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)
AUC0-∞	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)
CLR	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)

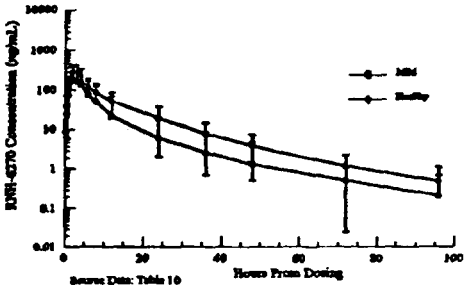
Table 7.2.3.1:1 Descriptive Statistics of RNH-6270 Plasma Pharmacokinetic Parameters Following Oral Administration of the 10 mg CS-866 Tablet

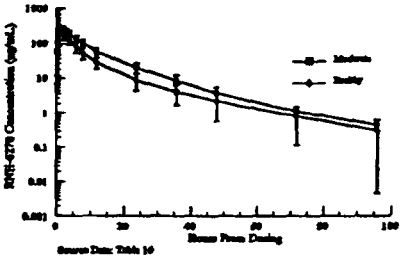
Dose Group	Descriptive Statistics	$AUC_{0-t_{last}}$ (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max}* (hrs)	$t_{1/2}$ (hrs)
Hepatically Impaired – All patients	N	12	12	12	12	12
	Arithmetic Mean	2414.2	2425.8	267.38	2.00	15.23
	±SD	615.2	619.9	47.89		4.73
	CV%	25.5	25.6	17.9		31.1
Hepatically Impaired – Mild	N	4	4	4	4	4
	Arithmetic Mean	2212.7	2227.0	260.35	2.00	14.43
	±SD	1005.26	1019.55	43.79		1.53
	CV%	45.4	45.8	16.8		10.6
Hepatically Impaired – Moderate	N	8	8	8	8	8
	Arithmetic Mean	2514.9	2525.2	270.90	2.00	15.62
	±SD	356.2	352.9	52.35		5.80
	CV%	14.2	14.0	19.3		37.2
Healthy Subjects	N	12	12	12	12	12
	Arithmetic Mean	1698.8	1708.1	256.26	2.00	16.27
	±SD	456.8	458.4	67.24		4.36
	CV%	26.9	26.8	26.2		26.8

Source: Section 10.2, Table 11

*T_{max} is reported as median, not mean.

Figure 7.2.3.1:1 Mean (S.D.) Plasma RNH-6270 Concentration - Time Profiles of Patients with Mild Hepatic Impairment vs. Matched Healthy Subjects Following Oral Administration of the 10 mg CS-866 Tablet





7.2.3.2 Plasma Pharmacokinetics Following Intravenous Administration

Mean plasma concentrations over time by patient group and matched controls following iv administration of RNH-6270 are presented in Section 10.2, Table 13.

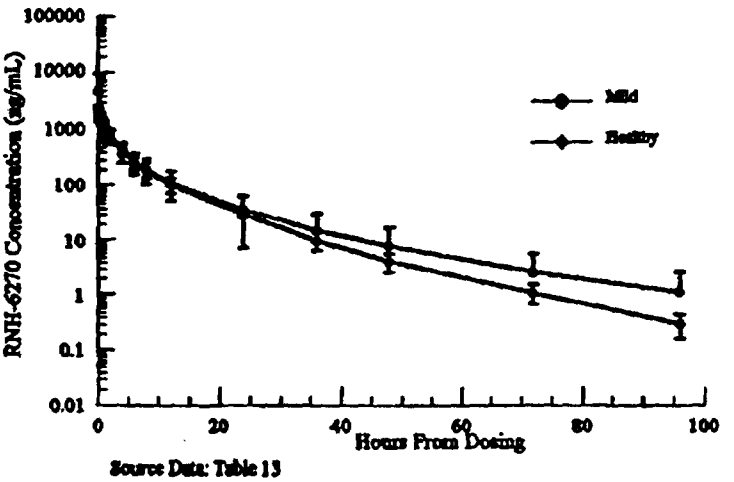
Table 7.2.3.2:1 Descriptive Statistics of RNH-6270 Plasma Pharmacokinetic Parameters Following Intravenous Administration of the 8 mg RNH-6270 Solution

Dose Group	Descriptive Statistics	AUC_{0-hr} (ng.h/mL)	$AUC_{0-\infty}$ (ng.h/mL)	C_{max} (ng/mL)	T_{max}* (hrs)	$t_{1/2}$ (hrs)	CL (L/hr)
Hepatically Impaired – All patients	N	12	12	12	12	12	12
	Arithmetic Mean	6908.2	6924.4	2651.17	0.17	14.02	1.23
	±SD	1593.4	1609.1	3026.72	N/A	1.71	0.30
	CV%	23.1	23.2	114.2	N/A	12.2	24.2
Hepatically Impaired – Mild	N	4	4	4	4	4	4
	Arithmetic Mean	6779.8	6806.0	4496.25	0.13	16.02	1.31
	±SD	2490.0	2521.8	5161.30	N/A	1.01	0.47
	CV%	36.7	37.1	114.8	N/A	6.3	35.5
Hepatically Impaired – Moderate	N	8	8	8	8	8	8
	Arithmetic Mean	6972.4	6983.6	1728.63	0.17	13.02	1.19
	±SD	1148.2	1153.7	247.33	N/A	0.83	0.20
	CV%	16.5	16.5	14.3	N/A	6.4	16.9
Healthy Subjects	N	12	12	12	12	12	12
	Arithmetic Mean	5963.9	5975.2	2204.08	0.17	14.46	1.39
	±SD	1007.5	1008.3	302.19	N/A	2.62	0.25
	CV%	16.9	16.9	13.7	N/A	18.1	17.8

Source: Section 10.2, Table 12

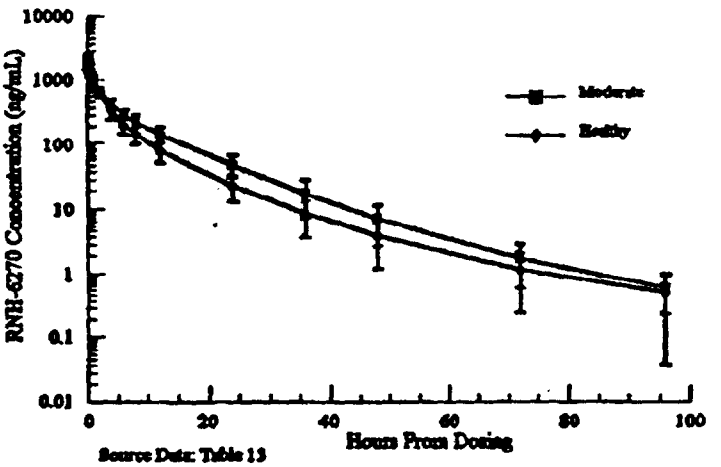
* T_{max} is reported as median, not mean.

Figure 7.2.3.2:1 **Mean Plasma RNH-6270 Concentration -Time Profiles of Patients with Mild Hepatic Impairment vs. Matched Healthy Subjects Following Intravenous Administration of the 8 mg RNH-6270 Solution**



Source Data: Table 13

Figure 7.2.3.2:2 **Mean Plasma RNH-6270 Concentration -Time Profiles of Patients with Moderate Hepatic Impairment vs. Matched Healthy Volunteers Following Intravenous Administration of the 8 mg RNH-6270 Solution**



Source Data: Table 13

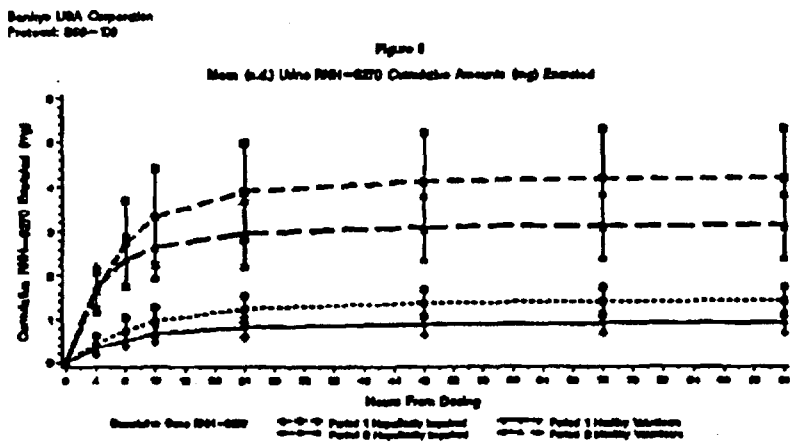
Table 7.2.3.3:1 **Mean Percent of RNH-6270 Excreted in Urine / Mean Renal Clearance Following Oral Administration of the 10 mg CS-866 Tablet**

Time Interval (hr)	Mean Percent of Dose Excreted Urine (% CV)			
	Hepatic Impaired - Mild	Hepatic Impaired - Moderate	Hepatic Impaired – All Patients	Healthy Volunteers
0-4	5.1 (51.1)	5.6 (47.9)	5.4 (46.9)	4.1 (39.6)
4-8	3.3 (67.6)	4.1 (44.6)	3.8 (49.7)	2.5 (41.0)
8-12	1.6 (67.0)	3.2 (16.6)	2.7 (38.9)	1.8 (61.0)
12-24	2.9 (63.2)	3.9 (31.2)	3.6 (40.8)	1.9 (41.1)
24-48	1.6 (80.9)	1.6 (41.6)	1.6 (53.8)	0.9 (45.3)
48-72	0.4 (75.3)	0.4 (52.2)	0.4 (57.3)	0.2 (52.8)
72-96	0.2 (51.3)	0.1 (95.2)	0.1 (80.2)	0.0 (141.4)
Total* (0-96)	15.1 (31.3)	18.9 (17.3)	17.6 (22.9)	11.5 (24.9)
CL_R (L/hr)	0.58 (28.7)	0.61 (24.6)	0.60 (24.8)	0.55 (17.7)

Source: Section 10.2, Tables 11 and 14

* Based on total amount of drug recovered over the 96 hour collection period, therefore, this may not reflect the sum of the intervals due to rounding.

Figure 7.2.3.3:1 **Mean (S.D.) RNH-6270 Urine Concentration at Each Collection Interval**



Reviewer's Summary:

1. 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.

2. It should be noted that no severe patients were included in this study.

3. Also, the study may lack adequate power. There is no equal number of subjects in each group, particularly, the number of subjects in the mild group is rather small (n=4).

4. After oral administration, the mean AUC is about 30% and 47% higher in mild and moderate hepatic impairment than healthy subjects, respectively. However, the Cmax was not affected in this study.

5. 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. The effect of liver impairment on the absorption and the metabolism process of the drug can explain the difference between oral and IV data. When the drug is given IV, no absorption process takes place nor there is exposure of the drug to hepatic metabolism.

6. In terms of urine data, the amount excreted in urine was consistently higher in patients than healthy subjects. The % of olmesartan dose 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 % of dose was 39.3 and 58.3% in mild and moderate hepatic disease, respectively, compared to 38.7% in control subjects.

7. The fraction unbound tends to be higher in patients compared to control group. The mean % fraction unbound was 0.34% and 0.41% in mild and moderate impairment, respectively, compared to 0.26% in control healthy subjects.

8. It should be noted that according to the sponsor's proposed label, no dose adjustment was recommended in patients with hepatic impairment.

Conclusion:

The drug should be carefully monitored in patients with hepatic impairment, especially in severe cases.

Vol. 70

Study # SE-866/07

Title:

MULTIPLE DOSE TOLERABILITY, SAFETY AND PHARMACOKINETIC STUDY OF THE ANGIOTENSIN IIANTAGONIST CS-866 IN YOUNG AND ELDERLY HYPERTENSIVE PATIENTS

Investigator:

[redacted]

Objective:

The objective of the trial was to evaluate the safety and tolerability of single and multiple oral doses of CS-866. Plasma and urine PK were also investigated.

Study Design:

This was a double-blind, placebo-controlled, parallel 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).

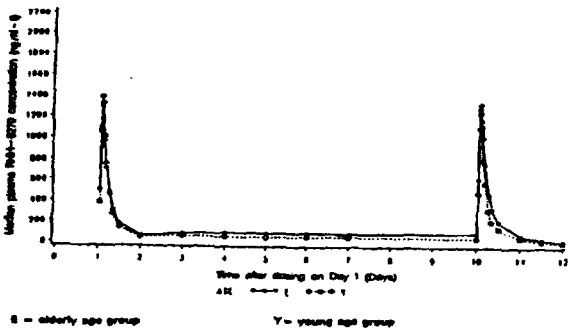
Formulation:

The lot # of the 20 mg tablets used in this study was 232; 204F.

Results:

Figure I and Table I summarise the pharmacokinetic results of this study.

Figure I. Median Plasma RNH-6270 Concentrations versus Time Profile



E = elderly age group Y= young age group

Table V. Summary of Pharmacokinetic Parameters

Age Group	E		Y	
Day	1	10	1	10
C_{max} [ng/ml] GM (GCV)	1310 (21.8)	1313 (22.2)	1288 (21.1)	1436 (29.5)
t_{max} [h] MD (Min, Max)	2.0 (—)	1.5 (—)	1.5 (—)	1.5 (—)
AUC(0-24) [ng.h/ml] GM (GCV)	7161 (23.2)	-	7772 (17.5)	-
$AUC_{ss,\tau}$ [ng.h/ml] GM (GCV)	-	6807 (22.6)	-	9078 (22.6)

- continued -

Age Group	E		Y	
Day	1	10	1	10
$t_{1/2}$ [h] GM (GCV)	-	10.58 (23.6)	-	12.85 (40.2)
Am(0-24) [µg] AM (SD)	5069 (1378)	4970 (1004)	3587 (877.0)	4863 (2096)
Am(0-48) [µg] AM (SD)	-	5403 (957.5)	-	5348 (2175)
Dose excreted (24h) [%] AM (SD)	7.9 (2.2)	7.8 (1.6)	5.6 (1.4)	7.6 (3.3)
Dose excreted (48h) [%] AM (SD)	-	8.5 (1.6)	-	8.4 (3.4)
CL_R [ml/min] GM (GCV)	11.4 (19.6)	11.9 (19.4)	7.5 (27.6)	8.3 (20.1)

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

Reviewer's Comments:

1. At steady state, the exposure in elderly as exemplified by mean AUC was about 33% higher than in young (6807 vs. 9078 ng.h/ml). However, in terms of Cmax, it was higher by only 9% in elderly compared to young (1313 vs. 1436 ng/ml).

2. No difference in the % of dose excreted in urine after multiple dosing between the two populations (7.8 % vs. 7.6 %)

3. Overall, the difference between young and elderly may have some clinical significance.

Conclusion:

The exposure to the drug appears to be greater in elderly than in young. Dose adjustment based on age may not be necessary. According to the sponsor's proposed label, no dose adjustment is necessary in elderly population.

Vol. 72

Study # SE-866/14

Title:

A PHARMACOKINETIC, SAFETY AND TOLERABILITY STUDY OF THE ORAL ANGIOTENSIN II-ANTAGONIST CS-866 IN YOUNG AND VERY ELDERLY PATIENTS WITH MILD TO MODERATE ESSENTIAL HYPERTENSION

Investigator:

Objective:

To evaluate PK parameters of RNH-6270 in plasma and urine after single and multiple dosing (10 mg o.d.}, comparing young {aged 18 to 45) and very elderly (75 years of age or more} patients.

Study Design:

This was a double-blind, placebo-controlled, parallel 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).

Formulation:

The lot # of the 10 mg tablets used in this study was 2233V97003 (=D97T02)

Results:

	Young		Elderly	
	Day 1	Day 10	Day 1	Day 10
C_{max} [ng/ml] GM (GCV)	216.58 (17.71)	254.53 (14.38)	279.95 (29.39)	289.50 (18.02)
t_{max} [h] MD (min, max)	2.0 (——	1.5 ——	2.0 ——	1.5 ——
AUC(0-24 h) [ng·h/ml] GM (GCV)	1218.25 (26.64)	-	1796.82 (26.36)	-
AUC_{tau} [ng·h/ml] GM (GCV)	-	1411.1 (17.4)	-	2035.4 (23.2)
$t_{1/2}$ [h] GM (GCV)	-	12.30 (23.10)	-	16.49 (47.56)
Am(0-24 h) [mg] AM (SD)	0.86 (0.29)	-	0.80 (0.19)	-
Am_{tau} [mg] AM (SD)	-	1.05 (0.27)	-	0.89 (0.21)
Dose excreted (24 h) [%] AM (SD)	10.82 (3.66)	13.25 (3.45)	10.07 (2.33)	11.16 (2.58)
CLR (ml/min) GM (GCV)	10.98 (42.41)	12.12 (27.41)	7.21 (30.78)	7.09 (26.44)

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

Figure I: Median RNH-6270 Plasma Concentration vs Time Profile by Age-Group after Multiple Dose (cf. Section 8.1, Figure 22.2; Section 8.2, Table 34)

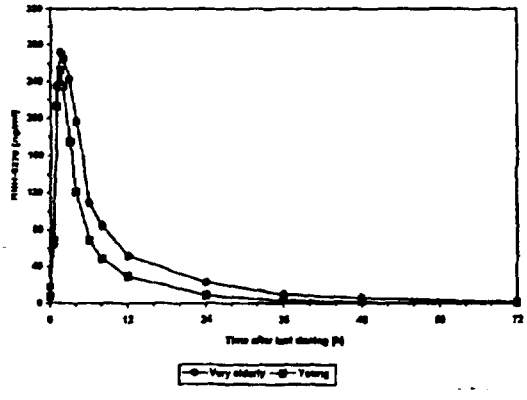
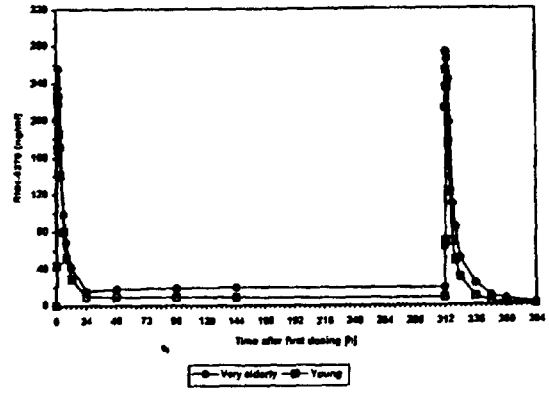


Figure II: Median RNH-6270 Plasma Concentration vs Time Profile by Age-Group after Single and Multiple Dose (Day 1 to Day 16; cf. Section 8.2, Table 34)



Reviewer's Comments:

1. At steady state, the exposure in elderly as exemplified by mean AUC was about 44% higher than in young (1411 vs. 2035 ng.h/ml). However, in terms of Cmax, it was higher by 13% in elderly compared to young (254 vs. 289 ng/ml).

2. No difference in the % of dose excreted in urine after multiple dosing between the two populations (13 % vs. 11 %)

3. Compared to the other study in elderly (#SE-866-14), this study shows slightly more exposure to the drug in the very elderly patients.

Conclusion:

Overall, the difference between young and elderly may have minimal clinical significance. According to the sponsor's proposed label, no dose adjustment is necessary in elderly population.

Vol. 68

Study # 866-110

Title

A Comparative PK Study of CS-866 Tablets in Healthy Adult Male and Female Volunteers

Investigator

Objective

To assess the PK of CS-866 tablets administered under fasting conditions to healthy adult male and female volunteers

Study Design

This was a single 20 mg dose of Benevas tablet administered orally to 18 males and 17 females. The drug was administered after a 12 hour fast. Blood and urine samples were collected over 72 hours for PK analysis.

Formulation:

The lot # of the 20 mg tablets used in this study was 293.

Results:

Figure 7.2.2:1 Mean (±SD) Plasma Concentrations Linear Scale

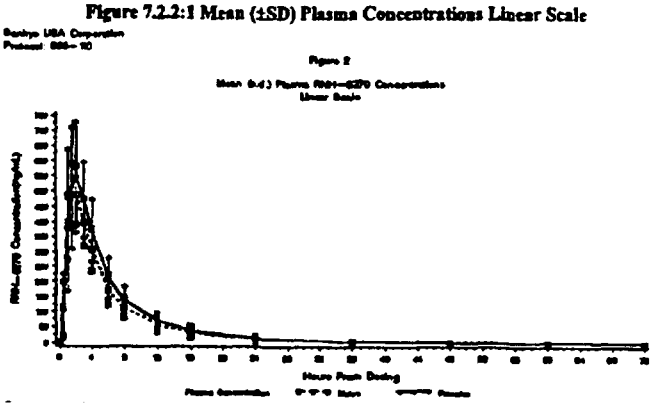


Table 7.2.2:1 Summary of Pharmacokinetic Parameters for RNH-6270

Parameter	Mean[1] (±SD)	
	Females (N=17)	Males (N=18)
AUC_{0-tqc} (ng·hr/mL)	3673.01 (±1032.47)	3134.63 (±645.99)
$AUC_{0-\infty}$ (ng·hr/mL)	3729.24 (±1039.09)	3167.28 (±658.15)
C_{max} (ng/mL)	574.59 (±180.03)	506.17 (±90.47)
T_{max} (hrs)	2.00	1.75
$t_{1/2}$ (hrs)	18.72 (±5.92)	14.80 (±4.78)
V/F (L)	122.28 (±42.78)	111.65 (±41.95)
CL/F (L/hr)	4.64 (±1.43)	5.26 (±1.07)
CL_R (L/hr)	0.55 (±0.17)	0.55 (±0.07)

Source: Section 10.2, Table 5

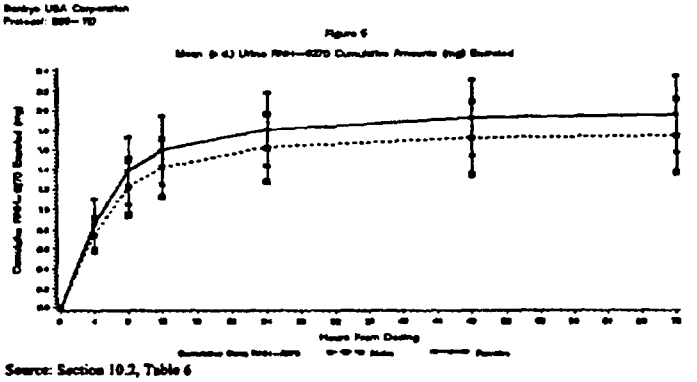
[1]The median for T_{max} is displayed; all other parameters are presented as mean values

Table 7.2.3:1 Mean Renal Clearance/Mean Percent of RNH-6270 Urine for Each Gender Group

Time Interval	Mean Percent (%CV) of Dose Excreted in Urine	
	Female RNH-6270	Male RNH-6270
0-4	5.3 (29.2)	4.7 (22.6)
4-8	3.3 (36.2)	3.0 (32.0)
8-12	1.3 (37.0)	1.2 (35.3)
12-24	1.4 (31.2)	1.3 (36.0)
24-48	0.7 (30.9)	0.6 (43.4)
48-72	0.2 (46.6)	0.2 (64.0)
Total (0-72)	12.2 (19.7)	10.9 (21.6)
CL_R (L/hr)	0.6 (30.0)	0.6 (12.3)

Source: Section 10.2, Tables 5 and 6

Figure 7.2.3:1 Mean (±SD) Urine RNH-6270 Cumulative Amounts Excreted



Source: Section 10.2, Table 6

Reviewer's Comments:

1. In females, the Cmax and AUC were about 17% and 13% higher than males. However, there was no difference in other PK parameters between females and males.

2. In terms of urine data, the amount excreted in urine was consistently higher in females than in males. However, there is little difference in the overall amount of drug excreted in urine. The mean % excreted in urine in female was 12.2% and in males was 10.9%.

Conclusion:

Overall, the difference between males and females can be considered of no clinical significance and thus no dosing adjustment is necessary.

Vol. 84

Study # SE 866/08

Title:

THE EFFECT OF THE COMBINATION OF THE ORAL ANGIOTENSIN II-ANTAGONIST CS-866 AND WARFARIN ON PHARMACODYNAMICS, PHARMACOKINETICS AND SAFETY IN HEALTHY, MALE SUBJECTS

Investigator

[redacted]

OBJECTIVES:

To investigate any possible influence on the Quick factor (in seconds and INR) after coadministration of warfarin and CS-866 in healthy volunteers. The secondary objectives are to investigate the pharmacodynamics (PTT) and PK of warfarin and RNH-6270.

Study Design:

This was 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, the 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. The details of study design is as follows:

Period: Time:	Period I Day 1 - 13	Period II Day 14 - 20	Period III Day 23 - 29
Sequence Group A Treatment	Warfarin	CS-866 Warfarin	Placebo Warfarin
Sequence Group B Treatment		Placebo Warfarin	CS-866 Warfarin
Pharmacokinetic/ - dynamic profile		Day 20 - 23	Day 29 - 32

Formulation:

The lot # of the 20 mg tablets used in this study was 220 and for warfarin was 5209

Assay:

The plasma concentration of warfarin was determined by . . The limit detection of this assay is µg/l. The calibration curve was linear from 25 µg to 1264 µg/ml. The inter and intra-assay precision (%CV) is approximately % as shown below as examples:

Table 1: Recalculated R-Warfarin concentrations [µg/l] of the calibration samples and statistical evaluation on both validation days.

calibration curve	25.3	50.6	253	506	758	1264
day 1	25.6	48.8	262	506	766	1231
day 2	24.8	52.7	251	491	792	1225
mean	25.2	50.7	256	499	779	1228
standard deviation	0.584	2.76	7.59	10.6	18.3	3.92
inter-assay precision [%]						
accuracy [%]						

Table 2: Recalculated S-Warfarin concentrations [µg/l] of the calibration samples and statistical evaluation on both validation days.

calibration curve	25.3	50.6	253	506	758	1264
day 1	25.0	51.5	253	509	768	1227
day 2	25.0	51.9	251	493	792	1227
mean	25.0	51.7	252	501	780	1227
standard deviation	0.024	0.294	1.56	11.0	17.3	0.073
inter-assay precision[%]						
accuracy [%]						

Table 5: Recalculated R-Warfarin concentrations [µg/l] and statistical evaluation of the validation samples on day 1.

sample no.	25.3	506	1264
1			
2			
3			
4			
5			
6			
mean	25.6	498	1214
standard deviation	1.11	9.07	23.0
intra-assay precision [%]			
accuracy [%]			

Table 6: Recalculated R-Warfarin concentrations [µg/l] and statistical evaluation of the validation samples on day 2.

sample no.	25.3	506	1264
1			
2			
3			
4			
5			
6			
mean	26.0	524	1293
standard deviation	1.42	13.2	21.0
intra-assay precision [%]			
accuracy [%]			

* : not used for calculation

Results:

The mean data are shown in the following Tables.

Table X: Mean Pharmacokinetic Parameters of RNH-6270 ± SD

Parameter	Sequence group		
	A (PII)	B (PIII)	Total
$C_{ss,max}$ [ng/ml]	680 ± 117	715 ± 284	697 ± 213
$C_{ss,min}$ [ng/ml]	22.64 ± 9.28	20.08 ± 7.62	21.30 ± 8.41
t_{max} [h]	1.79 ± 0.26	1.67 ± 0.39	1.73 ± 0.33
$t_{1/2}$ [h]	13.35 ± 5.38	12.50 ± 2.78	12.93 ± 4.21
$AUC_{ss,0-\tau}$ [ng*h/ml]	4064 ± 825	4162 ± 1388	4113 ± 1118

sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin

Table II: Mean Pharmacokinetic Parameters of Warfarin Enantiomers ± SD and Parametric 90% Confidence Intervals for Treatment Ratios

Parameter	E	CS-866 + warfarin	Placebo + warfarin	90% Confidence Interval		
				Lower limit	point estimator	upper limit
$AUC_{ss,0-24}$ [µg*h/l]	R	11887 ± 4956	12103 ± 4653	0.9031	0.9841	1.0292
	S	8676 ± 3549	8498 ± 3346	0.9716	1.0023	1.0340
$C_{ss,max}$ [µg/l]	R	687 ± 284	665 ± 229	0.9602	1.0186	1.0805
	S	539 ± 189	517 ± 171	1.0077	1.0376	1.0685
t_{max} [h]	R	1.9 ± 1.8	1.7 ± 1.5	0.8498	1.1500	1.6502
	S	1.4 ± 1.0	1.2 ± 0.6	0.8859	1.2182	1.5505

E = Enantiomer

Table VII: Mean Pharmacokinetic Parameters of Warfarin Enantiomers ± SD

Parameter	Sequence Group	R-Enantiomer µg/l]		S-Enantiomer µg/l]	
		Treatment			
		CS-866 + w	placebo + w	CS-866 + w	placebo + w
$C_{ss,max}$ [µg/l]	A	654 ± 240	633 ± 195	502 ± 213	460 ± 182
	B	721 ± 282	696 ± 264	576 ± 162	575 ± 144
	Total	687 ± 264	665 ± 229	539 ± 189	517 ± 171
$C_{ss,min}$ [µg/l]	A	362 ± 164	368 ± 113	224 ± 116	215 ± 102
	B	392 ± 204	411 ± 223	263 ± 106	283 ± 110
	Total	377 ± 182	389 ± 174	243 ± 110	249 ± 110
t_{max} [h]	A	2.0 ± 1.9	2.0 ± 2.0	1.1 ± 0.6	1.2 ± 0.7
	B	1.8 ± 1.7	1.3 ± 0.6	1.7 ± 1.2	1.1 ± 0.6
	Total	1.9 ± 1.8	1.7 ± 1.5	1.4 ± 1.0	1.2 ± 0.6
$AUC_{ss,0-24}$ [µg*h/l]	A	11560 ±4655	11473 ±3410	7895 ± 3635	7307 ± 3038
	B	12213 ±5427	12732 ±5726	9257 ± 3480	9689 ± 3332
	Total	11887 ±4956	12103 ±4653	8576 ± 3549	8498 ± 3346

w: warfarin
sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin

Table I: Mean Pharmacodynamic Parameters of Quick and PTT ± SD and 90% Confidence Intervals for Treatment Ratios

Parameter	F	CS-866 + warfarin	Placebo + warfarin	90% Confidence Interval		
				lower limit	point estimator	upper limit
$E_{ss,max}$ [INR]	Quick	1.6 ± 0.3	1.6 ± 0.3	0.9375	1.0000	1.0625
[s]	PTT	43.2 ± 4.0	42.7 ± 3.9	0.9235	0.9699	1.0255
$AUE_{ss,0-24}$ [INR*h]	Quick	37.4 ± 6.9	37.4 ± 7.6	0.9582	1.0028	1.0446
[s*h]	PTT	985.2 ± 91.1	975.7 ± 86.9	0.9452	0.9728	1.0090
$E_{ss,min}$ [INR]	Quick	1.5 ± 0.3	1.4 ± 0.3	0.9286	1.0000	1.0714
[s]	PTT	37.6 ± 3.8	37.9 ± 3.3	0.9609	1.0026	1.0521

F = Coagulation Factor

Table XI: Mean Quick Values ± SD by Sequence

A. Days with Single Measurements

Day	Period	Mean of Quick (INR) ± SD	
		Sequence group A	Sequence group B
Screening		1.09 ± 0.07	1.09 ± 0.08
Day 13	I	1.51 ± 0.11	1.48 ± 0.10
Day 14	II	1.54 ± 0.14	1.52 ± 0.13
Day 16		1.81 ± 0.18	1.85 ± 0.15
Day 18		1.68 ± 0.31	1.74 ± 0.25
Day 22		1.48 ± 0.28	1.54 ± 0.26
Day 23	III	1.46 ± 0.26	1.56 ± 0.35
Day 25		1.48 ± 0.27	1.56 ± 0.29
Day 27		1.48 ± 0.28	1.58 ± 0.34
Day 31		1.46 ± 0.33	1.52 ± 0.32
Day 32		1.48 ± 0.31	1.53 ± 0.30
SFU		1.08 ± 0.10	1.04 ± 0.09

SFU = Safety Follow-up
sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin

B. Kinetic Days

Day	Time after dosing [h]	Mean of Quick (INR) ± SD	
		Sequence group A	Sequence group B
Day 21	pre-dose	1.58 ± 0.28	1.71 ± 0.30
	2	1.45 ± 0.22	1.53 ± 0.26
	4	1.50 ± 0.26	1.62 ± 0.31
	8	1.60 ± 0.29	1.65 ± 0.29
	12	1.58 ± 0.30	1.64 ± 0.34
	24	1.58 ± 0.34	1.63 ± 0.33
Day 30	pre-dose	1.47 ± 0.34	1.55 ± 0.30
	2	1.48 ± 0.32	1.53 ± 0.27
	4	1.45 ± 0.33	1.53 ± 0.32
	8	1.50 ± 0.32	1.56 ± 0.33
	12	1.46 ± 0.31	1.53 ± 0.29
	24	1.53 ± 0.34	1.61 ± 0.34

sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin

Table XII: Quick [INR] Characteristics, Mean ± SD

Parameter	Sequence	Treatment	
	Group	CS-866 + warfarin	placebo + warfarin
$E_{ss,\ max}$ [INR]	A	1.65 ± 0.33	1.57 ± 0.33
	B	1.63 ± 0.35	1.72 ± 0.34
	Total	1.64 ± 0.33	1.64 ± 0.34
$E_{ss,\ min}$ [INR]	A	1.43 ± 0.21	1.39 ± 0.30
	B	1.46 ± 0.28	1.49 ± 0.26
	Total	1.45 ± 0.25	1.44 ± 0.28
$AUE_{ss,\ 0\text{-}24}$ [INR*h]	A	37.5 ± 6.8	35.6 ± 7.6
	B	37.3 ± 7.3	39.1 ± 7.5
	Total	37.4 ± 6.9	37.4 ± 7.6

sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin

Table XIV: Mean PTT Values ± SD by Sequence

Day	Time after dosing [h]	Mean of PTT [s] ± SD	
		Sequence group A	Sequence group B
Screening		35.1 ± 2.0	35.8 ± 1.8
Day 21	pre-dose	38.6 ± 4.6	41.2 ± 3.0
	2	38.9 ± 5.1	38.6 ± 3.3
	4	38.8 ± 5.2	39.9 ± 2.7
	8	39.7 ± 4.6	40.4 ± 2.4
	12	41.1 ± 5.3	41.4 ± 3.4
	24	41.2 ± 4.8	42.8 ± 3.7
Day 30	pre-dose	39.8 ± 3.4	41.8 ± 2.3
	2	39.8 ± 4.1	40.8 ± 2.5
	4	38.8 ± 4.2	40.2 ± 2.5
	8	39.7 ± 4.8	40.8 ± 2.7
	12	40.9 ± 4.8	43.3 ± 3.0
	24	40.0 ± 4.7	42.2 ± 3.8
Day 32		40.2 ± 4.1	40.3 ± 2.9
SFU		35.7 ± 3.4	34.7 ± 3.2

sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin
SFU = Safety Follow-up

Table XV: PTT Characteristics, Mean ± SD

Parameter	Sequence	Treatment	
	Group	CS-866 + warfarin	placebo + warfarin
$E_{ss,\ max}$ [s]	A	42.3 ± 4.9	42.0 ± 4.6
	B	44.1 ± 2.7	43.4 ± 3.2
	Total	43.2 ± 4.0	42.7 ± 3.9
$E_{ss,\ min}$ [s]	A	36.4 ± 4.7	37.2 ± 3.7
	B	38.8 ± 2.2	38.5 ± 2.8
	Total	37.6 ± 3.8	37.9 ± 3.3
$AUE_{ss,\ 0\text{-}24}$ [s*h]	A	965 ± 113	962 ± 102
	B	1006 ± 60	989 ± 70
	Total	985 ± 91	976 ± 87

sequence group A = PII: CS-866 + warfarin, PIII: placebo + warfarin
sequence group B = PII: placebo + warfarin, PIII: CS-866 + warfarin

Reviewer's Summary:

1. There was no difference in any of the PK parameters of warfarin PK for either R or S enantiomers when administered with benevas or placebo. For example the mean AUC for R-Warfarin was 11887 and 12103 ug.h/ml when administered with Benevas and placebo, respectively.

2. Similarly, Benevas had no effect on PTT values compared to placebo.

3. Furthermore, warfarin had no effect on any of the PK parameters of Benevas.

Conclusion:

There was no clinically significant drug interaction in this study in either direction.

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Study # SE-866/15

TITLE

THE EFFECT OF THE COMBINATION OF THE ORAL ANGIOTENSIN II-ANTAGONIST CS-866 AND DIGOXIN ON THE SAFETY, TOLERABILITY AND PHARMACOKINETICS IN HEALTHY, MALE SUBJECTS

Investigator:

[redacted]

OBJECTIVES

The primary object is to investigate any possible influence on the PK of digoxin after coadministration of CS-866 at steady state in healthy, male subjects. The secondary objective is to investigate the PK of the main metabolite of CS-866 (RNH6270).

Design:

This was 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.

Formulation:

The lot # of the 20 mg tablets used in this study was 2234V97009 and for digoxin was F3758A [redacted]

Assay:

Digoxin plasma concentration was determined by [redacted] with a detection limit of [redacted] ng/ml. The calibration curve is linear up 3 ng/ml. The precision (% CV) of the assay (niter and intra-assay) was in the range of [redacted] % as shown in the following Tables:

Table 1: Concentration of Digoxin [µg/l] in calibration samples tested along with samples from subjects of a drug interaction study (external study no. SE-866/15)

batch no.	fortified concentration [µg/l] 0.107	0.267	0.534	1.07	2.67	5.34
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
13	[illegible]					
mean	0.106	0.268	0.561	1.03	2.50	5.62
standard deviation	0.0028	0.0193	0.036	0.0505	0.0645	0.276
inter-assay precision [%]						
accuracy [%]						

#: rejected from calculation

Table 2: Concentration of Digoxin [µg/l] in validation samples tested along with samples from subjects of a drug interaction study (external study no. SE-866/15)

batch no.	fortified concentration [µg/l] 0.303	0.758	3.03
1			
1			
2			
2			
3			
3			
4			
4			
5			
5			
6			
6			
7			
7			
8			
8			
9			
9			
10			
10			
11			
11			
12			
12			
13			
mean	0.327	0.793	3.07
standard deviation	0.0292	0.0647	0.233
inter-assay precision [%]			
accuracy [%]			

#: rejected from calculation
n.a.: due to an instrument failure not analysed
n.s.: no signals

Results:

Figure I. Median Concentration of Digoxin (ng/ml) in Plasma After Multiple Dose (Periods II and III)

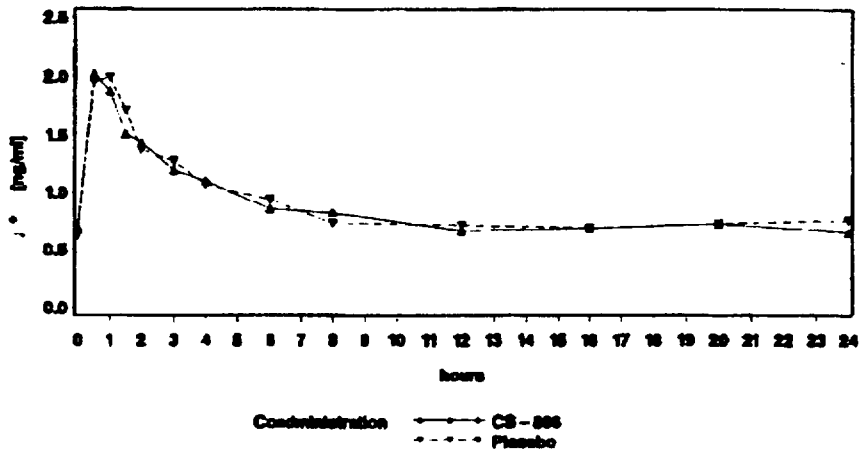


Table I. Pharmacokinetic Results of Digoxin, Geometric Mean (Geometric CV)

Pharmacokinetic parameter	Minimum	Maximum	Geometric mean coadministration CS-866	Geometric mean coadministration placebo
$AUC_{ss,\tau}$ (h*ng/ml)			20.74 (25.84)	20.97 (25.15)
$C_{ss,max}$ (ng/ml)			2.15 (26.16)	2.13 (26.00)
t_{max} (h)			1.0 (0.5-3.0)*	1.0 (0.5-3.0)*
$C_{ss,min}$ (ng/ml)			0.54 (33.94)	0.45 (123.33)
$C_{ss,\tau}$ (ng/ml)			0.86 (25.84)	0.87 (25.15)

* Median (Minimum-Maximum)

Table II. Pharmacokinetic Results of RNH-6270, Geometric Mean

Pharmacokinetic parameter	Geometric mean (range) coadministration with digoxin
$AUC_{ss,\tau}$ (h*ng/ml)	2683 (1356 - 4517)
$C_{ss,max}$ (ng/ml)	440 (208 - 741)
t_{max} (h)*	2.0 (1.0 - 3.0)
$C_{ss,min}$ (ng/ml)	16.6 (7.17 - 26.3)
$t_{1/2}$ (h)**	12.2 (7.0 - 26.3)

* Median **N=22

Reviewer's Comments:

1. Concomitant administration of Benevas with digoxin had essentially no effect on the pharmacokinetics of digoxin. Except for Css, min, which was marginally higher when digoxin was administered concomitantly with Benevas as compared with placebo.

2. The AUC for digoxin was 20.74 and 20.97 ng.h/ml when administered with Benevas and placebo, respectively.

3. It would have been preferable is the sponsor also investigated the effect of digoxin on the PK of olmesartan.

Conclusion:

No clinically significant drug interaction was observed in this study. The focus of this study was mainly on the effect of Benevas on the PK of digoxin. It should be noted that the effect of digoxin on the PK of olmesartan is unknown.

Vol. 91

Study # SE-866/04

EFFECTS OF THE ANGIOTENSIN II-ANTAGONIST CS-866 IN SALT-DEPLETED HYPERTENSIVE PATIENTS (SINGLE DOSE)

Investigator:

[redacted]

Objectives:

The primary objective is to assess the dose-response relationship of CS-866 in association with a low sodium diet on blood pressure in hypertensive patients. The secondary objective is to assess the effect on the renin-angiotensin system.

Study Design:

In this study 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. Patients received one of the following treatment sequences as shown below:

Group I:

	Day 1	Day 8	Day 15	Day 22
A:	2.5 mg	10 mg	40 mg	Placebo
B:	2.5 mg	10 mg	Placebo	40 mg
C:	2.5 mg	Placebo	10 mg	40 mg
D:	Placebo	2.5 mg	10 mg	40 mg

Group II:

	Day 6	Day 13	Day 20	Day 27
E:	5 mg	20 mg	80 mg	Placebo
F:	5 mg	20 mg	Placebo	80 mg
G:	5 mg	Placebo	20 mg	80 mg
H:	Placebo	5 mg	20 mg	80 mg

Formulations:

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

Results:

Table IV. Mean 24 h Diastolic Blood Pressure Values (± S.D.) for Dose Groups [mmHg] (Appendix 4, Listing 13; Section 8.2, Table 4)

Group 1 (8 patients)			Group 2 (8 patients)		
Dose Group	Mean dBP	Median dBP	Dose Group	Mean dBP	Median dBP
Placebo	88.17 ± 15.08	89.5	Placebo*	79.14 ± 13.93	80.0
2.5 mg	84.34 ± 15.49	84.5	5 mg	76.52 ± 15.54	77.0
10 mg	81.31 ± 15.88	80.0	20 mg*	70.69 ± 14.88	71.0
40 mg	81.82 ± 14.87	83.0	80 mg	70.21 ± 15.64	70.0

* 7 in these groups (see Section 4)

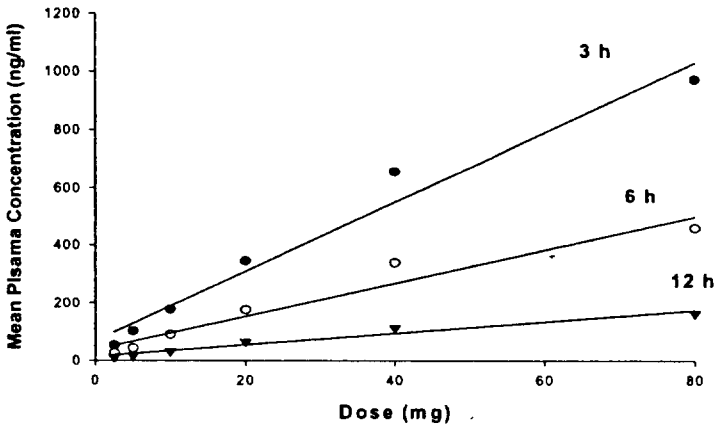
Table V. Conventional Diastolic Blood Pressure Values of Group 1, Group 2 (means ± S.D. of 8 patients, 2 measurements each) [mmHg] (Appendix 4, Listing 15; Section 8.2, Tables 5.13 - 5.15)

	Group 1 (n = 16)		Group 2 (n = 16)
Screening:	103.31 ± 6.24	Screening:	103.06 ± 7.53
Pre-Phase:		Pre-Phase:	
Day -3	106.31 ± 5.69	Day -3	104.88 ± 5.21
Day -2	106.25 ± 4.60	Day -2	104.00 ± 3.93
Day -1	106.94 ± 5.79	Day -1	103.38 ± 3.32
Mean Pre-Phase:*	106.50 ± 5.28	Mean Pre-Phase:*	104.08 ± 4.19
Close-Out Visits: (Day 2)		Close-Out Visits: (Day 2)	
Placebo	95.94 ± 6.82	Placebo	88.43 ± 08.12
2.5 mg	97.69 ± 5.63	5 mg	90.69 ± 11.57
10 mg	89.38 ± 5.69	20 mg	78.64 ± 08.92
40 mg	90.38 ± 8.86	80 mg	76.50 ± 13.03

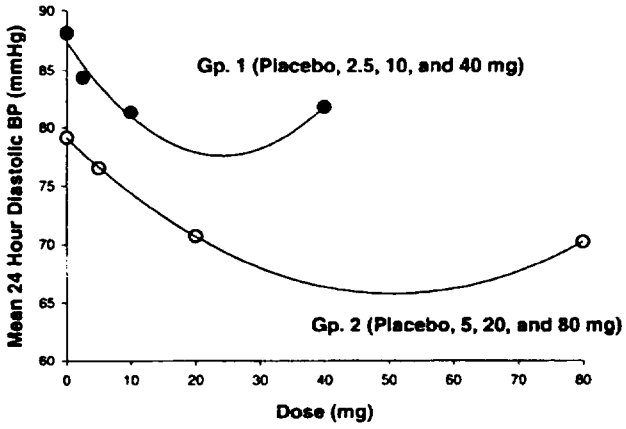
*n = 48

Reviewer's Summary:

This study lacks the adequate power to establish the dose-response relationship for this drug. The mean plasma concentrations at 3, 6, and 12 hours appear to be dose proportional in all subjects. The Figure below shows the relationship Between Dose and Mean Plasma Concentration of Olmesartan at 3, 6, and 12 hours in 8 subjects.

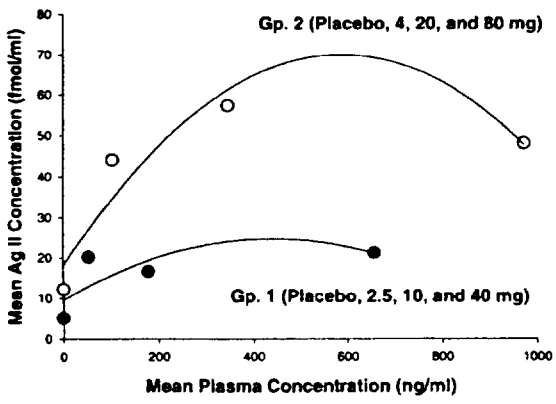


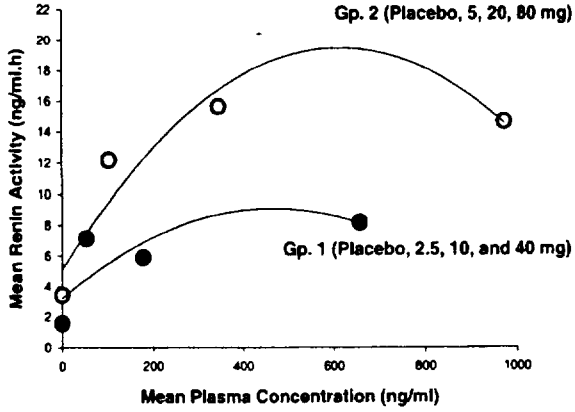
There appears to be some relationship between 24 hour diastolic blood pressure and dose in each group. The Figure below shows the relationship Between Dose and Mean 24 Hours Diastolic Blood Pressure (n=8)



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). This results in two different profile for each group with two different baselines (**see Figures**). The reason for this marked difference is unknown. Similarly, two markedly different baselines and curves where observed for renin activity and angiotensin plasma concentrations. There was a weak relationship between dose and/or olmesartan plasma concentration and renin activity and angiotesnin plasma concentration. The relationship starts plateau after the second dose in each group (see Figures below).

Relationships Between Plasma Concentration and Angiotensin II (left) and Renin (right) plasma concentration (n=8).





Conclusions:

This study lacks of adequate power to establish the dose-response relationship for this drug. Overall, there is a reduction of about 10 mmHg in each group from the respective baseline with increase in dose.

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Vol. 90

Study # SE-866/03

Title:

COMPARISON OF THE ANGIOTENSIN II-ANTAGONIST CS-866 WITH THE ACE INHIBITOR ENALAPRIL IN HEALTHY MALE SUBJECTS CHALLENGED WITH ANGIOTENSIN I (SINGLE DOSE)-

Investigator:

[redacted]

Objectives:

The primary objective of this trial was to assess the inhibitory effect of CS-866 on the pressor action of exogenous angiotensin (Ang I) and to compare this with the effect of enalapril. The safety and tolerability of CS-866 was a further consideration, as was the response of plasma components of the RAS {plasma renin activity and Ang II levels).

Study Design:

This phase I study was designed as a randomized, double-blind, double-dummy, placebo-controlled, four-way crossover trial, assessing the inhibitory effect of the angiotensin (Ang) II-antagonist CS-866 on the pressor action of exogenous angiotensin I (Ang I) after single-dose administration in healthy male subjects, compared to enalapril. There were two groups of eight subjects. These subjects received four doses of trial medication (2.5, 10 or 40 mg CS-866 or placebo in group 1 and 5, 20 mg CS-866, 20 mg enalapril or placebo in group 2) in one of eight possible sequences (A-H). Two subjects were assigned to each sequence.

Before the first administration of trial drug, an individual Ang I response curve was plotted for each subject, in order to determine which concentration of Ang I was required to increase systolic blood pressure (sBP) by the 2.5 to 40 mg. This dose was then used in each of the subsequent trial periods. Each trial period lasted for 24 hours with each subject receiving one single dose of study drug. During this time several Ang I challenges were made and blood samples were drawn for the assessment of pharmacokinetic and pharmacodynamic parameters.

Formulations:

The lot #s of the 2.5, 5, 10, and 20 mg tablets used in this study are 217, 218, 219, 220 respectively.

Treatment Regimen and Dosage

Each group consisted of 8 subjects. Treatments were in one of the following sequences:

Group I

	Period I	Period 2	Period 3	Period 4
A:	2.6 mg	10 mg	40 mg	placebo
B:	2.5 mg	10 mg	placebo	40 mg
C:	2.5 mg	placebo	10 mg	40 mg
D:	placebo	2.6 mg	10 mg	40 mg

Group 2:

	Period 1	Period 2	Period 3	Period 4
E:	5 mg	20 mg	enalapril	placebo
F:	5 mg	20 mg	placebo	enalapril
G:	5 mg	placebo	20 mg	enalapril
H:	placebo	5 mg	20 mg	enalapril

(A-H are the different treatment sequences, two subjects were assigned to each sequence). Each dose consisted of two tablets and a capsule.

Results:

The results clearly demonstrate that CS-866 is significantly more effective at inhibiting an Ang I-induced increase in sBP than placebo. This is true for all doses used including the lowest one, 2.5 mg. Statistical tests also show that there is no significant difference In efficacy between CS-866 and enalapril (the difference at 20 mg CS-866 is borderline significant). The graphs of change in sBP suggest that there is no substantial gain in inhibitory potency when increasing the dose beyond 10 to 20 mg. There was a less than proportional increase in the plasma concentrations of olmesartan especially at the higher dose. This data was based on the plasma concentration at 2 hours (Cmax) and $AUC_{0\text{-}24}$ hour. In contrast, pharmacodynamic results lack clear proportionate increases in parameters examined over the range of doses studied.

Table. Systolic Blood Pressure percentage response of the area above the Curves (AACs) by treatments

Subject group	Medication	AAC		
		Mean ± S.D.	Median	(Min, Max)
1	placebo	385 ± 267	290	[redacted]
2	placebo	380 ± 291	376	[redacted]
1	2.5 mg CS-866	1162 ± 606	1279	[redacted]
2	5 mg CS-866	1381 ± 635	1494	[redacted]
1	10 mg CS-866	1710 ± 236	1590	[redacted]
2	20 mg CS-866	1601 ± 333	1810	[redacted]
1	40 mg CS-866	1660 ± 755	1968	[redacted]
2	20 mg enalapril	1328 ± 517	1366	[redacted]

Table IV. Exploratory Results of Pairwise Statistical Testing of AACs (Section 8.2, Table 11.5)

CS-866 Dose	Median difference[a] (p-value)	
	vs. Placebo	vs. Enalapril
2.5 mg	850 (0.031) [b]	-87 (0.603) [bb]
5 mg	1300 (0.016) [b]	-87 (0.945) [b]
10 mg	1303 (0.016) [b]	225 (0.118) [bb]
20 mg	1400 (0.008) [b]	428 (0.055) [b]
40 mg	1539 (0.031) [b]	602 (0.328) [bb]

[a] Difference in medians in independent samples;
[b] Placebo, Group 1 ; [bb] Placebo, Group 2
[b] Wilcoxon signed-rank test ; [bb] Wilcoxon rank-sum test

Table V. Pharmacokinetic Parameters of RNH-6270 in Plasma by Medication (Section 8.3, Appendix 5, Tables 2.1, 2.2 and 3.9 - 3.13)

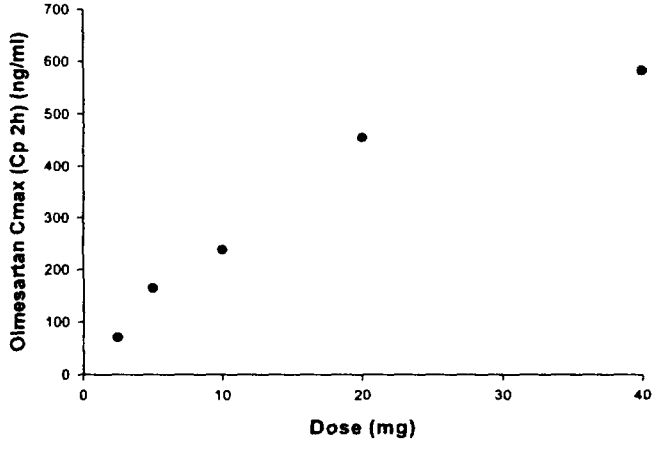
Dose of CS-866 (mg)	Pharmacokinetic Parameters		
	AUC(0-24) [ng.h/ml] (geom. mean (geom. CV))	C_{max} [ng/ml] (geom. mean (geom. CV))	t_{max} [h] (median (min, max))
2.5 (n=8)	440 (20.7)	70 (32.6)	2 [redacted]
5 (n=8)	1015 (10.0)	163 (24.9)	2 [redacted]
10 (n=7)	1498 (24.4)	233 (26.8)	2 [redacted]
20 (n=8)	3121 (18.9)	463 (28.2)	2 [redacted]
40 (n=7)	4878 (15.4)	567 (33.8)	2 [redacted]

Reviewer's Summary and Findings:

This was a double-blind, double-dummy, placebo-controlled, single dose, four-way crossover in healthy subjects. There were two groups of 8 subjects. In each group, 2 patients received placebo. Each patient 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, enalapril (20 mg), 5 and mg Benevas tablets. 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.

The following are further analysis of the data conducted by the reviewer. Based on this, the mean plasma concentrations of olmesartan at 2 hours (Cmax) appears to be dose proportional in both groups of subjects (**Figure 1**).

Figure 1 Relationship Between Dose and Olmesartan Plasma Concentration at 2 hours (Cmax)



There was some relationship between reduction in blood pressure (BP) and dose (**Figures 2A and 2B**). For example, in Group 1, the mean reduction in blood pressure following 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 2 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 2A. Mean Systolic Blood Pressure-Time Profiles in Group 2 Following 20 mg Benevas and 20 mg Enalapril Compared to Placebo (n=8)

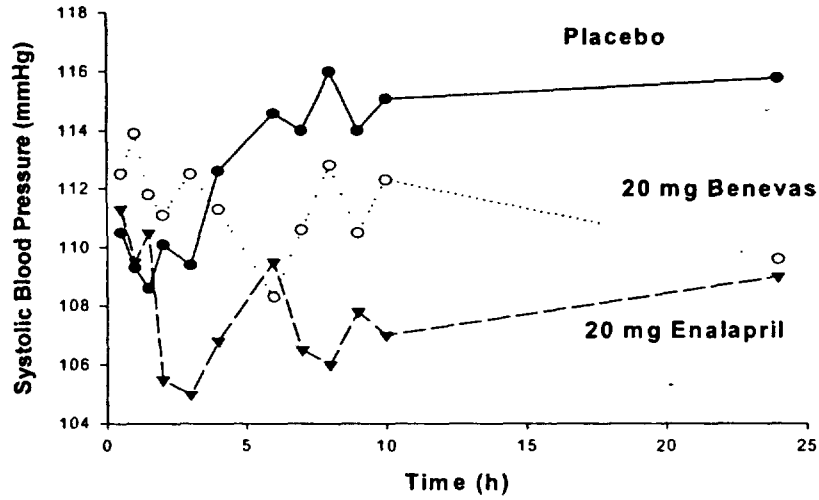
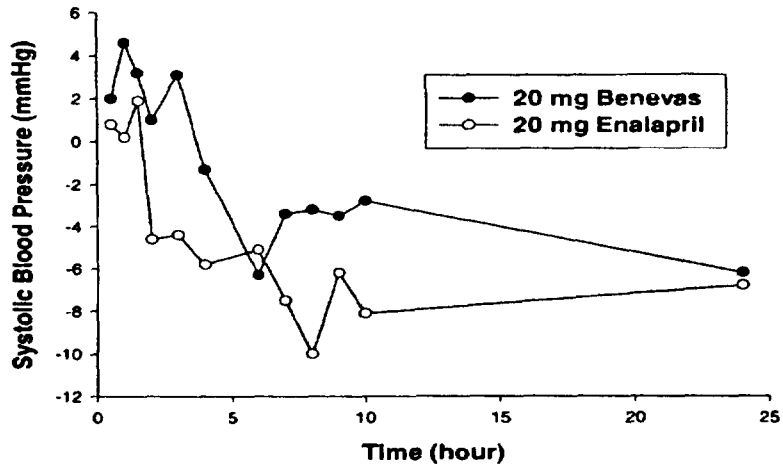
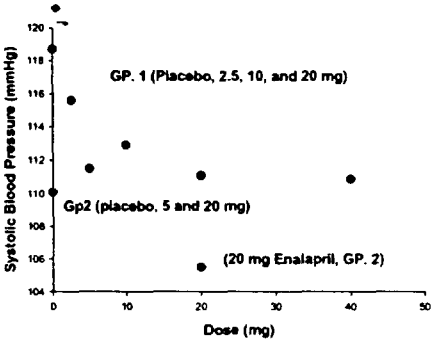


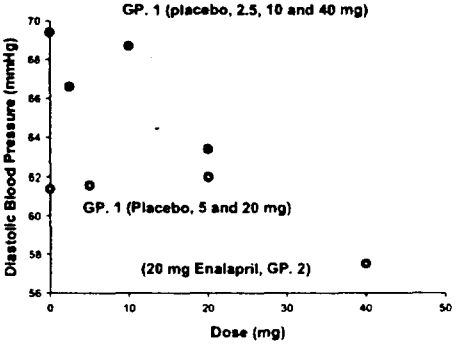
Figure 2B. Reduction in Systolic Blood Pressure After Placebo Subtraction (see Figure 2A for actual data).

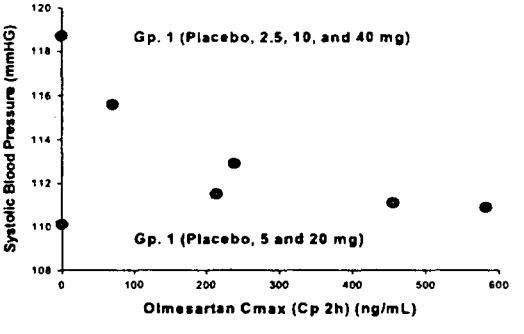


At 2 hours, the baselines for systolic and diastolic BP were markedly different between the two groups (**Figure 3-5**). In group 1, the mean baseline for the systolic BP was at 2 hour was 118.7 mmHg and in group 2 was 110.1 mmHg. Similarly, for diastolic BP, at 2 hours, it was 69.4 and 61.4 mmHg in group 1 and group 2, respectively. This results in two different curves for each group. The reason for this marked difference is unknown. In addition, there was some relationship between reduction in blood pressure, dose and plasma concentration, particularly at Cmax, which occurs at 2 hours.

Figures 3-5. 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)

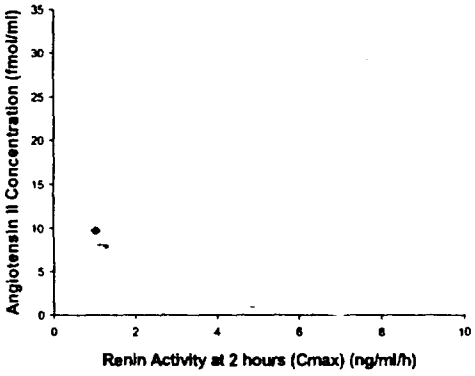


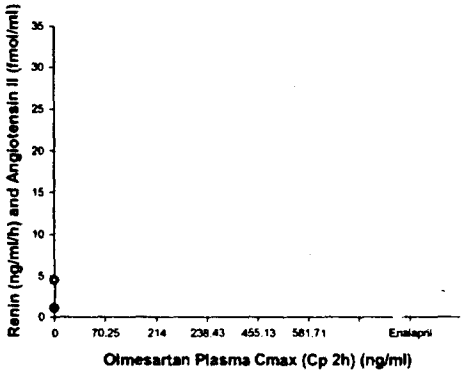




It appears that there is a linear relationship between renin activity and angiotensin II at 2 hours (Cmax) of drug administration (**Figures 6,7**). Enalapril, howerver, caused marked reduction in renin activity and angiotensin. There was non-linear relationship between olmesartan plasma concentration (e.g., Cmax) and renin or angiotensin plasma concentration.

Figures 6-7. 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)





Conclusion:

Overall, this study lacks of adequate power to establish a dose-response relationship for this drug (n=8 in each group).

Vol. 93

Report # 17240-1.01

Title:

Validation of [redacted] for the Quantitation of RNH-6270 in Plasma

Investigator/Site:

[redacted]

Method

A method was validated for the determination of RNH-6270 in human plasma by [redacted] RNH-6270 and an internal standard, RNH-6272, were extracted from plasma using [redacted]

Five standard curves assayed over a period of 9 days to determine the interday and intraday reproducibility. Recovery of RNH-6270 and stability was also determined. During the validation, quality control samples were [redacted]

Redacted 4

pages of trade

secret and/or

confidential

commercial

information

Conclusion:

The analytical assay used in this NDA to determine the plasma concentration of olmesartan (RNH-6270) is adequately sensitive, specific and reproducible.

Vol. 93 and 94

Report # 17240-2.01

Title:

Validation of [redacted] for the Quantitation of RNH-6270 in Human Urine

Investigator/Site:

[redacted]

Method

Isolation of RNH-6270 and RNH-6272 (internal standard) from human urine is accomplished by [redacted]

Six standard curves assayed over a period of 14 days was to determine the interday and intraday reproducibility. Recovery of RNH-6270 and stability also was determined. During the validation, quality control samples were

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Conclusion:

The analytical assay used in this NDA to determine olmesartan (RNH-6370) concentration in human urine is adequately sensitive, specific and reproducible.

Vol. 6 (Pharmtox/PK)

Study # GR-144-063

Title:

Inhibitory Effects of RNH-6270 on Drug-Metabolizing Enzymes Activities in Human Liver Microsomes

Investigator:

Analytical and Metabolic Research Laboratories, Sankyo Co., Ltd., Japan

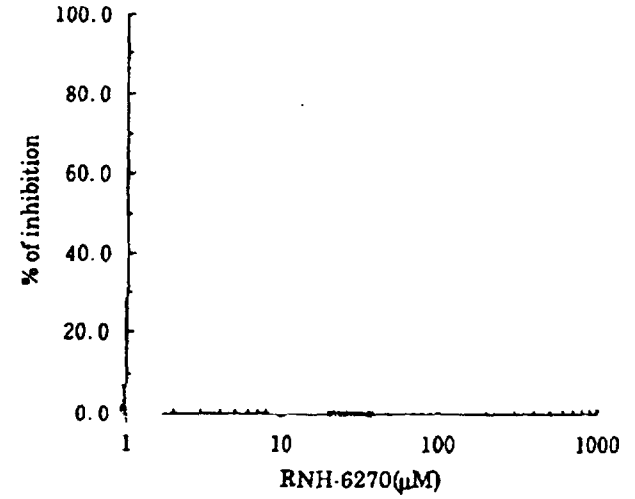
Method Experimental :

The inhibitory effects of RNH-6270 on the activities of various drug-metabolizing enzymes were investigated after addition to human liver microsome fraction at concentrations of 1, 10, 25, 50, 75, 100, 250 and 500 μM, using substrates specific to the isoforms of cytochrome P450 (P450). Effects of typical inhibitors of each P450 isoform were also investigated as a positive control. The following Table shows the summary of the experimental design:

Isozyme	Substrate	Final Concentration (substrate)	Protein Conc. (mg/ml)
CYP1A1 and 2	7-ethoxyresorufin	10 μM	0.5
CYP2A6	Coumarin	50 μM	0.2
CYP2C19	S-Mephentyoin	0.4 mM	1.0
CYP2C8 and 9	Tolbutamide	1 mM	0.5
CYP2D6	Bufuranol	10 μM	1.0
CYP2E1	Chlorzoxazone	0.4 mM	0.5
CYP3A4	Nifedipine	0.1 mM	0.5

Results:

The Data are shown in the next few pages:



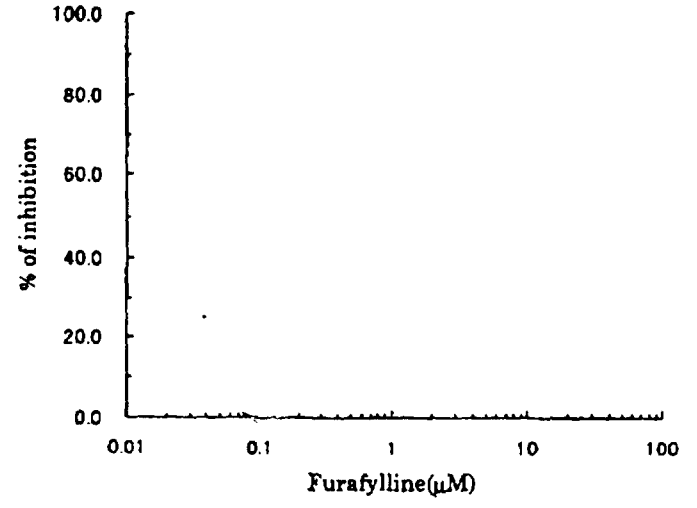
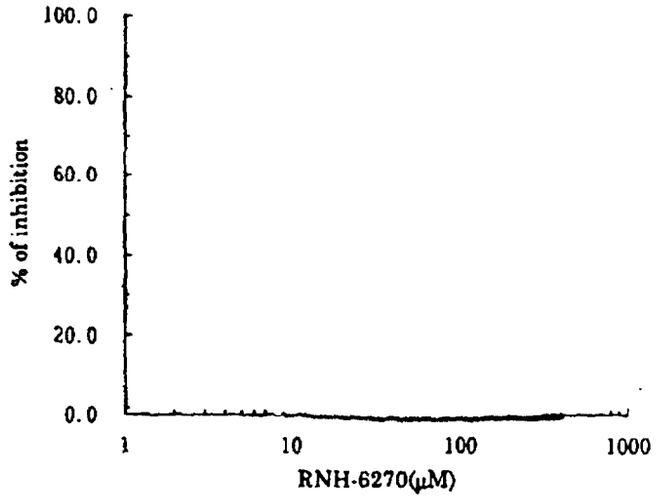


Figure 2 CYP1A1&2 inhibition(7-Ethoxyresorufin O-dealkylation) by RNH-6270 and furafylline using human liver microsomes



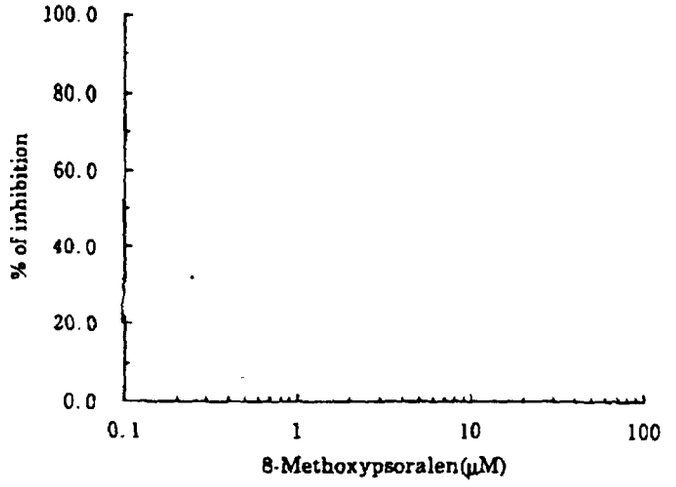


Figure 3 CYP2A6 inhibition(Coumarin 7-hydroxylation) by RNH-6270 and 8-metoxypsoralen using human liver microsomes

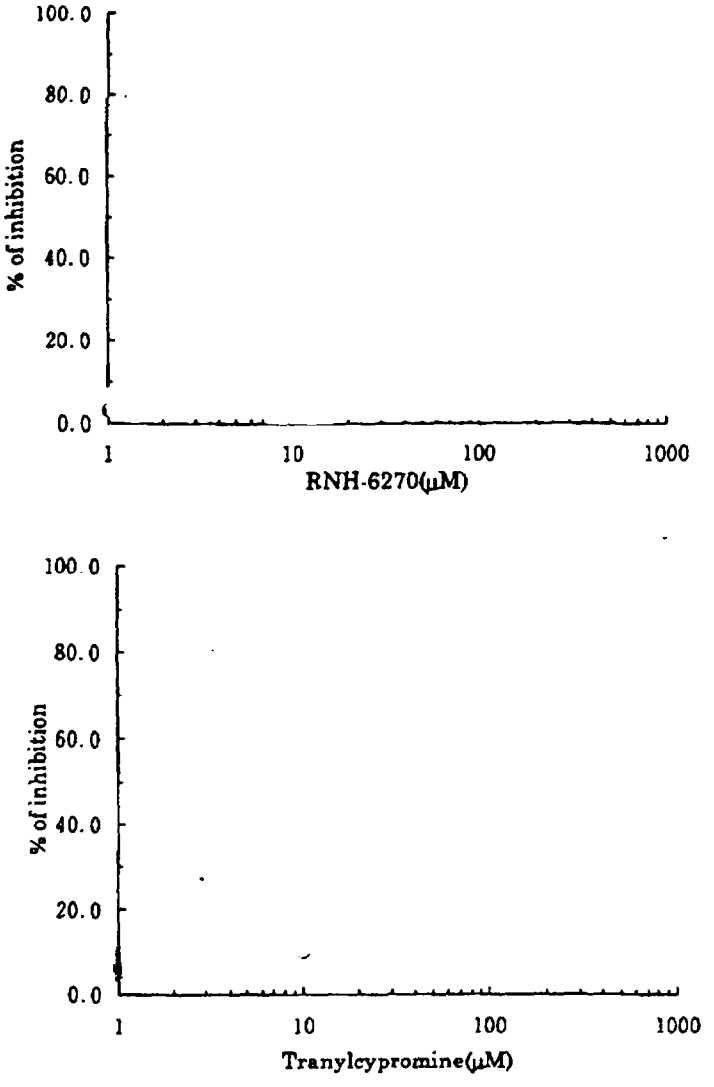


Figure 4 CYP2C19 inhibition(S-Mephenytoin 4'-hydroxylation) by RNH-6270 and tranylcypromine using human liver microsomes

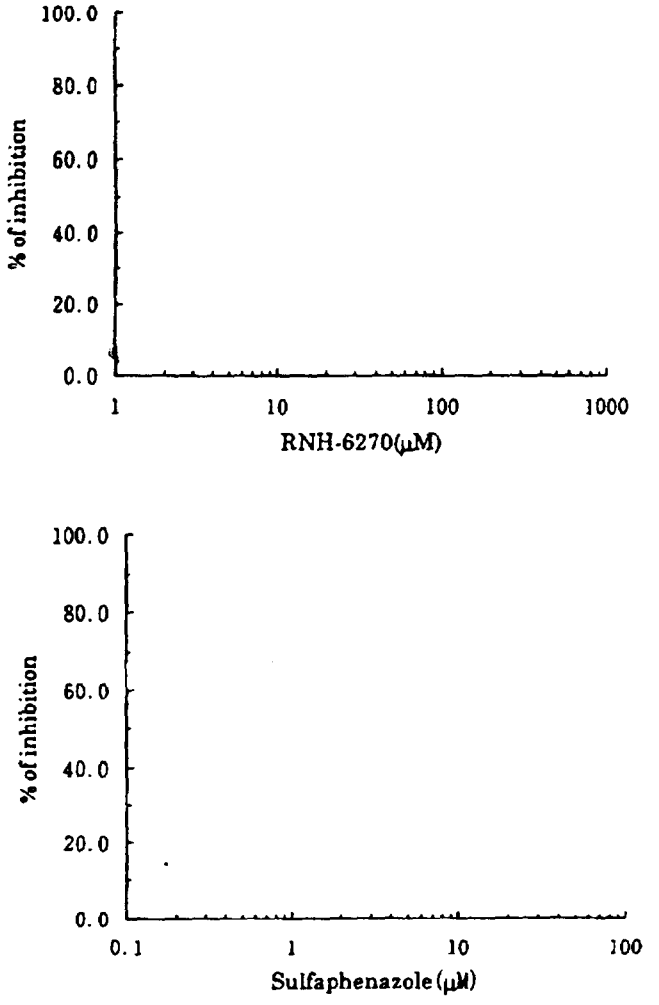


Figure 5 CYP2C8&9 inhibition(Tolbutamide hydroxylation) by RNH-6270 and sulfaphenazole using human liver microsomes

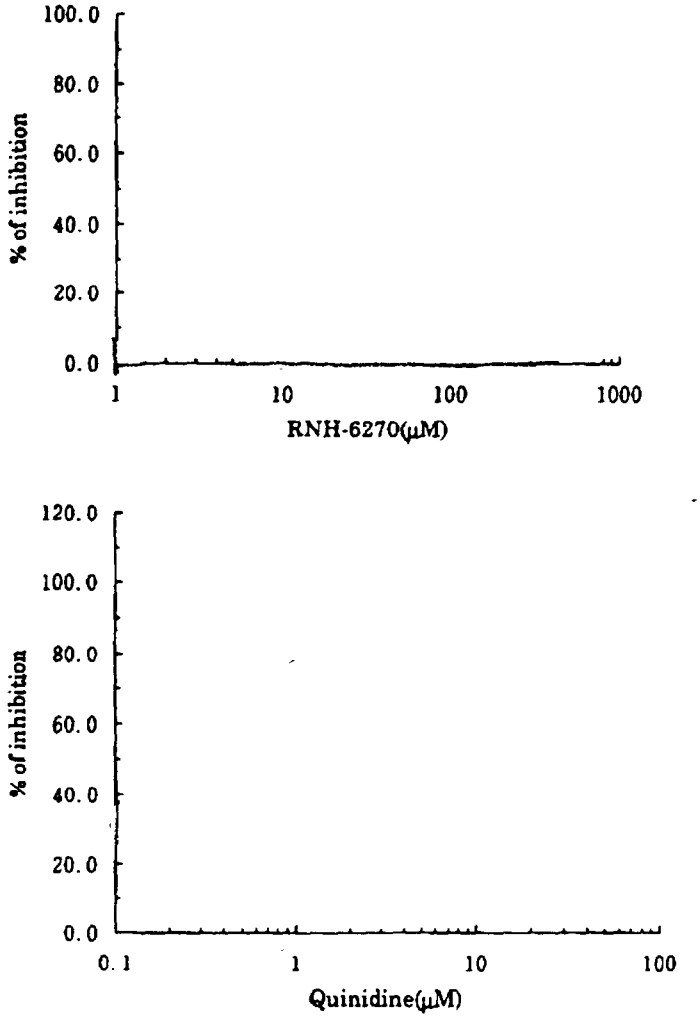


Figure 6 CYP2D6 inhibition(Bufuralol hydroxylation) by RNH-6270 and quinidine using human liver microsomes

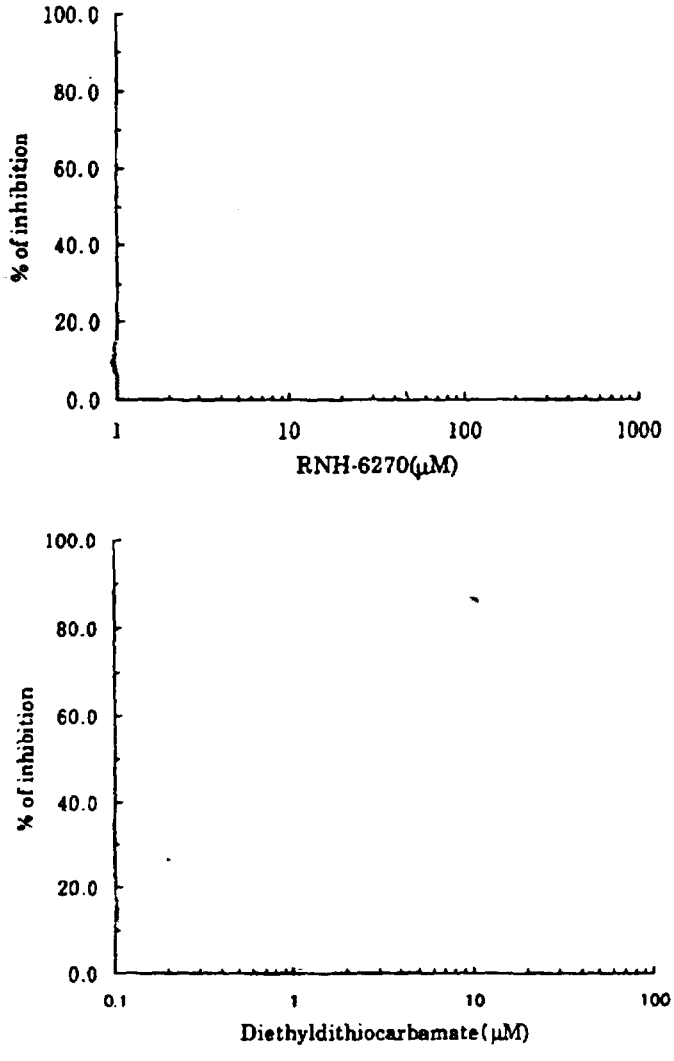


Figure 7 CYP2E1 inhibition(Chlorzoxazen 6-hydroxylation) by RNH-6270 and diethyldithiocarbamate using human liver microsomes

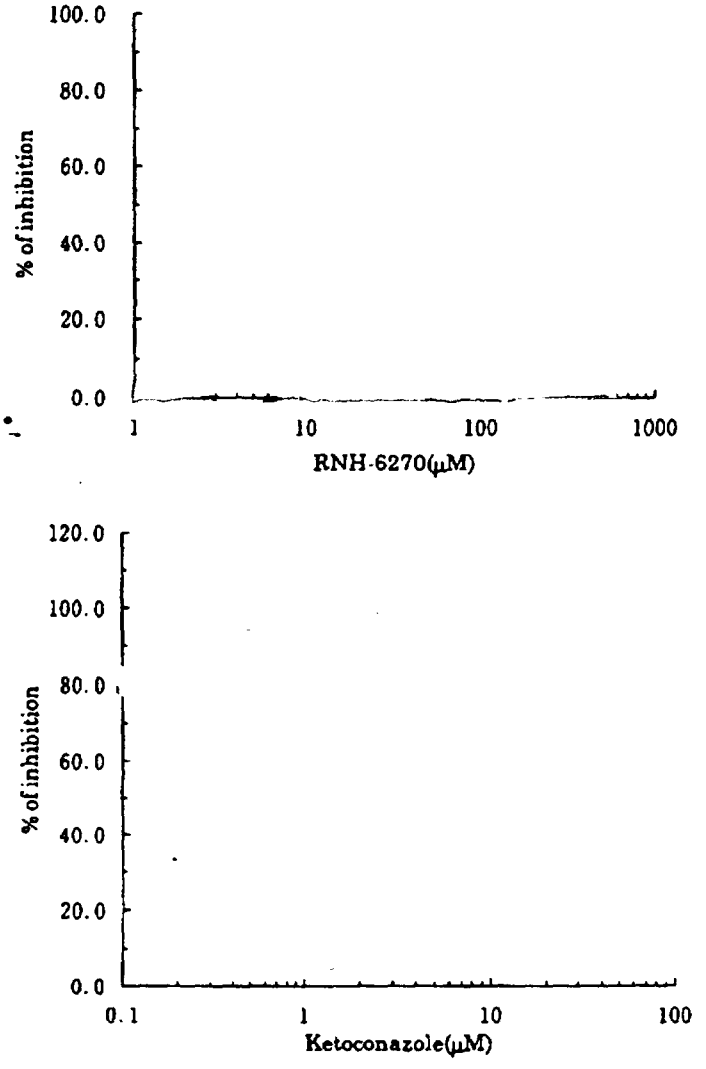


Figure 8 CYP3A4 inhibition(Nifedipine aromatization) by RNH-6270 and ketoconazole using human liver microsomes

Table 1 CYP1A1&2 inhibition (7-Ethoxyresorufin O-dealkylation) by RNH-6270 and furafylline using human liver microsomes

RNH-6270(μM)	Resorufin formation (pmol/min/mg)	Inhibition (%)
0	25.36	-
1	25.11	0.96
10	25.13	0.88
25	25.30	0.23
50	25.11	0.96
75	23.74	6.39
100	24.11	4.89
250	23.52	7.23
500	22.86	9.83

Furafylline(μM)	Resorufin formation (pmol/min/mg)	Inhibition (%)
0	10.21	-
0.05	9.62	5.77
0.1	10.45	-2.42
0.5	8.39	17.80
1	6.80	33.39
2.5	4.04	60.46
5	2.05	79.88
10	0.58	94.28
20	0.04	99.62

Table 3 CYP2C19 Inhibition (S-Mephenytoin 4'-hydroxylation) by RNH-6270 and tranylcypromine using human liver microsomes

RNH-6270(μM)	Hydroxymephenytoin formation (pmol/min/mg)	Inhibition (%)
0	21.35	-
1	20.69	3.09
10	21.15	0.91
25	19.40	9.13
50	20.54	3.79
75	18.72	12.29
100	20.49	4.04
250	13.98	34.54
500	14.92	30.10

Tranylcypromine (μM)	Hydroxymephenytoin formation (pmol/min/mg)	Inhibition (%)
0	19.95	-
1	18.73	6.08
10	17.98	9.88
25	13.66	31.50
50	10.63	46.72
75	8.91	55.31
100	6.97	65.06
250	3.22	83.86
500	1.70	91.48

Table 4 CYP2C8&9 inhibition (Tolbutamide hydroxylation) by RNH-6270 and sulfaphenazole using human liver microsomes

RNH-6270(μM)	Hydroxytolbutamide formation (pmol/min/mg)	Inhibition (%)
0	134.22	-
1	126.09	6.06
10	125.24	6.69
25	111.11	17.22
50	114.41	14.76
75	112.60	16.11
100	127.32	5.14
250	108.08	19.48
500	78.16	41.77

Sulfaphenazole (μM)	Hydroxytolbutamide formation (pmol/min/mg)	Inhibition (%)
0	68.13	-
0.1	70.46	-3.41
0.5	64.19	5.78
1	56.55	17.01
2.5	56.29	17.38
5	45.48	33.24
10	31.24	54.15
20	25.65	62.35

Table 5 CYP2D6 inhibition (Bufuralol hydroxylation) by RNH-6270 and quinidine using human liver microsomes

RNH-6270(μM)	Hydroxybufuralol formation (pmol/min/mg)	Inhibition (%)
0	9.68	-
1	9.69	-0.07
10	10.21	-5.47
25	10.13	-4.61
50	9.46	2.26
75	9.75	-0.66
100	9.48	2.03
250	9.64	0.42
500	8.71	10.03

Quinidine (μM)	Hydroxybufuralol formation (pmol/min/mg)	Inhibition (%)
0	9.17	-
0.1	6.35	30.76
0.5	3.20	65.12
1	2.15	76.52
2.5	1.37	85.06
5	1.01	88.97
10	0.53	94.22
20	0.44	95.24

Table 6 CYP2E1 inhibition (Chlorzoxazon 6-hydroxylation) by RNH-6270 and diethyldithiocarbamate using liver microsomes

RNH-6270(μM)	Hydroxychlorzoxazon formation (nmol/min/mg)	Inhibition (%)
0	2.35	-
1	2.12	9.50
10	1.88	20.10
25	1.91	18.83
50	2.31	1.54
75	1.80	23.29
100	2.12	9.61
250	1.99	15.18
500	2.15	8.35

Diethyldithiocarbamete (μM)	Hydroxychlorzoxazon formation (nmol/min/mg)	Inhibition (%)
0	3.67	-
0.1	3.17	13.65
0.5	2.73	25.59
1	2.53	31.07
2.5	1.60	56.37
5	0.87	76.23
10	0.53	85.48
20	0.29	92.04

Table 7 CYP3A4 inhibition (Nifedipine aromatization) by RNH-6270 and ketoconazole using human liver microsomes

RNH-6270(μM)	Oxidized nifedipine formation (pmol/min/mg)	Inhibition (%)
0	631.82	-
1	674.33	-6.73
10	651.87	-3.17
25	665.30	-5.30
50	670.11	-6.06
75	677.12	-7.17
100	702.05	-11.12
250	608.74	3.65
500	613.04	2.97

Ketoconazole(μM)	Oxidized nifedipine formation (pmol/min/mg)	Inhibition (%)
0	493.01	-
0.1	106.78	78.34
0.5	21.25	95.69
1	1.78	99.64
2.5	2.10	99.57
5	0.00	100.00
10	0.00	100.00
20	0.00	100.00

Reviewer's Summary:

- The activity of 7-ethoxyresorufin deethylase (CYP1A1, lA2) was inhibited by the addition of RNH-6270. This inhibition was only by 0.88% at 10 μM and by 9.83% a concentration of 500 μM. In contrast, furaphylline, the specific inhibitor of CYPlA1 and CYP1A2 showed increasing inhibition along the increase of the concentration, and the inhibition reached 99.62% at a concentration of 20 μM.

- There was no inhibitory effect of RNH-6270 at all on the activity of coumarin 7-hydroxylase (CYP2A6). On the other hand, 8-methoxypsoralene, the specific inhibitor of CYP2A6, showed 90.40% inhibition at a concentration of 20 μM.

- The activity of S-mephenytoin hydroxylate (CYP2CI9) was inhibited in the presence of RNH-6270 by 0.91% and 30.10% at concentrations of 10 μM and 500 μM, respectively. Tranylcypromine, the specific inhibitor of CYP2CI9, inhibited the activity of S-mephenytoin hydroxylase by 91.48% at a concentration of 500 μM.

- The activity of tolbutamide hydroxylase (CYP2C8, 9) was inhibited in the presence of RNH-6270 by 6.69% and 41.77% at concentrations of 10 μM and 500 μM, respectively. Sulfaphenazole, the specific inhibitor of CYP2C8 and CYP2C9, showed 62.35% inhibition at a concentration of 20 μM.

- The activity of bufurarol hydroxylase (CYP2D6) was not inhibited by RNH-6270 at a concentration of 10 μM, while it was inhibited by 10.03 % at a concentration of 500 μM. Quinidine, the specific inhibitor CYP2D6, inhibited thc activity of bufurarol hydroxylase by 95.24% at a concentration 20 μM.

- The activity of chlorzoxazone hydroxylase (CYP2E1) was inhibited in the presence of RNH-6270 by 20.10 % and 8.35% at concentrations of 10 μM and 500 μM, respectively. However, a large variation was found in the inhibition percentage, and no correlation was observed between the inhibitory effect and the RNH-6270 concentration. Diethyldithiocarbamate, the specific inhibitor of CYP2EI, inhibited thc activity of chlorzoxazone hydroxylase by 92.04% at a concentration of 20 μM.

- The activity of nifedipine oxidase (CYP3A4) was not inhibited by RNH-6270 in all experiments. Ketoconazole, the specific inhibitor of CYP3A4, inhibited the nifedipine oxidase by 78.34% and 100 % at concentrations of 0.1 μM and 5 μM, respectively.

Conclusions:

Olmesartan (RNH-6270) showed no inhibition on the activities of CYP2A6 and CYP3A4 even at the highest concentration examined (500 μM). Inhibition of the activities of CYPIA1 & 2, CYP2C19, CYP2D6 and CYP2EI were in the range of 8.35%-30.10%. CYP2C8 & 9 (tolbutamide hydroxylase activity), on the other hand, was found to be inhibited by 41.77% at this concentration,

Based on these data it can be concluded that olmesartan at clinically relevant concentrations has little effect on the activities of hepatic drug metabolizing enzymes *in vitro*.

Vol. 6 (Pharmtox/PK)

Study # RAM 140-053

Title:

Binding of ^{14}C-RNH-6270 to Serum Proteins *in vitro*

Objective:

The objective of the study is to determine the binding ratios of RNH-6270 to serum proteins of various animal species in vitro.

Method and Experimental Design:

^{14}C RNH-6270 (1 μg/ml - 100 μg/ml) was incubated with serum samples of mice, rats, dogs and humans at 37 °C for 5 min. After ultrafiltration, the radioactivity in the filtrate was measured to determine the free drug concentration. The binding ratio was calculated according to the total drug concentration and the free drug concentration.

To each 0.9 ml of the serum samples of various animal species, human serum albumin (HSA) solution (10 mg/ml), α1-acid glycoprotein (10 mg/ml) and globulin (10 mg/ml), 0.1 ml of ^{14}C-RNH-6270 was added (1, 10 and 100 μg/ml), and the mixture was incubated at 37°C for 5 min. In the binding experiments using purified human serum proteins, the concentration of RNH-6270 was fixed at 1 μg/ml. The samples were chilled with ice after incubation, and an aliquot of each mixture was transferred into a counting vial to measure the radioactivity, which served as the total drug concentration (C_{total}). Remaining incubation mixture was all transferred into an apparatus for ultrafiltration, and centrifuged until the filtrate of approximately 10% of the total volume is obtained. An aliquot of the ultrafiltrate was transferred into a counting vial, and measured for the radioactivity, which served as the free drug concentration (C_{free}). The samples in vials were solubilized in 1 ml of tissue solubilizer, added 15 ml of a toluene [redacted] and subjected to the measurement of the radioactivity by [redacted].
The binding experiments were conducted in duplicate, and the mean value was calculated. The ratio of the protein binding was calculated according to the following equation:

$$\text{Binding ratio (\%)} = \frac{C_{total}(\text{dpm}) - C_{free}(\text{dpm})}{C_{total}(\text{dpm})} \times 100$$

Results

Table I. Protein binding ratio of ^{14}C-RNH-6270 to mouse, rat, dog and human sera

RNH-6270 Concentration	Protein binding ratio (%)			
	Mouse	Rat	Dog	Human
1 μg/ml	95.4	98.6	95.7	98.8
10 μg/ml	96.6	99.0	95.5	99.3
100 μg/ml	94.4	96.6	94.0	99.1

Table II. Protein binding ratio of ^{14}C-RNH-6270 to human serum albumin, α_1-acidglycoprotein and globulin

Protein species	Protein binding ratio (%)
albumin	99.4
α_1-acid glycoprotein	96.0
globulin	13.3

Protein concentration: 10 mg/ml

Table III. Protein binding ratios of various concentrations of ^{14}C-RNH-6270 human serum albumin

RNH-6270 Conc. (μM)	Free form conc. (μM)	Bound form conc. (μM)	Protein binding ratio (%)
40	0.05	39.95	99.87
60	0.23	59.77	99.62
80	0.95	79.05	98.81
100	1.85	98.15	98.15
125	5.21	119.78	95.83
150	9.71	140.30	93.53
175	16.77	158.24	90.42
200	24.80	175.20	87.60
250	50.35	199.65	79.86
300	78.24	221.76	73.92

TableIV. Protein binding ratios of various concentrations of ^{14}C-RNH-6270 to human α_1-acid glycoprotein

RNH-6270 Conc. (μM)	Free form conc. (μM)	Bound form conc. (μM)	Protein binding ratio (%)
40	5.92	34.08	85.19
60	12.50	47.50	79.16
80	22.75	57.25	71.56
100	35.61	64.39	64.39
125	50.58	74.43	59.54
150	75.56	74.45	49.63
175	89.67	85.33	48.76
200	112.42	87.58	43.79
250	157.53	92.48	36.99
300	208.47	91.53	30.51

Table V. Inhibition of protein binding of RNH-6270 to human serum albumin by diazepam, digitoxin and warfarin

Competitor	RNH-6270 conc. (μM)	Protein binding ratio (%)	
		Absolute values	Relative values
Control	1	99.3	100.0
	100	93.2	100.0
Diazepam	1	99.4	100.1
	100	95.8	102.9
Digitoxin	1	99.4	100.1
	100	95.3	102.3
Warfarin	1	95.6	96.2
	100	85.7	92.0

Human serum albumin concentration: 100 μM
Competitor concentration: 100 μM

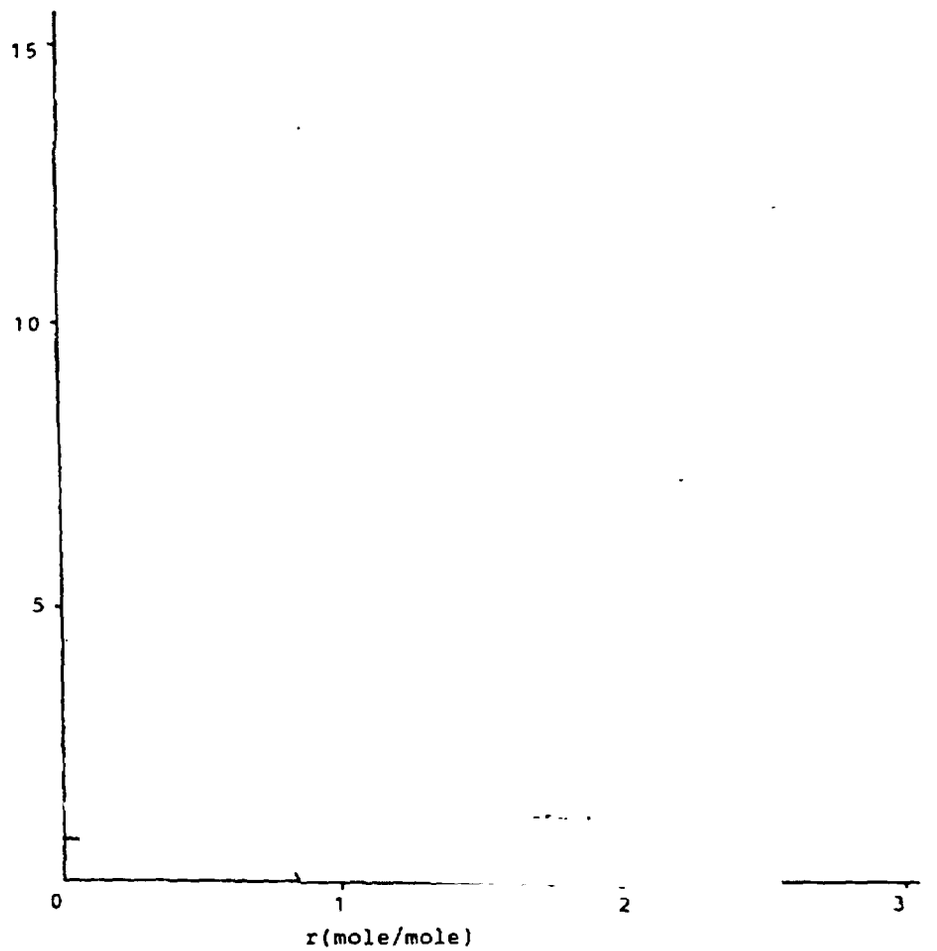


Fig. 2 Scatchard plot of protein binding of RNH-6270 to human serum albumin

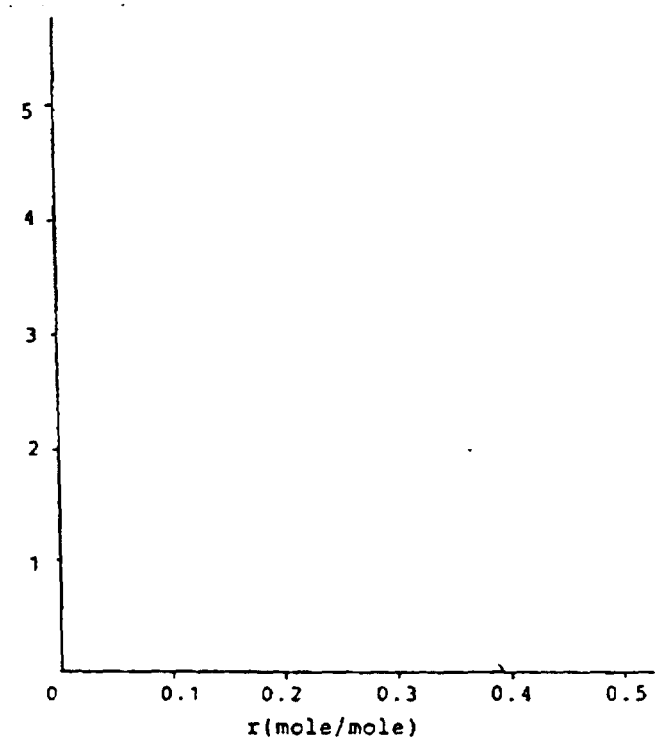
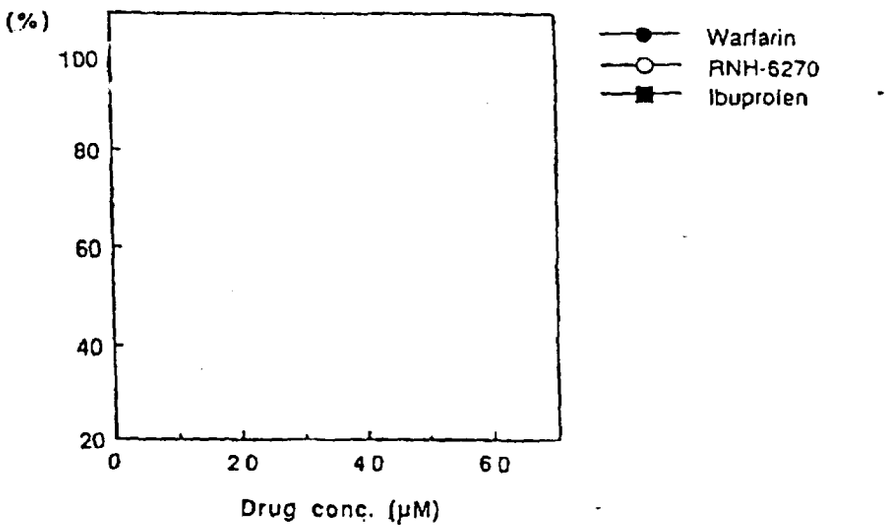
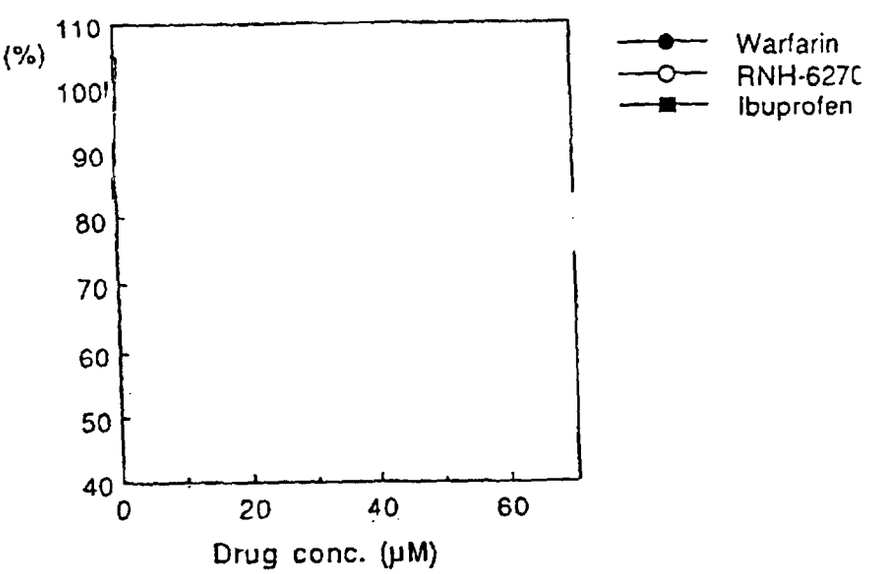


Fig. 3 Scatchard plot of protein binding of RNH-6270 to α_1-acid glycoprotein


(%)
100
80
60
40
20
0
20
40
60
Drug conc. (μM)
Warfarin
RNH-6270
Ibuprofen


(%)
110
100
90
80
70
60
50
40
0
20
40
60
Drug conc. (μM)
Warfarin
RNH-627(
Ibuprofen

Reviewer's Summary:

- The binding ratios of RNH-6270 at the concentrations of 1, 10 and 100 μg/ml were very high ranging from 94.0% to 99.3% in all animal species, including humans.

- The binding ratios of various concentrations of ^{14}C-RNH-6270 (40 μM-300 μM) to HSA solution at the constant concentration of 100 μM are almost constant (98.2% - 99.9%). The binding ratio showed a slight decrease at 125 μM, and further decreased as the concentration of RNH-6270 increased, reaching 73.9% at 300 μM.

- Based on the Scatchard plot, the binding to HSA is biphasic. However, the binding to α1-acid glycoprotein was monophasic.

- Adding the cocktail of highly protein bound drugs such as diazepam, digitoxin and warfarin, had no effect on the binding of olmesartan to HSA. However, it should be noted that warfarin caused slight reduction (4-6%) in binding of RNH-6270 to HAS (See above tables).

Conclusion:

Based on the above data, olmesartan is considered as a highly bound drug in animals and humans (94.0% - 99.3%). Highly bound drugs such as diazepam, digitoxin, and warfarin do not appear to cause any significant competitive effect on the binding of olmesartan to HSA.

Vols. 1.1, 1.2, and 31

Dissolution Methods:

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
Count of Samples:	6 each
Sampling Time:	5, 10, 15, 20, 30, 45, and 60 minutes

Results:

The following Tables and Figures show the mean and individual dissolution results for some of clinically used formulations:

TABLE 6.6.6.1a: Dissolution Results of CS-866 Tablets Used in Sankyo USA and Sankyo Europe GmbH Clinical Trials Under Standard Release Testing[a]

Date of Test	Tablet Strength	Lot No.	Units Tested	Range	Mean % Dissolved	% C.V.
08/25/98	5 mg	2232V98014	12	[redacted]	95.7	[redacted]
09/01/98	10 mg	2233V98016	12	[redacted]	95.4	[redacted]
09/01/98	20 mg	2234V98013	12	[redacted]	92.0	[redacted]
10/19/99	20 mg	2234V99013	6	[redacted]	96.0	[redacted]

[a] Dissolution Apparatus = Paddle (Ph. Eur.); Media = JP2; Temp = 37°C; Speed of Rotation/Flow = 50 rpm and Collection Times = 30 min.

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TABLE 6.6.6.1b: Dissolution Profiles of [redacted] and [redacted] CS-866 Tablets Manufactured by Sankyo Pharma GmbH Compared to CS-866 Tablets Manufactured by Sankyo Co., Ltd.

Formula	Conditions	Tablet Lot No.		Percent of Label Claim Dissolved in Minutes					
				5 min	10 min	20 min	30 min	45 min	60 min
Sankyo Co., Ltd.	Medium: Second fluid JP	D97/T02	Mean	40	65	81	89	94	97
			SD	2	2	1	1	1	1
			%CV			[redacted]			
	Paddle speed: 50 rpm								
Sankyo Pharma GmbH		2233V98019[a]	Mean	15	21	28	32	36	40
			SD	1	1	2	2	2	3
			%CV			[redacted]			
		2233V98017[a]	Mean	32	48	60	67	74	79
			SD	2	2	2	2	2	2
			%CV			[redacted]			
		2233V98018[a]	Mean	61	82	93	96	98	98
			SD	2	1	1	1	1	1
			%CV			[redacted]			

[a] Lot Numbers used in SE-866/22Sankyo Co., Ltd. Results

TABLE 6.6.6.2a: Dissolution Results of CS-866 Tablets Used in Sankyo USA and Sankyo Europe GmbH Clinical Trials Under Standard Release Testing[a]

Date of Test	Tablet Strength	Lot No.	Units Tested	Range	Mean %	% C.V.
2/13/95	2.5 mg	201F	6		103	
11/21/95	2.5 mg	217	6		105	
5/19/97	2.5 mg	290	6		102	
2/13/95	5 mg	202F	6		100	
11/21/95	5 mg	218	6		102	
5/19/97	5 mg	291	6		101	
8/11/97	5 mg	D97/T01	6		102	
2/13/95	10 mg	203F	6		100	
11/21/95	10 mg	219	6		102	
5/19/97	10 mg	292	6		102	
8/11/97	10 mg	D97/T02	6		101	
2/13/95	20 mg	204F	6		100	
8/29/95	20 mg	232	6		101	
11/21/95	20 mg	220	6		101	
5/19/97	20 mg	293	6		100	
8/11/97	20 mg	D97/T03	6		100	
5/19/97	40 mg	294	6		100	
9/10/99	20 mg	E99T03	6		100.7	

[a] Dissolution Apparatus = Paddle (JP Method 2); Media = JP1; Temp = 37°C; Speed of Rotation/Flow = 50 rpm and Collection Times = 30 min.

6.6.7 Appendices

6.6.7.1 List of Formulations

TABLE 6.6.7.1a: Clinical Formulations Used in CS-866 Clinical Trials

Process No./Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.†	Tablet Batch Size	Manufacturer
	Placebo	Tablet	143-005	231		Sankyo Co., Ltd.
		Tablet	141-011, 141-041	180		Sankyo Co., Ltd.
		Tablet	SE-866/03, SE-866/06 SE-866/08, SE-866/09 SE-866/18, SE-866/19 SE-866/20	224 2235V95021		Sankyo Co., Ltd
		Tablet	SE-866/09, SE-866/17	225 2235V95022		Sankyo Co., Ltd.
		Tablet	SE-866/09, SE-866/18 SE-866/19, SE-866/20	226 2235V95023		Sankyo Co., Ltd.
		Tablet	SE-866/10, SE-866/11 SE-866/15	296 2235V97001		Sankyo Co., Ltd.
		Tablet	866-101, SE-866/01, 866-102, SE-866/02, SE-866/04, SE-866/07	200F 2235V95001		Sankyo Co., Ltd.
		Tablet	866-204	222		Sankyo Co., Ltd.
		Tablet	866-204	223		Sankyo Co., Ltd.
		Tablet	866-305, 866-306	295		Sankyo Co., Ltd.
		Tablet	SE-866/10-01	2235V98001		Sankyo Pharma GmbH
		Tablet	SE-866/18, SE-866/19 SE-866/20	D97/T04 2235V97003		Sankyo Co., Ltd.
B, D	2.5	Tablet	SE-866/11, SE-866/12, SE-866/2T, 866-305	290 2231V97001		Sankyo Co., Ltd.
A, C		Tablet	SE-866/01, SE-866/04	201F 2231V95001		Sankyo Co., Ltd.
B, C		Tablet	SE-866/03, SE-866/09 866-204	217 2231V95003		Sankyo Co., Ltd.

TABLE 6.6.7.1a: Clinical Formulations Used in CS-866 Clinical Trials (Continued)

Process No./Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.†	Tablet Batch Size	Manufacturer
B, D	5	Tablet	SE-866/10, SE-866/11, SE-866/12, SE-866/14, SE-866/16, SE-866/21, 866-305, 866-306	291 2232V97001		Sankyo Co., Ltd.
A, C		Tablet	SE-866/01, SE-866/04	202F 2232V95001		Sankyo Co., Ltd.
B, C		Tablet	SE-866/03, SE-866/09, 866-204	218 2232V95003		Sankyo Co., Ltd.
D, E, G1		Tablet	[redacted]	2232V98014		Sankyo Pharma GmbH
B, D		Tablet	SE-866/10, SE-866/18, SE-866/19, SE-866/20	D97/T01 2232V97003		Sankyo Co., Ltd.
B, D	10	Tablet	SE-866/10, SE-866/11, SE-866/12, SE-866/17, SE-866/18, SE-866/19, SE-866/20, 866-109, 866-305, 866-306	292 2233V97001		Sankyo Co., Ltd.
A, C		Tablet	866-101, SE-866/01, SE-866/02, SE-866/04	203F 2233V95001		Sankyo Co., Ltd.
B, C		Tablet	SE-866/03, SE-866/06, SE-866/09, 866-204	219 2233V95003		Sankyo Co., Ltd.
G1, D, E		Tablet	SE-866/22	2233V98018		Sankyo Pharma GmbH
1, D, E		Tablet	SE-866/22	2233V98019		Sankyo Pharma GmbH
G2, D, E		Tablet	SE-866/22	2233V98017		Sankyo Pharma GmbH
D, E, G1		Tablet	[redacted]	2233V98016		Sankyo Pharma GmbH
B, D		Tablet	SE-866/14, SE-866/16, SE-866/18, SE-866/19, SE-866/20, SE-866/21, SE-866/22	D97/T02 2233V97003		Sankyo Co., Ltd.

TABLE 6.6.7.1a: Clinical Formulations Used in CS-866 Clinical Trials (Continued)

Process No./Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.†	Tablet Batch Size	Manufacturer
B, D	20	Tablet	866-116	E99T03		Sankyo Co., Ltd.
B, D		Tablet	143-005	230		Sankyo Co., Ltd.
B, C		Tablet	SE-866/03, SE-866/05, SE-866/06, SE-866/08, SE-866/09, 866-204	220 2234V95004		Sankyo Co., Ltd.
A, C		Tablet	SE-866/07	232 2234V95003		Sankyo Co., Ltd.
A, C		Tablet	866-101, SE-866/01, 866-102, SE-866/02, SE-866/04, 866-103, SE-866/07	204F 2234V95001		Sankyo Co., Ltd.
B, D		Tablet	866-108, SE-866/10, SE-866/12, SE-866/17, 866-110, 866-305, 866-306	293 2234V97001		Sankyo Co., Ltd.
D, E, G1		Tablet		2234V98013		Sankyo Pharma GmbH.
F, G1, H		Tablet	866-116	2234V99013		Sankyo Pharma GmbH
B, D		Tablet	SE-866/15, SE-866/18 SE-866/19, SE-866/20	D97/T03 2234V97009		Sankyo Co., Ltd.
B, D	40	Tablet	866-305, 866-306	294		Sankyo Co., Ltd.

TABLE 6.6.7.1a: Clinical Formulations Used in CS-866 Clinical Trials (Continued)

Process No./Change	Strength (mg)	CS-866* Dosage Form	Study No.	Lot. No.†	Tablet Batch Size	Manufacturer
MR145-091‡	1	Tablet	141-010	151		Sankyo Co., Ltd.
MR145-091	2	Tablet	141-010	152		Sankyo Co., Ltd.
MR145-091	4	Tablet	141-010, 141-011	153		Sankyo Co., Ltd.
MR145-091	8	Tablet	141-010, 141-011, 141-012	154		Sankyo Co., Ltd.
MR145-091	16	Tablet	141-010, 141-011, 141-041	155		Sankyo Co., Ltd.
	20	^{14}C-CS-866 powder	SE-866/13	D-970715		[redacted]
	20	Powder	SE-866/13	NH209		Sankyo Co., Ltd.
	20	Suspension	866-108	K97T05		Sankyo Co., Ltd.
	16	RNH-6270 solution	866-107, 866-108, 866-109	K97T01		Sankyo Co., Ltd.

*Except as noted
A = CS-866 Drug Substance.
B = CS-866.
C =
D =
E = Manufacturing excess.
F = Manufacturing excess
G1 = CS-866 Drug Substance.
G2 = CS-866 Drug Substance.
H = Commercial tablet formulation, different excipient to drug ratio, larger tablet weight, larger tablet size
† If more than one Lot No. is indicated the first Lot No. is the one assigned by the manufacturing site; the second Lot No. is the one subsequently assigned by the subsidiary.
‡ See Sankyo Co., Ltd. report MR145-091.

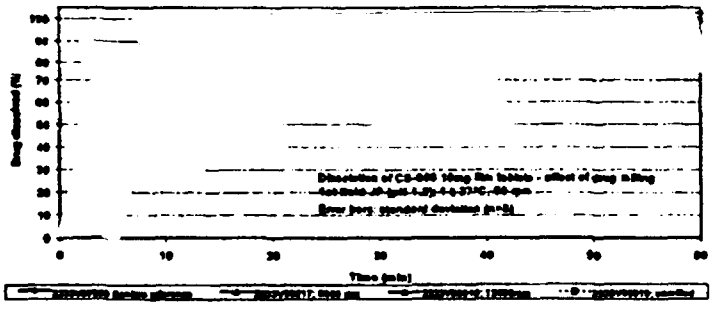
CS-866 20 mg: 2234V99005

Dissolution testing: 2nd fluid JP; 37°C; paddle speed 50 rpm					
time [min]	mean/n=6 [%]	s	[illegible]	min [%]	max [%]
5	38.4				
10	76.9				
15	86.4				
20	91.6				
30	96.6				
45	99.8				
60	101.1				
Dissolution testing: 2nd fluid JP; 37°C; paddle speed 75 rpm					
time [min]	mean/n=6 [%]	s	[illegible]	min [%]	max [%]
5	52.9				
10	77.9				
15	86.1				
20	90.5				
30	94.8				
45	97.9				
60	99.2				
Dissolution testing: 2nd fluid JP; 37°C; paddle speed 100 rpm					
time [min]	mean/n=6 [%]	s	[illegible]	min [%]	max [%]
5	60.1				
10	88.5				
15	87.3				
20	91.2				
30	95.4				
45	98.2				
60	99.7				

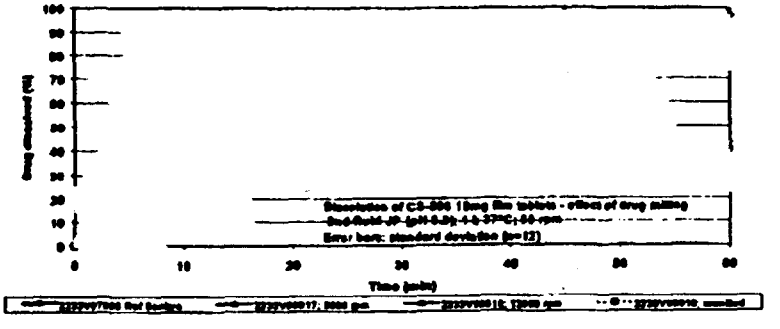
CS-866 40 mg: 2236V99005

Dissolution testing: 2nd fluid JP; 37°C; paddle speed 50 rpm					
time [min]	mean/n=6 [%]	s	s_rel [%]	min [%]	max [%]
5	29.5				
10	64.3				
15	77.2				
20	83.1				
30	89.5				
45	93.9				
60	96.3				
Dissolution testing: 2nd fluid JP; 37°C; paddle speed 75 rpm					
time [min]	mean/n=6 [%]	s	s_rel [%]	min [%]	max [%]
5	53.4				
10	72.8				
15	79.2				
20	83.6				
30	88.6				
45	92.7				
60	94.6				
Dissolution testing: 2nd fluid JP; 37°C; paddle speed 100 rpm					
time [min]	mean/n=6 [%]	s	s_rel [%]	min [%]	max [%]
5	59.1				
10	74.4				
15	81.2				
20	84.9				
30	89.6				
45	93.1				
60	94.9				

BE-Study medication SE-866/22



BE-Study medication SE-866/22



BE-Study medication SE-866/22

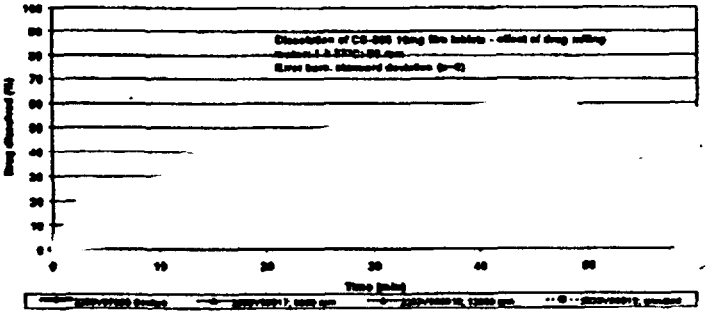


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Table 3.4.3. 1: Sankyo Co., Ltd. Clinical Development Formulations

Ingredient	2.5 mg tablet	5 mg tablet	10 mg tablet	20 mg tablet	40 mg tablet
CS-866	2.5 mg	5 mg	10 mg	20 mg	40 mg
Microcrystalline cellulose					
L-hydroxypropyl cellulose					
Lactose, monohydrate					
Hydroxypropyl cellulose					
Magnesium Stearate					
Tablet Core Weight					
Coating Mass					
Total Tablet Weight	110 mg	110 mg	110 mg	110 mg	110 mg
Tablet shape	Round	Round	Round	Round	Round
Tablet Core Dimensions	dia.	dia.	dia.	dia.	dia.

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Table 3.4.3. 2: Sankyo Pharma GmbH Commercial Formulations

Ingredient	5 mg tablet	10 mg tablet	20 mg tablet	40 mg tablet
CS-866	5 mg	10 mg	20 mg	40 mg
Microcrystalline cellulose				
L-hydroxypropyl cellulose				
Lactose, monohydrate				
Hydroxypropyl cellulose				
Magnesium Stearate				
Tablet Core Weight				
Coated Tablet Weight				
Tablet shape	Round	Round	Round	Oval
Tablet Core Dimensions				

Reviewer's Comments:

1. The tablets are rapidly dissolving with — % dissolved in 15 minutes.
2. The % CV for all formulations is —%.
3. The sponsor has tested the product with one dissolution medium only. The Agency is - usually requires three dissolution medium.

Conclusion:

Based on the data presented, the following dissolution method 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 —% (Q) in 30 minutes

Report

Dissolution Profiles: CS-866 Tablets, 20 and 40 mg

A dissolution profile study was conducted on 20 mg and 40 mg CS-866 Tablets manufactured by Sankyo Pharma GmbH to ascertain the similarity of dissolution profiles of these two dosage forms. The study was done to provide supportive information to NDA 21-286 in support of a Waiver of In Vivo Bioavailability/Bioequivalence Studies.

The following dissolution conditions were used for the profiles.

USP Apparatus 2, Paddle, 50 rpm.

Media Tested. One liter of media maintained at 37° C was used in all cases.

Purified Water
JP Fluid 1, pH 1.2
JP Fluid 2, pH 6.8

Samples:

CS-866 20 mg Tablets: Lot 2234V99013
CS-866 40 mg Tablets: Lot 2236V99011

Number of Tablets per dissolution profile: 12

Sampling Intervals: 5, 10, 20, 30, 45, and 60 minutes.

Assay: [redacted]

The study was performed at Sankyo Pharma GmbH, Pfaffenhofen, Germany.

The data are given in the Tables 1-6 and graphically in Figure 1.

The calculated similarity factors (Table7) for the dissolution of the 20 and 40 mg CS-866 Tablets demonstrates the similarity of the dissolution profiles of the two tablet strengths in different media.

Table 1

CS-866 20 mg Lot 2234V99013, Purified Water, 37°C, 50 rpm

Sample	Dissolution [%]					
	5 min	10 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Count of samples	12	12	12	12	12	12
Mean [%]	10.03	19.65	26.94	29.95	32.34	33.98
Rel. Std. [%]	17.8	4.8	3.1	1.8	1.5	1.6
Conf. limits[%]*						
from	8.89	19.05	26.41	29.61	32.03	33.63
to	11.17	20.25	27.47	30.29	32.65	34.33
*α = 0.05						

Table 2

CS-866 40 mg Lot 2236V99011, Purified Water, 37°C, 50 rpm

Sample	Dissolution [%]					
	5 min	10 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Count of samples	12	12	12	12	12	12
Mean [%]	7.93	16.36	20.47	22.08	23.32	24.13
Rel. Std. [%]	17.4	4.0	3.6	3.2	3.0	2.6
Conf. limits [%]*						
from	7.05	15.95	20.01	21.63	22.88	23.73
to	8.81	16.77	20.93	22.53	23.76	24.53
*α = 0.05						

Table 3

CS-866 20 mg Lot 2234V99013, 1st fluid JP (pH 1.2), 37°C, 50 rpm

Sample	Dissolution [%]					
	5 min	10 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Count of samples	12	12	12	12	12	12
Mean [%]	61.03	97.75	104.35	104.68	104.87	105.07
Rel. Std. [%]	22.9	2.5	0.8	0.7	0.7	0.9
Conf. limits [%]*						
from	52.16	96.2	103.82	104.19	104.37	104.49
to	69.90	99.3	104.88	105.17	105.37	105.65
*α = 0.05						

Table 4

CS-866 40 mg Lot 2236V99011, 1st fluid JP (pH 1.2), 37°C, 50 rpm

Sample	Dissolution [%]					
	5 min	10 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Count of samples	12	12	12	12	12	12
Mean [%]	51.01	92.05	104.08	104.65	104.78	104.92
Rel. Std. [%]	19.5	5.0	0.7	0.8	0.8	0.8
Conf. limits [%]*						
from	44.69	89.13	103.65	104.13	104.24	104.36
to	57.33	94.97	104.51	105.17	105.32	105.48
*α = 0.05						

Table 5

CS-866 20 mg Lot 2234V99013, 2nd fluid JP (pH 6.8), 37°C, 50 rpm

Sample	Dissolution [%]					
	5 min	10 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Count of samples	12	12	12	12	12	12
Mean [%]	37.49	73.92	89.51	94.52	97.28	98.19
Rel. Std. [%]	11.3	1.9	0.9	0.8	0.7	0.8
Conf. limits [%]*						
from	34.81	73.02	88.99	94.03	96.85	97.68
to	40.17	74.82	90.03	95.01	97.71	98.70
*α = 0.05						

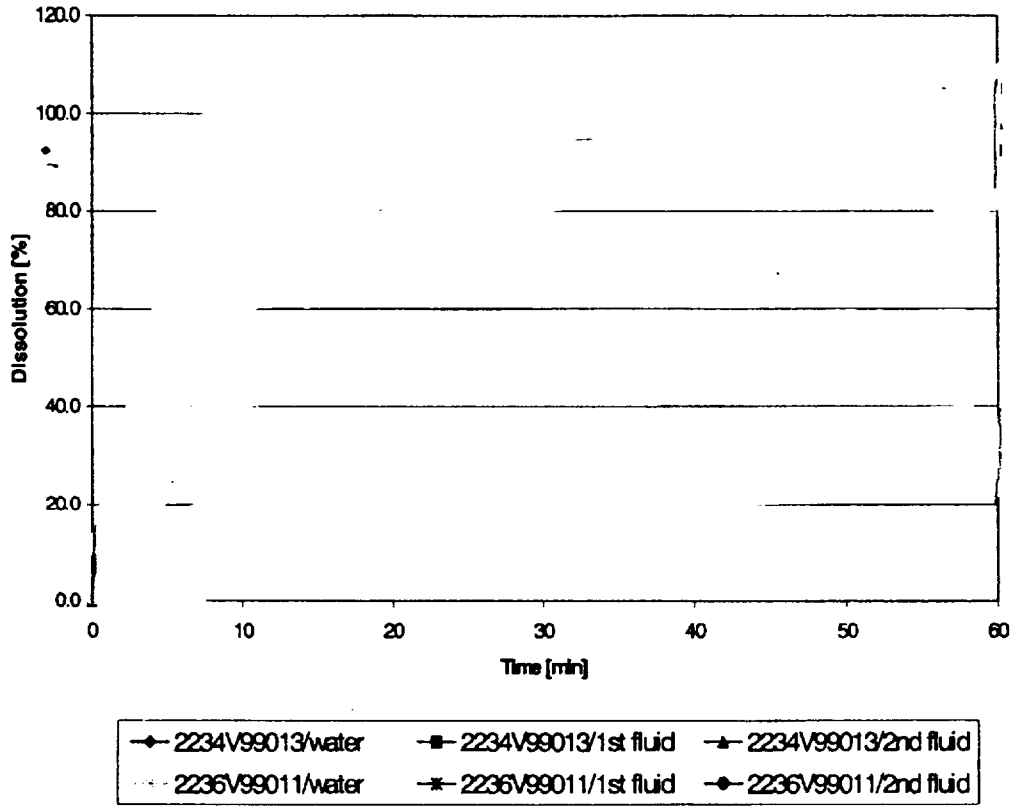
Table 6

CS-866 40 mg Lot 2236V99011, 2nd fluid JP (pH 6.8), 37°C, 50 rpm

Sample	Dissolution [%]					
	5 min	10 min	20 min	30 min	45 min	60 min
1						
2						
3						
4						
5						
6						
7						
8						
9						
10						
11						
12						
Count of samples	12	12	12	12	12	12
Mean [%]	29.82	64.14	80.12	85.84	90.37	92.52
Rel. Std. [%]	16.2	3.4	1.3	1.2	0.9	1.0
Conf. limits [%]*						
from	26.75	62.77	79.44	85.18	89.85	91.96
to	32.89	65.51	80.80	86.50	90.89	93.08
*α = 0.05						

Figure 1

Sankyo Pharma GmbH Dissolution Profiles for 20 and 40 mg CS-866 Tablets



Using these data, calculation of the f2 or similarity factor was made for the mean data in each of the three media. The similarity factors (f2) were calculated according to the equation given in the Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, dated August 2000. The calculated f2 values comparing the dissolution profiles of the 20 and 40 mg tablets in each of the three media are given below in Table 7. The guideline states that mean data should be used only when the variation is less than 20% at earlier time intervals. Only one of the early sampling intervals, the 5 minute sample of the 20 mg tablet in JP 1 fluid, has a variance larger than 20% and only by a small amount. The similarity factor was calculated for this

sample using individual values and was found to still exceed 50. Therefore, mean data were used for all calculations.

Table 7
Similarity Factors (f2) for Mean Dissolution Data

Dissolution Media	Similarity Factor (f2)
JP Fluid 1, pH 1.2	65.9
JP Fluid 2, pH 6.8	54.3
Purified Water	57.4

Based on the interpretation given the Guidance for Industry, Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System, dated August 2000, the data demonstrate the similarity the dissolution performance of the 20 and 40 CS-866 Tablets in all the media tested.

The differences in the dissolution rates of CS-866 tablets in the different media is explained by the solubility dependence of CS-866 with pH. The following table demonstrates the pH-solubility relationship.

Table 8
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.

Although the FDA guideline indicates that pH 4.5 media should be used for dissolution profiles, we utilized Purified Water, as the drug is almost totally insoluble around pH 4.

Solubility at pH 1.2 is very rapid and complete after approximately 20 minutes. At pH 6.8 the rate is significantly slower. For information, pH 6.8 was selected as the discriminating dissolution media for CS-866 Tablet release testing. The dissolution of both the 20 and 40 mg tablets is much slower in water. This is attributed to the limited solubility of the drug in water.

In summary, calculation of the similarity factors for 20 and 40 mg CS-866 Tablets demonstrates there are no differences in any of the three media studied.

Calculation of F2

Lot# (Ref) 2234V99013 (20 mg tablet)
Lot# (test) 2236V99011 (40 mg tablet)
2nd media (pH 6.8)

Time (min)	ref (%)	test (%)	R-T	(R-T)2
[redacted]				

	Sum
	91.43498
	0.104012
	10.40116
	1.017082
Similarity f2	**50.85409**

Conclusions:

1) Since the F2 is >50, the two dissolution profiles of the tow formulations are similar
2) Waiver for bioequivalant study is granted

APPEARS THIS WAY ON ORIGINAL

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