Table 161: Demographics - ITT and Per Protocol population Study SE- #866-11

		CS - 866			Placebo	Total
No of Pts.	**Age class**	**2.5mg**	**5mg**	**10mg**		
Safety(EFS)	Young	8	28	16	12	63
	Middle Aged	53	37	49	45	184
	Elderly	10	4	7	9	30
	Very Elderly	3	4	3	5	15
	Total	74	73	74	71	292
ITT	Young	8	27	16	12	62
	Middle Aged	53	37	49	43	162
	Elderly	9	4	7	9	29
	Very Elderly	3	4	3	4	14
	Total	73	72	74	68	287
Per Protocol	Young	7	26	16	12	59
	Middle Aged	42	33	42	40	157
	Elderly	7	2	4	6	19
	Very Elderly	0	1	0	2	3
	Total	56	61	61	60	238

EFS=Evaluable for Safety

Table 162:Demographics Gender Race, Age& Physical characteristics -ITT- 866-11

	Placebo	2.5mg	5mg	10mg	Total
Patients (N)	68	73	72	74	287
M/F	35/33	41/32	36/36	45/29	157/130
Age(years)	54.7±11.5	55.9±10.3	50.5±11.8	54.4±11.2	53.9±11.3
Height (cm)	169.1±8.9	169.1±9.1	168.9±9.1	171.0±8.5	169.6±8.9
Weight (kg)	80.9±14.6	80.2±14.1	82.4±16.2	85.0±14.1	82.2±14.5
Race	Caucasians	Caucasians	Caucasians	Caucasians	Caucasians

Taper off period for patients on previous anti-hypertensive therapy

Of the 287 randomized patients, 194(67.6%) had received previous antihypertensive medication at screening and required a taper-off period (Table 163).

Table 163: Taper-off Period - ITT - 866-11

	Plcbo	CS-866			
		2.5mg	5mg	10mg	
Taper-off Period	68	73	72	74	Total
Yes	49	52	48	45	194
No	19	21	24	19	93

18.8 Dose selection

There was no dose selection study carried out for this study. Different doses had been investigated in healthy volunteers or hypertensives in Japan, Europe and the US (N= 235; N=1200). These samples were considered large enough to derive a dosing regimen for this study. The dose levels used in this study 2.5, 5 and 10 mg were adopted based on previous animal and human data.

18.9 Analysis of Primary Efficacy

The primary efficacy variable in this study was the change from baseline in hourly-averaged ABPM data over a 24-hour period after treatment with olmesartan. ANCOVA showed no significant effect of the treatment by center interaction. Tables 164 and 165 show all 3 active doses, 2.5mg, 5.0mg, 10mg are different from placebo in ITT patients as measured by daytime dBP at week 12 and supported by 95% CI pairwise differences in change in mean daytime dBP using ABPM.

Table 164: Change in mean daytime dBP from wk 0-wk12 by treatment group –24 h ABPM –ITT- 866-11

Daytime dBP	Placebo N=68	2.5mg N=73	5mg N=72	10mg N=74
Mean (SD)	-4.53(9.01)	-7.65(8.14)	-8.35(9.21)	-10.55(8.94)
Adjusted mean	-3.53	-7.57	-8.82	-10.59

Table 165: 95% CI for pairwise differences to placebo in change in mean daytime dBP- ITT-866-11

	Lower CI	Point Estimate	Upper CI
2.5mg -placebo	-8.01	-4.04	-0.07
5mg -placebo	-9.32	-5.29	-1.26
10mg -placebo	-10.97	-7.05	-3.14

In contrast to the ITT population, analysis of per protocol population showed the 95% confidence limits to be significantly different from placebo (Table 166) only in the 5mg and 10 mg doses whereas the 2.5 mg was not significantly different from placebo.

Table 166: 95% CI for pairwise differences to placebo in change in mean daytime dBP- PP-Study SE #866-11

	Lower CI	Point Estimate	Upper CI
2.5mg -placebo	-8.13	-3.23	1.68
5mg -placebo	-9.54	-5.01	-0.50
10mg -placebo	-10.27	-5.74	-1.21

The pairwise comparisons on Diastolic and systolic blood pressure-Night time on ABPM are in Tables 167 and 168 below. They are similar to the daytime data.

Table 167:CI pairwise differences-placebo-change in mean night time dBP -ITT-Study SE- #866-11

	Lower CI	Point Estimate	Upper CI
2.5mg 0-week 12	-10.47	-6.79	-3.11
5mg 0-week 12	-10.99	-7.23	-3.48
10mg 0-wk12	-13.00	-9.33	-5.66

Systolic blood pressure - Night time

Table 168: CI for pairwise differences to placebo-change in mean night time sBP - ITT-866-11

	Lower CI	Point Estimate	Upper CI
2.5mg 0-wk12	-16.71	-11.18	-5.65
5mg 0-wk12	-16.45	-10.82	-5.18
10mg 0-wk12	-18.82	-13.32	-7.83

18.10 To evaluate the effect of CS-866 at dose levels of 2.5 mg, 5 mg, and 10 mg o.d on the ABPM minimum and maximum BP ratio after 4, 8, and 12 weeks of treatment the data on ITT patients are in Table 169 by treatment group. The minimum to maximum dBP ratio of 24 hr ABPM was about 0.5 in all treatment groups with very slight reduction in the active treatment groups. There is neither significant age class effect nor a significant treatment by age class interaction on the minimum maximum ratios. There is a slight reduction in the ration over time in the higher doses (Table 169).

Table 169: Minimum-maximum dBP ratio by dose (24h ABPM) -ITT-SE-#866-11

Week	Placebo	2.5mg	5mg	10mg
0	0.50	0.52	0.51	0.50
4	0.50	0.50	0.49	0.48
8	0.50	0.50	0.49	0.47
12	0.50	0.48	0.49	0.47

18.11 Secondary efficacy

The mean change in sitting diastolic blood pressure from baseline at trough in the treated groups compared to placebo from week 2 to week 12 is presented in Table 170 and Figure 61 below. The lowering of sitting diastolic blood pressure was evident from week 2 with 2.5mg CS-866 but the effect change was greater in the 10mg group. The maximum effect change was observed at week 4 using placebo-subtracted values and there is very little difference between the 5mg and 10mg dose using descriptive statistics (Figures 62 and 63). The effect change on SiDBP at trough for the 2.5 mg dose leveled off from week 2 until week 12 (Figures 61 and 62). There was a difference in the treatment effect between CS-866 (at doses 2.5, 5, and 10mg) and placebo when the effect was measured by changes in diastolic and systolic blood pressure (dBP) assessed by 24 hour ABPM after 12 weeks of treatment.

Secondary Efficacy (Table 170, Figs. 62, 63 and 67)

To assess the efficacy of CS-866 at dose levels of 2.5 mg, 5 mg and 10 mg o.d in terms of the dBP assessed by 24-hour ABPM after 4 and 8 weeks of treatment. (Table 170)

To assess the efficacy of CS-866 at dose levels of 2.5 mg, 5 mg and 10 mg o.d in terms of the dBP assessed by 24-hour ABPM after 4, 8 and 12 weeks of treatment.

To determine the dBP lowering effect of CS-866, at trough levels, at doses of 2.5 mg, 5 mg, and 10 mg o.d after 2, 4, 8, and 12 weeks of treatment.

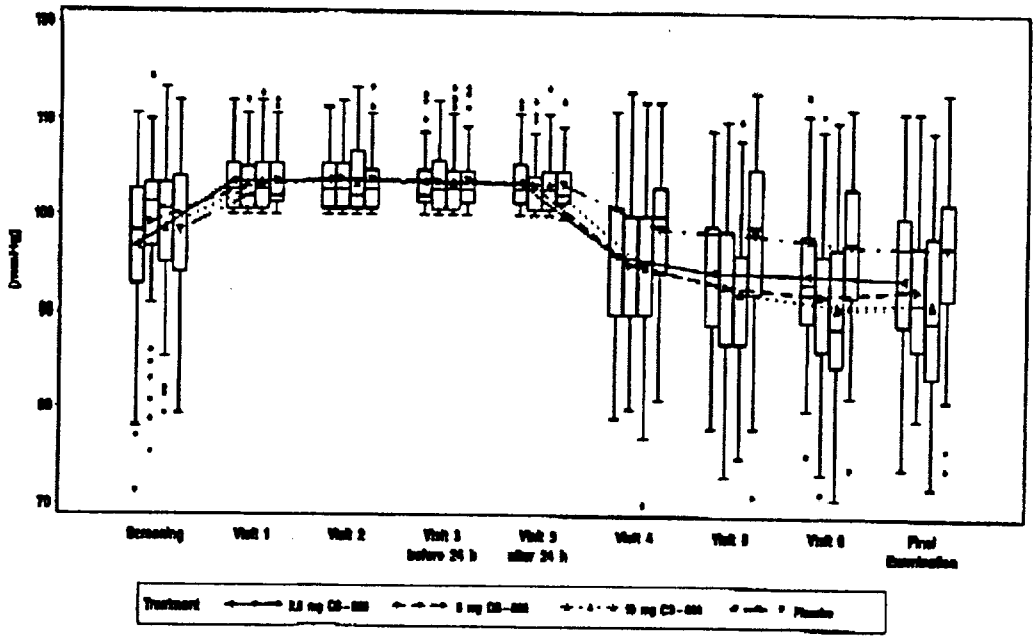
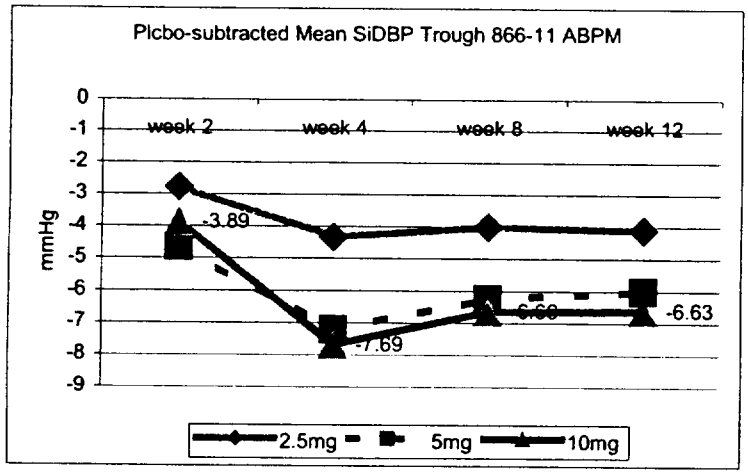


Figure 61 above: ABPM-4 treatment arms from baseline to week 12- 866-11 ITT – sponsor.

Table 170: Trough DBP ITT –866-11 (Figures 62 and 63)

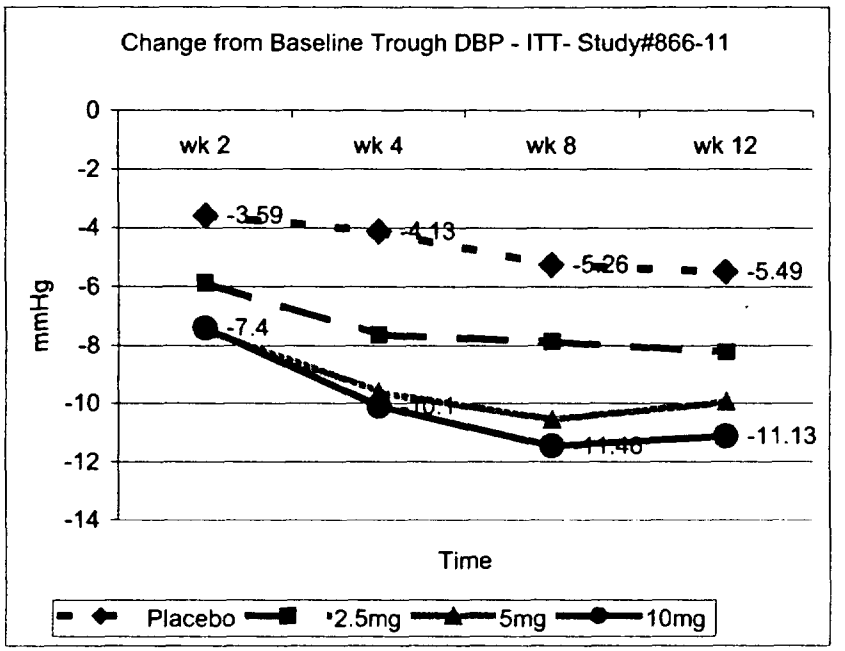
Troughdbp	wk 2	wk 4	wk 8	wk 12
Placebo	-3.59	-4.13	-5.26	-5.49
2.5mg	-5.87	-7.63	-7.87	-8.23
5mg	-7.44	-9.62	-10.57	-9.95
10mg	-7.4	-10.1	-11.46	-11.13

Figure 62: Trough dBP at final visit-efficacy end point 866-11-ITT



Values for 10mg shown. Note similarities between 5 and 10 mg curves.
Source: Reviewer

Figure 63: Change from baseline to endpoint ABPM 866-11

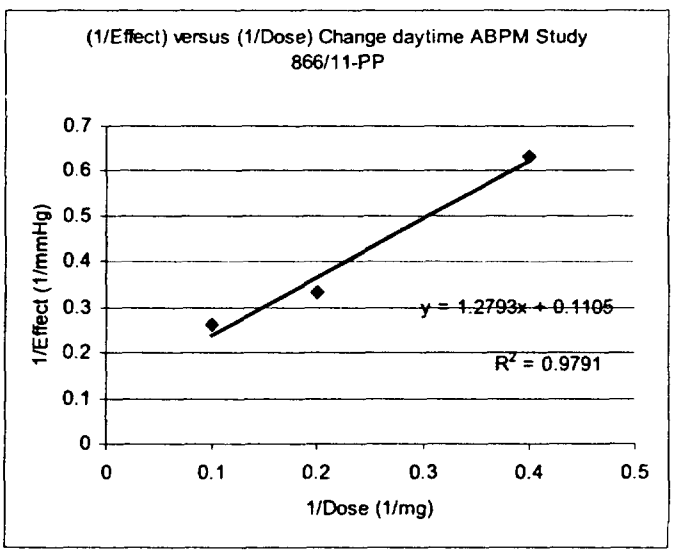


Change from baseline to Efficacy endpoint using ABPM 866-11

Values for placebo and 10mg shown. Source: Reviewer

The effect change versus dose using ABPM is shown in Figure 64 for the ITT population. The dose response has a correlation coefficient of (R^2) 0.8957 that is considered significant between the doses. Using the per protocol population, the effect change versus dose using ABPM daytime data also yielded similar trend with an R^2 of 0.9791 (Figure 64). The trends for the simultaneous upper and lower limits of confidence limits for the 2.5mg dose failed to cross but they crossed for the 5 and 10 mg dose groups before week 8 suggesting that there may be no difference between these two dose groups (Figure 65).

Figure 64:(1/Effect) versus (1/Dose) Sitting DBP ABPM (ITT #866-11)



Source: Reviewer

Figure 65: Simultaneous upper and lower CI limits for the 3 doses-SiDBP-866-11

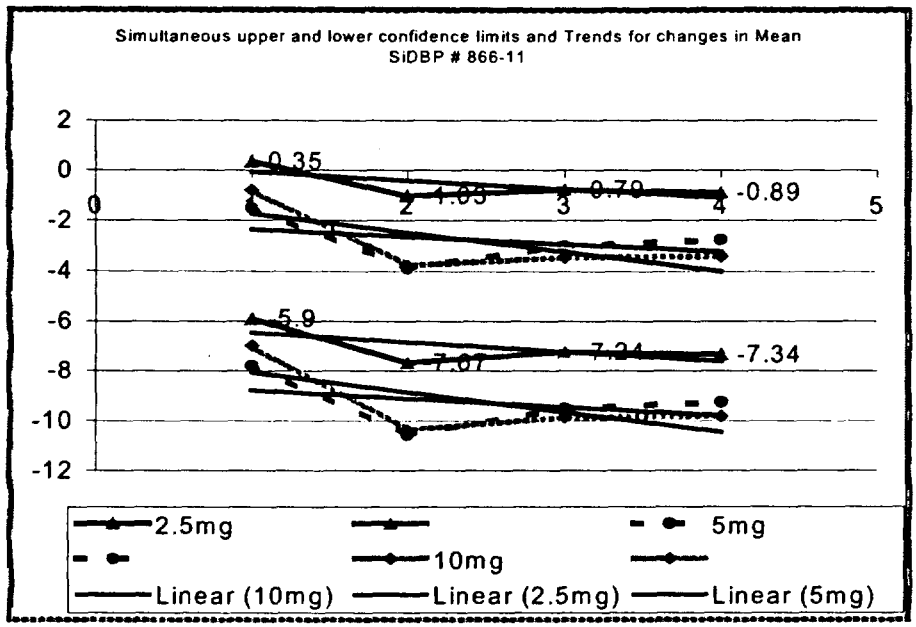


Figure 65 above :Confidence Limits/Trends of Mean SiDBP (ITT 866-11) by dose and time (1-12 weeks) 1,2,3,4 =weeks 2,4,8, and 12 respectively. Mean values and trends shown for upper/ lower confidence limits (2.5 mg). Note trend lines overlap for 5 and 10mg dose levels but not for 2.5mg dose level. Source: Reviewer

18.12: Pharmacokinetics

The pk parameters including AUC, Cmax show increasing geometric mean values with increasing doses of CS-866. The geometric mean values for the AUC $_{0\text{-}24}$ and Cmax were approximately doubled with doubling of the dose consistent with dose proportionality over the dose range examined (Figure 66). The mean of the pk parametrers across all age groups from young to very old however, showed that the AUC and C max were higher in the elderly compared to young patients – a finding that may have implications for labeling.

Figure 66: Pharmacokinetics - 866-11

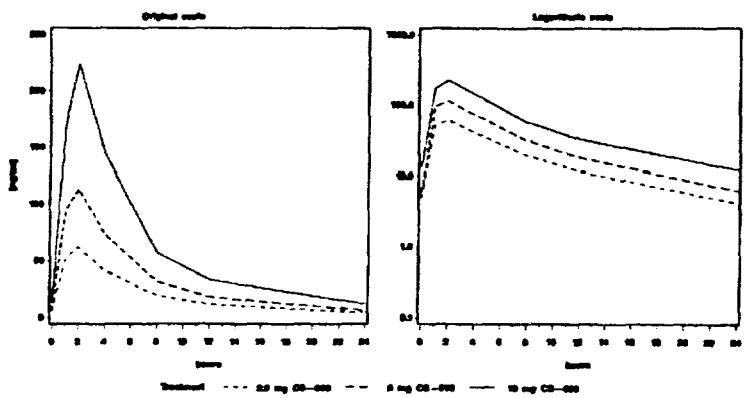


Table 171: Pharmacokinetics of olmesartan - ITT – Study SE-# 866-11

Parameter	2.5mg	5mg	10mg
AUC0-24	479(36.24)	818(33.93)	1666.25(35.38)
Cmax	68.07(32.61)	126.54(32.23)	244.18(24.45)
The steady state maximum concentrations were reached at a median time of 2 hours after administration-all doses of CS-866.			

18.13: Pharmacodynamics: Secondary efficacy variables

To investigate the correlation between change in dBP (visit 6/week 8) and RNH – 6270 concentration in plasma (visit6/week8)

To investigate the correlation between change in dBP (visit 6/week 8) and creatinine clearance (mean of visit 5/week 4 and visit 6/week8)

There is correlation (Pearson's) between AUC_{0-24} of the metabolite, RNH-6270, and change in diastolic BP among ITT patients (p value = 0.0230), whereas there was no correlation between change in diastolic BP and creatinine clearance, and between AUC_{0-24} and creatinine clearance (Table 172).

Table 172:Comparisons of Correlation coefficients between ITT &PP population

Correlation between	Sample	Correlation Coefficient	p-value
Change in dBP and AUC 0-24	ITT	-0.1572	0.0230
	PP	-0.10476	0.1652
Change in dBP and Creatinine Clearance	ITT	-0.06037	0.3762
	PP	-0.04457	0.5547
AUC 0-24 and Creatinine Clearance	ITT	-0.07473	0.2811
	PP	-0.03649	0.6297

18.14 Safety

Secondary objective: To assess the safety and tolerability of CS-866 at dose levels of 2.5 mg, 5 mg, and 10 mg o.d in terms of AEs, pulse rate, ECG and laboratory parameters over 12 weeks of treatment. There were no significant changes in the pulse rate and ECG of patients over the 12 weeks of treatment.

18.15 Clinical

There were no deaths in this study.

A total of 7 serious adverse events were observed during the placebo run-in period and there was no increase with increasing dose. Four of the 15 patients withdrawn were due to AEs , four were withdrawn due to withdrawal of consent, six due to lack of efficacy and an ABPM could not be performed on one patient.

18.16 Laboratory Safety

Three of 13 patients with AEs due to laboratory abnormalities received 2.5mg CS 866

o.d, 4 received 5mg and 2 received 10mg while 4 received placebo. Most frequent AE was increased triglycerides (4) followed by increased bilirubin, creatinine, uric acid and cholesterol. Although there is no definite signal from any of these abnormal lab values in this study, further information may be described in the integrated summary for safety.

18. 17 Hepatic enzyme abnormalities
Out of 10 patients with AEs for elevated (>2ULN) SGPT, SGOT or gamma GT, 4 patients received 5 mg olmesartan, 4 patients received 10 mg olmesartan, and 2 received placebo. None of the patients were discontinued because of increased liver enzymes. The safety follow up on these patients is not known.

Summary
This study was a randomized, placebo-controlled, ABPM study of patients on 3 doses of olmesartan versus placebo. After adjustment and unblinding, the study was still powered enough to detect a difference of about 5mmHg between the 4 groups. ABPM analysis conducted included all subjects randomized with available data at week 12. Analysis of the mean daytime ABPM measurements during this study showed that treatment with 5mg and 10 mg doses were statistically significant in reducing diastolic blood pressure after 12 weeks of treatment compared to placebo. The higher the dose the more effective was the treatment effect for both the ITT and PP population samples. Per protocol patients who received 2.5 mg olmesartan failed to show statistical superiority to placebo group in their treatment effect which is more compelling than the difference demonstrated for this group in the ITT sample.

Seating and standing blood pressures were reduced in all the active treatment groups compared to placebo albeit relatively small in the 2.5mg dose group in the ITT population. Analysis of the secondary blood pressure parameters also showed that treatment effects were manifest at 4 and 8- week time points which in turn confirmed the 12-week time point results. The minimum to maximum dBP ratio of 24 hour ABPM was about 0.5 (50%) in all treatment groups using the ITT population. This ratio suggests that these dose levels may not be entirely suitable for long term use considering that patients had 12 weeks of drug exposure. Age had no significant effect on efficacy at these dose levels although the plasma levels of the metabolite, RNH-6270, were higher in the elderly compared to the young.

There was a significant correlation between the change in dBP and AUC_{0-24} for the ITT population ($p=0.0230$) but there was no correlation between the change in dBP and creatinine clearance or the mean creatinine clearance and the AUC_{0-24} The geometric mean values for the AUC_{0-24} and Cmax were approximately doubled with doubling of the dose consistent with dose proportionality over the dose range examined (Figure 66 and Table 171). There were no deaths during the study and serious adverse events will be dealt with separately under integrated summary of safety.

CS-866 was well tolerated at the dosages of 2.5 mg, 5mg, and 10 mg o.d. during the 12-week trial period.

19.0 Study SE- #866-09
19.01 Title: A Multi-Center Double-Blind Dose-Finding Study of Oral CS-866 versus Placebo in Patients with Mild to Moderate Hypertension (Phase II).

Source documents: Study report: NDA 21-286, vol. 220 (Clinical);

Investigator: The Principal Investigator was K. O. Stumpe, MD, Bonn, Germany.
Sites: Total=60: 52 in Germany, 6 in the Czech Republic and 2 in Poland.

Study dates: April 10, 1996 (first subject screened) to June 6, 1997 (last completed).

19.1 Objectives: Primary objective
To determine diastolic blood pressure (DBP) lowering effects at trough levels of CS-866 2.5, 5, 10, 20, 40 and 80 mg once daily, with placebo control, compared to baseline in patients with mild to moderate hypertension.

Secondary objectives
1. Trough blood pressure lowering effects after 2, 4, 8 and 12 weeks of treatment; 2. Responder rate at each dose after 2, 4, 8 and 12 weeks of treatment (compared to baseline); 3. Peak blood pressure lowering effect (4 ± 1 hours after administration) after 2 weeks placebo (Visit 3) and week 12 (Visit 8); 4. Safety and tolerability by adverse events, physical and EKG exams, laboratory tests.

19.2 Study design
This study description was based upon the study report in volume 1 of NDA. An amendment to the study report provided further safety information (see Safety Results) and integrated audit certificates for the finalized protocol and Case Report Form.

This was a randomized, double-blind, placebo-controlled, 7-arm parallel group trial shown schematically in Figure 1. After a 4-week single-blind placebo run-in period, eligible subjects were randomly assigned to placebo or active drug (2.5, 5, 10, 20, 40 and 80 mg CS-866 once daily) for 12 weeks. Those already on antihypertensive therapy were tapered off drug for 1-2 weeks prior to the single-blind placebo run-in period.

19.3 Inclusion criteria
Eligible patients were males or nonpregnant females 18 to 75 years, with mild to moderate essential hypertension (mean sitting DBP $\geq$ 100 mm Hg and $\leq$ 114 mm Hg prior to placebo run-in--at screening or end of taper-off period--and the mean of the three sitting diastolic blood pressure measurements had to be between 100 and 114 mmHg inclusive at two of the three visits during the placebo run-in phase). Patients with essential hypertension were also eligible in whom it was medically justifiable to withdraw prior treatment (i.e., poor efficacy or tolerability).

19.4 Exclusion criteria

Pregnant or breastfeeding women or women of childbearing potential not using acceptable contraception;

Severe hypertension (sitting DBP $\geq$ 115 mm Hg and/or SBP > 200 mm Hg or stage III per WHO classification);

Secondary hypertension;

Symptomatic postural hypotension;

Atrial fibrillation, 2nd or 3rd degree AV block, cardiac arrhythmia requiring therapy, or bradycardia (< 50 bpm);

Patients with significant cardiovascular disease, such as a significant narrowing of the aortic or bicuspid valve, a severe obstruction of cardiac outflow (hypertrophic cardiomyopathy), severe heart failure or symptomatic coronary heart disease.

Patients with a history or clinical evidence of significant cerebrovascular, gastrointestinal, haematological or hepatic disease or myocardial infarction (in the past six months) or a previous history of any serious underlying disease, including immunocompromised patients and/or neutropenic patients that, in the opinion of the investigator, would interfere with the conduct of the study.

Patients with clinical evidence of renal disease (including renovascular occlusive disease, nephrectomy and/or renal transplant, serum creatinine level in excess of 150 µmol/l (= 1.7 mg/dl) or proteinuria '++' or more on dipstick evaluation).

Patients with clinically significant laboratory abnormalities including patients with ASAT/SGOT and ALAT/SGPT greater than 2 times the upper limit of the laboratory normal range. Patients with gamma-GT greater than 2 times the upper limit of the laboratory normal range were excluded only if ASAT/SGOT and/or ALAT/SGPT were greater than 1.5 times the upper limits.

Patients with insulin-dependent or poorly controlled diabetes.

Patients with known malabsorption syndromes.

Patients whose body weight exceeded -15%/+35% of the Modified Metropolitan Life Index (see Appendix III of the trial protocol, Appendix 1.1) or who weighed < 45 kg or > 110 kg.

Patients with a history of a wasting disease (cancer), autoimmune diseases, connective tissue diseases or major allergies.

Patients with psychiatric or emotional problems, which would invalidate the giving of Informed Consent or limit the ability of the patient to comply with study requirements.

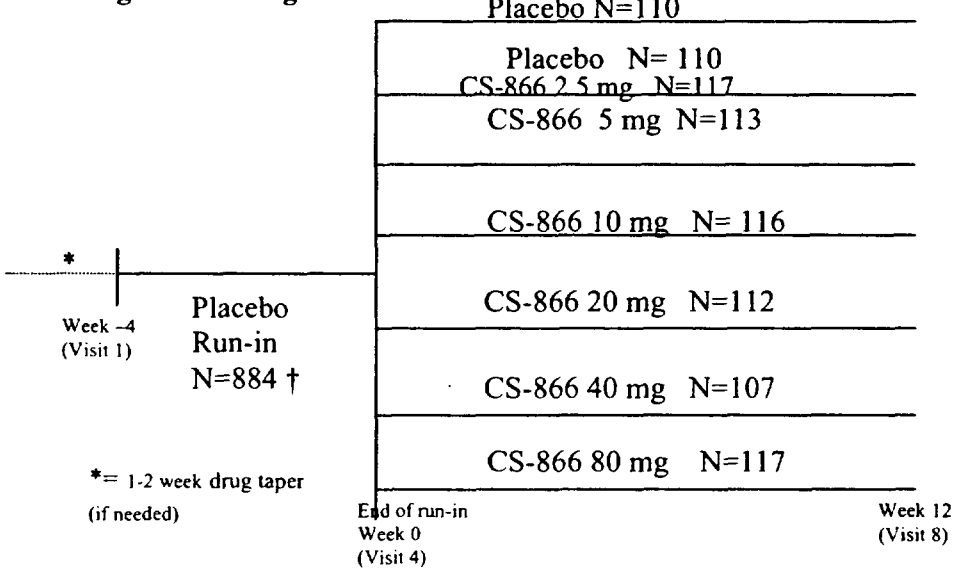
Patients with any history of alcoholic and/or drug abuse.

Patients having been treated for other indications with drugs or medication which may have influenced blood pressure and which cannot be withdrawn during the period of the study, e.g. a-blockers for the treatment of benign prostatic hypertrophy or intraocular b-blockers for the treatment of glaucoma.

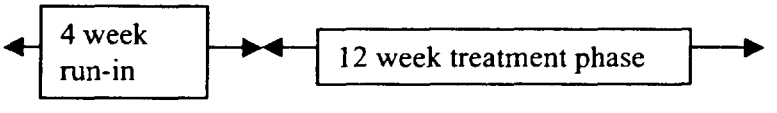
Patients with known hypersensitivity, lack of response or contraindication to angiotensin II-antagonists or hypersensitivity to related drugs (cross-allergy) or adjuvant hypersensitivity.

Patients unwilling or unable to tolerate discontinuation of their previous antihypertensive medication.
Patients who had donated 450 ml or more blood within the last three months.
Patients who had received an investigational drug within three months prior to entering the placebo run-in phase of the study.
Patients who had previously been enrolled in this study.
Patients who were unwilling or unable to provide Informed Consent or to participate

Figure 67:Design-SE-866-09



†Note: 92 patients were dropped prior to randomization.



Patients were followed weekly during the placebo run-in phase (Visits 1-4), and at Weeks 2, 4, 8 and 12 during the treatment phase (Visits 5-8, respectively); a safety followup visit (Visit 9, Week 14) was done 1-2 weeks after study completion.

19.5 Efficacy The primary efficacy parameter was the change from baseline in trough sitting diastolic blood pressure (DBP). Secondary efficacy parameters included: change in trough sitting systolic as well as standing systolic and diastolic blood pressures at weeks 2, 4, 8, and 12 weeks of treatment; response in sitting DBP at weeks 2, 4, 8 and 12 weeks; and trough-to-peak ratio in sitting DBP after 12 weeks of treatment. Safety parameters included adverse event collection, blood pressure/pulse monitoring, 12-lead EKG, and routine laboratory tests.
For Drug supplies, manufactured by Luitpold Pharma GmbH, Sankyo Group (Table 173).

Table 173. Drug Supplies Study SE #866-09

Substance	Batch #
Matching Placebo	224/225/226
CS-866 2.5 mg	217
CS-866 5 mg	218
CS-866 10 mg	219
CS-866 20 mg	220

Source: NDA 21-286 Study SE-866-09 Clinical Trial Report (Vol. 1) pdf. page 39

19.6 Sample Size Calculation

To demonstrate a difference between treatment and placebo of 3 mm Hg or greater in the primary efficacy parameter, a sample size of 100 evaluable patients was needed in each group. This sample size was calculated with a power of 80.8% and an assumed standard deviation of 6 mm Hg.

19.61 Statistical Methods

All statistical significance testing was two-sided and performed at a level of 5%. Trough DBP was analyzed using ANOVA including treatment, center, and treatment-by-center interactions as effects in the statistical model. Differences in parameters between active drug and placebo were estimated associated with 95% confidence intervals. Response rates were analyzed by a logistic regression model, including treatment and center (pool) as effects. The only confirmatory analysis was done on the primary efficacy parameter for the ITT population; other analyses were carried out on an exploratory basis.

Pooling of Centers

Trial centers with less than 21 evaluable patients were ascendingly ordered by numbers of evaluable patients and combined to center pools according to the following rule: smallest with largest with less than 21 patients, second-smallest with second-largest with less than 21 patients and so on to reach the target center size. For resulting center pools that consisted of less than 21 evaluable patients, the procedure was repeated until all center pools were sufficiently sized. Resulting ITT and PP pools were numbered and subsequently used for statistical evaluation together with sufficiently sized trial centers.

Changes to the Protocol

As of 2/23/96, it was decided that the baseline peak blood pressure measurement should be taken during the placebo phase (at Visit 3, Week –2), rather than following the first dose (Visit 4, Week 0). As of 3/4/96, the inclusion criterion for diastolic blood pressure was changed from a "mean of 3 sitting DBP measurements must be between 100 and 114 mm Hg inclusive at 3 measurements during the placebo run-in phase" to "between 100 and 114 mm Hg inclusive at 2 of the 3 visits during the placebo run-in phase."

19.7 Results

Table 174: Patient disposition-SE-#866-09

	N
Screened	938
Enrolled	884
Dropped prior to randomization	92
Randomized	792
Withdrawal	52
Adverse events	5
Lack of efficacy	27
Withdrew consent	8
Other	12
Completed	740
Intent-to-treat group	790
Per-protocol group (evaluable)	651

Source: NDA 21-286: Study SE-866-09 pdf. Pages 65- 66

Table 175: Patient disposition by treatment group SE-#866-09

	Plcbo	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg	Total
Randomized	110	117	113	116	112	107	117	792
Withdrawn	12	8	10	5	10	4	3	52
Completed	98	109	103	111	102	103	114	740
Per-protocol	85	92	90	99	91	90	104	651
ITT	110	116	113	116	111	107	117	790

Source: 21-286: SE-866-09: pdf. Page 65

The highest numbers of dropouts (or withdrawals) were in the placebo (12 subjects), 5 and 20 mg treatment groups (10 subjects each). Of 52 total dropouts, 27 occurred due to lack of efficacy. There was about 50% withdrawal because of lack of efficacy in most treatment groups except in placebo, where 9 patients (75%) were withdrawn.

Table 176: Withdrawals by treatment arms - Study SE-#866-09.

Reason for withdrawal	Placebo	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg	Total
Adverse Event	0	0	2	1	1	1	0	5
Lack of efficacy	9	3	4	3	6	1	1	27
Withdrawal of consent	3	2	2	0	0	1	0	8
Other reasons	0	3	2	1	3	1	2	12
Total	12	8	10	5	10	4	3	52

Source: SE-866-09: pdf. Page 50.

19.8 Baseline characteristics

Baseline demographics are shown in Table 177. All subjects were Caucasian. Mean ages ranged from 54 to 57; mean heights were 169-170 cm and mean weights were 79-81 kg. The median duration of hypertension, 3.3 years, was similar across treatment groups. 41 (CS-866 5 mg group) to 51 subjects (2.5 mg group) per group (40% of ITT population) required a taper-off period from prior antihypertensive medication.

Baseline blood pressure was defined as the mean of the three assessments performed during the placebo run-in phase. Mean (± SD) sitting DBP was 103-105 (3) mm Hg, mean (± SD) sitting SBP was 163-165 (12-14) mm Hg, and mean (± SD) sitting HR was 74-76 (7-8) bpm; there were no meaningful differences across treatment groups.

Table 177: Baseline characteristics (ITT population) - Study SE-866-09

	Placebo	CS-866					
		2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg
N	110	116	113	116	111	107	117
N ≥ 65 years (%N)	21 (19)	22 (19)	25(22)	16 (14)	19 (17)	27 (25)	24 (21)
Male (%N)	56 (51)	64 (55)	51 (45)	58 (50)	47 (42)	50 (47)	63 (54)
Smoker (%N)	22 (20)	25 (22)	20 (18)	22 (19)	26 (23)	25 (23)	23 (20)

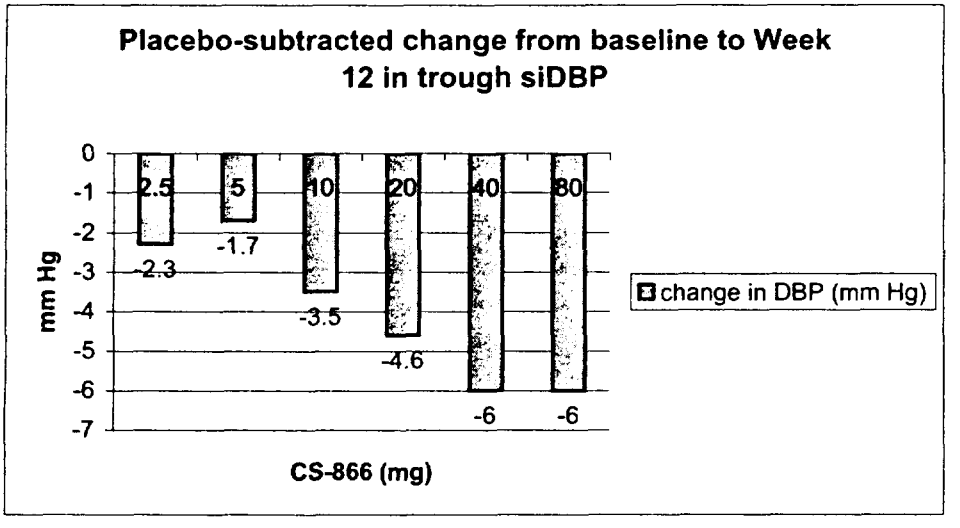
Source: 21-286: SE-866-09: pdf. Pages 70, 73, 81, 100.

19.9 Primary efficacy parameter: change from baseline in trough sitting DBP

Below is a graph showing placebo-subtracted decrease in trough sitting DBP (siDBP) from baseline to Week 12 (Source: SE 866 09: pdf. Page 73; statistical analysis pdf. Page 75). One can note a flattening of dose-response at 40 mg CS-866 and above; the change from baseline is statistically significant compared to placebo at CS-866 10 mg and above. In the per protocol (evaluable) population, the statistical analysis showed similar results (i.e. statistical significance at doses of 10 mg and above).

Only 11 trial centers had 21 ITT patients or more. In order to perform the statistical analysis, the other 49 trial centers were pooled into 12 ITT trial center pools consisting of 25 to 35 patients from 4 to 5 trial centers each. Treatment effects (p=0.0001) and center pool effects (p=0.0001) were statistically significant; the interaction was not statistically significant (p=0.7196).

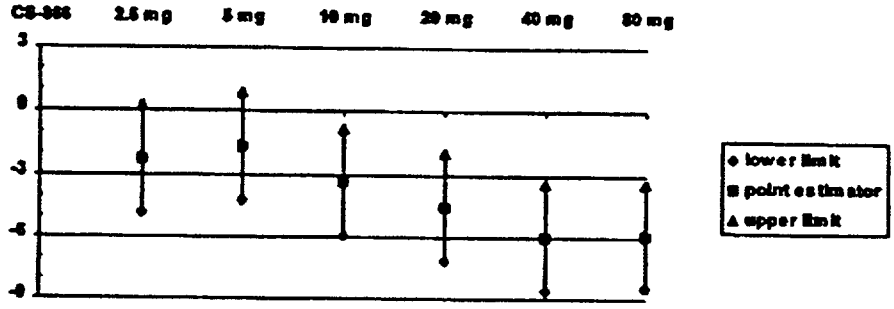
Figure 68: Change from baseline at week 12 – ITT- SiDBP - 866-09



These data pertain to ITT. Final values are at week 12 or LOCF for withdrawals.

Confidence Intervals on Treatment Differences CS-866 compared to placebo: 5% total level of significance.

Figure 69: Confidence Intervals on treatment diferrences - 866-09



19.10 Secondary Efficacy Parameters

Figure 70: Trough sitting DBP over time: (Source: Table XII: pdf. Page 78)

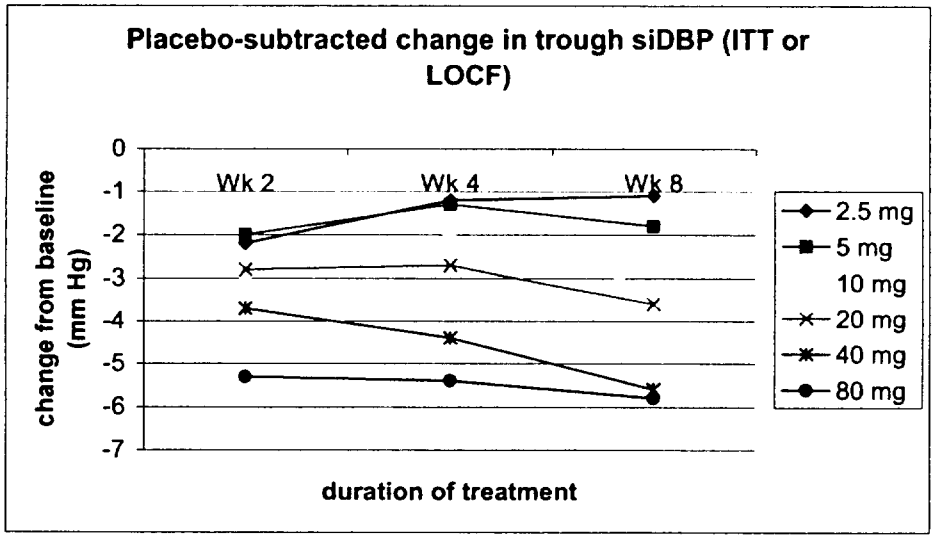


Figure 71: Placebo-subtracted mean change from baseline trough SiSBP (ITT and LOCF) Study #866-09

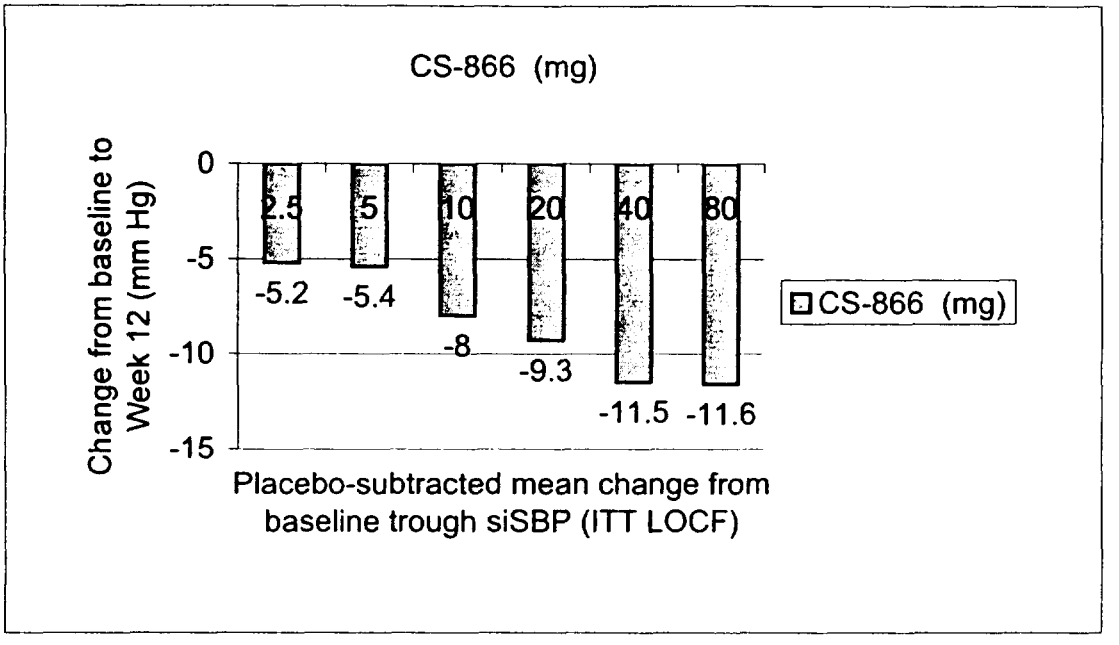


Table 178: Changes from baeline trough SiSBP by dose – ITT- Study #866-09

Table XVI: Last Values and Decreases under Treatment in Mean Sitting sBP [mmHg] at Trough by Treatment Group - ITT Population (Appendix 4, Listing 14.1; Section 8.2, Table 17.1.4)

Mean ± S.D.	Placebo (N=110)	2.5 mg (N=116)	5 mg (N=113)	10 mg (N=116)	20 mg (N=111)	40 mg (N=107)	80 mg (N=117)
Baseline value	162.9 ± 13.1	164.6 ± 11.1	162.7 ± 12.8	163.3 ± 12.5	164.2 ± 13.9	164.4 ± 12.3	164.8 ± 13.0
Last value under treatment*	153.8 ± 12.4	150.3 ± 13.6	148.3 ± 14.0	146.2 ± 13.8	145.9 ± 15.9	143.8 ± 13.2	144.0 ± 14.7
Decrease under treatment	9.1 ± 10.8	14.3 ± 11.3	14.5 ± 10.3	17.1 ± 11.7	18.4 ± 12.5	20.6 ± 13.2	20.7 ± 14.2

* = 12-week value for completers or LOCF for withdrawals

19.21 Responders (SiDBP)

Below is a table of response rates from this study (ITT population). It can be seen that the response rates increase with dose as well as duration of treatment (even in the placebo group). Results were similar in the PP population; it should be noted that response rates were higher in the 20 mg treatment group for the PP population.

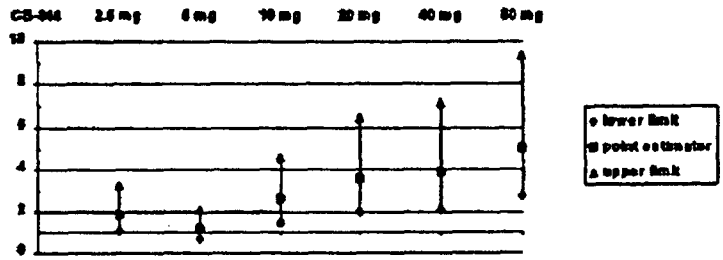
Table 179: Response rate by dose and visit – ITT – Study SE 866-09

Visit or LOCF	Plcbo (N=110)	2.5 mg (N=116)	5 mg (N=113)	10 mg (N=116)	20 mg (N=111)	40 mg (N=107)	80 mg (N=117)
Visit 5/Week 2	20.0	28.4	29.2	37.1	36.9	38.3	47.0
Visit 6/Week 4	38.2	43.1	46.9	52.6	54.1	60.7	64.1
Visit 7/Week 8	41.8	48.3	54.0	63.8	68.5	72.0	76.1
Visit 8/Week 12	45.5	59.5	50.4	66.4	72.1	73.8	77.8

Source: responders: SE-866-09: Table X: pdf. Page 76

Figure 72:CI for odds ratio of CS 866 versus placebo in DBP response

Figure IV: 95% Confidence Intervals for Odds Ratios of CS-866 Treatment Groups [Dosage in mg] versus Placebo in dBP Response to Treatment - ITT Population (Section 8.2, Table 15.1.4)



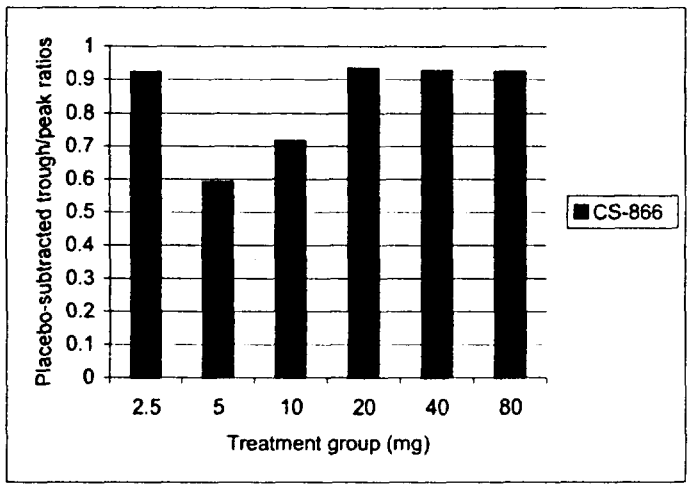
Trough-to-Peak (siDBP): Trough and peak measurements can be found in SE 866-09: Table XIV: pdf. Page 79. Trough-peak ratios

Table 180 Trough/Peak ratios – ITT - Study 866-09

Table XIV: Trough and Peak Measurements of Mean Sitting dBP [mmHg] by Treatment Group - ITT Population (actual values) (Appendix 4, Listing 14.2; Section 8.1, Figure 4.1; Section 8.2, Table 12.1)

Mean ± S.D.	Placebo (N = 91)	2.5 mg (N = 103)	5 mg (N = 100)	10 mg (N = 102)	20 mg (N = 95)	40 mg (N = 97)	80 mg (N = 106)
Trough Visit 3 / Week -2	104.0 ± 3.1	104.2 ± 2.9	104.1 ± 3.1	104.3 ± 3.1	104.2 ± 3.0	104.2 ± 2.7	104.9 ± 3.1
Trough Visit 8 / Week 12	94.0 ± 7.3	91.8 ± 7.7	92.0 ± 7.4	91.3 ± 6.6	88.6 ± 7.2	88.0 ± 7.8	88.9 ± 8.0
Decrease Trough	10.1 ± 7.3	12.4 ± 7.7	12.1 ± 7.6	13.1 ± 6.8	15.6 ± 6.9	16.2 ± 8.0	16.0 ± 7.9
Peak Visit 3 / Week -2	103.6 ± 3.6	103.8 ± 3.4	104.2 ± 3.2	104.2 ± 3.4	104.0 ± 3.0	103.9 ± 3.2	104.1 ± 3.9
Peak Visit 8 / Week 12	82.7 ± 8.3	80.0 ± 7.7	89.7 ± 8.2	88.0 ± 7.2	87.1 ± 7.6	86.3 ± 7.8	86.8 ± 8.2
Decrease Peak	11.0 ± 7.6	13.5 ± 7.3	14.4 ± 7.8	15.2 ± 6.9	16.9 ± 7.2	17.6 ± 8.2	17.4 ± 7.7
Trough-to-peak ratio	0.93 ± 0.82	0.89 ± 0.76	0.87 ± 0.79	1.09 ± 2.72	1.00 ± 0.55	0.83 ± 1.19	0.92 ± 0.41

Figure 73: Plcbo.-subtracted trough/peak change from baseline to wk 12 Study #866-09



19.22 Safety/tolerability

There were no deaths during this trial. After randomization, 283 patients reported 438 adverse experiences. In addition, 5 patients were withdrawn due to adverse experiences. The most frequent AEs during treatment phase were 51 reports of influenza-like symptoms followed by increased gamma-GT, headache and hypertriglyceridemia.

Table 181: Withdrawals due to AE Study SE-866-09:

Randomization number	Treatment group	AE	Onset (days after randomization)	Severity	Outcome
360	CS-866 20 mg	Migraine	40	Moderate	Recovered
384	CS-866 40 mg	Headache	57	Severe	Recovered
604	CS-866 20 mg	Ischemic changes on ECG	56	Moderate	SAE— unstable angina
780	CS-866 10 mg	Elevated liver enz.	14	Moderate	Recovered
947	CS-866 5 mg	Sternalgia	41	Moderate	Recovered

Six serious AE were reported during this trial; 3 of these occurred post-randomization (one is patient #604, reported above). The other two included an ankle fracture (placebo group- rand. # 591) and retinal hemorrhage (rand. # 121) For further discussion, the reader is referred to the Integrated Summary of Safety.

Summary

CS-866 appears to lower trough sitting DBP significantly greater than placebo, after 12 weeks, at 10 mg and above.

Placebo-subtracted trough-peak ratios appear similar at 20 mg and above.

Response rates increase with time and dose (also noted with placebo group).

Response rates for CS-866 are significantly greater than placebo (95% CI) at doses of 10 mg and above.

19A Study SE-#866-23 (Felodipine v CS 866)
This was a 381 patient, double-blind, 12 week, dose-titration non-inferiority study of CS-866 (20 and 40 mg daily) and felodipine (5 and 10 mg daily). There were 374 completers; 4 were discontinued due to adverse events (one of these was an already-mentioned SAE in the felodipine group: atrial fibrillation, one developed a headache on felodipine, and there were two laboratory adverse events with onset at Week 0 visit).

In 12 patients, treatment-emergent liver function test elevations were reported: 5 patients were in the felodipine group, and 7 were in the CS-866 group. In the CS-866 group, most elevated liver function tests had decreased by the next follow-up visit or by the safety follow-up visit (except for one patient with slightly elevated liver tests).

Other laboratory abnormalities reported in patients receiving CS-866 included hypertriglyceridemia (values > 400 mg/dl noted in 8 patients), hyperglycemia (1 patient with serum glucose 140 mg/dl which resolved) and erythrocyturia (1 patient; this resolved on a follow-up visit). One felodipine patient (230531/352) was noted to have proteinuria (100 mg/dl on dipstick) which resolved. Other than above or the patient with atrial fibrillation, there were no relevant ECG or physical examination findings.

ECG Changes
In the integrated safety summary there is no separate analysis of ECG changes. To this reviewer, there appeared to be no gross pattern of ECG changes seen with CS-866. One patient in SE-866/23 (on felodipine) and one patient in SE-866/10 (on CS-866 5 mg: discontinued due to this adverse event) developed atrial fibrillation.

20.0 Study SE- #866-03
20.01 Title: "Comparison of the Angiotensin II–Antagonist CS-866 with the ACE Inhibitor Enalapril in Healthy Male Subjects Challenged with Angiotensin I (Single Dose)"

Source documents: Study report: NDA 21-286, vol. 90 (hpbio)
Investigators: The Principal Investigator was H. Brunner, MD.
Site: This was a one-site study conducted in Lausanne, Switzerland.
Study dates: January 4, 1996 to March 20, 1996.

20.1 Objectives: The primary objective of this study was to assess the inhibitory effect of CS-866 on the pressor activity of exogenous angiotensin I compared to enalapril. Secondary objectives were 1. To evaluate safety and tolerability in healthy male subjects; and 2. To evaluate drug effects on plasma renin activity and angiotensin II levels.

20.2 Study design: This description was based upon the study report.
This Phase I study was a 9-week randomized, double-blind, double-dummy, single-dose, dose-escalating, placebo-controlled, four-way crossover trial. Subjects received a single dose per treatment period of 4 trial medications (CS-866 2.5 mg, 10 mg 40 mg and placebo in group 1; CS-866 5mg, 20 mg, enalapril or placebo in group 2) in one of eight possible sequences. The treatment periods lasted 24 hours and were separated by a 2-week washout period. The dose level was increased from one treatment period to the next; in group 2, enalapril 20 mg was given as the last treatment (after CS-866 20 mg or placebo). Before receiving study medication, an angiotensin I (Ang I) dose-systolic blood pressure (SBP) curve was generated for each subject in order to determine the dose of intravenous (i.v.) bolus Ang I required to raise SBP 25-40 mm Hg. During each treatment period, fasting baseline blood samples were drawn for RNH-6270, Angiotensin II (Ang II) and plasma renin activity (PRA). The subjects then received Ang I . Study medication was given; iv bolus Ang I was repeated 1, 2, 4, 6, 10, and 24 hours(twice after 24 hours) post-dose and BP/HR measurements were taken at baseline, 0.5, 1.5, 3, 5, 7, 8, and 9 hours post-dose. Blood samples for RNH-6270, Ang II and PRA were drawn at 1, 2, 4, 8, and 24 hours post-dose. The subjects were discharged and readmitted 3 more times after interim 2-week washout periods (following each study medication). A safety follow-up visit was scheduled 1-2 weeks after study completion.

20.3 Inclusion criteria
Eligible subjects were healthy normotensive (DBP$\leq$ 90 mm Hg and SBP$\leq$ 140 mm Hg) males, 20 to 35 years, with normal baseline electrocardiograms.

20.4 Exclusion criteria
(1) History or suspicion of alcohol/drug abuse; (2) Clinically relevant metabolic, renal, hepatic, immunologic, cardiovascular, or hematologic disease; (3) History of angioneurotic edema; (4) Medication use within 7 days prior to trial start; (5) Blood donation within 3 months; (6) Gastrointestinal disease which might influence drug absorption; (7) Clinically significant laboratory abnormalities including transaminase levels greater than twice the upper limit of normal, or gamma GT greater than twice the

upper limit of normal with transaminases greater than 1.5 times the upper limit of normal; (8) Concurrent use of other medications that influence blood pressure; (9) Symptomatic postural hypotension; (10) Insulin-dependent or poorly controlled diabetes; (11)Active smoker; (12) Recent participation in a clinical trial; (13) History of hepatitis B or C; (14) Positive results for HIV, hepatitis, or drug screening; (15) Allergy or contraindication to antiotensin II-antagonists or ACE inhibitors; (16) Body weights exceeding -15%/+35% of average according to the Modified Metropolitan Life Insurance Tables;

Efficacy parameters included: systolic blood pressures, PRA, Ang II, and RNH-6270. Safety monitoring included: adverse event collection, physical examination (at end of study), blood pressure/pulse monitoring, 12-lead ECG, and routine laboratory tests.

20.5 Drug supplies, manufactured by Luitpold Pharma GmbH, Sankyo Group, are shown in Table 182.

Table 182: Drug Supplies - SE-#866-03

Substance	Batch #
Enalapril 20 mg	2235V95017
Enalapril matching placebo	2235V95016
CS-866 2.5 mg/5 mg /10 mg /20 mg	217, 218, 219, 220
CS-866 matching placebo	224

Source: NDA 21-286 Study SE-866-03 Clinical Trial Report: page 12 (pdf. Page 21)

20.6 Patient Disposition: Sixteen males were recruited; other than one dropout because of bronchopneumonia after completing period I (CS-866 2.5 mg), all completed the trial.

20.7 Baseline characteristics

Of the sixteen males, mean ages for the two groups ranged from 24-26 years (age range 22-30 years); mean height was 178-182 cm, and mean weights were 73-81 kg. 12 (75%) were nonsmokers. There did not appear to be significant differences between the two groups.

20.8 Results

Shown below are two graphs (Figures 74 and 75) of systolic blood pressure curves following angiotensin I challenge:

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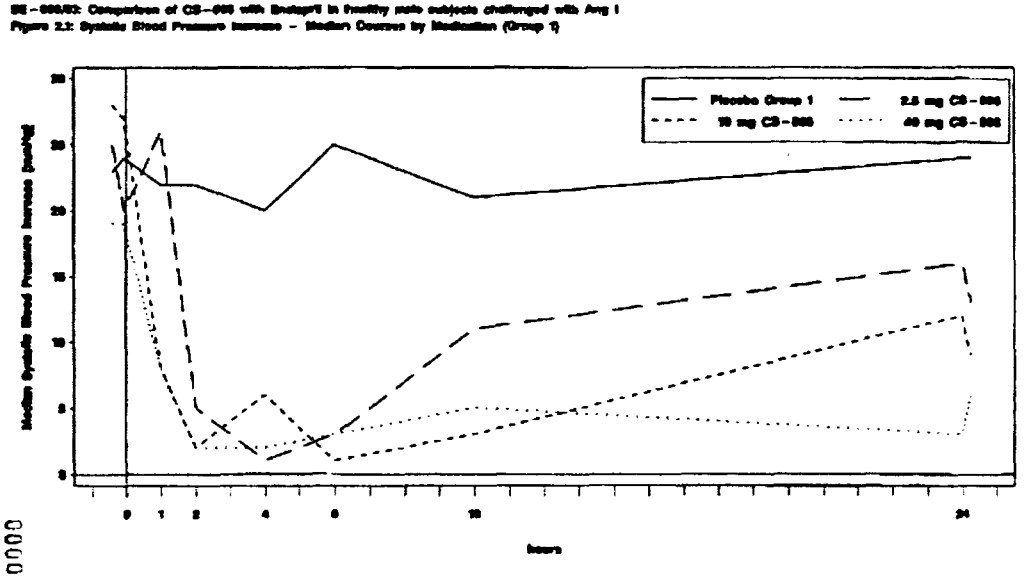
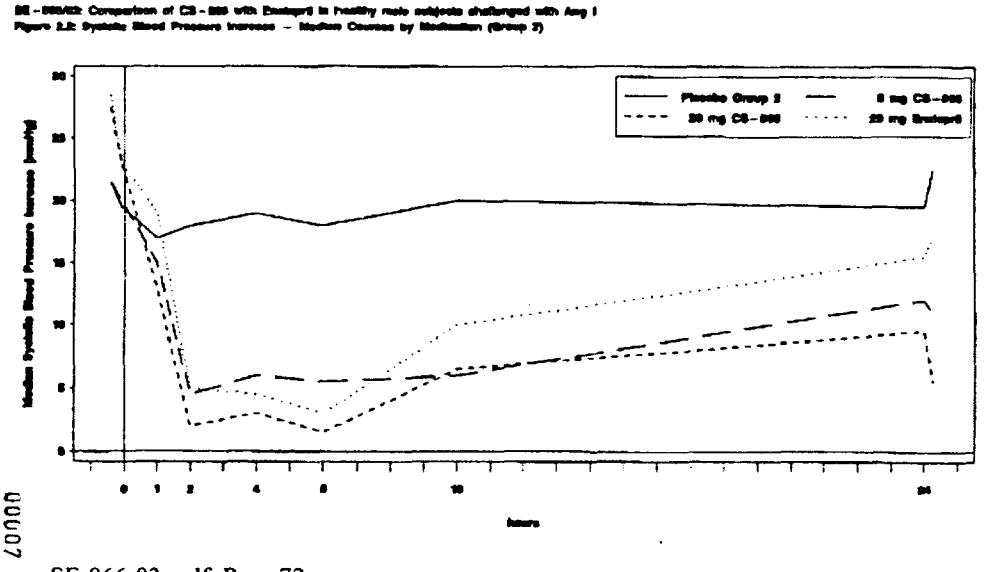
Figure 74: Median SBP increase with Ang I challenge (Group I) 866-03



Source: SE-866-03: pdf. Page 71

Figure 75: Median SBP increase with Ang I challenge (Group 2) 866-03



Source: SE-866-03: pdf. Page 72

20.9 Results

It can be seen that the initial increase in systolic blood pressure is sustained in the placebo group and suppressed within 2 hours in all of the active treatment groups. In the 2.5 mg CS-866 and enapril groups, systolic blood pressure rises by 24 hours; in group 1 there appears to be a dose-response in inhibitng the rise in systolic blood pressure, with the smallest 24th hour increase in systolic BP in the 40 mg CS-866 group.

Exploratory statistics were done for the median area above the curve (AAC) for SBP response to Ang I challenge.AAC for all doses of CS-866 were found to be significantly different compared

with placebo and no dose was signifcantly different compared with enalapril.

Table 183 Median differences in AAC (SBP response to Ang I) 866-03

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

CS-866 Dose	Median difference[#] (p-value)	
	vs. Placebo	vs. Enalapril
2.5 mg	850 (0.031) [b]	-87 (0.603) [bb]
5 mg	1300 (0.016) [b] [bb]	-87 (0.945) [b]
10 mg	1303 (0.016) [b]	225 (0.118) [bb]
20 mg	1400 (0.008) [b] [bb]	429 (0.055) [b]
40 mg	1539 (0.031) [b]	602 (0.325) [bb]

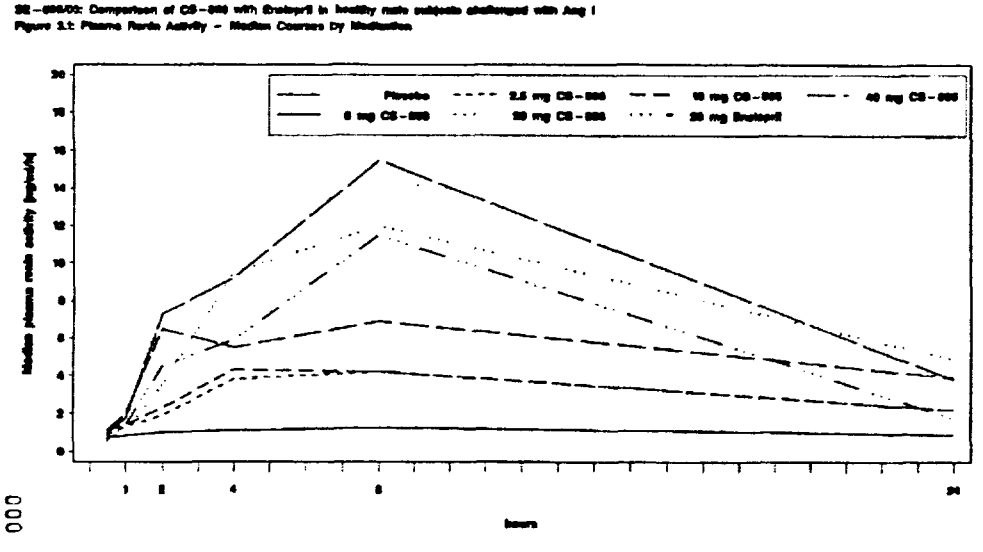
[#] Difference in medians in independent samples;
[b] Placebo, Group 1 ; [bb] Placebo, Group 2
[b] Wilcoxon signed-rank test ; [bb] Wilcoxon rank-sum test

Secondary objectives:

Effects on plasma renin activity and angiotensin II levels:

One would expect AT receptor blockade to result in a decrease in aldosterone secretion and an increase in circulating plasma renin and angiotensin II (because of the interruption of the negative feedback control of renin release). For ACE inhibitors, one would expect a decrease in angiotensin II as well as an increase in plasma renin (Figures 76-78). These effects can be seen in this study where the angiotensin II curve is flat in the enalapril group.

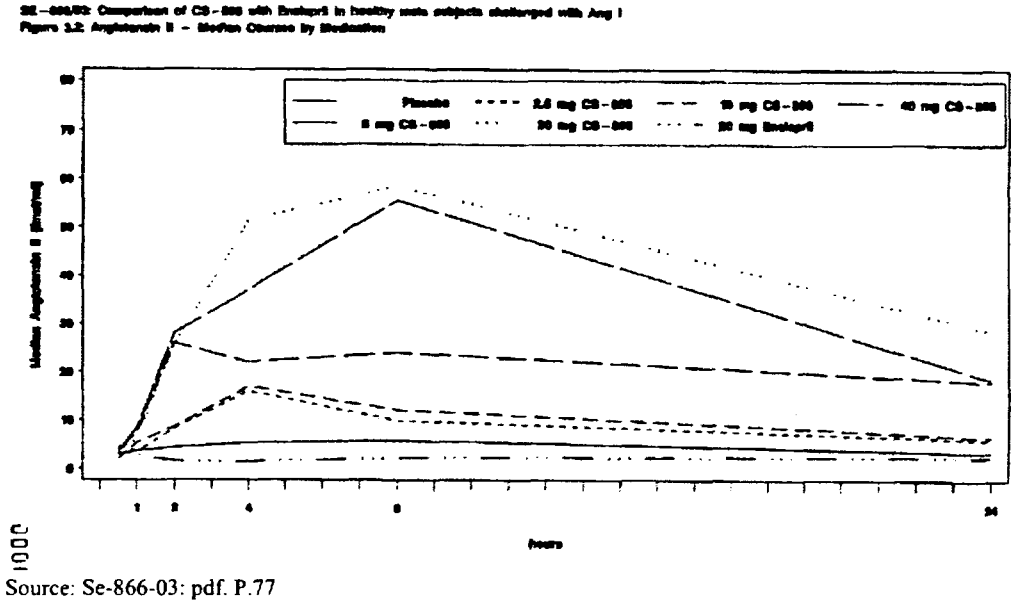
Figure 76: Median plasma renin activity after Angiotensin I challenge 866-03



(Source: SE-866-03: pdf. Page 76)

One can see a flattened curve in the placebo group, and elevated median plasma renin activity in all active treatment groups (Figures 76-77).

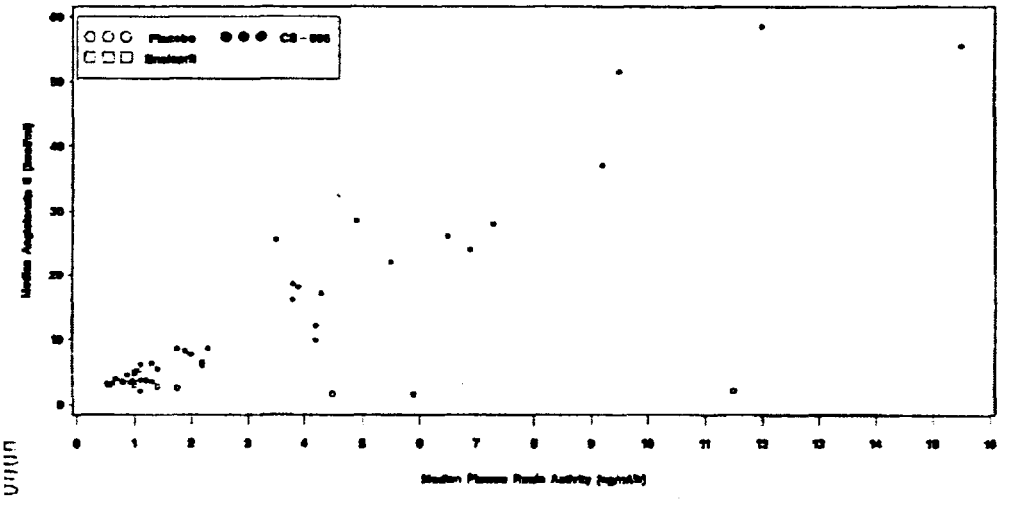
Figure 77: Median Angiotensin II levels by medication 866-03



Source: Se-866-03: pdf. P.77

A Spearman correlation coefficient of median renin vs median angiotensin II levels was 0.937.

Figure 78: Median plasma renin activity vs. Angio II levels by medication866-03



20.10 Pharmacokinetc parameters of RNH-6270

One can see from table 184 that there is an increase in Cmax and AUC (0-24) with increasing dose. Median tmax appears to be unchanged regardless of dose.

Table 184: Pharmacokinetc parameters of RNH-6270

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
5 (n=8)	1015 (10.0)	163 (24.9)	2
10 (n=7)	1498 (24.4)	233 (26.8)	2
20 (n=8)	3121 (18.9)	463 (28.2)	2
40 (n=7)	4878 (15.4)	867 (33.8)	2

Source: SE-866-03: pdf. Page 49

20.11 Safety/tolerability

Aside from one dropout due to bronchopneumonia, there were nine adverse events in six subjects (Table 185). Because of the small numbers in this trial, no definitive safety conclusions can be made. For further discussion, the reader is referred to the Integrated Summary of Safety.

Table 185 Adverse events Study SE 866-03

Table VI. Adverse Event Description (Section 8.3, Appendix 4, Listing 22, 23)

Subject			Adverse Event			
Number	Treatment	Treatment phase	Diagnosis	Severity	Drug relation	Outcome
3	40 mg	Period 3	Chest pain	mild	unrelated	recovered
6*	2.5 mg	Period 1	Bronchopneumonia	moderate	remote	recovered
11	40 mg	Period 4	Hypertriglyceridaemia	mild	remote	recovered
17	Placebo	Period 1	Pallor and Tachycardia	mild	remote	recovered
20	Placebo	Period 2+3	Hypertriglyceridaemia	mild	remote	recovered*
20		Safety Follow-up	Lymphocytes atypical and Granulocytosis	mild	remote	recovered
26	Placebo	Period 4	Bilirubin increased	mild	remote	recovered

* Subject withdrew from the trial
* Although outcome was reported as unknown, AE ended on 29.02.1996.

Comments

This was Phase I study comparing effects of CS-866 and enalapril 20 mg on Angiotensin I-induced rise in SBP as well as renin and angiotensin II levels.

Conclusions

There appears to be a dose-related CS-866 suppression of the Angiotensin I-induced rise in systolic blood pressure.

In this study, all active treatments (CS-866 and enalapril) were associated with elevations in plasma renin activity; CS-866 doses were associated with elevations in angiotensin II levels.

Cmax and AUC (0-24) increased with CS-866 across the dose range studied; tmax was unchanged across the dose range.

21.0 Study SE- #866-04
21.01 Title "Effects of the angiotensin antagonist II CS-866 in salt-depleted hypertensive patients (Single dose)"

21.1 Study objectives: Primary Objective:
To assess the dose-response relationship of CS-866 in association with a low sodium diet on blood pressure in mild to moderately hypertensive patients.

Secondary objective
To evaluate the safety and tolerability of CS-866 in the patients after single dosing by monitoring adverse events, ECG, laboratory parameters, and renin-angiotensin system (RAS) endocrine values.

Duration of trial: Twenty seven (27) days composed of 5 days of treatment, a 3 day pre-phase period, after treatment, an oral dose of 40mg furosemide given on the third day the patients received next dose, and a 24 hour ambulatory blood pressure measurement (Table 186). Throughout the 24 hours after dosing the concentration of RNH-6270, plasma renin activity and angiotensin II levels were measured.

21.2 Study design: This phase II study was designed as a randomized, double blind, placebo-controlled, 4 way cross over trial assessing the effects of angiotensin II antagonist CS-866 after single dose administration in salt-depleted male or female hypertensive patients, aged between 18 and 65 years. There were two dosage groups with 8 patients each receiving different doses of CS-866 (2.5mg, 5mg, 10mg, 20mg, 40mg, and 80mg , respectively) or placebo in four treatment groups.

21.3 Trial design
There were 2 groups, each group consisted of 8 patients, 6 of them receiving CS-866 and 2 receiving placebo. Group I received 2.5mg, 10mg, 40 mg and placebo and Group II received 5mg, 20mg, and 80 mg, and placebo. In every period there were 8 patients in each of the two groups. The patients were assigned randomly, in blocks of 4, to one of the possible treatment sequences.

For safety, a randomized, dose rising scheme was preferred which placed placebo in a trial period. The first protocol amendment expanded the eligible patient population (Male and female Caucasian hypertensive patients (mean value of SiDBP between 100 and 114 mmHg during the pre-phase; 18-65 years old) to include female as well as male patients and the second amendment removed Day 3 from each trial period. Drug administration was by the oral route and each dose was taken in the morning before meals. For treatment sequences- see Table 186.

Table 186: Treatment sequences – CS-866 in mg Study 866-04

Group I	Day 1	Day 8	Day 15	Day 22
A	2.5	10	40	Placebo
B	2.5	10	Placebo	40
C	2.5	Placebo	10	40
D	Placebo	2.5	10	40
Group II	**Day6**	**Day13**	**Day20**	**Day27**
E	5	20	80	Placebo
F	5	20	Placebo	80
G	5	Placebo	20	80
H	Placebo	5	20	80
A-H = different treatment sequences, consisting of 2 patients each.				

21.4 The parameters examined on the subjects were as follows
24 hour diastolic blood pressure **AUC**
Mean 24 hour diastolic blood pressure
Mean diastolic blood pressure during daytime (7-19h)
Last measurement of diastolic blood pressure before medication
Diastolic blood pressure 2 hours after medication
Diastolic blood pressure 6 hours after medication
Diastolic blood pressure 12 hours after medication
Last measurement of diastolic blood pressure in the 24 hour period

21.41 Additionally, 24 hour ABPM measurements were recorded continuously on day 1 of each trial period and 24 hour profiles were also recorded at the following intervals:
20 minute intervals from 6.00am to 12.00pm and
30 minute intervals from 1200 pm to 6 am..
PD assessments: Plasma Renin and Angiotensin II levels were measured.
PK assessments: Blood samples were taken at pre-specified intervals for estimating levels of the main metabolite, RNH-6270.

21.5 Results
Eight patients completed the trial in each group. Demographics and baseline data showed a balance between the treatment groups and placebo (Table 186). The ABPM and the conventional diastolic BP are presented in Tables 187 and 188, respectively. There were two protocol violations and results of 2 patients were excluded from the efficacy, PK and PD analyses.

Table 186 Demographics –Study #866-04

Table 1. Demographic Data (Appendix 3, Listing 7)

Subject number	Sex	Age [years]	Height [cm]	Weight [kg]	Smoking habits	Alcohol consumption
1	female	47	150	53	2	3
2	female	40	164	67	2	3
3	female	43	168	63	2	3
4	male	63	180	70	1	1
5	male	48	172	88	2	1
6	female	47	165	65	2	3
7	female	43	158	53	1	3
8	female	52	158	70	2	3
9*	male	28	184	82	1	2
Mean pat. no. 1-8		48.1	160.6	68.2		
17	male	47	184	74	1	2
18	male	58	173	86	1	1
19	male	59	178	72	1	1
20	female	64	164	60	1	2
21	female	64	163	60	1	2
22	female	44	158	62	2	3
23	female	65	156	68	2	2
24	male	42	198	81	2	2
Mean pat. no. 17-24		52.9	164.5	70.4		

*: Drop-out
Smoking: 1 = smoker 2 = non-smoker
Alcohol: 1 = sometimes 2 = rarely 3 = never

Table 187: Mean 24 hr. Diastolic blood pressure by dose groups Study - #866-04

Group I (8 patients)			Group II (8 patients)		
Dose group	**Mean SiDBP**	**Median SiDBP**	**Dose group**	**Mean SiDBP**	**Median SiDBP**
Placebo	88.17±15.08	89.5	Placebo	79.14±13.93	80
2.5mg	84.34±15.49	84.5	5mg	76.52±15.54	77
10mg	81.31±15.88	80	20mg	70.69±14.88	71
40mg	81.82±14.87	83	80mg	70.21±15.64	70

21.51 The mean 24 hour diastolic blood pressure AUC shows a dose dependent reduction from 2.5mg to 20 mg (Figure 79a) and this is not evident above 20mg dose (Figure 80). Figure 81 shows that CS-866 medication is more effective in lowering the diastolic blood pressure than placebo. There is very little difference in the magnitude of effect between the 20mg (-8.45mmHg) and 80 mg dose (-8.93mmHg) (Table 187). The plateau effect of the dose response relationship after 20mg is shown in Figure 81 and supports the pairwise comparison test results. The antihypertensive efficacy of CS-866 is evident in this small number of patients at doses of 10mg and higher using cuff measurements (Table 188). It is noteworthy that increasing the single dose from 2.5mg to 10mg and from 5 to 20 mg lowered the dBP more than increasing the dose from 10 to 40mg or 20 to 80 mg (Table 187), respectively. The mean 24 hour dBP was lowered by 8.45 mmHg with an oral dose of 20mg CS-866 as compared to placebo (Figure 81).

Figure 79: 24 hr DBP AUC in patients receiving 2.5-20mg Study #866-04

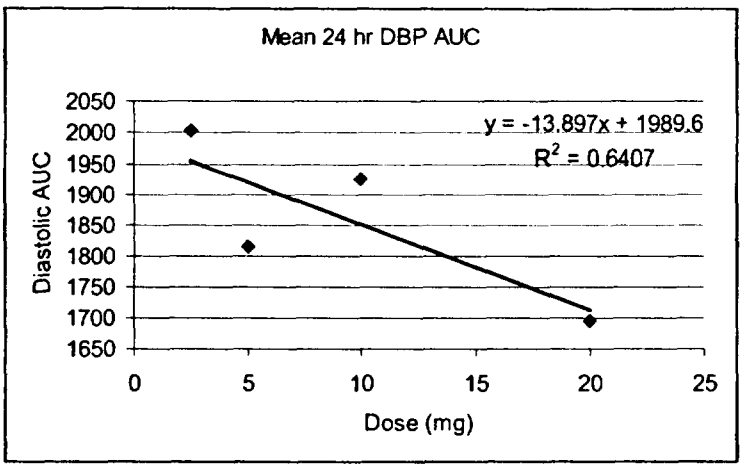


Figure 80: 24 hr DBP AUC in patients receiving 2.5-80mg Study #866-04

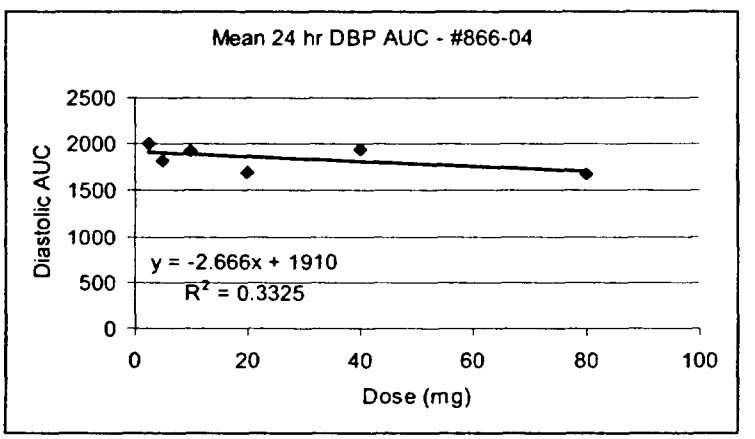
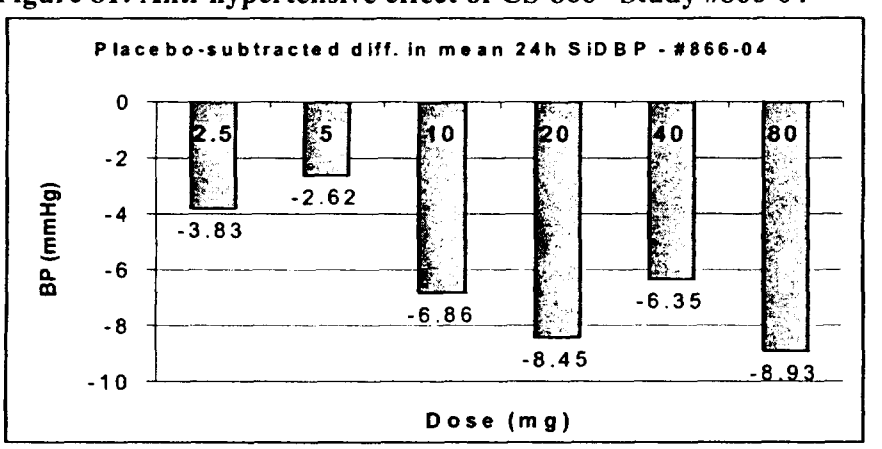


Figure 81: Anti-hypertensive effect of CS-866 –Study #866-04



Graphs in Figures 79a-81: Reviewer

Table 188: Cuff Diastolic BP by dose of groups I and II –Study #866-04

Group 1 (16 patients)		Group II (16 patients)	
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±8.12
2.5mg	97.69±5.63	5mg	90.69±11.57
10mg	89.38±5.69	20mg	78.64±8.92
40mg	90.38±8.86	80mg	76.50±13.03

The 24hour ABPM measurements that were continuously recorded on day 1 of each trial are presented in Figures 82 and 83. They support the finding of lowering of blood pressure by olmesartan compared to placebo. The dose response curve shows a plateau referred to above.

The results of linear regression between AUC of metabolite and dose yielded an R-Square of 0.04 and an adjusted R-Square of 0.005 for group 1 and 0.06 and 0.026 for group II (Sponsor) suggesting a roughly linear corellation between dose and AUC of metabolite.

Figure 82:ABPM pattern in salt depleted subjects-CS866- 2. 5, 10, 40mg - #866-04

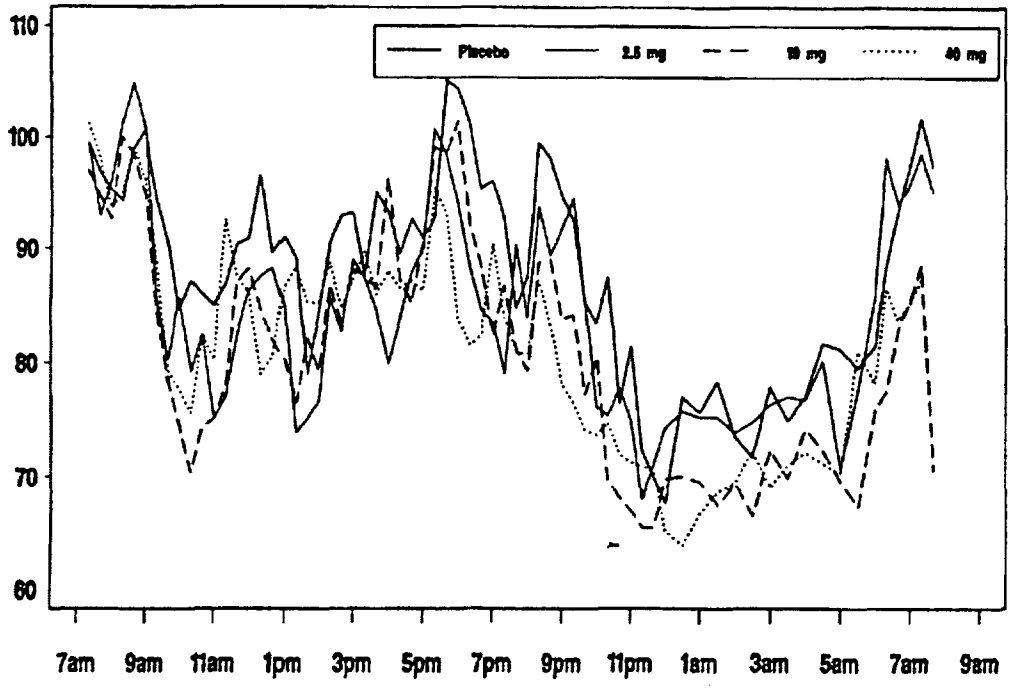
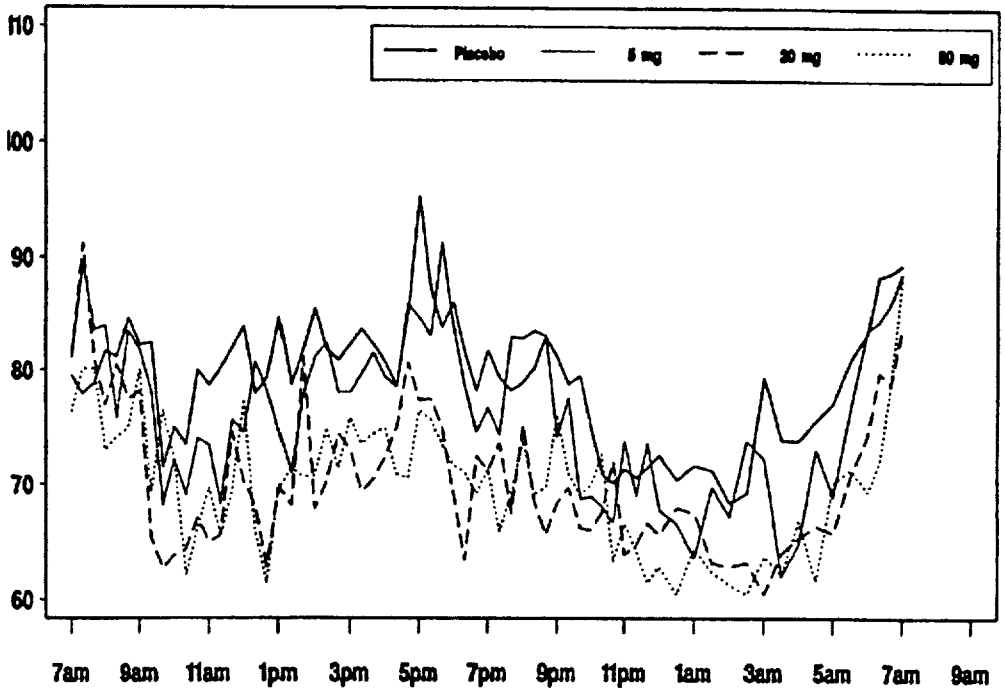


Figure 83: ABPM pattern in salt depleted subjects on CS-866 5, 20, 80mg 866-04



21.6 Pharmacokinetics

Plasma concentrations of the active metabolite RNH-6270 were assessed pre-dose and at 3,6, and 12 hours after dosing in each treatment period. There is a roughly linear correlation between CS-866 dose and RNH-6270 concentration (Figures 84-86). The estimated half-life of the active metabolite RNH–6270 was 3-6 hours. The graphsin Figures 84-86 have been determined from 3-6 points by the Medical Reviewer to show correlation between the dose given and the concentration of metabolite in both groups.

Figure 84: RNH-6270 concentration 12 hours after dosing Group II –Study #866-04

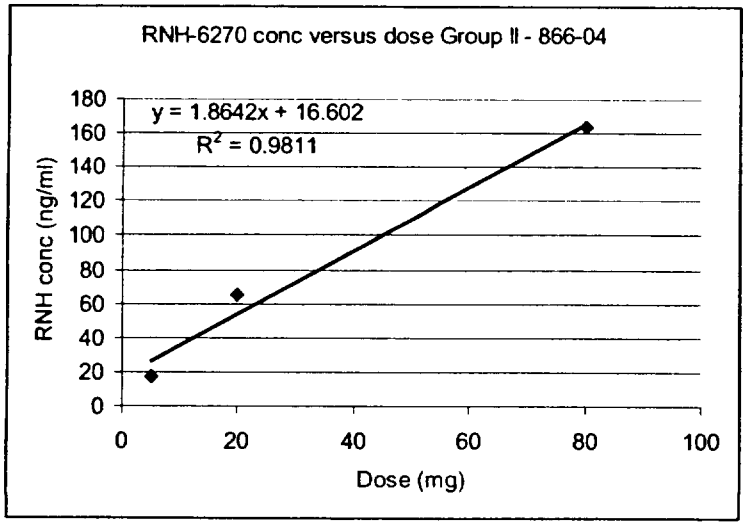


Figure 85: RNH-6270 concentration 12 hours after dosing Group I –Study #866-04

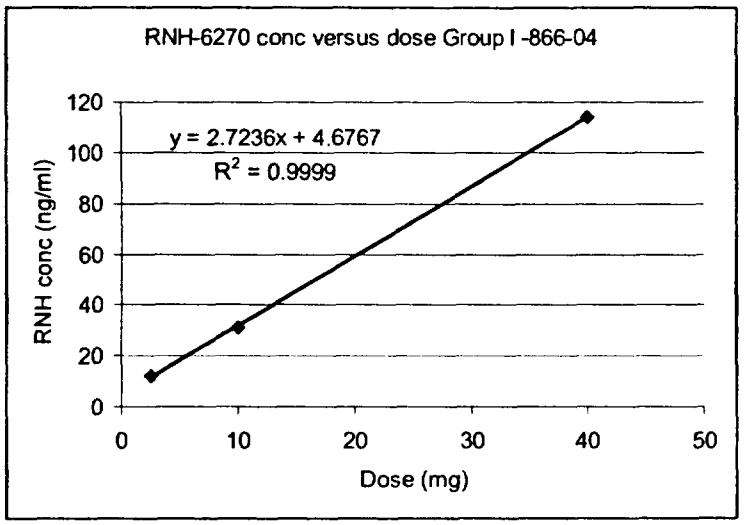
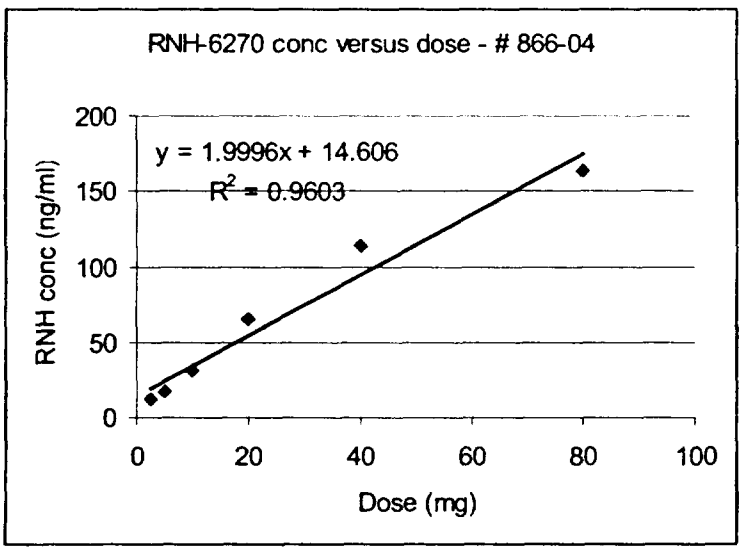


Figure 86: RNH-6270 conc. 12 hours after dosing. Groups I and II –Study #866-04



Figures 87-89 show increased renin concentrations in patients given CS-866 compared to placebo and Figure 90 shows increased Angiotensin II levels in patients given CS-866 compared to placebo. The maximum concentrations occurred 3 hours after dosing.

Figure 87: Plasma Renin activity 24 h post dosing – Study #866-04

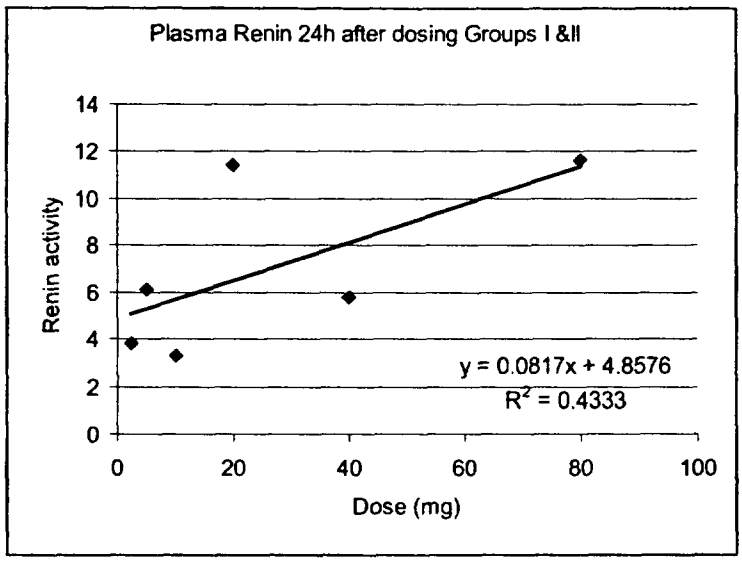


Figure 88: Plasma Renin activity 24 h post dosing Group 1 Study #866-04

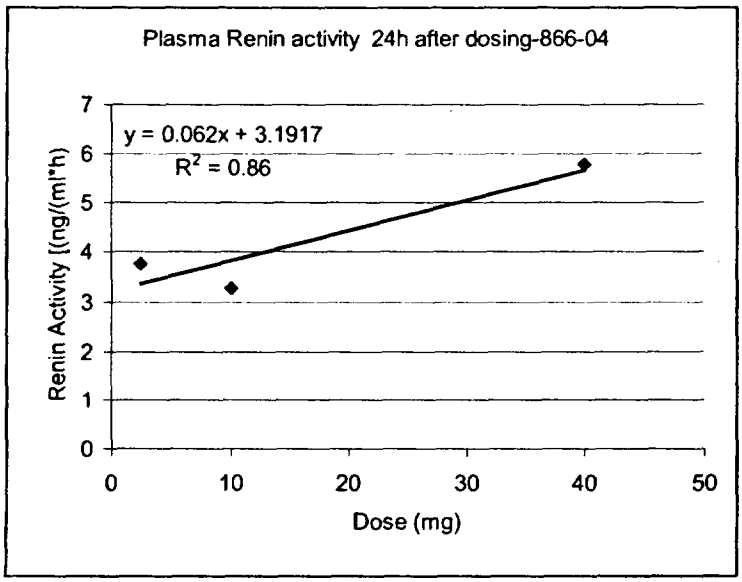


Figure 89: Plasma Renin activity 24 h post dosing Group II Study #866-04

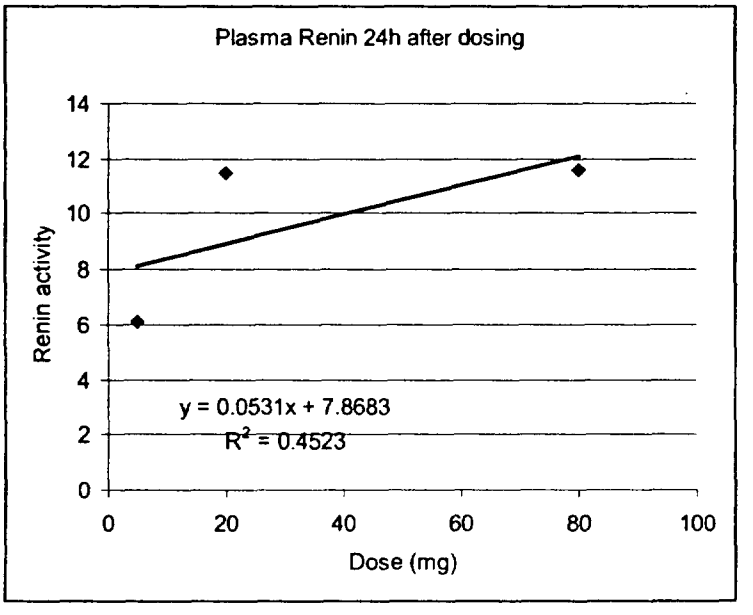
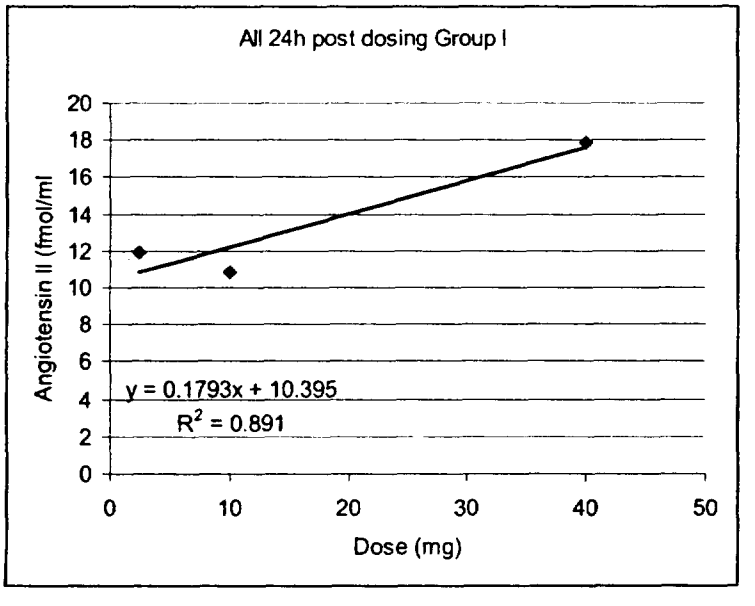


Figure 90: Angiotensin II 24 hrs post dosing 2.5, 10, and 40 mg – Study #866-04



21.7 Safety

This will be discussed under integrated safety section of NDA.

21.8 Pharmacodynamics: For additional information, see biopharmaceutics review.

SUMMARY AND CONCLUSIONS

Increased levels of renin and Angiotensin II levels were observed in salt-depleted hypertensive patients given CS-866 compared to placebo. The maximum concentration of renin occurred 3 hours after dosing. There is a roughly linear correlation between CS-866 dose and the concentration of the active metabolite, RNH-6270. The estimated half-life of the active metabolite RNH–6270 was 3-6 hours. There were no significant safety issues.

APPEARS THIS WAY
ON ORIGINAL

22.0 Risk benefit of olmesartan

22.01 Integrated Summary of Benefits and Risks

Olmesartan (CS-866) is a pro-drug that, after oral intake, is rapidly hydrolyzed to the active drug, RNH-6270, a selective AT_1 angiotensin II receptor antagonist. The clinical experience with olmesartan includes 3732 subjects in 11 studies, from which ??? were included in the safety analysis.

The generally accepted benefits of treating hypertensive patients are preventive: 1. prevention of target organ effects/damage (e.g. hypertensive renal disease, left ventricular hypertrophy, hypertensive heart disease/diastolic dysfunction/congestive heart failure); 2. Cardiac risk factor reduction; and 3. Prevention of stroke. These benefits are to be weighed against the risk of drug-related adverse events, either inherent in the angiotensin II (AT_1) antagonist class, or specific to this particular drug.

22.02 Benefits

The benefits of olmesartan are, according to the sponsor, the following:

- Olmesartan, unlike losartan, does not require metabolic conversion by cytochrome P450 for activation.
- RNH-6270 is eliminated, via urine and feces, essentially unchanged in humans. Therefore, no dosing adjustment is needed for patients with mild to moderate renal or hepatic impairment.
- RNH-6270 has an elimination half-life of about 13 hours, which would allow once daily administration.
- Bioavailability was not affected by food.
- In the 7 placebo-controlled studies, olmesartan in dosages of 2.5 mg, 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg QD was significantly more effective than placebo in lowering sitting and standing diastolic and systolic blood pressure at the primary study time point.
- Antihypertensive effect was seen as early as 1 week following initiation of treatment with maximum benefit occurring by 4 weeks. Significant differences in blood pressure compared to placebo could be seen within 2-4 weeks of starting treatment.
- The reduction in blood pressure was not associated with clinically significant changes in heart rate.
- The blood pressure lowering effect, with and without HCTZ, could be maintained up to one year of treatment. There was no evidence of tachyphylaxis with long-term treatment.
- There was no evidence of rebound after cessation of treatment.

In addition, please see the integrated review of efficacy.

22.03 Risks

According to the sponsor, the following safety profile was seen with olmesartan:

- The most common adverse events in patients treated with CS-866 were headache, upper respiratory tract infections, and influenza-like symptoms, all of which occurred at similar or slightly higher frequencies in patients treated with placebo. The only

adverse event that was reported in at least 1% of CS-866 treated patients and occurred at a significantly higher rate in the CS-866 group compared with the placebo group **was dizziness.**

- The rate of withdrawals due to adverse events was 1.6% in patients who received CS-866 whereas it was 0.7% with placebo.

The most frequently reported adverse event leading to discontinuation of therapy was dizziness, which resulted in withdrawal of 6 (0.2%) CS-866 treated patients and none of the placebo patients.
The question of mutagenicity and/or carcinogenicity remains outstanding and is being addressed by the Carcinogenicity Assessment Committee (CAC).
Small decreases in hemoglobin and hematocrit were noted; this finding is consistent with that seen in this drug class.
A higher incidence of marked CPK elevations were seen with olmesartan, compared with placebo (1.04% in the total CS-866 group vs. 0.39% with placebo). The sponsor relates most of these CPK elevations to physical activity (see Integrated Summary of Safety).
The overall rate of liver enzyme elevations appears to be similar to placebo; however, a dose-related effect of liver enzymes cannot be excluded (see Integrated Summary of Safety, Tables 41, 41a,41b).
Drugs that act directly on the renin-angiotensin system during the second and third trimesters of pregnancy have been associated with fetal and neonatal injury and death. Other than limited information about one pregnancy (see Integrated Summary of Safety), there is no human pregnancy experience and this drug should not be used in pregnancy.
It is also not known whether olmesartan is excreted in human breast milk. Because of the potential adverse effects on the nursing infant, olmesartan should not be prescribed to a breastfeeding mother.

Appendix 1: Inclusion criteria for clinical placebo-controlled trials

Placebo-Controlled Studies	
866-204 866-305 866-306	Male or female outpatients 18 years of age or older with essential hypertension (sitting DBP 100 to 115 mm Hg).
SE-866/06 SE-866/09	Male or female Caucasian outpatients aged 18 to 75 years with essential hypertension (sitting DBP 100 to 114 mm Hg).
SE-866/10 SE-866/11	Male or female Caucasian outpatients over 18 years of age with essential hypertension (sitting DBP 100 to 114 mm Hg).
866-204	Mean daytime DBP ≥90 mm Hg as determined by ABPM.
SE-866/06 SE-866/11	Mean 24-hour DBP ≥84 mm Hg as determined by ABPM, with at least 30% of DBP readings >90 mm Hg during daytime.
866-204 866-305 866-306	Female patients with a negative serum pregnancy test result at screening, not lactating, no plans to become pregnant during the study, and who met one of the following criteria: postmenopausal for at least 1 year (6 months for 866-204); hysterectomy or tubal ligation at least 6 months before giving informed consent; if of childbearing potential, willing to practice an adequate method of birth control throughout the entire study period.
SE-866/06 SE-866/09 SE-866/10 SE-866/11	Female patients with a negative pregnancy test result within 48 hours before enrollment, no plans to become pregnant during the study, and who met one of the following criteria: postmenopausal for at least 1 year; hysterectomy or surgical sterilization at least 3 months before enrollment; if of childbearing potential, willing to practice an adequate method of birth control throughout the entire study period.

Appendix 2: Clinical Pharmacology and Phase 2/3 Studies of Olmesartan

oavailability/Bioequivalence	Protocol	N	n•	Dose (mg)	Exposure
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	866-108	24	24	20 (tab), 20 (PO susp), 16 RNH-6270 (iv), 16 RNH-6270 PO	Single dose, Crossover (4x)
A Radio-labelled, Pharmacokinetic and Dose Recovery Study of the [14]C-labelled Oral Angiotensin II-Antagonist CS-866 in Healthy, Adult Volunteers	SE-866/13	6	6	20	Single dose
A Randomized, Open-Label, Two-Way Crossover Bioequivalence Study of CS-866 Tablets in Healthy Adult Volunteers	866-116	30	30	20 (different formulations)	Single dose, Crossover (2x)
	SE-866/12	24	24	20 (total dose, administered as different formulations)	Single dose, crossover (4x)
Bioequivalence Study of CS-866 Tablets (10 mg) in Healthy, Male Volunteers	SE-866/22	24	24	10 (different formulations)	Single dose, Crossover (4x)
Pharmacokinetic (PK) Studies					
Baseline PK Studies, Initial Safety and Tolerability: Healthy Volunteers					
Δ Randomized, Double-Blind, Placebo-	866-101	40	25	10, 20, 40,	Single dose

Bioavailability/Bioequivalence	Protocol	N	n•	Dose (mg)	Exposure
Controlled Ascending, Single Dose, Tolerance Study of Oral CS-866 in Healthy Adult Male Volunteers				80, 160	
A Randomized, Double-Blind, Placebo-Controlled Ascending, Multiple Dose, Safety and Tolerance Study of Oral CS-866 in Healthy Adult Male Volunteers	866-102	30	30	20, 40, 80	Multiple dose (10 days)
An Open-Label, Ascending Single Dose, Safety and Tolerance Study of Intravenously Administered RNH-6270 in Healthy Adult Male Volunteers	866-107	34	34	1, 2, 4, 8, 16, 32 RNH-6270 (iv)	Single dose
Tolerability and Safety of the Angiotensin II-Antagonist CS-866 in Healthy, Male Subjects (Single Dose)	SE-866/01	63	42	10, 20, 40, 80, 160, 240, 320	Single dose
Tolerability and Safety of the Angiotensin II Antagonist CS-866 in Healthy, Male Subjects (Multiple Dose)	SE-866/02	24	18	40, 80	Multiple dose (14 days)
A Pharmacokinetic Dose Proportionality Study Following Multiple Daily Doses of 2.5, 5, 10, and 40 mg CS-866 in Healthy Volunteers	SE-866/21	30	30	2.5, 5, 10, 20, 40	Multiple dose (7 days), Crossover (5x)
Phase I Clinical Study of CS-866 - Preliminary Investigation	141-010	10	10	1, 2, 4, 8, 16, 32	Single dose
Phase I Clinical Study of CS-866 - Single Administration in Fasting	141-011	27	18	4, 8, 16,	Single dose
Phase I Clinical Study of CS-866 - Repeated Administration	141-041	10	7	16	Multiple dose (7 days)

•n=received olmesartan (CS-866)

	Protocol	N	n•	Dose (mg)	Exposure
Phase I Clinical Study of CS-866 - 40 mg Repeated Administration Study	143-005	10	7	40	Multiple dose (8 days)
Phase I Study of CS-866 - Determination of Unchanged Compound in Blood and Glucuronide in Urine from Healthy Volunteers – A Pilot Study in Healthy Volunteers	GR 142-026	??	??	8, 16, 24	??
Population Subsets(Intrinsic Factors)					
A Comparative Pharmacokinetic Study of CS-866 blets and RNH-6270 Intravenous Solution	866-109	24	24	10 (PO CS-866), 8 (IV RNH-6270)	Single dose (PO), then 10 day washout

dministered to Patients with Impaired Liver and Healthy Volunteers					followed by single dose (iv)
A Comparative Pharmacokinetics Study of CS-866 Tablets in Healthy Adult Male and Female Volunteers	866-110	35	35	20	Single dose
Multiple Dose Tolerability, Safety and Pharmacokinetic Study of the Angiotensin II-Antagonist CS-866 in Young and Elderly Hypertensive Patients	SE-866/07:	37 ‡	24	80	Multiple dose (10 days)
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	SE-866/14:	44 †	36	10	Multiple dose (14 days)
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	SE-866/16	34	34	10	Multiple dose (7 days)
Population Subsets (Extrinsic Factors)					
A Comparative Bioavailability Study of CS-866 blets in the Presence and Absence of Food in ealthy Adult Male Volunteers	866-103	25	25	20	Single dose, crossover (3x)
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	SE-866/05	24	24	20	Multiple dose (5 days), crossover (2x)
The Effect of the Combination of the Oral Angiotensin II-Antagonist CS-866 and Warfarin on Pharmacodynamics, Pharmacokinetics and Safety in Healthy, Male Subjects	SE-866/08	26 *	24	40	Multiple dose (7 days), Crossover (2x)
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	SE-866/15	24	24	20	Multiple dose (7days), crossover (2x)
Phase I Clinical Study of CS-866-Effects of Meals on Bioavailability	141-012	6	6	8	Single dose, crossover (2x)
Human Pharmacodynamic (PD) Study Reports					
Study: Comparison of the Angiotensin II-ntagonist CS-866 with the ACE Inhibitor	SE-866/03	16	16	2.5, 5, 10, 20, 40	Single Dose, crossover (4x)

ıalapril in Healthy .Ⅵale Subjects Challenged with Angiotensin I (Single Dose)					
Study SE-866/04: Effects of the Angiotensin II-Antagonist CS-866 in Salt-Depleted Hypertensive Patients (Single Dose)	SE-866/04	17 ‡	16	2.5, 5, 10, 20, 40, 80	Single Dose, crossover (4x)

•n=received olmesartan (CS-866)

†8 subjects dropped on Day 1 (7 = BP criteria, 1=Consent) prior to taking study medication.

‡One patient dropped during run-in. *2 dropped out prior to receiving study medication.

Appendix 2 continued

	Protocol	N	n•	Dose (mg)	Exposure
A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of CS-866 Using Ambulatory Blood Pressure Monitoring in Hypertensive Patients	866-204	334	286	5, 20, 80	8 Weeks
A Randomized, Placebo-Controlled, Parallel-Group Study of CS-866 with Long-Term Safety Evaluation in Patients with Essential Hypertension	866-305	526	435	2.5, 5, 10, 20, 40	8 Weeks + long-term double-blind extension (through Month 12)
.ʌ Randomized, Placebo-Controlled, Dose-Titration Study of CS-866 with Long-Term Safety Evaluation in Patients with Essential Hypertension	866-306	457	341	5, 10, 20	8 Weeks +Long-term Open Label period (6 Months)
Safety, Tolerability and Efficacy of the Angiotensin II-Antagonist CS-866 in Patients with Mild to Moderate Hypertension	SE-866/06	76	50	20, 80	6 Weeks
A Multi-Centre Double-Blind Dose-Finding Study of Oral CS-866 Versus Placebo in Patients with Mild to Moderate Hypertension	SE-866/09	792	682	2.5, 5, 10, 20, 40, 80	12 Weeks
A Multi-Centre Double-Blind Long Term, Safety, Efficacy and Tolerability Study of the Oral Angiotensin II-Antagonist CS-866 in Patients with Mild to Moderate Essential Hypertension	[redacted]	619	526	5, 10, 20	12 Weeks (+ 2 week placebo wash-out +Long-term extension (52 weeks))
Evaluation of the Antihypertensive Effect of Once-Daily Therapy of the Oral Angiotensin II-Antagonist CS-866 Versus Placebo Using Non-Invasive 24-Hour Ambulatory Blood Pressure Monitoring	SE-866/11	292	221	2.5, 5, 10	12 Weeks

Comparison of the Efficacy and Safety of the Oral Angiotensin II-Antagonist CS-866 with That of Atenolol in Patients with Moderate to Severe Hypertension Under Persistent Treatment of Hydrochlorothiazide	SE-866/17	328	164	10, 20	12 Weeks
A Multi-Centre, Double-Blind, Efficacy, Tolerability and Safety Study of the Oral Angiotensin II-Antagonist CS-866 Versus Atenolol in Patients with Mild to Moderate Essential Hypertension	SE-866/18	326	165	10, 20	12 Weeks
A Multi-Centre, Double-Blind, Efficacy, Tolerability and Safety Study of the Oral Angiotensin II-Antagonist CS-866 Versus Losartan in Patients with Mild to Moderate Essential Hypertension	SE-866/19	316	160	10, 20	24 Weeks
A Multi-Centre, Double-Blind, Efficacy, Tolerability and Safety Study of the Oral Angiotensin II-Antagonist CS-866 Versus Captopril in Patients with Mild to Moderate Essential Hypertension	SE-866/20	291	148	5, 10, 20	12 Weeks

Appendix 3: Patient Accounting:Clinical Pharmacology Studies

Clin. Pharm.	X-0ver	Placebo	CS-866	Comparator	Total
866-101		15	25		40
866-102		9	21		30
866-103		0	25		25
866-107 (RNH)		0	34		34
866-108	X	0	24		24
866-109		0	24		24
866-110		0	35		35
866-116	X	0	30		30
SE-866/01		21	42		63
SE-866/02		6	18		24
SE-866/-03	X	16	16	8	16
SE-866/04	X	16	16		16
SE-866/05		0	24		24
SE-866/07		12	24		36
SE-866/08	X	24	24		24
SE-866/12		0	24		24
SE-866/13		0	6		6
SE-866/14		0	36		36
SE-866/15	X	24	24		24
SE-866/16		0	34		34
SE-866/21		0	30		30
SE-866/22		0	24		24
Total		143	560	8	623

*Total does not equal the "sum of the parts" because of 4 crossover studies, where subjects are counted as both placebo and active treatment.

Appendix 4: Other Clinical Pharmacology Studies: Not included in integrated safety database

Study	X over	PBO	CS-866	Comparator	Total
	--	0	10	--	10
	--	9	18	--	27
	--	3	7	--	10
	--	3	7	--	10
	--	0	6	--	6
Total	--	15	48	--	63

Appendix 5: Patient Accounting—Phase 2/3 trials

Phase 2/3	Placebo	CS-866	Comparator	CS-866 + HCTZ	Total
866-204	48	286			334
866-305	91	435			526
866-306**	116	341			457
SE-866/06	26	50			76
SE-866/09	110	682			792
SE-866/10	93	526			619
SE-866/11	71	221			292
SE-866/17		164	164		328
SE-866/18		165	161		326
SE-866/19		160	156		316
SE-866/20		148	143		291
SE-866/23*		187	194		381
Total without SE-866/23	555	3178	624		4357
Total including SE-866/23	555	3365	818		4738

*Not included in the safety database. **These numbers refer to the short-term phase

Appendix 6: Patient Narratives
INTEGRATED SAFETY NARRATIVES
Narratives of Deaths

Four olmesartan -exposed subjects died, and in no case was the death attributed by the investigator to study treatment. I have found no compelling evidence for rejecting their attributions. The following are the reported case narratives:

D1- Patient 000398, a 70 year old Caucasian female with a history of congenital nasopharyngeal hemangioma, and Parkinson's disease received olme 20 mg qd for about 9 months in study SE-866/10. She was then hospitalized with gastrointestinal (GI) bleeding and anemia, and olme was discontinued. Bleeding was believed to be sourced in the nasopharyngeal hemangioma. During the hospitalization her cerebral condition declined. Oral feeding became difficult, a gastrostomy tube was introduced, and the patient's condition deteriorated suddenly. An ileus was diagnosed and the patient died during preparation for exploratory surgery. Autopsy was refused. The suspected diagnosis was GI perforation and subsequent shock. The investigator judged both ileus and anemia as not related to the study medication, and reasonably so.

D2- Patient 000293, a 68 year old Caucasian male with a history of hypertension and dyspepsia, received olme 10 mg qd in study SE-866/19. One week after randomization he experienced worsening of pre-existing epigastric pain, and self-terminated olme about 2 weeks later. Weight

loss and difficulty in swallowing solid food led to a diagnosis of esophageal carcinoma, from which the patient died. The investigator judged this event to be unrelated to olme, and reasonably so.

D3- Patient 000153, a 73 year old Caucasian male with a history of hypertension and cardiomegaly received olme at a highest dose of 20 mg qd in combination with HCTZ 12.5 mg qd in study SE-866/19. Three months later he experienced left hemiparesis and was discontinued from the study. He was diagnosed with CT-documented cerebral infarct, and new atrial fibrillation. His recovery was slow, and he died 4 months later. The investigator reportedly commented that lack of efficacy during the trial may have remotely contributed to the stroke. Elsewhere he noted that Afib was considered the probable cause of the stroke, and reasonably so.

D4- Patient 001040 (a 40 year old Hispanic male who received 5 mg olme QD in study 866-204) was murdered.

Narratives of Dropouts
Erectile Dysfunction
Erectile dysfunction was the cause of discontinuation in two men exposed to olme at 5-40 mg/d. One[3] was a 55 year old who complained of this symptom beginning on day 14. Impotence persisted for more than 2 months after discontinuation of drug. His concomitant simvastatin exposure was plausibly contributory, and the investigator judged the relationship to olme as remote. The other[4] was a 54 year old whose impotence started after 9 days of treatment. Although he discontinued olme after 57 days it appears that this event actually resolved on treatment, albeit during the last day of treatment. The investigator reported the event as possibly related to treatment.

Changes in liver functional indices:

The overall rate of dropout associated with increases in liver functional indices was comparable in olme and control groups (i.e. 0.2-0.3%).

Increases in GGT, SGOT, and SGPT resulted in discontinuation of 2 patients exposed to olme at 10-80 mg/d[5]. Pre-treatment GGT was already elevated in both. Elevations continued 3-6 months after drug discontinuation, and the events were investigator-attributed to alcohol use.

Increased CK resulted in discontinuation of two patients[6] exposed to a highest olme dose of 20 mg/d. In one of these (patient 003313) CK was already 2.8 times the ULN at pre-treatment (566 U/L), and it rose to 11.6 times the ULN at week 4, and then post-discontinuation fell to below the

[3] patient 002330 in study 866-305

[4] patient 003338 in Study 866-306

[5] patient 000780 from Study SE-866/09; and patient 001135 from Study 866- 204.

[6] patients 003313 and 003077 in Study 866-306.

highest pre-treatment level. Possible nondrug causes of this CK elevation include physical activity (there was temporal coincidence with the initating of a jogging regimen), and concomitant disease (the patient was discovered to have a CNS tumor (meningioma) plausibly contributing to CK elevation).
The investigator attributed this as only remotely relatable to drug.

In patient 003077 the CK was, at 566 U/ L, already more than 3 times the ULN at pre-treatment, but it rose to 1373 U/L at week 4. CK returned to below the pre-treatment level, and yet thereafter the investigator discontinued drug for reasons attributed to elevated CK. Also, lovastatin exposure (10 mg QD) was potentially confounding.

Patient 433 in Study SE-866/18 was a 50 year old Caucasian male who received olme 10 mg. Pre-treatment (one month prior) LFTs were normal, although there is a suggestion of pre-treatment gastrointestinal complaint since hepatic and abdominal sonography was undertaken (for reasons that are not clear) during the placebo run-in; these diagnostics yielded normal results.

Although total bilirubin remained normal throughout the study, there were subsequently various on-treatment transaminase and alkaline phosphatase elevations. At post-randomization day 5 days there were elevations of SGPT (1.5 times ULN) and SGOT (2.0 times ULN). At post-randomization week 4 there were considerably higher levels of SGPT (22.0 times ULN), SGOT (10.4 times ULN), along with elevation of GGT (4.9 times ULN) and alkaline phosphatase (1.7 times ULN). Olme was discontinued the next day, and a repeat sonogram was again normal. Post-discontinuation followup data were as follows: Two months after the last olme dose the SGPT had fallen to 7.6 times ULN, SGOT had fallen to 3.9 times ULN, GGT had fallen to 1.4 times ULN, and the alkaline phosphatase had returned to normal. By 4 months after discontinuation the GGT had also normalized, and lesser elevations of SGPT (5.0 times ULN) and SGOT (2.6 times ULN) were still present. Twelve months after discontinuation the SGPT, SGOT, GGT, and AP were all within normal limits. There was no hepatitis testing or additional diagnostic evaluation. The patient denied alcohol use. The investigator attributed the event as definitely related to olme, based on the lack of exposure to known hepatotoxins and the temporal relationship of increases and subsequent decreases in the enzymes. A potentially interacting factor was the suggestion of gastrointestinal symptomology prior to randomization.

Dizziness
Patient 003378 (Study 866-306) was a 64 year old Caucasian male taking 20 mg olmesartan. At week 8 he experienced severe transient dizziness that was judged to be definitely associated with olmesartan. BP was 110/70 mm Hg, and the symptom resolved that day, but the patient desired to discontinue the trial. Two weeks earlier systolic BP had been observed to fall with orthostatitic postural change (mean standing BP was 125/86 mm Hg, while sitting BP was 109/81).

A 68 year old Caucasian female with history of diabetes mellitus received olme 10 mg/d and had severe dizziness on day 12. No symptom-associated BP is available. She was withdrawn on day 14, and dizziness resolved 1 day later (at which time sitting DBP was 90 mm Hg). The event was investigator-attributed as remotely related to olme.

Patient 000406 (Study SE-866/20) was a 51 year old Caucasian female who received olme 5 mg/dy. On day 3 she experienced severe dizziness and severe dry mouth. Associated BPs are not available. Drug was discontinued and dizziness resolved 11 days later (dry mouth resolved within just two days). Mean sitting DBP was 111 mm Hg the day after medication was discontinued (i.e. higher than pre-treatment). The investigator assessed both events as definitely related to olme.

Breast cancer

One patient was diagnosed with breast cancer after about a year of receiving olmesartan 5 mg/d. Another patient was diagnosed with breast cancer after 113 days of 40 mg/d olmesartan. One other woman (patient 000125 in study SE-866/11) received a breast cancer diagnosis after 64 days of olme 10 mg/d. It is plausible that the disease clinically pre-existed exposure to olme since she had elevated serum alkaline phosphatase levels before (and during) olme exposure, which resolved post-mastectomy. The investigator reported that he believed the tumor was likely to have been present prior to the study, and that it had (for reasons that apparently were not argued in detail) a remote possibility of having been affected by olme.

Rash

Discontinuations for rash, pruritis, or urticaria were less frequent in the olme groups (0.1%) than in controls (0.3%). Nonetheless there are data supportive of olme-induced rash, insofar as there was a case with positive de-challenge and positive re-challenge.

A 60 year old Caucasian male (study 866-305's patient 002449) took olme 40 mg/d with resultant onset of welts and pruritus on day 25. There was no facial edema, involvement of the mucosa, fever, or lymphadenopathy. The welts gradually resolved after olme's discontinuation, re-appeared within 2 hours of re-challenge, and then gradually resolved again.

A 49 year old Caucasian female (patient 000287 of study SE- 866/19) had
a history of rhinitis and eczema. She experienced urticaria 14 days after beginning olme 10 mg/d, and these resolved without specific treatment 18 days after discontinuation.

A 49 year old Caucasian female (patient 000172 of study SE-866/20) experienced a generalized pruritic rash 3 days after beginning olme 5 mg/d.
Olme was discontinued for this 43 days later, and the rash resolved in the subsequent 5 days.

A 53 year old Caucasian female with history of asthma and ulcerative colitis
(patient 000351 of study SE-866/19) reported a rash 4 days after starting
olme 10 mg/d, and this drug was discontinued 18 days later. The rash resolved 22 days after discontinuation. There is at least theoretic possibility of a confounding rash-contributing effect of her chronic mesalamine therapy.

Appendix 7: Narratives of serious adverse events

Cerebrovascular accident

Patient 153 from study SE866-19 was a 73 year old Caucasian male with history of enlarged heart (not further specified) and newly documented atrial fibrillation. There was no previous history of cardiovascular or cerebrovascular events, but a family history of fatal stroke in the subject's mother. He received olme 20 mg/d and HCTZ 12.5 mg/d, and developed hemiparesis on day 90 with CT-

documented cerebral infarct. Atrial fibrillation was considered the probable cause of this event. He was begun on warfarin with only a slow and partial subsequent recovery, and then death four months after discontinuation of olme. The investigator did not attribute the stroke to olme, but did point to the possibility of a remote contribution of antihypertensive inefficacy during the trial (pre-treatment BPs of 170/102 and maximum on-therapy values of 172/106).

Angina

Angina resulted in hospitalization of 4 olme-treated patients and no placebo patients. Three of these patients discontinued. After evaluation, chest pain was deemed non-cardiac in one, and revealed no evidence of active cardiac ischemia in 2 others. One patient was observed to be evolving an acute MI (patient 003225 in Study 866-306, who received olme 20 mg/d). Another[7] (a 71 year old woman with a history of hyperlipidemia and cigarette smoking) seemed to have had transient cardiac ischemia secondary to a sudden rise in BP to 180/110 mm Hg while taking olme 20 mg/d.

Narratives from first safety update

Narratives of Deaths

During the period 1/2/00- 8/1/00 one olme-associated death was reported among subjects in whom therapy has been as yet unblinded.

The olme-associated death occurred in patient 100847/0427 of study [redacted] an 81 year old Caucasian female with history of generalized atherosclerosis. On day 262 of therapy with olme 5 mg/d patient experienced a cerebral infarction and dropped out of the study. At one point (?when) she was noted to have persistent atrial fibrillation. She experienced generally adequate BP control during the study. The general condition of the patient improved, but about 2 months later the patient died with death attributed to "an influenza-type reaction".

One additional death was reported in a subject whose therapy is as yet blinded (patient 100711/0793 from study [redacted] whose death was apparently in the context of a fractured femur and intestinal ischemia), and another death was reported in a placebo patient.

[7] patient 000819 in Study SE- 866/10.

Appendix 8: Narratives of Dropouts or other Serious Adverse Events
Transient Ischemic Attack

Patient S70123/8207 from study 866-321 was a 67 year old Caucasian female with a history of diabetes mellitus who received once daily treatment with olme 20 mg plus HCTZ 12.5 mg. About 3 weeks after enrollment she experienced a CT scan-negative transient ischemic attack (TIA) during which BP was 203/112. BPs had reportedly averaged 146- 56/70-84 during the trial. She was anticoagulated with heparin and warfarin, and neurological symptoms disappeared completely the next day without recurrence, although study drugs were discontinued. The investigator, on the basis of the one emergency department BP reading, judged this AE to be possibly related to lack of efficacy of study medications, although the case for this is weakened by evidence of good prior BP control.

Elevated Liver Enzymes

Patient T- I from study 146-006 was a 69 year old Asian female with history of daily ethanol consumption, pre-treatment AST elevation (for at least the prior 4 months), chronic GGT elevations, and "biliary polyp" (undefined). She received olme 10 mg/d plus amlodipine 5 mg/d, and after about 9 weeks she dropped out with asymptomatic LFT elevations during which the ratio of AST/ALT was greater than 2. There was sonographic evidence of slightly fatty liver, but reportedly no signficant history of bilirubin elevation, alkaline phosphatase elevation, recent foreign travel, blood transfusion, or positive hepatitis B or C serology. Peak levels were as follows: AST 975 U/L (ULN <33 U/ L), ALT 315 U/L (ULN <42 U/ L) and LDH 841 U/L (ULN <229 U/ L). These changes reportedly resolved within 5 days. It remains ambiguous as to whether olme had any causal contribution since the AST/ALT findings are suggestive of at least some component of ethanol-induced hepatitis, and amlodipine alone has been associated with cholestasis as well as transient liver enzyme elevations.

It is not clear whether this was treatment emergent.

Appendix 9: References
Selected Review Articles

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