 0.02	0.04 ± 0.02	0.04 ± 0.02

mean ± SD or median (range)

Figure 8. Study 866-127: RNH-6270 Cp (mean ± SD)



The HCTZ in the combination tablets were bioequivalent. (See table.)

Table 39. Study 866-127: HCTZ Point Estimates and 90 % CI

	AUC $_{(0-t)}$	AUC $_{(0-\infty)}$	Cmax
A vs. B	1.01 (0.95 – 1.08)	1.01 (0.95 – 1.07)	1.03 (0.96 – 1.11)
A vs. C	1.05 (0.99 – 1.13)	1.04 (0.90 – 1.10)	1.06 (0.90 – 1.14)
B vs. C	1.04 (0.98 – 1.11)	1.03 (0.97 – 1.09)	1.02 (0.95 – 1.10)

HCTZ PK and plasma concentrations are shown in the table and figure below.

Figure 9. Study 866-127: HCTZ Cp (mean ±SD)

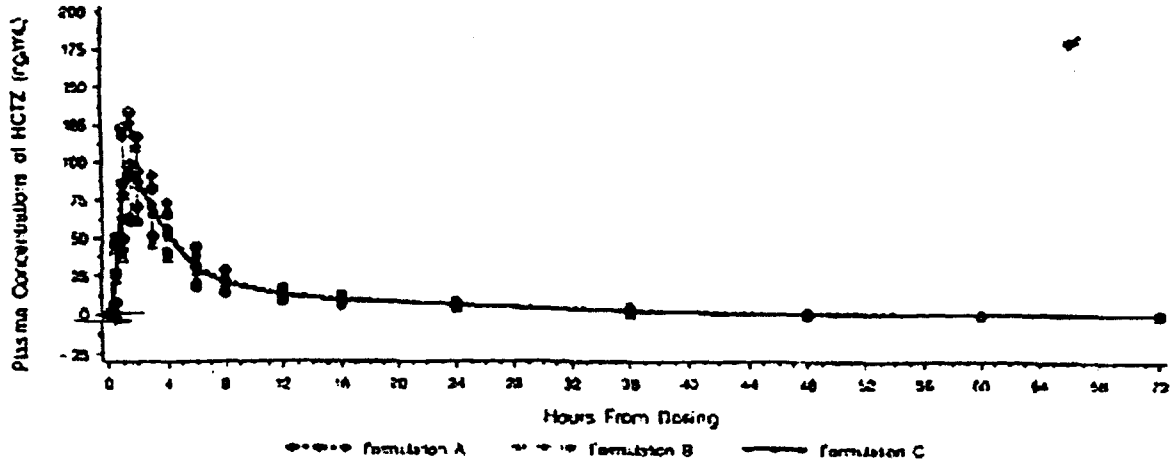


Table 40. Study 866-127 HCTZ PK parameters

Formulation	A	B (20/12.5 mg)	C (40/12.5 mg)
AUC $_{(0-t)}$ (ng*h/mL)	638 ± 171	630 ± 168	603 ± 151
AUC $_{(0-\infty)}$ (ng*h/mL)	679 ± 167	675 ± 166	654 ± 155
Cmax (ng/mL)	105 ± 30	104 ± 35	101 ± 33
Tmax (h)	1.5 (1.0 – 2.0)	1.5 (1.0 –3.0)	1.5 (1.0 – 3.0)
T ½ (h)	10.9 ± 2.0	10.6 ± 2.3	10.6 ± 1.5
k_{el}	0.07 ± 0.01	0.07 ± 0.01	0.07 ± 0.01

mean ± SD or median (range)

Headache was the most common AE reported.

Sponsor's Conclusions: The three dose strengths of CS-866 were dose proportional. HCTZ in the three formulations were bioequivalent.

Reviewer's Conclusions: The reviewer agrees with the sponsor's conclusions. The wide confidence intervals for RNH-6270 are likely because the study is underpowered.

6.2.3 Drug Interaction

6.2.3.1 SE-866 CMB/01: Interaction study between RNH-6270 and HCTZ using 20 mg of CS-866 and 25 mg of HCTZ tablets

Study: SE-866 CMB/01 Volume: 1.55 p. 1 – 3397

Title: The effect of the combination of the oral angiotensin II antagonist CS-866 and hydrochlorothiazide on pharmacokinetics, safety, and tolerability in healthy male subjects

Principal investigator:
Study site:

First patient enrolled: January 12, 2000
Last patient completed: April 27, 2000

Objectives: *Primary* - To assess the influence of CS-866 on the PK of HCTZ and the influence of HCTZ on RH-6270 at steady state.
Secondary – Evaluate the PK parameters of RNH-6270 and HCTZ in urine at steady state to assess the safety and tolerability of the different treatments using ECG, BP, pulse rate (abbreviated PR by the sponsor), and laboratory safety tests.

Study design: randomized, open-label, three-way crossover

Duration: 38 days: 7 treatment days (x 3 treatments) plus a 7 day washout period

Population: Twenty-four healthy male subjects were enrolled, however 23 completed the study. One subject withdrew due to an SAE.

Table 41. Study SE-866 CMB/01: Demographics of enrolled subjects

Males	24
Age (yrs)	32 ± 6 (21 – 42)
Weight (kg)	74 ± 12 (59 – 94)
Height (cm)	178 ± 8 (164 – 191)
Race n (%)	24 (100 %) Caucasian

mean ±SD (range)

Procedure: Subjects were randomized to receive one of three treatments for seven days. A 7-14 day washout period separated each treatment. Blood and urine were collected for pharmacokinetic assessments on the last dosing day (Day 7) of each treatment period.

Other medications: Other medications, including OTC medications were not allowed for seven days prior to and during the study.

Treatment: One dose was taken daily at 8:00 am (± 1 hour) for seven days following an overnight fast of ~12 hours. The dose was taken with 200 mL of water. On Day 7 of each treatment period, breakfast was served after the 4 hour blood sample, lunch was served seven hours after dosing and another meal was served 11 hours after dosing.

A) 20 mg CS-866 tablet
B) 25 mg HCTZ tablet (HCTZ [redacted]
C) 20 mg CS-866 tablet + 25 mg HCTZ tablet

Formulation:

- 20 mg CS-866 film-coated tablet – batch #2234v99001, manufactured by Sankyo Pharma GmbH
- 25 mg HCTZ tablet (HCTZ- [redacted] – batch #7080275t, manufactured by [redacted]

Assay: RNH-6270 was determined in plasma b[redacted] Concentrations of HCTZ were determined in plasma using a validated [redacted] method.

Table 42. Study se-866 cmb/01: Assay quality control

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270	[redacted]	[redacted]	[redacted]	[redacted]
HCTZ	[redacted]	[redacted]	[redacted]	[redacted]

Concentrations of RNH-6270 and HCTZ were determined in urine using a validatec [redacted] method.

Table 43. Study se-866 cmb/01: Assay quality control in urine

Drug	Precision	Accuracy	Linearity	Sensitivity
RNH-6270	[redacted]	[redacted]	[redacted]	[redacted]
HCTZ	[redacted]	[redacted]	[redacted]	[redacted]

Pharmacokinetics: Plasma samples for RNH-6270 and HCTZ were collected predose and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 hours after the last dose on Day 7. Samples were also collected predose on Days 1, 5 and 6 for RNH-6270 (treatments A and C) and HCTZ (treatments B and C).

Urine was collected on Day 7 at the following periods after the last dose: 0-4 h, 4-8 h, 8-12 h, and 12-24 h. Concentrations of HCTZ in urine were determined for Treatments B and C. Concentrations of RNH-6270 in urine were determined for Treatments A and C.

Primary PK parameters were derived from the plasma concentrations. Predose and terminal values below the LOQ were set to zero.

Equivalence of the PK parameters, AUC and Cmax were investigated using the two one-sided test approach by Schuirmann. SAS ver 6.12 was used for the analysis.90 % confidence intervals were constructed.

Results: The RNH-6270 in the two formulations were not bioequivalent. Although the point estimates were near unity, the confidence intervals were outside of the accepted 0.80 – 1.25.

Table 44. Study se866cmb/01: RNH-6270 Point Estimates (geometric mean) and 90 % CI

	$AUC_{(ss,t)}$	Cmax
C vs. A	1.02 (0.67 – 1.55)	1.00 (0.60 – 1.64)

The median plasma concentrations for RNH-6270 are shown in the figure below.

Figure 10. Study se-866 cmb/01: RNH-6270 Cp (median)

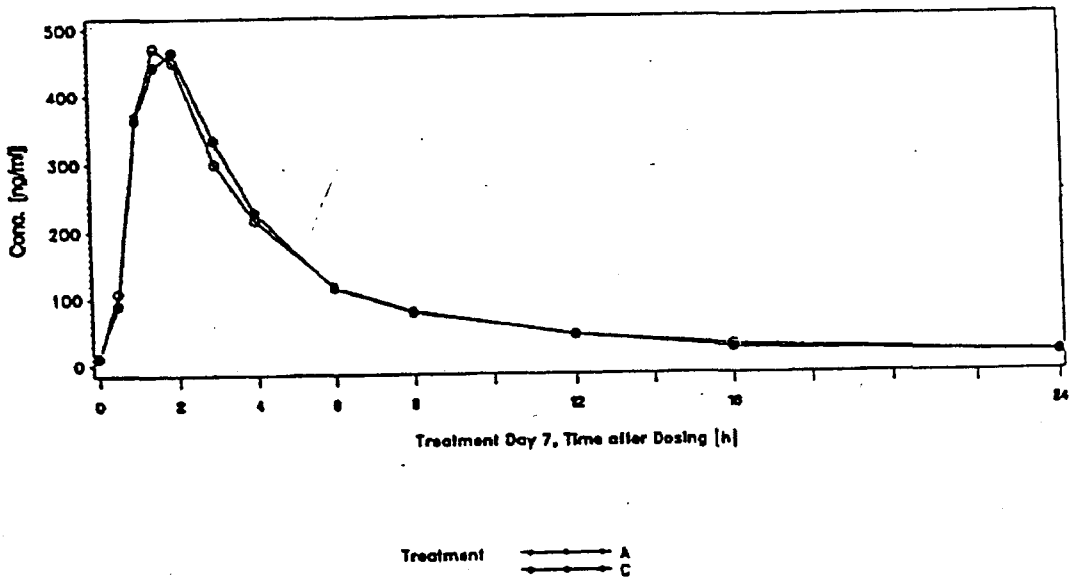


Table 45. Study se866cmb/01: RNH-6270 PK parameters (n=23)

Formulation	A (single)	C (combination)
$AUC_{(ss,t)}$ (ng*h/mL)	1755.1 (96 %)	1790.4 (93 %)
Cmax (ng/mL)	343.2 (128 %)	341.8 (118 %)
Tmax (h)	1.5 (0 –3.0)	1.5 (1.0 – 3.0)

Geometric mean (CV %)

The HCTZ in the two formulations were not bioequivalent. The bioavailability of HCTZ in the combination product is 20 % less than the single entity.

Table 46. Study se866cmb/01: HCTZ Point Estimates (geometric mean) and 90 % CI

	AUC $_{(ss,t)}$	Cmax
C vs. B	0.79 (0.58 – 1.08)	0.79 (0.60 – 1.04)

Figure 11. Study se-866 cmb/01: HCTZ Cp (median)

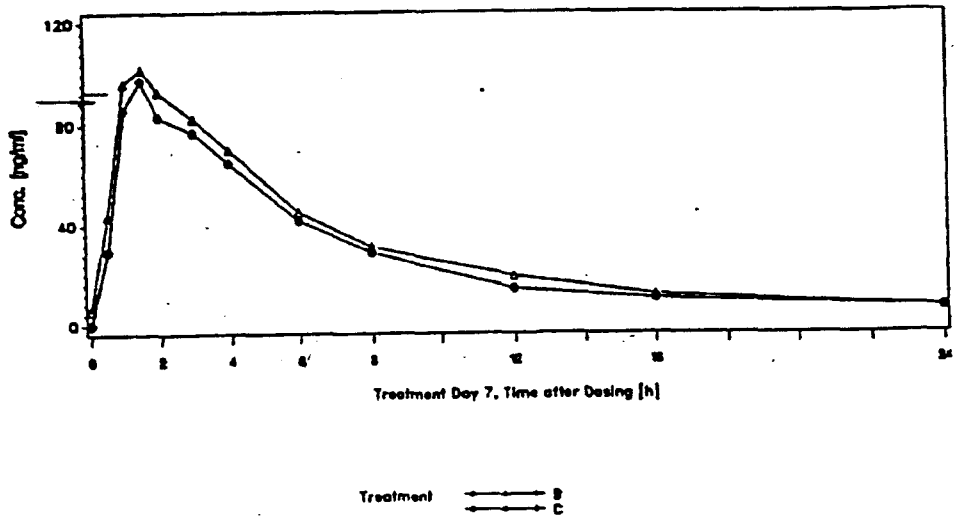


Table 47. Study se866cmb/01: HCTZ PK parameters (n=23)

Formulation	B (single)	C (combination)
AUC $_{(ss,t)}$ (ng*h/mL)	686.4 (44 %)	541.8 (91 %)
Cmax (ng/mL)	109.0 (50.0 %)	86.0 (73 %)
Tmax (h)	1.5 (0 –2.0)	1.5 (1.0 – 4.0)

Geometric mean (CV %)

Six subjects were excluded from the PK analysis because concentrations for RNH-6270 and or HCTZ were lower after monotherapy (Treatment A (CS-866) or B (HCTZ)) compared to combination treatment (Treatment C) or vice versa. The sponsor felt that these subjects' concentrations were inconsistent with the other subjects' concentrations.

LOWER AFTER COMBINATION THERAPY

1007 and 1010 - RNH-6270 and HCTZ plasma concentrations and urinary excretion were lower after combination treatment versus monotherapy.

1016 – RNH-6270 plasma concentrations and urinary excretion were lower after combination treatment compared to monotherapy. Plasma concentrations of HCTZ were

also considerably lower after combination treatment compared to monotherapy, but urinary excretion of HCTZ was essentially identical after either treatment.

LOWER AFTER MONOTHERAPY

1009 – HCTZ concentrations after monotherapy were below the LOQ and urinary HCTZ excretion was very low.

1022 – RNH-6270 and HCTZ plasma concentration and urinary excretion was lower after monotherapy compared to other subjects and compared to combination treatment.

1023 – RNH-6270 plasma concentrations and urinary excretion were lower after monotherapy compared to other subjects and compared to combination therapy. This subject also had higher plasma concentrations of HCTZ after monotherapy compared to combination therapy. Urinary excretion of HCTZ after monotherapy was low compared to other subjects.

After the sponsor removed the data of six subjects (1007, 1009, 1010, 1016, 1022 and 1023), the RNH-6270 AUC and Cmax PK parameters for the single entity were bioequivalent to that when given together. The same was true for HCTZ. However, rather than a 20 % decrease in bioavailability, there was only a 10 % decrease in bioavailability of HCTZ when given with CS-866 compared to HCTZ alone.

Sponsor's Conclusions: Coadministration of CS-866 with HCTZ had little effect on the pharmacokinetics of RNH-6270. Coadministration resulted in a decrease in the bioavailability of HCTZ of up to 20 %. The sponsor concludes that because of wide intra-subject variability, this decrease in bioavailability is unlikely to be of clinical significance.

Reviewer's Comments: Although the point estimates for RNH-6270 AUC and Cmax were near unity, the confidence intervals were outside of the accepted 90 % confidence interval of 0.80 – 1.25. This is most likely due to the high inter-subject variability. Rather than exclude the six subjects with anomalous concentrations, the sponsor should have accounted for the inter-subject variability and recruited more subjects.

Reviewer's Conclusions: This drug-drug interaction study found that HCTZ does not affect the pharmacokinetics of RNH-6270, however CS-866 decreased the bioavailability of HCTZ by up to 20 %. There is wide inter-subject variability in the pharmacokinetics of RNH-6270 and HCTZ.

6.3 Dissolution

Volume: 1.29 p. 33 – 74

Procedure: The sponsor tested twelve tablets in each dissolution profile. All [redacted] strengths of CS-866/HCTZ film-coated tablets ([redacted] mg, 20/12.5 mg, 40/12.5 mg, [redacted] g and 40/25 mg) manufactured by Sankyo Pharma GmbH were tested. Sampling times were at 10, 20, 30, and 45 minutes. The three media tested were water, JP fluid 1 (pH 1.2) and JP fluid 2 (40.83 g KH2PO4 + 5.6 g NaOH dissolved in 6 L purified water, pH 6.8). The paddle (USP Apparatus II) was used at a speed of 50 rpms.

Due to the hydrolysis of CS-866 to RNH-6270, the dissolution rate of CS-866 was corrected for the amount of RNH-6270 formed during the dissolution test. The amount of RNH-6270 was calculated as a percent of CS-866 and was added to the amount of CS-866. See below for more details.

Dissolution of CS-866

[redacted]	C – Content CS-866 [%] W – Weighing CS-866 Standard [mg] F_1 – Purity CS-866-Standards [%] F_2 – Water CS-866-Standards [%] D – Dose of CS-866 in Tablets [mg] A – Area CS-866 in Sample I – Area Int STD in Sample A_s – Area CS-866 in Standard I_s – Area Int STD in Standard Dil – Dilution Factor 2 for CS-866/HCTZ [redacted] mg and 40mg/25mg
[redacted]	V_0 – Volume of dissolution media [ml] V_s – Volume of stock standard solution [ml] D_1 – Dilution of stock standard solution D_2 – Dilution of sample

Calculation of RNH-6270

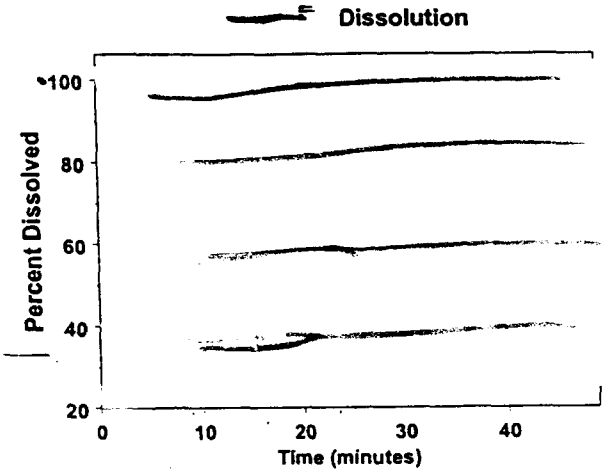
[redacted]	C_1 – Content RNH-6270 [%] W – Weighing CS-866 Standard [mg] F_1 – Purity CS-866-Standards [%] F_2 – Water CS-866-Standards [%] D – Dose of CS-866 in Tablets [mg] A – Area CS-866 in Sample I – Area Int STD in Sample A_s – Area CS-866 in Standard I_s – Area Int STD in Standard $RRF_{RNH-6270}$ – Relative Response Factor for RNH-6270* Dil – Dilution Factor 2 for CS-866/HCTZ [redacted] mg and 40mg/25mg

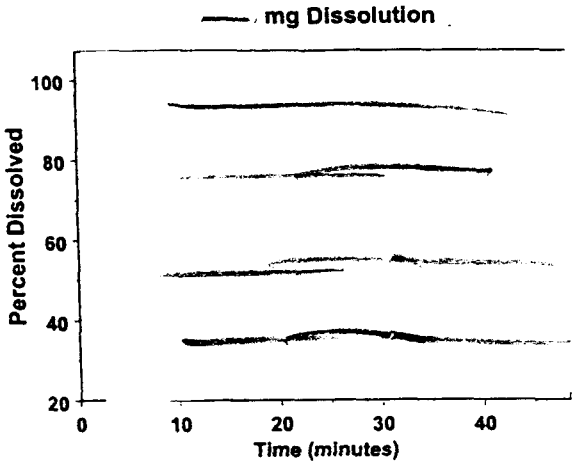
* The RRF for RNH-6270 was determined in the method validation

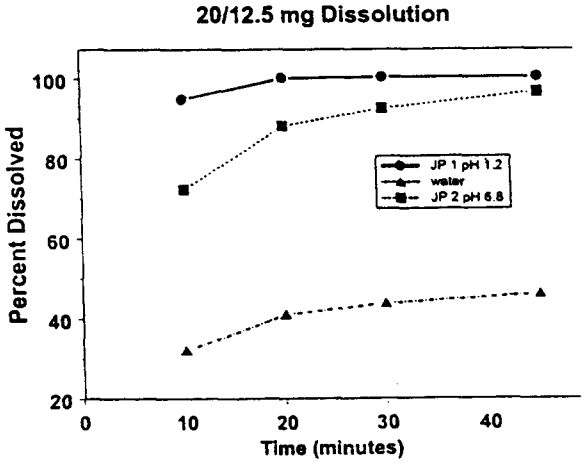
Calculation of CS-866 hydrolysed to RNH-6270

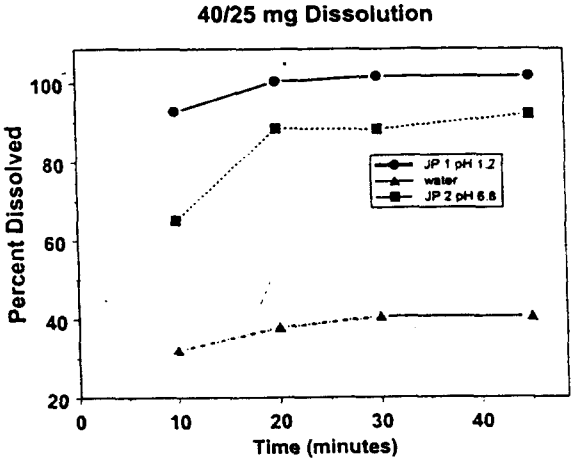
[redacted]	C_1 – Content RNH-6270 [%] MW_{CS-866} – Molecular weight of CS-866: [redacted] $MW_{RNH-6270}$ – Molecular weight of RNH-6270:

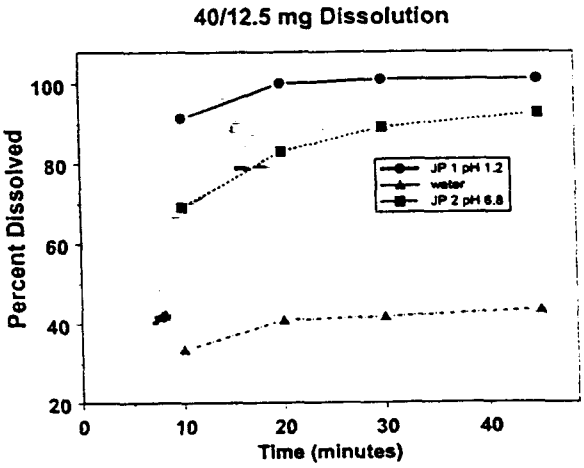
Results: The graphs below shows the CS-866 mean dissolution data over time for three media.



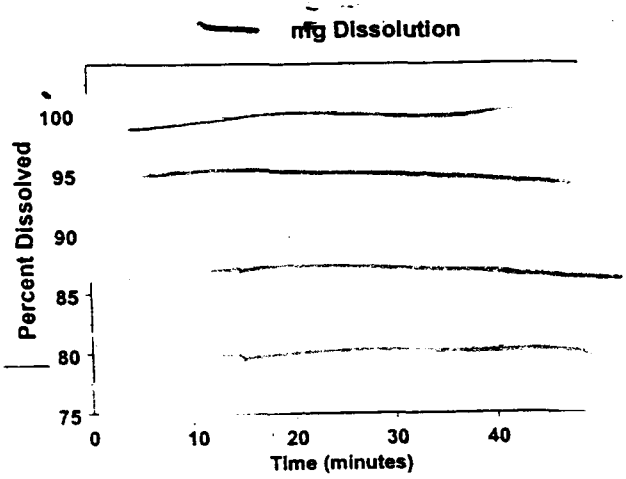


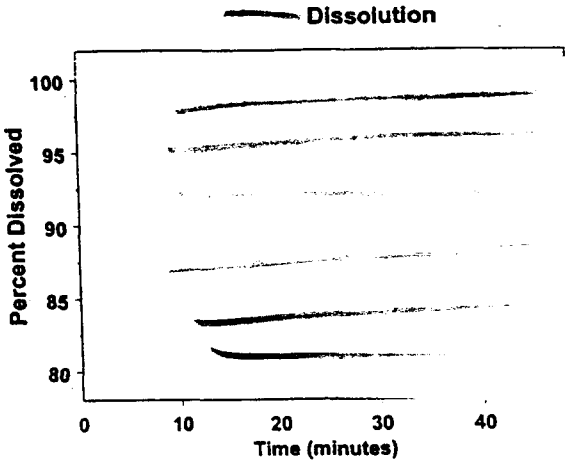


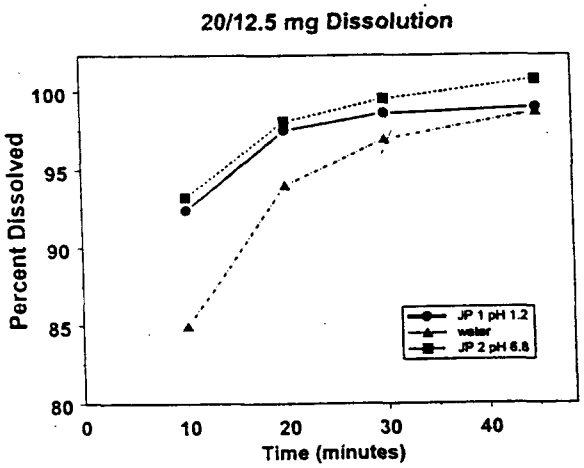


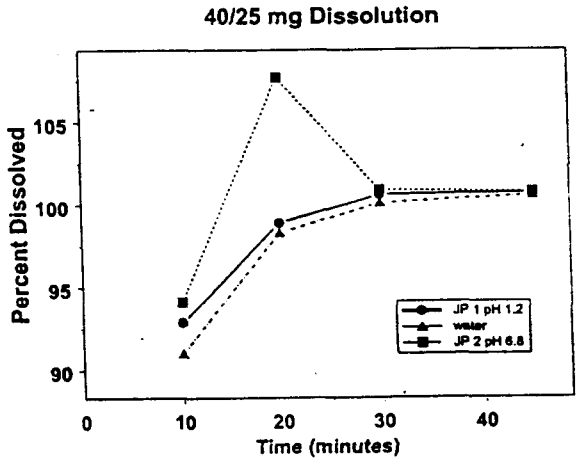


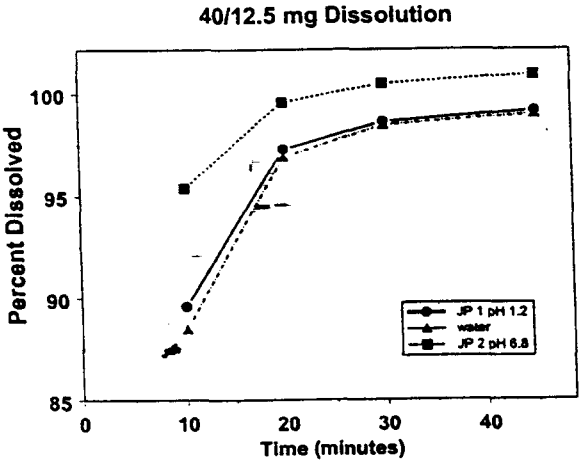
The graphs below shows the HCTZ mean dissolution data over time for three media.











Dissolution Specifications:

The approved dissolution methodology and specifications for Benicar (olmesartan medoxomil) are:

Medium: 1000 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q NLT — , at 30 minutes

The sponsor's proposed dissolution specifications for the combination product are:

Sponsor's Recommended Dissolution Specifications and Methodology for CS-866

20/12.5 mg tablet
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less thar — a*

40/12.5 mg and 40/25 mg tablet
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than — at —

Sponsor's Recommended Dissolution Specifications and Methodology for HCTZ
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q not less than — at —

It is noted that the sponsor should not have corrected for the — degradation. After review of the stability data (see CMC review), it was decided that the sponsor may not meet the specifications Q= — at — A product with a release of only — is less likely to meet bioequivalence than a product with a release of 100 %. Since a higher specification is better, the following is recommended for the combination product:

CS-866
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q NLT — at —

HCTZ
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q NLT — at —

Waiver Request:

The sponsor demonstrated bioequivalence (BE) between the to-be-marketed formulation tablet of 20/12.5 mg and the single entities (study 866-126). The sponsor is requesting a waiver from doing the human BE study for the 40/25 mg tablet. The following data support the waiver:

- The pharmacokinetics of both drugs are linear over the dosage range.
- The dissolution profiles of the reference (20/12.5 mg tablet) and test product (40/25 mg tablet) are similar. The reviewer's calculated similarity factors (f2) for CSS-866 are between 50 –100 (see table below).

Table 48. Similarity factor (f2) for CSS-866 20/12.5 mg and 40/25 mg

Medium	f2
Water	75.4
pH 6.8	75.4

- The f2 was not calculated for CSS-866, pH and for HCTZ because dissolution was greater than , by
- The 40/12.5 mg tablet (reference) is proportionately similar to the 40/25 mg tablet (see table below). The difference in HCTZ is accounted for in the lactose.

Table 4.3. 1: Quantitative formulation of the Sankyo Pharma GmbH CS-866HCTZ commercial tablets

Ingredient	tablet	20/12.5 mg tablet	40/12.5 mg tablet	tablet	40/25 mg tablet
CS 866[1]		20 mg	40 mg		40 mg
Hydrochlorothiazide		12.5 mg	12.5 mg		25 mg
Microcrystalline cellulose					
Lactose, [illegible]					
Hydroxypropyl cellulose					
Magnesium Stearate					
Tablet Core Weight					
Coated Tablet Weight					
Tablet shape	Round	Round			Oval
Tablet Core Dimensions	6.5 mm dia.	8.5 mm dia.			15 x 7 mm

Reviewer's Conclusions:
A biowaiver can be granted for the 40/25 mg tablet.

Dissolution Specifications:

The following dissolution specifications are recommended:

CS-866
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C

Apparatus: USP II (paddle)
Speed: 50 rpm
Specifications: Q NLT — at 45 minutes

- **HCTZ**
  Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
  Apparatus: USP II (paddle)
  Speed: 50 rpm
  Specifications: Q NLT — at 15 minutes

6.3.1 Individual dissolution data

The individual dissolution data for **CS-866** are shown in the pages that follow.

[illegible]ng CS-866 / HCTZ tablet

lot 3138v01006
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

lot 3138v01006
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

* = Missed sample, no data

[redacted] mg CS-866/ HCTZ tablet

- lot 3138v01006

Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

[redacted] mg CS-866 / HCTZ tablet

lot 3148v01002
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

lot 3148v01002
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

[redacted] mg CS-866 / HCTZ tablet

lot 3148v01002
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

20/12.5 mg CS-866 / HCTZ tablet

lot 3139v01004
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	94.79	100.02	100.35	100.42
Std. Deviation	1.71	0.91	0.92	1.02

lot 3139v01004
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	32.05	40.96	43.70	46.07
Std. Deviation	2.08	0.90	0.76	1.28

20/12.5 mg CS-866 / HCTZ tablet

lot 3139v01004
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	72.25	88.04	92.51	96.62
Std. Deviation	2.93	1.43	1.26	1.02

40/25 mg CS-866 / HCTZ tablet

lot 3149v01002
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	92.65	100.43	101.71	101.71
Std. Deviation	3.61	1.33	1.08	1.35

lot 3149v01002
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	32.04	37.76	40.49	40.49
Std. Deviation	1.49	1.05	0.88	0.94

40/25 mg CS-866 / HCTZ tablet

lot 3149v01002
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	65.06	88.38	88.13	91.98
Std. Deviation	3.07	15.41	0.77	1.13

40/12.5 mg CS-866 / HCTZ tablet

lot 3140v01005
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	91.44	100.20	101.13	101.27
Std. Deviation	3.73	1.17	1.21	1.00

lot 3140v01005
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	33.55	40.93	41.68	43.47
Std. Deviation	1.58	1.35	0.73	1.66

40/12.5 mg CS-866 / HCTZ tablet

lot 3140v01005
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% CS-866 Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	69.14	83.12	89.21	92.68
Std. Deviation	2.86	1.10	1.18	0.78

The individual dissolution data for **HCTZ** are shown in the pages that follow.

[redacted] mg CS-866/ HCTZ tablet

lot 3138v01006
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

lot 3138v01006
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

* = Missed sample, no data

[redacted] mg CS-866 / HCTZ tablet

lot 3138v01006 [redacted]
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1	[redacted]			
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

mg CS-866 / HCTZ tablet

lot 3148v01002
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

lot 3148v01002
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

mg CS-866 / HCTZ tablet

lot 3148v01002
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean				
Std. Deviation				

20/12.5 mg CS-866 / HCTZ tablet

lot 3139v01004
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	92.41	97.52	98.60	98.95
Std. Deviation	2.72	1.93	1.29	1.09

lot 3139v01004
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	84.93	94.01	96.93	98.66
Std. Deviation	6.08	2.85	2.10	1.56

20/12.5 mg CS-866 / HCTZ tablet

lot 3139v01004
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	93.24	98.08	99.53	100.75
Std. Deviation	3.08	2.21	1.59	1.29

40/25 mg CS-866 / HCTZ tablet

lot 3149v01002
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	92.86	98.89	100.61	100.74
Std. Deviation	3.11	1.44	1.21	1.48

lot 3149v01002
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	90.99	98.30	100.10	100.55
Std. Deviation	3.17	1.73	1.31	1.30

40/25 mg CS-866 / HCTZ tablet

lot 3149v01002
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	94.11	107.70	100.87	100.76
Std. Deviation	3.85	19.04	0.60	1.16

40/12.5 mg CS-866 / HCTZ tablet

lot 3140v01005
Medium: 900 mL, JP fluid 1, pH 1.2, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	89.57	97.26	98.63	99.15
Std. Deviation	3.68	1.79	1.50	1.21

lot 3140v01005
Medium: 900 mL, purified water, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	88.45	96.89	98.45	98.98
Std. Deviation	2.40	1.54	1.30	1.11

40/12.5 mg CS-866 / HCTZ tablet

lot 3140v01005
Medium: 900 mL, JP fluid 2, pH 6.8, 37°C
Apparatus: USP II (paddle)
Speed: 50 rpm

Sample	% HCTZ Dissolved			
	10 minutes	20 minutes	30 minutes	45 minutes
1				
2				
3				
4				
5				
6				
7				
8				
9				
10				
11				
12				
Mean	95.37	99.58	100.49	100.93
Std. Deviation	3.23	1.28	1.13	1.17

6.4 Batches used in pharmacokinetic studies and 866-318 (pivotal study)

Table 49. Batch numbers for to-be-marketed combination tablet

Strength		20/12.5 mg	
Lot no.	**3138V01006**	**3139V01004**	**3140V01005**
Clinical study		866-126	
	866-127	866-127	866-127

Table 50. Batch numbers for 10 mg CS-866 tablet

Lot no.	B99T19
Clinical study	866-318

Table 51. Batch numbers for 20 mg CS-866 tablet

Lot no.	B99T20	2234v99001
Clinical study	866-126	Se-866cmb01
	866-318	

Table 52. Batch numbers for 12.5 mg HCTZ capsule

Lot no.	015103
Clinical study	866-126
	866-134

Table 53. Batch numbers for 12.5 mg HCTZ over-encapsulated to-be-marketed capsule

Lot no.	1006138/02
Clinical study	866-134

Table 54. Batch numbers for 12.5 mg HCTZ tablet

Lot no.	2145601
Clinical study	866-126

Table 55. Batch numbers for 25 mg HCTZ tablet (HCTZ

Lot no.	7080275t
Clinical study	Se-866cmb01

6.5 Formulations used in the studies

TABLE 6.5.7.1a: Formulations Used in CS-866HCTZ Clinical Trials

Process No./Change	Strength (mg)	CS-866HCTZ Dosage Form*	Study No.	Lot. No.	Tablet Batch Size	Manufacturer
A	[redacted]	Tablet	S66-127	3138V01006	[redacted]	Sankyo Pharma GmbH
A	20/12.5	Tablet	S66-126, 866-127	3139V01004	[redacted]	Sankyo Pharma GmbH
A	40/12.5	Tablet	S66-127	3140V01005	[redacted]	Sankyo Pharma GmbH

* CS-866/HCTZ combination tablet
A Commercial process

TABLE 6.5.7.1b: Formulations Used in CS-866 Tablets in Combination with HCTZ Preparations in Clinical Trials

Process No./Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.†	Tablet / Capsule Batch Size	Manufacturer
	Placebo	Tablet	SE-866/19	224 2235V95021	[redacted]	Sankyo Co., Ltd.
		Tablet	SE-866/17	225 2235V95022	[redacted]	Sankyo Co., Ltd.
		Tablet	SE-866/19	226 2235V95023	[redacted]	Sankyo Co., Ltd.
		Tablet	SE-866/10	296 2235V97001	[redacted]	Sankyo Co., Ltd.
		Tablet	866-305, 866-306	295	[redacted]	Sankyo Co., Ltd.
		Tablet	SE-866/10-01	2235V98001	[redacted]	Sankyo Pharma GmbH
		Tablet	866-318	B99T22	[redacted]	Sankyo Co., Ltd.
		Tablet	SE-866/19	D97T04 2235V97003	[redacted]	Sankyo Co., Ltd.
		Capsule	866-318	100690-02/5	[redacted]	[redacted]
		Capsule	866-318	100690-07/5	[redacted]	[redacted]
		Capsule	866-419	100698-01	[redacted]	[redacted]
A, B	2.5	Tablet	866-305	290	[redacted]	Sankyo Co., Ltd.
A, B	5	Tablet	866-305, 866-306, SE-866/10	291 2232V97001	[redacted]	Sankyo Co., Ltd.
B, C, D		Tablet	SE-866/10-01	2232V98014	[redacted]	Sankyo Pharma GmbH
A, B		Tablet	SE-866/10, SE-866/19	D97T01 2232V97003	[redacted]	Sankyo Co., Ltd.
A, B	10	Tablet	866-305, 866-306, SE-866/10, SE-866/17, SE-866/19	292 2233V97001	[redacted]	Sankyo Co., Ltd.
B, C, D		Tablet	SE-866/10-01	2233V98016	[redacted]	Sankyo Pharma GmbH
A, B		Tablet	SE-866/19	D97T02 2233V97003	[redacted]	Sankyo Co., Ltd.
A, B		Tablet	866-318	B99T19	[redacted]	Sankyo Co., Ltd.

TABLE 6.5.7.1b: Formulations Used in CS-866 Tablets in Combination with HCTZ Preparations in Clinical Trials (Continued)

Process No./Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.†	Tablet Batch Size	Manufacturer
A, B	20	Tablet	866-108, 866-305, 866-306, SE-866/10, SE-866/17	293 2234V97001		Sankyo Co., Ltd.
B, C, D		Tablet	SE-866/10-01	2234V98013		Sankyo Pharma GmbH.
A, B		Tablet	SE-866/19	D97T03 2234V97009		Sankyo Co., Ltd.
C, D		Tablet	SE-866CMB/01	2234V99001		Sankyo Pharma GmbH
A, B		Tablet	866-126, 866-318	B99T20		Sankyo Co., Ltd.
A, B		Tablet	866-321	E99T03		Sankyo Co., Ltd.
A, B		Tablet	866-419	B00T17		Sankyo Co., Ltd.
A, B	40	Tablet	866-305, 866-306	294		Sankyo Co., Ltd.
A, B		Tablet	866-318	B99T21		Sankyo Co., Ltd.
A, B		Tablet	866-419	E99T06		Sankyo Co., Ltd.
NA	20	Suspension	866-108	K97T05		Sankyo Co., Ltd.
NA	16	RNH-6270 solution	866-108	K97T01		Sankyo Co., Ltd.

*Except as noted

A = [redacted]

B = [redacted]

C = [redacted]

D = [redacted]

NA= Not Applicable

† If more than one Lot No. is indicated the first Lot No. is the one assigned by the manufacturing site; the second Lot No. is the one subsequently assigned by the subsidiary.

TABLE 6.5.7.1c: Formulations Used in CS-866 Tablets in Combination with HCTZ Preparations in Clinical Trials*

Strength (mg)	HCTZ Dosage Form	Study No.	Lot. No.†	Tablet/Capsule Batch Size	Manufacturer
Placebo	Capsule	866-318	100690-02/5 100690-07/5	[redacted]	[redacted]
	Capsule	866-419	100698-01		
12.5	Tablet	866-126	2145601	Commercial	
	Capsule	866-126	015103	Commercial	
	Capsule	866-134	015103	Commercial	
	Capsule	866-134	015103 106138/02		
	Capsule	866-305	706602	Commercial	
	Capsule	866-306	706602	Commercial	
	Capsule	866-318	006901 100690-08/5		
	Capsule	866-321	012301	Commercial	
	Capsule	866-419	010801	Commercial	
	Tablet	SE-866/19	2000201	Commercial	
25	Tablet	866-419	K5406	Commercial	
	Tablet	SE-866CMB/01	7080275T	Commercial	
	Tablet	SE-866/10, SE-866/10-01	203890	Commercial	
	Tablet	SE-866/10 SE-866/10-01	203900	Commercial	
	Tablet	SE-866/17	7080275	Commercial	
	Tablet	SE-866/19	2000502	Commercial	

* Study 866-134 did not include the use of CS-866 tablets. This was a bioequivalence study of market-image versus overencapsulated market-image hydrochlorothiazide capsules.

† If more than one Lot No. is indicated the first Lot No. is the one assigned by the manufacturer; the second Lot No. is the lot number assigned by the [redacted], during overencapsulation with [redacted] capsule.

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/s/

Nhi Nguyen
4/10/03 03:04:05 PM
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Patrick Marroum
4/10/03 03:23:09 PM
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