CENTER FOR DRUG EVALUATION AND RESEARCH

APPROVAL PACKAGE FOR:

APPLICATION NUMBER
21-286

Clinical Pharmacology and Biopharmaceutics Review

Clinical Pharmacology/Biopharmaceutics Review

NDA: 21-286, N-BB
Benicar™ (Olmesartan medoximil)
Sankyo Pharma Development

Submission Date: May 7, 2001

Reviewer: Gabriel J. Robbie

Type of Submission: Dissolution data supporting bioequivalence of 1 x 5-mg tablet and 4 x 5-mg tablets versus 1 x 20-mg tablet of olmesartan medoximil.

BACKGROUND:

The sponsor is seeking an in vivo bioequivalence study waiver linking Benicar™ 5-mg tablet (new strength) with 20-mg tablet. In a teleconference on April 6, 2001, the Agency advised the sponsor to compare dissolution of 4 x 5-mg tablets versus 1 x 20-mg tablet to overcome assay sensitivity problems. The sponsor has since identified that the [redacted] method was sufficiently sensitive for assay of one 5-mg tablet. Nevertheless, the sponsor has submitted dissolution data comparing both 1 x 5-mg tablet and 4 x 5-mg tablets versus 1 x 20-mg tablet in 3 media.

DISSOLUTION METHOD:

In vitro dissolution testing of 1 x 5-mg, 4 x 5-mg, and 1 x 20-mg Benicar® tablets were performed by testing either one or 4 tablets in USP Apparatus 2 (paddle) at a paddle speed of 50 rpm in 3 different media: water, pH 1.2 and pH 6.8. Dissolution media was sampled at 10, 20, 30, 45 and 60 minutes.

RESULTS:

The results of the dissolution study in 3 media are presented in the table below and in Figure 1 on the following page.

Time	Mean % Dissolved in pH 1.2 (CV%)			Mean % Dissolved in Water (CV%)			Mean % Dissolved in pH 6.8 (CV%)		
(min)	1 x 5-mg	4 x 5-mg	1 x 20-mg	1 x 5-mg	4 x 5-mg	1 x 20-mg	1 x 5-mg	4 x 5-mg	1 x 20-mg
10	99.9 (	98.6 (	97.0 (	31.3 (	24.6 (	18.2 (	85.3 (	77.5 (	73.5 (
20	102.4 (	102.2 (	103.1 (	42.4 (	31.6 (	25.7 (	96.4 (	89.0 (	90.0 (
30	102.1 (	102.7 (	103.5 (	49.4 (	35.1 (	28.8 (	99.2 (	93.6 (	94.5 (
45	102.1 (	102.9 (	103.6 (	56.6 (	37.8 (	31.4 (	100.9 (	96.1 (	97.2 (
60	102.4 (	103.1 (	103.7 (	61.4 (	40.1 (	33.1 (	101.3 (	97.4 (	98.3 (

Dissolution at pH 1.2 and pH 6.8 was rapid while, dissolution of olmesartan in water was slow and incomplete because of pH dependent solubility. The similarity factor 'f2' cannot be calculated for dissolution in pH 1.2 and pH 6.8 because of rapid dissolution within 10 minutes. The sponsor intends to use pH 6.8 as the dissolution specification

medium. At pH 6.8, dissolution of 1 x 5-mg tablet was faster than 4 x 5-mg tablet, while, dissolution of 4 x 5-mg tablets was similar to 1 x 20-mg tablet.

Since the dissolution of 4 x 5-mg tablets was similar to 1 x 20-mg tablet and since dissolution of Benicar™ tablets is rapid and ➖% dissolution is expected to be achieved in 15 minutes at pH 6.8, an in vivo bioequivalence study waiver can be granted.

RECOMMENDATIONS:

Based on the similarity of dissolution of 4 x 5-mg and 1 x 20-mg tablets of Benicar™ and because ➖% dissolution is expected in 15 minutes at the dissolution specification medium of pH 6.8, the Office of Clinical Pharmacology and Biopharmaceutics recommends granting an vivo bioavailability/bioequivalence waiver for the 5-mg strength.

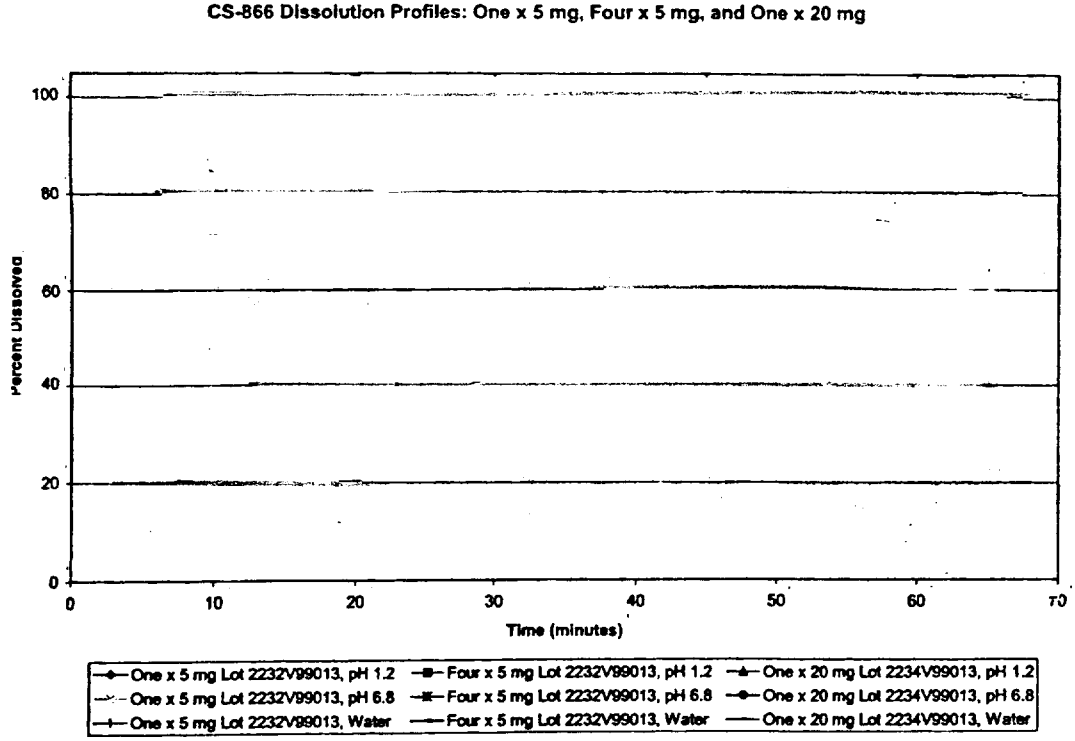
/S/

Gabriel J. Robbie, Ph. D.

RD/FT by Patrick J. Marroum, Ph. D.

Cc: NDA 21-286, HFD 110, HFD 860 (Mehta, Robbie), CDER document room: Attn: Biopharm (CDER)

Figure 1



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/s/

Gabriel Robbie
5/31/01 03:49:18 PM
BIOPHARMACEUTICS

Patrick Marroum
5/31/01 04:30:19 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

NDA 21-286 [N-BB] **SUBMISSION DATES:** March 27, 2001
Benicar™ (olmesartan medoxomil) Tablets
5 and 20 mg

SANKYO PHARMA DEVELOPMENT **REVIEWER:** Emmanuel O. Fadiran, Ph.D.

TYPE OF SUBMISSION: NDA Amendment

BACKGROUND:
Benicar™ (olmesartan medoxomil, CS-866), a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT_1 subtype angiotensin II receptor antagonist under review for the treatment of hypertension. The sponsor submitted clinical data and dissolution data on the 20 mg tablet to the original NDA and during the review process was requested to submit *in vitro* dissolution data on the 40 mg. The comparative *in vitro* dissolution data on the 20 and 40 mg tablets was used for the waiver of bioequivalence study for the 40 mg tablet. The sponsor also plans to market a 5 mg tablet and this supplement provides the data obtained from a comparative dissolution study conducted between the 5 and 20 mg tablet in three different media.

SYNOPSIS:

Comparative dissolution profiles were generated using in Purified Water, buffer media at pH 1.2 and pH 6.8. The following dissolution conditions were used for the profiles:

USP Apparatus 2, Paddle, 50 rpm
Volume of media: 1000 ml used for 20 mg tablets
500 ml used for 5 mg tablets [redacted]

The sponsor stated that Purified Water was used instead of buffer pH 4.5 recommended in the guidance because olmesartan is practically insoluble around pH 4. Additionally, the sponsor reported that the solubility of olmesartan is pH dependent (see Table 1 below).

The similarity factors (f2) resulting from the comparative dissolution profile in various media (re-calculated by the reviewer) are summarized for Benicar tablets, 5 and 20 mg, in Table 2 while the dissolution profiles are summarized in Figure 1.

Table 1:

Solubility of CS-866 at Various pH Values

Buffer	pH[1]	Solubility in µg/mL
JP-1 (pH 1.2)	1.23	568
2.0	2.04	112
4.0	3.99	0
Water	5.67	8
6.0	6.00	24
JP-2 (pH 6.8)	6.82	128
8.0	7.76	424

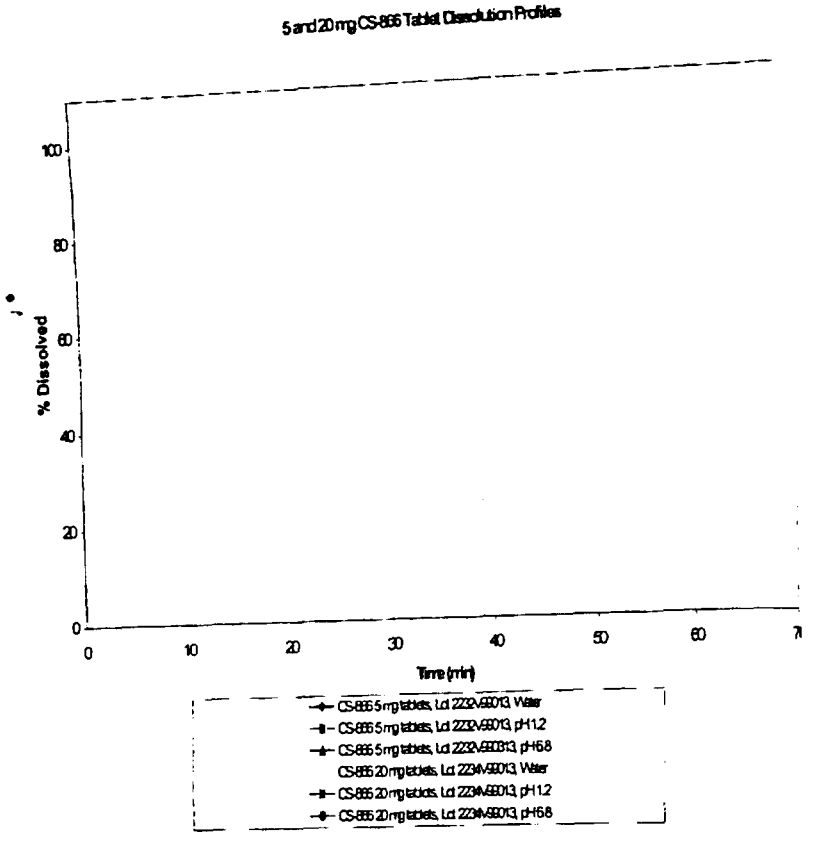
Note 1: pH of the solution after saturating the solution.

Table 2: Similarity factors (f2) comparing dissolution profiles of the 5 mg and 20 mg tablets

	Media		
	Buffer pH 1.2	Buffer pH 6.8	Purified Water
Similarity factor (f2) (Calculated by reviewer)	N/A*	56.5	37.3
Similarity factor (f2) (Reported by sponsor)	57.7	63.7	37.3

*f2 not calculated, —— % dissolved in 10 minutes for both 5 and 20 mg tablets

Figure 1



COMMENTS:

1. The sponsor did not perform the dissolution profile comparison under identical conditions as specified in the Dissolution Testing Guidance and General BA/BE Guidance. For the request for a biowaver to be granted, the dissolution profile comparison must be conducted using the identical dissolution procedures for both strengths of the formulation.
2. To overcome the assay sensitivity problem using [redacted] it is recommended that the sponsor should use an [redacted] assay. The sensitivity of an [redacted] assay will allow for determination of olmesartan from 5 mg tablet using 1000 ml of the dissolution media.
3. If [redacted] method could not be developed, it is recommended that the sponsor should compare 5 x 4 mg tablet with 20 mg of olmesartan in order to overcome the assay sensitivity problem with using one 5 mg tablet.
4. The sponsor should perform the dissolution profiles comparison using the same dissolution procedures (three media, same volume) as recommended in the guidance and submit the dissolution data with a biowaiver request to the Agency for review.

RECOMMENDATIONS:

The dissolution profile comparison for the 5 and 20 mg tablets was performed under different conditions and the similarity factor result in water is outside the acceptable range. The sponsor is requested to conduct the dissolution profile comparison for the two tablets strengths under identical conditions (three media, same volume) and submit the dissolution data with a biowaiver request to the Agency for review.

CONCLUSIONS:

The Division of Pharmaceutical Evaluation I has completed the review of the sponsor's submission and recommends that the sponsor be requested to conduct the dissolution profile comparison for the 5 mg and 20 mg olmesartan tablets under identical conditions and submit the dissolution data with a biowaiver request to the Agency for review. Please forward the above comments to the sponsor.

/S/

Emmanuel O. Fadiran, Ph.D.
Division of Pharmaceutical Evaluation I

/S/

FT Initialed by P. Marroum, Ph.D. ----------

cc: NDA 21-286, HFD-110, HFD-860 (Fadiran, Mehta), HFD 110 (Zielinski, Srinivasachar), BIOPHARM - CDR

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW

NDAs: 21-286
Category: IS

Submission Date:
July 25, 2000
September 28, 2000
October 25, 2000
November 9, 2000
November 27, 2000
December 15, 2000

Generic Name:	**Olmesartan Medoxomil**
Brand Name:	**BENEVAS™**
Formulations:	**20 AND 40 MG Film Coated tablets**
Indication:	**Essential Hypertension**
Sponsor:	**Sankyo Pharmaceuticals Japan**
Type of Submission:	**NDA (NME)**
Reviewer:	**Sayed Al-Habet, Ph.D.**
Date of Review:	**November 14, 2000**

TABLE OF CONTENTS

Synopsis:

BENEVAS™ (olmesartan medoxomil), a prodrug, is hydrolyzed to olmesartan during absorption from the gastrointestinal tract. Olmesartan is a selective AT1 subtype angiotensin II receptor antagonist. The drug has been developed for the treatment of patients with essential hypertension. The usual recommended starting dose of BENEVAS ™ is 20 mg once daily when used as monotherapy. For patients requiring further reduction in blood pressure, the dose may be increased to 40 mg once daily or 20 mg twice daily. BENEVAS ™ may be administered with or without food.

The molecular weight Olmesartan medoxomil is 558.59. It is practically insoluble in water and sparingly soluble in methanol. The pKa is 4.14 and the partition coefficient (log P) between buffer (pH 7.0) and n-octanol is 0.73.

Major Studies:

In this NDA 28 clinical Pharmacology and Pharmacokinetics studies were submitted. Out of these 28 studies 20 were identified as relevant and reviewed. The most relevant studies were related to: dose proportionality, absolute bioavailability, bioequivalence, effect of food, metabolism, renal impairment, hepatic impairment, elderly, gender, and drug interactions (warfarin, digoxin, and antacid).

RECOMMENDATION

1. Based on the information submitted to us, this NDA is ACCEPTABLE to the Office of Clinical Pharmacology and Biopharmaceutics.

2. Waiver for the bioequivalence study for the 40 mg strength is granted. This is based on the *in vitro* dissolution data which showed that the dissolution profiles of the 20 mg and the 40 mg formulations are similar in three media. The f2 values were >50 in the three media.

3. The following dissolution methodology and specifications are recommended:

Apparatus II:	USP (Paddles)
Speed:	50 rpm
Medium:	1000 mL (250 ml 0.2 N KH_2PO_4 + 118 ml NaOH 0.2 N filled with water to 1000 ml)
Specification:	Not less than [redacted]% (Q) in 30 minutes

COMMENTS TO THE CLINICAL DIVISION/LABELLING

1. The sponsor is proposing to market 20 mg and 40 mg tablets. These tablets are not scored. Therefore, it is difficult to titrate the dose, if necessary.

2. It should be noted that the recommended doses of 20 mg and 40 mg are the plateau of the dose-response relationship for this drug (the details of this will be provided by the Clinical Division).

3. No data is available in patients with severe hepatic impairment (study # SE-866-109). The selected dose in the study (i.e., 10 mg dose) was rather low. The starting recommended dose for this drug is 20 mg. The plasma concentrations were generally higher at all time points in mild and moderate hepatic impairment patients than healthy subjects. There is no equal number of subjects in each group as follows: 12 healthy subjects, 4 mild and 8 moderate hepatic impairment. The number of subjects in the mild group is rather small. According to the sponsor's proposed label,

4. Similar to the hepatic study, the dose used in the renal impairment study was also 10 mg given once daily for 7 days (study # SE-866-16). In this study, the exposure of olmesartan in patients with severe renal impairment was 3-fold higher than control. According to the sponsor's proposed label,

5. The drug is not completely absorbed. Therefore, in the sponsor's proposed label (page 2, Pharmacokinetics section-line 1), the word should be deleted.

Executive Summary
Clinical Pharmacology and Biopharmaceutics

Background:

BENEVAS (olmesartan medoxomil), is a selective A_{T1} subtype angiotensin II receptor antagonist. It is a prodrug that is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Its molecular weight is 558.59 and is practically insoluble in water and sparingly soluble in methanol. BENEVAS is available for oral use as film-coated tablets containing 20 mg or 40 mg of olmesartan medoxomil.

Absorption:

Following oral administration of Benevas, the absolute bioavailability of olmesartan tablet is approximately 26%. The peak serum concentration (Cmax) of olmesartan after oral administration is reached after 1 to 2 hours. Food does not affect the bioavailability of olmesartan.

Dose proportionality:

Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. The pharmacokinetics of olmesartan is linear following single and multiple doses up to 80 mg. There is trend for less than proportional increase in Cmax and AUC as the dose is increased beyond 80 mg. Steady state levels of olmesartan are achieved within 3 to 5 days and no accumulation in serum occurs with once-daily dosing.

Metabolism and Elimination:

Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose is recovered in urine while the remainder is eliminated in feces via the bile. The volume of distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

Special Population:

Elderly:

The pharmacokinetics of olmesartan were studied in the elderly (>65 years). Overall, the exposure to olmesartan as expressed by AUC was approximately 33% to 44% higher than the young patients of <65 years of age.

Gender:

Minor differences were observed in the pharmacokinetics of olmesartan in females compared to males. AUC and Cmax were increased 10-15% in females over those in males. This conclusion was based on a single 20 mg dose study in healthy subject.

Renal and Hepatic Impairment:

After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min) compared to subjects with normal renal function. Also, the AUC and Cmax were increased in patients with moderate hepatic impairment compared to those in matched controls. The increase in AUC was approximated 1.6 fold. It should be noted that no severe hepatic impairment patients were studied.

Drug Interactions:

No significant drug interactions were reported in studies in which olmesartan medoxomil was co-administered with digoxin or warfarin in healthy volunteers. The bioavailability of olmesartan was not significantly altered by the co-administration of antacids [Al(OH)3/Mg(OH)2]. Olmesartan medoxomil is not metabolized by the cytochrome P450 system and has no effects on P450 enzymes; thus, interactions with drugs that inhibit, induce or are metabolized by those enzymes are not expected.

Dose Response (PK/PD):

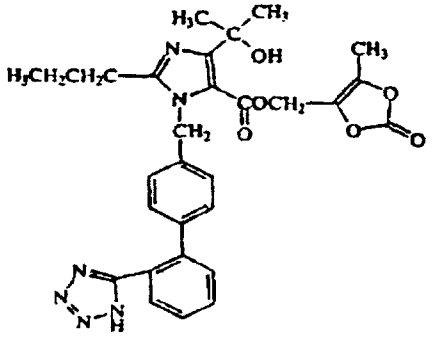
Based on two preliminary Phase II studies, the PK/PD relationship was inconclusive. After single doses of 2.5 to 40 mg olmesartan medoxomil, the pressor response was reduced compared to placebo. No clear dose-response relationship was apparent. Plasma concentrations of angiotensin I, angiotensin II and plasma renin activity increased after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Again, the data was variable and inconclusive. In a comparative pilot study (n=8), 20 mg dose of enalapril caused marked reduction in blood pressure, renin and angiotesin II level compared to 20 mg Benevas dose. It should be noted that the recommended doses of 20 mg and 40 mg are the plateau of the dose-response relationship for this drug (the details of this will be provided by the Clinical Division).

SUMMARY REVIEW
OF PHARMACOKINETICS AND BIOAVAILABILITY
(Question Based Review, QBR)

A) BACKGROUND:

What are the Physico-Chemical Properties of Olmesartan?

Olmesartan medoxomil is described chemically as (5-methyl-2-oxo-1,3-dioxolen-4-yl) methyl 4-(1-hydroxy-1-methylethyl)-2-propyl-1[[2'-(1H-tetrazol-5-yl) biphenyl-4-yl]methyl] imidazol-5-carboxylate. Its structural formula is:



Olmesartan medoxomil is a white to light yellowish-white powder or crystalline powder with a molecular weight of 558.59. It is practically insoluble in water and sparingly soluble in methanol. BENEVAS ™ is available for oral use as film-coated tablets containing 20 mg or 40 mg of olmesartan medoxomil. The pKa is 4.14 and the partition coefficient (log P) between buffer (pH 7.0) and n-octanol is 0.73.

What is the Indication of Olmesartan?

BENEVAS™ (olmesartan medoxomil) has been developed for the treatment of patients with essential hypertension.

What is the Mechanism of Action of Olmesartan?

Olmesartan binds competitively and selectively to AT1 receptors. Therefore, it blocks the vasoconstrictor effects of angiotensin II by selectively blocking the binding of angiotensin II to the AT1 receptor in vascular smooth muscle. Angiotensin II is the principal pressor agent of the renin-angiotensin system, with effects that include vasoconstriction, stimulation of synthesis and release of aldosterone, cardiac stimulation and renal reabsorption of sodium.

How Will Olmesartan be Supplied?

BENEVAS ™ will be available for oral use as film-coated tablets containing 20 mg or 40 mg of olmesartan medoxomil.

What is the Proposed Dosage and Administration of Olmesartan?

The usual recommended starting dose of BENEVAS ™ is 20 mg once daily when used as monotherapy. For patients requiring further reduction in blood pressure, the dose may be increased to 40 mg once daily or 20 mg twice daily. BENEVAS ™ may be administered with or without food.

What Assay Method Was Used?

Methods employed for quantitation of olmesartan and other metabolites included [redacted] and [redacted] respectively. [redacted] was used to quantitate ^{14}C from radiolabeled Benevas, while [redacted] was used for metabolic profiling of radiolabeled drug. All analytical methods were rigorously validated prior to use.

B) CLINICAL PHARMACOLOGY STUDIES:

What is the Bioavailability of Olmesartan ?

The absolute bioavailability of the active metabolite, olmesartan (RNH-6270) after oral administration was investigated in a four-way crossover study in 21 normal subjects comparing single oral doses of olmesartan medoxomil (Benevas, CS-866) tablets and olmesartan medoxomil (Benevas, CS-866)) suspension and olmesartan (RNH-6270) oral solution, to a single intravenous administration of olmesartan (RNH-6270) solution (study # 866-108). The calculated mean bioavailability of olmesartan (the active metabolite) following oral administration of 20 mg Benevas was 25.6% from the tablet, 21.4% from the suspension and 4.6% from the oral solution. The reasons for the low bioavailability from the solution is because the parent compound (CS-866) in the tablet and suspension formulations was present as methyl ester of RNH-6270 and there are 16 mg equivalents of RNH-6270 in 20 mg of CS-866.

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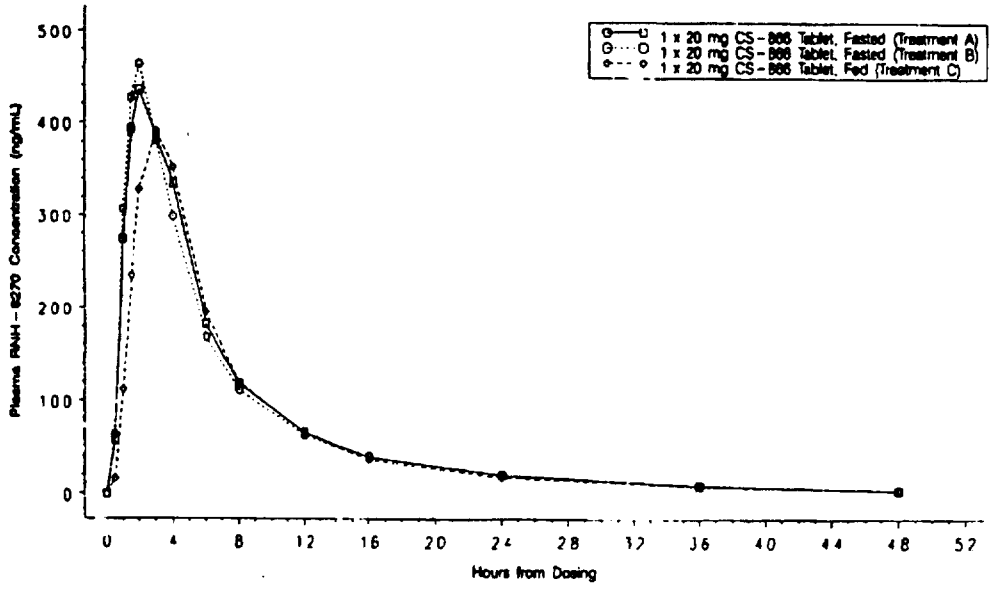
ON ORIGINAL

Is There Any Effect of Food on Olmesartan Absorption and Bioavailability?

The pharmacokinetics of olmesartan following oral administration of 20 mg single dose of Benevas without food compared to administration of Benevas 30 minutes following a standard meal were investigated in the 3-way crossover study in 24 normal subjects (study # 866-103). In this study Benevas was administered twice without food and once with food. The effects of food on the pharmacokinetics of olmesartan were minimal (**Figure 1**). Food slightly prolonged Tmax and marginally reduced Cmax and $AUC_{0-\infty}$ by approximately 10%.

Figure 1. Mean Plasma Concentration-Time Profiles of Olmesartan in Two Repeated Fasted State (Treatments A and B) and With Food (Treatment C) in 24 subjects.



Is There Bioequivalence Among Formulations Used During Benevas Development?

The bioequivalence of the commercial 20 mg Benevas tablet (Lot# 2234V99013) was compared to the investigational 20 mg Benevas (Lot # E99T03). The study was conducted after a single oral dose of 20 mg tablet in 30 normal subjects (study # 866/116). The commercial tablet was essentially identical to the investigational tablet with respect to excipients, however, their relative ratios and final tablet size were different (**Table 1**).

Table 1. Composition of Benevas 20 mg Tablets Used in Study # 866-116

Ingredients	Research Tablets (% of core weight)	Commercial Tablets (% of core weight)
CS-866 (mg)	20 (19.0)	20 (9.5)
Microcrystalline cellulose (mg)		
Low substituted hydroxypropyl cellulose (mg)		
Lactose monohydrate (mg)		
Hydroxypropylcellulose (mg)		
Magnesium stearate (mg)		
Tablet core weight (mg)		
Film Coat (mg)		
Total weight (mg)	**110**	**218**
Shape	Round	Round
Diameter		
Color	White	White

Mean AUC and Cmax values were slightly higher for the commercial tablets compared to the investigational tablets (**Table 2**). As shown in the Table below, the 90% CI were within the regulatory allowable limits of 0.8-1.25 for both the AUC and Cmax. Therefore, the two formulations are considered bioequivalent.

Table 2. PK and BE Parameters Following 20 mg a Single Dose of Benevas Tablets Used in Study # 866-116:

Parameter	Commercial Tablet (n=30)	Research Tablet (n=30)	Point Estimate	90% CI
AUC_{0-t} (ng/ml.h)	3608.12 (856.22)	3284.46 (805.23)	1.10	(1.031, 1.17)
$AUC_{0-\infty}$ (ng/ml.h)	3696.46 (928.26	3344.19 (841.50)	1.10	(1.036, 1.18)
Cmax (ng/ml)	589.70 (119.26)	524.63 (138.08)	1.15	(1.061, 1.24)
Tmax (h)	1.50	1.50	-	-
Half life (h)	19.45 (12.16)	17.45 (8.66)	-	-

On December 15, 2000, the sponsor has submitted *in vitro* dissolution data for the 20 and 40 mg tablets The data showed that the dissolution profiles of the 20 mg and the 40 mg formulations are similar in three media. The f2 values were >50 in the three media. Based on this, waiver for the bioequivalence study for the 40 mg strength is granted.

What is the Elimination Pathways of Olmesartan (Metabolism and Excretion)?

In Vivo Metabolism:

The mass balance of Benevas (CS-866) was investigated following administration of a single 20 mg oral dose of ^{14}C-CS-866 (ca. 100 mCi) given as a solution to six human subjects (study # 866/13). The drug was rapidly absorbed with a peak plasma concentration of radioactivity occurring within 0.5 to 2 hours after administration. RNH-6270 was the only radio-labeled components observed in plasma. Mean cumulative recovery of radioactivity amounted to 12.6% of the administered dose in urine and 77.2% in feces after 312 hours. Essentially all radioactivity was accounted for as unchanged olmesartan. The overall radioactive recovery from both urine and feces averaged 89.77% (range: [redacted] %). It should be noted that, overall, the radioactivity in blood was approximately 50% of that in plasma. **Figures 2-4** show the mean data.

Figure 2. Median Plasma Concentration-Time Profile of Radioactivity and Olmesartan (RNH-627).

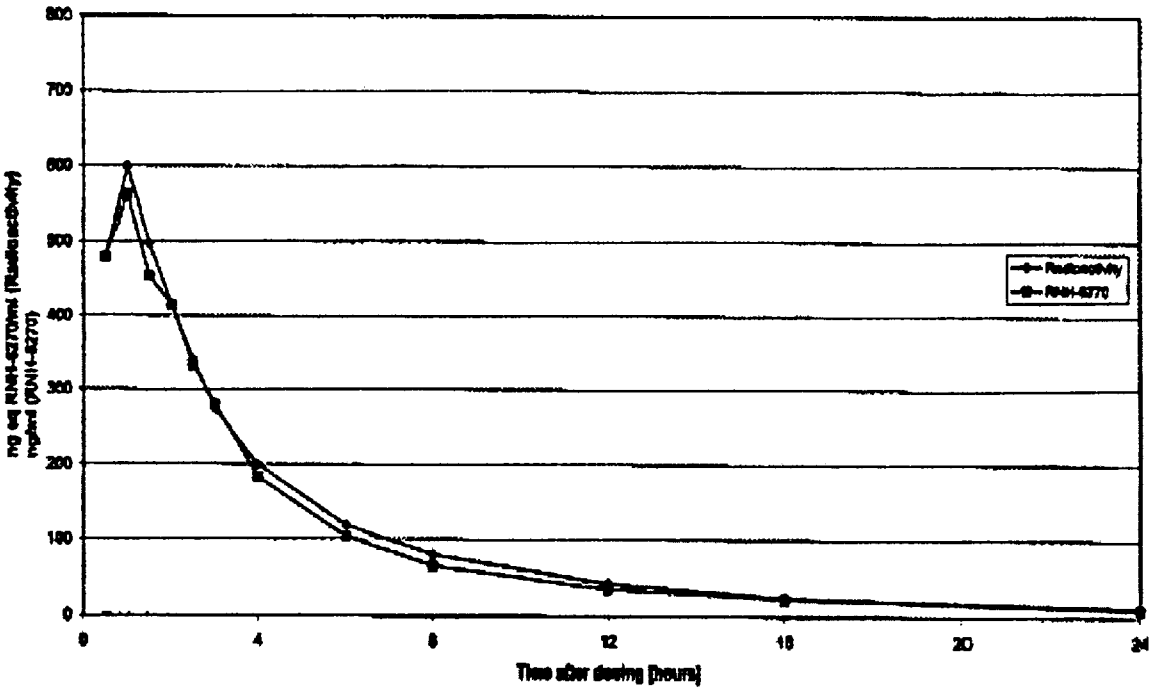


Figure 3. Median Plasma and Blood Concentration-Time Profile of Radioactivity.

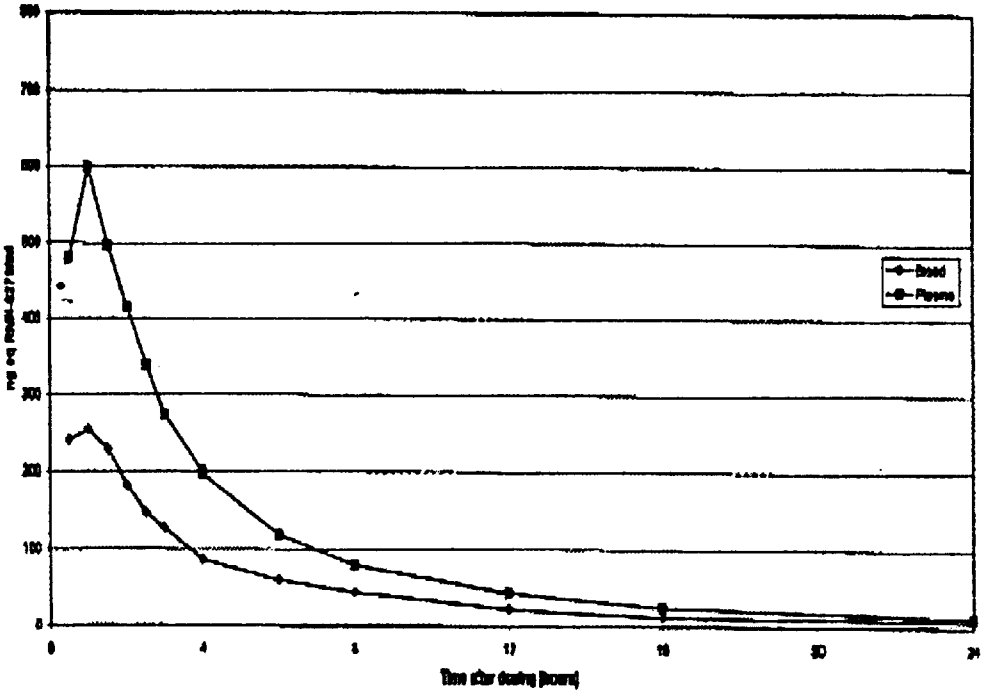
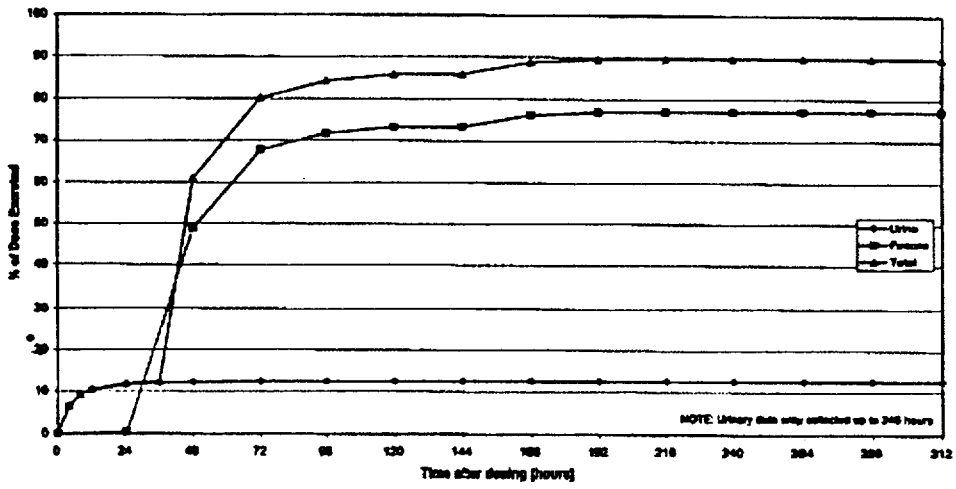
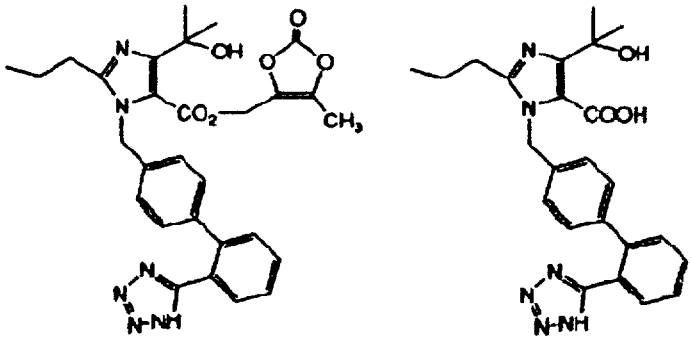


Figure 4. Mean Cumulative Excretion of Radioactivity in Urine and faeces.



Benevas (Olmesartan medoxomil) is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. The metabolic fate of the hydrolyzed dioxolenyl-based side-group is illustrated in **Figure 5.**

Figure 5. Chemical structures of the prodrug-CS-866 (Benevas-Olmesartan medoxomil) and its metabolite RNH-6270 (Olmesartan)



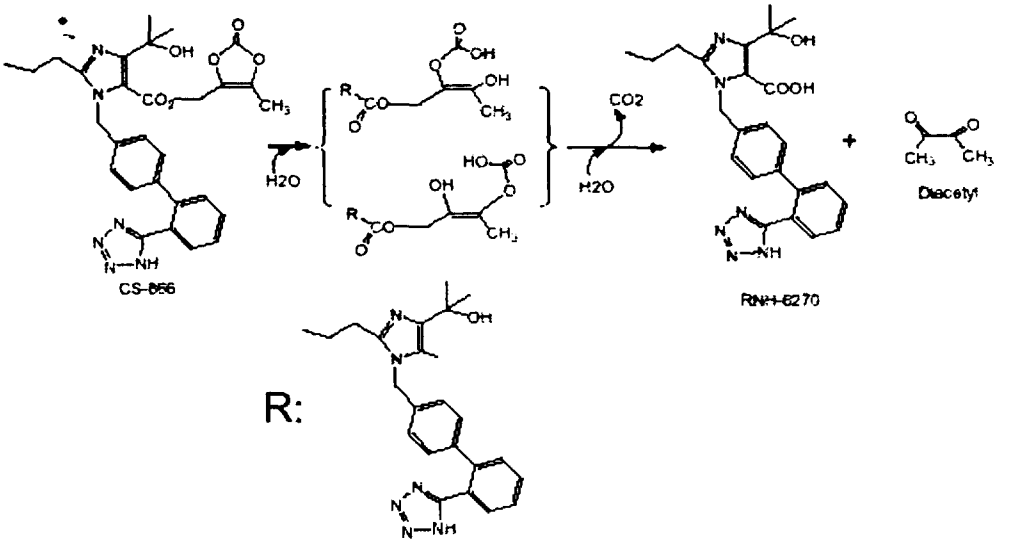
Parent drug (prodrug)
CS-866 (M.W. 558)
(Benevas)
(Olmesartan medoxomil)

Metabolite
RNH-6270 (M.W. 446)
Olmesartan

In Vitro Metabolism:

In vitro, Benevas is hydrolyzed by human serum albumin and by esterases in mouse, rat, dog, rabbit, monkey, and human plasma ((studies # GR-143-036 and GR 143-098). The activity of human plasma was 10.58 nmol/min/mg. Studies to characterize the plasma esterase responsible for hydrolysis of Benevas indicated that it was arylesterase. **Figure 6.** shows the proposed metabolic pathway of Benevas.

Figure 6. Proposed Mechanism For the Hydrolysis of CS-866 (Benevas-Olmesartan medoxomil) to RNH-627o (Olmesartan)



What is the Active Moiety?

Benevas (CS-866, Olmesartan medoxomil) is a prodrug and must be activated by hydroysis to olmesartan (RNH-6270), the active moiety.

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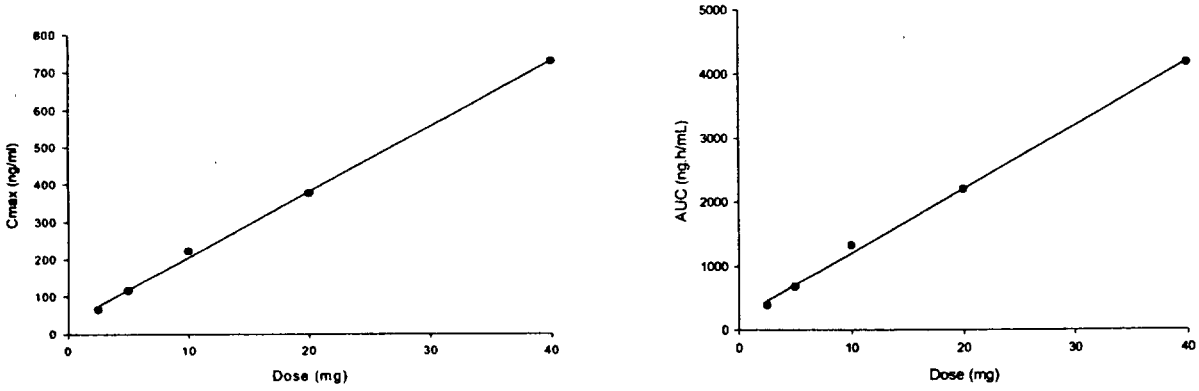
What is the Degree of the Plasma Protein Binding of Olmesartan?

The *in vitro* plasma protein binding of olmesartan is approximately 99% over a wide concentration range of [redacted] µg/ml (studies # GR 143-079, RAM 140-053).

What is the PK of Olmesartan Relative to Dose ? (i.e., is There Dose Proportionality?)

The following three main studies were conducted to investigate the dose-proportionality following oral administration of Benevas: 866-101, 866-102, SE-866/01, and 866/21. All of these studies have shown a dose proportional increase in Cmax and AUC with an increase in Benevas dose up to 80 mg. The most robust study was study #866/21 which was a multiple dose (7 days) five-way crossover in 30 subjects at doses range from 2.5 to 40 mg. Each dose period was for 7 days separated by 7-14 days washout period. Overall, within experimental errors, there was dose proportional increase in steady state Cmax and AUC up to 40 mg dose. In addition, there was no evidence of drug accumulation after multiple doses. A similar conclusion was made from study # 866-102. **Figures 7-9** show the dose proportionality for Cmax and AUC at steady state up to 40 mg.

Figure 7. Relationship Between Dose Cmax (left) and AUC (right) of Olmesartan multiple dose (7 Days) Oral administration of Benevas (study # 866-21). Data is the mean of 30 subjects.



The most comprehensive study was study # 866/01. Unlike study # 21, this was a parallel single dose rising study, where a group of six subjects received the drug at one of the following dose levels: 10, 20, 40, 80, 160, 240, and 320 mg. From this study, there is clear evidence of dose proportional in Cmax and AUC up to 80 mg dose as shown in (**Figure 8**). However, with further increase in dose, the relationship tends to plateau as shown in (**Figure 9**). This means that there is a less than proportional increase, especially in Cmax, at a dose higher than 80 mg. In addition, the mean plasma elimination half-life ranged from 12 to 14 hours over the enire dose range in this study. Urine collections

showed that approximately 5% to 10% of the dose was excreted as olmesartan.

Figure 8. Relationship Between Dose AUC (left) and Cmax (right) of Olmesartan After Oral administration of Benevas ONLY up to 80 mg Dose From Study # 866/01

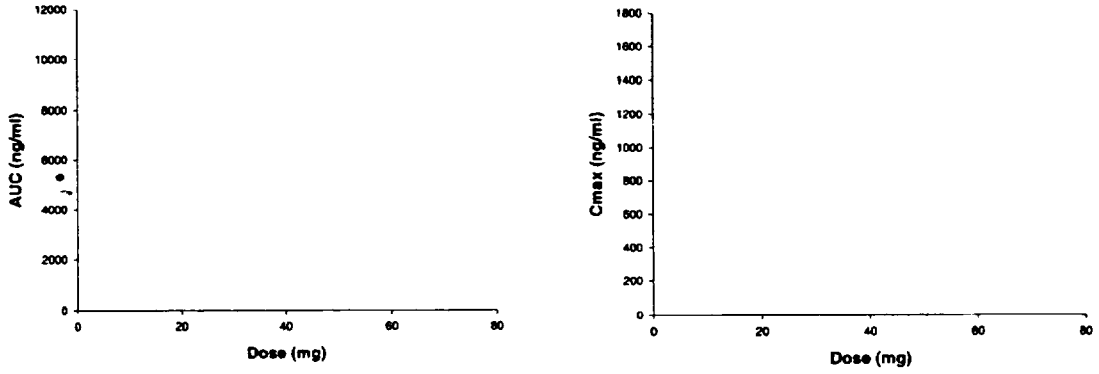
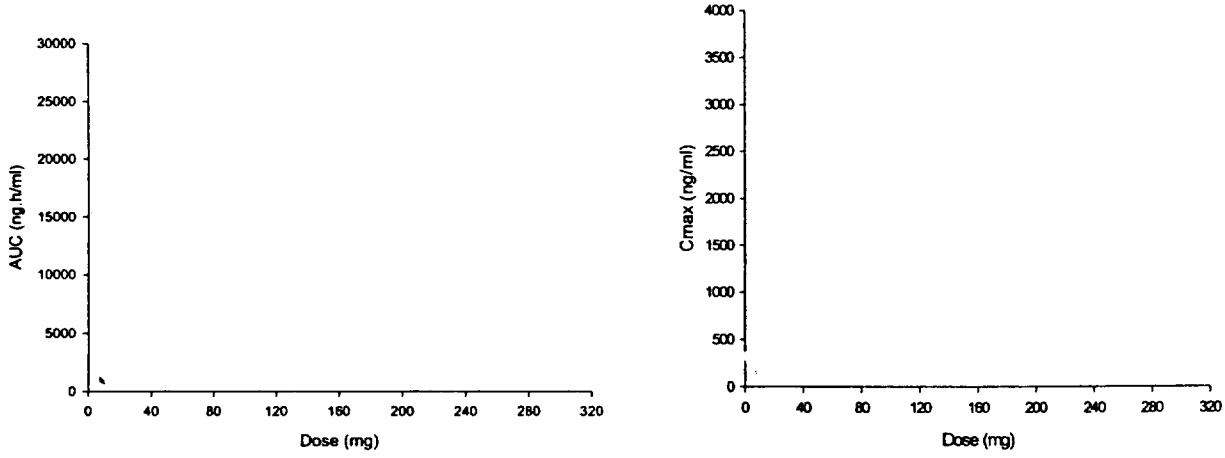


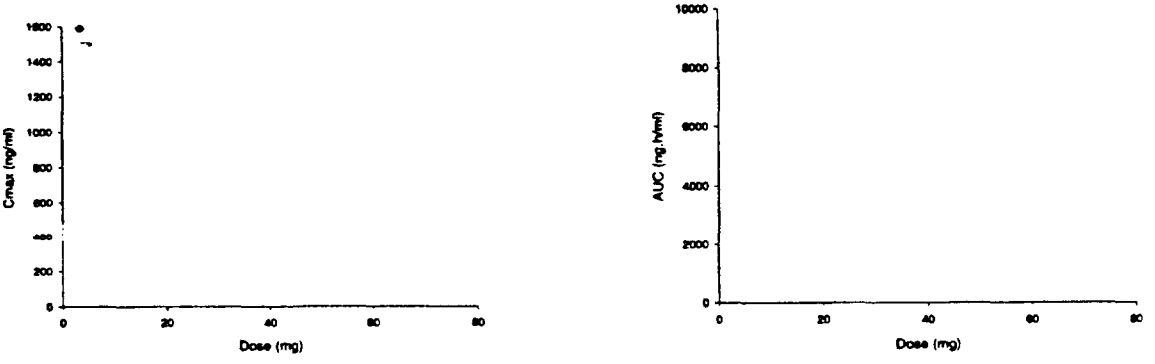
Figure 9. Relationship Between Dose AUC (left) and Cmax (right) of Olmesartan After Oral administration of Benevas for ALL doses up to 320 mg (study # 866-01)



In study # 866-102, the drug was administered daily as a single dose for 10 consecutive days to 10 subjects at each dose level (20, 40, and 80 mg). Within acceptable experimental errors and usual variability, the data show a dose proportional increase in Cmax and AUC up to 80 mg (**Figure 10**). However, it should be noted that the Cmax and

AUC for the 20 mg dose is somehow slightly at the higher end. This makes the dose proportionality between the 20 and 40 mg doses less apparent. The half-life remains constant at all doses. No difference in the data between Day 1 and day 10, which confirms that there is no drug accumulation. In terms of urine data, the percent of dose excreted in urine was about 10% on Day 1 and Day 10 at all doses. This also suggests that there is no accumulation of the drug after multiple dosing.

Figure 10. Relationship Between Cmax (left), AUC (right) and Benevas Dose in Day 1 (close circles) and Day 10 (open circles) in 10 Subjects (study # SE 866-102)



One additional note is that the drug also exhibits linear PK characteristics following IV administration up to 32 mg (study # SE-866-107).

What is the Pharmacokinetics of Olmesartan in Special Populations?

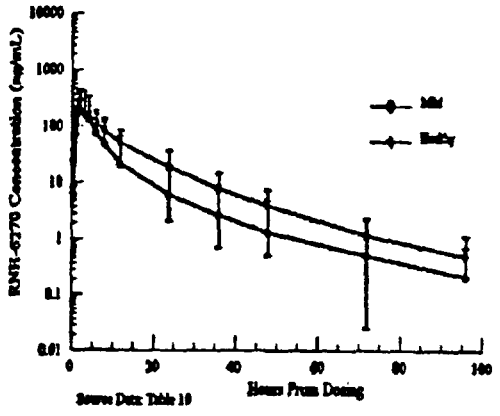
A) Hepatic Disease

The effect of hepatic disease on the PK of olmesartan was investigated after a single 10 mg dose. The drug was orally administered on Day 1 and followed by 8 mg intravenous dose after a washout period of 10 days (study # 866-109). The study was conducted in 24 subjects with varying degree of hepatic impairment as follows: 12 healthy (Childs Pugh score <5), 4 mild (Childs Pugh score 5-6), and 8 moderate (Childs-Pugh score 7-9). Blood and urine were collected over 96 hours. Subjects ranged in age from 44 to 65 years.

It should be noted that no severe patients were included in this study. Also, the study may lack adequate power due to small number of subjects particularly, the number of subjects in the mild group is rather small (n=4). In addition, there was no equal number of subjects in each group. More importantly, the selected dose of 10 mg may be considered low, since the recommended initial dose is 20 mg. However, for safety reasons in these patients, this dose can be acceptable.

After oral administration, the mean AUC is about 30% and 47% higher in mild and moderate hepatic impairment than healthy subjects, respectively (**Tables 3 and 4 and Figure 11**. However, the Cmax was not affected in this study. The plasma concentrations were generally higher at all time points in hepatic patients compared to the control group. As expected, after intravenous administration, there was little difference in the AUC and Cmax among the groups. In this case, the AUC was about 14% and 17% higher in mild and moderate hepatic impairment than healthy subjects, respectively. In terms of urine data, the amount excreted in urine was consistently higher in patients than healthy subjects. The percent of dose of olmesartan excreted in urine over 96 hours was 15.1% in mild and 18.9 % in moderate hepatic impairment. However, in healthy subjects, it was 11.5%. After IV administration, the percent of dose was 39.3% and 58.3% in mild and moderate hepatic disease, respectively, compared to 38.7% in control subjects. The fraction unbound tends to be higher in patients compared to control. The mean percent fraction unbound was 0.34% and 0.41% in mild and moderate, respectively, compared to 0.26% in control healthy subjects.

Figures 11. Mean (SD) Plasma concentration-Time Profiles of Olmesartan in Healthy Subjects and Patients With Hepatic Impairment Following a Single 10 mg Oral Dose of Benevas Tablets (study # SE-866-109)



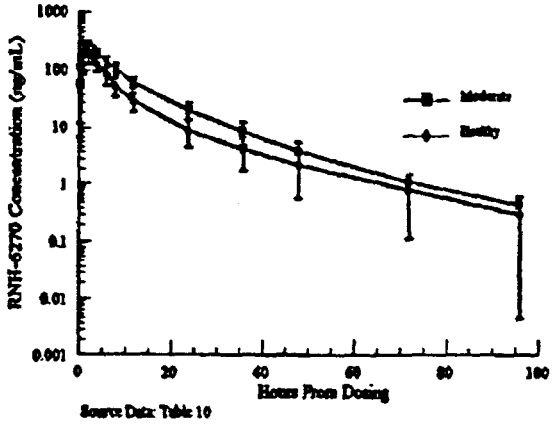


Table 3. Mean (%CV) PK Parameters of Olmesartan in Healthy Subjects and Patients With Hepatic Impairment Following a Single 10 mg Oral Dose of Benevas Tablets

Parameters	Healthy (n=12)	Mild (n=4)	Moderate (n=8)
$AUC_{0-\infty}$ (ng.h/ml)	1708 (26.8)	2227 (45.8)	2525 (14.0)
Cmax (ng/ml)	256 (26.2)	260 (16.8)	271 (19.3)
Half life (h)	16.3 (26.8)	14.4 (10.6)	15.6 (37.2)
Urine (%)	11.5 (24.9)	15.1 (31.3)	18.9 (17.3)

Table 4. Point Estimate and 90% CI For Patients With Hepatic Disease and Healthy Matched Controls Following Oral Administration a Single 10 mg Dose of Benevas Tablet

Parameter	Mild (n=4)/Control (n=4) Point Estimate (90% CI)	Moderate (n=8)/Controls (n=8) Point Estimate (90% CI)
$AUC_{0-\infty}$	1.06 (0.54-2.09)	1.65 (1.43-1.90)
Cmax	0.94 (0.56-1.56)	1.13 (0.88-1.44)
Half life	0.86 (0.74-1.00)	0.98 (0.66-1.47)
CL	0.99 (0.79-1.25)	0.82 (0.73-0.92)
CL_R	1.10 (0.70-1.72)	1.07 (0.96-1.21)
Urine (%)	1.17 (0.57-2.40)	1.77 (1.53-2.04)

B) Renal Disease

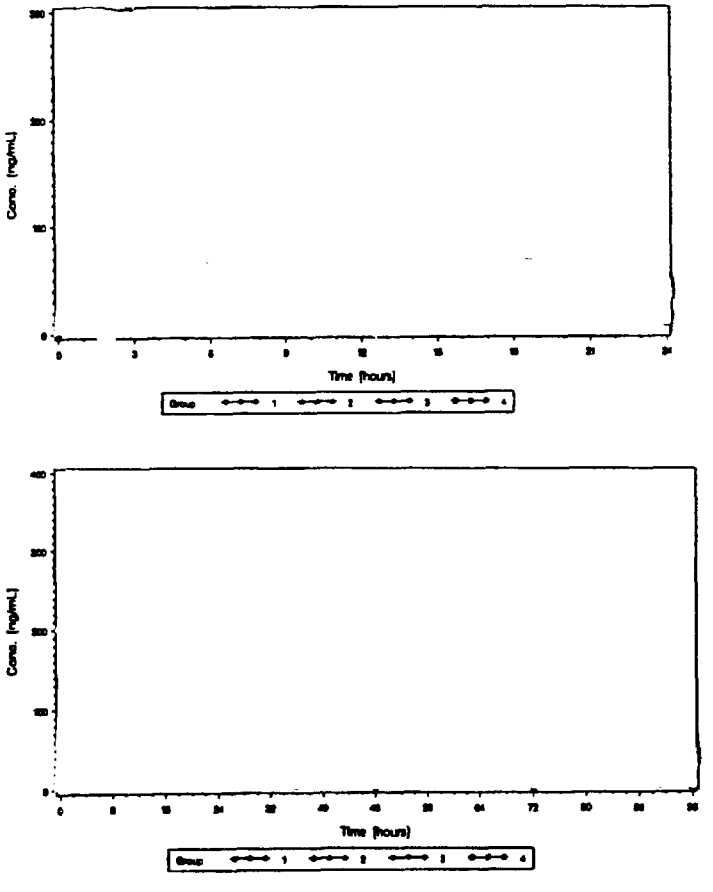
The effect of renal impairment on the PK of olmesartan was investigated at multiple 10 mg dose for 7 days. The study was conducted in 34 subjects of 25 to 75 years of age with varying degree of renal functions as follows: 8 normals (CLcr >60 ml/min), 8 mild (Clcr 40-59 ml/min), 9 moderate (Clcr 20-39 ml/min), and 9 severe (CLcr <20 ml/min) (study # SE-866/16). PK profiles were assessed on Day I and Day 7 (for 24 and 96 h after drug administration). Additional trough plasma samples were collected on Days 3, 4, 5 and 6 for RNH-6270 assay.

As in the hepatic impairment study, the selected dose of 10 mg may be considered low, since the recommended initial dose is 20 mg. However, for safety reasons in these patients, this could be acceptable. At steady state, the exposure to the drug, as exemplified by AUC, in severe renal impairment was about 3.3 fold higher than in normal subject. In the same token, the effect on Cmax was less pronounced. This was about 56% (or 1.56 fold) higher in severe renal impairment compared to normal subjects (**Table 5 and Figure 12**). Similarly, the percent of dose excreted in urine was associated with the severity of the renal impairment. These were in the same magnitude of that of the plasma data. Furthermore, Cmax and AUC were consistently higher in all renal impairment patients compared to normal subjects after both single dose and multiple dose administration. As expected, there was a strong negative correlation between $AUC_{(0-\infty)}$ (P=0050) and $Cmax_{(ss)}$ (P=0.011) and creatinine clearance. No change in the elimination half-life was noted in any of the groups irrespective of either renal function and/or duration of drug administration. Based on these data, dose adjustment is recommended in patients with renal impairment, especially in the severe cases. This needs to be discussed with the clinical division and the sponsor. At present, the lowest available tablet strength of the drug is 20 mg unscored tablet. Therefore, it is not possible to give a smaller dose in renal impairment patients.

Table 5. Geometric mean (%CV) PK parameters grouped by severity of renal impairment (study # 866-16)

Parameter	Severe CLcr <20 (ml/min)	Moderate Clcr <39 (ml/min)	Mild CLcr <59 (ml/min)	Normal CLcr>60 (ml/min)
AUC (ng.h/ml)	3779 (40.5)	2468 (32.9)	2197 (37.4)	1355 (18.1)
Css	360 (32.2)	320 (30.9)	294 (40.0)	231 (28.0)
Half Life (h)	18.0 (30.5)	18.9 (42.8)	19.3 (47.6)	18.7 (37.1)
CL_R	0.05 (111.4)	0.12 (41.3)	0.26 (72.3)	0.52 (41.5)
Urine (%)	2.96	3.91	7.61	9.63

Figures 12. Olmesartan Plasma concentration-Time Profiles After 10 mg Single Dose (Upper) and Daily for 7 Days (Lower) in Subjects With Varying Degrees of Renal Impairment



Gender:

The effect of gender on the PK of olmesartan was investigated at a single 20 mg dose administered orally to 18 males and 17 females (study# 866-110). In females, the Cmax and AUC were about 17% and 13% higher than males. The AUC averaged 3729.24 ng/ml.h in females and 3167.28 ng/ml.h in males, while Cmax averaged 574.59 ng/ml and 506.17 ng/ml in females and males, respectively. However, there was no difference in other PK parameters between females and males. In terms of urine data, the amount excreted in urine was consistently higher in females than males. However, there was little difference in the overall amount of drug excreted in urine. The mean percent excreted in urine in female was 12.2% and in males was 10.9%. Overall, the difference between males and females is of no clinical significance. Based on these results, dose adjustments is not necessary relative to gender.

D) Young and Elderly Hypertensive Patients

The exposure to olmesartan as expressed by the AUC in elderly patients of 65 years or older was approximately 33% to 44% higher than the young patients of <65 years of age. This conclusion was based on two studies (# SE-866/07 and SE- 66/14). Study # 07 was a double-blind, placebo-controlled in a group of young (18 –45 years) and elderly (65-75 years) hypertensive patients. In each group, 12 patients received a daily dose of 80 mg (4 x 20 mg) Benevas tablets for 10 days and six received placebo. The PK was determined after a single dose (Day 1) and steady-state (Day 10). Study # 14, was somewhat similar, double-blind, placebo-controlled in a group of young (18 –45 years) and very elderly (>75 years) hypertensive patients. In each group, 18 patients received a daily dose of 10 mg Benevas tablets for 14 days and six received placebo. The PK was determined after a single dose (Day 1) and steady-state (Day 14).

What Drugs Could Potentially Interact with Olmesartan?

A) *In vitro:*

Pooled human liver microsome fractions were used to examine the effects of olmesartan on the activities of several cytochrome P450 isozymes *in vitro*, including CYP1A1 and 2, CYP2A6, CYP2C19, CYP2C8 and 9, CYP2D6, CYP2E1 and CYP3A4 (study # GR 144-063). At concentrations representative of maximum plasma concentrations of olmesartan typically observed *in vivo* (approximately 10 mM), olmesartan had essentially no effect on the activity of any of the isozymes studied except for an approximate 20% inhibition of CYP2E1.

B) *In vivo* Drug-Drug Interaction Studies:

i) Is There Any Effect of Olmesartan on Other Drugs?

Warfarin (study # 866/08) Olmesartan has minimal influence on either the pharmacokinetics or pharmacodynamics of warfarin. Except for Tmax, which was slightly prolonged, the pharmacokinetic parameters of the R- and S-warfarin enantiomers were essentially unchanged by the concomitant administration of Benevas (**Table 6**).

This was based on a double-blind, placebo-controlled, two-way crossover in 24 healthy subjects. All subjects received an individualized dose of warfarin alone for a run-in-period of two weeks (day 1-13) to obtain values of 1.4 to 1.8 for International Normalized ratio (INR). After the run-in-period, a group of 12 subjects received Benevas 40 mg (2x 20 mg) tablets or placebo daily for one week in a crossover design (Either Day 14-20 or Day 23-29). The PK or PD (INR and Partial thromboplastin time-PTT) were done on Day 20-23 or day 29-32.

Table 6. Mean (± SD), Point Estimates and 90% CI for Warfarin R-and S-enantiomers PK Parameters Following Oral Administration of Benevas and Warfarin

Parameter	Warfarin Enantimore	Benevas + Warfarin	Placebo + Warfarin	Point Estimate (90% CI)
AUC_{0-24}	R	11887 ± 4956	12103 ± 4653	0.96 (0.90, 1.03)
(ug.h/ml)	S	8576 ± 3549	8498 ± 3346	1.00 (0.97, 1.03)
Cmax	R	687 ± 264	665 ± 229	1.02 (0.96, 1.08)
(ug/ml)	S	539 ± 189	517 ± 171	1.04 (1.01, 1.07)
Tmax (h)	R	1.9 ± 1.8	1.7 ± 1.5	1.15 (0.65, 1.65)
	S	1.4 ± 1.0	1.2 ± 0.6	1.22 (0.89, 1.55)

Digoxin (study #866/15). Concomitant administration of Benevas with digoxin had essentially no effect on the pharmacokinetics of digoxin. Except for $C_{ss,min}$, which was marginally higher when digoxin was administered concomitantly with Benevas as compared with placebo. Equivalence was statistically demonstrated for all digoxin PK parameters tested (**Table 7**)

These data were based on a double-blind, placebo-controlled, two-way crossover in 24 healthy subjects. In this study, all subjects entered a run-in-period and received 0.375 mg dose of digoxin daily for 10 days. After this period, while on daily digoxin doses, all subjects received either 20 mg dose of Benevas or placebo for 7 days in a crossover

design. It should be noted that the PK analysis was conducted only for digoxin. In other word, the study focuses only on the effect of Benevas on the PK of digoxin. Therefore, the effect of digoxin on the PK of olmesartan is unknown.

Table 7. Mean (%CV), Point Estimates and 90% CI for Digoxin PK Parameters Following concomitant Oral Administration of Benevas and Digoxin

Parameter	Benevas + Digoxin	Placebo + Digoxin	Point Estimate (90% CI)
$AUC_{0\text{-}24}$(ng.h/ml)	20.74 (25.84)	20.97 (25.15)	1.01 (0.97, 1.05)
Css, max (ng/ml)	2.15 (26.16)	2.13 (26.00)	0.99 (0.90, 1.08)
Css, min (ng/ml)	0.54 (33.94)	0.45 (123.33)	0.83 (0.58, 1.20)
Css, avg (ng/ml)	0.86 (25.84)	0.87 (25.15)	1.01 (0.97, 1.05)
Tmax (h)	1.0	1.0	--

ii) Is There Any Effect of Other Drugs on Benevas?

$Al(OH)3/Mg(OH)_2$ Antacid:

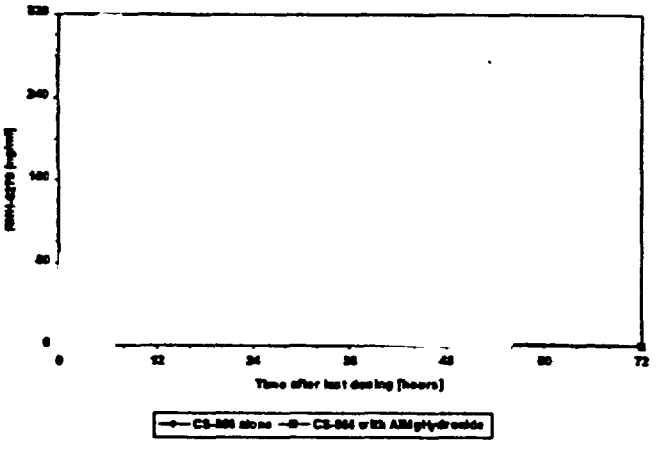
The bioavailability of olmesartan was slightly diminished (~10 %) by the coadministration of Benevas with the antacid, $Al(OH)3/Mg(OH)_2$, compared to CS-866 alone (**Table 8 and Figure 13**). Renal excretion of olmesartan was correspondingly slightly lower following coadministration of Benevas with antacid compared to Benevas alone (6.9% vs. 9.2%).

This was based on a two-way crossover trial in 24 subjects (study # SE 866-05). In this study, antacid was administered at a dose of 400 mg four time daily for 8 days. On days 4-8 a single dose of 20 mg Benevas was administered daily. After a washout period of 7-14 days, a single daily 20 mg dose of Benevas was administered alone for five days.

Table 8. Mean (%CV), Point Estimates and 90% CI for Olmesartan PK Parameters Following Concomitant Oral Administration of Benevas and Antacid

Parameter	Benevas + Antacid	Benevas Alone	Point Estimate (90% CI)
AUCss (ng/h/ml)	1630 (27)	1858 (35)	1.14 (1.03, 1.26)
$AUC_{0\text{-}24}$ (ng.h/ml)	1537 (48)	1962 (33)	1.28 (1.13, 1.45)
Cmax (ng/ml)	289 (23)	313 (36)	1.08 (0.97, 1.21)
Tmax (h)	2.0	2.0	--
Half Life (h)	10.5 (28)	11.6 (33)	--

Figure 13. Plasma concentration-Time Profiles of Olmesartan With and Without Antacid in 24 subject. (study # SE 866/05)

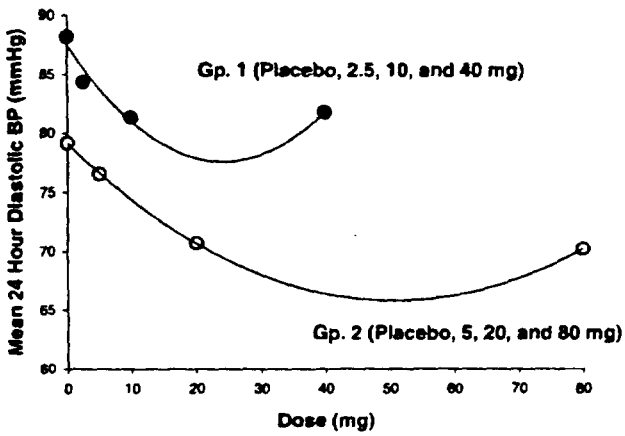


Is There any PK/PD Relationship With Benevas?

Two pilot PK/PD studies were conducted in 8 subjects each (study # SE-866/04 and SE-866/03). In study #SE-866/04 the drug was administered in a double-blind, placebo-controlled, four-way crossover design to 16 salt depleted patients. Each patient was involved in four treatment periods. Group 1 (n=8) received the following single doses: placebo, 2.5, 10, and 40 mg and Group 2 (n=8) received the following doses: placebo, 5, 20, and 80 mg. All patients were placed on a low-sodium diet of 3 to 4 g/ml 3 days prior to drug administration. Blood samples for PK were collected only at pre-dose and at 3, 6, and 12 hours post dose. For response, blood pressure and relevant biochemical (pharmacodynamic) were monitored.

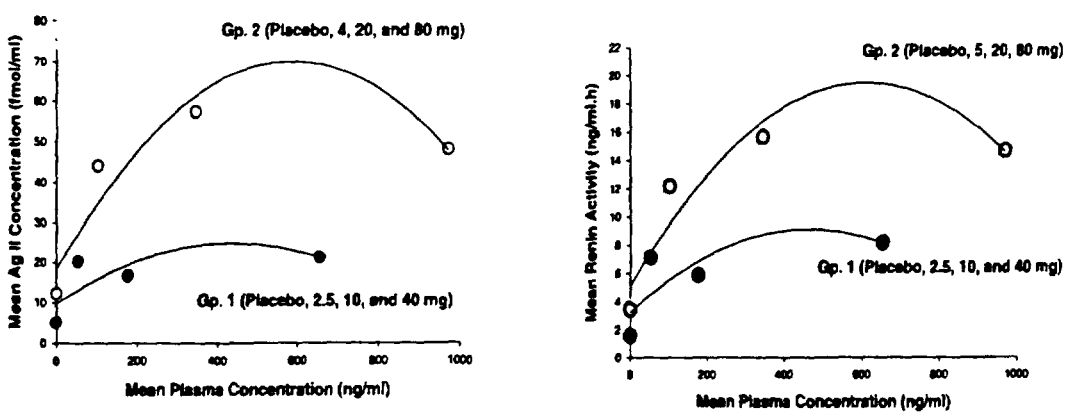
This study (#04) lacks the adequate power to establish the dose-response relationship for this drug. It appears that there is some relationship between 24 hour diastolic blood pressure and dose in each group (**Figure 14**).

Figure 14. Relationship Between Dose and Mean 24 Hours Diastolic Blood Pressure (n=8) (study # 866/04).



Overall, there is a reduction of about 10 mmHg in each group from the respective baseline with increase in dose. However, it should be noted that the baselines are markedly different between the two groups (i.e., 88 mmHg in Group 1 and 79 mmHg in group 2). Similarly, two markedly different baselines in each group were observed for renin activity and angiotensin plasma concentrations (**Figures 15).**

Figure 15. Relationships Between Plasma Concentration and Angiotensin II (left) and Renin (right) plasma concentration (n=8) (study # 866/04)



There was a weak relationship between dose and/or olmesartan plasma concentration and renin activity and angiotesnin plasma concentration. The relationship starts to plateau after the second dose in each group.

The second study (#SE-866/03) was double-blind, double-dummy, placebo-controlled, single dose, four-way crossover in healthy subjects. There was two groups of 8 subjects. In each group, 2 patients received placebo. Each patient was involved in four treatment periods. Group 1 (n=8) received the following single doses: placebo, 2.5, 10, and 40 mg Benevas tablets and Group 2 (n=8) received the following doses: placebo, 5 mg and 20 mg Benevas tablets and 20 mg enalapril. Blood samples for PK and PD (e.g., renin and angiotensin II) were collected at 1, 2, 4, 8, and 24 hours after dosing. For response, blood pressure was monitored throughout.

There was a relationship between reduction in blood pressure (BP) and dose (**Figures 16 A and B**). For example, in Group 1, the mean reduction in blood pressure following a 20 mg Benevas dose was very apparent compared to placebo. The 20 mg dose of enalapril was superior to 20 mg dose of Benevas. For better clarity, the effect of placebo was subtracted from each treatment as shown in **Figure 16 B**. Again, based on this preliminary data, it can be concluded that the there was some reduction in blood pressure with 20 mg Benevas. However, the effect is more pronounced with 20 mg enalapril.

Figure 16A. Mean Systolic Blood Pressure-Time Profiles in Group 2 Following 20 mg Benevas and 20 mg Enalapril Compared to Placebo (n=8) (study # 03)

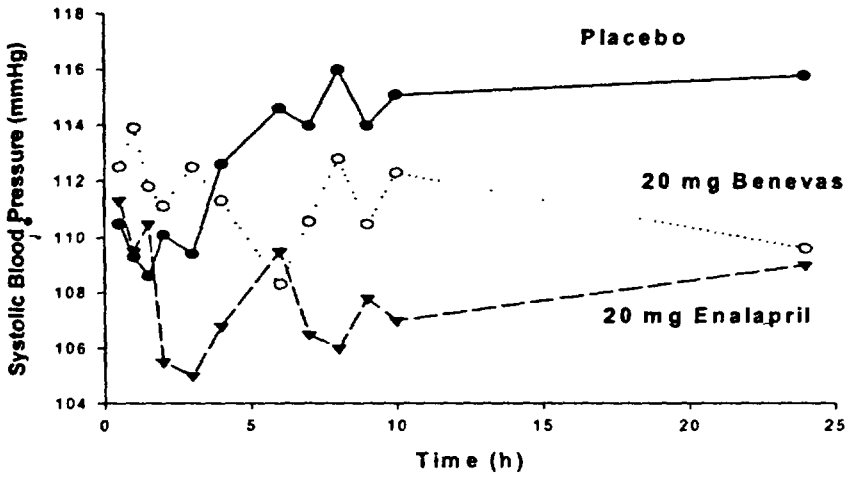
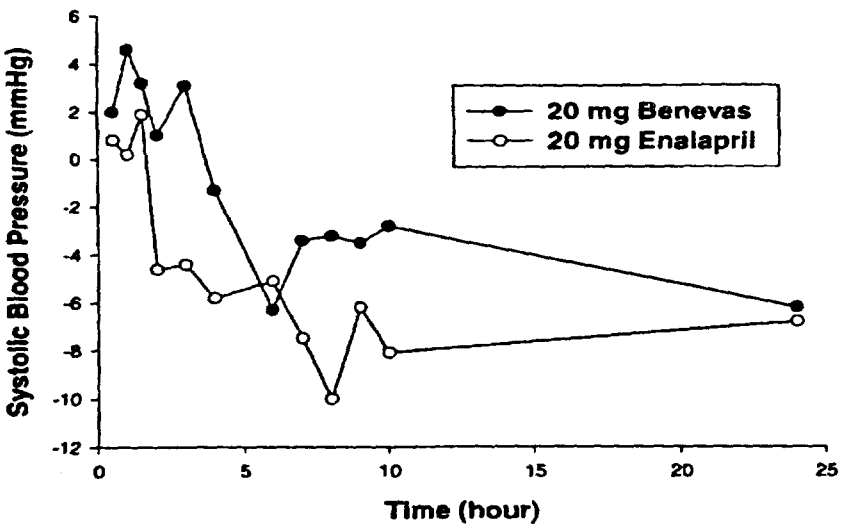
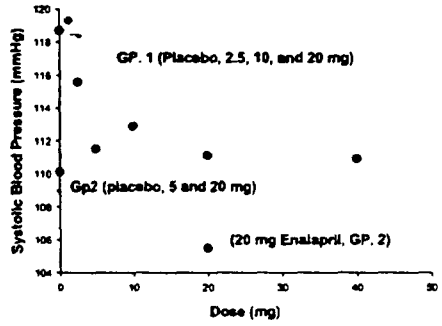


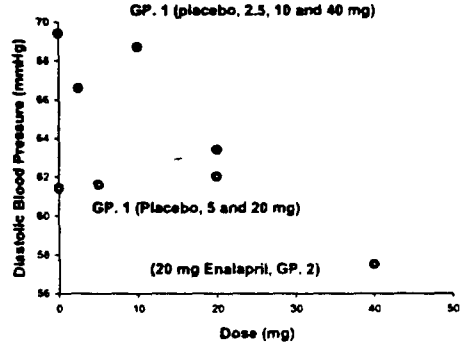
Figure 16B. Reduction in Systolic Blood Pressure After Placebo Subtraction (see Figure 16A for actual data) (study # 03).

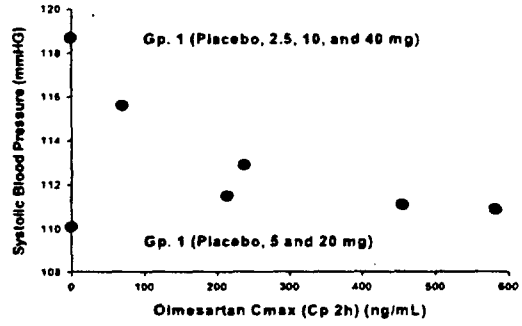


At 2 hours, the baselines for systolic and diastolic BP were markedly different between the two groups (**Figure 17**). This Figure shows that in group 1 the mean baseline for the systolic BP at 2 hour was 118.7 mmHg and in group 2 was 110.1 mmHg. Similarly, for diastolic BP, at 2 hours, it was 69.4 and 61.4 mmHg in group 1 and group 2, respectively.. In addition, there was some relationship between reduction in blood pressure, dose and plasma concentration, particularly at Cmax, which occurs at 2 hours (**Figures 17**).

Figures 17. Relationship Between Systolic (left), Diastolic (right) blood Pressure and Dose. The lower Figure shows the relationship Between Systolic Blood Pressure and Plasma Concentration at 2 hours (cmax) (study # 03)

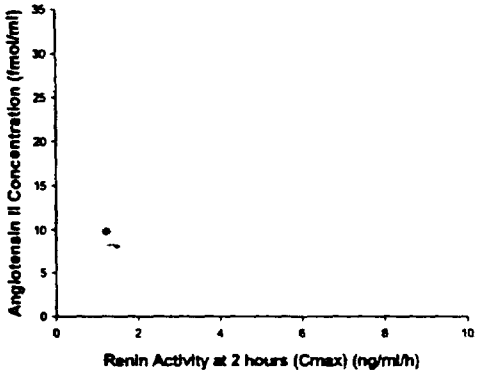


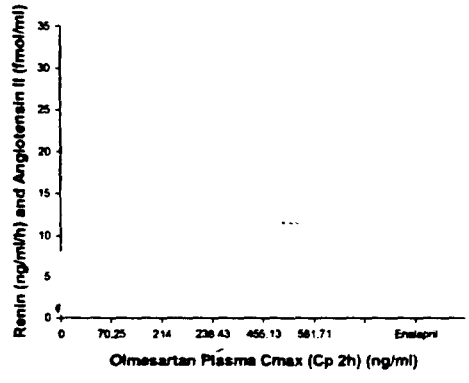




It appears that there is a linear relationship between renin activity and angiotensin II at 2 hours (Cmax) of drug administration (**Figures 18**). Enalapril, howerver, caused marked reduction in renin activity and angiotensin. There was a non-linear relationship between olmesartan plasma concentration (e.g., Cmax) and renin and angiotensin plasma concentration. Overall, this study lacks of adequate power to establish a dose-response relationship for this drug (n=8 in each group).

Figures 18. Relationship Between Rennin Activity at 2 hours and Angiotensin II Concentration at 2 hours (left) and Olmesartan Plasma Concentration at 2 hours (Cmax) and Renin and Angiotesin Concentration at 2 hours (right)





ClinPharm/Biopharm Briefing on: December 21, 2000.

Briefing Attendees: Drs. Patrick Marroum, Chandra Sahajawalla, Mehul Mehta, Hank Malinowski, Jerry Fetterly, Florian Zielinski, Akinwole Williams, Agnes Westelinck, Shari Targum, and Shiew-Mei Huang

Reviewed by:

/S/

Sayed Al-Habet, Ph.D.
Office of Clinical Pharmacology and Biopharmaceutics
Division of Pharmaceutical Evaluation I

/S/

RD/FT initialed by Patrick Marroum, Ph.D. _____

cc: NDAs # 21-286: HFD-110, HFD-860 (Al-Habet and Mehta), and Drug files (Biopharm File, CDR).

Appendix I

Sponsor's Proposed Label

12 pages redacted from this section of the approval package consisted of draft labeling

Appendix II

Individual Studies/Reports

Vol. 31

Study No. 866-108

Title

A Randomized, Open Label, Four-Way Crossover Study Using Single Doses of RNH-6270 Solution Intravenously, RNH-6270 Solution Orally, CS-866 Tablets Orally and CS-866 Suspension Orally to Assess Bioavailability in Healthy Adult Volunteers

Investigator:

Objective

To determine the absolute bioavailability of the active metabolite (RNH-6270) of the prodrug CS-866 when administered orally.

Study Design:

This study was a single center, randomized, open-label, four-way crossover trial. Each subject was randomly assigned to a pre-specified treatment sequence.

Subjects were confined to the clinical study unit beginning, the evening before each dose until approximately 72 hours afterwards. Subjects were ultimately administered all four formulations. Dosing occurred every seven days, such that there was a four-day washout period following the dosing interval prior to the administration of the next formulation. Pharmacokinetic assessment included plasma (15-17 collection time-points) and urine (seven collection intervals) sample analysis during each post-dose evaluation period.

Subject Enrollment

The age range for the 24 male subjects enrolled in the study was 19 to 45 years (27.5 4. 7.03, inclusive. They ranged in weight from 122 to 206 pounds (165.3 + 20.8), and in height from 66 to 76 inches (70.8 + 2.8). Racially, the study group was comprised of 14 Black subjects (58%) and 10 Caucasian subjects (42%).

Drug Administration

During each dosing period, subjects were administered one of four different formulations following an overnight fast: 20 mg CS-866 tablet PO, 20 mg CS-866 suspension PO, 16 mg RNH-6270 solution iv, or 16 mg RNH-6270 solution PO.

Formulations:

The formulations used in this study are shown below. It is important to note that that the parent compound (CS-866) in the tablet and suspension formulations is present as methyl ester of RNH-6270. There are 16 mg equivalents of RNH-6270 in 20 mg of CS-866.

Test product, dose, mode of administration and batch number:

Test product	Dose	Mode of Administration	Batch No.
CS-866 Tablet	20 mg	po	293
CS-866 Suspension	20 mg	po	K97T05
RNH-6270 Solution	16 mg	po	K97T01
RNH-6270 Solution	16 mg	iv	K97T01

Results:

REDACTIONS MADE BY APPLICANT

Table 7.2.3.1:5 Summary of Pharmacokinetic Parameters for RNH-6270

[redacted]	$AUC_{0-\infty}$ (ng·h/mL)	AUC_{0-t} (ng·h/mL)	C_{max} (ng/mL)	T_{max}[1] (hrs)	$t_{1/2}$ (hrs)	V (L)	CL (L/hr)
CS-866 TABLETS ORALLY							
N	23	23	23	23	23	21	21
MEAN	3543.85	3311.83	494.97	2.00	18.06	34.92	1.31
S.D.	961.04	775.89	86.74	_	8.23	20.71	0.25
%CV	27.44	23.43	17.52	_	45.60	59.31	19.22
CS-866 SUSPENSION ORALLY							
N	23	22	23	23	22	20	20
MEAN	2713.66	2620.31	368.96	2.00	16.06	30.75	1.29
S.D.	771.78	756.37	94.73	_	5.72	12.44	0.25
%CV	28.42	28.82	25.67	_	35.62	40.46	19.00
RNH-6270 SOLUTION iv							
N	21	21	21	21	21	21	21
MEAN	12902.84	12844.75	4542.37	0.17	13.22	25.34	1.31
S.D.	2723.13	2737.82	760.95	_	4.79	12.66	0.25
%CV	21.27	21.31	16.75	_	36.30	49.96	19.22
RNH-6270 SOLUTION ORALLY							
N	22	21	22	22	21	20	20
MEAN	478.99	380.86	20.56	3.00	27.87	49.61	1.29
S.D.	143.83	182.00	8.77	_	22.42	49.59	0.25
%CV	30.03	31.33	33.92	_	80.44	100.76	19.00

[1] The median for T_{max} is displayed in the mean row.

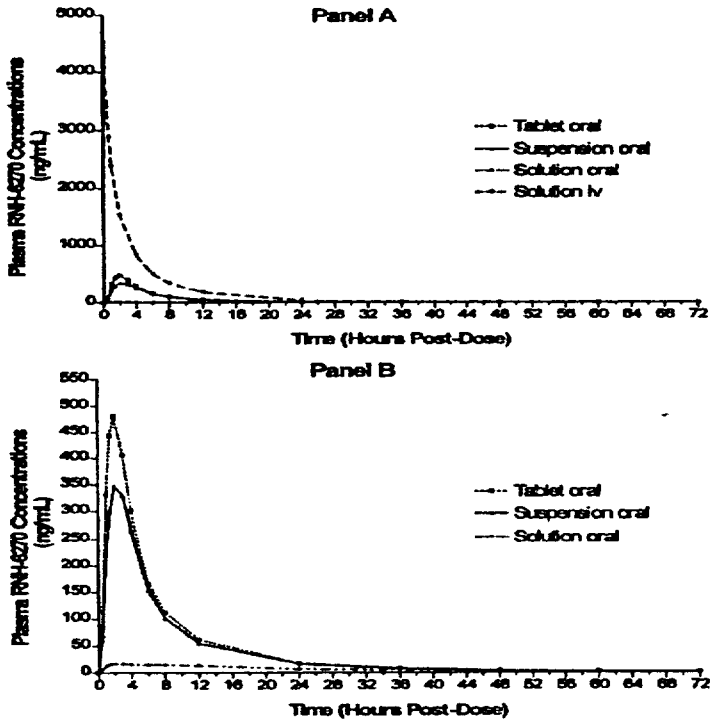
Reference: Section 10.2, Table 6

Table 7.2.3.2:1 Absolute Bioavailability of RNH-6270 following Oral Administration of CS-866 or RNH-6270

[redacted]	F (%)		
	CS-866 Tablets	CS-866 Suspension	RNH-6270 Solution
N	21	20	20
Mean	25.6	21.4	4.3
S.D.	3.86	4.09	0.56
%CV	15.11	19.13	13.51

Reference: Section 10.2, Table 7

Figure 7.2.3.1:1 Mean Plasma RNH-6270 Concentration-Time Profiles following Four Individual Treatments: Panel A (All Four Treatments), Panel B (Oral Treatments only).



Reviewer's Summary:

1. The administered doses in all arms are not the same. The dose for the oral and IV solutions was 16 mg and for tablets and suspensions was 20 mg.

2. Oral administrations of tablet or suspension resulted in similar plasma concentration time profiles for olmesartan. The mean (± SD) Cmax was 495 (± 87) ng/mL for the tablets (20 mg dose) and 368 (± 95) ng/mL for the suspension (20 mg dose) and the Tmax 2 hours. In sharp contrast, The mean (± SD) Cmax after oral solution of 16 mg dose was 20 (± 7) ng/mL. This is markedly lower than that after 20 mg dose of oral suspension. In addition, the Cmax with the suspension was ~25% lower than of the tablets. The reasons for these unexpected discrepancies are due to the fact that the parent compound (CS-866) in the tablet and suspension formulations was present as methyl ester of RNH-6270 and there are 16 mg equivalents of RNH-6270 in 20 mg of CS-866.

3. The calculated mean bioavailability of RNH-6270 was 25.6 (± 3.86)% from the tablet, 21.4 (± 4.09) % from the suspension, and only 4.5 (± 0.96) % from the oral solution.

4. Total urinary excretion was greatest following iv administration averaging 35.8 % of the administered dose; next came the tablet and suspension averaging 9.5 % and 8.3 %, respectively followed lastly by the oral solution which averaged 1.6 % of the administered dose.

Conclusions:

The mean bioavailability of 4.5% after oral solution is markedly lower than that after tablets (25.6%) and suspension (21.4%). The reasons for the low bioavailability from the solution is because the parent compound (CS-866) in the tablet and suspension formulations was present as methyl ester of RNH-6270 and there are 16 mg equivalents of RNH-6270 in 20 mg of CS-866

Vol. 89

Study # SE-141-012

Title:

Effects of Meals on Bioavailability

Investigator:

[redacted]

Toshiaki Amamoto

Objectives

To compare the pharmacokinetics of CS-866 after single oral administration in the fasting state with that after meals in healthy adult male volunteers, and to investigate the effects of meals.

Subjects:

Subjects were 6 healthy Japanese adult males.

Meals:

Subjects in the group with administration in the fasting were made to fast from 11:00 p.m. on the day before administration until 4 hours after administration of the study drug. Subjects in the group with postprandial administration were to finish breakfast by 30 minutes before administration. Subsequently, ordinary meals of the same content (daily calorie: 1,800 to 2,400 kcal, salt content: 8 to I 0 g) were served to all subjects at designated times. The following Table shows the food contents:

Breakfast menu

	Weight (g)	Energy (Kcal)	Protein (g)	Fat (g)	Carbohydrate (g)	Salt (g)
3 butter-enriched dinner rolls	105	293	9.2	5.4	51.9	1.3
Regular milk	180	113	5.6	6.1	8.6	0.2
1 boiled egg	50	76	6.0	5.1	0.4	0.2
Orange juice	165	66	0.8	0.2	17.3	0.0
Butter (containing salt)	8	60	0.0	6.5	0	0.2
Strawberry jam	14	37	0.1	0.0	9.4	0.0
Total	522	645	21.7	23.3	87.6	1.9
% (Kcal)			13	32	54	

Study Design:

A randomized open-label 2-way cross-over study with single oral administration in the fasting or after meals. The study drug was CS-866, and the dose was 8 mg tablet (lot # TT154). The study was conducted in 2 groups each of 3 subjects (6 subjects in total) with the same method in each period. The washout period was I week.

Formulation:

The lot # for the 8 mg table used in this study was TT154.

Results:

The mean data are shown in the following Table and Figures.

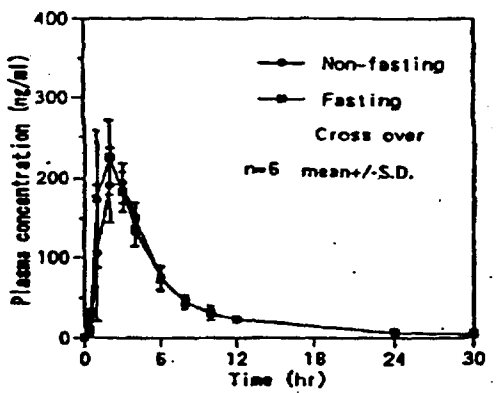
Protocol registration No. 141-012

Table 4

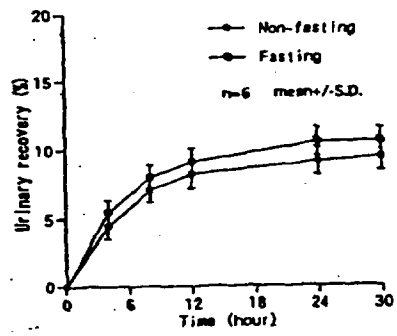
Pharmacokinetic parameter (plasma RNH-6270)

Administration condition	Phase	Subject No.	C_{max} (ng/ml)	T_{max} (hr)	$t_{1/2}$ (hr)	$AUC_{(0-30hr)}$ (ng · hr/ml)
In fasting	1	41	244.0	2.0	6.5	1213.7
		42	214.2	1.0	7.0	1431.3
		43	298.7	2.0	7.5	2010.4
	2	44	212.3	2.0	8.0	1125.3
		45	283.9	2.0	7.5	1243.0
		46	126.9	2.0	6.6	723.1
n=6		mean	226.7	1.8	7.2	1291.1
		sd(n-1)	58.6	0.4	0.6	423.2
Postprandial	2	41	231.6	3.0	6.5	1222.5
		42	222.9	2.0	7.6	1252.1
		43	248.6	2.0	8.5	1441.6
	1	44	179.1	3.0	6.5	1059.7
		45	190.1	2.0	8.6	1044.9
		46	205.7	3.0	5.7	1251.6
n=6		mean	211.4	2.5	7.2	1212.1
		sd(n-1)	28.3	0.5	1.2	146.4

Plasma concentrations of RNH-6270



Urinary recovery of RNH-6270



Reviewer's Comments:

1. This is a small pilot study in 6 Japanese subjects. The drug was administered in at a dose of 8 mg in two-way crossover design with or without food.

2. The administered dose is very low since the initial recommended dose is 20 mg daily.

3. Food had no effect on the bioavailability of olmesartan. However, the Tmax was slightly prolonged (1.8 vs. 2.5 hour) when the drug was administered with food.

4. No difference in urine excretion was noted between treatments.

Vol. 79

Study # SE 866-103

Title:

A Comparative Bioavailability Study of CS-866 Tablets in the Presence and Absence of Food in Healthy Adult Male Volunteers

Investigator:

Objective

To compare the bioavailability of CS-866 tablets administered in the fasted state versus CS-866 tablets administered in the fed state to healthy adult male volunteers.

Design:

Randomized, balanced, open-label, three-way crossover of single oral doses of CS-866 in the fasted state (on two separate occasions) and in the fed state. A complete Latin square design was employed.

Treatments:

Treatment A and B were administered in the fasted state and Treatment C in the fed state.

Enrollment

Twenty-five (25) healthy adult male subjects between the ages of 19 and 45 years old were enrolled and 24 completed the study.

Study Duration:

Subjects were confined m the clinical study unit from 12 hours prior to through 48 hours following each drug administration with a one week washout between each dosing.

Pharmacokinetic Sampling

Plasma samples for analysis of plasma RNH-6270 concentrations were collected prior to and at 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, 24, 36 and 48 hours following each drug administration.

Urine samples for analysis of urine RNH-6270 concentrations were collected prior to and 0-4, 4-8, 8-12, 12-24, 24-36 and 36-48 hours following each drug administration.

Formulation:

The lot # for the 20 mg tablets used in this study was 204F.

Results:

The mean data are shown in the following Tables and Figure.

Mean (S.D.) RNH-6270 Plasma Pharmacokinetic Parameters Following CS-866 Administration

Pharmacokinetic Parameters	First Administration, Fasted Arithmetic Mean (S.D.)	First Administration, Fasted Arithmetic Mean (S.D.)*	Second Administration, Fasted Arithmetic Mean (S.D.)	Treatment A Arithmetic Mean (S.D.)
Cmax (ng/mL)	499.5 (152.7)	468.3 (97.12)	482.1 (144.5)	499.7 (164.3)
Tmax (hr)	2.02 (0.667)	1.98 (0.561)	1.94 (0.450)	2.00 (0.676)
AUC(0-t) (ng*hr/mL)	3072 (738.1)	3024 (662.2)	3127 (947.9)	3131 (770.3)
AUC(0-inf) (ng*hr/mL)	3148 (761.0)	3101 (687.6)	3219 (961.9)	3211 (786.8)
T1/2el (hr)	10.71 (3.159)	10.71 (3.159)	11.66 (2.924)	10.71 (2.786)
Kel (1/hr)	0.0692 (0.0165)	0.0692 (0.0165)	0.0624 (0.0127)	0.0682 (0.0144)
LN(Cmax)	6.177 (0.2662)	6.127 (0.2181)	6.135 (0.3024)	6.173 (0.2786)
LN[AUC(0-t)]	8.000 (0.2587)	7.988 (0.2433)	8.003 (0.3148)	8.020 (0.2473)
LN[AUC(0-inf)]	8.024 (0.2581)	8.013 (0.2432)	8.034 (0.3065)	8.046 (0.2463)

	Treatment A Arithmetic Mean (S.D.)*	Treatment B Arithmetic Mean (S.D.)	Treatment C Arithmetic Mean (S.D.)
Cmax (ng/mL)	468.4 (114.5)	482.0 (131.2)	450.9 (104.1)
Tmax (hr)	1.96 (0.569)	1.96 (0.440)	2.77 (0.932)
AUC(0-t) (ng*hr/mL)	3084 (702.1)	3067 (921.7)	2883 (740.1)
AUC(0-inf) (ng*hr/mL)	3163 (720.5)	3156 (941.4)	2986 (755.3)
T1/2el (hr)	10.71 (2.786)	11.66 (3.281)	12.64 (6.289)
Kel (1/hr)	0.0682 (0.0144)	0.0635 (0.0155)	0.0606 (0.0139)
LN(Cmax)	6.123 (0.2321)	6.140 (0.2916)	6.084 (0.2415)
LN[AUC(0-t)]	8.009 (0.2322)	7.982 (0.3228)	7.934 (0.2641)
LN[AUC(0-inf)]	8.034 (0.2317)	8.012 (0.3152)	7.970 (0.2611)

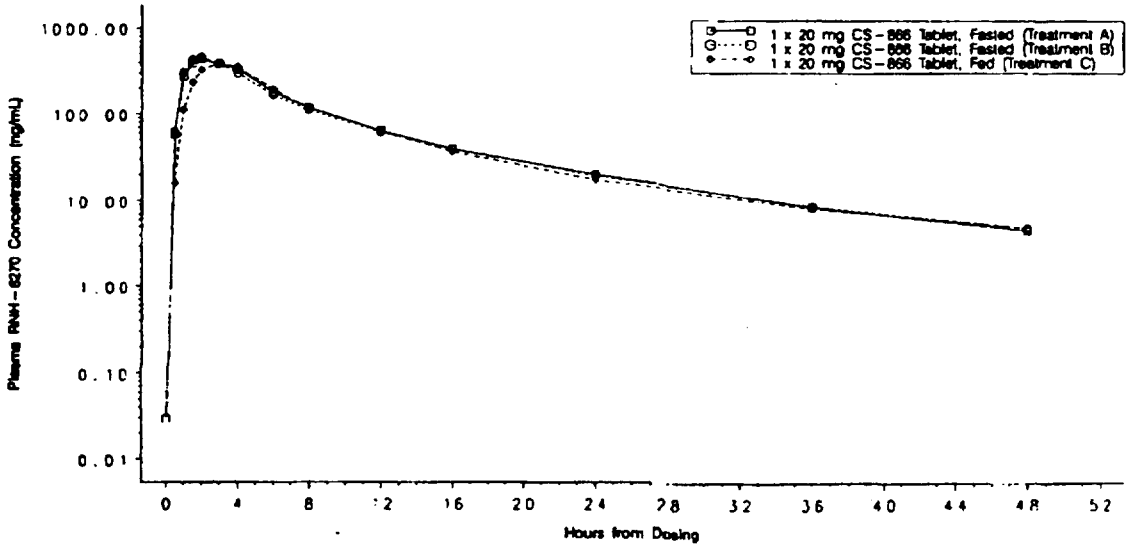
Treatment A = 1 x 20 mg CS-866 Tablet, Fasted
Treatment B = 1 x 20 mg CS-866 Tablet, Fasted
Treatment C = 1 x 20 mg CS-866 Tablet, Fed
*Mean pharmacokinetic parameter values excluding RNH-6270 concentration at Hour 4, Subject 215, Treatment A.

Mean (S.D.) RNH-6270 Urine Pharmacokinetic Parameters Following CS-866 Administration

	Treatment A Arithmetic Mean (S.D.)	Treatment B Arithmetic Mean (S.D.)	Treatment C Arithmetic Mean (S.D.)
Total Amount Excreted (mg)	1.606 (0.345)	1.576 (0.455)	1.494 (0.355)
Total Percent of Dose Excreted (%)	10.59 (2.274)	10.39 (3.002)	9.844 (2.338)
Maximum Excretion Rate (mg/h)	0.157 (0.033)	0.162 (0.058)	0.147 (0.039)
Time of the Maximum Excretion Rate (h)	2.5 (1.4)	2.3 (1.1)	3.7 (2.0)

Mean Plasma RNH-6270 Concentrations Versus Time

Semi-Log Scale



Reviewer's Summary:

1. There was no difference in the PK parameters for repeat dosing at fasting state.

2. Food had no effect on the bioavailability (i.e., AUC) of olmesartan. However, the Cmax was slightly lower with food (~470 ng/ml vs. 450 ng/ml). In addition, the Tmax was slightly prolonged (~1.9 vs. 2.7 hour) when the drug was administered with food.

3. The % of dose excreted in urine over 48 hours was similar among the three treatments (~10%)

Conclusion:

Based on this study, there was no food effect on the PK of olmesartan. Therefore, the drug can be taken with or without food.

Vol. 38

Study No. 866-116

Title

A Randomized, Open-Label, Two-way Crossover Bioequivalence Study of CS-866 Tablets in Healthy Adult Volunteers.

Investigator:

Objectives

To determine the relative bioequivalence of RNH-6270 following oral administration of two different tableted formulations of CS-866 (lot # 2234V99013 and E99T03).

Study Design

Fifteen healthy (male and female) subjects each were randomly assigned to receive one of the two different formulations (either 20 mg market-image CS-866 tablets or 20 mg investigational CS-866 tablets) at each of two different dosing intervals. The study required each eligible subject to spend approximately 176 hours at the clinical facility (88 hours during each of two separate visits). Each subject was ultimately administered both formulations. Dosing occurred every fourteen days, such that there was an eleven-day washout period following the dosing interval prior to the administration of the next formulation. Subjects were questioned for the occurrence of adverse events during each study period. Pharmacokinetic assessment included plasma (15 collection time-points) sample analysis during each dosing interval.

Drug Administration

On Day 1, subjects were administered a single 20 mg market-image CS-866 or 20 mg investigational CS-866 tablet orally (po) according to a predetermined randomization schedule. Following an eleven day washout period, subjects received the alternate CS866 tablet formulation in a two-way crossover design.
Formulations:

Formulations:

The lot #s of the formulations the commercial tablet was 2234V99013 and for investigational tablet was E99T03. The commercial tablet was essentially identical to the investigational tablet with respect to excipients, however, their relative ratios and final tablet size were different (see Table below). It should be noted that the batch size of the commercial tablets was over [redacted]

Composition of Benevas 20 mg Tablets

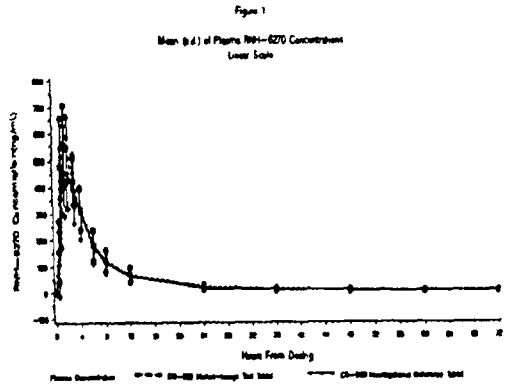
Ingredients	**Research Tablets (% of core weight)**	**Commercial Tablets (% of core weight)**
CS-866 (mg)	20 (19.0)	20 (9.5)
Microcrystalline cellulose (mg)	[redacted]	[redacted]
Low substituted hydroxypropyl cellulose (mg)		
Lactose monohydrate (mg)		
Hydroxypropylcellulose (mg)		
Magnesium stearate (mg)		
Tablet core weight (mg)		
Film Coat (mg)		
Total weight (mg)	**110**	**218**
Shape	Round	Round
Diameter		
Color	White	White

Results

The mean data are shown in the Table and Figure below.

PK and BE Parameters Following 20 mg a Single Dose of Benevas Tablets:

Parameter	Commercial Tablet (n=30)	Research Tablet (n=30)	Point Estimate	90% CI
AUC_{0-t} (ng/ml.h)	3608.12 (856.22)	3284.46 (805.23)	1.10	(1.031, 1.17)
$AUC_{0-\infty}$ (ng/ml.h)	3696.46 (928.26	3344.19 (841.50)	1.10	(1.036, 1.18)
Cmax (ng/ml)	589.70 (119.26)	524.63 (138.08)	1.15	(1.061, 1.24)
Tmax (h)	1.50	1.50	-	-
Half life (h)	19.45 (12.16)	17.45 (8.66)	-	-



Mean (+SD) Cmax values following oral administration were 589.70 (±119.26) and 524.63 (-±138.08) ng/mL for the market-image and the investigational CS-866 tablet formulations, respectively. As shown in the Figure (below), mean plasma RNI-l 6270 concentrations were marginally higher for the market-image CS-866 test tablets at each timepoint following dosing when compared with mean plasma RNH-6270 concentrations for the investigational CS-866 reference tablets. Mean (+SD) AUC values were 3696.46 (± 928.26) and 3344.19 (± 841.50) ng.h/mL for the market-image and the investigational CS-866 tablet formulations, respectively.

The ratio point estimates for AUC (0-inf), AUC (0-t) and Cmax were 1.10, 1.10 and 1.15, respectively. Despite the marginally higher values for the market-image formulation, the two formulations were deemed bioequivalent, since CIs surrounding these ratios were within the 0.8, 1.25.

Conclusions

1. The commercial tablet was essentially identical to the investigational tablet with respect to excipients, however, their relative ratios and final tablet size were different.

2. The two formulations were bioequivalent. The 90% CI limits for the AUC and Cmax were within 80-125%.

3. It should be noted that the sponsor on December 15, 2000 has submitted *in vitro* dissolution data for the 20 and 40 mg tablets The data showed that the dissolution profiles of the 20 mg and the 40 mg formulations are similar in three media. The f2 values were >50 in the three media. Based on this, waiver for the bioequivalence study for the 40 mg strength is granted.

APPEARS THIS WAY
ON ORIGINAL

Vol. 35

Study # SE-866/13

Title:

A RADIOLABELLED, PHARMACOKINETIC AND DOSE RECOVERY STUDY OF THE ^{14}C- LABELLED OPAL ANGIOTESNIN II- ANTAGONIST CS-866 IN HEALTHY ADULT VOLUNTEERS

Investigator:

[redacted]

Objectives:

The primary objective of the study was the investigation of the absoption, excretion and metabolism, and the PK profile of ^{14}C CS-866 in healthy male subjects. The secondary objective was to assess safety and tolerability of CS-866.

Study Design:

This phase I study was an open-label, single-dose study in six healthy, male Caucasian volunteers, aged between 49 sad 54 years. The subjects received a single oral dose of 19.85 or 19.86 mg [^{14}C] CS-866 (ca. 99 μCi).

Subjects fasted for at least 10 hours overnight prior to dosing. Blood, urine and fecal samples were collected in appropriate intervals over 216 hours. All blood, plasma, urine and faecal samples were assayed for radioactivity.

Results:

The mean data are shown in the tables and figures below:

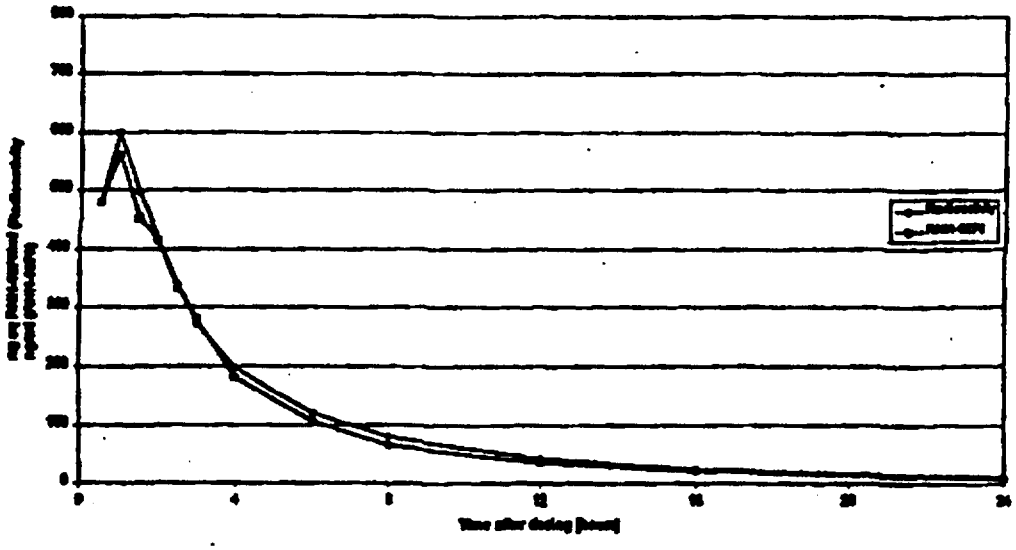
Table I: Total Excretion of Radioactivity in Urine and Faeces [% of Dose]

	Subject No.						Descriptive Statistics				
	1	2	3	4	5	6	Mean	SD	Min	Median	Max
Urine	12.86	13.84	16.31	9.84	12.85	10.16	12.68	2.96		12.71	
Faeces	79.40	64.58	78.10	77.09	73.50	89.59	77.21	8.18		78.10	
Total	91.96	78.12	94.41	87.83	86.35	89.76	89.77	7.63		89.80	

Table II: Pharmacokinetic Parameters for RNH-6270 in Plasma and Urine

Subject No.	C_{max} [ng/ml]	t_{max} [h]	AUC (0-tz) [ng*h/ml]	AUC (0-∞) [ng*h/ml]	$t_{½}$ [h]	A_e [µg]	% of dose excreted in urine	Cl_R [ml/min]
1	732.8	0.5	2540	-	-	1384	8.72	-
2	829.0	1.0	2797	2808	18.02	2129	13.42	12.64
3	750.0	1.0	3252	3273	8.11	2084	13.13	10.61
4	889.4	1.0	1964	-	-	2013	12.69	-
5	853.3	1.0	3059	3165	13.14	1961	12.48	10.43
6	416.6	2.0	1799	-	-	1676	10.56	-

Figure I: Median Plasma Concentration Vs Time Curves of Radioactivity and RNH-6270



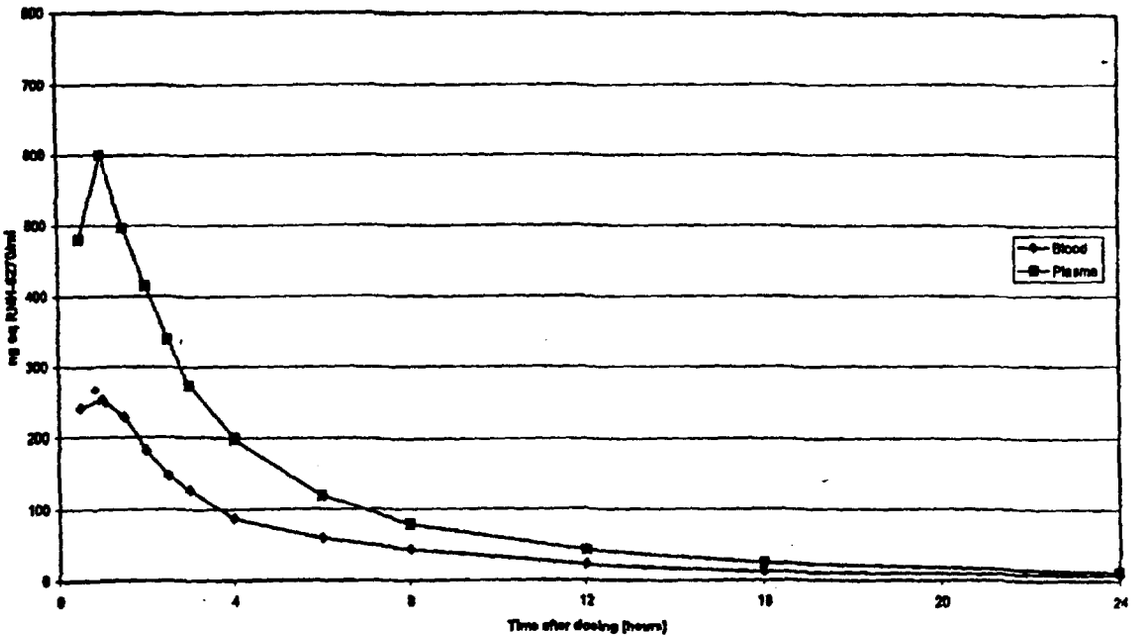
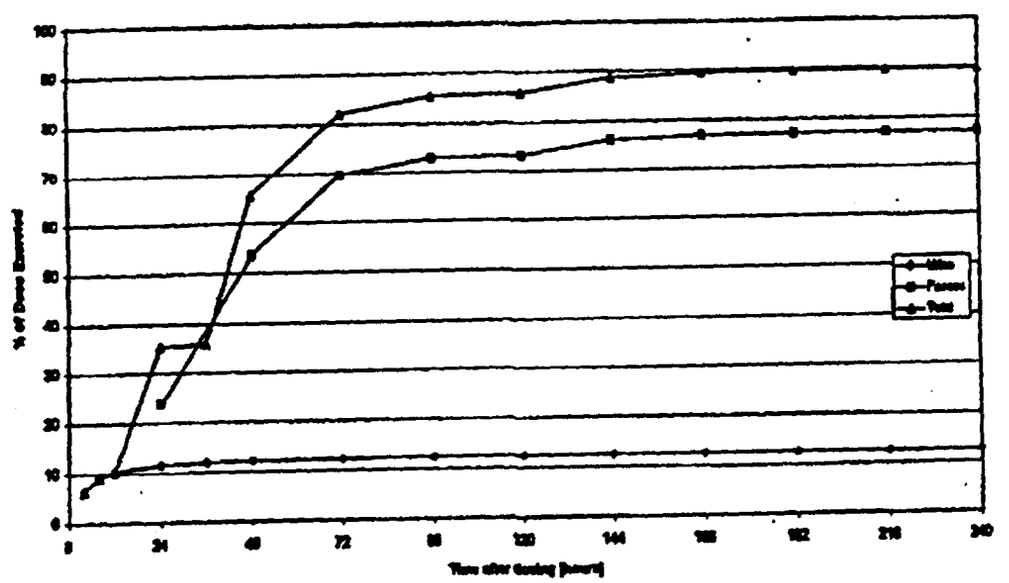


Figure II: Mean Cumulative Excretion of Radioactivity with Time in Urine and Faeces



Reviewer's Summary:

1. The drug was rapidly absorbed with a peak plasma concentration of radioactivity occuring within 0.5 to 2 hours after administration.

2. RNH-6270 was the only radio-labeled components observed in plasma.

3. The mean cumulative recovery of radioactivity amounted to 12.6% of the administered dose in urine and 77.2% in feces after 312 hours.

4. Essentially all radioactivity was accounted for as unchanged olmesartan. The overall radioactive recovery from both urine and feces averaged 89.77% (range: [redacted] %).

5. It should be noted that, overall, the radioactivity in blood was approximately 50% of that in plasma.

APPEARS THIS WAY
ON ORIGINAL

Vol. 59

Study # SE-866/21

Title:

A PHARMACOKINETIC DOSE PROPORTIONALITY STUDY FOLLOWING MULTIPLE DAILY DOSES OF 2.5, 5, 10, 20 AND 40 MG CS-866 IN HEALTHY VOLUNTEERS

Investigator:

[redacted]

Objective:

To evaluate the dose proportionality at steady state of CS-866 in plasma of healthy, male volunteers.

Study Design:

This phase I study was a randomized, open-label, five-way crossover study (five-period, Williams design (2 Latin squares), 7-day dosing periods separated by a washout period of 7-14 days). CS-866 was administered in five different doses {2.5, 5, 10, 20 and 40 mg) to 30 subjects. After the last dose of a dosing period (7 days), blood samples were collected for a period of 60 hours.

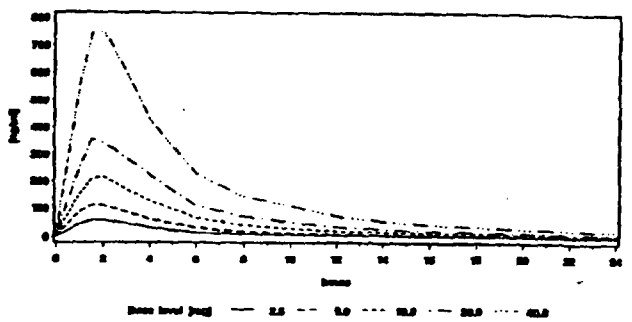
Formulations:

The lot #s of the 2.5, 5, and 10 mg tablets used in this study are 2231V97001, 2232V97001, and 2233V97003, respectively.

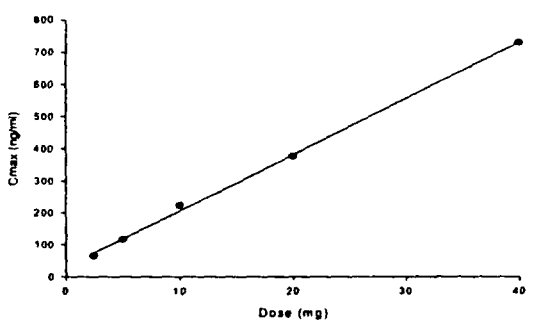
Results:

The mean data are shown in the Tables and Figures below:

Figure II. Concentration of RNH-6270 [ng/ml] in Plasma. Course of Median (by Dose Level)



Relationship Between Dose Cmax (left) and AUC (right) of Olmesartan multiple dose (7 Days) Oral administration of Benevas.



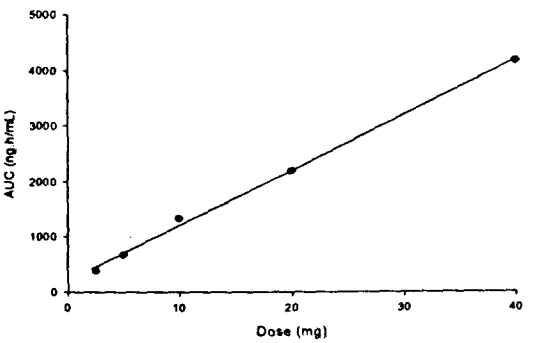


Table I. Pharmacokinetic Results of RNH-6270, Geometric Mean (Range)

Pharmacokinetic parameter	2.5 mg	5 mg	10 mg	20 mg	40 mg
$AUC_{ss,0-24}$ (h*ng/ml)	329	608	1214	2009	3852
$C_{ss,max}$ (ng/ml)	85	116	223	376	729
t_{max} (h) *	1.5	1.5	1.75	1.5	1.5
$t_{1/2}$ (h)	11.1	11.2	11.2	10.7	10.2
$AUC_{ss,tau}$ (h*ng/ml)	351	659	1307	2171	4136
$AUC_{ss,0-\infty}$ (h*ng/ml)	383	670	1325	2191	4189
$C_{ss,av}$ (ng/ml)	13.7	25.3	50.8	83.7	160.5
$C_{ss,min}$ (ng/ml)	1.6	3.0	6.5	9.2	17.7

*: Median instead of geometric mean

Reviewer's Summary:

1. This is the most robust study to investigate the dose proportionality of Benevas. In this study, Benevas was administered orally to 30 subjects in a five-way crossover design at dose ranges from 2.5 to 40 mg in all subjects. Each dose period was for 7 days separated by 7-14 days washout period. All subjects completed the study.

2. In this study, there was no evidence of drug accumulation after multiple doses.

3. Overall, within experimental errors, there is dose proportional increase in steady state Cmax and AUC up to 40 mg dose.

4. Although the dose range is low, the most recommended dose proposed by the sponsor is 20 mg and the maximum dose is 40 mg. Therefore, the drug follows a linear PK over the recommended dose range.

Vol. 56

Study # SE-866/01

Title:

TOLERABILITY AND SAFETY OF THE ANGIOTENSIN II ANTAGONIST CS-866 IN HEALTHY, MALE SUBJECTS (SINGLE DOSE)

Investigator:

[redacted]

Objective:

The objective of the trial was to evaluate the safety and tolerability of a single oral dose of CS-866.

Study Design:

This study was designed as a double-blind, placebo controlled, randomized trial comparing CS-866 with placebo after a single dose in healthy, male subjects aged between 18 and 45 years. Seven dosage groups were used (10, 20, 40, 80, 160, 240, and 320 mg) with six subjects receiving active treatment and three receiving placebo in each group. The trial lasted for four days per subject, administration of trial medication was on Day 1. Blood samples were drawn up to 72 hours after intake of trial medication, and urine samples were collected up to 48 hours after dosing for PK determinations.

Formulations:

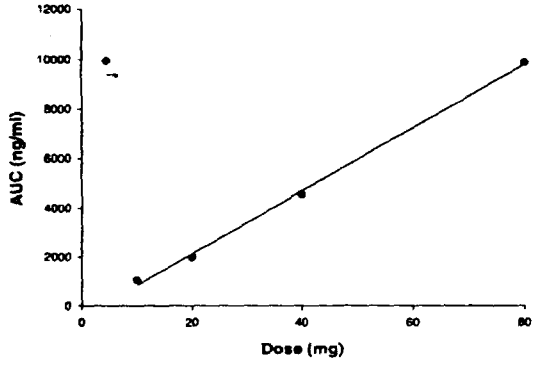
The lot #s of the 2.5, 5, 10, and 20 mg tablets used in this study are 201F, 202F, 203F, 204F respectively. The drug was administered as follows:

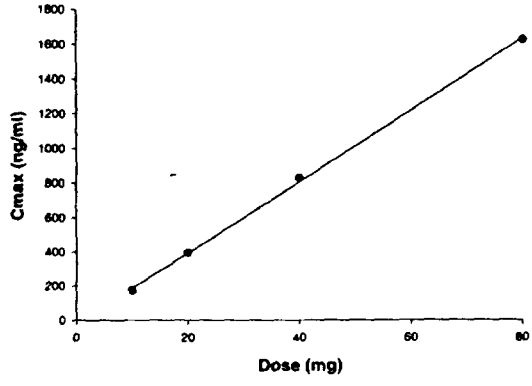
Dosage	Composition	Amount per bottle
Placebo	Placebo	
10 mg	Placebo CS-866 2.5 mg	
20 mg	Placebo CS-866 2.5 mg	
40 mg	CS-866 2.5 mg	
80 mg	CS-866 5.0 mg	
160 mg	CS-866 10.0 mg	
240 mg	CS-866 10.0 mg CS-866 20.0 mg	
320 mg	CS-866 20.0 mg	

Results:

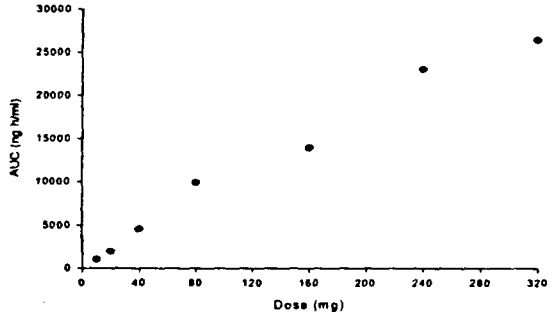
The mean data are shown in the Tables and Figures below:

Relationship Between Dose AUC (left) and Cmax (right) of Olmesartan After Oral administration of Benevas only up to 80 mg Dose





Relationship Between Dose AUC (left) and Cmax (right) of Olmesartan After Oral administration of Benevas for all Doses (i.e., up to 320 mg Dose)



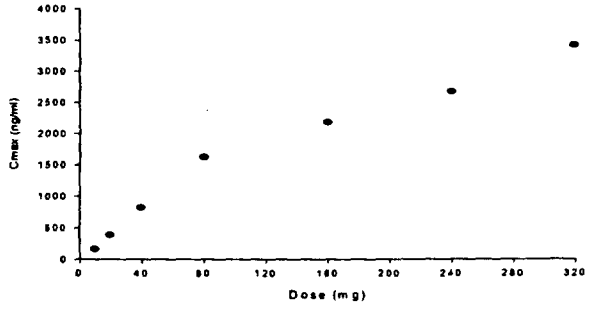


Table III. Pharmacokinetic Parameters (Appendix 5)

Dose	C_{max} [ng/ml] GM(GCV)	t_{max} [h] MD(Min,Max)	$AUC_{0-\infty}$ [ng · h/ml] GM(GCV)	$t_{1/2}$ [h] GM(GCV)	% of dose [%] AM(SD)	Cl_R [ml/min] GM(GCV)
10 mg	171.6 (36.7)	2.0 —	1044.22 (30.9)	12.38 (38.6)	10.86 (3.28)	13.76 (13.4)
20 mg	393.3 (20.9)	1.0 —	1971.76 (14.8)	12.34 (7.9)	10.99 (1.12)	15.37 (14.7)
40 mg	828.1 (38.9)	2.0 —	4534.47 (47.7)	12.37 (48.6)	9.61 (4.07)	10.87 (48.2)
80 mg	1625 (33.3)	2.0 —	9872.37 (33.7)	12.03 (32.1)	10.52 (4.24)	11.16 (19.9)
160 mg	2184 (32.2)	1.5 —	13903.63 (29.2)	12.24 (33.6)	6.26 (2.78)	8.99 (42.4)
240 mg	2668 (25.8)	2.0 —	23011.85 (33.2)	13.81 (50.1)	5.72 (3.51)	7.15 (51.0)
320 mg	3407 (48.7)	2.0 —	26413.27 (51.9)	13.28 (58.9)	6.68 (1.75)	10.97 (27.8)

GM: Geometric mean; GCV: Geometric coefficient of variation [%]; MD: Median; AM: Arithmetic mean; SD: standard deviation; % of dose: percentage of dose administered excreted as RNH-6270

CS-866 was absorbed rapidly after oral dosing since the individual times required to attain peak plasma concentrations of RNH-6270 were between 1-2 hours for doses up to 160 mg and between 1-4 hours for doses of 240 mg and 360 mg.

Reviewer's Summary:

1. This is the most comprehensive study to investigate the dose proportionality of olmesartan. However, this is unlike study # 21 which is a parallel (not crossover) single dose rising study. In this study a group of six subjects received the drug at one of the following dose levels: 10, 2,40, 80, 160, 240, and 320 mg.

2. There is clear evidence of dose proportional increase in Cmax and AUC up to 80 mg dose. As expected, with further increase in dose, the relationship tends to plateau.

3. The mean plasma elimination half-life ranged from 12 to 14 hours over the entire dose range in this study. Urine collections showed that approximately 5% to 10% of the administered dose of CS-866 was excreted as RNH-6270.

Conclusion:

The drug exhibits linear PK characteristics (dose proportionality) up to 80 mg dose. Beyond this dose the relationship tends to be less than dose proportional.

Vol. 46

Study # 866- 101

Title

A Randomized, Double-Blind, placebo-Controlled Ascending, Single Dose, Tolerance Study of Oral CS-866 in Healthy Adult Male Volunteers

Investigator:

[redacted]

Objective:

To determine the safety and tolerance of single oral doses of CS866 given to healthy adult male volunteers

Study Design:

Five dosage levels (10, 20, 40, 80 and 160 mg) were studied in a randomized, double-blind, ascending, single-dose manner. Forty (40) healthy adult male subjects between the ages of 19 and 40 years old were enrolled and completed the study. Eight subjects (5 received CS-866 and 3 received placebo) were enrolled at each of five dosage levels. Blood and urine samples for PK were collected over 48 hours following drug administration.

Formulations:

The lot #s of the 10 and the 20 mg tablets used in this study are 203F and 204F, respectively.

Results:

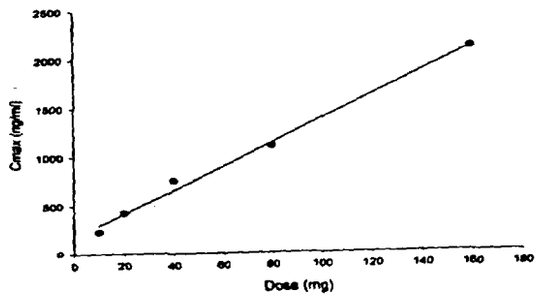
The mean data are shown in the Following Tables and Figures:

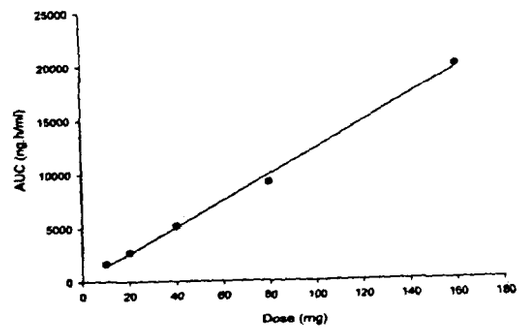
Mean (S.D.) RNH-6270 Plasma Pharmacokinetic Parameters
Following CS-866 Administration

	10 mg	20 mg	40 mg	80 mg	160 mg
Cmax (ng/mL)	224 (45.2)	419 (56.2)	752 (223)	1,100 (280)	2,100 (532)
Tmax (h)	2.4 (0.9)	2.5 (0.9)	1.4 (0.5)	2.0 (0.0)	2.8 (1.1)
AUC(0-t) (ng·h/mL)	1,590 ±(248)	2,610 ±(468)	5,000 ±(1,260)	8,780 ±(2,620)	19,000 ±(3,980)
AUC(0-inf) (ng·h/mL)	1,630 (266)	2,680 (479)	5,160 (1230)	9,160 (2,760)	19,900 (4370)
Kel (hr^{-1})	0.0602 (0.0111)	0.0609 (0.0145)	0.0547 (0.0097)	0.0567 (0.0198)	0.0516 (0.0161)
Tl/2el (h)	11.8 (2.27)	12.1 (3.77)	13.0 (2.64)	13.2 (3.41)	14.7 (5.05)

Mean (S.D.) RNH-6270 Urine Pharmacokinetic Parameters
Following CS-866 Administration

	10 mg	20 mg	40 mg	80 mg	160 mg
Total Amount Excreted (mg)	0.903 (0.193)	1.59 (0.484)	2.99 (0.649)	4.73 (0.949)	10.2 (2.15)
Percent of Dose Excreted	11.90 (2.549)	10.46 (3.193)	9.839 (2.138)	7.789 (1.564)	8.388 (1.767)
Max. Excretion Rate (mg/h)	0.083 (0.015)	0.151 (0.035)	0.277 (0.052)	0.491 (0.081)	0.808 (0.175)
Time of Max. Excretion Rate (h)	3.6 (2.2)	2.8 (1.8)	2.8 (1.8)	2.0 (0.0)	4.4 (2.2)





Reviewer's Comments:

1. In terms of design, this study is similar to study # 866-01. In other words, this was also a parallel single dose rising study, where a group of five subjects received the drug at one of the following dose levels: 10, 20, 40, 80, and 160.

2. Considering experimental errors and the usual level of variability, there is an overall impression for a dose proportional increase in Cmax and AUC up to 160 mg.

3. The mean percentage of dose excreted in urine of RNH-6270 was ~8 to ~12%. This was independent of dose.

APPEARS THIS WAY
ON ORIGINAL

Vol. 48

Study # 866- 102

Title

A Randomized, Double-Blind, placebo-Controlled Ascending, Multiple Dose, Safety and Tolerance Study of Oral CS-866 in Healthy Adult Male Volunteers

Investigator:

[redacted]

Objective:

To determine the safety and tolerance of multiple oral doses of CS866 given to healthy adult male volunteers

Study Design:

This was a randomized, double-blind, placebo-controlled, ascending, multiple-dose study investigating three doses (20, 40, and 80 mg) of CS-866 given once daily in the morning for 10 days. Thirty healthy adult male subjects between the ages of 19 end 38 years old were enrolled, and 29 completed the study. Ten subjects in each of three dosage levels were randomly assigned to treatment such that seven received CS-866 and three received placebo.

Blood samples for PK were collected over 24 hours after dosing on Days 1 and 10, and at 36 and 48 hours after the Day 10 dose. In addition, plasma samples for analysis of RNH-5270 were drawn before the daily dose on Days 4, 6 and 8. Urine was collected over 24 hours after Day 1 and Day 6 dosing and over 48 hours after Day 10 dosing.

Formulation:

The lot # of the 20 mg tablets used in this study is 204F.

Results

The mean data are shown in the following Tables and Figures:

Plasma Pharmacokinetic Parameters[a] for RNH-6270 after Administration of CS-866 Once Daily for 10 Days

Parameter	20 mg	40 mg	80 mg
Day 1			
Cmax (ng/mL)	479 (210)	693 (77.7)	1380 (454)
Tmax (h)	1.7 (0.8)	2.4 (1.0)	1.9 (0.7)
$AUC_{0\text{-}24}$ (ng·h/mL)	2613 (675)	4229 (500)	9330 (3128)
Day 10			
Cmax (ng/mL)	507 (57.8)	732.7 (160)	1379 (255)
Tmax (h)	1.7 (0.5)	1.9 (0.4)	1.8 (0.8)
$AUC_{216\text{-}240}$ (ng·h/mL)	2950 (378)	4366 (626)	9382 (2056)
Cmin (ng/mL)	18.6 (5.24)	35.3 (15.7)	61.6 (21.5)
Cavg (ng/mL)	123 (15.8)	182 (26.1)	391 (85.7)
FI(Cmin)	28.5 (10.0)	22.9 (11.3)	24.1 (10.7)
FI(Cavg)	3.98 (0.297)	3.83 (0.656)	3.46 (0.872)
T½el (h)	14.9 (5.89)	14.5 (7.48)	14.1 (7.04)
Kel (1/h)	0.0527 (0.0196)	0.0558 (0.0191)	0.0582 (0.0228)

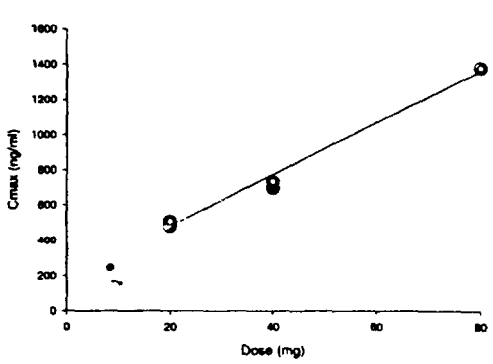
Abbreviations: Cmax, maximum observed concentration during the dosing interval; Tmax, the time from dosing at which Cmax occurred; AUC, area under the RNH-6270 concentration versus time curve; Cmin, minimum observed concentration during the dosing interval; Cavg, average concentration during the dosing interval; FI, fluctuation index; T½el, apparent terminal half-life; Kel, apparent elimination rate constant.
[a] Presented as mean ± standard deviation

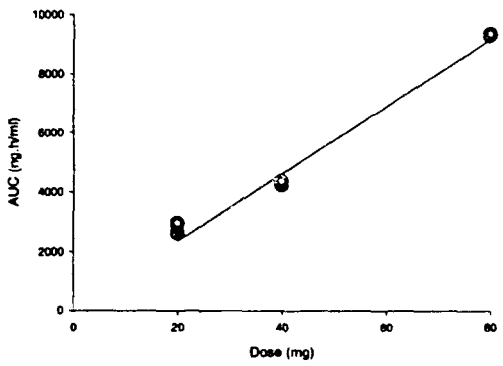
Urine Pharmacokinetic Parameters[a] After Administration of CS-866 Once Daily for 10 Days

Parameter	20 mg	40 mg	80 mg
Day 1			
Total amount excreted (0-24 h) (mg)	1.60 (0.47)	2.90 (0.51)	4.60 (1.05)
% of dose excreted	10.5 (3.11)	9.57 (1.67)	7.58 (1.73)
Maximum excretion rate (mg/h)	0.180 (0.069)	0.304 (0.082)	0.466 (0.095)
Time of maximum excretion rate (h)	2.0 (0.0)	3.1 (2.0)	2.0 (0.0)
Day 6			
Total amount excreted (0-24 h) (mg)	1.83 (0.342)	3.01 (0.630)	5.39 (1.47)
% of dose excreted	12.1 (2.25)	9.93 (2.08)	8.88 (2.42)
Maximum excretion rate (mg/h)	0.223 (0.062)	0.364 (0.087)	0.562 (0.079)
Time of maximum excretion rate (h)	2.0 (0.0)	3.7 (2.1)	2.7 (1.6)
Day 10			
Total amount excreted (0-48 h) (mg)	1.99 (0.468)	3.26 (0.644)	5.96 (1.13)
% of dose excreted	13.1 (3.09)	10.7 (2.12)	9.81 (1.86)
Maximum excretion rate (mg/h)	0.229 (0.064)	0.358 (0.088)	0.593 (0.048)
Time of maximum excretion rate (h)	2.0 (0.0)	2.0 (0.0)	2.7 (1.6)
CLr (L/h)	0.671 (0.107)	0.752 (0.140)	0.642 (0.0946)

[a]Presented as mean (standard deviation)

Relationship Between Cmax (left), AUC (right) and Benevas Dose in Day 1 (close circles) and Day 10 (open circles) in 10 Subjects.





Reviewer's Comments:

1. Within acceptable experimental errors and usual variability, the data show a dose proportional increase in Cmax and AUC up to 80 mg. However, it should be noted that the Cmax and AUC for the 20 mg dose is somehow slightly at the higher end. This makes the dose proportionality between the 20 and 40 mg doses less apparent.

2. The half-life remains constant at all doses.

3. No difference in the data between Day 1 and day 10, which confirms that there is no drug accumulation.

4. In terms of urine data, the percent of dose excreted in urine was about 10% on Day 1 and Day 10 at all doses. This also suggests that there is no accumulation of the drug after multiple dosing.

Conclusion:

The drug exhibits linear PK characteristics up to 80 mg dose. This observation is consistent with other studies. There was no apparent change in either half-life or in the percent of dose excreted in urine with increasing doses. Again, this is consistent with the principles of linear (dose independent) PK. Furthermore, there was no evidence of drug accumulation over 10 days of dosing.

Vol. 52

Study # SE-866-107

Title:

An Open label Ascending Single Dose, Safety and Tolerance Study of Intravenously Administered RNH-6270 in Healthy Adult Male Volunteers

Investigator:

Objective:

The objective of the study is to determine the safety and tolerability of intravenously administered RNH-6270 in healthy subjects.

Study Design:

This was open-label, ascending single dose, safety and tolerance study at IV doses of 1, 2, 4, 8, 16, and 32 mg. Blood and urine samples were collected 48 hours following start of infusion. In this study, thirty-for (34) subjects (6 dose groups, 2 groups of subjects and four groups of 6 subjects)

Formulation:

The lot #s of the IV solution used in this study was K97T01.

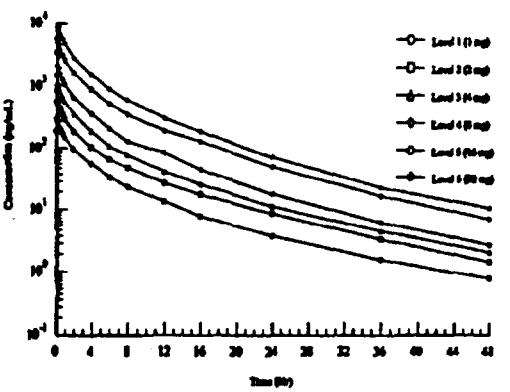
Results:

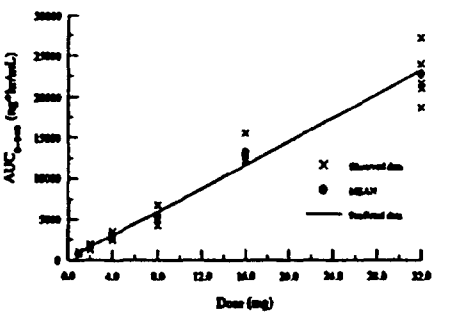
The mean data are shown in the following Tables and Figures:

Table 11.4.3.1:1 Descriptive Statistics of Pharmacokinetic Parameters for Plasma RNH-6270

Dose Group	Descriptive Statistics	$AUC_{0-t_{last}}$ (ng*hr/mL)	$AUC_{0-\infty}$ (ng*hr/mL)	C_{max} (ng/mL)	T_{max} (hr)	$t_{1/2}$ (hr)
1 mg RNH-6270 (n=6)	Arithmetic Mean	818.6	830.8	268.12	0.18	10.58
	±SD	97.2	100.0	19.28	0.03	1.04
	CV%	11.9	12.0	7.2	17.8	9.8
2 mg RNH-6270 (n=5)	Arithmetic Mean	1635.8	1654.3	543.05	0.19	9.21
	±SD	271.4	275.7	71.12	0.04	1.45
	CV%	16.6	16.7	13.1	19.2	15.8
4 mg RNH-6270 (n=6)	Arithmetic Mean	2879.5	2906.3	1091.83	0.21	9.14
	±SD	394.6	401.2	77.77	0.04	0.84
	CV%	13.7	13.8	7.1	20.9	9.2
8 mg RNH-6270 (n=6)	Arithmetic Mean	5336.6	5370.0	2078.50	0.20	8.89
	±SD	830.8	834.4	200.01	0.04	1.37
	CV%	15.6	15.5	9.6	21.0	15.4
16 mg RNH-6270 (n=5)	Arithmetic Mean	13113.4	13197.7	4829.20	0.17	8.29
	±SD	1353.6	1333.9	402.35	0.00	1.43
	CV%	10.3	10.1	8.3	0.0	17.2
32 mg RNH-6270 (n=6)	Arithmetic Mean	22501.3	22624.5	9206.67	0.20	8.30
	±SD	2909.8	2916.9	2262.20	0.04	0.84
	CV%	12.9	12.9	24.6	21.0	10.1

Reference: Appendix 16.1.9.3



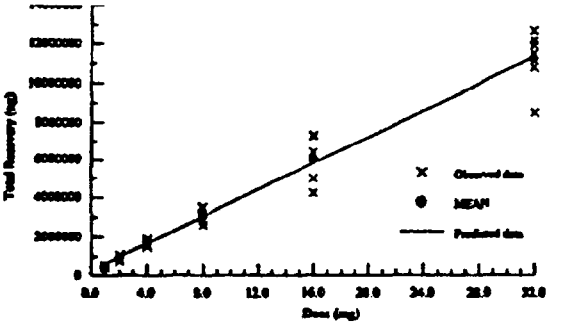


11.4.3.1:2 Regression Analysis of Mean Plasma RNH-6270 $AUC_{0-\infty}$ vs.Dose ($AUC_{0-\infty}$ = 208.64 + 715.49 DOSE, R^2 = 0.968, p = 0.557 for intercept).

Table 11.4.3.2:1 Mean Renal Clearance / Mean Percent of RNH-6270 Excreted in Urine for Each Dose Group.

Time Interval (hr)	Mean Percent of Dose Excreted in Urine (%CV)					
	1.0 mg RNH-6270	2.0 mg RNH-6270	4.0 mg RNH-6270	8.0 mg RNH-6270	16 mg RNH-6270	32 mg RNH-6270
0-4	27.2 (13.3)	25.2 (21.0)	25.9 (12.3)	22.2 (17.8)	23.3 (9.7)	20.3 (17.1)
4-8	9.1 (23.7)	8.9 (19.1)	6.8 (42.1)	8.3 (17.6)	6.9 (63.2)	6.6 (23.5)
8-12	6.1 (12.4)	3.7 (30.9)	3.7 (47.4)	2.9 (52.1)	2.8 (37.7)	3.9 (33.1)
12-24	4.5 (46.7)	4.7 (57.8)	5.1 (20.1)	4.0 (33.6)	3.4 (62.3)	3.2 (35.8)
24-36	1.8 (23.1)	1.8 (41.0)	1.4 (31.4)	1.1 (38.2)	1.0 (37.3)	0.8 (42.0)
36-48	0.4 (102.8)	0.7 (29.6)	0.5 (23.5)	0.3 (44.5)	0.4 (51.7)	0.3 (61.5)
TOTAL (0-48)	49.1 (12.5)	45.1 (13.3)	43.3 (9.9)	38.9 (11.7)	37.6 (22.9)	35.0 (13.3)
Cl_R (L/hr)	0.6 (15.8)	0.6 (16.3)	0.6 (19.5)	0.6 (17.3)	0.5 (29.3)	0.5 (21.9)

Reference: Appendices 16.1.9.3 and 16.1.9.5



RE 11.4.3.2:2 Regression Analysis of Mean Total Urinary Recovery of RNH-6270 vs. Dose
(Total Urinary Recovery = 289.57 + 344.28 DOSE,
$R^2 = 0.961$, $p = 0.134$ for intercept).

Reviewer's Comments:

1. There was a perfect dose-proportionality increase in plasma level as exemplified by AUC. Unlike the PO data, there was minimal variability in the IV data. It is noteworthy to point out that doses administered after IV were much lower than after oral administration. The lowest dose after IV was 1 mg and for analytical reasons this dose is too low to be given by oral administration.

2. Overall, both oral and IV data show a linear PK of the drug up to the maximum proposed dose (40 to 80 mg).

3. In terms of urine data, although there is a linear relationship between the amount recovered in urine and dose (see Figure), the % of dose excreted in urine over 48 hours tends to decrease with increasing the dose. At 1 mg the % of dose excreted was 49%, while after 32 mg dose was 35% (see Table).

Conclusion:

The drug exhibits linear PK characteristics up to 32 mg IV dose.

Vol. 82

Study # SE-866/05

Title:

THE EFFECT OF AN ANTACID (ALUMINIUM MAGNESIUM HYDROXIDE) ON THE PHARMACOKINETICS AND SAFETY OF THE ORAL ANGIOTENSIN II-ANTAGONIST CS-866 IN HEALTHY MALE SUBJECTS

Investigator:

Objectives:

The objective of the trial was the determination of the effect of a concomitant administration of aluminum magnesium hydroxide on the Pharmacokinetics of the pharmacologically active metabolite RNH-6270. The safety and tolerability of CS-866 with and without concomitant administration of aluminum magnesium hydroxide was also addressed.

Study Design:

This phase I study was designed as an open-label, randomized, two-way crossover trial assessing the effect of an antacid (aluminum magnesium hydroxide) on the PK and safety of CS-866 in 24 healthy, male subjects aged between 18 and 45 years. There were two sequence groups with 12 subjects each. Sequence group I received 800 mg aluminum magnesium hydroxide q.i.d, over eight days with co-administration of 20 mg CS-866 o.d. on Days 4-8. After a wash-out period of 7-14 days, 20 mg CS-866 o.d. alone was administered for five days. Sequence group II received both treatments in reverse order.

Formulation:

The lot # of the 20 mg tablets used in this study is 220.

Results and Conclusions:

1. The data show no statistically or clinically significant difference in any of the PK parameters when the drug was administered with or without the antacid. It should be noted, however, that Cmax and AUC were slightly lowered (~10%) with antacid.

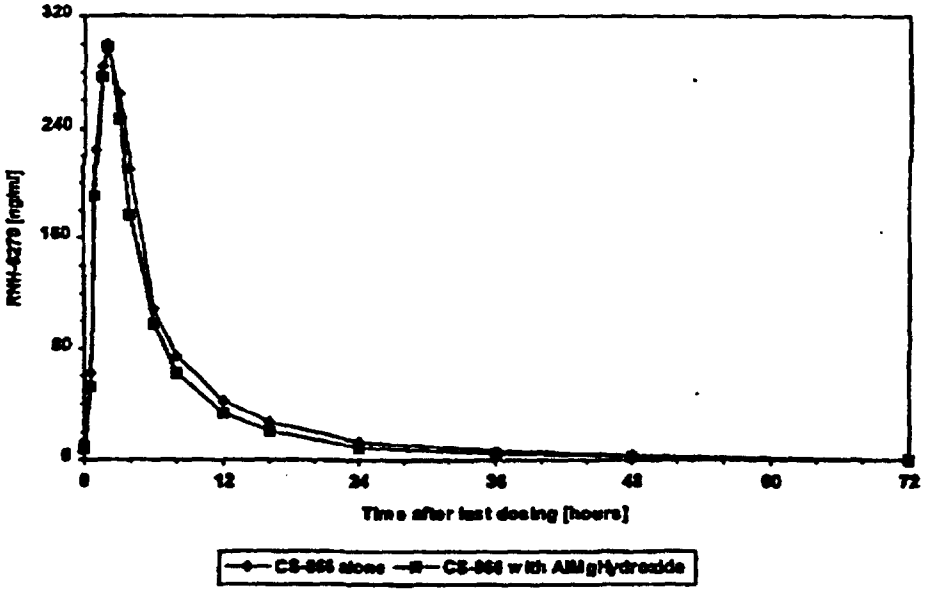
2. Similarly, no significant difference was observed in the urine excretion data.

Table I: Overall Sample Characteristics of Pharmacokinetic Parameters in Plasma after Multiple Dose by Treatment

Pharmacokinetic parameter in plasma after multiple dose	20 mg CS-866 o.d. + 800 mg aluminium magnesium hydroxide q.i.d. (= treatment 1)	20 mg CS-866 o.d. alone (=treatment 2)
$AUC_{ss,\tau}$ [ng*h/ml] *	1630 (27%)	1858 (35%)
C_{max} [ng/ml] *	289 (23%)	313 (36%)
t_{max} [h] **	2.0 (1.5 to 3.0)	2.0 (1.0 to 3.0)
$t_{\frac{1}{2}}$ [h] *	10.5 (28%)	11.6 (33%)

* = geometric mean (geometric coefficient of variation)
** = median (minimum to maximum)

Figure I: Median Plasma RNH-6270 Concentration versus Time Curve after Multiple Dose by Treatment



Vol. 76

Study # SE-866/16

Title:

A COMPARATIVE PHARMACOKINETIC, SAFETY AND TOLERABILITY TRIAL OF THE ORAL ANGIOTENSIN II ANTAGONIST CS-866 IN SUBJECTS WITH VARYING DEGREES OF RENAL IMPAIRMENT AND HEALTHY VOLUNTEERS

Investigator:

Objectives:

1. The primary objective of the trial was to evaluate the PK parameters of RNH-6270 in plasma and urine after single and multiple daily oral doses of 10 mg CS866 in patients with varying degrees of renal impairment and healthy volunteers.

2. Safety and tolerability of CS-866 after multiple dosing.

Study Design:

This was a multiple dose study in 34 (25 to 75 years of age) subjects with varying degree of renal functions as follows: 8 normals (CLcr >60 ml/min), 8 mild (Clcr 40-59 ml/min), 9 moderate (Clcr 20-39 ml/min), and 9 severe (CLcr <20 ml/min). Each group received a single daily oral 10 mg dose of Benevas tablet for 7 days. PK profiles were assessed on Day I and Day 7 (for 24 and 96 h after drug administration). Additional trough plasma samples were collected on Days 3, 4, 5 and 6 for RNH-6270 assay.

Formulation:

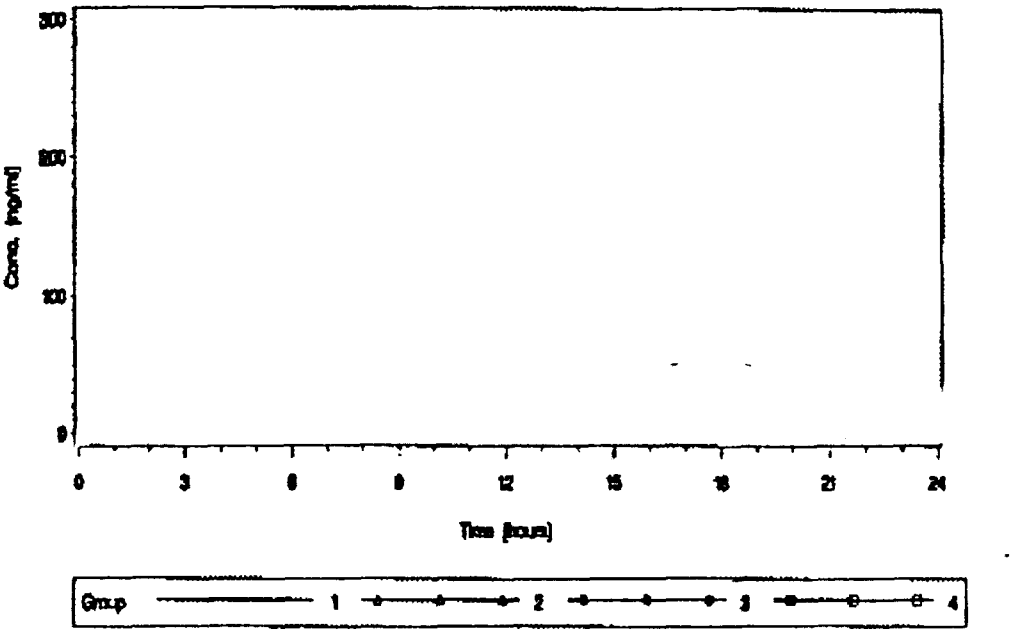
The batch # of the 10 mg tablets used in this study is 2233V97003.

Results:

Mean (%CV) PK parameters grouped by severity of renal impairment.

Parameter	Severe CLcr <20 (ml/min)	Moderate Clcr <39 (ml/min)	Mild CLcr <59 (ml/min)	Normal CLcr>60 (ml/min)
AUC (ng.h/ml)	3779 (40.5)	2468 (32.9)	2197 (37.4)	1355 (18.1)
Css	360 (32.2)	320 (30.9)	294 (40.0)	231 (28.0)
Half Life (h)	18.0 (30.5)	18.9 (42.8)	19.3 (47.6)	18.7 (37.1)
CLR	0.05 (111.4)	0.12 (41.3)	0.26 (72.3)	0.52 (41.5)
Urine (%)	**2.96**	**3.91**		**7.61**
9.63				

Olmesartan Plasma concentration-Time Profiles After 10 mg Single Dose (upper) and Daily for 7 Days (lower) in Subjects With Varying Degrees of Renal Impairment



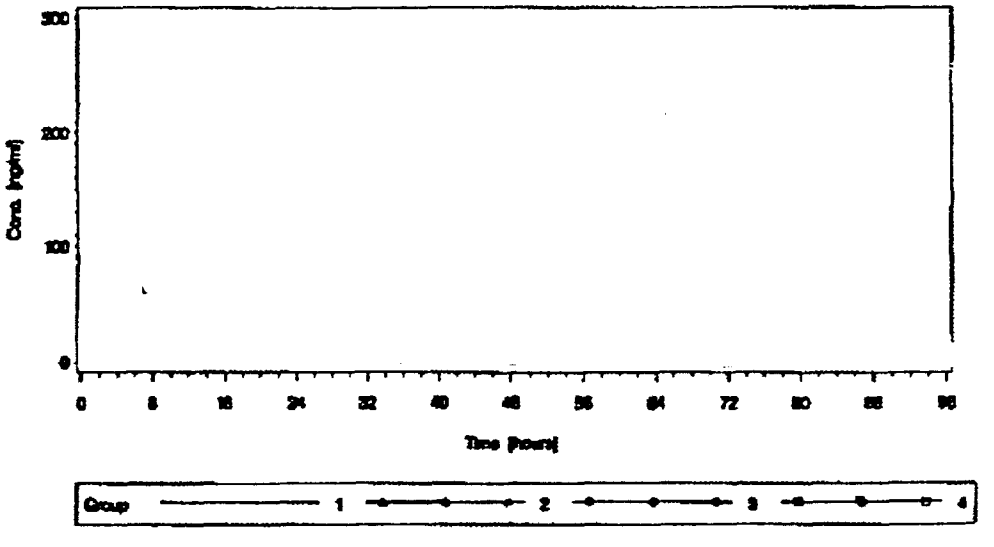
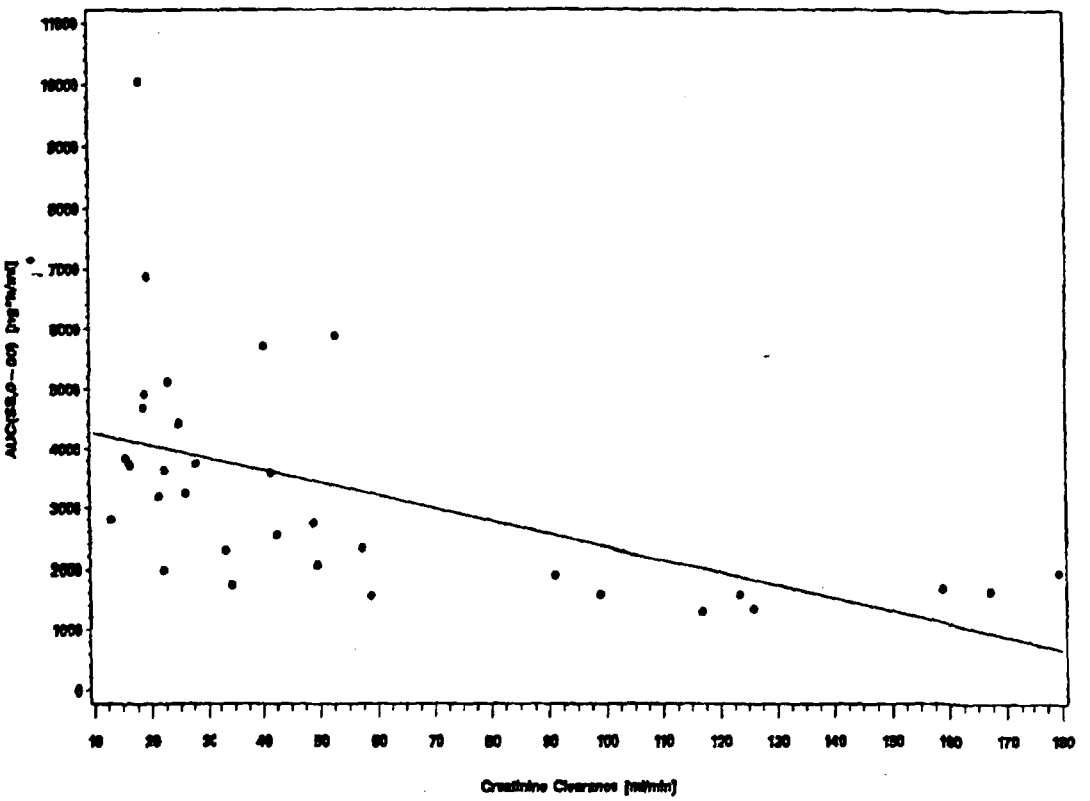


Figure 2.1.4: Linear Regression Plot of Creatinine Clearance on AUC(0,8-00)



APPEARS THIS WAY
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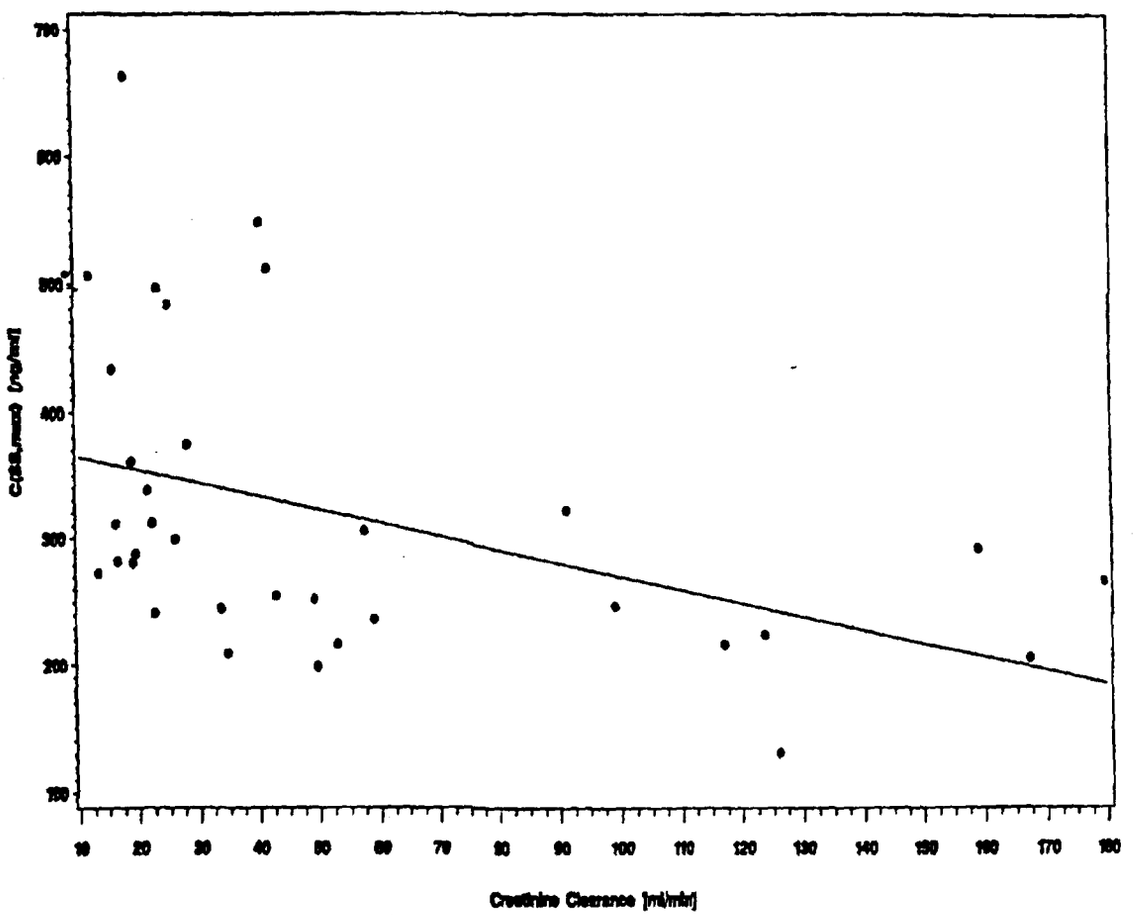
Figure 23.8: Linear Regression Plot of Creatinine Clearance on C(SS,max)



Reviewer's Summary:

1. The classification of subjects relative to renal function (CLcr) is somehow different from that of the FDA Guidance for renal impairment. According to the guidance, the CLcr for normals, mild, moderate and severe renal impairment is >80, 50-80, 30-50, and <30 ml/min, respectively.

2. The selected dose of 10 mg may be considered low, since the recommended initial dose is 20 mg. However, for safety reason in these patients, this dose can be accepted.

3. At steady state, the exposure to the drug, as exemplified by AUC, in severe renal impairment was about 3.3 fold higher than in normal subject. In the same token, the effect on the Cmax was less pronounced. This was about 56% (or 1.56 fold) higher in severe renal impairment compared normal subjects.

4. Similarly, the % of dose excreted in urine was associated with the severity of the renal impairment. These were in the same magnitude of that of the plasma data.

5. Furthermore, the Cmax and AUC were consistently higher in all renal impairment patients than normal subjects after both single dose and multiple dose administration.

6. As expected, there was a strong negative correlation between $AUC_{(0-\infty)}$ (P=0050) and $Cmax_{(ss)}$ (P=0.011) and creatinine clearance. This implies that these PK parameters increase with decrease creatinine clearance.

7. No change in the elimination half life was noted in any of the groups irrespective of either renal function and/or duration of drug administration.

Conclusion:

According to the sponsor's proposed label, the starting dose in severe renal impairment is 20 mg with close monitoring. However, based on these data, we recommend dose adjustment in all patients with renal impairment, especially in the severe cases. This needs to be discussed with the clinical division and the sponsor. At present, the lowest available tablet strength of the drug is 20 mg unscored tablet. Therefore, it is not possible to give a smaller dose in renal impairment patients.

Vol. 64

Study # SE- 866-109

Title

A Comparative PK Study of CS-866 Tablets and R.NH-6270 Intravenous Solution Administered to Patients with Impaired Liver Function and Healthy Volunteers.

Investigator:

Objective

To compare the relative PK of CS-866 administered orally as a tablet and RNH-6270 administered as an intravenous infusion in male patients with hepatic impairment and matched healthy adult male volunteers.

Study Design:

This study was a single center, open-label, comparative PK study of a single oral dose of CS-866 (tablet) followed by an IV dose of R.NH-6270 administered to 24 male subjects with varying degree of hepatic impairment as follows: 12 healthy (Childs Pugh score <5), 4 mild (Childs Pugh score 5-6), and 8 moderate (Childs-Pugh score 7-9). All subjects were first administered one 10 mg tablet of CS-866 on Day 1 following a twelve hour overnight fast. After a 10 day washout period, each participant received 8 mg of RNH-6270 by slow (5 minutes) intravenous infusion. Blood and urine were collected over 96 hours. Subjects ranged in age from 44 to 65 years.

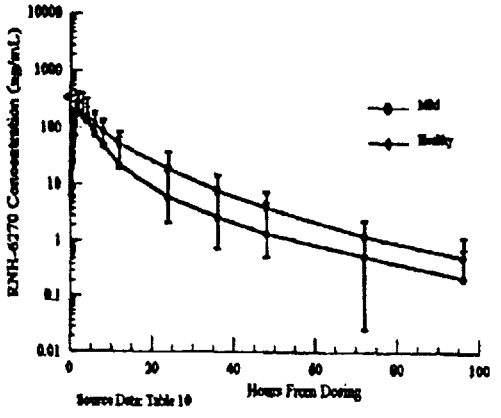
Formulations:

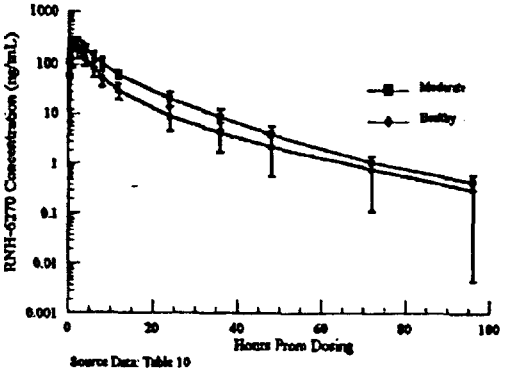
The lot # of the 10 mg tablets used in this study was 292 and for the IV solution was K97T01. The constituents of the IV solution are sodium chloride, sodium hydroxide, active charcoal, and water. The concentration of the IV solution is 80 mg/ampule.

Results:

The mean data are shown in the following Tables and Figures:

Mean (SD) Plasma concentration-Time Profiles of Olmesartan in Healthy Subjects and Patients With Hepatic Impairment Following a Single 10 mg Oral Dose of Benevas Tablets





Mean (%CV) PK Parameters of Olmesartan in Healthy Subjects and Patients With Hepatic Impairment Following a Single 10 mg Oral Dose of Benevas Tablets

Parameters	**Healthy (n=12)**	**Mild (n=4)**	**Moderate (n=8)**
AUC0-∞ (ng.h/ml)	1708 (26.8)	2227 (45.8)	2525 (14.0)
Cmax (ng/ml)	256 (26.2)	260 (16.8)	271 (19.3)
Half life (h)	16.3 (26.8)	14.4 (10.6)	15.6 (37.2)
Urine (%)	11.5 (24.9)	15.1 (31.3)	18.9 (17.3)