ıarmacodynamics, Pharmacokinetics and ɔafety in Healthy, Male Subjects					
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-Antagonist CS-866 with the ACE Inhibitor Enalapril in Healthy Male Subjects Challenged with Angiotensin I (Single Dose)	SE-866/03	16	16	2.5, 5, 10, 20, 40	Single Dose, crossover (4x)
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.

ase 2/3 Studies:	**Protocol**	**N**	**n•**	**Dose (mg)**	**Exposure**
.. Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of CS-866 Using Ambulatory Blood Pressure Monitoring in Hypertensive Patients	866-204	33 4	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	52 6	435	2.5, 5, 10, 20, 40	8 Weeks + long-term double-blind extension (through Month 12)
A Randomized, Placebo-Controlled, Dose-Titration Study of CS-866 with Long-Term Safety Evaluation in Patients with Essential Hypertension	866-306	45 7	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	SE-866/09	79 2	682	2.5, 5, 10, 20, 40, 80	12 Weeks

ild to Moderate Hypertension					
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	SE-866/10 (+	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
A 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 sential 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

1.10 Mechanism of action

Olmesartan medoxomil is rapidly and completely bioactivated by ester hydrolysis to olmesartan during absorption from the gastrointestinal tract. Olmesartan appears to be eliminated in a biphasic manner with a terminal elimination half-life of approximately 13 hours. The pharmacokinetics of olmesartan is linear following single oral doses of up to 320 mg and multiple oral doses of up to 80 mg. Steady state levels of olmesartan are achieved within 3 to 5 days and no accumulation in plasma occurs with once-daily dosing.

Olmesartan inhibits the pressor effects of angiotensin I infusion and following administration of single doses of 2.5 to 40 mg, the pressor response was significantly reduced compared to placebo. The duration of the inhibitory effect was dose-related.

The pressor effect was inhibited by ~ 80-95% at peak with up to 90% inhibition persisting for 24 hours.
Plasma concentrations of angiotensin I, angiotensin II and plasma rennin activity (PRA) increased after single and repeated administration of olmesartan medoxomil to healthy subjects and hypertensive patients. Repeated administration of up to 80 mg olmesartan medoxomil had minimal influence on aldosterone levels and no effect on serum potassium. For individual reviews of studies see Biopharm and clinical pharmacology reviews in this NDA.

The volume distribution of olmesartan is approximately 17 L. Olmesartan is highly bound to plasma proteins (99%) and does not penetrate red blood cells. The protein binding is constant at plasma olmesartan concentrations well above the range achieved with recommended doses.

The peak plasma concentration (C_{max}) of olmesartan after oral administration is reached after 1 to 2 hours. Following the rapid and complete conversion of olmesartan medoxomil to olmesartan during absorption, there is virtually no further metabolism of olmesartan. Total plasma clearance of olmesartan is 1.3 L/h, with a renal clearance of 0.6 L/h. Approximately 35% to 50% of the absorbed dose are recovered in urine while the remainder is eliminated in feces via the bile.
Studies on mechanism of action of CS-866 are presented in Table 7.

Table 7: Studies on mechanism of action, clinical pharmacology, PK/PD.

Study	Design	Objective	N	Population	Synopsis of Review
866-21	Parallel/5 way crossover	Dose linearity PK	30	HV	>10mg CS866 was less than proportional to dose range (2.5 –40mg)
-01	R,DB,PC,SD	Dose linearity PK	63	HV	Near proportionality observed over dose range, 10,20,40,80,160,240,320mg. CS-866 resulted in increased plasma AII and Renin levels but not Angiotensin I or aldosterone levels
-101	R,DB,PC,SD	Dose linearity PK	40	HV	Dose dependent increases for AUC, Cmax,Ae
-102	R,DB,PC, MD	Dose linearity PK	29	HV	Dose dependent accumulation of drug at steady state
-02	R,DB,PC, MD	PK/PD	24	HV	~10% of drug renally excreted
-05	R,OL,2-way crossover	Antacid effect	24	HV	No differences in elimination in antacid combination (t1/2)

Study	Design	Objective	N	Population	Synopsis of Review
-16	OL. PK	Renal impaired	34	RI+HV	Exposure at steady state was ~3 fold higher in renal impaired (CLcr<20ml/min) p=0.0001
-109	OL,2 way crossover	Hepatic impaired	24	HI+HV	Liver impaired patients had increased AUC_0- ∞ (p<0.001) compared to matched controls. Similarly increased urinary recovery of RNH-6270 in impaired group.
-07	R,DB,PC,PL	Young/Elderly	36	HY	Accumulation of RNH-6270 ~33% higher in elderly (p=0.006) compared to young
-14	Analyte	Young/Very Elderly	42	HY	t1/2 prolonged in very elderly compared to young; (p<0.03)
-110	OL,SD	Gender PK	35	HY	10-15% urinary increase in females (N=18)
-08	R,DB,PC,2 way crossover	Warfarin interaction	24	HV	PK of R &S enantiomers unchanged+co-administration of CS- 866
-15	R,DB,PC,2 waycrossover	Digoxin interaction	24	HV	No significant effect on PK of digoxin when co-administered.
-04	R,DB,PC,4 waycrossover	Salt depleted patients	16	HY	Increased renin and AII levels in patients given CS866 compared to placebo; max levels occurred 3 hours after dosing
-03	R,DB,4-way crossover	CS 866 Vs Enalapril 2.5mg-40mg	15	HY	< 20mg of CS866 inhibited pressor response better than enalapril (p=0.055); No effect >20mg
-012 &103	R,OL, 3 way crossover	Food effect	6/24	HV	Minimal to no food effect
RAM-140-053		Plasma protein binding (in vitro)	-	-	Plasma protein binding of RNH-6270 >99% regardless of renal function
GR-144-063		In vitro drug interaction	-	-	---

HV=Healthy volunteers; HY=Hypertensives; RI=Renal impaired; HI=Hepatic impaired
SD=single dose MD =multiple dose; OL=Open label;

2.0 Integrated review of efficacy of CS-866

The efficacy database analyzed for this review includes data from all placebo controlled clinical studies. In evaluating the overall efficacy of olmesartan, the Medical Reviewer used the electronic archive, including the SAS database, supplied by the Sponsor with the submission of NDA 21-286. In addition to reviewing data in the Integrated summary of efficacy, the Medical Reviewer looked at efficacy data of all individual studies.

2.01 Results of antihypertensive therapy with CS-866

The effect of CS-866 in dosages of 2.5mg, 5 mg, 10 mg, 20 mg, 40 mg, and 80 mg administered once daily to patients with hypertension was statistically significantly superior to placebo in lowering sitting diastolic and sitting systolic blood pressure ($p<0.001$ for each dose at pre-specified primary time points). Additionally, it was also effective in lowering standing systolic blood pressure ($p<0.002$) at primary study time points (weeks 6, 8, and 12) compared to placebo. Dose related effects were observed for SiDBP and StDBP in all the controlled studies (Figures 1a and 1b; pp 15 and 17 below).

Based on the primary analysis group of 2,693 ITT patients, the treatment effect due to CS-866 was evident by week 1 at 2.5 mg dose. After 6 to 12 weeks of therapy there was a statistically significant lowering of diastolic blood pressure compared to placebo (Figures 1a, 1b, and 2). A dose response curve was observed from 2.5mg to 20mg and then leveled off in Caucasians, whereas in blacks the dose response extended to 40 mg for SiDBP (Figures 7c, 9,10). There is no significant difference in heart rates when data are combined for all the treated groups compared to placebo (Table 8) but there appears to be a dose-related decrease in pulse rate in non-blacks (Figure 3).

Table 8: Mean change-baseline-trough at primary study time points – Total of 2, 693 ITT patients

Vital signs	Plcbo	2.5mg	5mg	10mg	20mg	40mg	80mg
N	548	281	598	447	436	195	188
SiDBP	-6.8	-10.3	-11.2	-13.9	-13.9	-13.8	-14.1
SiSBP	-5.5	-11.9	-12.9	-16.9	-17.6	-18.6	-18.5
p-value*		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
HR	-0.3	-0.4	-0.6	-1.3	-0.9	-1.4	-1.4
p-value		1.0	0.885	0.331	0.960	0.828	0.953
StDBP	-5.80	-8.60	-9.09	-11.0	-11.47	-12.67	-13.19
StSBP	-7.43	-11.04	-12.55	-15.30	-15.41	-17.89	-18.59
p-value*		<0.01	<0.001	0.112	0.361	0.998	<0.001

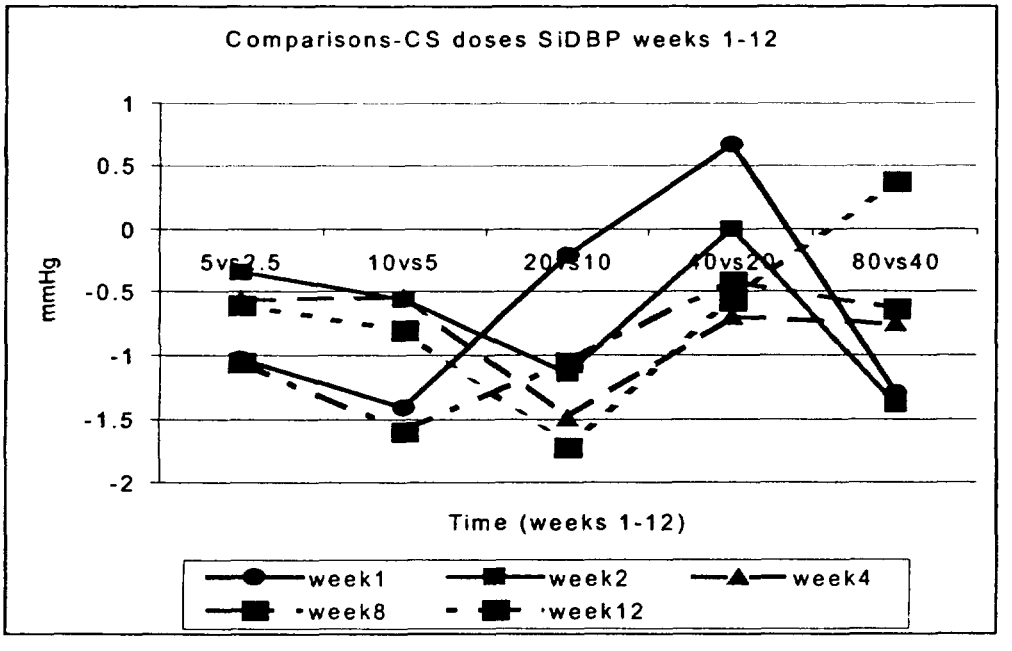
*p-value for diastolic BP. See Figure 7

2.02 Anti-hypertensive effect of CS-866 continued

In all controlled studies of olmesartan, antihypertensive effect was evident as early as 1 week after initiation of therapy for sitting and standing blood pressure changes (Figures 1b, 2, and 6).

Two weeks after initiation of treatment with all doses of CS-866 used in the trials, a dose effect on SiDBP was observed compared to placebo (Figures 1a,1b & 3). Similarly a dose effect was seen for standing diastolic blood pressure. At the primary efficacy endpoint the placebo-subtracted effects for 10mg and 20 mg doses were similar (-7.1mmHg) (Table 8) suggesting that these 2 dose levels are indistinguishable. Furthermore, pairwise comparisons between the two doses showed no statistical significance (p=0.947) using cuff measurements. However, using ABPM these two doses are different (Figures 7a and 7b). To determine whether 10 or 20 mg dose is preferable for initiation of treatment, ANCOVA model with centralized baseline vital sign as covariate, and study and dose as factors was used. The p-value based on t-test comparing the difference in effect between 20 mg and 10 mg at week 12 showed a statistically significant difference (p=0.004) (Figure 1a). Therefore, 20 mg dose can be used as a starting dose because it is preferable to 10 mg dose. Comparisons between 40mg and 20mg, on one hand and 80 mg and 40 mg on the other hand showed no statistical differences (p=0.51 and 0.698, respectively). Assuming 20 mg olmesartan is the starting dose of choice in mild-to-moderate hypertension, the patient's blood pressure should be monitored every 2 weeks. If uncontrolled, the patient should be titrated up to 40 mg of drug. In uncontrolled patients, HCTZ 12.5 mg or 25mg may be added to olmesartan and the patient monitored every week for 2 weeks before a final dosing regimen is established. The long- term (12 months) studies using 20 mg monotherapy showed that treatment effect can be maintained for at least 1 year. The drug was found to be safe and tolerable.
The response rates are presented in Table 14.
Based on data from relatively small numbers of Blacks and Hispanics (~8 %), 10 mg and 20 mg doses showed no statistically significant treatment effect at primary end points compared to placebo (Figures 8 and 9). However, it would appear clinically reasonable to initiate treatment in this group with 20 mg and then titrate upwards to 40mg, and if uncontrolled add HCTZ (Figures 7c, 8 and 9; pages 23-24).

Figure 1a: Comparisons of CS-866 doses in SiDBP-ITT- ISE



Pairwise comparisons for the different doses are presented in Tables 9 and 10.

Table 9: Pairwise comparisons-trough SiDBP: change from baseline at end points

		Plcbo (548)	CS-866 (2145 patients)				
	N /LS Mean	Plcbo	2.5mg	5mg	10mg	20mg	40mg
Placebo	548 /–5.62						
2.5	281 /-9.61	<0.001					
5	598 /-9.81	<0.001	1.0				
10	447 /-11.66	<0.001	0.019	0.006			
20	436 /-12.23	<0.001	<0.001	<0.001	0.947		
40	195 /-13.11	<0.001	<0.001	<0.001	0.396	0.883	
80	188 /-14.02	<0.001	<0.001	<0.001	0.029	0.176	0.938
P values are based on Tukey-Kramer test. LS Mean based on ANCOVA model.							

Table 10: Change from baseline at efficacy variable time point: Pairwise comparisons-trough – SiSBP. Integrated summary of efficacy.

		Plcbo (548)	CS-866 (2145 patients)				
	N /LS Mean	Plcbo	2.5mg	5mg	10mg	20mg	40mg
Placebo	548 /–5.62						
2.5mg	281 /-11.26	<0.001					
5mg	598 /-12.39	<0.001	0.902				
10mg	447 /-14.48	<0.001	0.019	0.130			
20mg	436 /-115.12	<0.001	<0.003	0.015	0.990		
40mg	195 /-17.58	<0.001	<0.001	<0.001	0.082	0.303	
80mg	188 /-17.97	<0.001	<0.001	<0.001	0.050	0.167	1.000
p-values are based on Tukey-Kramer test. LS Mean based on ANCOVA model.							

2.03 Comparator studies

Except for captopril that was less effective than CS-866 (p=0.01), all comparators studied showed no significant differences in efficacy and responder's rate compared to olmesartan (Tables 11 and 12).

Table 11: Mean change-baseline at trough sitting dBP at week 12 - ITT population

	CS-866(mmHg decrease)	Comparator (mmHg decrease)	Confidence Interval (2 sided -95%)
SE-866-17	-17.3	-17.2 Atenolol + HCTZ	1.23
SE-866-18	-14	-14.3 Atenolol	-1.2,1.7
SE-866-19	-10.6	-8.5 Losartan	-3.6,-0.6
SE-866-20	-9.9	-6.8 Captopril	-4.8,-1.5
(SE-866: upper limit of the 97.5% CI. 18,19, 20: 2 sided 95% CI.) Balanced demographics between the groups.			

Table 12: Responder's Rate - ITT population – CS-866 compared with comparators

Visit	CS-866	Comparator	2 sided 95% CI
Week 24	113/152 (72%)	Losartan 108/152 (71%)	-9.6,10.5 NS
Week 12	77/144(53%)	Captopril 54/142 (38%)	4.0,26.9 p=0.01
Week 12	128 (78%)	Atenolol 127 (79%)	NS
Week 12	CS 866+HCTZ 141/164(86.0%)	Atenolol +HCTZ 139/164 (84.8%)	NS
NS= No significant difference between the 2 treatment groups. Only Captopril showed a difference.			

Figure 1b: SiDBP over time-all studies-Sponsor

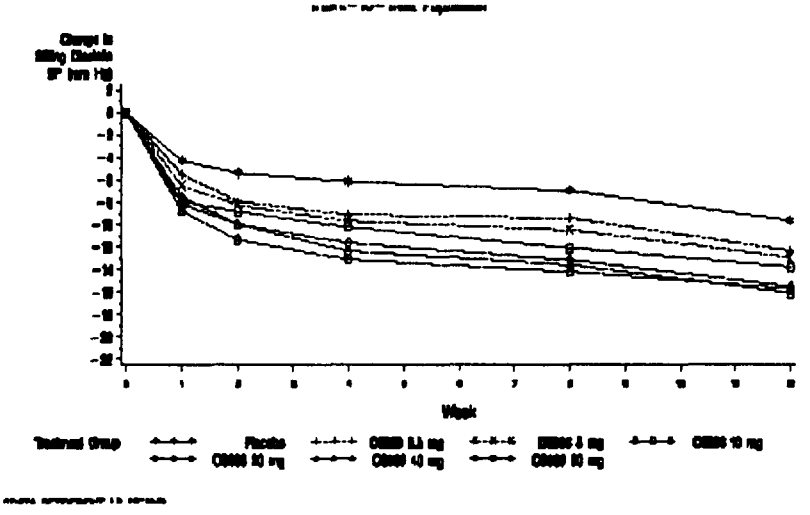


Figure 2: StDBP over time-all studies - Sponsor

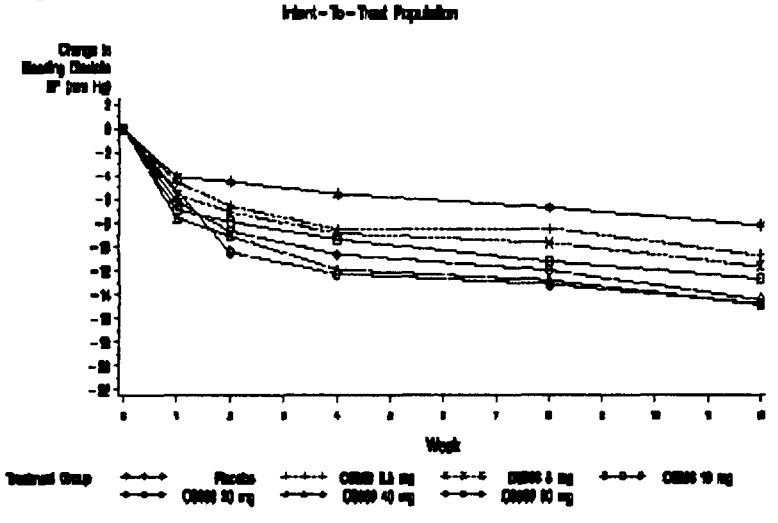
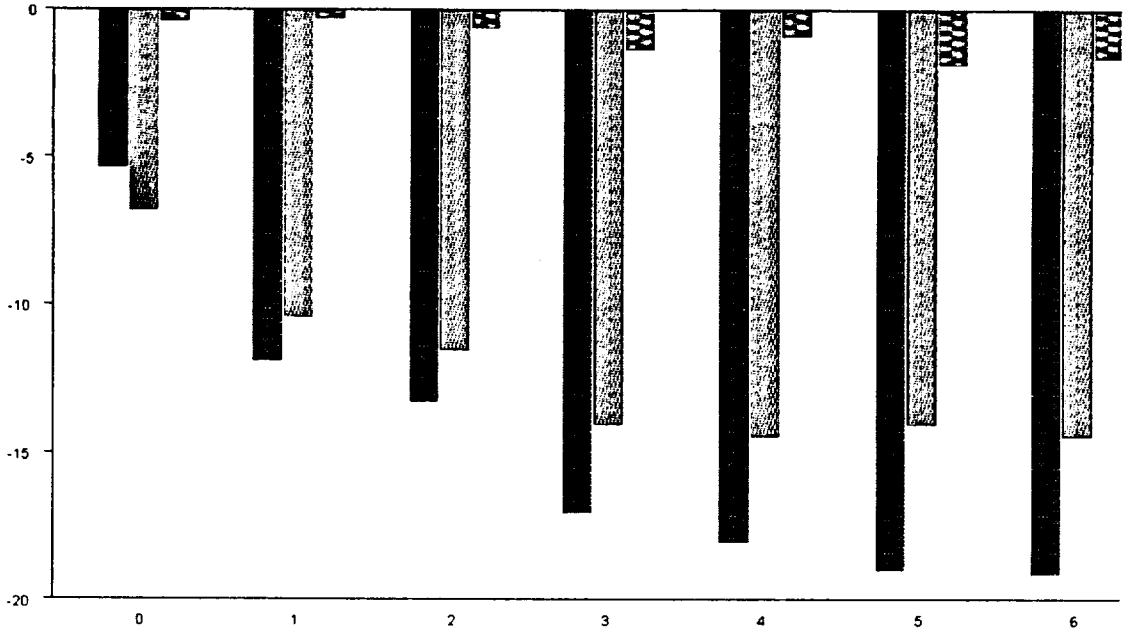


Figure 3: Caucasians CS-866 SiDBP, SiSBP and HR - Source Reviewer
0=Plcbo;1-6=2.5,5,10,20,40, and 80mg, respectively. Red=Systolic;Green=Diastolic; Blue=HR.



2.1 Dosing Regimen suitability and ABPM – once versus twice daily dosing
ABPM data for 537 patients (Plcbo, 140; CS-866, 397 73/2.5mg; 114/5mg; 74/10mg; 66/20mg and 70 patients received 80mg) are analyzed in studies 204,06, and 11. The mean values at baseline for DBP and SBP were similar among treatment groups. CS-866 in dosages of 2.5mg, 5mg, 10mg, 20mg and 80mg once daily dosing showed a dose response up to 20mg using ABPM (Figure 6, 7a and 7b). All doses evaluated were statistically significantly superior to placebo in lowering diastolic and systolic blood pressure ($p<0.009$) throughout the 24 hour dosing interval, during day and night time measures (Figures 7a and 7b and Table 13). There was no compelling evidence to suggest that twice daily dosing was better than once daily dosing (Table 13; see study #204). In studies #SE 866-11 where the trough-to-peak ratios were not corrected for placebo the once daily dosing showed relatively low ratios of about 50% for all doses (5mg, 10mg, 20mg) at week 12 using ABPM. Using cuff in study #866-10, the uncorrected trough to peak ratios, however, for 5mg, 10mg and 20mg were 96%, 98%, and 100%, respectively,. In study # 204 the corrected trough-to-peak ratios for once daily dosing ranged between 51.8% to 62.6% for 20 mg, whereas for twice daily dosing the ratio ranged from 60.2% to 74.3%. Since the sponsor will not market 80 mg o.d. dose, the trough to peak ratios, of 72% to 79% was observed. There is sufficient evidence that once daily dosing with 20 mg adequately maintained drug effect for almost 24 hours. However, the corrected trough-to-peak ratio for 20 mg dose bid appears to be better (75%) than the once daily dosing (Table 13). There is, however, no clinical advantage of twice daily dosing compared to once daily dosing despite the slightly better trough to peak ratio (See review of study #204). No significant differences in heart rates are detected between the treatment groups.

Table 13: ABPM Placebo-controlled Trough-to-Peak Ratio- # 866-204 -Caucasians

	CS-866 (Total dose in each group)					
	5mg		20mg		80mg	
	OD	BID	OD	Bid	OD	BID
DBP	63.9%	62%	62.6%	74.3%	79.1%	69.4%
SBP	70.1%	68.9%	51.8%	60.2%	72.3%	62.6%

OD=once daily; BID=twice daily; DBP= Diastolic BP; SBP = Systolic blood pressure

Figure 4: Change in standing Systolic BP from baseline over time-Sponsor

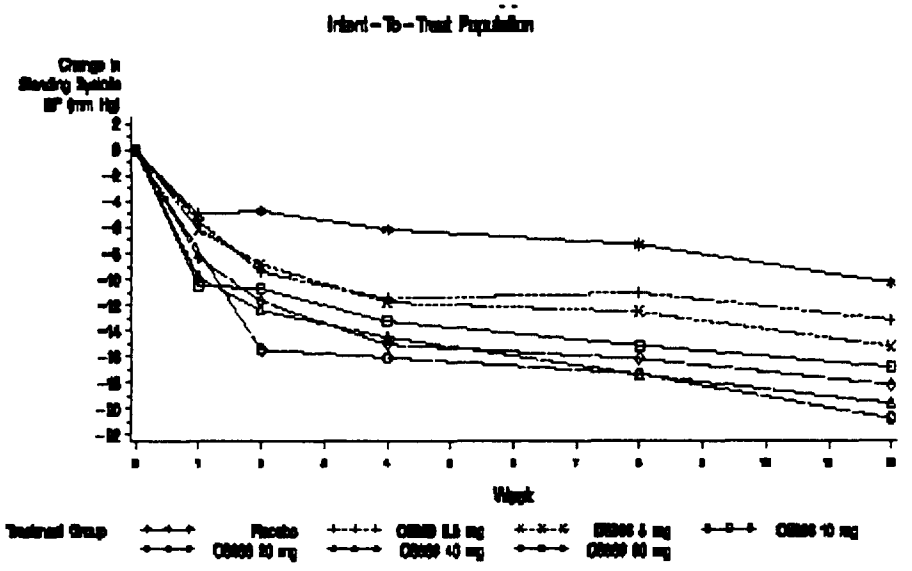
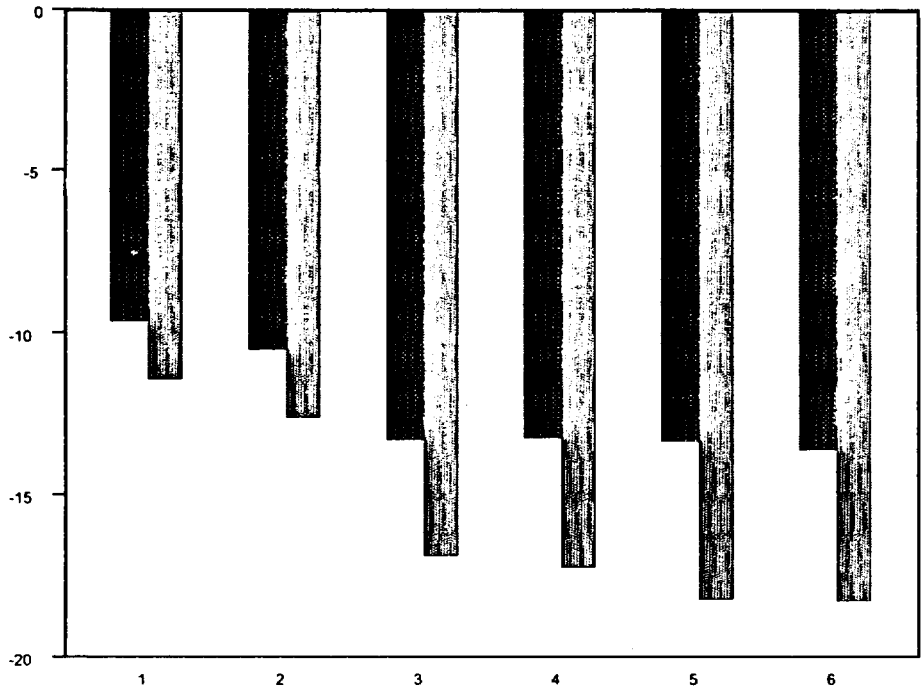
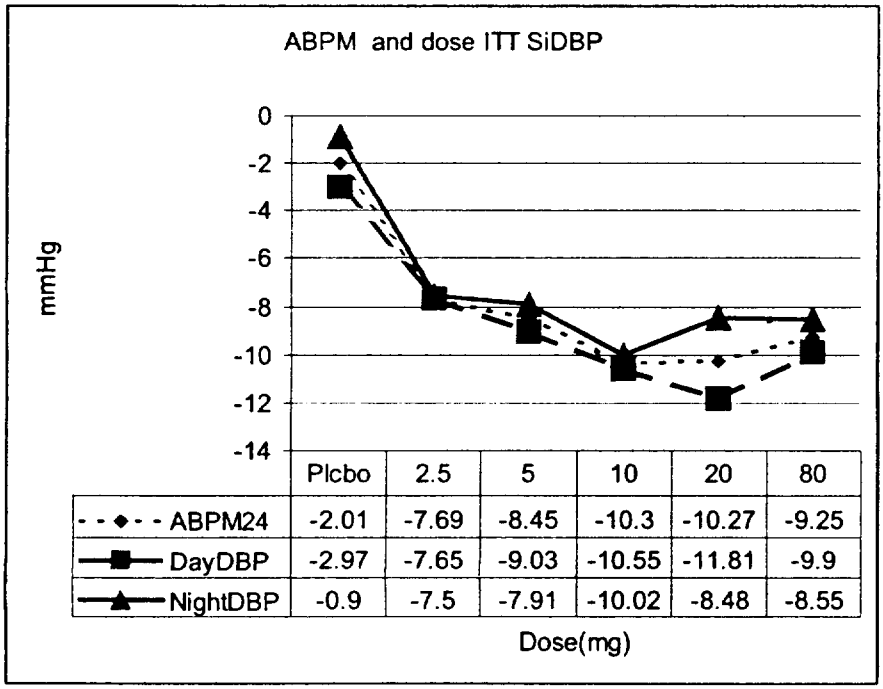


Figure 5: ABPM and dose response- See figures 7a/7b for day and night time



1-6=2.5mg, 5mg, 10mg, 20mg, 40mg, and 80mg, respectively.
Red=Systolic;Green=Diastolic;

Figure 6: All patients on CS-866 showing dose response-Source Reviewer



	Plcbo	2.5	5	10	20	80
ABPM24	-2.01	-7.69	-8.45	-10.3	-10.27	-9.25
DayDBP	-2.97	-7.65	-9.03	-10.55	-11.81	-9.9
NightDBP	-0.9	-7.5	-7.91	-10.02	-8.48	-8.55

2.2 ABPM

The ABPM data support results from cuff measurements to a large extent in the controlled studies except for the 40 mg tablet that no ABPM studies were carried out.. Increasing the dose from 20 mg to 80 mg showed no additional therapeutic benefit (Figures 5, 7a & 7b). The blood pressure lowering effect of olmesartan was maintained throughout the 24-hour period, as shown by ambulatory blood pressure monitoring (Figures 7a and 7b). The placebo-adjusted reductions in daytime mean systolic and diastolic blood pressure after treatment with 20 mg BENICAR were -13 and -9 mm Hg, respectively. QD dosing was as effective as BID dosing. Figures 7a and b represent hourly averaged ABPM placebo-adjusted data at different efficacy time-points (6,8 and 10 weeks) from 3 studies (204,06,11).

Figure 7a: Placebo-subtracted ABPM Daytime-ISE –Sitting diastolic BP

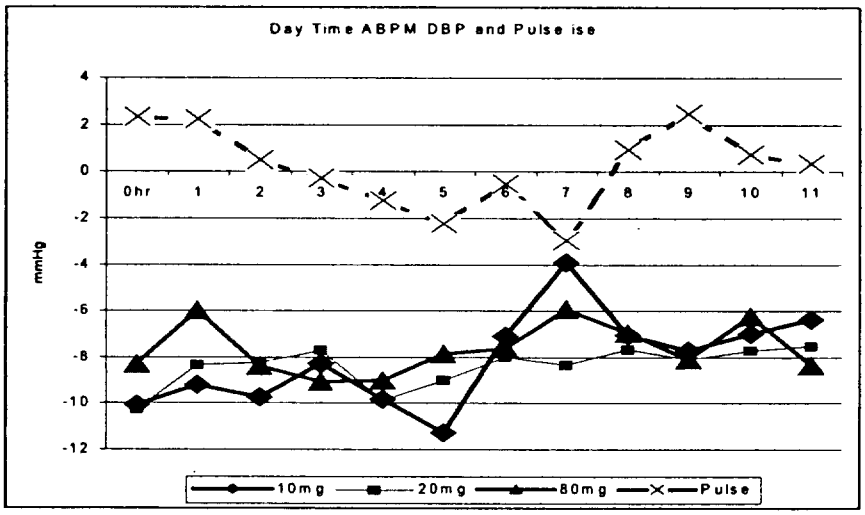
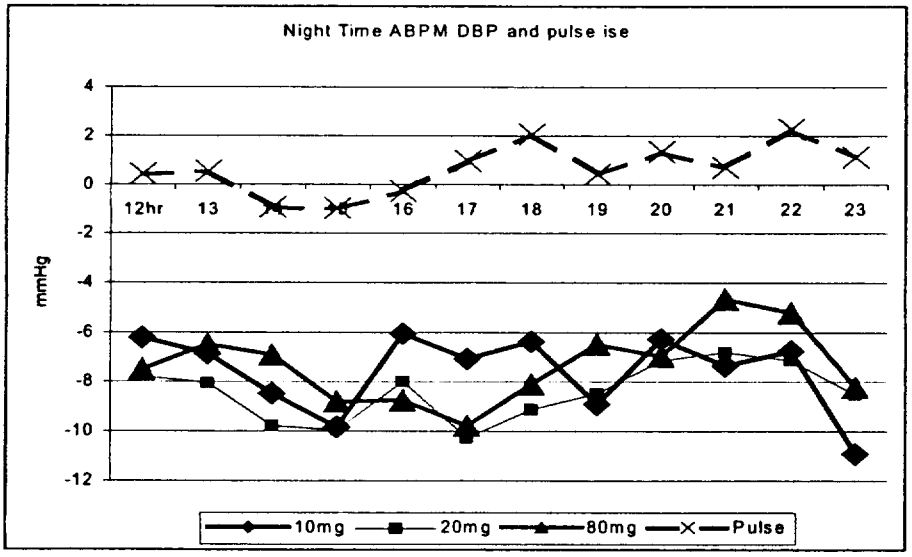


Figure 7b: Placebo-subtracted ABPM Night time –ISE-Sitting diastolic BP



2.3 Controlled blood pressure and Responder Rates

Controlled blood pressure was defined as sitting DBP<90mmHg or sitting SBP<140mmHg at the primary study time point. These are more stringent than responder rates. The controlled DBP rate for each of the CS-866 dose groups (33% -52%) was significantly higher compared to placebo (23%) ($p<0.001$). Doses higher than 10mg were not statistically significantly different from one another suggesting that the beginning of the optimal dose range is 10mg. In contrast, doses below 10 mg showed a statistically significant difference betrween them ($p<0.032$). For sitting systolic BP, the controlled blood pressure rate for each of the doses was 27% to 43% compared to 16% for placebo group ($p<0.001$). Considering this as a measure of efficacy, doses of 10mg or higher were effective in controlling DBP and SBP. At these dose levels, the controlled DBP rate was about 50% and the SBP rate was about 40%. These figures are more conservative than responder rates in Table 14 below.

Table 14: DBP and SBP responder rates -ITT- population

		CS-866 (mg)					
	Placebo	**2.5mg**	**5mg**	**10mg**	**20mg**	**40mg**	**80mg**
N	548	281	598	447	436	195	188
Responders DBP responder rate	201 37%*	150 53%	334 56%	316 71%	313 72%	131 67%	135 72%
Responders SBP responder rate	165 30%*	137 49%	336 56%	293 66%	287 66%	132 68%	126 67%

* = $p<0.001$ for all CS-866 doses versus placebo. Note higher responder rates with higher doses for SBP compared to lower doses.

2.4 Gender and Age

The mean change from baseline in SiDBP and SiSBP at the primary study time point was statistically significantly greater ($p<0.001$) in CS-866 treated patients compared to placebo regardless of the gender. The reduction was in both sitting DBP and SBP for both genders. There was no difference in the heart rates regardless of treatment and gender. Similar statistically significant changes in all the standing vital signs were observed in the CS-866 treated group compared to placebo regardless of gender (Table 15). Mean sitting blood pressure values were higher in the older age groups (>65 years) compared to the younger age groups (<65 years). The magnitude of the change from baseline in sitting SiSBP among CS-866 treated patients is somewhat smaller in older patients >65 years compared to patients under 65 years.

2.5 Race

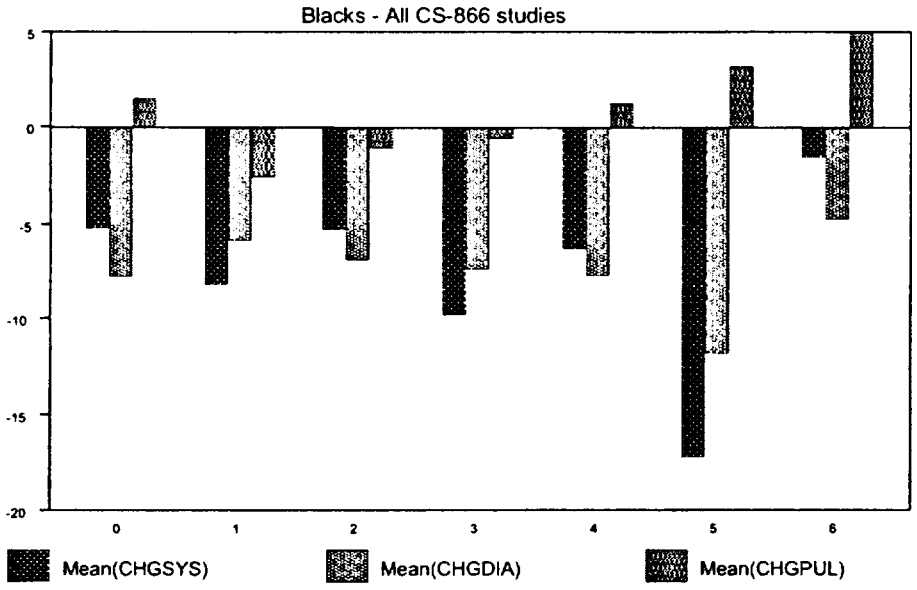
Based on the total number of Hispanics, the effects of CS-866 on blood pressure at trough were similar to blacks in some respects using data from integrated data on efficacy.(Figures 3, 7c.; See SE 866 #306). The blacks and Hispanics, however, do not appear to respond as well to olmesartan as Caucasians at 20mg dose level and below. (See statistical review for analysis of data from integrated summary of efficacy and race).

Table 15:Differences between CS-866 treated and Plcbo-age and gender –all studies

	Male		Female	
Change from baseline	**Placebo (N=311)**	**CS-866(N=1113)**	**Placebo (N=237)**	**CS-866(N=1032)**
Gender				
SiDBP	-6.60	-11.88	-7.2	-13.52
p-value		<0.001		<0.001
SiSBP	-4.58	-14.70	-6.65	-16.48
p-value		<0.001		<0.001
Heart rate*(NS)	-0.07	-0.96	-0.69	-0.89
StDBP	-5.77	-10.81	-6.55	-12.39
p-value		<0.001		<0.001
StSBP	-5.65	-14.40	-8.17	-16.03
p-value		<0.001		<0.001
Age and gender				
Placebo/CS-866	<65 years (N=440/1681)		>65years (N=108/464)	
SiDBP	-6.26	-12.33	-9.14	-13.88
p-value		<0.001		<0.001

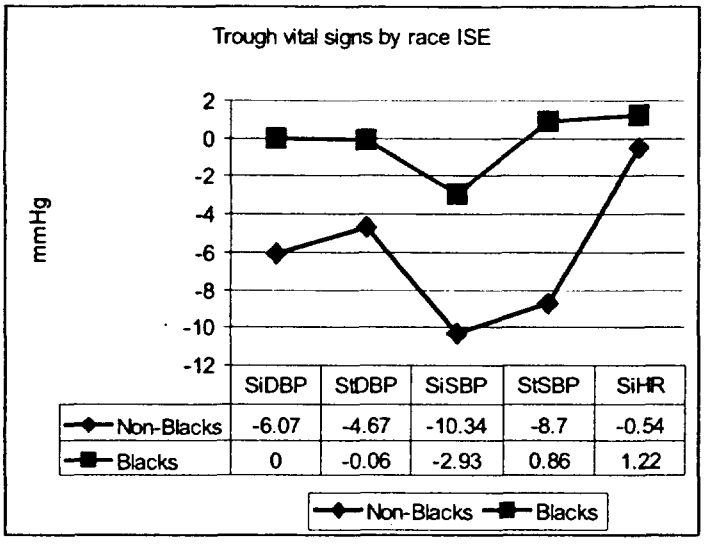
NS= Not statistically significant.

Figure7c: Mean sitting changes Blacks SiSBP (CHGSYS), SiDBP (CHGDIA) and SiPR (CHG)



0=placebo;1=2.5mg;2=5.0mg;3=10mg;4=20mg;5=40mg;6=80mg. Source:Reviewer

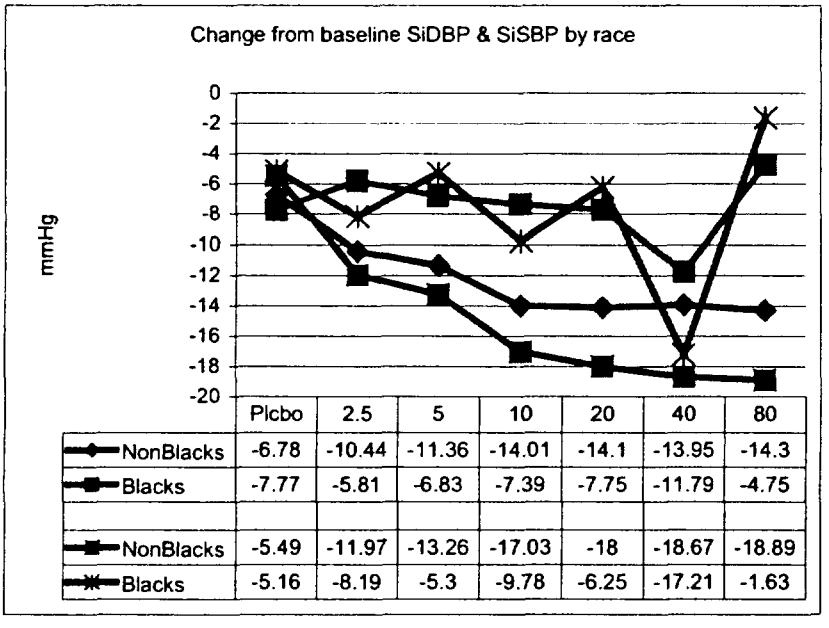
Figure 8: Trough vital signs double blind phase-ISE - Source of graph: Reviewer



	SiDBP	StDBP	SiSBP	StSBP	SiHR
Non-Blacks	-6.07	-4.67	-10.34	-8.7	-0.54
Blacks	0	-0.06	-2.93	0.86	1.22

2593 non-blacks (552 placebo and 2071 CS-866); 100 Blacks (26 placebo and 74 CS-866)

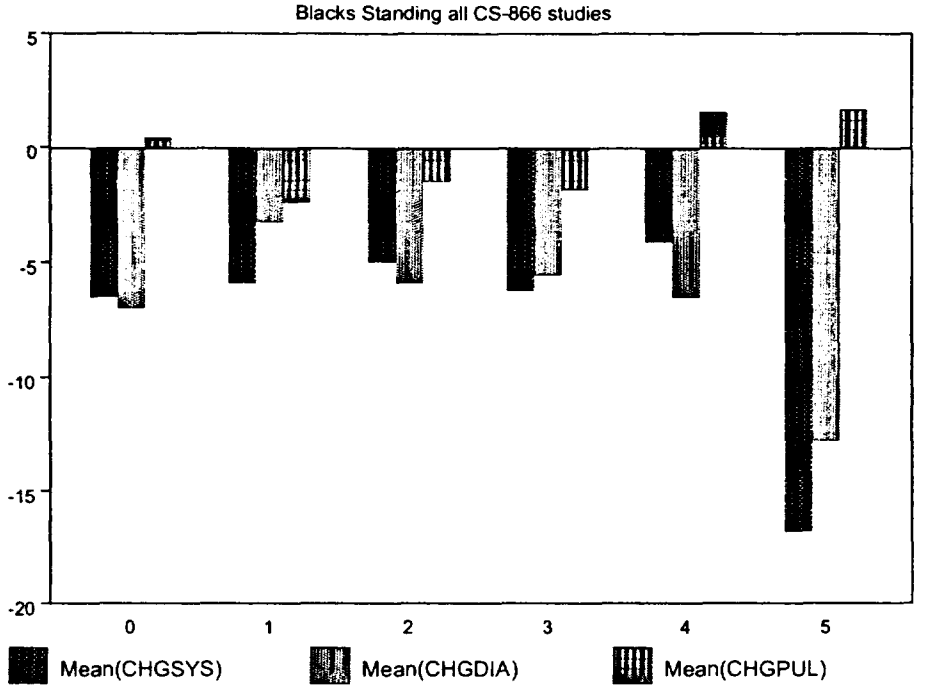
Figure 9:Trough SiDBPand SiSBP by race - ITT –N=2593 non-blacks; 100 blacks



	Plcbo	2.5	5	10	20	40	80
NonBlacks	-6.78	-10.44	-11.36	-14.01	-14.1	-13.95	-14.3
Blacks	-7.77	-5.81	-6.83	-7.39	-7.75	-11.79	-4.75
NonBlacks	-5.49	-11.97	-13.26	-17.03	-18	-18.67	-18.89
Blacks	-5.16	-8.19	-5.3	-9.78	-6.25	-17.21	-1.63

The lower 2 curves are from non-blacks (SiDBP and SiSBP being the lowermost), and the upper 2 curves are from blacks (SiDBP and SiSBP). All curves at primary study time point. Source of graph-Reviewer.

Figure10:StDBP, StSBP,& HR in 100 black patients - Source - Reviewer



0=placebo;1=2.5mg;2=5mg;3=10mg;4=20mg;5=40mg;6=80mg. Source Reviewer

N=100 (74 received CS-866; 26 on placebo).

2.6 There are 2 safety issues that will be discussed in integrated summary of safety.

a) Hepatic Insufficiency: Increases in $AUC_{0-\infty}$ and C_{max} were observed in patients with moderate hepatic impairment compared to those in matched controls. While decreases in the plasma clearance of olmesartan occurred, there was a compensatory increase in the renal clearance of olmesartan with an attendant increase in the percent of the dose eliminated via the kidney. The increase in AUC approximated 1.6 fold, which is less than that observed when the dose is increased from 20 to 40 mg in normal volunteers. The starting dosage for patients with mild to moderate hepatic impairment does not need to be adjusted.

b) Renal Insufficiency: In patients with renal insufficiency serum concentrations of olmesartan were elevated compared to subjects with normal renal function. After repeated dosing, the AUC was approximately tripled in patients with severe renal impairment (creatinine clearance <20 mL/min) compared to subjects with normal renal function. The pharmacokinetics of olmesartan in patients undergoing hemodialysis has not been studied. No dosage adjustment is necessary in patients with mild to moderate (>20 mL/min) renal insufficiency; in patients with severe renal impairment olmesartan may be initiated with a starting dose of 20 mg, however, patients should be closely monitored. (See **DOSAGE AND ADMINISTRATION IN PACKAGE INSERT**).

SUMMARY

- Antihypertensive effectiveness of CS-866 was derived from integrated analysis of data from changes in vital signs of 2693 ITT patients (2,145 CS-866 and 548 placebo) enrolled in 7 randomized, double-blind, placebo-controlled studies.
- Following 6 to 12 weeks treatment with 2.5mg, 5mg, 10mg, 20mg, 40mg and 80mg of CS-866 once daily, four large controlled studies (#204,305,306, &11) showed a statistically significant difference in lowering sitting and standing diastolic BP compared to placebo ($p<0.001$).
- Similarly there was a statistically significant difference for sitting systolic blood pressure ($p<0.002$) at the primary efficacy time point for the controlled studies.
- Evidence of antihypertensive effect was observed as early as 1 week after initiation of CS-866 treatment with maximum benefit occurring by 4 weeks. The blood pressure lowering effect was maintained for up to one year with 20 mg dose regardless of HCTZ combination.
- CS-866 doses at 10 mg or higher produced higher response rates compared to placebo particularly in respect of diastolic and systolic blood pressure.
- The optimal therapeutic dosing range is between 10 mg and 40 mg o.d. for all the demographic subgroups. For non-blacks, there is no statistically significant difference between treatment effect (SiDBP and SiSBP) when 20 mg and 40 mg doses were compared.
- Using ABPM, the doses evaluated, (2.5mg, 5mg, 10mg, 20mg, and 80 mg o.d.) showed a statistically significant lowering of diastolic and systolic blood pressure over a period of 24 hours dosing interval both during the day and at night time compared to placebo ($p<0.009$). This is in agreement with results obtained with cuff measurements.
- Based on cuff blood pressure measurements, there was a dose response relationship between CS-866 dose and the magnitude of the change from baseline over the entire range of the doses evaluated (2.5 mg to 80 mg) and only up to 20 mg based on ABPM. There was no additional therapeutic benefit above 40 mg even though the 40mg dose was not evaluated on ABPM.
- Once or twice daily dosing appears to be effective based on ABPM data in studies 204 and 11.
- Comparative efficacy studies showed CS-866 to be as effective as atenolol in lowering diastolic blood pressure, and when CS-866 was given in combination with HCTZ it was equally as effective as atenolol combined with HCTZ in lowering diastolic and systolic blood pressure.
- CS-866, at the doses evaluated, was statistically more effective in lowering DBP and SBP compared to losartan and captopril and also in yielding higher responder rates.
- CS-866 at the dose of 20 mg was less effective in Black and Hispanic patients compared to non-blacks. These racial groups, assuming the numbers are large enough to make conclusions, will benefit from upward titration to 40 mg CS-866 and from combination of CS-866 with HCTZ if hypertension is uncontrolled.

RECOMMENDATIONS

At the present time, we estimate olmesartan's therapeutic benefit to risk relationship as being acceptable for the proposed patient population. The clinical controlled studies have

demonstrated adequate efficacy for the proposed indication of lowering blood pressure. We recommend that Benicar should only be approved for the treatment of mild to moderate hypertension provided it is not mutagenic, and that other labeling issues are resolved.

APPEARS THIS WAY
ON ORIGINAL

3.0 Integrated review of safety
Safety Review: Olmesartan
3.01Materials Utilized in Review
In evaluating the safety of olmesartan, the Medical Reviewer used the electronic archive, including the SAS database, supplied by the Sponsor with the submission of NDA 21-286. In addition to reviewing the data in the Integrated Summary of Safety, the Medical Reviewer looked at the Safety Update and the individual studies as needed. The safety database analyzed in this review represented data from all completed studies as of January 1, 2000; where possible, information from the Safety Update (i.e.,deaths, serious adverse events) will also be presented.

The approach used to characterize the safety profile of olmesartan consisted of examination of the entire database for deaths, discontinuations, serious adverse events, as well as routine safety data (treatment emergent adverse events, laboratory tests, vital signs and ECG data).

3.2 Background - Pharmacologic Class
According to the Sponsor, "CS-866 is a novel, orally active angiotensin (Ang) II antagonist. The active metabolite of CS-866, RNH-6270, blocks the vasoconstrictor effects of Ang II by selectively blocking its binding to the AT1 receptor, which is found in many tissues, including vascular smooth muscle." Ang II receptor blockers, with increased specificity and selectivity in blocking the circulating and tissue effects of Ang II at the receptor level, would have potential advantages over ACE inhibitors, including a lower incidence of bradykinin-related adverse events such as cough or angioedema.

3.3 Post-Marketing Experience
Olmesartan has not been approved/marketed elsewhere; therefore, there are no available postmarketing safety data for review.

3.4 Use in Pediatric Population
Olmesartan has not been studied in population less than 18 years of age.

3.5 Other Preclinical Issues (Mutagenicity)
There is an outstanding question of positive mutagenicity testing that will be further evaluated by the Carcinogenicity Assessment Committee (CAC). Please see the review by the assigned Pharmacologist for further details.

4.0 Description of clinical data sources
4.1 Primary source data
Clinical Pharmacology: This program consisted of 22 studies that explored bioavailability/tolerance/biopharmaceutics, special populations (includingSE-866/16, a renal impairment study), and drug/food interactions. (Appendices 2 and 3 present an overview of the Clinical Pharmacology program and patient accounting, respectively.

4.2 Phase 2/3 Clinical Efficacy/Safety Studies consisted of 7 placebo-controlled short term (6-12 week) monotherapy studies (866-204, 866-305, 866-306 Dose-Titration, SE-

866/06 ABPM, SE-866/09, SE-866/10, SE-866/11), 2 placebo-controlled double-blind long term extensions (866-305 and SE-866/10), one 4 month open-label (866-306) extension, 3 active-controlled 12 week monotherapy studies (SE-866/18, /19 and /20), one active-controlled long-term (additional 12 week) study (SE-866/19), and one 12 week active-controlled moderate to severe hypertension study (SE-866/17). In total, this program consisted of 11 controlled clinical trials.

4.3 Exclusions from Database

Excluded from the integrated Safety Database were SE-866/23 (a study report was submitted with the safety update) as well as 63 subjects in Phase I Clinical Pharmacology Studies from Japan

4.4 Safety Populations studied and their characteristics

4.4.1 Demographics

Demographic data for the Phase 2/3 trials, as well as placebo-controlled monotherapy trials, are presented below in Table 16. The placebo-controlled monotherapy study population appears to be fairly well-balanced except for a slightly younger age and slightly more male predominance in the placebo group. This study population was mostly Caucasian and mostly under 65 years of age. Note that the active control population is also100% Caucasian

Table 16: Demographics: Phase 2/3 trials*:

	Placebo	**CS-866**	**Comparator**
N	555 n (%)	3177 n (%)	624 n (%)
Age (years)			
Mean (SD)	55.2 (11)	55.6 (11)	56.0 (11)
Range	23-88	22-92	19-92
≤30	5 (1)	35 (1)	6 (1)
31-40	48 (9)	249 (8)	37 (6)
41-50	141 (25)	778 (2)	162 (26)
51-60	202 (36)	1079 (34)	211 (34)
61-64	49 (9)	360 (11)	67 (11)
65-74	86 (15)	516 (16)	115 (18)
≥75	24 (4)	160 (5)	26 (4)
Sex			
Males	316 (56.9)	1658 (52.2)	325 (52.1)
Females	239 (43.1)	1519 (47.8)	299 (47.9)
Race			
Caucasian	492 (88.6)	2856 (89.9)	624 (100)
Black	26 (4.7)	124 (3.9)	
Asian	2 (0.4)	15 (0.5)	
Hispanic	32 (5.8)	176 (5.5)	
Other	3 (0.5)	6 (0.2)	

	Placebo	CS-866	Comparator
Weight (kg)			
Mean (SD)	83(15)	82 (15)	79 (14)
Range	49-134	40-185	99-246
Height (cm)			
Mean (SD)	171 (9)	170 (9)	169 (9.3)
Range	142-201	130-202	136-196

*Includes protocols:866-204, 866-305, 866-306, SE-866/06, 09-11, 17-20
(Source: dataset: Demographics)

Table 17: Demographics: Placebo-Controlled Monotherapy Studies

	Placebo	CS-866
N	555	2540
	n (%N)	n (%N)
Age (years)		
Mean (SD)	50 (19)	55 (11)
Range	22-72	22-92
≤30	5 (1.0)	25 (1.0)
31-40	48 (8.6)	213 (8)
41-50	141 (25.4)	640 (25)
51-60	202 (36.3)	855 (34)
61-64	49 (8.8)	292 (11)
65-74	86 (15)	383 (15)
≥75	24 (4.3)	132 (5.2)
Sex		
Males	316 (57)	1340 (53)
Females	239 (43)	1200 (47)
Race		
Caucasian	492 (88.6)	2219 (87)
Black	26 (4.7)	124 (5)
Asian	2 (0.4)	15 (0.6)
Hispanic	32 (5.8)	176 (7)
Other	3 (0.5)	6 (0.2)
Weight (kg)		
Mean (SD)	76 (13)	83 (15)
Range	55-95	44-185
Height (cm)		
Mean (SD)	173 (7)	170 (10)
Range	164-186	130-202

*Includes studies 06, 09, 10, 11, 204, 305 and 306.
Sponsor's analysis: Table 19: ISS and Demographics database

4.5 Extent of Exposure to olmesartan

The two tables to follow list duration of exposure by dose in the Phase 2/3 Clinical Trials. Most of the exposure to CS-866 appears to be in total daily doses up to 20 mg. There appears to be less exposure of patients to the 40 and 80 mg total daily doses; in addition, there is no long-term (>26 week) exposure of patients to the 80 mg dose.

Table 18: Drug Exposure - Phase 2/3 Clinical trials.

	CS-866 Total Daily Dose						
Duration	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg	Total
1 Day to 12 Weeks	97	667	596	496	127	140	1105
>12 Wks-26 Wks	114	143	268	394	172	100	1274
>26 Wks-39 Weeks	9	3	7	4	1	0	88
>39 Wks-52 Weeks	35	75	68	76	29	0	283
>52 Weeks	27	144	161	154	42	0	528
Total Patients	282	1032	1100	1124	371	240	3278
Total Pt/Months	1406	4178	4808	5136	1646	543	17717

Data from 11 Phase 2/3 Clinical trials. Does not include : SE-866/23
Source: Sponsor: ISS: Table 4: pdf. Page 387.

Table 19: Cumulative frequency - Phase 2/3 clinical trials.

Cumulative Frequency							
	CS-866						
Duration	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg	Total
≥ 1 Day	282	1032	1100	1124	371	240	3278
>12 Weeks	185	365	504	628	244	100	2173
>26 Weeks	71	222	236	234	72	0	899
>39 Weeks	62	219	229	239	71	0	811
>52 Weeks	27	144	161	154	42	0	528

Data/Source: See above Table 3.

4.6 Adequacy of Safety Database

The safety database appears to be adequate for the demographic population as noted in Table 19 except for reduced long term exposure to 40 and 80mg dose levels.

4.7 Human Pharmacokinetic Considerations

The Medical Reviewer failed to identify pharmacokinetic findings useful in explaining the occurrence of adverse events observed during clinical trials of olmesartan. The reader is referred to the Biopharmaceutics review for the human pharmacokinetics of olmesartan and detailed information on the subject.

5.0 Deaths

As of July 12, 2000, six deaths were reported ; five of these patients received olmesartan and one received captopril. In the four month safety update, three additional deaths were reported, all occurring in the long-term extension study ——— '; one patient received olmesartan, one placebo, and one patient's therapy remained blinded. No deaths

were reported in any clinical pharmacology studies. The following table provides a summary of deaths by treatment and study.

Table 20: Deaths: Phase 2/3 Studies (See Patient Narratives)

Study	Patient ID	Treatment group	Sex	Age	Race	AE	Comment	Day after Randomized Dose
866-204 (PBO Controlled)	001040	CS-866 5 mg	M	40	Hispanic	Homicide	Patient. was victim	57
SE-866-10 (PBO Controlled)	000398	CS-866 20 mg	F	69	Caucasian	Ileus, anemia		311
SE-866-19 (Active C)	000093	CS-866 10 mg	F	60	Caucasian	Cardiac Failure	Pt. died 11 days post last dose study drug.	174
SE-866-19 (Active C)	000153	CS-866 20 mg + HCTZ 12.5 mg	M	73	Caucasian	CVA: Last BP 162/100		90
SE-866-19(Active C)	000293	CS-866 10 mg	M	68	Caucasian	esophageal CA		14
SE-866-20 (Active C)	000014	Captopril 12.5 mg	M	72	Caucasian	MI		24
—	100847/0427	CS-866 5 mg	F	81	Caucasian	CVA: Last BP 160/85 HR 82	Died in nursing home ~ 2 months later: cause of death listed as "influenza-type reaction."	262
—	100953/0505	Placebo	M	67	Caucasian	Sudden death	Avg BP 125/85 prior to event; ECGs reported NL.	Approx.7 months
—	100711/0793	Blinded	M	90	Caucasian	S/p fractured R. femur; post-op ischemic small/large bowel;	Underwent subtotal colectomy and partial small bowel resection—did not recover.	Approx.6 months
866-411	Patient # S50064/4061	Blinded	M	56	Caucasian	Multiple blunt trauma	Hit by car	1

5.1 Serious Adverse Events

There were 128 total serious adverse events (including death) in the adverse event database. No Serious AE were noted in the CS-866 2.5 BID and 10 mg BID groups, respectively. There was one patient in the Clinical Pharmacology Program who

developed a serious AE (see corresponding section); one serious adverse event was also noted in Study SE-866/23 (see corresponding section).

Table 21: Serious Adverse Events (Incidence ≥ 0.1% for Olmesartan Treatment Group) in Placebo-Controlled Monotherapy Studies;Primary Term: Short-term*

Serious Adverse Event: Primary Term	Placebo N=555 n (%)	Olmesartan N=2540 n (%)
Angina Pectoris	0 (0.0)	4 (0.2)
Breast Cancer - Female	0 (0.0)	2 (0.1)
Cerebrovascular Disorder	1 (0.2)	2 (0.1)

*Data from Studies 204, 6, 9, 11; Studies 305 and 306 through Week 8; Study 10 through Week 12 visit. Source: Sponsor: Table 69 (ISS): pdf. Page 1004.Not included: SE-866/23

Table 22: Serious Adverse Events (Incidence ≥ 0.1% for Olmesartan Treatment Group) in Long-term Placebo-Controlled or Open-label Studies Primary Term**

Serious AE: Primary Term	Placebo* N=154	Olmesartan* N=1305 (n (%))
Chest Pain	0	4 (0.3)†
Hypovolemia	0	1 (0.1)
Hypertension	0	1 (0.1)
Vertigo	0	2 (0.2)
Convulsions	0	1 (0.1)
Parkinsonism aggravated	0	1 (0.1)
Goiter	0	1 (0.1)
Gastroenteritis	0	2 (0.2)
Diarrhea	0	1 (0.1)
GI Reflux	0	1 (0.1)
GI hemorrhage	0	1 (0.1)
Rectal hemorrhage	0	1 (0.1)
Ileus	0	1 (0.1)
Pancreatitis	0	1 (0.1)
Hearing decreased	0	1 (0.1)
Tachycardia	0	1 (0.1)
Cholecystitis	0	1 (0.1)
Dehydration	0	1 (0.1)
Hyponatremia	0	1 (0.1)
NPN increased	0	1 (0.1)
Arthralgia	0	1 (0.1)
Arthritis	0	1 (0.1)
Pathological fracture	0	1 (0.1)
Angina pectoris	0	3 (0.2)
Myocardial infarction	0	2 (0.2)
Endocarditis	0	1 (0.1)
Breast cancer malignant female	0	2 (0.2)
Adenocarcinoma NOS	0	1 (0.1)

Serious AE: Primary Term	Placebo* N=154	Olmesartan* N=1305 (n (%))
Malignant neoplasm	0	1 (0.1)
Cerebrovascular disorder	0	1 (0.1)
Abnormal vision	0	1 (0.1)
Hematoma	0	1 (0.1)
Anemia	0	1 (0.1)
Orchitis	0	1 (0.1)
Sepsis	0	1 (0.1)

Source: Table 71: ISS ¶Preferred term for "creatinine, blood increased."
* Includes Placebo + HCTZ; olmesartan +HCTZ respectively.
**Data from studies 10, 305 and 306. Only events that occurred or continued into long-term treatment are included. Each patient is counted once in each treatment received and counted only once within a total group. For study 306, those were randomized to placebo and continued into long-term phase are counted once in each of the total groups. † 3 (chest pain) were in olmesartan alone.

Table 23: Serious Adverse Events (Incidence ≥ 0.1% for Olmesartan Treatment Group) in Active-Controlled Monotherapy Studies, by Primary Term:**

Serious AE: Primary Term	Comparator* N=460 n (%)	Olmesartan N=473 n (%)
Back pain	0	1 (0.2)
Chest pain	0	1 (0.2)
Abdominal pain	0	1 (0.2)
Arthropathy	0	1 (0.2)
Breast cancer- female	0	1 (0.2)
Esophageal carcinoma†	0	1 (0.2)
Surgical intervention	3 (0.7)	3 (0.6)
Renal calculus	0	1 (0.2)
Cerebrovascular disorder‡	0	1 (0.2)

*Includes: losartan, captopril and atenolol. **Data from Studies 18, 19 (through Week 12) and 20. Source:Sponsor: ISS: Table 73. †This olmesartan patient (#000293) is the same patient listed under Deaths (see Table 5) ‡According to the Patient Listings (Table 74, ISS), this patient had a cerebral infarction.

Table 24: Number (%) of Patients with Serious Adverse Events in SE/866-17 (Active-Controlled Study—Moderate to Severe Hypertension

Serious AE: Primary Term	Atenolol + HCTZ* N=164 n (%)	Olmesartan + HCTZ* N=164 n (%)
Surgical intervention	0	1 (0.6)
Renal calculus	0	1 (0.6)

Source:Sponsor: ISS Table 77; pdf. Page 1059.

5.11 Serious Adverse Events: Clinical Pharmacology:

One serious AE was reported (Protocol SE/866-16 renal impairment) in a 57 year old Caucasian male (ID #016014) on CS-866 10 mg who developed progression of renal insufficiency/uremia (with hospitalization) 14 days after the first randomized dose.

5.12 Other Serious Adverse Events: Safety Update

SE-866/23: No deaths occurred in this study. One serious adverse event was reported (Patient # S230984/0659): atrial fibrillation in a 54 year-old Caucasian male in the felodipine treatment group. (This patient was one of two patients discontinued because of AE). For that patient, vital signs were : Screening May 25, 1999 BP 142/102 , pulse 70; prior to hospitalization (July 16,1999) vital signs: (Visit 5 July 12, 1999) BP 148/90, pulse 62.

Table 25: Other Serious Adverse Events (excluding Deaths) from Safety Update

Serious Adverse Event:	Placebo	Comparator	Olmesartan	Unknown°
Chest Pain				1
Congestive heart failure				1
Syncope				1
Scrotal Ulcer				1
Complete heart block				1
Cough/Breathlessness		1		
Accidental injury		1		
Pneumonia			1	

Source: Sponsor: 4-month Safety Update . °Treatment blinded as of Safety Update.

Table 26: IND Safety Reports: Serious Adverse Events (ongoing studies—not integrated into safety summary)

Study #	Drug	AE #	Rand. #	AE term	FDA Serial #	Initial Report Date
[redacted]	Placebo + HCTZ 12.5 mg QD	005	0162	GI neoplasm Malignant	093	May 26, 1999
[redacted]	CS-866 5 mg QD	001	NA	Dyspnea	043	September 22, 1997

Source: Sponsor: ISS: Table 8.4.5.4a

5.2 Discontinuations

In placebo-controlled monotherapy trials, 1.6% (40 /2540) of CS-866 treated patients and 0.7% (4 /555) of patients who received placebo discontinued as a result of adverse events.

Discontinuations: Phase 2/3 Clinical Studies

Table 27: Adverse Events That Resulted in Discontinuation (Incidence ≥ 0.1% in Olmesartan -Treated Patients): Placebo-Controlled Monotherapy Studies

Primary Term	Placebo N=555 n (%)	CS-866 N=2540 n (%)
Dizziness	0	6 (0.2)
Angina pectoris	0	4 (0.2)
Hypertension	1 (0.2)	2 (0.1)
Headache	0	2 (0.1)
Nausea	0	3 (0.1)
Increased liver enzymes•	0	2 (0.1)
CPK increased	0	2 (0.1)
Breast Cancer	0	2 (0.1)
Impotence	0	2 (0.1)

Includes studies: 204, 06, 09, 11; 305 and 306 through Week 8; Study 10 through Week 12. For patients receiving more than one treatment, discontinuation is counted in the treatment group immediately prior to discontinuation. For Total CS-866 each patient is counted only once. Source: ISS: Table 58, 59 (patient listings). •Includes: GGT increased, SGOT increased, SGPT increased

5.21 Discontinuations: Clinical Pharmacology Studies
Of 623 patients in the safety database, 9 patients did not complete their respective studies (614 were completers). Of the 9 dropouts, all were in a CS-866 treatment group (i.e., none were placebo dropouts). Reasons for dropout included: Protocol violation (2 subjects); low systolic blood pressure (1 subject), concomitant medication (1 subject), bronchopneumonia (1 subject), and subject request (1 subject), lost to follow up (1 subject), lack of efficacy (1 subject) and poor veins leading to inadequate sampling (1 subject). The subject who developed hypotension , or low systolic blood pressure (Study 866-102, subject 000178) was in the CS-866 80 mg treatment group; the event occurred day 4 after first randomized dose.

5.22 Adverse Events That Resulted in Discontinuation (Incidence ≥ 0.2% in Olmesartan-Treated Patients): Long-term Active-controlled Study (SE-866/19):
One patient discontinued from the long-term CS-866 group (CS-866 + HCTZ) due to a hemiparesis (see Serious Adverse Events).

5.23 Adverse Events That Resulted in Discontinuation (Incidence ≥ 0.2% in Olmesartan-Treated Patients): Active-controlled Study in Moderate-Severe Hypertension (SE-866/17)
One patient discontinued from the CS-866 + HCTZ treatment group due to a renal calculus.

Table 28: Clinical Adverse Events That Resulted in Discontinuation (Incidence ≥ 0.2% in Olmesartan-Treated Patients) All Studies in Hypertensive Patients:

Primary Term	Comparator* N=1179 n (%)	CS-866 N=3278 n (%)
Angina pectoris	0	6 (0.2)
Dizziness	1 (0.1)	10 (0.3)
Hypertension†	2 (0.2)	2 (0.2)
Nausea	4 (0.3)	5 (0.2)
Hepatic function abnormalities‡	3 (0.3)	6 (0.2)
Breast neoplasm malignant	0	5 (0.2)

Includes: 204, 6, 9, 10, 11, 17-20, 305, 306 both short and long-term
†Includes: hypertension and hypertension aggravated
‡Includes: gamma GT, SGOT, SGPT increased, hepatic enzymes increased, hepatic function abnormal, hepatitis, and bilirubinemia. Source: Sponsor: ISS: Table 68, Table 8.4.5.3.2d.

Table 29: Adverse Events That Resulted in Discontinuation (Incidence ≥ 0.2% in Olmesartan-Treated Patients): Long-term Placebo-Controlled/Open Label Studies

Primary Term	Placebo* N=154 n (%)	CS-866* N=1305 n (%)
Angina pectoris	0	2 (0.2)
Breast cancer - female	0	2 (0.2)

Includes studies 10, 305, 306. For patients receiving more than one treatment, discontinuation is counted in the treatment group immediately prior to discontinuation.
*The total N includes placebo +HCTZ, CS-866 + HCTZ, respectively. However, above noted discontinuations occurred in the CS-866 alone group.

Table 30: Adverse Events leading to Discontinuation (Incidence ≥ 0.2% in Olmesartan-Treated Patients): Active-controlled Studies

Primary Term	Comparator* N=460 n (%)	CS-866 N=473 n (%)
Chest Pain	0	1 (0.2)
Malaise	0	1 (0.2)
Hypertension	0	1 (0.2)
Dizziness	1 (0.2)	4 (0.8)
Headache	3 (0.7)	2 (0.4)
Leg cramps	0	1 (0.2)
Dry mouth	0	2 (0.4)
Nausea	4 (0.9)	2 (0.4)
Atrial arrhythmia	0	1 (0.2)
Tachycardia	0	1 (0.2)
Hepatic function abnormal	0	1 (0.2)
Hepatitis	0	1 (0.2)
Myalgia	0	1 (0.2)
Breast cancer - female	0	1 (0.2)
Esophageal carcinoma	0	1 (0.2)
Cough	0	1 (0.2)
Dyspnea	0	1 (0.2)
Pruritis	0	1 (0.2)
Rash	0	1 (0.2)
Urticaria	0	1 (0.2)
Cerebrovascular disorder	0	1 (0.2)
Flushing	0	1 (0.2)
Varicose vein	0	1 (0.2)

Includes: Studies #18, 19 (through week 12) and 20. *Comparators include losartan, captopril, atenolol Source: Table 62, 63

5.24 Treatment Emergent Adverse Events

Below are listings for treatment emergent adverse events. This reviewer selected listing where the incidence was at least 1-2% for the olmesartan treatment group.
The most common adverse event that occurred more frequently than placebo was dizziness.

Of the listed adverse events in placebo-controlled monotherapy studies, only Dizziness and Influenza-like Symptoms appeared to have some possible relationship with dose (see Table 31.

In this same analysis population, there was one report of facial edema in CS-866 (5 mg; total incidence 0.1%) and none in the placebo group. The incidence of cough in this population was 0.7% (4/555) in the placebo group and 0.9% (22/2540) in the olmesartan group. The incidence of hyperkalemia was 0% in the placebo group and 0.1% (3/2540) in the olmesartan group; the incidence of increased NPN (creatinine) was 0.5% (3/555) in placebo and 0.3% (8/2540) in the olmesartan group.

In the placebo-controlled monotherapy studies, the incidence of impotence was 0 in the placebo group and 0.4% (10/2540) in the CS-866 treatment group. Impotence is highlighted in Study 866-305 where the incidence of this adverse event is 0 in the placebo group and 1.1% (5/435) in the active treatment group; 2 patients in this study were withdrawn due to this adverse event. However, these two patients were also on simvastatin as concomitant therapy.
In Study 866-306, the incidence of impotence was 0% in the placebo group and 1.2% (4/341) in the active treatment group.

Table 31: Adverse Events (Incidence ≥ 1.0 % for Olmesartan Treatment Group) in Placebo-Controlled Monotherapy Studies, by Primary Term:**

	Placebo N=555 n (%)	**CS-866 N=2540 n (%)**
Influenza-like symptoms	16 (3)	79 (3)
Back pain	8 (1)	41 (2)
Headache	40 (7)	141 (6)
Dizziness	5 (0.9)	70 (3)
Gamma-GT increased	13 (2)	57 (2)
CPK increased	6 (1)	40 (2)
Upper Respiratory Infection	27 (5)	83 (3)
Pharyngitis	9 (2)	33 (1)
Bronchitis	10 (2)	51 (2)
Rhinitis	9 (2)	40 (2)
Hematuria	10 (2)	49 (2)
Sinusitis	11 (2)	29 (1)
Hyperglycemia	15 (3)	32 (1)
Hypertriglyceridemia	6 (1)	29 (1)
Inflicted injury	7 (1)	34 (1)
Diarrhea	4 (0.7)	27 (1)

Includes: 204, 06, 09, 11, 305 and 306 through Week 8, Study 10 through Week 12.
Source: Table 25

Table 32: Adverse Events (Incidence ≥ 2.0 % for Olmesartan Treatment Group) in Long-term Placebo-Controlled or Open-Label Studies, by Primary Term:**

	Placebo* N=300 n (%)	CS-866* N=1402 n (%)
Influenza-like symptoms	12 (4)	81 (8)
Back pain	16 (5)	116 (8)
Chest pain	6 (2)	37 (3)
Peripheral edema	6 (2)	36 (3)
Pain	6 (2)	34 (2)
Fatigue	4 (1)	28 (2)
Headache	32 (11)	123 (9)
Dizziness	7 (2)	76 (5)
Vertigo	3 (1)	26 (2)
Diarrhea	5 (2)	48 (3)
Gastroenteritis	1 (0.3)	32 (2)
Nausea	3 (1)	31 (2)
Dyspepsia	8 (3)	29 (2)
Abdominal pain	3 (1)	25 (2)
Gamma-GT increased	12 (4)	39(3)
SGPT increased	6 (2)	31 (2)
SGOT increased	6 (2)	29 (2)
CPK increased	8 (3)	38 (3)
Hyperuricemia	7 (2)	35 (3)
Hyperglycemia	2 (0.7)	34 (2)
Arthralgia	2 (0.7)	38 (3)
Arthritis	2 (0.7)	36 (3)
Myalgia	7 (2)	25 (2)
Skeletal pain	2 (0.7)	21 (2)
Upper Respiratory Infection	28 (9)	134 (9)
Bronchitis	18 (6)	109 (8)
Rhinitis	10 (3)	66 (5)
Sinusitis	10 (3)	48 (3)
Pharyngitis	5 (2)	42 (3)
Coughing	5 (2)	39 (3)
Inflicted injury	9 (3)	72 (5)
Hematuria	8 (3)	58 (4)
Urinary tract infection	4 (1)	33 (2)

*Includes drug or placebo + HCTZ Data from studies: 10, 305, 306—both short and long term. Source: Table 32

Table 33: Adverse Events (Incidence ≥ 2.0 % for Olmesartan Treatment Group) in Active-Controlled Monotherapy Studies, by Primary Term**

Primary Term	Comparator* N=460 n (%)	CS-866 N=473 n (%)
Influenza-like symptoms	28 (6)	27 (6)
Fatigue	16 (3)	14 (3)
Back pain	11 (2)	11 (2)
Pain	3 (0.7)	9 (2)
Headache	27 (6)	28 (6)
Dizziness	19 (4)	24 (5)
Diarrhea	17 (4)	17 (4)
Dyspepsia	13 (3)	11 (2)
Abdominal pain	5 (1)	10 (2)
Nausea	11 (2)	10 (2)
Lliver/biliarysystem disorders	7 (2)	13 (3)
Pharyngitis	15 (3)	11 (2)
Rhinitis	9 (2)	11 (2)
Upper respiratory infection	11 (2)	11 (2)
Coughing	14 (3)	9(2)
Bronchitis	8 (2)	8 (2)
Surgical intervention	4 (0.9)	9 (2)

*losartan, captopril or atenolol. Includes studies: 18, 19 through Week 12, and 20.
Source: Tables 43, 44:ISS

Table 34: Adverse Events (Incidence ≥ 2.0 % for Olmesartan Treatment Group) in Clinical Pharmacology Studies in Hypertensive Patients, by Primary Term**

	Placebo N=12 n (%N)	CS-866 N=94 n (%N)
Headache	4 (33.3%)	11 (11.7%)
Tachycardia	0	2 (2.1)
Bilirubinemia	0	3 (3.2)
SGPT increased	0	2 (2.1)
Hypertriglyceridemia	0	4 (4.3)
Hypoproteinemia	0	4 (4.3)
Albuminuria	0	8 (8.5)

**Includes Studies 07, 14, 16. Source: Sponsor: Table 55: ISS

Table 35: Adverse Events (Incidence ≥ 2.0 % for Olmesartan Treatment Group) in Clinical Pharmacology Studies in Normotensive Volunteers, by Primary Term**

	Placebo N=51 n (%N)	CS-866 N=280 n (%N)
Back Pain	0	6 (2.1)
Fatigue	0	9 (3.2)
Hypotension	4 (7.8)	23 (8.2)
Dizziness	1 (2.0)	25 (8.9)

	Placebo N=51 n (%N)	CS-866 N=280 n (%N)
Headache	3 (5.9)	42(15.0)
Auto-Antibody Response	0	5 (1.8)
Nausea	1 (2.0)	8 (2.9)
Tachycardia	9 (17.6)	14 (5.0)
SGOT increased	0	5 (1.8)
SGPT increased	0	12 (4.3)
CPK increased	2 (3.9)	6 (2.1)
Skeletal pain	0	6 (2.1)
Somnolence	0	5 (1.8)
Rhinitis	1 (2.0)	8 (2.9)
Procedural site reaction	0	7 (2.5)

**Includes studies: 01, 02, 12, 13, 21, 101, 102, 103, 109 (CS-866 only), 110, 116.

In the placebo-controlled monotherapy trials, the Medical Reviewer could find only two adverse events that occurred with higher frequency at higher doses.

Table 36: Dose-Relationship to dizziness and influenza-like symptoms

	Placebo	2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg
N	555 n (%)	282 n (%)	884 n (%)	527 n (%)	566 n (%)	195 n (%)	240 n (%)
Dizziness	5 (0.9)	2 (0.7)	25 (2.8)	10 (1.9)	17 (3)	8 (4.1)	12 (5)
Influenza-like symptoms	16 (2.9)	8 (2.8)	19 (2.1)	18 (3.4)	17 (3)	7 (3.6)	10 (4.2)

Source: Sponsor: ISS: Table 25

5.3 Laboratory Values: Hematology

Table 37: Change from baseline at Primary Study Time Points: Placebo-controlled Monotherapy Studies

Hemoglobin (g/dl)	Placebo (N=464)	Total CS-866 (N=2239)
Mean change from baseline	0.03	-0.25
Range	[redacted]	
Hematocrit (%)		
N	458	2225
Mean change from baseline	0.76	-0.26
Range	[redacted]	

Includes data from 204, 06, 09, 11; Studies 305 and 306 through Week 8 visit, and Study 10 through Week 12 visit. Baseline= pre-randomization visit. Source: Sponsor: ISS: Table 80A

5.31 Means

RBC: In the placebo-controlled monotherapy studies, there were slight decreases in mean hemoglobin (0.2-0.3 g/dL) from baseline to primary study time points; mean hematocrit either remained unchanged or varied by one point during these periods. Mean RBC

counts either remained unchanged or decreased by 0.1 (x 10^6). Red cell indices (MCV, MCH, MCHC) did not significantly change.

WBC: In the placebo-controlled monotherapy studies, mean WBC counts varied within 0.2 (x 10^3). Two patients on olmesartan (SE-866/09, 51/000527, 2.5 mg and SE-866/10, 22/000009, 5 mg) were noted to have transient leukopenia (WBC counts 2.1-2.2 x 10^3 range); however, both had normal subsequent counts.

Platelets were abnormal in 2 (0.67%) placebo-treated patients and 17 (1.21%) of those treated with CS-866. For patients on placebo and drug, most decreased platelet counts appeared to be transient, with most subsequent values being normal or similar to pre-treatment values. The Medical Reviewer could find one patient on placebo (SE-866/10, site 10, #000282) and 4 patients on olmesartan (SE-866/11, site 9, #000270 on 5 mg; SE-866/10, site 26 #000328 on 5 mg and site 40, #000424 on 5 mg; and site 53 #000363 on 10 mg, where baseline platelet counts were normal and final platelet counts were in the 50,000-100,000 range (Source: ISS: Table 91).

Chemistry: Sodium
One patient in SE-866/10 (CS-866 5 mg group; #0119/100167) developed hyponatremia with seizure as a Serious Adverse Event. Otherwise this Medical Reviewer did not note any significant changes related specifically to sodium.

Renal Effects
Since the focus of pre-clinical toxicology was the kidney, this reviewer will mention effects related to renal function.

Albuminuria: In the placebo-controlled monotherapy trials albuminuria as a treatment-emergent adverse event was reported in the following frequency:

Table 38: Incidence of albuminuria in placebo-controlled monotherapy trials

	Placebo	CS-866						
	N=555 n (%)	2.5 mg N=282 n (%)	5 mg N=884 n (%)	10 mg N=527 n (%)	20 mg N=566 n (%)	40 mg N=195 n (%)	80 mg N=240 n (%)	Total CS-866 N=2540 n (%)
Albuminuria	7 (1.3)	2 (0.7)	6 (0.7)	2 (0.4)	3 (0.5)	0	3 (1.3)	16 (0.6)

Source: ISS: Table 24

In study SE-866/09 two patients (CS-866 80 mg group) were reported as having albuminuria as an adverse event. In study SE-866/06 100 mg/dl proteinuria was reported in 3 CS-866 patients as occurring on a single occasion, then resolving. No pattern to proteinuria is noted in study 866-204.

Creatinine: In the placebo-controlled monotherapy studies, creatinine (mg/dL) was reported as change from baseline (with minimum and maximum values):

Table 39: Change from baseline in creatinine[1]

	Placebo	CS-866					
		2.5 mg	5 mg	10 mg	20 mg	40 mg	80 mg
Creatinine (mg/dL)							
N	466	252	639	477	507	177	217
Mean change from baseline	0	0	0	0	0	0	0
Range							

Source: ISS: Table 81: includes studies 204, 06, 09, 11, 305 and 306 through Week 8, Study 10 through Week 12.

In study 866-305, increased creatinine as a treatment-emergent adverse event was noted in 0 placebo patients and 1.2% (5/435) of CS-866 treated patients from Day 1 through Month 12. In one patient this event occurred after initiation of HCTZ, and the highest value for these patients was a creatinine of 1.5 mg/dL.

5.4 Liver Function

Mean changes from baseline in liver enzymes are presented in Table 40. Six patients receiving CS-866 (± HCTZ) and three placebo patients were discontinued because of abnormal hepatic function in the controlled trials. In the placebo-controlled monotherapy trials, the following patients were discontinued because of elevated liver function tests (of CS-866 treated patients):

1. One patient in 866-204 (#1135, randomized to CS-866 40 mg BID, discontinued at Week 4, elevated GGT noted during placebo run-in, attributed to alcohol, GGT 3 months after discontinuation remained elevated at 440 U/L);
2. One patient (long-term) in 866-305 (#18/2137, randomized to CS-866 5 mg + open-label HCTZ 25 mg, elevated ALT level (54 U/L) noted pre-randomization, AST/ALT levels at Month 9 noted at 112/57, patient withdrawn 1 month later with levels still elevated;
3. One patient in SE-866/09 (#780, randomized to CS-866 10 mg, onset Day 14 post-randomization, elevated AST, ALT, GGTP, lasted 5 months).

The Medical Reviewer could not find information regarding re-challenge with drug.

Table 40:Change from baseline-Primary Study End Points: Plcbo-controlled Monotherapy[2]

	Placebo	CS-866					
		2.5 mg	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**
SGPT (ALT) (U/L)							
N	466	252	638	477	506	176	216

[1] The Medical Reviewer noted one patient on olmesartan 5 mg (SE-866/09 #32/000762) with a screening creatinine of 1.4 mg/dL and a transient creatinine of 2.2 mg/dL at visit 7 (study day 57) with subsequent levels similar to baseline.

[2] Analysis of elevated liver enzymes was complicated by: 1.Frequent attribution to alcohol as etiology; 2. In several circumstances the baseline liver enzymes were elevated. Data from those patients with normal baseline liver enzymes whose levels increased > 2 times ULN is being analyzed further.

Mean change from baseline	0	0	0	1	0	0	1
Range	[redacted]						
SGOT (AST) (U/L)							
N	466	253	638	477	506	176	216
Mean change from baseline	0	0	0	0	-1	0	1
Range	[redacted]						
GGT (U/L)							
N	466	253	639	476	507	177	217
Mean change from baseline	1	0	2	2	1	0	-2
Range	[redacted]						
Alkaline phosphatase (U/L)							
N	465	251	635	476	504	175	216
Mean change from baseline	1	1	0	0	-1	0	-1
Range	[redacted]						
Total bilirubin (mg/dL)							
N	463	251	633	475	503	175	214
Mean change from baseline	0	0	0	0	0	-0.1	0
Range	[redacted]						

Source: Sponsor: ISS: Table 81

Included in this submission was an analysis performed by the sponsor of SGOT or SGPT > 3 Times the Upper Limit of Normal or > 3 times the baseline value. While the incidence of the total CS-866 group is similar to placebo, a dose-dependent drug effect at doses above 10 mg could not be excluded; the total N at 40 mg and above is less than that of the placebo group.

Table 41: SGOT or SGPT > 3 Times ULN or > 3 Times Baseline Value

	Placebo	**CS-866**						
		2.5 mg	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**Total**
N	555	282	884	527	566	195	240	2540
Frequency	2	0	2	3	4	0	0	9
Percentage	0.36	0	0.23	0.57	0.71	0	0	0.35

Source: ISS: Table 144

The Sponsor was asked to provide a subanalysis of patients in the placebo-controlled monotherapy trials with normal baseline liver enzymes (SGOT, SGPT, GGT) who developed elevated liver enzymes > 2 times the upper limit of normal. The following was provided:

Table 41a. SGOT, SGPT, GGT > 2 times Upper Limit of Normal(Placebo-controlled monotherapy)*

		CS-866 Total Daily Dose						
SGOT	**Placebo**	**2.5**	**5 mg**	**10 mg**	**20 mg**	**40 mg**	**80 mg**	**Total**
N	517	264	820	488	527	184	226	2365
Frequency°	1	1	6	3	4	0	2	16
Percent°	0.19	0.38	0.73	0.61	0.76	0.00	0.88	0.68
SGPT								
N	482	240	759	451	487	176	217	2194
Frequency°	3	2	8	8	6	0	1	25
Percent°	0.62	0.83	1.05	1.77	1.23	0.00	0.46	1.14
GGT								
N	426	215	717	402	455	158	197	2011
Frequency°	1	3	17	12	9	3	1	45
Percent°	0.23	1.40	2.37	2.99	1.98	1.90	0.51	2.24

*Patients with normal baseline values and subsequent values > 2 times upper limit of normal
Includes: 204, 6, 9, 11, 305 and 306 through week 8 visit; study 10 through week 12 visit. A patient is counted once in each treatment received; for total CS-866 each patient is counted only once.
°A patient is counted once in each dose group in which the abnormality occurred.

As noted in Table 41a, there is a higher frequency of increased liver enzymes in the CS-866 treatment group compared to placebo; this finding is consistent across SGOT, SGPT, and GGT.

Table 41b: SGOT, SGPT, GGT > 2 times Upper Limit of Normal (Long-term Placebo-controlled or Open-Label)*

SGOT	**Total Placebo** (89 received HCTZ)	**Total CS-866** (439 received HCTZ)
N	278	1304
Frequency°	1	17
Percent°	0.36	1.30
SGPT	**Total Placebo**	**Total CS-866**
N	261 (81 received HCTZ)	1207 (406 received HCTZ)
Frequency°	3	30
Percent°	1.15	2.49
GGT	**Total Placebo**	**Total CS-866**
N	236 (73 received HCTZ)	1168 (391 received HCTZ)
Frequency°	3	33
Percent°	1.27	2.83

°A patient is counted once in each dose group in which the abnormality occurred. For study 306, patients randomized to placebo who continued into long-term may be counted once in each of the total groups
*Patients with normal baseline values and subsequent values > 2 times upper limit of normal
Includes: studies 10, 305 and 306, both short and long-term.
A patient is counted once in each treatment received; within a total group each patient is counted only once.

5.41 In 866-204, 3 patients on active treatment and 1 on placebo had elevations in liver function tests ; the placebo patient had minimal elevations (SGPT and SGOT < 50 U/L). The other patients (#1401 on 20 mg QD, #1135 on 40 mg BID, #1392 on 80 mg QD) had abnormal GGT values on screening—271, 121, 79 respectively—and values over 200 (264, 387, 208 respectively) by Week 2 of treatment. For patients 1401 and 1135, the last GGT value remained elevated (345, 440 respectively) by Week 8. For patient #1392 on CS-866 80 mg QD, the investigator felt that the GGT fluctuations were probably drug-related and there was no history of alcohol use.

5.42 In 866-306, the rate of treatment-emergent increases in AST or ALT during double-blind therapy was 0.9% (1/116) for placebo and 2.1% (7/341) for the combined CS-866 treatment groups. According to the sponsor, alcohol was a factor in etiology of 4/7 patients and other concomitant medication was identified for 1/7 patient. The sponsor also notes a higher rate of increased GGT in the placebo group (3/116, or 2.6%) compared to CS-866 (6/341, or 1.8%).

In SE-866/09, elevated SGOT, SGPT or GGTP were observed in 5 placebo (4.5%) and 33 (4.9%) CS-866 treated patients. Onset of elevation was noted at Visits 5-9; in 5 cases (3 CS-866 and 2 placebo) etiology was noted to be alcohol.

In SE-866/10, 5 patients on CS-866 5 mg, 6 patients on CS-866 10 mg, 13 patients on CS-866 20 mg daily and 3 patients on placebo developed clinically relevant elevated liver enzyme (AST, ALT, GGTP) tests (none in this grouping were discontinued from the trial).

In SE-866/11, 8 patients on CS-866 (4 patients on 5 mg and 4 patients on 10 mg daily) and 2 patients on placebo developed elevated liver enzymes. In this group 6 out of the 8 patients on drug treatment normalized their liver enzyme elevations by the final observation.

5.43 CPK

According to the sponsor, the frequency of marked abnormalities of CPK(>1000 U/L) was 1.04% in the CS-866 group and 0.39% in the placebo group (an almost 3-fold higher incidence in the drug-treated group). In the placebo-controlled monotherapy trials, one placebo patient and 11 CS-866 treated patients had marked abnormalities in CPK levels. There appeared to be no dose-response relationship for the CS-866 patients. The sponsor claims that CPK values were already high at baseline for 7 of the 11 patients on active drug. In all 11 patients on CS-866, the markedly abnormal CK values were transient, and either normalized or were no longer markedly abnormal (i.e. > 1000 U/L) while the patients were still receiving study drug. The investigator associated these elevations with physical activity in 7 of the 11 patients. Data for CPK were not obtained in the active-control trials; in addition, the isozyme determinations were mostly of the MM type.

In study 866-204, 12 patients (4%) on active therapy and 1 patient (2%) on placebo had elevations in CPK; in 9/12 patients on active treatment, these elevations were transient and resolved while these patients continued therapy. Ten out of these 12 patients were male (83%). In 11/12 of patients on active therapy, the elevated CPK was attributed to "physical activity." One female patient (1177, CS-866 20 mg QD) with myalgias on Day 23 of treatment and CPK elevations was discontinued from treatment after Week 4; muscle pains resolved 24 days after discontinuing drug, while CPK decreased from 1147 U/L to 560 U/L on drug, to 669 U/L off drug. Another patient (#003228, site 31, 866-306, had a screening CPK of 212 and a Week 8 CPK of 1096 (U/L) on olmesartan 5 mg (no subsequent CPK noted in Table 91).

Increased CPK, however, resulted in discontinuation of only one patient (003077,CS-866 20 mg) in study 866-306.

In the long-term placebo-controlled and open-label trials, seven additional patients administered CS-866 had marked abnormalities of CPK. In all 7 CS-866 patients, the CPK values were already high at baseline or the markedly abnormal CPK values were transient, and normalized while the patients were still receiving study drug. The CPK

elevations in 5 of the 7 CS-866 patients were associated by the investigator with physical activity.

5.5 Vital Signs (Heart Rate)
In the vital signs database, there were small mean decreases in heart rate (< 2 bpm) without evidence of a dose-response relationship (See integrated summary of efficacy Figure 3 in Caucasians which a showed a trend but may not be statistically significant or clinically meaningful).

5.6 Withdrawal /Abuse Potential
Withdrawal effects were evaluated in an interim analysis of study [redacted] where patients completing SE-866/10 with mean DBP ≤ 90 mm Hg could enter [redacted] (a 2 week placebo washout period followed by 52 weeks of study drug). The primary objective of this interim analysis was to investigate BP effects consistent with rebound hypertension after cessation of drug therapy. A secondary objective was to assess safety data for this 2 week placebo washout period, especially adverse events related to sympathetic overactivity. As noted in results of study [redacted] there appears to be no evidence for rebound effects.

According to the sponsor, "there were no cases of rebound hypertension reported in any phase 2 or phase 3 study."

5.7 Human Reproduction Data
One patient (Study 866-306, Patient # 003168), a 35 year old Black female with a history of bilateral tubal ligation, became pregnant after completing the double-blind portion (CS-866 5 mg group) and entering the open-label extension (CS-866 20 mg daily, titrated to CS-866 40 mg daily and 12.5 mg HCTZ added). As of Month 4, BP reported as 144/102 mm Hg. After 85 days of open-label therapy, the patient reported a positive home pregnancy test and delayed menses. This patient was withdrawn from the study (early termination BP 137/93 mm Hg) and underwent an elective first trimester abortion. The status of the fetus was unreported in this submission.

5.8 Other analyses

5.9 Adverse Events by Gender
In the placebo-controlled monotherapy trials, the following adverse events occurred with a higher frequency in one gender or the other. Except for Urinary Tract Infection (which occurred with a higher frequency in females), the rest of these occurred more frequently in the male population compared to females. However, it should also be noted that the adverse event rates in the males given CS-866 are not higher than that seen in the males given placebo.

Table 42: Adverse Events where there was ≥ 1% difference in rates by Gender

	Male		Female	
	Placebo N=316 n (%)	**CS-866 N=1340 n**	**Placebo N=239 n (%)**	**CS-866 N=1200 n (%)**

		(%)		
Headache	27 (9)	61 (5)	13 (5)	80 (7)
↑ Gamma GT	10 (3)	42 (3)	3 (1)	15 (1)
CPK increased	5 (2)	32 (2)	1 (0.4)	8 (0.7)
Hyperglycemia	13 (4)	25 (2)	2 (0.8)	7 (0.6)
Urinary Tract Infection	2 (0.6)	3 (0.2)	3 (1)	18 (2)

Source: Table 8.4.12.2a: Sponsor

5.10 Adverse Events by Age

In the placebo-controlled monotherapy trials, the only adverse event that was increased in the elderly (≥ 65 years of age) treated with olmesartan was dizziness, which occurred in 49/2025, or 2.4% of those < 65 years of age, and in 21/515, or 4.1% of those ≥ 65 years old. (Source: Table 8.4.12.1a: ISS: Sponsor)

5.11 Adverse Events by Race

Listed below are adverse events where Black and Non-black CS-866 treated patients differed by ≥ 2% and where Adverse Events in at least one CS-866 group is greater than placebo. It can be seen that there are increased rates of headache, increased CPK, cough, rhinitis, hyperglycemia and glycosuria in the Black vs. nonBlack groups. However, an analysis by race is limited by the relatively small numbers of non-Caucasian patients in the database (this is particularly true regarding numbers of Black patients on placebo).

Table 43: Adverse Events by Race (Black and non-Black)

	Non-Black		**Black**	
	Placebo N=529 n (%)	**CS-866 N=2416 n (%)**	**Placebo N=26 n (%)**	**CS-866 N=124 n (%)**
At Least One AE	219 (41)	995 (41)	18 (69)	76 (61)
Chest pain	2 (0.4)	20 (0.8)	1 (4)	5 (4)
Headache	37 (7)	124 (5)	3 (12)	17 (14)
CPK increased	4 (0.8)	28 (1)	2 (8)	12 (10)
Hyperglycemia	15 (3)	27 (1)	0	5 (4)
Glycosuria	3 (0.6)	4 (0.2)	0	4 (3)
Rhinitis	9 (2)	34 (1)	0	6 (5)
Cough	3 (0.6)	15 (0.6)	1 (4)	7 (6)

Source: ISS: Table 8.4.12.3a, Table 167

5.13 Overdose Experience

There were no reports associated with this submission regarding accidental overdosage.

5.14 Conclusions

1. Of the treatment-emergent clinical adverse events in the placebo-controlled monotherapy studies, dizziness (3% olmesartan, 0.9% placebo) and back pain (2% olmesartan, 1% placebo) occurred more frequently in olmesartan compared with placebo. In the long-term studies (double-blind and open-label), most common adverse events (> 2 %) were influenza-like symptoms, back pain, dizziness, arthralgias, arthritis, and skeletal pain.
2. Dizziness and angina were the most common (>0.1% and greater than comparator) clinical adverse events leading to study discontinuation in the Phase 2/3 studies.
3. There was an increased frequency of dizziness as well as influenza-like symptoms at higher doses of olmesartan. Dizziness as an adverse event is also seen with valsartan, candesartan, and losartan.
4. The percentage of SGOT/SGPT elevations (> 3 Times baseline or Upper Limit Normal) appears to be higher in the olmesartan 10 mg and 20 mg treatment group compared with placebo; however, the event rates are low. A dose-related rise in liver function tests in some patients cannot be excluded.
5. The frequency of marked (>1000 U/L) CPK elevations was approximately 3-fold higher in the olmesartan-treated group compared with placebo.
6. In this review,the question of mutagenicity/carcinogenicity will be further assessed by the CAC of the Agency. From a safety standpoint, the event rates for cancer are too low (and the length of treatment relatively short) for an adequate clinical assessment.

INDIVIDUAL CLINICAL PLACEBO-CONTROLLED STUDIES

6.0 Study SE-#866-204

6.01 Title A Randomized, Double-Blind, Placebo-Controlled, Dose-Ranging Study of CS-866 Using Ambulatory Blood Pressure Monitoring in Hypertensive Patients

Design Summary

This placebo-controlled, parallel-group, double-blind, multicenter study randomized 334 subjects (adults with essential hypertension marked by average cuff DBP $\geq$ 100 mm Hg and $\leq$ 115 mm Hg and mean daytime DBP by ABPM of $\geq$ 90 mm Hg) to 8 weeks of placebo or one of 6 orally administered olmesartan arms: once-daily olmesartan at 5, 20, or 80 mg/d; or twice-daily olmesartan at 2.5, 10, or 40 mg BID. The primary endpoint was an evaluation for monotonic, non-decreasing, antihypertensive effect with respect to reduction from pre-treatment mean 24 hour DBP (ABPM derived) for once-daily olmesartan and placebo.

6.1 Enrollment (866-204)- Inclusion Criteria

Adult (>18 years of age) patients of both genders with essential hypertension (average cuff DBP > 100 mm Hg and $\leq$ 115 mm Hg and ABPM mean daytime DBP of $\geq$ 90 mm Hg) were to be eligible for enrollment if they manifested:

- no more than a 7 mm Hg difference between the qualifying BPS.

- body weight within 30% of ideal

- normal screening laboratory values.

Excluded from enrollment were to be:

- pregnant or lactating women and women of childbearing potential (defined as women who have not undergone a hysterectomy or tubal ligation in the prior 6 months, and has not been post-menopausal) who did not plan to continue using an acceptable contraceptive method throughout the study (i.e. oral, injectable or implantable hormonal contraceptives, intrauterine device, diaphragm plus spermicide, or female condom).

- those with physical findings of serious cardiovascular (other than hypertension), renal, endocrine, pulmonary, metabolic, hepatic, neurologic, hematologic/ oncologic, or gastrointestinal disorders.

- those within 6 months of AMI, cerebrovascular accident, or transient ischemic attack.

- those with angina pectoris, congestive heart failure, arrhythmia that required medication, seizure disorder, the active presence of malignancy, pheochromocytoma or renal vascular disease.

- history of drug abuse or alcohol addiction during the previous two years.

- history of classic allergic response to drugs of the angiotensin II antagonist class

- history of angioneurotic edema

- non-dominant arm <24 or >42 cm in circumference (arm extended, upper arm midpoint circumference)

- requirement for any agent with antihypertensive activity (diuretics, β-blockers, α- and β-blocker combinations, calcium channel blockers, ACE-inhibitors, peripheral vasodilators), potassium supplements, salt substitutes, carbonic anhydrase inhibitors, coronary vasodilators, cardiac glycosides, antiarrhythmic agents, anticoagulants, psychotropic agents, sympathomimetics, or anti-Parkinson drugs.

6.2 Treatment (SE-#866-204)
Prior antihypertensives were to be discontinued for 7 days, followed by a 14-day single-blind placebo run-in period. Patients were randomized to 8 weeks of placebo or once-daily oral olmesartan at 5, 20, or 80 mg/d, or twice-daily oral olmesartan at 2.5, 10, or 40 mg bid. Patients who were assigned to the olmesartan once-daily doses took olmesartan for the morning dose and matching placebo for the evening dose.

If the daily average sitting cuff DBP was> 120 mm Hg, or the daily average sitting cuff SBP was >200 mm Hg the patient was to be discontinued.

6.3 Endpoints (866-204)
The prespecified primary endpoint was an intent-to-treat evaluation for monotonic non-decreasing antihypertensive effect with respect to reduction from pre-treatment mean 24 hour DBP (ABPM) for once-daily olmesartan and placebo. Patients were randomized in a 1: 1: 1: 1: 1: 1: 1 ratio. Black and non-Black subsets were to be analyzed separately (with recognized limitations of power for the assessment of effect in Blacks).

ABPM was to be conducted using a [redacted]
The ABPM-derived 24 hour DBP was : [redacted]

Trough-to-peak ratios were evaluated as follows: BP response was defined as change from pre-treatment to last visit, findings in the last hour of recording were defined as trough, peak was defined as the maximum BP response was, and response was adjusted for placebo response.

The safety endpoints were:
- history and physical examination
- BP and HR in supine and sitting position
- 12-lead ECG
- chest radiograph.
- AE.

6.4 Samples for laboratories and urinalysis were obtained pre-treatment, on day 1, and at weeks 1, 2, 4, 6 and 8.

Table 44: Schedule of procedures- study 866-204

EVENT	Screen	Days -21 to -2	Day -1	Day 1 t=0	Day 1 t=4	Day 8	Day 15	Day 29	Day 43	Day 57	Day 58
Informed Consent	●										
Medical History	●										
Chest X-ray	●										
Physical Examination	●			●							●
Blood Pressure Cuff t=0 hrs		●	●	●	●	●	●	●	●	●	
ABPM			●			○	○	○	○	●	
12-Lead ECG	●			●				●			●
Hematology	●			●		●	●	●	●		●
Blood Chemistry	●			●		●	●	●	●		●
Urinalysis	●			●		●	●	●	●		●
Pregnancy	●			●							●
Adverse Events		●	●	●	●	●	●	●	●	●	●
Compliance		●	●	●		●	●	●	●	●	●

6.5 Statistics (866-204)

The prespecified primary analysis was an intent-to-treat evaluation for an effect of once-daily olmesartan dosing to monotonically lower mean 24 hour DBP, as measured by ABPM. Testing was to be two-sided at an alpha level of 0.05. Bartholomew's test for ordered alternatives in the one-way analysis of variance was used. Black and non-Black populations were to be analyzed as separate studies.

6.6 Datasets (866-204)

Included in the intent-to-treat dataset were those patients who had received at least one dose of randomized drug, had an evaluable pre-treatment ABPM at baseline and at least one scheduled study visit after the pre-treatment visit.

Exploratory secondary analyses were also conducted (including those undertaken on

modified datasets), but without formal hypothesis testing.

Results other than Efficacy per se (866-204)
Validation of data. (study #866-204)
Reportedly no bias was introduced by including the data from Dr. Fiddes' center 12.
Covariates (866-204)
The treatment groups were reasonably balanced at pre-treatment baseline.See tables.

Table 45: Pre-treatment characteristics of *non-black* subjects(# 866-204)

		OLMESARTAN GROUP					
		Once-daily			Twice-daily		
covariate	Placebo	5 mg/d	20 mg/d	80 mg/d	2.5 mg BID	10 mg BID	40 mg BID
	n= 41	n= 39	n= 39	n= 41	n= 43	n= 41	n= 45
mean age (yr)	53.7	56.1	52.3	52.4	53.6	53.0	56.4
% male	61.0	66.7	66.7	68.3	62.8	63.4	66.7
% female	39.0	33.3	33.3	31.7	37.2	36.6	33.3
mean weight (lb)	181.7	186.0	189.3	186.8	189.3	185.7	187.9
mean 24 hr DBP (ABPM)	94.2	96.3	95.1	94.8	93.8	94.4	95.2
mean 24 hr SBP (ABPM)	149.3	150.2	148.8	148.6	147.1	148.2	152.1
	n = 42	n= 41	n = 41	n = 42	n = 43	n =44	n =46
mean cuff SiDBP	103.5	104.5	104.1	104.2	103.5	103.8	104.3
mean cuff SiSBP	157.0	156.0	154.7	155.0	154.4	155.0	160.0

[source: sponsor's table 7, Table 12A and Table 14A]

Table 46: Pre-treatment characteristics of *black* subjects (study # 866-204)

		OLMESARTAN GROUP					
		Once-daily			Twice-daily		
covariate	Placebo	5 mg/d	20 mg/d	80 mg/d	2.5 mg BID	10 mg BID	40 mg BID
	n= 5	n= 4	n= 2	n= 4	n= 6	n= 4	n= 3
mean age (yr)	50.2	58.5	46.7	38.9	53.6	48.4	50.5
% male	40.0	50.0	50.0	75.0	100.0	25.0	100.0
% female	60.0	50.0	50.0	25.0	0.0	75.0	0.0
mean weight (lb)	198.0	163.0	211.0	156.5	195.5	197.8	212.3
mean 24 hr DBP (ABPM)	93.6	96.7	103.1	95.4	99.1	98.4	92.1
mean 24 hr SBP (ABPM)	148.9	155.7	159.7	143.4	151.3	148.6	141.0
	n = 5	n = 4	n = 3	n = 4	n = 6	n = 4	n = 3
Mean cuff DBP (sitting)	101.1	104.4	105.3	103.6	103.9	105.5	103.5
mean cuff SBP (sitting)	146.2	152.5	163.5	146.8	155.3	149.0	147.0

[source: sponsor's table 107, Table 112A and Table 114A]

6.7 Patient disposition (866-204)

There were 334 patients randomized (302 non-Black patients and 32 Black patients), of which 36 (10.8%) discontinued. The dropouts were reasonably well-distributed across dose groups. In the following descriptions of the attributed causes of dropouts, each subject is counted only once.

Table 47: All dropouts: number and mean rate (# 866-204; all-randomized dataset)

		Once-daily olmesartan			Twice-daily olmesartan		
	PLACEBO (n = 48)	5 QD mg (n = 45)	20 mg QD (n = 45)	80 mg QD (n = 48)	2.5 mg BID (n = 50)	10 mg BID (n = 48)	40 mg BID (n = 50)
Adverse event	2 (4%)	2 (4%)		1 (2%)		1 (2%)	2 (4%)
Patient request		1 (2%)	4 (9%)		1 (2%)	2 (4%)	1 (2%)
Uncontrolled BP	3 (6%)						
Non-compliance					1 (2%)		
Investigator Judgement	2 (4%)	1 (2%)		1 (2%)	1 (2%)	1 (2%)	1 (2%)
Lost to follow-up					1 (2%)	1 (2%)	
Protocol violation		1 (2%)		2 (4%)			1 (2%)
Did not meet ABPM entry criteria	1 (2%)						
other				1 (2%)			
Total dropouts	8 (17%)	5 (11%)	4 (9%)	5 (10%)	4 (8%)	5 (10%)	5 (10%)

[source: sponsor's Table 3c] Each subject is counted only once in this analysis.

6.7.1 Datasets (866-204)

As prespecified, the dataset upon which the primary analysis was undertaken was a reasonable reduction of the all-randomized dataset such that only those who had received at least one dose of randomized medication and who had at least one on-therapy BP evaluation were included (with treatment assignment as per the intent-to-atreat principle. Th distribution of subjects in this dataset (abbreviated as "ITT") is shown IN Table 48 below.

Table 48: Distribution of all randomized subjects (# 866-204)

	PLCBO.	QD GROUPS			BID GROUPS		
		5 mg	20 mg	80 mg	2.5 mg	10 mg	40 mg
Non-Black	43	41	42	43	43	44	46
Black	5	4	3	5	7	4	4
Total	48	45	45	48	50	48	50

Source: sponsor's Table 6.1.1.3-1

Table 49: Number of Patients in the ITT dataset (study 866-204)

		ITT for ABPM	ITT for cuff BP
Non-Black	302	289	299
Black	32	29	29

source: sponsor's Table 7.1-1

6.8 Efficacy results - Primary endpoint (study 866-204)

Non-Black patients: In this subgroup (i.e. non-Black patients) the monotonic trend for increasing antihypertensive response (vis a vis the reduction from pre-treatment mean 24 hour DBP) with higher doses was reportedly statistically significant for once-daily dosing ($p < 0.0001$). The integrated 24 hour mean response to 80 mg was not higher than that of 20 mg. The results of the ITT analysis were as follows:

Table 50: Mean change from pretreatment 24 hour DBP
(Non-blacks, ABPM, study 866-204)

GROUP	CHANGE IN 24 HOUR DBP BY ABPM
Placebo	0.8
5 mg qd	-9.3
20 mg qd	-11.2
80 mg qd	-9.9

Source- sponsor's Table 7.5.1.1-1

Once-daily olmesartan decreased diastolic BP as early as week 1 for all groups except the 5 mg/d group. The effect of twice-daily dosing was reportedly also statistically significant (nominal $p < 0.0001$), as was (at the same nominal significance level) the decrease in daytime and nighttime DBP, mean 24 hour SBP, and mean daytime and nighttime DBP and SBP.

Systolic BP effect was also evident. Olmesartan decreased the mean 24 hour, daytime and nighttime SBP, at reportedly low nominal p values (< 0.0001).

In non-black patients receiving once-daily dosing the diastolic trough-to-peak BP ratios ranged from 63-64% for the low and middle dose groups, and was 79% for the high dose (80 mg/d) group, while the systolic trough-to-peak BP ratios were 70% for the 5 mg/d group, 52% for the 20 mg/d group, and 72% for the 80 mg/d group.

Again in non-black patients, descriptive comparison of once-daily with twice-daily dosing shows some evidence of higher point-estimated trough-to-peak BP ratios with divided twice-daily dosing, but this is not consistently demonstrated (i.e. the low and high doses do not reproduce this finding). See my interpretation in the comment section below.

Table 51: ABPM trough-peak ratio in non-blacks (ITT, # 866-204)

5 mg total dose		20 mg total dose		80 mg total dose		
QD	**BID**	**QD**	**BID**	**QD**	**BID**	
Diastolic BP						
63.9%	62.0 %	62.6 %	74.3%	79.1%	69.4%	
Systolic BP						
70.1%	68.9 %	51.8 %	60.2%	72.3%	62.6%	

Source: sponsor's Table 21

The data were inadequate for estimating trough-to-peak ratios in the Black population (due to small sample size, large variability, and in many instances opposite directions of change at trough vs peak).

Additional mean data (including cuff data) are presented in tabular and graphical form on the following pages.

Table 52: Mean changes from pre-treatment DBP at the last observation (mmHg)
(Non-Black Patients; ITT; study 866-204)

GROUP	24 hour dbp	daytime dbp	nighttime dbp
Placebo	0.8	-0.1	1.7
5 mg qd	-9.3	-10.5	-8.2
20 mg qd	-11.2	-12.8	-9.6
80 mg qd	-9.9	-10.4	-9.4
2.5 mg bid	-7.9	-8.8	-7.1
10 mg bid	-10.7	-11.5	-9.9
40 mg bid	-10.7	-13.0	-8.4

Source- sponsor's Table 7.5.1.1-1

The last observation was week 8 in completers, and earlier in dropouts.

Table 53: Mean changes in SBP at the last observation (mmHg) (Non-Black Patients; ITT; study 866-204)

GROUP	24-hour sbp	daytime sbp	nighttime sbp
Placebo	1.1	0.3	1.9
5 mg qd	-14.3	-15.9	-12.8
20 mg qd	-15.2	-17.3	-13.2
80 mg qd	-14.8	-16.1	-13.5
2.5 mg bid	-11.2	-12.6	-9.7
10 mg bid	-15.3	-16.1	-14.6
40 mg bid	-16.1	-19.3	-12.9

source- sponsor's Table 75.1.1.2

The last observation was week 8 in completers, and earlier in dropouts.

Figure 11: ABPM-based DBP changes from pre-treatment, at last visit (Non-Blacks, ITT, sponsor's fig 711)

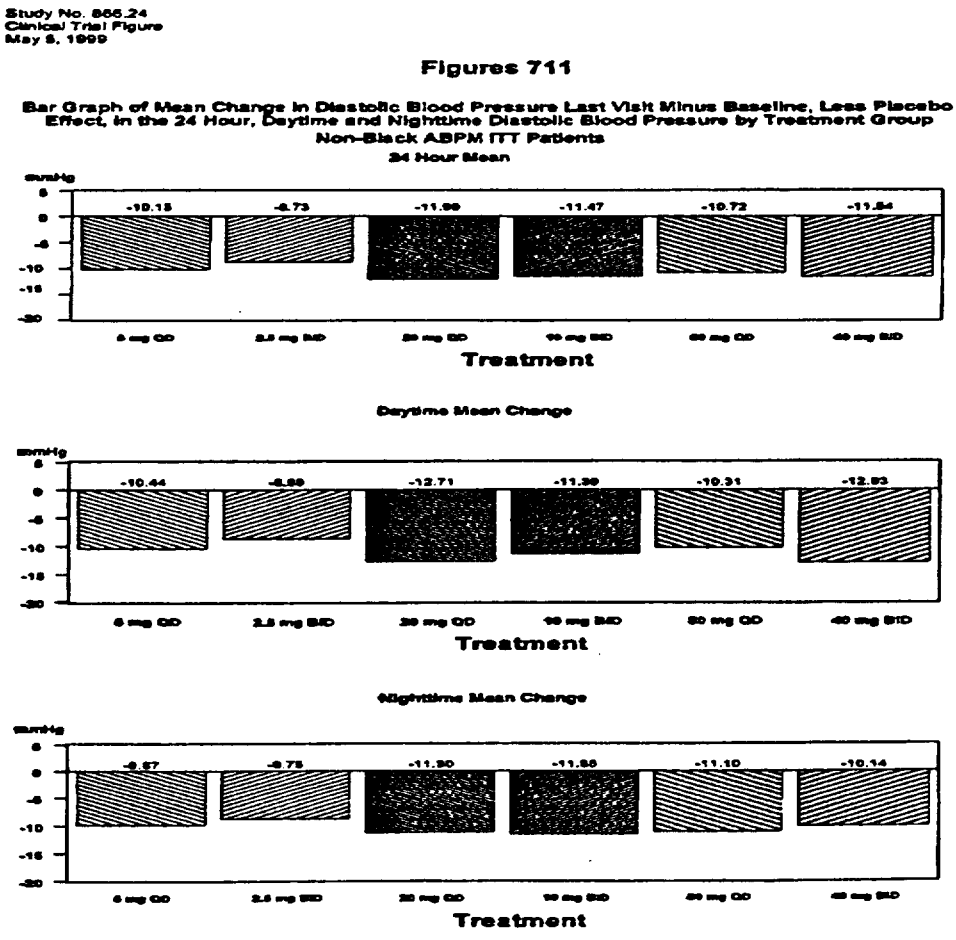


Figure 12: ABPM-based DBP changes from pre-treatment, at last visit
(Non-Blacks, ITT; sponsor's fig 710)

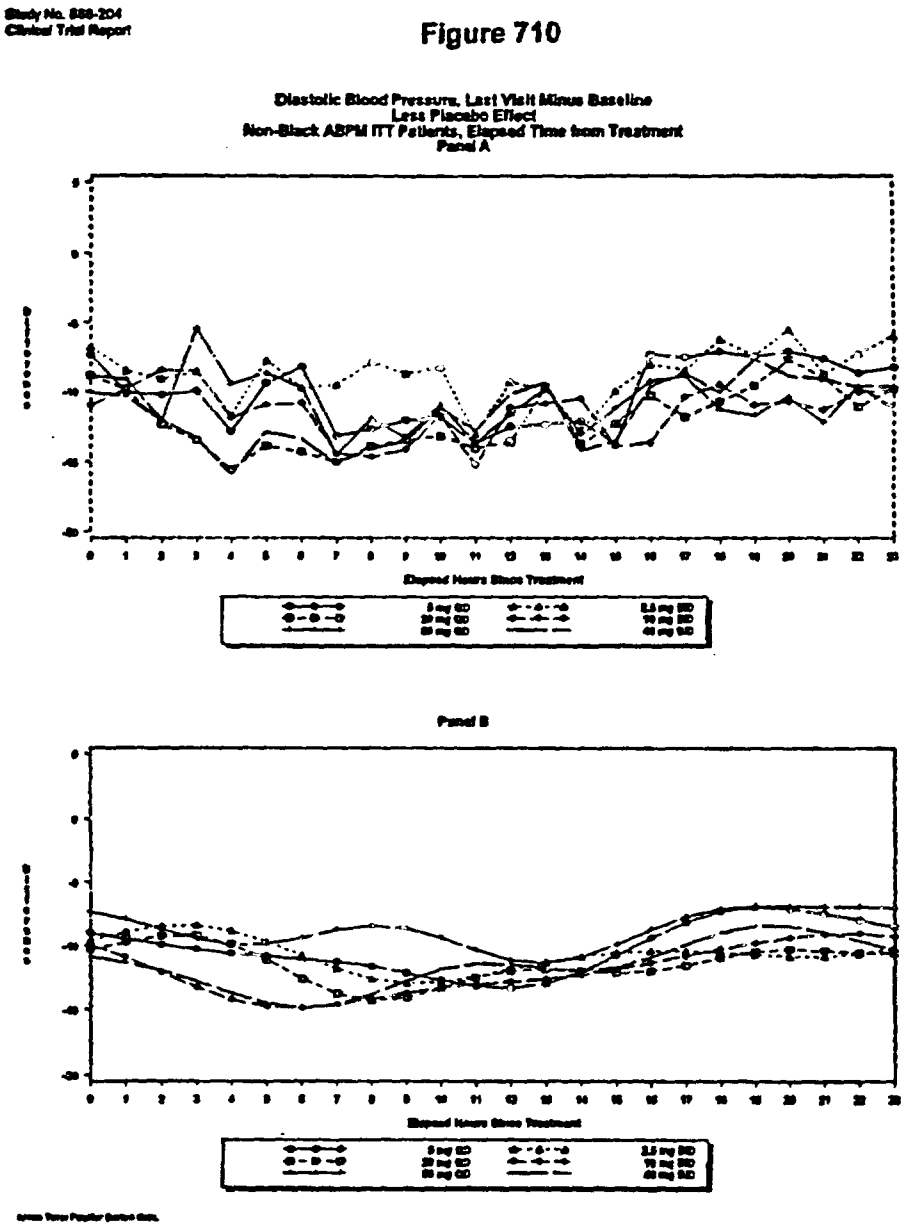


Table 54: Cuff-based DBP changes from pre-treatment at week 8 – Study #204
(Non-Blacks, ITT; sponsor's table 35A)

See next page

Study No. 666-204
Clinical Trial Report
April 2, 1998; v0.1

Figure 13:
Timecourse of cuff-based sitting DBP changes from pre-treatment-SE - #204
(Non-Blacks, ITT; sponsor's fig 740)

Table 35A
Cuff Measurement Results
Mean Change in Diastolic BP From Baseline[1] to Week 8
Non-Black, Cuff Intent-to-Treat Patients Within Visit Windows[2]

		5 mg Total Dose			20 mg Total Dose			80 mg Total Dose		
	Placebo	QD	BID	Comb.	QD	BID	Comb.	QD	BID	Comb.
Total Randomized	43	41	43	84	42	44	86	43	46	89
					Sitting (mm Hg)					
Mean	101.0	96.4	92.7	94.5	92.6	92.1	92.3	91.5	92.3	91.9
±SD	±7.0	±7.8	±9.2	±8.7	±8.7	±9.4	±9.0	±11.9	±9.6	±10.6
Mean Change	-2.2	-8.4	-10.6	-9.6	-11.4	-11.8	-11.7	-12.7	-11.9	-12.3
±SD	±6.1	±6.6	±7.8	±7.3	±8.4	±7.6	±8.0	±10.7	±8.8	±9.7
n	37	37	39	76	38	39	77	39	43	82
					Supine (mm Hg)					
Mean	99.5	96.2	89.9	93.0	91.1	87.9	89.5	89.5	89.8	89.6
±SD	±7.4	±7.2	±9.5	±9.0	±9.2	±8.5	±8.9	±11.2	±9.5	±10.3
Mean Change	-2.1	-7.0	-11.3	-9.2	-10.5	-13.4	-12.0	-12.5	-11.9	-12.2
±SD	±6.5	±7.0	±8.6	±8.1	±9.0	±8.5	±7.9	±9.3	±8.9	±9.0
n	37	37	39	76	38	39	77	39	43	82