Table 99: Screening failures - 866-10

ITT Population	N	%
Number of patients screened	**645**	**100**
Number of screening failures (Total)	45	6.97
Dropouts prior to randomization		
Adverse event	1	3.8
Withdrawal of consent	9	34.6
Randomization Criteria not met	8	30.8
Concomitant Medication	1	3.8
Others	7	25.9
Total	26	100
Withdrew after a single dose	9	
Termination of study by sponsor(Center 37)	10	
Total	19	

Table 100: Withdrawal of ITT Patients by treatment group - 866 -10

No of patients	Placebo	5mg	10mg	20mg	Total
Randomized	93	178	177	171	619*
Withdrawn	33	19	18	12	**82+11**
Completed	56	153	153	156	518

*19 patients withdrew without post-randomization data.

11.73 Demographics and group comparability

All the randomized patients were Caucasians and had been diagnosed with essential hypertension prior to randomization (Table 102). The mean age of the ITT population was 54 years. Males were diagnosed earlier with hypertension at a median age of 52 compared to 55 years for females (Tables 101 - 102). Table 102 presents the age distribution of the ITT and PP patients. Of 85 very elderly ITT patients 73 (85.9%) completed the trial. No significant differences in baseline measurements were seen among the 4 treatment groups including age, race including arm used for BP measurement: the right arm use [(e.g. BPDIA3= 41% (<90mmHg), and left arm (BPDIA3=41.5% (<90mmHg)] (Table 101). Previous duration of hypertension and concomitant medications revealed no differences and the percentages of non-completers in the placebo and treated ITT groups showed no significant imbalance in demographic characteristics, age class, and baseline variables (Table 101). Comparisons of ITT and PP populations confirmed group comparability (Tables 97 and 102). The rate of withdrawal was comparable in both periods. In period I (V1-V8) - the short active treatment 12-week period, withdrawal was 8.9% and in period II withdrawal rate was 7.1% after the 40-week long extension period.(V9-14). Apart from an excess of females randomized compared to males, there is essentially, no other differences were seen between treatment groups (age, concomitant medication or previous intake of anti-hypertensive agents, exposure to drug, weight, and duration of hypertension and BMI).

Table 101: Demographics - ITT - 866-10

	Placebo		5mg		10mg		20mg	
	M	F	M	F	M	F	M	F
Age(yrs) N Mean Median SD	46 58 55.5 12.72	43 62.14 66.0 13.43	75 56.04 56.0 11.21	97 61.7 2 60.0 13.0	87 54.94 56.0 11.21	104 63.07 64.0 12.49	70 56.27 58.0 13.06	98 62.12 63.0 14.31
Race: Caucasian	100%		100%		100%		100%	
GenderN (%) Male Female Total	46(7.7%) 43(7.2%) 89(14.8%)		75(12.5%) 97(16.2%) 172(28.7%)		67(11.2%) 104(17.3%) 171(28.5%)		70(11.7%) 98(16.3%) 168(28.0%)	Total (N) 258 342 600
Weight (kg) SD	83.75± 10.95	74.7 ± 11.6	85.06 ± 13.07	72.6 7± 11.2 8	89.7 6± 19.1 5	73.32 ± 14.22	86.32± 12.38	76.66± 14.70
*Age-Hptn diagnosis	51.97	55.7 7	51.05	55.8 2	49.5 2	57.12	52.09	55.29

*Mean years in months

Table 102: Demographics - Comparisons between ITT and PP - 866-10

	Placebo		5mg		10mg		20mg	
	ITT	PP	ITT	PP	ITT	PP	ITT	PP
Age(yrs)								
N	89	44	172	113	171	126	168	135
Mean	58.97	58.50	59.24	58.65	59.88	59.34	60.52	59.87
Median	57.0	59.0	58.0	58.0	60.0	56.5	60.0	59.0
SD	13.35	13.80	12.84	12.43	12.34	12.27	13.80	13.90
Race: Caucasian	100%		100%		100%		100%	
Hptn. (months)	65.28	61.20	68.31	69.88	69.04	68.98	76.06	74.30
Gender N %)								
Male	46 (7.7%)	21(%)	75 (12.5%)	51 (%)	67 (11.2%)	49 (%)	70 (11.7%)	60(%)
Female	43 (7.2%)	23(%)	97 (16.2%)	62 (%)	104 (17.3%)	77 (%)	98 (16.3%)	78(%)
Total	89 (14.8%)	44(%)	172 (28.7%)	113 (%)	171 (28.5%)	126 (%)	168 (28%)	138
*Age-Hptn diagnosis	53.40	53.34	53.57	52.86	54.14	53.57	54.20	53.76

11.75 Adequacy of Clinical Experience and Quality of Data

Based on sample size of all studies in this NDA there is adequate clinical experience for a drug of this class,. The quality of data in this study is adequate in respect of group comparability despite the statistical analyses that pre-specified analysis of ITT patients and instead used PP patients. Most patients in the four treatment groups were 100% compliant during the randomized double-blind period of the trial.

11.8 Analysis of Efficacy

Primary efficacy endpoint is the "change from baseline in sitting diastolic blood pressure (SiDBP) at trough level of CS-866 at dose levels of 5mg, 10mg, and 20mg o.d. after 12 weeks of treatment compared to placebo in the ITT population". Review of primary efficacy is therefore based on analyses of data at the end of the 12-week, double blind period or LOCF values where applicable.

The final on-therapy changes from baseline in trough SiDBP by dose for ITT patients compared to placebo at visit 4 and at week 12 are presented in Tables 103, 104 and Figure 48. Table 105 shows a statistically significant interaction when data are pooled across centers (p=0.0548) and when the interaction is between the treatment and ITT patients (p=0.0237). Table 106 shows the statistical effects of removal of centers with anomalous results.

Table 103: Mean Seated baseline DBP, SBP, HR-Trough -at visits 2-4 - ITT - 866-10

Trough	Placebo (N=89)	5mg (N=172)	10mg (N=171)	20mg (N=166)
DBP (mean±SD)	104.62±3.29	104.41±2.86	104.53±2.96	104.90±3.18
SBP (mean±SD)	163.21±11.77	163.56±12.01	164.31±11.28	165.70±12.30
HR (mean±SD)	75.20±8.48	74.78±7.02	74.25±6.73	74.51±6.60

Visits 2-4 Placebo-run-in period.

Table 104: Mean SiDBP, SiSBP - Plcbo subtracted differences week 12 - ITT

Baseline value	Placebo	5mg	10mg	20mg
SiDBP				
N	89	172	171	166
Mean	-10.20	-15.17	-15.91	-16.84
Placebo-subtracted		-4.97	-5.71	-6.64
Difference frombaseline	0.0001	0.0001	0.0001	0.0001
p-value	(-11.66, -8.74)	(-7.09,-2.84)	(-7.84,-3.58)	(-8.77,-4.51)
95%CI				
Individual p-values		0.0001	0.0001	0.0001
SiSBP				
N	89	172	171	166
Mean	-11.21	-19.23	-19.12	-21.03
Placebo-subtracted		-8.02	-7.91	-9.82
SiPR Trough				
N	89	172	171	166
Mean Visits 2-4	75.20±6.48	74.78±7.02	74.25±6.73	74.51±6.60
Mean Visit 8	75.17±8.60	73.65±6.26	73.22±7.88	73.50±7.51
Source- Reviewer; SiPR=Sitting Pulse rate, SiDBP=Sitting diastolic BP; SiSBP=Sitting systolic BP				

p-value for overall treatment effect p<0.0001.

Table 105: Decrease from baseline Mean SiDBP- Trough - visit 8 -ITT

Source	N	Treatment	Mean ±SD	p-value
ITT Protocol	89*	Placebo	-10.2 ±7.96	
ITT Protocol	172*	5mg	-15.15 ±7.55	
ITT Protocol	171*	10mg	-15.93 ±6.66	
ITT Protocol	166*	20mg	-16.93 ±7.30	
ITT Pool*Treatment	600 *			0.0548
Center Number	46 DF=1			0.0001
Treatment	3 DF=3			0.0001
CenterNo*Treat	122			0.0001
ITT Pool	13			0.0001
Treatment	3			0.0001
ITT*Treat	39 centers			0.0237

ITT=Intent – to-Treat; DF=Degrees of Freedom; * Randomized Population.

Table 106: Interaction and removal of centers 866-10

Center/Pooled center removed*	**P-values of treatment* pooled center interaction**
None	0.02737
Center 2	0.0976
**Center 5,20,22,55	0.1862
Center 5	0.0569
Center 20	0.0989
Center 22	0.0440
Center 55	0.0090
Center 2 and 20	0.3471
Center 2 and pooled 5,20,22,& 55	0.6126

*Center 37 was removed from study and efficacy analysis because the investigator refused to be audited. **Anomalous results

Individual p-values for difference from placebo to week 12 (V 8) for 5mg, 10mg and 20mg=0.0001 are presented in Table 107 below. The treatment effect versus dose shows a dose response for the seated diastolic blood pressure at end of study (R^2=0.8957). Graph not shown.

Table 107: Decrease in mean SiDBP-trough from baseline-wk 12 (visit 8) PP

Treatment	Placebo	5mg	10mg	20mg
N	44	113	126	135
Least square means 95%CI	-12.54	-16.10	-16.35	-18.27
Difference from placebo-95%CI		-3.56 (-6.25,-0.87)	-3.81 (-6.47,-1.15)	-5.73 (-6.73,-3.09)
Individual p-values		0.0064	0.0028	0.0001
Difference from baseline p-values	0.0001	0.0001	0.0001	0.0001

ANOVA and Dunnett's many to one procedure used for above data.

Figure 48:Plcbo-subtracted difference-DPB/SBP by dose-wk12

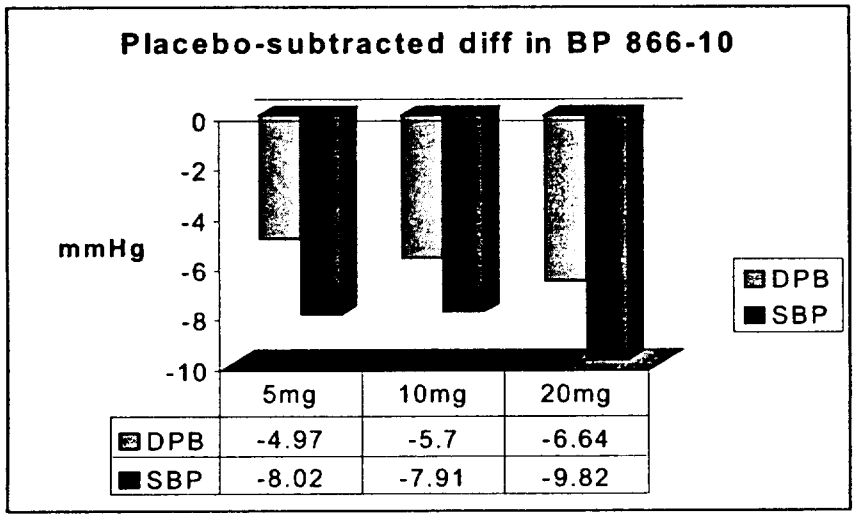
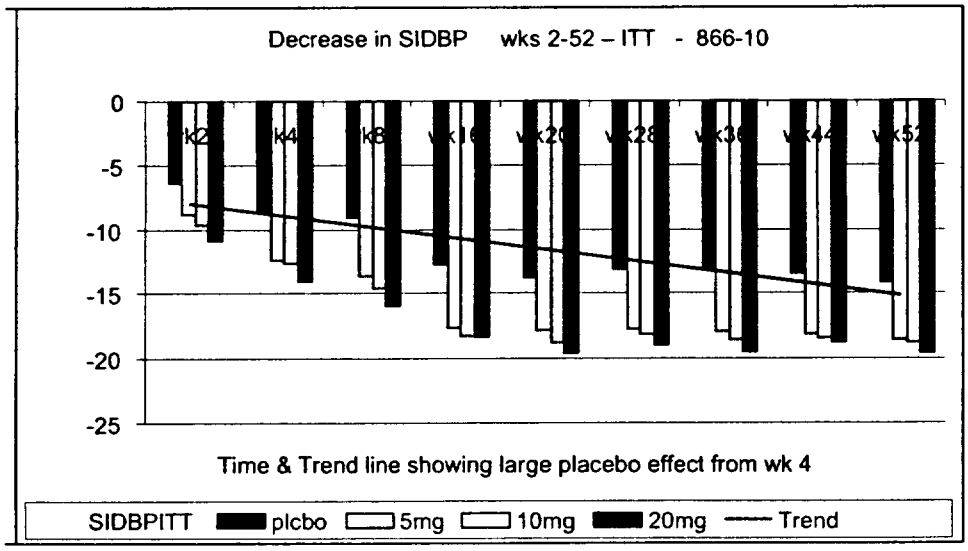
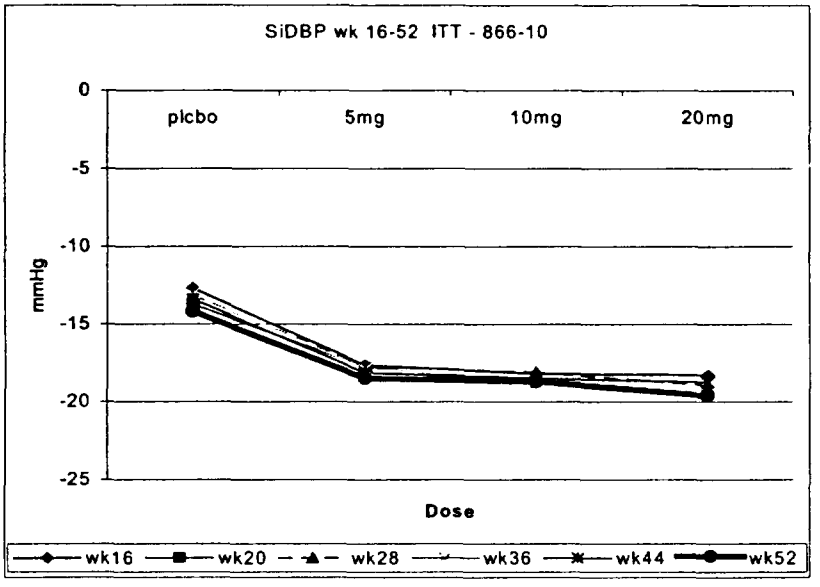


Figure 49: Decrease mean SiDBP-trough from baseline-v14 at 52 wks-Reviewer.



Source Reviewer. Y-axis = mmHg in Figure 49.
Figure 50: SiDBP- 16 to 52 weeks – ITT - 866-10



11.81 Primary efficacy conclusion

This study shows a dose response as measured by lowering of both diastolic and systolic blood pressure (Figures 48-50). The 3 doses 5mg, 10mg and 20 mg of CS-866 given once daily showed a statistically significantly greater reduction in diastolic blood pressure than placebo after 12 weeks of treatment of ITT patients p=0.0001) and for ITTPool* Treatment (p=0.0548) (Tables 104 and 105); p=0.0001 for overall treatment effect. These results were also confirmed using the PP population.

11.82 Secondary Efficacy

Efficacy after week 12 as measured by SiDBP and SiSBP- Extension period

At the end of week 52, a total of 326 patients were receiving CS-866 alone compared to 31 on placebo whereas 161 were receiving a combination of CS-866 and HCTZ or HCTZ alone (Figures 49 and 50).

Using paired t-tests after week 12, the blood pressure lowering effect of CS-866 monotherapy, supplemented with HCTZ in the uncontrolled population (Table 109), showed statistically significant changes in diastolic BP reduction including the placebo group (Table 109). The anomalous results in several centers and the significantly large placebo effect between 16 weeks and 52 weeks makes interpretation of the data in this study rather difficult to interpret with confidence. The lowering of diastolic BP in period 1 is significant but after 16 weeks the treatment effect levels off to the extent that there is little difference between the 3 dose levels and placebo. Lowering of systolic blood pressure was not observed among the monotherapy group but with additional HCTZ significant changes were observed (Table 109).

11.83 To determine suitability of once a day dosing regimen, the ratio of trough to peak BP measurements are presented below (Table 108). Figure 51 shows similarity in Trough to Peak ratios between ITT and PP sample populations suggesting that data from either population can be used for analysis of efficacy. On their own, however, the ratio of unity or near unity observed for all the dose groups is not proof of efficacy but an indication that the drug effect is not markedly reduced for 24 hours. This suggests suitability of the once daily dosing regimen (Table 108 and Figure 51) as opposed to twice daily dosing (See study # 866-204 for comparison between qd and bid dosing).

Table 108:Trough/Peak BP; Trough/Peak Ratios at visits 3 & 8 - ITT and PP 866-10

ITT				PP			
Placebo	N	Mean±SD	Median	Placebo	N	Mean±SD	Median
Trough @ visit 3	88	104.56± 3.54	104.17	Trough @ visit 3	44	104.9±3.62	102.67
Trough @ visit 8	77	92.71±7.26	92.33	Trough @ visit 8	44	91.68±6.69	90.17
Decrease in trough	76	11.79±7.42	12.00	Decrease in trough	44	12.61±7.34	12.87
Peak @ visit 3	87	103.37±4.02	102.67	Peak @ visit 3	44	103.14±3.49	102.50
Peak @ visit 8	75	91.86±9.01	91.33	Peak @ visit 8	44	90.63±9.82	88.67
Decrease in Peak	73	11.35±8.96	12.67	Decrease in Peak	44	12.52±10.33	14.17
Trough/Peak Ratio	**71**	**1.24 ± 1.10**	**1.00**	**Trough to Peak Ratio**	**43**	**1.14 ± 1.07**	**0.91**
5mg CS-866				5mg CS-866			
Trough @ visit 3	171	104.42± 2.98	104.00	Trough @ visit 3	112	104.09±2.79	103.50
Trough @ visit 8	166	89.02±7.81	88.67	Trough @ visit 8	113	88.27±7.54	87.67
Decrease in trough	164	15.35±7.28	15.33	Decrease in trough	112	15.75±7.29	15.67
Peak @ visit 3	171	103.56±3.41	103.00	Peak@ visit 3	112	103.22±3.23	100.67
Peak @ visit 8	165	87.18±7.74	88.87	Peak @ visit 8	113	86.23±7.71	80.67
Decrease in Peak	164	16.37±7.25	16.00	Decrease in Peak	112	18.93±7.31	12.50
Trough/Peak Ratio	**161**	**0.96 ± 0.36**	**0.95**	**Trough to Peak Ratio**	**110**	**0.93 ± 0.30**	**0.94**
10mg CS-866				10mg CS-866			
Trough @visit 3	171	104.62±3.18	104.67	Trough @ visit 3	126	104.34±3.17	104.00
Trough @ visit 8	161	88.65±6.57	88.00	Trough @ visit 8	126	88.25±6.35	88.00
Decrease in trough	161	15.97±6.58	15.33	Decrease in trough	126	16.09±6.64	15.33
Peak @ visit 3	171	103.48±3.94	102.67	Peak @ visit 3	126	103.44±3.62	102.67
Peak @ visit 8	161	88.95±6.62	87.33	Peak @ visit 8	126	88.66±6.74	87.33
Decrease in Peak	161	16.68±6.73	16.00	Decrease in Peak	126	16.79±6.83	15.00
Trough/Peak Ratio	**161**	**0.95 ± 0.51**	**0.95**	**Trough to Peak Ratio**	**126**	**0.96±0.51**	**0.95**
20mg CS-866				20mg CS-866			
Trough @ visit 3	168	104.96±3.38	104.33	Trough @ visit 3	136	105.6±3.38	104.33
Trough @ visit 8	161	87.20±6.31	86.67	Trough @ visit 8	135	88.80±6.26	83.33
Decrease in trough	161	17.71±6.36	17.67	Decrease in trough	135	18.26±6.46	14.67
Peak @ visit 3	168	104.14±3.88	103.33	Peak @ visit 3	135	104.20±3.96	103.67
Peak @ visit 8	161	85.48±7.02	85.00	Peak @ visit 8	135	85.25±6.54	84.67
Decrease in Peak	161	18.62±7.09	18.67	Decrease in Peak	135	18.95±6.77	19.00
Trough/ Peak Ratio	**161**	**1.00 ± 0.42**	**0.93**	**Trough to Peak Ratio**	**135**	**1.01±0.41**	**0.97**
SD=Standard deviation				SD=Standard deviation			

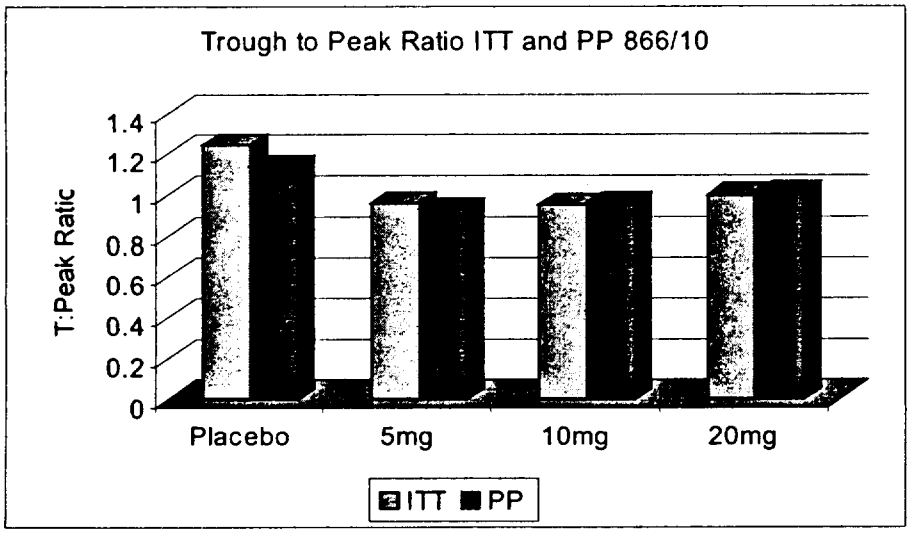
Visit 3=week 1; Visit 8=week 12. The trough to peak ratios between ITT and PP are similar. Once daily dosing appears adequate.

Table 109: Changes in Mean Trough SiDBP, SiSBP and SiHR-v 8-14 866-10

Treatment	N	T prob>|T| Diastolic	Systolic BP	Pulse Rate
20mg	115	0.0946	0.4553	0.2015
10mg	118	0.0285	0.7190	0.9797
5mg	131	0.0673	0.8523	0.5663
Placebo	58	0.0407	0.3435	0.1196
20mg+12.5HCTZ	30	0.0001	0.0223	0.8313
10mg+12.5HCTZ	30	0.0001	0.0242	0.8997
5mg+12.5HCTZ	29	0.0001	0.0001	0.2561
Plcbo/12.5HCTZ	12	0.0041	0.0389	0.8425
20mg+25HCTZ	27	0.0001	0.0001	0.4887
10mg+25HCTZ	23	0.0001	0.0071	0.1132
5mg+25HCTZ	8	0.0013	0.0387	0.3437
Placebo+25HCTZ	19	0.0001	0.0001	0.2478

Paired T test to detect changes over time by HCTZ dose and Treatment

Figure 51: Comparison between trough and peak ratios- ITT/PP -866-10

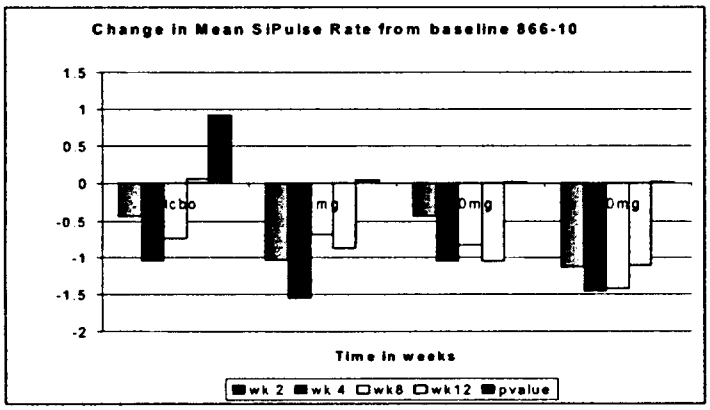


Source: Reviewer. Note similarity between both population samples at all doses.

11.84 Pulse Rate and CS-866 To determine the effect on pulse rate of CS-866 at dose levels of 5, 10, 20 mg o.d at trough after 2, 4, 6, 8, 12, (SiDBP and PR only), 16, 20, 36, 44, 52 weeks of treatment compared to baseline. There is a dose-related decrease in sitting pulse rate at trough (Figure 52). There is also a statistically significant reduction in sitting pulse rate from baseline at weeks 4 and 12 in the active treatment groups only compared to placebo (e.g. week 12 p= 0.05, 0.01 and 0.01 for 5mg, 10mg, and 20mg, respectively). This reduction is not evident in patients on active treatment or placebo between weeks 20 and 52. At week 16, the patients who received 20 mg CS-866 still showed a statistically significant reduction of sitting pulse rate at trough at week 16 (p=0.0895, N=168) compared to placebo. When the effect of additional HCTZ was

removed, analysis of data still showed reduction in sitting pulse rate at trough for several weeks after week 12.

Figure 52: Pulse rates at wks 2, 4, 8,12 and p-values - ITT - CS-866 only- 866-10



Y-axis =beats per minute and last column in each treatment group is p-value.
Graph by Reviewer

11.85 Response rates

The response rate at each dose level of 5mg, 10mg, and 20mg o.d. of CS-866 after 2, 4, 8, and 12 weeks of treatment for Periods I and II,. for both ITT and PP populations, are presented in Tables 110 and 111 below. Table 112 shows response rates from baseline to the end of study at 52 weeks (p=0.0001). The addition of HCTZ to CS-866 increased response rates and also increased number of patients showing reduction in diastolic and systolic blood pressure over time. There is a significant placebo effect (p=0.04) and HCTZ alone also has a significant effect (p=0.004) presumably because placebo patients and low dose patients had been given HCTZ (See statistical review).

11.86 Comparison of Response rates between ITT and PP samples - 866-10

Table 110: Responder Rates - Mean sitting diastolic BP - Visits 5-8 (ITT) 866-10

Period 1		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**	
Treatment Group		N	%	N	%	N	%	N	%
Placebo	NR	69	77.5	54	60.7	55	61.8	41	46.1
	R	20	22.5	35	39.3	34	38.2	48	53.9
5mg CS-866	NR	100	58.1	58	33.7	56	32.6	45	26.2
	R	72	41.9	114	66.3	116	67.4	127	73.8
10mgCS-866	NR	94	55.0	70	40.9	42	24.6	31	18.1
	R	77	45.0	101	59.1	129	75.4	140	81.9
20mgCS-866	NR	79	47.0	53	31.5	34	20.2	21	12.5
	R	69	53.0	115	68.5	134	79.8	147	87.5

R=Responder; NR=Non-Responder

Table 111: Responder Rates - Mean sitting diastolic BP - Visits 5-8 (PP) 866-10

Period 1		**Visit 5**		**Visit 6**		**Visit 7**		**Visit 8**	
Treatment Group		N	%	N	%	N	%	N	%
Placebo	NR	31	70.5	26	59.1	23	52.3	13	29.5
	R	13	29.5	18	40.9	21	47.7	31	70.5
5mg CS-866	NR	63	55.8	36	31.9	36	31.9	28	24.8
	R	60	44.2	77	68.1	77	68.1	85	75.2
10mgCS-866	NR	66	52.4	52	41.3	31	24.6	18	14.3
	R	60	47.6	74	58.7	95	75.4	108	85.7
20mgCS-866	NR	59	43.7	40	29.6	22	16.3	11	8.1
	R	76	56.3	93	70.4	113	83.7	124	91.9

R=Responder; NR= Non-Responder

Table 112: Responder Rates baseline-Visit 14 –Mean SiDBP Trough (ITT/LOCF)

Treatment	Estimate	S.E.	Odds Ratio	p-value
Placebo	0.0000	0.0000	1.0000	-
5mg	1.0242	0.2874	2.2874	0.0004
10mg	1.5758	0.5072	4.8344	0.0001
20mg	1.7841	0.3185	5.9539	0.0001

11.87 This section will deal with evaluation of the rate of patients currently in treatment compared to the randomized patients after 16, 20, 28, 36, 44, and 52 weeks of treatment. Among the patients requiring HCTZ in period II, the placebo group constituted the largest proportion of withdrawals followed by patients on 10 mg CS-866. Withdrawals took place throughout the duration of both periods I and II. Out of a total of 82 (13.7%) patients who withdrew from the study, 43 (7.2%) withdrew during the phase 1 study and 39(6.5%) withdrew during period II study. The data for lack of tachyphylaxis cannot be easily analyzed. The issue of tachyphylaxis was not specified in the protocol.

11.88 Age and efficacy To investigate the effects of age on efficacy, safety and tolerability of CS-866 at dose levels of 5, 10, and 20 mg o.d. over 52 weeks of treatment. No effect was observed between age and efficacy.

11.89: Drug exposure: The mean exposure to study drug is shown in Table 113 below.

Table 113: Drug exposure in days - ITT - 866-10

Treatment	N	Mean Exposure	SD	Minimum – Maximum (days)
Placebo	93	271	138	6-513
5mg	178	331	95	1-436
10mg	177	334	95	1-401
20mg	171	346	73	15-386

11.89 Tolerability

CS-866 was well tolerated and safe for the dosages of 5mg, 10mg and 20 mg o.d over the 52 week treatment period (Tables 114-118). See safety section 11.90 below and integrated review of safety.

11.90 SAFETY

11.91 Deaths

Of the 171 patients randomized to 20 mg CS-866, one patient died from what was described as "ileus" during the double blind treatment phase (SAE026).
Narrative below and in Appendix 6. SAE-026 was a 70 year old, hypertensive, female Caucasian patient (100626/0398), randomized to 20mg o.d of olmesartan that she took for 310 days. The patient was hospitalized for gastric bleeding with an admission Hemoglobin level of 5.8g/dl, increased LDH level of 265 U/l, decreased folic acid level of 1.6ng/ml and normal coagulation data. A diagnosis of Anemia was made and she was transfused. She subsequently died of an "ileus" of the small intestine. The study

medication was discontinued on admission. At the last study visit, the sponsor stated that there were no signs of an ileus and for this reason concluded that the SAE was not related to the study medication. There were no biochemical data, such as potassium levels, to explain the possible etiology of the ileus and there is no evidence of an associated peritonitis that may cause death. However, previous medical history of the patient included Parkinson's disease for which the patient received several medications.

There were 26 dropouts in the 12-week double blind period. The frequencies of the SAEs were not dose related (4 patients on placebo; 10, 10 and 5 patients on 5mg, 10mg, and 20 mg CS-866 once daily dosing, respectively,).

No significant changes in patients with normal ECG were recorded during the treatment phase.

11.92 Adverse Events

A total of 1073 adverse events were reported among 619 EFS randomized patients. There were 919 treatment/patient combinations even though there were only 619 patients (Randomized, Randomized plus 12.5mg HCTZ, and randomized plus 25 mg HCTZ). The commonest treatment emergent adverse events are in tables 114 and 115 below.

Table 114: Commonest Treatment-emergent adverse events ITT - 866-10

Bronchitis	77	Hyperuricemia	13
Dizziness	29	Vertigo	12
Gastroenteritis	17	Diarrhea	11
Headache	28	Gastritis	8
Back pain	28	Cervical spine-Syndrome	8
Influenza-like symptoms	15	Urinary tract infection	8
Hypertriglyceridemia	21	Dyspepsia	7

Table 115: AEs with duration of more than 6 months 866-10

Drug exposure (days)	Adverse event >6 months
188-346	DIZZINESS AND VERTIGO
182-343	HEADACHE
334	DIARRHOEA
182-308	HYPERTRIGLYCERIDAEMIA
287-308	HYPERCHOLESTEROLAEMIA
295	HYPERGLYCAEMIA
251	INFECTION TBC
236	DISTURBED SLEEP
219	DEPRESSION
211	BACK PAIN
198	INCREASED GAMMA-GT

Source: Reviewer

Table 116: Frequencies of AEs with dose and gender - 866-10

Placebo M/F	Males (mg)			Females(mg)		
	5	10	20	5	10	20
*Headache 0/0	6	4	7	5	5	8
*Dizziness 2/4	-	2	8	6	8	7
Hypertriglycerides 5/3	7	9	9	-	4	4
Back Pain 9/6	11	15	18	28	29	11
Hyperuricemia3/5	3	8	4	3	6	-
Gamma GT 3/0	7	5	5	4	-	-

Source: Reviewer

The most frequent treatment emergent adverse events by dose and gender are summarized in Table 117 below.

Table 117: Frequent(>2%) Treatment-Emergent AEs-dose and gender--ITT-866-10

Placebo Males	Plcbo Female	20 mg Males	20 mg Females	10 mg Males	10 mg Females	5 mg Males	5 mg Females
influenza-like symptoms	Hyperuric emia	vertigo	bronchitis	back pain	back pain	bronchitis	back pain
inflicted injury	hypertrigl yceridemi a	sweating increased	back pain	bronchitis	bronchitis	back pain	bronchitis
infection fungal	dizziness	neuralgia	influenza-like symptoms	influenza-like symptoms	dizziness	Hyperuricem ia	influenza-like symptoms
Hyperuricemi a	cystitis	influenza-like symptoms	headache	hypertriglyc eridemia	influenza-like symptoms	influenza-like symptoms	dizziness
hypertriglycer idemia	bronchitis	Hyperuricem ia	dizziness	Hyperuricem ia	headache	gamma-gt increased	gastroenteritis
hypercholester olaemia	back pain	hypertriglyc eridemia	gastroenteriti s	vertigo	coughing	hypertriglyc eridemia	urinary tract infection
gastroenteritis		headache	inflicted injury	gamma-gt increased	gastroenteriti s	headache	headache
gamma-gt increased		haematuria	pharyngitis	thrombocyto penia	hypertriglyc eridemia	Hematuria	nausea
dizziness		gastroenteriti s	vertigo	headache	Hyperuricem ia	neuralgia	conjunctivitis
bronchitis		gamma-gt increased	urinary tract infection	Hematuria		pharyngitis	gamma-gt increased
back pain		bronchitis	coughing	sinusitis		diarrhea	sinusitis
arthritis		back pain	hypercholest erolaemia	npn increased		gastritis	vertigo
		arthralgia		hypercholest erolaemia		gastroenteriti s	arthralgia
				gastritis			coughing
				dizziness			enteritis
				diarrhea			gastritis
				arthritis			hypercholeste rolaemia
				angina pectoris			hyperuricaemi a
							neuralgia

Placebo Males	Plcbo Female	20 mg Males	20 mg Females	10 mg Males	10 mg Females	5 mg Males	5 mg Females
							pharyngitis

Source: Reviewer- based on safety database for this study.

11.93 Serious Adverse Events

There were 33 SAEs requiring hospitalization during the treatment phase of this study. Twenty nine (29) events were due to CS-866 and 4 to HCTZ. Three out of the 4 patients given placebo had no HCTZ and 1 had 25 mg of HCTZ. Eleven of the 33 SAEs were regarded as severe, 21 moderately severe and 10 mild. Table 27 lists serious adverse events in patients on CS–866 by sex (Total of 29 patients plus 4 on HCTZ=33).

Table 118: Serious Adverse Events by Gender - ITT - 866-10

SERIOUS ADVERSE EVENTS - 866-10	
Males N=12	**Females N=17**
ALCOHOL PROBLEM	VERTIGO
PARKINSONISM	CONVULSIONS
CHOLECYSTITIS	GOITRE
MYOCARDIAL INFARCTION	ANGINA PECTORIS
	BACK PAIN
DIARRHOEA	GI HAEMORRHAGE/ANEMIA
ORCHITIS	
ARTHRALGIA	ANGINA PECTORIS
DIABETES MELLITUS	HYPERTENSION
RECTAL CARCINOMA	POST-MENOPAUSAL
BURSITIS	BLEEDING
	TRIGEMINAL NEURALGIA
	BREAST CANCER
	SARCOMA
	MENORRHAGIA

Source: Reviewer

SUMMARY

This study shows a dose response.CS-866 at doses of 5, 10 and 20 mg o.d.showed a statistically significantly greater reduction in diastolic and systolic blood pressure compared to placebo after 12 weeks of treatment [(p=0.05 for ITTPool* Treatment (p=0.0548) (Tables 104-105)]; and p=0.0001 for overall treatment effect. These results were also confirmed on analysis of the per protocol (PP) population.

During the 40-week extension period that followed the 12-week double blind treatment phase, blood pressure lowering effect of CS-866 monotherapy was not significantly sustained without concomitant HCTZ therapy. Supplemented with HCTZ, statistically significant changes in diastolic BP reduction were observed that could be due to additional HCTZ effect or to the relatively large placebo effect (Table 109). CS-866 did not significantly lower systolic BP during the extension period but with addition of HCTZ, significant treatment effects were observed. The protocol did not specify how to treat HCTZ effect statistically.

The trough to peak ratio was near unity or unity in both the ITT and PP population samples. This supports suitability of once a day dosing regimen.

There is a dose-related decrease in sitting pulse rate at trough that is statistically significant in the active treatment groups compared to placebo (e.g.at week 12, p-value = 0.05, 0.01 and 0.01 for 5mg, 10mg, and 20mg, respectively). This reduction in pulse rate is not evident in actively treated patients from weeks 20 to 52. However, at week 16, the patients who received 20 mg CS-866 still showed a statistically significant reduction in sitting pulse rate at trough (p=0.0895, N=168) compared to placebo. Without additional HCTZ, analysis of data still showed a reduction in sitting pulse rate at trough for several weeks after week 12.

CS 866 is well tolerated and safe at the doses studied.

12.0 Study # [redacted]
Materials used in this review Electronic submission (volumes 263-267)
12.01 Title:"A multi-center, 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" Prolongation of study #866-10.

Source documents: Study Report NDA 21-286 Study # [redacted]
Principal Investigator: Professor K.O. Stumpe M.D.
Sites: This study was conducted in 41 sites in Europe.
Study Dates: October 26 1998 – 2001
12.1 Amendments to Protocol: July 10 1998 re-safety: and re-statistics - HCTZ was added as an extra term for ANOVA.

12.2 Study Objectives: Primary
"To investigate if there are any changes in blood pressure consistent with the occurrence of rebound hypertension and tachyphylaxis in patients with mild-to-moderate hypertension".
Secondary objective
To assess the safety data for the 2-week period covered by the interim analysis, paying particular attention to adverse events related to sympathetic overactivity and hence rebound hypertension and tachyphylaxis.

12.3 Study design
The first 2 weeks of this phase III study was a double blind, randomized, placebo-controlled, multi-center extension study covered by the interim analysis. The study was to be conducted in 41 investigational sites. It was planned to randomize all mild to moderately hypertensive patients experiencing a response to treatment who completed study 866-10. Total duration of study - 54 weeks.Eligible patients had mean sitting Diastolic Blood Pressure (SiDBP) <90mm Hg at week 52 from the previous study 866-10. They were suspended for a period of 2 weeks from treatment and during this period they all received placebo o.d in a single blind fashion. Interim analyses were performed to evaluate rebound hypertension and ascertain lack of tachyphylaxis among patients receiving CS-866 throughout study 866-10. Thereafter the patients were randomized to the same doses of 5, 10 and 20 mg CS-866 or placebo or HCTZ where appropriate once daily for 52 weeks. Patients on monotherapy were given HCTZ to a maximum dose of 25 mg if it became necessary at a later date. For this study, the total duration of Period I was the 2 weeks of placebo, and Period II. lasted for 52 weeks. Interim visits and HCTZ interim visits were as for 866-10. For this interim visit, only visits 1 and 2 (week 0) were of interest because the aim of this interim analysis was to contribute to safety profile of drug in hypertensive patients who had not adhered to long-term self-medication.

12.4 Primary efficacy
To compare the diastolic blood pressure changing effect of placebo at trough level on patients undergoing long-term therapy with CS-866 doses of 5mg, 10mg, and 20mg o.d. and placebo after 2 weeks compared to baseline data of study #866-10 of hypertensive patients using conventional cuff blood pressure monitoring.

Tachyphylaxis is defined as a falling off of the effects produced by a drug during continuous use or constantly repeated administration.

12. 5 Patient disposition

A total of 454 out of 526 patients completed study ——— . Figure 1 shows disposition of patients during the 2 week placebo period of study when medication was stopped (Figure 47a). The patients who completed ——— ' include a subset of patients completing study # 866-10 (Table 96), and the treatment groups and demographics were in essence comparable with respect to demographics except the age difference (Tables 96 and 100; 119 and 120).

Figure 53 (See Fig 47 on page 110): Patient disposition during the 2 week placebo period covered by interim analysis- Study ———

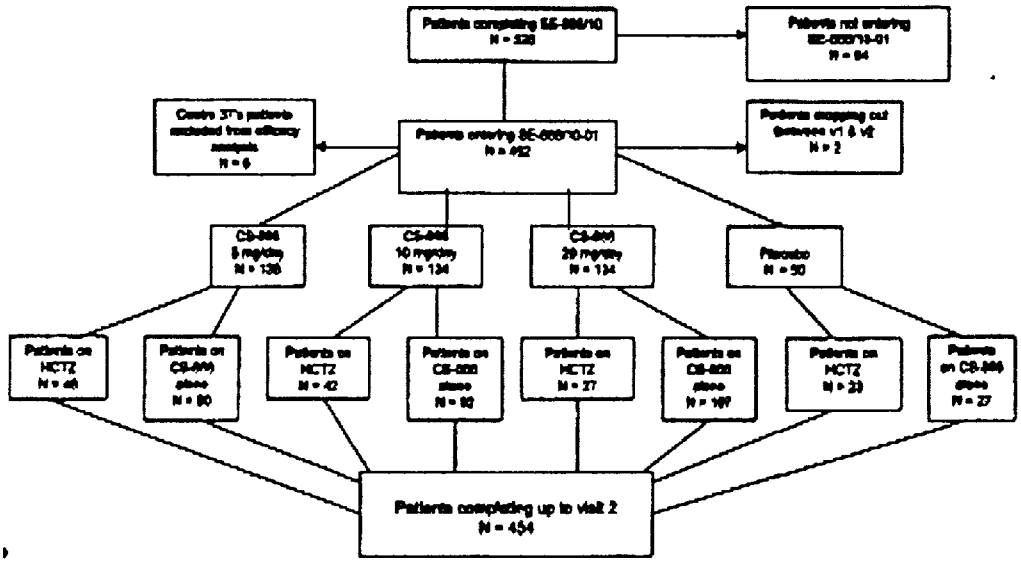


Table 119: Number of patients per analysis set ———

N	Placebo	5mg	10mg	20mg	Total
Safety set	53	136	137	136	462
ITT	50	136	134	134	454

12.6 Eight patients did not complete the 2-week placebo period covered by the interim analysis. Six of these patients were from center 37 where the investigator refused to be audited.

Table 120: Demographics of subset from study #866-10 - ITT - ——

	Placebo	5mg	10mg	20mg
No of patients	50	136	134	134
Age (yrs)	60.2±12.8	59.9±12.1	60.6±12.3	60.8±12.8
Gender(M/F)	25/25	61/75	51/83	59/75
Height	167.1±8.9	167.9±9.0	167.8±8.1	167.5±9.0
Weight	77.1±11.2	77.5±12.7	79.8±14.8	80.0±13.9
Body Mass	27.7±3.9	27.5±3.9	28.3±4.4	28.5±4.0

Males were diagnosed with hypertension at the younger median age of 52.5years compared to 55 years for females.

12.7 Efficacy

Baseline blood pressure used to determine eligibility was defined in the protocol as the mean of 3 BP assessments at visits 2, 3, and 4 performed during study 866-10 for those patients who completed the study.

Rebound hypertension was also defined as the rapid return of blood pressure to pre-treatment levels with signs and symptoms of sympathetic overactivity and possibly hypertensive encephalopathy, cerebrovascular accidents or other cardiovascular events.

It was originally planned to determine the number of patients in each treatment group that had a sitting dBP equal to or above their 866-10 baseline value at the end of the 2 week placebo period of study —— and to evaluate the number of patients with symptoms of sympathetic overactivity. The proposed primary analysis was not carried out because of the relatively few patients (e.g <6% in respect of SiDBP) with expected outcomes (Tables 120 and 121).

The purpose of the initial 2-week washout period in —— study was to find out what happens when CS-866 was withdrawn in terms of efficacy and safety. It would be expected that patients on active treatment would be expected to have a loss of treatment effect and that this effect should be greater than the placebo effect. This greater loss will support a pharmacological effect of CS-866 before withdrawal. To detect this, a within group analysis was performed using the paired t test at the end of study 866-10.

During the 2-week placebo period, mean sitting diastolic blood pressure increased for all treatment groups including placebo group. The greatest increase for diastolic and systolic blood pressure was in the 20mg group in the ITT population (Table 122).

Table 121: Disposition of patients with BP and pulse rates at visit 2 equal to or above baseline values of 866-10 by treatment group or adverse events

Treatment	Placebo	5mg	10mg	20mg
N	50	136	134	134
Number of patients with SiDBP> baseline (%)	3(6)	4(2.9)	4(3)	7(5.2)
Number of patients with SiSBP> baseline (%)	10(20)	31(22.8)	30(22.4)	27(20.1)
Number of patients with SiPR> baseline (%)	21(42)	67(49.3)	66(49.3)	57(42.5)
Number of patients with StDBP> baseline (%)	8(16)	14(10.3)	17(12.7)	18(13.4)
No of patients with Adverse events	0(53)	0(136)	1(137)	1(136)

Table 122: Change in mean sitting diastolic BP at trough from baseline of 866-10 to visit 2 of study -ITT

Treatment	Placebo	5mg	10mg	20mg
N	**50**	**136**	**134**	**134**
Number of patients with SiDBP> baseline (%)	3(6)	4(2.9)	4(3)	7(5.2)
LS mean (95% CI)	-8.95 (-10.46,-7.43)	-10.61 (-11.60,-9.61)	-9.85 (-10.86,-8.85)	-10.21 (-11.30,-9.13)
Difference from baseline p-value	0.0001	0.0001	0.001	0.0001
Difference from placebo 95% CI of difference)		-1.66 (-3.42,0.10)	-0.91 (-2.68,0.86)	-1.27 (-3.07,0.54)
Individual p-values for differences from placebo		0.0643	0.3141	0.1690
No of patients with Adverse events	0(53)	0(136)	1(137)	1(136)

Model adjusted for pooled center and HCTZ dose at end of study #866-10. p-value for overall treatment effect was 0.2861

Table 123: Change in mean SiDBP at trough from end of study SE-866/10 to visit 2 of study — (change over 2 week placebo washout period)-ITT —

Treatment	Placebo	5mg	10mg	20mg
N	50	136	134	134
LS mean (95% CI)	9.61 (7.96,11.26)	9.02 (7.94,10.11)	9.43 (8.33,10.52)	10.30 (9.12,11.48)
Difference from end of study 866-10 p-value	0.0001	0.0001	0.001	0.0001
Difference from placebo 95% CI of difference)		-0.59 (2.51,1.33)	-0.18 (2.11, 1.75)	0.69 (-1.27,2.66)
Individual p-values for differences from placebo		0.5485	0.8511	0.4885
Number of patients with adverse events	0(53)	0(136)	1(137)	1(136)

12.8 Results

The mean SiDBP was significantly lower at visit 2 of study — than at baseline of study 866-10 for all treatment groups including placebo group. There are no significant differences between the active treatment groups regardless of HCTZ addition (p=0.2971). Similar results are observed for the secondary efficacy variables including SiSBP, SiPR, and StDBP. There is no significant difference in the change in mean sitting pulse rates at trough from baseline during the 2-week period of — suggestive of a lack of tachycardia associated with sympathetic overactivity.

12.9 Safety

During the two-week placebo period no patient was withdrawn due to adverse events. There were 2 treatment-emergent adverse events suggestive of sympathetic overactivity that implied rebound hypertension. One occurred in the 10mg and another in the 20mg groups.

SUMMARY

Although there was no compelling evidence of either rebound hypertension or tachyphylaxis, there was a significant loss of treatment effect during the 2-week placebo washout period of study — in all treatment groups. The loss was greatest in the 20mg group. It is conceivable that the 2-week placebo period was not long enough to detect significant differences between the treatment groups. Furthermore a large placebo effect was observed in the previous study #866-10.

In spite of the selection bias for study — that enrolled only responders from study 866-10, the results failed to demonstrate efficacy following a 2-week placebo period. However there were no serious adverse events and no patient was withdrawn in the immediate period following the cessation of drug administration.

13.0 Positive-control study SE-# 866-18 (Atenolol v.CS-866)
13.01 Study Design (SE-866-18)
This atenolol-controlled, double-blind, parallel group, dose-titrated monotherapy trial randomized (at a ratio of 1:1) 326 subjects (patients with mild-to-moderate essential hypertension (DBP 95-114 mmHg inclusive) to once-daily oral starting doses of olmesartan 10 mg or atenolol 50 mg for 12 weeks
Doses were to be doubled after 4 weeks if DBP was ≥90 mmHg and/or had decreased by less than 10 mmHg from pre-treatment. The primary endpoint was the change from pre-treatment mean sitting trough DBP at week 12.

13.1 Enrollment (SE-866- 18)
Patients had to meet all of the following inclusion criteria:
- Patients with essential hypertension in whom it was medically justifiable to withdraw treatment (poor tolerability or efficacy of previous treatment, or for verification that treatment was still necessary).

- mean sitting dBP between 95 and 114 mmHg (inclusive) at screening (before entry into the placebo run-in phase).

- Male or female, adult, out-patients aged over 18 years.

- A female of non-childbearing potential was defined as one who had been post-menopausal for at least one year, or was surgically sterilized or had a hysterectomy at least three months prior to trial start. A female of childbearing potential could be enrolled provided she: had a negative pregnancy test within 48 hours before starting the trial and was routinely using adequate contraception (combined estrogen/ progesterone oral contraceptive pill or the intrauterine coil) prior to and during the trial and agreed not to attempt to become pregnant during the trial.

Patients were to be excluded for any of the following reasons:

- Females who were pregnant or planned a pregnancy during the time of the trial, were breast feeding, or were of childbearing potential and not using acceptable methods of contraception (combined estrogen/ progesterone oral contraceptive pill or the intrauterine coil).

- Patients with any type of known secondary or malignant form of hypertension (e. g. renal, renovascular or adrenocortical disease, phaeochromocytoma, hyperthyroidism, iatrogenic), including renal arteriosclerosis.

- Patients with severe arterial hypertension defined as sitting dBP
> 115 mmHg and/ or sbp > 200 mmHg or classified as stage III according to WHO classification.

- 2nd or 3rd degree AV-block (in the absence of a pacemaker), atrial fibrillation, cardiac arrhythmia (requiring therapy) or bradycardia

< 50 beats/ min at rest).

- 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, hematological or hepatic disease or myocardial infarction, which occurred in the past six months, PTCA or CABG (within 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 trial or the patient's well-being, patients with intracerebral or subarachnoid haemorrhage event, patients with ejection fraction ≤40 %, patients with unstable angina or angina requiring other therapy than nitrates.

- Patients with clinical evidence of renal disease (including renovascular occlusive disease, nephrectomy and/ or renal transplant, serum creatinine level in excess of 1. 7 mg/ dl or proteinuria '++ ' or ≥100 mg/ dl on dipstick evaluation.

- Patients with impaired liver function suggesting a severe liver disorder.

- Patients with clinically significant laboratory abnormalities including patients with ASAT/ SGOT and ALAT/ SGPT greater than two times the upper limit of the laboratory normal range. Patients with *GGT greater* than two 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 known malabsorption syndromes.

- Patients whose BW exceeded -15% /+ 35% of the Modified Metropolitan Life Insurance Tables.

- Patients with psychiatric or emotional problems, which would invalidate the giving of informed consent or limit the ability of the patient to comply with trial requirements.

- Patients with any history of alcohol and/ or drug abuse.

- Patients having been treated for other indications with drugs or medication that may influence blood pressure and which could not be withdrawn during the period of the trial, e. g. alpha blockers for the treatment of benign prostatic hypertrophy or intra-ocular beta blockers for the treatment of glaucoma.

- Patients with known hypersensitivity, lack of response or contraindication to Ang II-antagonists or blockers 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 trial.

- Patients who had previously been enrolled in this trial.

- Patients who were unwilling or unable to provide written informed consent or to participate satisfactorily for the entire trial duration.

- Patients with asthma or any history of obstructive disease of the respiratory system

13.2 Treatment (SE-866- 18)
Taper off any previous antihypertensive medication occurred for one to two weeks, after which there was three-week placebo run-in period.

The following were to be the rules for concomitant (nonrandomized) therapies: antihypertensives, tricyclic antidepressants, neuroleptics, long-acting nitrates, and potassium supplements were to be disallowed.

13.3 Endpoints (SE-866-18)
Efficacy was assessed by the difference from pre-treatment to week 12 in mean sitting DBP values (cuff measurements) at trough. Peak BP effects were also assessed at 4 hours after drug administration during week 4.

Patients visited the trial site at weeks 2, 4, 8 and 12 during the treatment period, with safety follow-up plans for weeks 13 and 15 when new or unresolved AE appeared at week 12. Laboratory assessments (biochemistry, hematology) and 12-lead ECG were also obtained.

13.4 Statistics (SE-866-18)
The primary endpoint was assessed using analysis of covariance techniques, with treatment, center and pre-treatment mean trough sitting DBP included as effects in the model. The null hypothesis was that the change from pre-treatment in mean trough sitting DBP at Week 12 in the olmesartan group was not more than 3.5 mmHg less than the change in the atenolol group.

The primary dataset included all randomized patients who had both a pre-treatment sitting DBP value and at least one on-therapy value. Analyses were conducted by the intent-to-treat principle with the last observation carried forward when data were missing at week 12.

No interim analyses were carried out.
The power calculation employed the following assumptions:
- 1-sided alpha = 0.05
- power = 90%
- variability = standard deviation 10 mmHg
- detection threshold = 3.5 mmHg
- expected difference 0 mmHg

13.5 Results (SE-866- 18)
The pre-treatment characteristics of the treatment groups were roughly comparable. All patients were Caucasians. See table 124 below.

Table 124: Distribution of pre-treatment covariates (ITT, study SE-866-18)

covariate	Olmesartan	Atenolol
Gender (male/female)	74/91	81/80
Age (years)	55.5	55.8
Weight (kg)	75.3	76.7
Smoking		
Yes	36	44
Ex-smoker	30	28
No	99	89
Alcohol		
Excessive	1	0
Regular	23	22
Sporadic	70	73
Never	71	66

Patient Disposition (SE-866-18)
There were comparable rates of dropping out in the two groups, as shown in the table below.

Table 125: Drop outs (ITT, SE-866-18)

Reasons for dropout	Olmesartan N = 165	Atenolol N = 161
AE	3 (1.8%)	4 (2.5%)
entry criteria not fulfilled	2 (1.2%)	3 (1.9%)
disallowed concomitant medication	1 (0.6%)	-
Other	2 (1.2%)	3 (1.9%)
Total	8 (4.8%)	10 (6.2%)

As shown in table 126 below, similar proportions of patients titrated to the higher dose at week 8 in both of the treatment groups.

Table 126:Distribution of patients by dose (ITT, SE-866-18)

Week	Olmesartan		Atenolol	
	10 mg	20 mg	50 mg	100 mg
week 2	165	0	161	0
week 4	165	0	161	0
week 8	109	56	108	53
week 12	108	57	108	53

13.6 Efficacy results (866-18)

As shown in the tables below, there were decreases in sitting levels of both DBP & SBP from as early as two weeks after start of treatment, and these became more pronounced during the next 2 weeks. The BP measurements at week 8 were similar to those observed at Week 12. There was no evidence to suggest that olmesartan was inferior to atenolol with regard to change in DBP.

Table 127: Mean sitting trough DBP(mmHg) change (ITT, SE-#866-18)

	Olmesartan (N=165)	Atenolol (N=161)
Pre-treatment	100.8	101.1
Week 4 change	-11.7	-12.1
Week 8 change	-14.2	-13.9
Week 12 change	-14.0	-14.3

Table 128: Mean sitting trough DBP (mmHg) over time (ITT, SE-#866-18)

	Olmesartan		Atenolol	
	10 mg	20 mg	50 mg	100 mg
Pre-treatment	100.8		101.0	
Week 2	89.7		89.0	
Week 4	88.5		88.5	
Week 8	83.4	91.4	84.8	90.9
Week 12	83.4	91.0	84.0	90.6

Table 129: Mean sitting trough SBP (mmHg) change over time (ITT, SE-#866-18)

	Olmesartan (N=165)	Atenolol (N=161)
Pre-treatment	161.1	160.5
Week 4 change	-18.6	-15.8
Week 8 change	-21.2	-17.1
Week 12 change	-20.7	-17.2

Comments (866-18)

At the dose regimens studied there was no evidence to suggest that olmesartan had inferior antihypertensive efficacy, relative to atenolol.

14.0 Study SE- # 866-19 (Losartan v. CS-866)

14.01 Study Design (SE-866- 19)

This losartan-controlled, double-blind, parallel group, dose-titrated trial randomized 316 subjects (patients with mild-to-moderate essential hypertension (DBP 95-114 mmHg inclusive) to once-daily oral starting doses of olmesartan 10 mg or losartan 50 mg for 12 weeks. After 4 weeks doses were to be doubled as needed for BP control, and after 12 weeks hydrochlorothiazide (HCTZ) was added as needed (starting dose of 12.5, with optional doubling). The primary endpoint was the change from pre-treatment mean sitting trough DBP at week 12.

14.1 Enrollment (SE-866- 19) Inclusion criteria

- adults (>18 years) with essential hypertension (mean sitting dBP between 95 and 114 mmHg inclusive), BP variation of not more than 6 mmHg,
and medically justifiable to discontinue any prior antihypertensive treatment.
- females of childbearing potential (not post-menopausal for at least one year, surgically sterilized or hysterectomized at least three months prior to the trial) who had a negative pregnancy test within 48 hours before starting the trial and was routinely using adequate contraception (combined estrogen/progesterone oral contraceptive pill or the intrauterine coil) prior to and during the trial, and who agreed not to attempt to become pregnant during the trial.

Exclusion criteria

- known secondary or malignant form of hypertension, sitting DBP ≥ 115 mmHg and/or sBP > 200 mmHg, or classified as stage III severe hypertension according to WHO classification.

- 2nd or 3rd degree AV-block (in the absence of pacemaker), atrial fibrillation, cardiac arrhythmia requiring therapy, or resting HR < 50 beats/min, or other significant cardiovascular disease (such as a significant narrowing of the aortic or bicuspid valve, severe obstruction of cardiac outflow, severe CHF, symptomatic CAD, LVEF ≤ 40%, unstable angina, angina requiring other therapy than nitrates; MI, PTCA or CABG in the prior 6 months).

- significant cerebrovascular, gastrointestinal, hematological or hepatic disease which occurred in the past six months; a previous history of any serious underlying disease, including immunocompromised, intracerebral or subarachnoid bleed event, renovascular occlusive disease, nephrectomy, renal transplant, serum creatinine >150 μmol/l, proteinuria '++' or ≥ 100 mg/dl on dipstick.

- significant hepatic disease which occurred in the past six months, impaired liver function suggesting a severe liver disorder, ASAT/SGOT and ALAT/SGPT greater than two times the upper limit of normal , γ-GT > two times the upper limit of normal if ASAT/SGOT and/or ALAT/SGPT were greater than 1.5 times the upper limits.

- poorly controlled diabetes, malabsorption syndromes, body weight exceeds -15% or +35% of normal, psychiatric problems, alcohol and/or drug abuse, requirement for continued treatment with medication which may influence BP.

- known hypersensitivity, lack of response or contraindication to Ang II-antagonists or β-blockers or hypersensitivity to related drugs.

14.2 Treatment (SE-866- 19)
Patients were discontinued from pre-existing antihypertensive medication over a period of at least 1 week, then entered a placebo run-in period of 3 weeks. Patients were randomized to once-daily oral starting doses of olmesartan 10 mg or losartan 50 mg for 12 weeks (double-dummy technique was used). Doses were to be doubled after 4 weeks if DBP was ≥90 mmHg or had decreased by less than 10 mmHg from pre-treatment. After week 12 dBP remained uncontrolled HCTZ 12.5 mg was added. At weeks 16, or 20 the HCTZ could be doubled as needed.
The following concomitant medications were to be disallowed:
- tricyclic antidepressants
- neuroleptics
- long-acting nitrates
- potassium supplements.

14.3 Endpoints (SE-866- 19)
The primary endpoint was the change from pre-treatment mean sitting trough DBP at week 12. BP recordings were performed at trough (24 hours), and also at peak at week 4. Patients visited the trial site at Weeks two, four, eight, 12, 16, 20 and 24 during the treatment period. A safety follow- up visit was scheduled between Weeks 25 and 27 for patients with new or unresolved Adverse Events at Week 24.

14.4 Statistics (SE-866- 19)
The power calculation employed the following assumptions:
- 1-sided alpha = 0.05
- power = 90%
- variability = standard deviation 10 mmHg
- detection threshold = 3.5 mmHg
The primary dataset included all randomized patients who had at least one on-therapy value. Analyses were conducted by the intent-to-treat principle with the last observation carried forward when data were missing at week 12.
No interim analyses were carried out.

14.5 Results (SE-866-19)
As shown in the table 130, the treatment groups were roughly comparable. All patients were Caucasians.

Table 130: Distribution of pre-treatment covariates (ITT, SE-#866-19)

	Olmesartan	Losartan
Gender (female/male)	79/81	67/89
Age (years)	57.3	56.7
Weight (kg)	79.1	78.7
Smoking		
Yes	31	26
Ex-smoker	39	53
No	90	77
Alcohol		
Excessive	2	1
Regular	44	39
Sporadic	90	99
Never	24	17

Disposition (SE-866-19)

As shown in the table below, the number and distribution of dropouts were roughly comparable.

Table 131: Dropouts (ITT, SE-#866-19)

Reason for dropout	Olmesartan (N=160)	Losartan (N=156)
AE	12	11
Inefficacy	3	5
Withdrew consent	1	3
Entry criteria not fulfilled	2	0
Disallowed concomitant medication	1	1
Other reason	3	3
Total	22	23

As shown in table 132 below, a higher proportion of patients titrated to the higher dose at week 4 in the losartan group compared with the olmesartan group.

Table 132: Distribution of patients, by dose (ITT, study SE-866-19)

	Week 2	Week 4	Week 8	Week 12	Week 16	Week 20	Week 24
Olmesartan							
10 mg	155	92	92	79	72	71	71
20 mg	0	66	66	42	35	32	32
20 mg + 12.5 mg HCTZ	0	0	0	37	34	31	30
20 mg + 25 mg HCTZ	0	0	0	0	17	24	25
All	155	158	158	158	158	158	158
Losartan							
50 mg	150	56	56	40	35	35	35
100 mg	0	96	96	63	50	44	44
100 mg + 12.5 mg HCTZ	0	0	0	49	44	36	36
100 mg + 25 mg HCTZ	0	0	0	0	23	37	37
All	150	152	152	152	152	152	152

14.6 Efficacy results (SE-866-19)

As shown in the tables below, a trough antihypertensive effect was seen as early as 2 weeks after starting treatment. At the doses studied, olmesartan tended to have no lesser mean trough effect than did losartan.

Table 133: Trough sitting DBP changes (mmHg) (ITT, SE-#866-19)

	Olmesartan (N=158)	Losartan (N=152)
Pre-treatment	101.3	101.9
Week 2 change	-8.4	-6.2
Week 4 change	-9.1	-6.4
Week 8 change	-10.9	-8.3
Week 12 change	-10.6	-8.5
Week 16 change	-11.7	-10.4
Week 20 change	-13.4	-11.3
Week 24 change	-12.9	-11.6

Table 134: Timecourse of mean trough sitting Diastolic BP (mmHg), according to dosegroup (ITT, SE-866-19)

	Olmesartan			Losartan		
	10 mg	20 mg	20 mg plus HCTZ	50 mg	100 mg	100 mg plus HCTZ
Week 0	96.6	--	--	98.7	--	--
Week 2	92.5	--	--	95.5	--	--
Week 4	86.6	98.8	--	88.1	99.1	--
Week 8	87.1	93.7	--	89.6	95.2	--
Week 12	85.5	92.2	98.3	86.9	91.4	99.7
Week 16	84.86	90.2	94.5	85.3	89.2	95.4
Week 20	84.8	89.0	90.0	85.8	88.9	92.7
Week 24	85.9	89.4	89.8	85.5	89.82	91.9

Table 135: Mean sitting trough SBP changes (ITT, SE-#866-19)

	Olmesartan (N=158)	Losartan (N=152)
Pre-treatment	159.2	159.7
Week 2 change	-12.1	-7.6
Week 4 change	-13.0	-9.5
Week 8 change	-14.4	-10.9
Week 12 change	-14.9	-11.6
Week 16 change	-16.1	-14.8
Week 20 change	-18.7	-15.3
Week 24 change	-17.8	-15.6

Comments (study #866-19)

At the dose regimens studied there was no evidence to suggest that olmesartan had inferior antihypertensive efficacy, relative to losartan.

15.0 Study SE- #866-20 (Captopril v CS-866)
15.01 Study Design (SE-866- 20)
This captopril-controlled, double-blind, parallel group, dose-titrated monotherapy trial randomized 291 subjects (patients with mild-to-moderate essential hypertension (DBP 95-114 mmHg inclusive) to oral starting doses of olmesartan (5 mg once-daily) or captopril (12.5 mg twice daily at its starting dose) for 12 weeks. After 4 weeks doses were to be doubled as needed for BP control, and after 8 weeks the doses could be doubled again). The primary endpoint was the change from pre-treatment mean sitting trough DBP at week 12.

Enrollment (SE-866- 20)
Entry (inclusion and exclusion) criteria were essentially those described above under trial SE-866-19.

Treatment (SE-866- 20)
Patients were discontinued from any pre-existing antihypertensive medications over at least one week, and then entered into a placebo run-in period of 3 weeks. Eligible patients were then randomized to oral starting doses of olmesartan (5 mg once-daily) or captopril (12.5 mg twice daily at its starting dose), using a double-dummy technique, for 12 weeks. The dose was to be doubled after 4 weeks if dBP was ≥90 mmHg or had decreased by less than 10 mmHg from pre-treatment. After 8 weeks, the dose could be doubled again as needed.
The following concomitant drugs were to be disallowed:
- antihypertensives
- tricyclic antidepressants
- neuroleptics
- long-acting nitrates
- potassium supplements

Endpoints (SE-866-20)
The primary endpoint was the change from pre-treatment mean sitting trough DBP at week 12. Cuff BP recordings were performed at trough (24 hours after the last administration of olmesartan, or 12 hours after the last administration of captopril), and also at peak (4 hours after drug administration) at week 4. Patients visited the trial site at weeks 2, 4, 8 and 12 during the treatment period. A safety follow-up visit was scheduled between weeks 13 and 15 for patients with new or unresolved AE at week 12.

15.1 Statistics (SE-866-20)
ANCOVA techniques were used for the primary analysis. No interim analyses were undertaken. The primary dataset included all randomized patients who had at least one on-therapy value. Analyses were conducted by the intent-to-treat principle with the last observation carried forward when data were missing at week 12.

The power calculation employed the following assumptions:
- 1-sided alpha = 0.05
- power = 90%

- variability = standard deviation of 10 mmHg
- detection threshold = 3.5 mmHg

15.2 Results (SE-866-20)

covariates (SE-866-20)

As shown in table 136 below, pre-treatment covariates were distributed comparably in the two groups.

Table 136: Distribution of pre-treatment covariates (ITT, study SE-866-20)

	Olmesartan	Captopril
Gender (male/female)	81/67	80/63
Age (years)	57.7	56.1
Height (cm)	168.2	168.9
Weight (kg)	79.1	80.0
Smoking		
Yes	26	25
Ex-smoker	45	57
No	77	61
Alcohol		
Excessive	0	1
Regular	49	50
Sporadic	79	76
Never	20	16

Disposition of subjects (SE-866-20)

As shown in table 137 below, there was a slightly higher dropout rate in the captopril group.

Table 137: Dropouts (ITT, study SE-866-20)

Reasons for dropout	Olmesartan (N=148)	Captopril (N=143)
AE	8 (5.4%)	10 (7.0%)
disallowed concomitant medication	1 (0.7%)	1 (0.7%)
Expiry of medication/termination of trial	16 (10.8%)	16 (11.2%)
Other reason	0	3 (2.1%)
Total	25 (16.9%)	30 (21.0%)

As shown in table 138 below, a larger proportion of patients received a second dose-doubling in the captopril group.

Table 138: Distribution of patients, by titrated dose (ITT, SE-866-20)

Week	Olmesartan (mg)			Captopril (mg)		
	5	10	20	12.5	25	50
week 2	142	--	--	139	--	--
week 4	72	72	--	32	110	--
week 8	60	49	35	20	44	78
week 12	60	48	36	20	44	78

15.3 Efficacy results (SE-866-20)

At the doses studied, there tended to be larger mean BP reductions from pre-treatment at trough in the olmesartan group. See the tables below.

Table 139: Trough sitting DBP mean changes (mmHg) (ITT, SE-#866-20)

	Olmesartan (N=148)	Captopril (N=143)
Pre-treatment mean	101.1	102.1
week 4 change	-8.3	-4.6
week 8 change	-10.1	-5.3
week 12 change	-9.9	-6.8

Table 140: Timecourse-mean trough sitting DBP (mmHg) (ITT, SE-866-20)

	Olmesartan (mg)			Captopril (mg)		
Week	5	10	20	12.5	25	50
2	93.2	--	--	97.6	--	--
4	87.1	98.2	--	90.3	99.7	--
8	84.9	91.2	99.4	88.8	92.1	101.2
12	86.8	92.1	96.4	89.2	92.5	98.9

Table 141: Trough Sitting SBP mean changes (ITT, SE-#866-20)

	Olmesartan (N=148)	Captopril (N=143)
Pre-treatment mean (mmHg)	161.3	161.3
Week 4 change	-12.4	-6.1
Week 8 change	-15.1	-6.5
Week 12 change	-14.7	-7.1

Comments (study 866-20)

At the dose regimens studied there was no evidence to suggest that olmesartan had inferior antihypertensive efficacy, relative to captopril.

16.0 Study SE-#866-06
16.01 Title: "Safety, Tolerability and Efficacy of the Angiotensin II-antagonist CS-866A in patients with Mild to Moderate Hypertension (Phase II study)".

Source documents: Study report: NDA 21-286, vol. 216 (Clinical); vol. I-VI

Site and Investigator: This study was conducted at a single site in Görlitz, Germany. The Principal Investigator was P U Witte, MD, PhD.

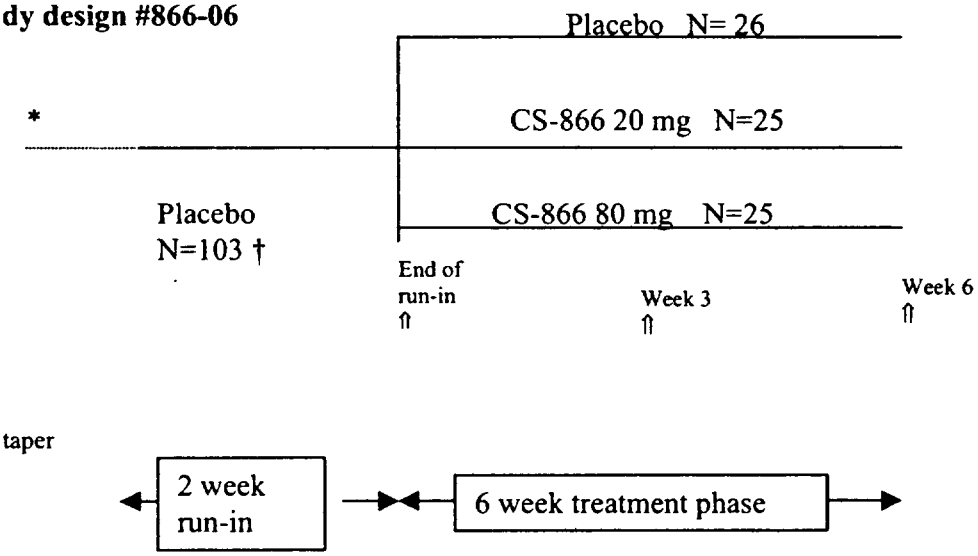
Study dates: January 16, 1996 to June 26, 1996.

Objectives: The primary objective of this study was to evaluate the safety and tolerability of CS-866 after 6 weeks of treatment. Measured parameters included adverse events, blood pressure/pulse, laboratory values, and 12-lead electrocardiograms (ECG). A secondary objective was to assess efficacy via 24-hour ambulatory blood pressure monitoring (24 hour ABPM).

16.1 Study design: This study description was based upon the protocol and study report. No amendments were made to the protocol. This was a randomized, double-blind, placebo-controlled, 3-arm parallel group trial shown schematically in Figure 54. After a 2-week single-blind placebo run-in period, eligible subjects were randomly assigned to placebo or active drug (20 or 80 mg CS-866) for 6 weeks. Those already on antihypertensive therapy were tapered off drug for 1-2 weeks prior to the single-blind placebo run-in period.

Eligible patients were to be males or females 18 to 75 years, with mild to moderate essential hypertension (mean sitting DBP $\geq$ 100 mm Hg and $\leq$ 114 mm Hg) and baseline (end of run-in) mean 24 hour DBP $\geq$ 84mm Hg on ABPM with at least 30% of daytime readings (8:00 to 20:00 hours) > 90 mm Hg. Women were to have a negative pregnancy test at the time of screening; all patients were to have a normal ECG.
Exclusion criteria included: (1) History or suspicion of alcohol/drug abuse; (2) Pregnant or breastfeeding women or women of childbearing potential who are not using acceptable contraception; (3) Severe hypertension with sitting DBP $\geq$ 115 mm Hg and/or SBP > 200 mm Hg or stage III per WHO classification; (4) Secondary hypertension; (5) Renal disease; (6) Gastrointestinal, hematologic or hepatic disease known to interfere with the absorption, distribution, metabolism or excretion of drugs; (7) Clinically significant laboratory abnormalities; (8) Concurrent use of other medications that influence blood pressure; (9) Symptomatic postural hypotension; (10) Insulin-dependent or poorly controlled diabetes; (11) Severe coronary disease, myocardial infarction within 6 months, or clinically significant congestive heart failure or valvular defects; (12) Wasting, autoimmune or connective tissue diseases; (13) History of hepatitis B or C; (14) Positive results for HIV, hepatitis, or drug screening; (15) Allergy or contraindication to antiotensin II-antagonists; (16) Body weights exceeding -15%/+35% of average according to the Modified Metropolitan Life Insurance Tables;

Figure 54: Study design #866-06



†Note: 27 patients were dropped prior to randomization.

Patients were seen at baseline (Day 1), and on Days 21, 22, 42, and 43; they also underwent a safety follow-up visit 1-2 weeks after study completion. In addition, trough blood samples for CS-866 were drawn on Days 22 and 43. Blood samples for RNH-6270, the main metabolite of CS-866, were drawn on Day 1 (prior to the first dose of active treatment), Day 22, and Day 43 (24 hours after the last drug dose).

As this was primarily a safety/tolerability study in subjects receiving multiple doses of CS-866, the primary parameters were safety data: adverse event collection, blood pressure/pulse monitoring, supine 12-lead ECG (done at baseline, on Days 21, 43, and during the safety followup visit), and routine laboratory tests.

A secondary parameter was efficacy via 24 hour ABPM. The analyses performed were purely exploratory; mean 24-hour diastolic and systolic blood pressures, daytime (8:00 to 20:00) and nighttime (20:00 to 8:00) means were calculated. A response to treatment was defined as decrease in either mean DBP ($\geq$ 10 mm Hg) or mean SBP ($\geq$15 mm Hg). Results were presented for ITT and per-protocol groups.
Drug supplies, manufactured by Luitpold Pharma GmbH, Sankyo Group, are shown in Table 142 below.

Table 142: Drug Supplies #866-06

Substance	Batch #
Placebo	FT224
CS-866 10 mg/20 mg	FT 219, FT 220

Source: NDA 21-286 Study SE-866-06 Clinical Trial Report (Vol. 1): page 23

16.2 Results

Table 143 presents disposition of subjects. One subject in the CS-866 20 mg group was excluded from the per protocol (evaluable) analysis because of noncompliance; 9 subjects were excluded from the per protocol group because of missing ABPM measurements. Of those considered evaluable, 24 were in the placebo group, 19 subjects were in the CS-866 20 mg group, and 21 in the 80 mg group, respectively.

Table 143: Disposition of subjects

	N
Entered placebo run-in	103
Dropped prior to randomization	27
Reasons : Did not meet criteria for randomization DBP too high on ABPM	25 2
Randomized	76
Completed	74
Per-protocol group (evaluable)	64

Source: NDA 21-286: Study SE-866-06 Clinical Trial Report (Vol. 1): pages 46, 51.

Baseline characteristics

Baseline demographics and vital signs are shown in Table 144. All subjects enrolled were Caucasian. Most subjects (84-88.5%) were on antihypertensive treatment and 20 subjects in each treatment group underwent a drug taper-off period prior to the placebo run-in; the rest stopped taking their medication prior to screening. (Most common antihypertensive medications were selective beta-blockers and converting enzyme-inhibitors). Baseline (end of run-in) vital signs are given for the ITT population; there appeared to be no significant differences in baseline ABPM results in the per protocol vs. ITT groups (Tables 147-150 after Conclusion). There appears to be a higher percentage of males in the 80 mg group, otherwise, baseline characteristics are similar between groups.

Table 144: Baseline characteristics (ITT) Study #866-06

	Placebo (N=26)	CS-866 20 mg (N=25)	CS-866 80 mg (N=25)
Age (years) ±SD	48.7 ± 9.4	53.2 ± 8.3	50.3 ± 10.1
Height (cm) ± SD	166.7 ± 9.4	170.8 ± 8.8	169.9 ± 8.6
Weight (kg) ±SD	74.2 ± 13.7	77.5 ± 11.4	80.0 ± 13.5
% Male	46	56	60
Mean (±SD) sitting DBP	101.3 (6.5)	102.8 (5.2)	101.2 (4.6)
Mean (±SD) sitting SBP	155.2 (16)	161.5 (18.3)	154.6 (15.1)
Mean (±SD) sitting HR (bpm)	79.7 (9.4)	79.1 (12.7)	79.4 (12.9)

Source: 21-286: SE-866-06 : pages 47, 200-201. BP in mmHg.SD=Standard Deviation

16.3 Primary objective

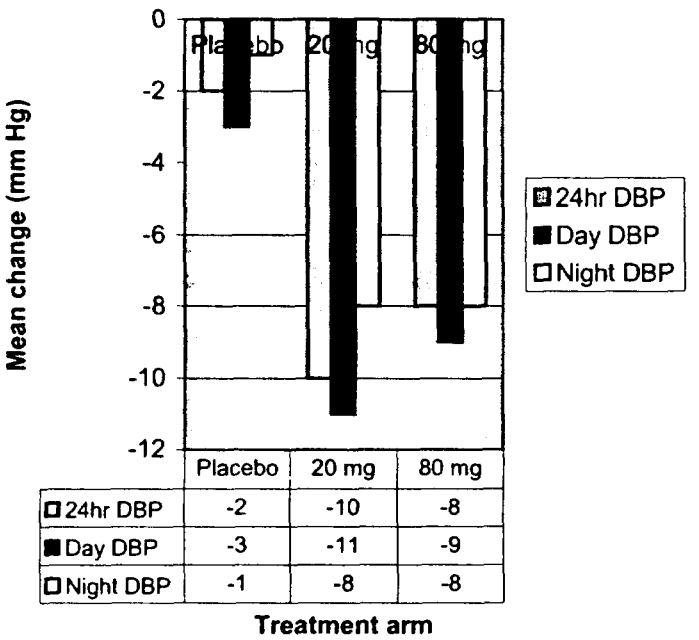
Safety/tolerability

There were no serious adverse events during this study. One patient (#6) on 20 mg CS-866 was dropped on Day 21 because of a 2 day history of leukocytosis and an elevated bilirubin; these findings resolved by the safety followup visit. Otherwise, there were no dropouts related to adverse events. No adverse event was significantly greater than placebo or related to dose. However, 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.

Secondary objectives:

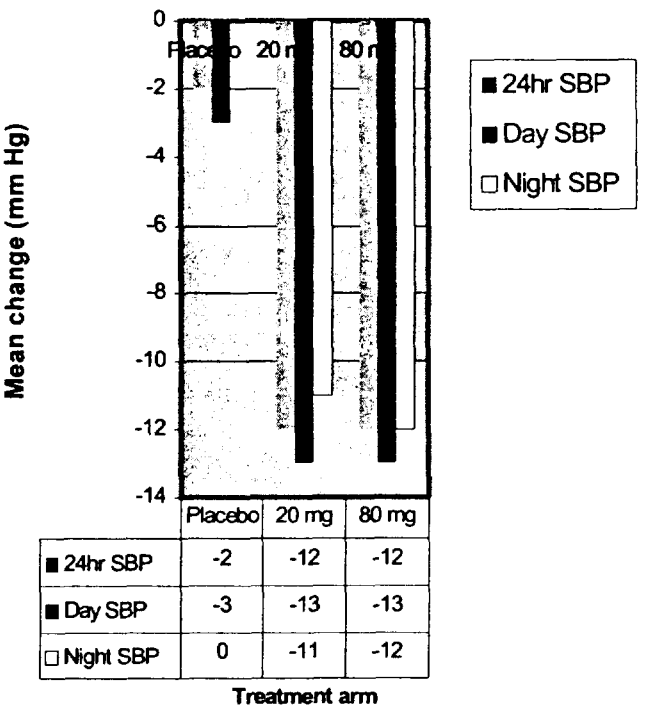
Twenty-four hour ABPM results –ITT- population are displayed graphically below in **Figures 55, 56, 57, 58 ABPM - 866-06**

Change from baseline to Day 21 in ABPM Mean Diastolic Blood Pressure (ITT)

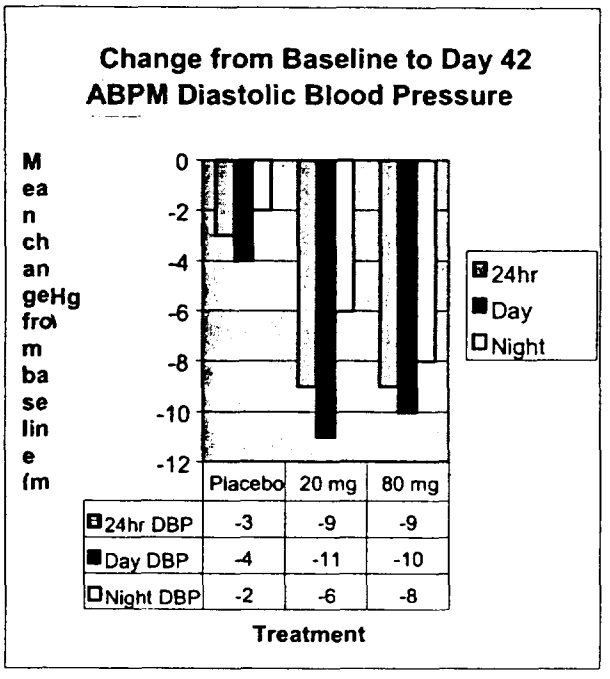


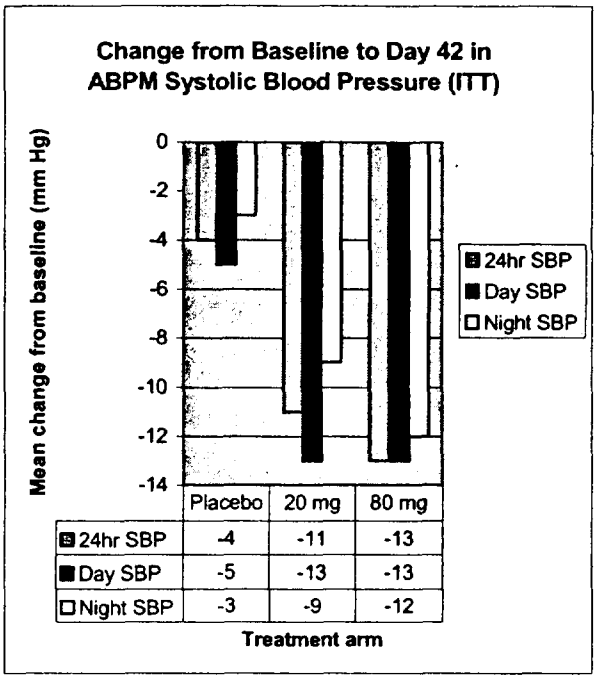
	Placebo	20 mg	80 mg
24hr DBP	-2	-10	-8
Day DBP	-3	-11	-9
Night DBP	-1	-8	-8

Change from baseline to Day 21 in ABPM Mean Systolic Blood Pressure (ITT)



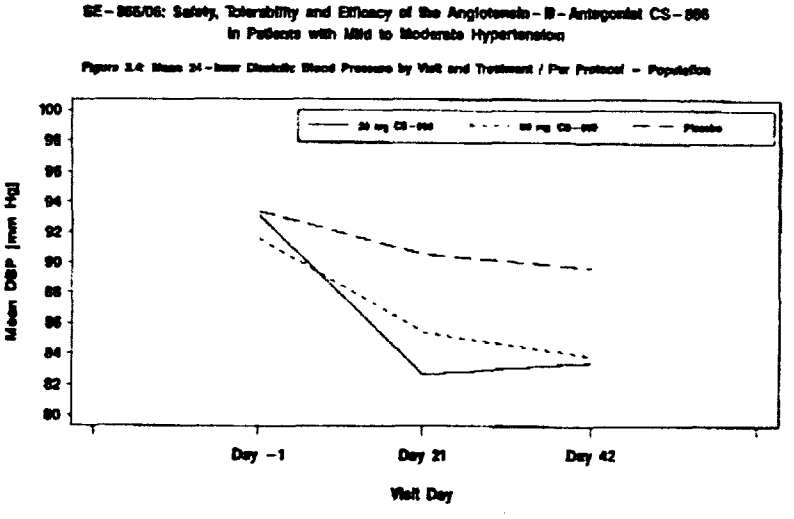
	Placebo	20 mg	80 mg
24hr SBP	-2	-12	-12
Day SBP	-3	-13	-13
Night SBP	0	-11	-12





For the per protocol evaluable group, results suggest that CS-866 20 mg is more effective than the 80 mg dose. An example is illustrated below (Figure 59). Furthermore, in the analysis of variance for the per protocol subjects, it would appear that the 80 mg, unlike the 20 mg dose, does not even beat placebo (Table 145). Whether this can be explained by patient selection (see patients excluded from the per protocol analysis), or increased variability (standard deviation), results for the 80 mg dose remains an unusual finding in this trial. It is also unclear why the 80 mg dose does not beat placebo for Daytime DBP in the per protocol group. Source: Se-866-06: page 88

Figure 59: Change from baseline ABPM Study #866-06



Source: SE-866-06: page 55 (ANOVA)

Table 145: ABPM changes from baseline to Day 42/43 (SE-866/06)

Table VIII: Analysis of variance and Scheffé-Test for changes in 24-hour ABPM from Day -1/1 to Day 42/43

		ITT (N = 76)		PP (N = 64)	
Time Average	Source #	diastolic BP	systolic BP	diastolic BP	systolic BP
24 hours	Treatment	0.0104	0.0508	0.0395	0.1771
	20 mg CS-866 vs. Placebo	***	nd	***	nd
	80 mg CS-866 vs. Placebo	***	nd	ns	nd
	20 mg CS-866 vs. 80 mg CS-866	ns	nd	ns	nd
Daytime	Treatment	0.0158	0.1045	0.0262	0.1871
	20 mg CS-866 vs. Placebo	***	nd	***	nd
	80 mg CS-866 vs. Placebo	ns	nd	ns	nd
	20 mg CS-866 vs. 80 mg CS-866	ns	nd	ns	nd
Night-time	Treatment	0.0267	0.0342	0.1234	0.2060
	20 mg CS-866 vs. Placebo	ns	ns	nd	nd
	80 mg CS-866 vs. Placebo	***	***	nd	nd
	20 mg CS-866 vs. 80 mg CS-866	ns	ns	nd	nd

\# The row named 'Treatment' describes the resulting p-value of the factor Treatment from the Analysis of Variance. The following three rows describe the results from the corresponding pairwise comparison of Scheffé-Test.
*** Comparison significant at the 0.05 level
ns Comparison not significant
nd Scheffé-Test not performed

16.5 Responders

Response rates are shown in Table 146. For both systolic and diastolic blood pressures, the ITT population shows an increase in response rate from the 20 to 80 mg groups; the PP group shows an unexpected decrease in response rate between the 20 and 80 mg groups. The placebo group appears to show consistent results.
Source: SE-86-06: page 56 (response rate)

Table 146: 24 hour responder rate – Study #866-06

Table X: 24-hour ABPM (systolic/diastolic) responder rate

	20 mg CS-866 group			80 mg CS-866 group			Placebo group		
	R	P	%	R	P	%	R	P	%
sBP/ITT-population	10	25	40.0	11	25	44.0	2	26	7.7
sBP/PP-population	8	19	42.1	8	21	38.1	2	24	8.3
dBP/ITT-population	10	25	40.0	12	25	48.0	2	26	7.7
dBP/PP-population	9	19	47.4	9	21	42.1	2	24	8.3

R = Responder P = Patients

Summary

This was a randomized, double-blind, placebo-controlled, parallel-group study evaluating safety, tolerability and efficacy using ABPM of CS-866 20 mg and 80 mg.

Conclusions

Active treatment appeared to be well tolerated. There were no serious adverse events in this trial.

ITT results for 24 hour ABPM showed that CS-866 20 and 80 mg were effective in lowering systolic and diastolic BP compared to placebo and that the 80 mg group did not appear significantly different from the 20 mg group; however, results for daytime diastolic BP were inconsistent. Inconsistent, too, were the 80 mg group results in the per protocol population.

For reference, results for ITT and per protocol population are presented below in tables 147-150 (Source: SE-866-06: pages 52-53).

Tables 147-150: Mean ABPM results Study #866-06

Table IV: Mean Systolic Blood Pressure (24 h-ABPM) ± s.d., PP-Population

sBP (mmHg)	PP Sample	Day			Change under Treatment Day21 - Day-1	Change under Treatment Day42 - Day-1
Time Average	Treatment	-1/1	21/22	42/43		
24 hours	20 mg CS-866	148 ± 10	134 ± 16	135 ± 14	-14 ± 9	-13 ± 10
	80 mg CS-866	144 ± 10	135 ± 17	134 ± 19	-8 ± 13	-11 ± 15
	Placebo	146 ± 10	142 ± 13	140 ± 12	-3 ± 10	-6 ± 12
Daytime	20 mg CS-866	154 ± 12	140 ± 17	139 ± 16	-14 ± 11	-15 ± 12
	80 mg CS-866	150 ± 11	141 ± 18	139 ± 20	-10 ± 16	-11 ± 18
	Placebo	151 ± 10	147 ± 12	146 ± 14	-4 ± 11	-6 ± 14
Night-time	20 mg CS-866	140 ± 11	128 ± 16	121 ± 13	-12 ± 9	-10 ± 10
	80 mg CS-866	136 ± 11	128 ± 17	127 ± 18	-9 ± 12	-11 ± 13
	Placebo	139 ± 12	136 ± 15	134 ± 13	-3 ± 12	-5 ± 13

Table V: Mean Diastolic Blood Pressure (24 h-ABPM) ± s.d., PP-Population

dBP (mmHg)	PP Sample	Day			Change under Treatment Day21 - Day-1	Change under Treatment Day42 - Day-1
Time Average	Treatment	-1/1	21/22	42/43		
24 hours	20 mg CS-866	83 ± 6	83 ± 9	83 ± 9	-11 ± 6	-10 ± 8
	80 mg CS-866	82 ± 6	86 ± 11	84 ± 11	-6 ± 9	-8 ± 9
	Placebo	83 ± 6	81 ± 7	80 ± 7	-3 ± 7	-4 ± 7
Daytime	20 mg CS-866	89 ± 7	86 ± 9	87 ± 9	-11 ± 7	-12 ± 7
	80 mg CS-866	87 ± 7	90 ± 11	88 ± 12	-6 ± 9	-8 ± 10
	Placebo	89 ± 6	86 ± 7	95 ± 9	-3 ± 7	-5 ± 9
Night-time	20 mg CS-866	86 ± 7	77 ± 9	79 ± 9	-9 ± 6	-7 ± 7
	80 mg CS-866	86 ± 6	79 ± 11	78 ± 11	-6 ± 10	-7 ± 10
	Placebo	86 ± 7	84 ± 9	84 ± 8	-2 ± 7	-3 ± 8

Table VI: Mean Systolic Blood Pressure (24 h-ABPM) ± s.d., ITT-Population

sBP (mmHg)	ITT Sample	Day			Change under Treatment Day21 - Day-1	Change under Treatment Day42 - Day-1
Time Average	Treatment	-1/1	21/22	42/43		
24 hours	20 mg CS-866	148 ± 12	136 ± 16	136 ± 13	-12 ± 9	-11 ± 11
	80 mg CS-866	144 ± 9	132 ± 18	132 ± 18	-12 ± 15	-13 ± 15
	Placebo	146 ± 10	144 ± 15	142 ± 14	-2 ± 12	-4 ± 13
Daytime	20 mg CS-866	154 ± 13	141 ± 17	140 ± 14	-13 ± 11	-13 ± 14
	80 mg CS-866	150 ± 10	137 ± 19	137 ± 20	-13 ± 17	-13 ± 18
	Placebo	152 ± 10	149 ± 14	146 ± 14	-3 ± 12	-5 ± 14
Night-time	20 mg CS-866	141 ± 12	130 ± 16	131 ± 13	-11 ± 9	-9 ± 10
	80 mg CS-866	138 ± 10	126 ± 19	125 ± 18	-12 ± 14	-12 ± 13
	Placebo	139 ± 12	139 ± 17	136 ± 15	-0 ± 14	-3 ± 14

Table VII: Mean Diastolic Blood Pressure (24 h-ABPM) ± s.d., ITT-Population

dBP (mmHg)	ITT Sample	Day			Change under Treatment Day21 - Day-1	Change under Treatment Day42 - Day-1
Time Average	Treatment	-1/1	21/22	42/43		
24 hours	20 mg CS-866	83 ± 6	84 ± 8	84 ± 8	-10 ± 6	-9 ± 8
	80 mg CS-866	81 ± 5	83 ± 12	83 ± 11	-8 ± 10	-9 ± 9
	Placebo	83 ± 6	81 ± 8	80 ± 8	-2 ± 7	-3 ± 7
Daytime	20 mg CS-866	89 ± 7	88 ± 9	88 ± 9	-11 ± 7	-11 ± 8
	80 mg CS-866	86 ± 6	86 ± 12	87 ± 12	-8 ± 11	-10 ± 10
	Placebo	89 ± 5	86 ± 7	95 ± 8	-3 ± 7	-4 ± 9
Night-time	20 mg CS-866	86 ± 7	78 ± 9	79 ± 9	-8 ± 7	-8 ± 6
	80 mg CS-866	85 ± 6	77 ± 12	77 ± 12	-8 ± 10	-8 ± 10
	Placebo	86 ± 7	85 ± 9	84 ± 8	-1 ± 8	-2 ± 8

17.0 Study SE-#866-17
17.01 Title "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"

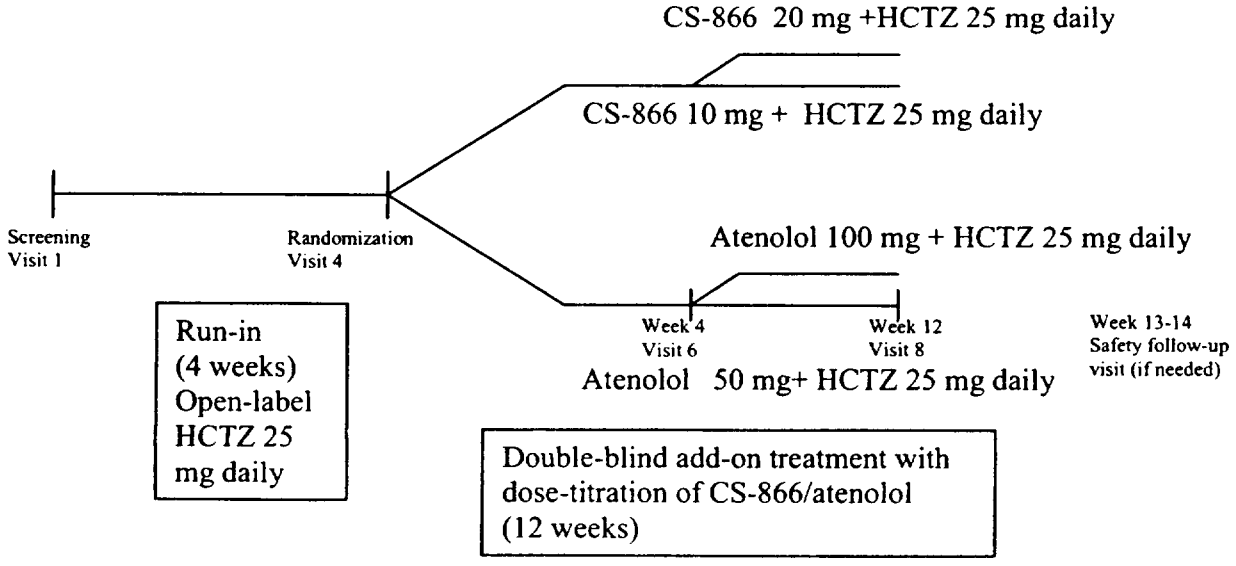
Source documents: Study report: NDA 21-286, vol. 294, 298, 302, 307 (clinistat)

Investigators: The Principal Investigator was P. U. Witte, MD, Ph.D. This was a 300 patient multicenter study.

Study dates: February 12, 1998 to April 28, 1999.

17.1 Objectives: Primary
To assess the non-inferiority of individually optimized doses CS-866 against atenolol after 12 weeks of treatment in lowering trough diastolic blood pressure (DBP).
Secondary objectives
(1) To assess non-inferiority of individually optimized doses of CS-866 against atenolol after 4 and 8 weeks of treament with respect to effects on trough DBP;
(2). To assess non-inferiority of individually optimized doses of CS-866 against atenolol after 4, 8 and 12 weeks of treatment with respect to effects on trough SBP;
(3). To compare individually optimized final doses of CS-866 and atenolol after 12 weeks of treatment;
(4). To compare responder rate of each dose level of CS-866 and atenolol after 4, 8, and 12 weeks of treatment; (5). To assess safety and tolerability of CS-866 compared to atenolol with respect to AE, pulse rate, ECG and laboratory parameters.

17.2 Study design: This description was based upon the study report. This Phase III study design is shown in Figure 60 below.
Figure 60: Study design - Study SE- #866-17



Eligible subjects were males and nonpregnant females over 18 years old with moderate to severe hypertension (105 ≤ DBP≤ 120 mm Hg or pretreated 100 ≤ DBP ≤ 120 mm Hg). Exclusion criteria included: (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 (>10 cigarettes daily); (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;

The primary efficacy variable was the change from baseline to Visit 8 (week 12 or final examination) in mean trough sitting DBP.
Safety monitoring included: adverse experience collection, physical examination (at end of study), blood pressure/pulse monitoring, 12-lead ECG, and routine laboratory tests. If the sitting DBP > 120 mm Hg or sitting SBP > 200 at any time, the patient was to be withdrawn from the study.

17.3 Statistical analysis: Three analysis populations were defined. The safety set consisted of all patients who received double-blind medication at least once. The full analysis set consisted of all patients who received double-blind medication at least once and returned for at least one study visit; missing data was handled as Last Observation Carried Forward (LOCF). The valid set consisted of patients in the full analysis set excluding those who withdrew for any reason, who violated inclusion/exclusion criteria, and who had serious deviations from the protocol.
ANOVA techniques were used to analyze the primary efficacy variable. Trial centers with no more than 12 subjects in the full analysis set were pooled, by country, for all center-specific evaluations on the full or valid analysis set. CS-866 plus HCTZ was declared to be non-inferior to atenolol plus HCTZ if the upper limit of the 95% once-sided confidence interval for the difference in the least squares means is less than or equal to 3.5 mm Hg.
Secondary endpoints were presented as descriptive statistics without formal analysis.Patients were classified as responders if their mean sitting DBP at trough had decreased to < 90 mm Hg and/or their mean sitting DBP had decreased by 10 mm or more from the mean at baseline.No interim analysis was performed.

Sample Size Calculation: A total of 282 patients (141 in each treatment group) gave 90% power to show that CS-866 is at least as effective as atenolol with respect to the

mean reduction in sitting dBP at trough after 12 weeks of treatment. This sample size calculation assumes that the residual standard deviation was 10 mmHg and that the maximum clinically allowable difference between the mean reduction in trough dBP levels in the two treatment groups consistent with non-inferiority is 3.5 mmHg and the type I error (one-sided) is 0.05.
Drug supplies, manufactured by Luitpold Pharma GmbH, Sankyo Group, are shown in Table 151.

Table 151: Drug Supplies SE-#866-17

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)

Changes in Trial Conduct or Planned Analyses:
According to the protocol, it was planned to utilize MS-Access database for data entry and transfer the data to SAS datasets for statistical analysis. However, the data were instead directly entered into SAS. In addition to 95% one-sided confidence intervals, 97.5% one-sided confidence intervals were calculated to satisfy ICH E9 guidelines adopted in 1998, after the trial design had been finalized.

17.4 Results

Patient Disposition

Table 152 displays patient disposition in this study (Source: SE-866-17 pdf. Page 64).

Table 152: Patient Disposition – Study SE #866-17

Screened	393		
Enrolled into HCTZ run-in	351		
Screening Failures	42		
Dropouts—HCTZ only	23		
	Total	CS-866	Atenolol
Randomized	328	164	164
Completed	318	158	160
Withdrawal	10	6	4
Due to AE	2	1	1
Withdrew consent	5	4*	1
Other	3	1	2

Source: SE-866-17: pdf. Page 64 *One patient had two reasons: AE, Withdrew consent
Dropouts/ Protocol deviations
Source: SE-866-17: Table VIII pdf. Page 71

All randomised patients were evaluable for the safety set and the full analysis set, i.e. both sets are identical in this trial. Forty-six patients, 14% of the randomized patients, were excluded from the valid cases set due to major protocol violations.

17.5 Baseline characteristics

In the ITT (full analysis set), all patients were Caucasian, and about 46-50% were males. In 67% of the full analysis set a taper-off period was necessary; there was no meaningful difference between the two treatment groups. There were also no meaningful differences between the two groups in background medical and surgical histories. The mean (± SD) age was 55-56 (10) years, mean weight was 82 (13) kg, mean height was 169 (9) cm. There were no meaningful differences between the two treatment groups.

17.6 Compliance

Treatment compliance was checked by pill counts. If compliance was not 80-120% during the open-label HCTZ run-in period, the patient was excluded. Mean compliance was 99.0% in the CS-866 group and 99.4% in the atenolol group. Median compliance was 100% in both groups. Two patients in the CS-866 and one patient in the atenolol group were excluded because of noncompliance.

17.7 Efficacy: Primary objective

Table 153: Change from baseline in Mean sitting DBP [mmHg] (± SD)

Visit	CS-866 (N=164)	Atenolol (N=164)
Baseline*	105.0 (4)	105.3 (4)
Final Visit/Week 12	87.3 (7.2)	87.5 (7.2)
Change from Baseline	-17.7 (7)	-17.8 (7.3)
Adjusted mean	-17.3	-17.2

* Baseline is defined as after open-label treatment with HCTZ 25 mg daily and prior to randomization. Source: SE-866-17: Table XIII: pdf. Page 76.

ANOVA showed significant effects of the trial center pool and the baseline value ($p < .001$) but no significant treatment effect ($p=.9075$).

Table 154: Treatment comparison: CS-866 v Atenolol

Treatment comparison	Point estimator of difference between adjusted means	95% upper confidence limit	97.5% upper confidence limit
CS-866 – Atenolol	-0.08	1.02	1.23

Table 155: Treatment comparison: CS866 v Atenolol at 2,4, and 8 wks SE #866-17

Visit		CS-866 (N=164)	Atenolol (N=164)
Visit 4/ Week 0	Mean dBP [mmHg] (SD)	104.8 (4.2)	105.1 (4.4)
Visit 5/ Week 2	Mean dBP [mmHg] (SD)	93.1 (8.7)	93.0 (8.8)
Change	Mean dBP [mmHg] (SD) Adjusted Mean	-11.9 (6.7) -11.6	-12.3 (7.4) -12.0
Visit 6/ Week 4	Mean dBP [mmHg] (SD)	90.6 (8.0)	89.8 (8.9)
Change	Mean dBP [mmHg] (SD) Adjusted Mean	-14.4 (6.5) -13.7	-15.5 (7.9) -14.7
Visit 7/ Week 8	Mean dBP [mmHg] (SD)	87.3 (7.6)	87.6 (6.8)
Change	Mean dBP [mmHg] (SD) Adjusted Mean	-17.7 (7.1) -17.4	-17.7 (6.5) -17.2

Table 155: Number & Rate of Responders by Visit &Treatment Group

Visit / Week	CS-866 (N=164)	Atenolol (N=164)
5 / 2	90 (54.9%)	94 (57.3%)
6 / 4	120 (73.2%	122 (74.4%)
7 / 8	140 (85.4%)	145 (88.4%)
Final Visit / 12	141 (86.0%)	139 (84.8%)

Full Analysis Set (Section 8.2, Table 40.1)

Of the CS-866 patients in the full analysis set, 43 (26.2%) concluded the trial receiving high dose treatment, compared to 46 atenolol patients (28.1%).

17.8 Heart rates analyses

Table 156: Heart Rate at baseline and Final visit-CS-866-17

	CS-866	Atenolol
Visit 4 (baseline)		
N	164	164
Median heart rate (min.-max.)	73.3	75.0
Final visit		
N	160	162
Median heart rate (min.-max.)	73.3	72 .0

Source: SE-866-17: Table 31: pdf. Page 111

There is a slight decrease in median heart rate in the atenolol treatment group compared to baseline. Since the median heart rate for atenolol is 72 bpm in the Final Visit, it appears that 50% or more patients in atenolol group were not maximally beta-blocked.

17.9 Safety/tolerability

There were no deaths during this trial. Five patients experiences 6 serious adverse experiences, 2 patients reported SAE during HCTZ run-in period, 2 patients developed SAE during treatment with CS-866, and 1 during treatment with atenolol. 5 patients (1 in CS-866 and 4 in atenolol) reported hepatic enzyme elevations; one of these developed into an SAE and led to trial discontinuation.

Nine patients (4 in CS-866 and 5 in atenolol) developed treatment-emergent AE due to clinically relevant changes in laboratory values (excluding liver enzyme elevations); 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.

Summary

This was a 12 week, 328 patient comparative (non-inferiority) study of HCTZ +CS-866 (10 and 20 mg) and HCTZ + atenolol (50 and 100 mg) in patients with moderate-to-severe hypertension.

Conclusions

The study was successful in demonstrating what it was designed to demonstrate. However, the full dose-response curves of CS-866 and atenolol were not compared. In addition, all patients were on background HCTZ therapy; the role of HCTZ may impact a direct comparison between CS-866 and atenolol.

18.0 Study SE-#866-11

18.01 Title "To assess the efficacy of CS-866 at dose levels of 2.5 mg, 5 mg and 10 mg once daily in mild - to - moderate hypertensive patients using the diastolic blood pressure (dBP) assessed by 24 hour ABPM after 12 weeks of treatment compared to baseline.

Principal Investigator: P.U.Witte, M.D.,Ph.D.
Sites: This study was conducted at 12 sites in Germany and Czech Republic.
Study Dates: June 1997 to February 1999.

18.1 Study Objectives: Primary Objective

"To assess the antihypertensive effect and safety of olmesartan administered to hypertensive patients once daily over a relatively long time (55 weeks) using ABPM as a measure for blood pressure monitoring.

Secondary Objectives

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.
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.
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.
To investigate the correlation between change in dBP (visit 6/week 8) and RNH – 6270 concentration in plasma (visit 6/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/week 8).
To investigate the correlation between RNH-6270 plasma levels (visit 6/week 8) and creatinine clearance (mean of visit 5 /week4 and visit 6/week 8), in the active groups.
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.
To investigate the effects of age on the efficacy safety and tolerability of CS-866 at dose levels of 2.5 mg, 5 mg , and 10 mg o.d over 12 weeks of treatment.

18.2 Study design

This was a phase III, multi-center, randomized, double blind, placebo-controlled, parallel group study in subjects with mild-to-moderate hypertension (95<SiDBP<110mmHg). Patients on previous antihypertensive therapy were tapered off their medication for at least 2 weeks (taper-off period) before the 2-week placebo run-in period. After the placebo run-in period, eligible patients were randomized to receive 2.5, 5, 10 mg CS-866 or placebo once daily for 12 weeks. After 12 weeks of treatment, completing patients entered an optional safety follow-up visit period of 2/3 weeks. The entire study lasted about 20 weeks. The total duration of the trial for each ITT patient was 16 weeks (inclusive of a 2-week placebo run-in phase) plus a 2-week pre-run in taper-off period.

An optional safety follow-up examination was carried out about 2 weeks after the last administration of the trial medication.

18.3 Inclusion criteria

The patients were taken from a healthy non-obese population over 18 years. Inclusion and exclusion criteria were applied to determine eligibility of patients enrolled and randomized as specified in protocol. The total number of patients projected to be randomized was 264 with 66 patients in each of the 4 treatment groups.

To be eligible for treatment phase, some of the patients' requirements include the following:

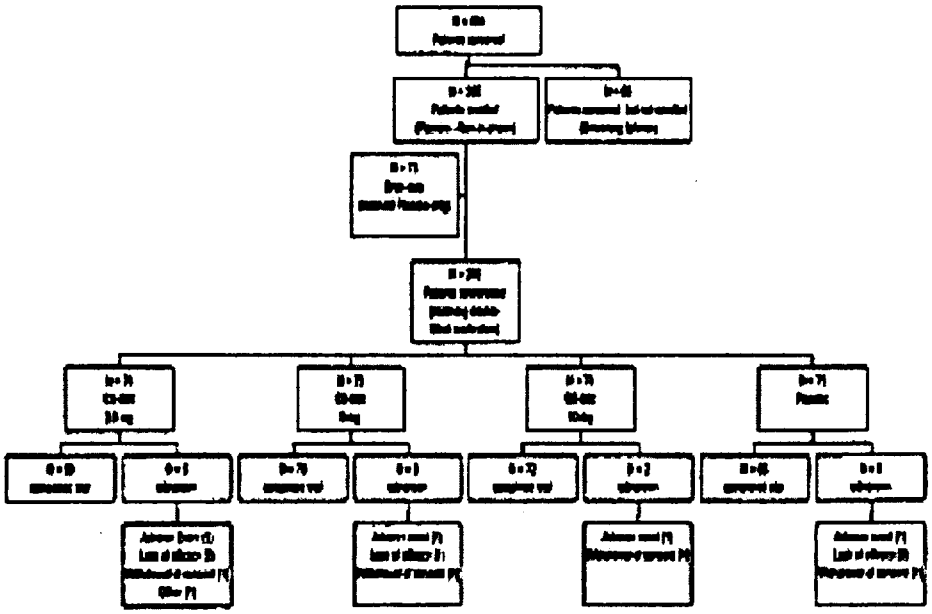
Newly diagnosed hypertensive with mean SiDBP between 100 and 114 mmHg inclusive at screening.

Hypertensive patients on previous therapy must have sitting diastolic BP between 100 and 114 mmHg at the end of the taper-off period.

All hypertensive patients must have a mean of 3 sitting DBP between 100 and 114mmHg inclusive of at least 2 measurements during the placebo run-in period.

All patients after a 2 week placebo run-in phase, the average 24-hour DBP had to be at least 84mmHg determined by 24 hour ABPM performed at visit 3 (week 0).

Figure 61: Study SE- #866-11



18.4 Primary efficacy: The primary efficacy analysis is performed on the ITT basis using the final on-therapy change from baseline value on trough SiDBP after 12 weeks.

18.5 Statistical analyses: Primary efficacy analysis
Statistical analyses: Primary hypothesis (866-11)
There is no difference in the treatment effect between CS-866 (at doses 2.5, 5, and 10mg) and placebo when the effect is measured by the change in diastolic blood pressure (dBP) assessed by 24 hour ABPM after 12 weeks of treatment compared to baseline.

The confirmatory statistical analysis was performed on the primary parameter of change in mean daytime dBP from week 0 to week 12 on the ITT sample. The statistical analysis used parametric ANCOVA model with fixed effects center and treatment and baseline mean daytime dBP as a covariate. The secondary parameters concerning the ABPM were also analyzed using similar ANCOVA model but excluded the center x treatment interaction terms. Pearson's and Spearman's correlation coefficients with 95% confidence intervals were obtained for patients in the groups combined between change in mean daytime dBP and AUC, change in mean daytime dBP and mean creatinine clearance and AUC and mean creatinine clearance, all at times specified in the protocol.

Sample size calculation
For primary efficacy variable, there are 3 comparisons of interest corresponding to each active dose compared to placebo. The sample size calculation was based on 90% power to detect a difference of 5mmHg between each group and placebo (α=0.05). Adjusting tests for multiple comparisons gives 0.017 as the significance level for each test. This study was powered accordingly to detect a difference of 5mmHg between each active group and placebo.

18.6 Results
Patient disposition
Out of a total of 454 patients screened, 365 patients were enrolled, 73 (20%) dropped out during the placebo run-in period leaving 292 evaluable patients for safety (Table 157). Fifteen patients were withdrawn, and 277 patients completed the trial. The overall disposition of patients (287 ITT, 238 PP and 292 EFS) during the double-blind period, by age class and treatment, is presented in Tables 157-160.

Table 157: Disposition of Patients by Age class, Treatment group and Withdrawals

Patients	Age class	Plcbo	CS-866			Total
			2.5mg	5mg	10mg	
Randomized (EFS)	Total	71	74	73	74	292
	Young	12	8	28	15	63
	Middle Aged	45	53	37	49	184
	Elderly	9	10	4	7	30
	Very elderly	5	3	4	3	15

Patients	Age class	Plcbo	CS-866			Total
			2.5mg	5mg	10mg	
ITT	Total	68	73	72	74	287
	Young	12	5	27	15	62
	Middle Aged	43	63	37	49	182
	Elderly	9	9	4	7	29
	Very elderly	4	3	4	3	14
Per Protocol	Total	60	56	61	61	238
	Young	12	7	25	15	59
	Middle Aged	40	42	33	42	157
	Elderly	6	7	2	4	19
	Very elderly	2	0	1	0	3
Withdrawn	Total	5	5	3	2	15
	Young	0	0	2	0	2
	Middle Aged	3	3	1	2	9
	Elderly	0	1		0	1
	Very elderly	2	1		0	3
Completed	Total	66	69	70	72	277
	Young	12	8	26	15	61
	Middle Aged	42	50	36	47	175
	Elderly	9	9	4	7	29
	Very elderly	3	2	4	3	12
Of the 292 randomized, 15 were withdrawn leaving 277 randomized patients for efficacy analysis. See Table 2 for reasons.						

Table 158: Summary Table-Patient disposition by treatment group-Study# 866-11

No. of patients	Placbo	CS-866			Total
		2.5mg	5mg	10mg	
Placebo run-in	71	74	73	74	292
Randomized					
ITT	68	73	72	74	287
Per Protocol	60	56	61	61	238
Withdrawn(%ITT)	5	5	3	2	15
Completed	66	69	70	72	277
Of the 292 randomized, 15 were withdrawn leaving 277 randomized patients for efficacy analysis.					

Out of 292 patients enrolled, 277 completed the study, 15 were withdrawn (Table 158). The reasons for withdrawal are given in Table 159. Table 160 gives the age class of those withdrawn and completers. Efficacy data from evaluable patients (238/292; 81.5 %) at the end of study were comparable to data from 292 ITT patients in nearly all respects.

There were also no significant differences between the ITT and PP population groups with respect to demographics, baseline ABPM or vital signs (Tables 161-162).

Table 159: Reasons for withdrawal by dose group-ITT- 866-11

Reasons for withdrawal(N)	CS - 866			Plcbo	Total
	2.5mg	5mg	10mg		
Adverse Event (4)	1	1	1	1	4
Loss of efficacy(6)	2	1	0	3	6
Withdrawal of consent(4)	1	1	1	1	4
Concomitant Medication(0)	0	0	0	0	0
Others(1)	1	0	0	0	1
Total	5	3	2	5	15

Table 160: Enumeration of subjects by age class and dose – ITT- 866-11

		CS - 866			Placebo	Total
No of Pts.	Age class	2.5mg	5mg	10mg		
Randomized	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
Withdrawn	Young	0	2	0	0	2
	Middle Aged	3	1	2	2	9
	Elderly	1	0	0	0	1
	Very Elderly	1	0	0	3	3
	Total	5	3	2	5	15
Completed	Young	8	26	15	12	61
	Middle Aged	50	36	47	42	175
	Elderly	9	4	7	9	29
	Very Elderly	2	4	3	3	12
	Total	69	70	72	66	277

18.7 Demographics and treatment group comparability

There is no significant difference between the treatment groups and also between ITT and PP population groups (Table 161). According to *"CPMP guidelines on hypertension"* a minimum of 28 BP measurements during daytime is mandatory and 52 in total. In this study 48 patients had fewer measurements than 28. 17 patients were excluded from the PP analysis on the basis that the numbers of measurements were less than 26 during daytime and less than 48 in total (Tables 161 and 162). Gender, race and physical characteristics of the patients are presented in Table 162. All the patients were Caucasians and the treatment groups were comparable in age, sex and physical characteristics.