Figure 740

Mean Change from Baseline in Cuff Sitting Diastolic BP By Treatment & Week
Non-Black, Cuff ITT Patients within Visit Windows

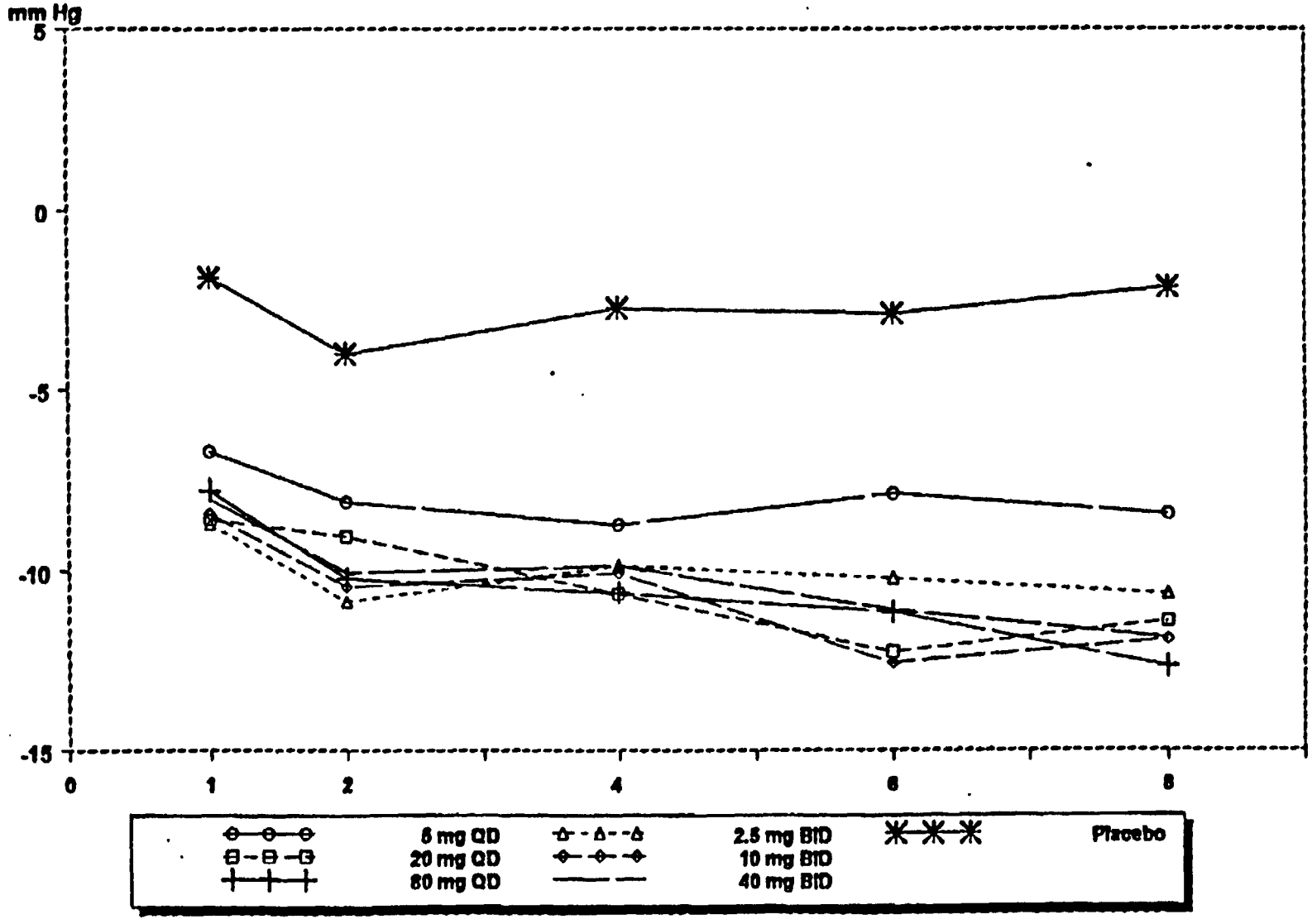

Figure 15: ABPM-based SBP changes from pre-treatment, at last visit
(Non-Blacks, ITT; sponsor's fig 712)

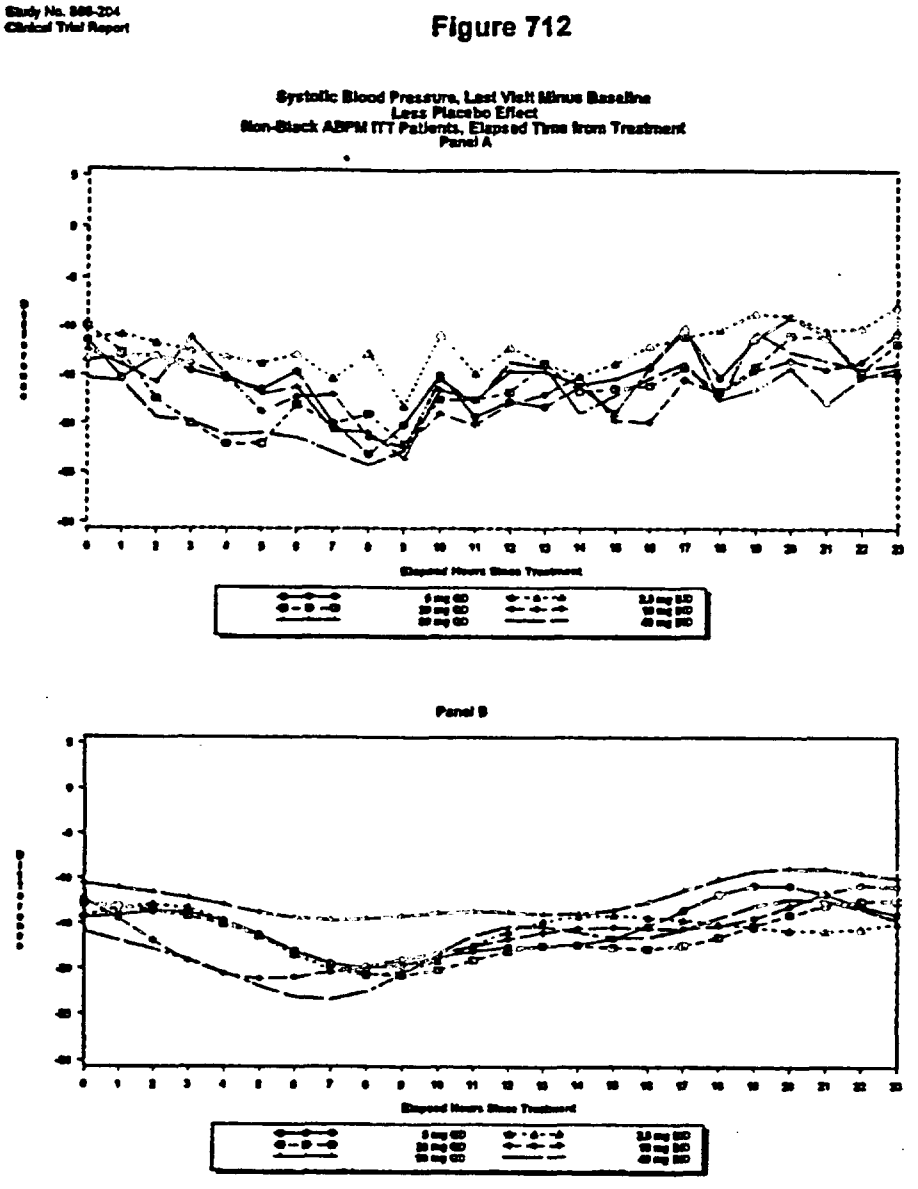

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Table 35B
Cuff Measurement Results
Mean Change in Systolic BP From Baseline[1] to Week 8
Non-Black, Cuff Intent-to-Treat Patients Within Visit Windows[2]

		5 mg Total Dose			20 mg Total Dose			80 mg Total Dose		
	Placebo	QD	BID	Comb.	QD	BID	Comb.	QD	BID	Comb.
Total Randomized	43	41	43	84	42	44	86	43	46	89
					Sitting (mm Hg)					
Mean	155.6	143.5	141.3	142.4	140.4	137.0	138.7	140.2	142.0	141.1
±SD	±16.6	±13.1	±14.7	±13.9	±17.3	±16.3	±17.6	±16.2	±21.3	±19.6
Mean Change	-1.6	-12.1	-13.7	-12.9	-14.5	-16.3	-15.4	-14.2	-17.1	-15.7
±SD	±10.9	±14.0	±12.5	±13.2	±13.1	±13.9	±13.5	±16.6	±18.5	±17.5
n	37	37	39	76	38	39	77	39	43	82
					Supine (mm Hg)					
Mean	155.1	144.3	141.1	142.7	142.9	135.6	139.3	139.7	141.1	140.4
±SD	±17.6	±13.5	±13.2	±13.4	±17.2	±16.7	±17.2	±19.5	±21.4	±20.4
Mean Change	-2.4	-13.0	-14.6	-13.8	-12.5	-17.2	-14.9	-15.4	-17.0	-16.2
±SD	±12.0	±16.3	±11.7	±14.1	±15.7	±11.5	±13.9	±17.4	±20.8	±19.2
n	37	37	39	76	38	39	77	39	43	82

6.9 HR effects (study 866-204)

As shown below, the changes from pre-treatment HR for all groups were relatively small and without statistical significance.

Table 56: Mean changes in HR at the last observation (bpm)

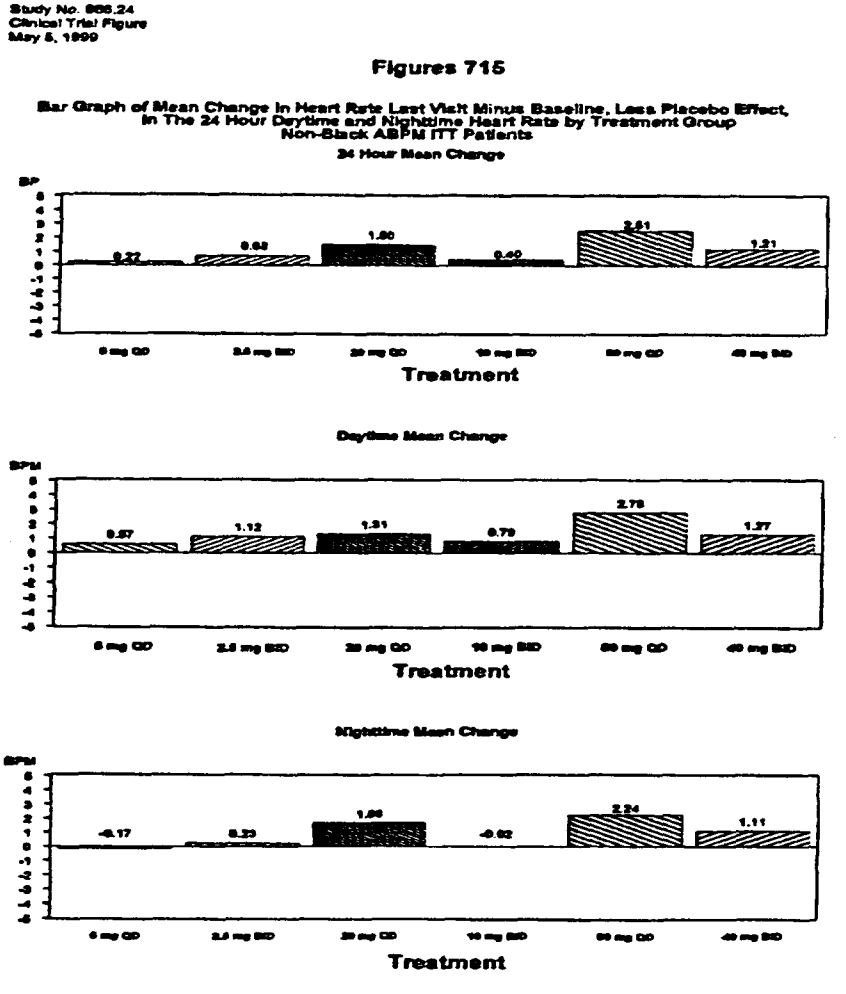
(Non-Black Patients; ITT; study 866-204)

GROUP	24 hr hr	daytime hr	nighttime hr
Placebo	-0.6	-0.3	-0.9
5 mg QD	-0.4	0.2	-1.1
20 mg QD	0.9	1.0	0.8
80 mg QD	1.9	2.4	1.3
2.5 mg BID	0.1	0.8	-0.7
10 mg BID	-0.2	0.5	-0.9
40 mg BID	0.6	0.9	0.2

Source- sponsor's Table 75.1.1-3

These were based on ABPM recordings as last observed at Week 8 in completers, or earlier in dropouts. (Figure 16: Non-Blacks, ITT; sponsor's fig 715)

Figure 16: ABPM-based Heart rate changes last visit -ITT-Study 866-204



6.10 Efficacy in Blacks (866-204)

For the primary endpoint, in the small group of Black subjects there was a statistically nonsignificant trend towards the same outcome as non-black subjects.

Blacks subjects were relatively few in number, therefore pooled analyses across placebo-controlled studies would be a more efficient means of examining for differential responsivity of this demographic subgroup. Means results of these and other analyses are shown below.

Table 57: Distribution of Black patients with ABPM data

(Black Patients; ITT; study 866-204)

GROUP	day -1	week 1	week 2	week 4	week 6
Placebo	5	2	1	2	0
5 mg QD	4	3	0	0	0
20 mg QD	3	1	1	0	0
80 mg QD	5	1	2	0	1
2.5 mg BID	7	0	3	2	0
10 mg BID	4	1	1	0	1
40 mg BID	4	1	1	0	1

Source- sponsor's Table 7.5.1.3-2

Table 58: Mean changes in DBP in Black patients; ITT; study 866-204)

GROUP	24 hr dbp	daytime dbp	nighttime dbp
Placebo	1.4	0.4	2.5
5 mg QD	-2.7	-7.1	1.7
20 mg QD	-12.8	-13.1	-12.5
80 mg QD	-3.1	-5.5	-0.7
2.5 mg BID	-6.3	-3.0	-9.6
10 mg BID	-3.2	-2.1	-4.3
40 mg BID	-9.5	-11.3	-7.6

Source- sponsor's Table 7.5.1.1-4

Table 59: Mean changes in SBP in Black patients (mm Hg; ITT; study 866-204)

GROUP	24 hr sbp	daytime sbp	nighttime sbp
Placebo	2.9	2.0	3.9
5 mg QD	-6.4	-12.7	-0.2
20 mg QD	-17.4	-21.7	-13.1
80 mg QD	0.8	-2.0	3.7
2.5 mg BID	-7.9	-3.4	-12.5
10 mg BID	-4.9	-3.6	-6.1
40 mg BID	-13.4	-16.0	-10.8

Source- sponsor's Table 7.5.1.1-5

Table 60: Mean changes in HR in Black patients (bpm; ITT; study 866-204)

GROUP	24 hr hr	daytime hr	nighttime hr
Placebo	1.5	3.8	-0.9
5 mg QD	1.0	1.9	0.0
20 mg QD	-6.7	-11.9	-1.4
80 mg QD	4.0	0.8	7.2
2.5 mg BID	2.2	3.5	0.9
10 mg BID	-5.0	-3.2	-6.8
40 mg BID	6.5	9.0	4.0

Source- sponsor's Table 7.5.1.1-6

Comments (study 866-204)

1. Convincing evidence for antihypertensive efficacy with once-daily dosing of olmesartan was provided by this trial.

2. There was no evidence of additional efficacy obtained by using an 80 mg qd dose, relative to a 20 mg qd dose.

3. I do not find support for an argument in favor of twice-daily dosing insofar as only one of the once-daily doses yielded point-estimated trough-to-peak BP ratios that were even qualitatively relatively lower than twice-daily effect, and apparently (as per preliminary report of the safety reviewer) without undue cost of symptomatic hypotension at peak.

APPEARS THIS WAY
ON ORIGINAL

7.0 Study SE-#866-305
7.01 Title: "A Randomized, Placebo-Controlled, Parallel-Group Study of CS-866 with long-term Safety Evaluation in Patients with Essential Hypertension".

Source documents:	Study report: NDA 21-286, vols. 170, 174, 178, 182, 186.
Sites:	This study was conducted at 54 sites.
Study dates:	August 19, 1997 (date of first enrollment) to February 11, 1999 (last completed).

7.1 Objectives: The objectives of this study were to assess 1) The efficacy and safety of CS-866 after 8 weeks of treatment; and 2) The long-term safety of CS-866 after 1 year of treatment, with and without concomitant hydrochlorothiazide.

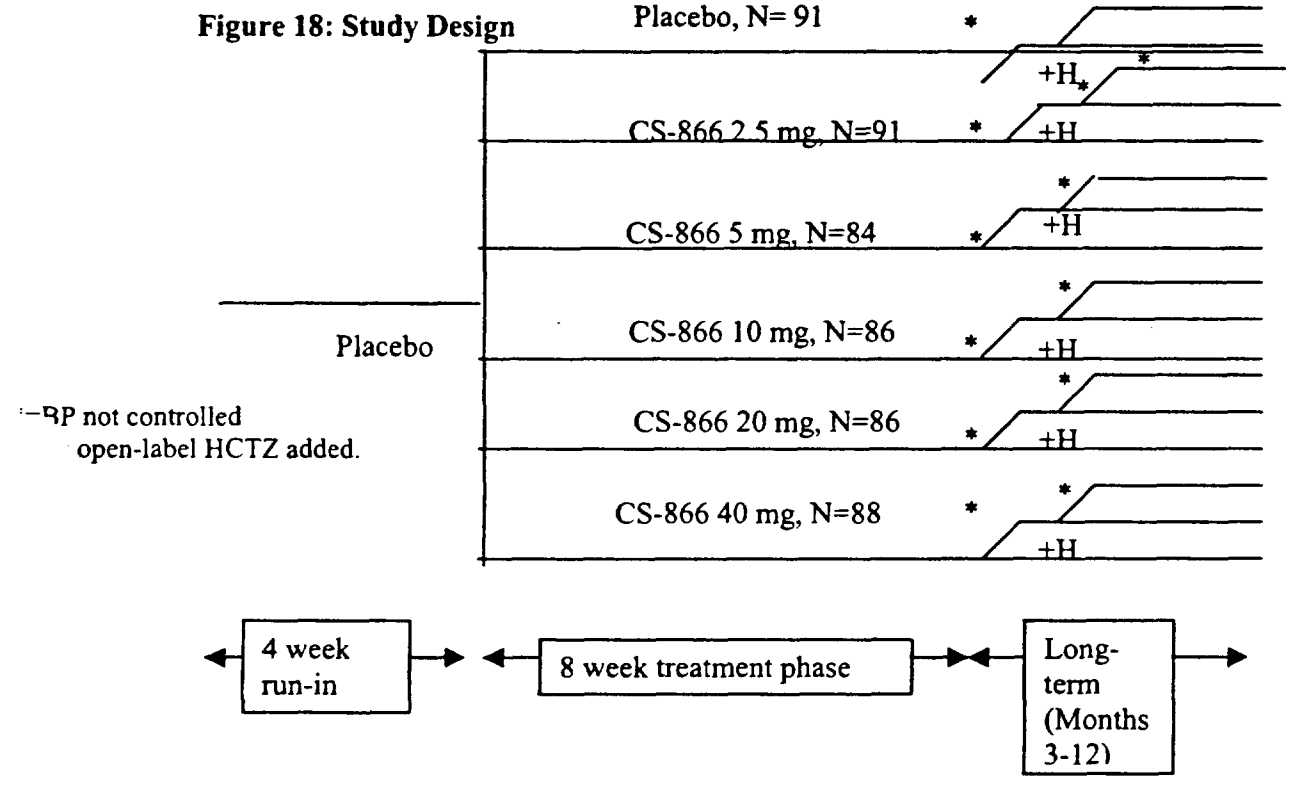
Study design: This study description was based upon the study report and protocol in Sponsor's Appendix 12.1.1. There were two changes after the start of enrollment: (1) the study was originally planned to include 420 patients; the size was apparently increased due to rapid enrollment; (2) the Sponsor originally planned to file with 6-month safety data but subsequently decided to obtain 12 month safety information. Two protocol amendments are noted: Amendment I (11/7/97): clarified wording regarding pregnancy testing during the exit visit; Amendment II (1/30/98): replaced serious adverse event definition with an updated Agency version, and changed the After-hours phone number.

This was a randomized, double-blind, placebo-controlled, parallel group trial shown schematically in Figure 1. After a 4-week placebo run-in period, eligible patients were randomly assigned to placebo or active drug (2.5, 5, 10, 20, or 40 mg CS-866) for 8 weeks. For the long-term double-blind phase (Week 8 through Month 12), patients continued on their respective randomized dose of study drug or placebo. During this phase, those with inadequately controlled blood pressure (BP), i.e., an average sitting diastolic blood pressure (DBP) $\geq$ 95 mm Hg at two consecutive visits or $\geq$ 105 mm Hg at any one visit, had open-label 12.5 mg HCTZ once daily added to their regimen; if DBP still remained uncontrolled, then the daily dose of HCTZ was titrated up to 25 mg.

Eligible patients were to be males or females 18 years or older, with essential hypertension (mean sitting DBP $\geq$ 100 mm Hg and $\leq$ 115 mm Hg with a difference of $\leq$ 7 mm Hg between sitting DBP at both Week 3 and Week 4 placebo run-in visits), at least 80% compliance during the placebo run-in and body weights within 50% of the ideal body weight for height and frame according to the 1983 Metropolitan Life Insurance table. Women were to have a negative pregnancy test at the time of screening. Exclusion criteria included: (1) serious medical disorder(s) limiting the evaluation of efficacy/safety of CS-866; (2) history of myocardial infarction, angina, coronary angioplasty or bypass surgery, heart failure, cerebrovascular accident, or transient ischemic attack within 6 months prior to enrollment; (3) clinically significant cardiac conduction defects, atrial fibrillation, atrial flutter, accessory bypass tract, or arrhythmia requiring medication; (4) Secondary hypertension; (5) Requirement for Excluded Medications (Protocol Appendix G), including cardiovascular agents, central nervous system agents, and chronic use of adrenergic agents. (6) Clinically significant laboratory

values (decreased hemoglobin, decreased granulocytes, decreased platelets, increased creatinine/SGOT/SGPT, >1+ proteinuria with values prespecified in the protocol); (7) A history of drug or alcohol abuse within 3 years before enrollment in this study (8) A history of allergic response to any angiotensin II antagonist or thiazide diuretic. (9) Participation in another drug study within 28 days before signing informed consent for this study or plans to participate in another drug study during the course of this study. (10) Previous administration of CS-866. (11) Involvement in the study as ancillary personnel.

Figure 18: Study Design



Withdrawal criteria included mean sitting DBP > 120 mm Hg or systolic BP (SBP) > 200 mm Hg on a single visit. For those subjects on drug or placebo plus HCTZ 25 mg daily the withdrawal criteria were (1) mean sitting DBP> 95 mm Hg on any two consecutive visits; mean sitting DBP> 105 mm Hg at any one visit. In addition, females who were found to be pregnant were to be immediately withdrawn.

Efficacy and safety evaluations were performed on Day 1, at Weeks 1, 2, 4, and 8, and at Months 3, 4, 6, 9, and 12.

All efficacy variables were measured during the short-term (8-week) treatment phase. The primary efficacy parameter was the change from baseline to Week 8 in sitting DBP for the Intent-to-Treat (ITT) patient population (last observation carried forward) who received CS-866 compared to those on placebo.

Secondary efficacy parameters were the change from baseline in: (1) mean sitting DBP at Weeks 1, 2, and 4; (2) mean standing DBP at Weeks 1, 2, 4, and 8; (3) mean sitting SBP at Weeks 1, 2, 4, and 8; (4) mean standing SBP at Weeks 1, 2, 4, and 8; another efficacy parameter was the proportion of responders, defined as those achieving DBP < 90 mm Hg or > 10 mm Hg decrease from baseline.
A given CS-866 regimen was considered to be effective if there was a statistically significant (one-sided $p<0.025$) greater mean reduction from baseline in mean trough sitting diastolic blood pressure compared to placebo at Week 8. A successful diastolic blood pressure response was defined as a mean trough sitting diastolic blood pressure <90 mm Hg or a decrease from baseline of at least 10 mm Hg at Week 8.

Safety assessments included baseline through Month 12 evaluations for adverse events, physical examinations, routine laboratory parameters, and 12-lead electrocardiograms.

The ANCOVA model used to analyze the primary efficacy variable and most secondary efficacy variables required at least one measurement per treatment per center. Patients were enrolled at 53 of the 54 investigational sites. Because some of the centers enrolled only a few patients, this criterion was not met by all centers. Thus, small centers were pooled so that at all time points there would be at least one analysis-qualified randomized patient with analyzable data per treatment group in all pooled centers.
The following rule was used for pooling: a center had to have at least one intent-to-treat patient in each treatment group. These patients had to have Day 1, Week 1, Week 2, Week 4, and Week 8 vital signs data. Centers meeting this criterion on their own were not pooled. Centers not meeting this criterion were pooled.

The ANCOVA model was also used to analyze secondary efficacy variables. For response rates, the proportion of patients in each treatment group achieving a successful response after 8 weeks of treatment was to be analyzed by means of a one-way logistic model with treatment as the factor. This analysis was to be performed for those patients who completed 8 weeks of treatment.

7.2 Sample Size Calculation
According to the Sponsor, the sample size was calculated based on the primary efficacy variable, mean change from baseline in sitting diastolic blood pressure. A difference of 5 mm Hg in sitting diastolic blood pressure between two treatment groups was utilized as the minimum treatment difference to be detected with 90% power at a significance level of 0.05, assuming a standard deviation of 9 mm Hg. Seventy patients were required for each treatment arm.

Drug supplies are shown in Table 61. [redacted] supplied CS-866 and matching placebo; [redacted] purchased HCTZ 12.5 mg from [redacted]

Table 61: Drug Supplies-Study #866-305

Substance	Batch #
Placebo	295
CS-866 2.5 mg	290
CS-866 5 mg	291
CS-866 10 mg	292
CS-866 20 mg	293
CS-866 40 mg	294
HCTZ 12.5 mg	706602

Source: NDA 21-286 Study 866-305 Clinical Trial Report (Vol. 1): page 23

Laboratory [redacted] provided [redacted]

7.3 Results

In the submission, data were presented for all patients randomized (APR), the ITT population, and evaluable patients. For purposes of brevity, baseline characteristics of the ITT population will be presented in this review; no significant differences in baseline characteristics were noted when compared to the APR and evaluable patients. Unless otherwise noted, results will be presented for the ITT population. Using prespecified pooling criteria, the original 54 centers were re-grouped into 38 "pseudo-centers."

Table 62 presents subject disposition. Four patients were withdrawn early due to a protocol deviation (1 patient each in 2.5, 5, 20 mg CS-866 and placebo, respectively); in addition, efficacy data were analyzed including and excluding site #7 because this site used aneroid rather than mercury sphygmomanometers for the first nine randomized patients (the sponsor kept the site open). Excluding site #7 did not change the results. In analyzing the data, the Sponsor has pooled those centers with small enrollments (see above for pooling criteria).

Table 62: Patient disposition –Study #866-305

	N		N
Screened	815	Entered placebo run-in	699
Screening failures	116	Withdrawn from run-in	173
Did not meet lab criteria	22	Did not meet lab criteria	3
Did not meet other criteria	32	Did not meet BP criteria	110
Patient request	29	Did not meet other criteria	5
Investigator judgement	9	Patient request	27
Lost to follow up	15	Uncontrolled BP	9
Noncompliance/uncooperative	4	Adverse event	3
Uncontrolled BP	2	Investigator judgement	5
Other	3	Lost to follow-up	8
		Noncompliant/uncooperative	3
Randomized	526	Intent-to-Treat	517
Entered long-term period	480	Evaluable	477
Completed 1 year study period	370		

Source: NDA 21-286: Study 866-305 Clinical Trial Report (Vol. 1): pages 47-48 (Vol.2, Tables 1, 2): 137-150.

*"Intent to Treat" was defined as patients who received at least one dose of randomized study medication and had at least one usable post-baseline observation.

**Evaluable: Patients meeting evaluability criteria as described in the Clinical Report.

Randomized: Patients who received at least one dose of randomized study medication.

Note: patient ##19/2142, who received study drug instead of placebo during the run-in phase, was counted as a randomized patient who was withdrawn for a protocol deviation.

Table 63: Patient Disposition during the 8 week short-term period

	Placebo (N)	CS-866 (N)				
		2.5 mg	5 mg	10 mg	20 mg	40 mg
Randomized	91	91	84	86	86	88
Discontinued	14	4	7	5	6	10
Completed	77	87	77	81	80	78

Source: NDA 21-286: Study 866-305 Clinical Trial Report (Vol.1): page 48

7.4 The most common reason for discontinuation was patient request (7 placebo; 14 CS-866) followed by uncontrolled blood pressure as defined by protocol (4 placebo; 2 CS-866), adverse event (0 placebo; 5 CS-866), and investigator judgment (0 placebo; 5 CS-866). Other reasons for discontinuation among 3 patients in the placebo group and 6 patients in a CS-866 dose group were: did not meet other entry criteria, noncompliance/lack of cooperation, protocol violation, and lost to follow-up.

7.5 Baseline characteristics: Baseline demographics are shown below:
There appears to be a higher percentage of males in the placebo group; otherwise, there appear to be no differences in baseline demographic data across the six treatment groups.

Table 64: Baseline characteristics (ITT population) Study #866-305

	Placebo	CS-866				
		2.5 mg	5 mg	10 mg	20 mg	40 mg
N	88	91	80	85	85	88
Mean age (+ SD)	54.5 (10.3)	54.6 (10.7)	53.0 (10.7)	54,1 (10.9)	54.3 (12.0)	54.3 (10.2)
Race n (%N)						
Caucasian	71 (81)	71 (78)	69 (86)	60 (71)	57 (67)	62 (71)
Black	7 (8)	8 (9)	6 (8)	9 (11)	12 (14)	12 (14)
Asian	0	1 (1)	0	1(1)	1(1)	1(1)
Hispanic	9(10)	11(12)	5(6)	14(17)	14(17)	13(15)
Other	1(1)	0	0	1(1)	1(1)	0
Gender n (%N)						
Male	64 (73)	47 (52)	48 (60)	51 (60)	49 (58)	56 (64)
Prior HTN medication*	77 (88)	82 (90)	75 (94)	71 (84)	77 (91)	78 (89)

Source: NDA 21-286, Study 866-305: Volume 2, Table 11b (page 202)

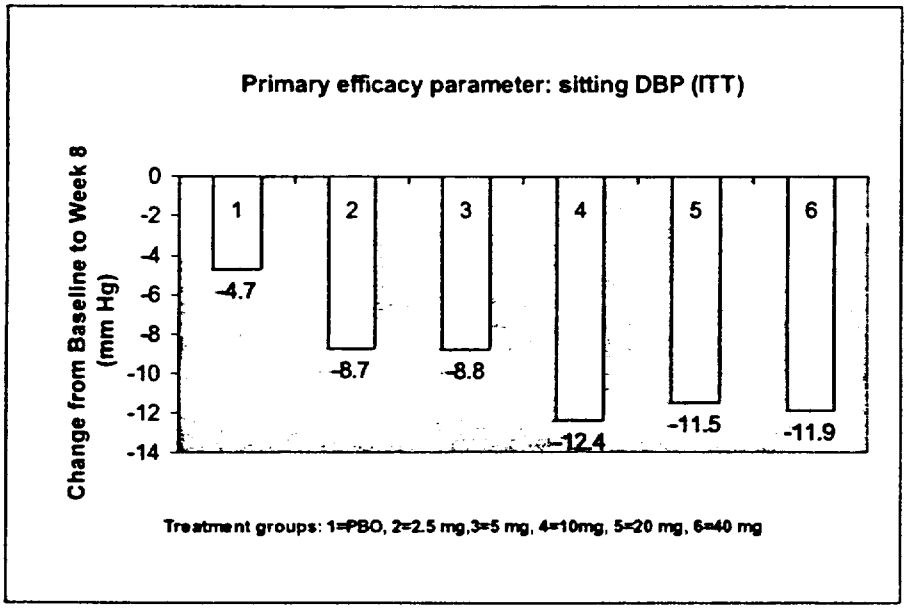
*Within the previous 90 days.
Mean heights (ITT) were 66-68 inches (range 55-79 inches) and mean weights were 186-200 lbs (range 107-304 lbs); there were no meaningful differences between the treatment groups in mean height and weight. Baseline vital signs for the ITT population revealed a mean sitting DBP (mm Hg) ranging from 103.2 + 3.24 (placebo group) to 103.6 + 3.05 (40 mg group); mean sitting SBP (mm Hg) ranging from 152.6 + 13.53 (5 mg group) to 155.0 + 15.19 (20 mg group); and HR (bpm) ranging from 73.4 (20 mg group) to 74.8 (10 mg group). There were no significant differences between the six treatment groups in baseline vital signs. (Source: NDA 21-286: 866-305: Volume 2, Table 12b, page 210).

7.6 Primary efficacy parameter (ITT LOCF All sites)
Table 65: Primary efficacy parameter

		CS-866				
	Placebo	**2.5 mg**	**5 mg**	**10 mg**	**20 mg**	**40 mg**
N	88	91	80	85	85	88
Mean Change (±SD) from baseline to Week 8	-4.1 (8.8)	-8.7 (7.8)	-8.8(8.3)	-12.4 (8.4)	-11.5 (7.8)	-11.9 (7.9)
95% CI	--	(-7.0, -1.7)	(-6.9, -1.4)	(-11.2, -5.8)	(-10.5, -5.0)	(-11.1, -5.8)
p-value*	--	0.001	0.002	0.001	0.001	0.001

*Using a step down procedure
Source: 866-305: Table 17a: page 231

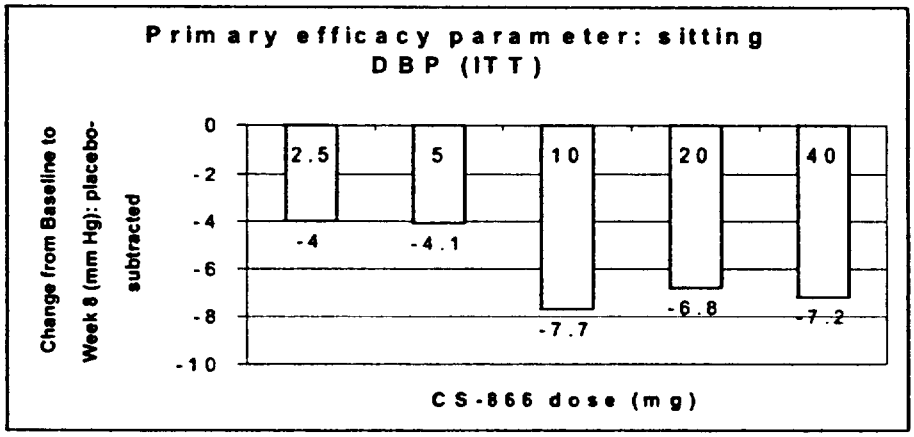
Figure 19: Change from baseline to Week 8 in trough sitting DBP; Figure 20 shows placebo-subtracted values. An effect plateau is noted in doses above 10 mg.
Source: NDA 21-286: 866-305: Volume 2, Table 17a (page 231)



All doses significantly different from placebo at $p < .01$

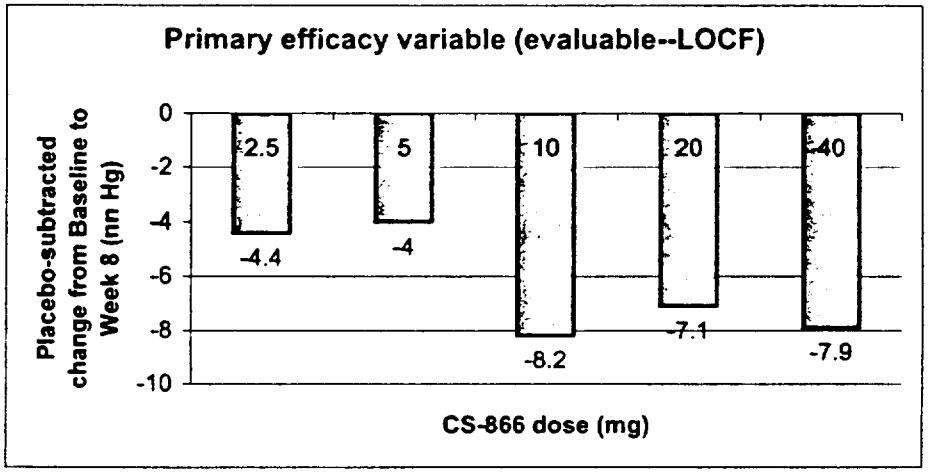
Figure 20: Placebo-subtracted mean change from baseline to Week 8: Sitting DBP (ITT LOCF) Study #866-305
Source: NDA 21-286: 866-305: Volume 2, Table 17a (page 231)--above table

Data for evaluable population show a similar flattening of the dose-response curve seen



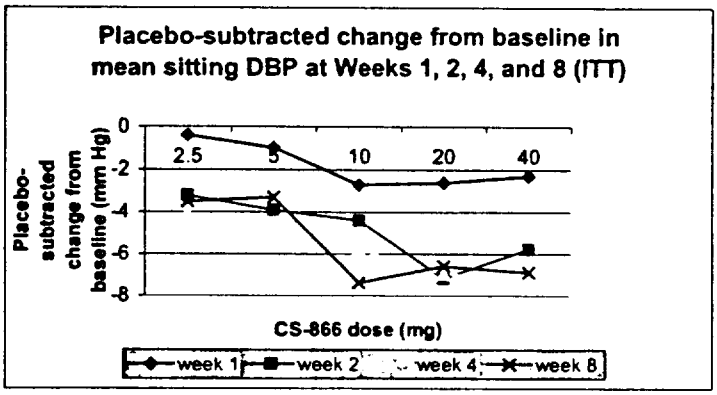
over CS-866 10 mg.

Figure 21: Primary efficacy variable (evaluable population)Study # 866-305



Source: NDA 21-286: 866-305: Volume 2 (page 308)

Figure 22: Change in SiDBP - wks 1,2,4,8 - ITT - Study #866-305
Source: NDA 21-286: CS-866-305: Volume 2 (pages 229-230; 259-260;235-236; 265-266)



The mean change from baseline in sitting SBP was significantly different at all doses compared to that of placebo beginning at Week 2 (see Table 7).

Figure 23: Change in SiSBP - wks 1,2,4,8 - ITT - Study #866-305

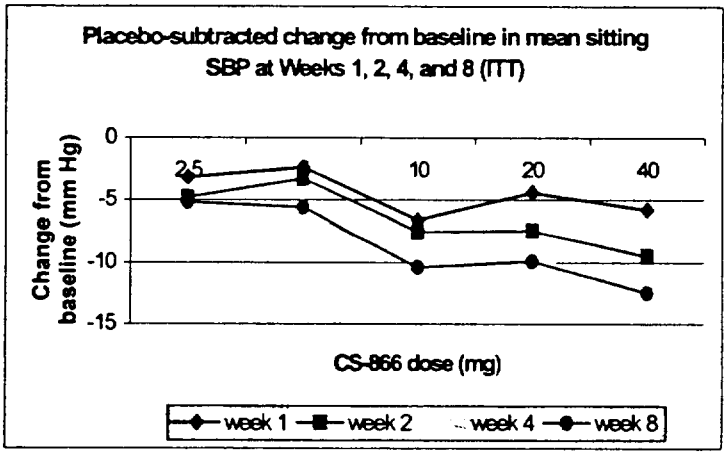


Figure 24:Change in StDBP wks 1,2,4,8 – ITT – Study #866-305

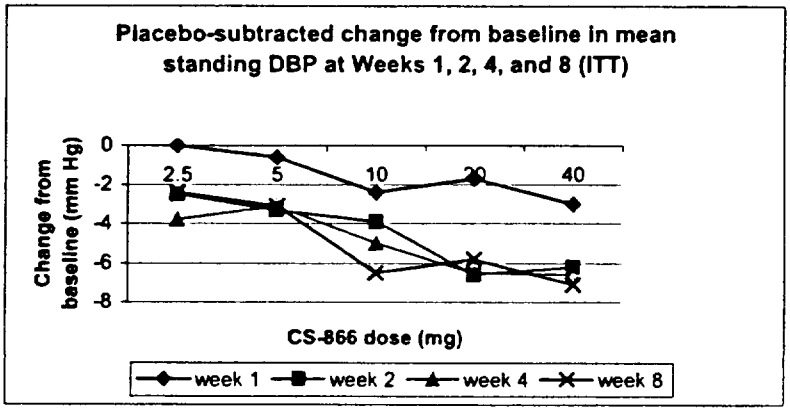


Figure 25: Change in StSBP - wks 1,2,4,8 - ITT - Study #866-305
Source: NDA 21-286:866-305: Volume 2 (Table 18b: pages 265-266)

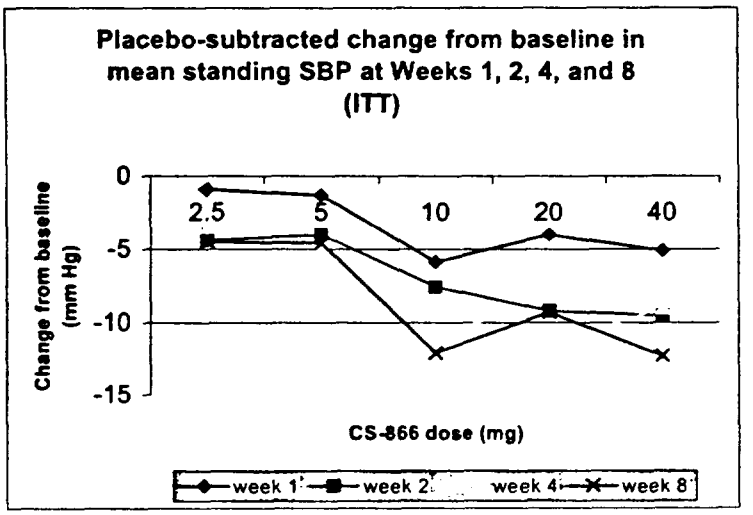


Table 66: Mean change from baseline in siDBP: Weeks 1, 2, & 4 (ITT: All Sites)

		CS-866				
	Placebo	**2.5 mg**	**5 mg**	**10 mg**	**20 mg**	**40 mg**
Week 1: N	88	90	80	85	85	87
Mean ± SD	-5.6 (6.5)	-6 (6.5)	-6.6 (5.4)	-8.3 (7.2)	-8.2 (7.8)	-7.9 (7.3)
LS Mean	-6.4	-5.3	-6.3	-8.8	-8.0	-7.9
95% CI (vs. PBO):	--	(-1.1, 3.3)	(-2.2, 2,4)	(-4.6, -0.1)	(-3.9, 0.6)	(-3.7, 0.7)
p value	--	.83	.54	.02	.08	.09
Week 2: N	86	91	80	83	82	85
Mean ± SD	-5.4 (6.2)	-8.6 (6.2)	-9.3 (6.6)	-9.8 (6.0)	-12.6 (7.1)	-11.2 (8.3)
LS Mean	-5.2	-8.2	-9.1	-9.5	-11.8	-10.8
95% CI (vs. PBO):	--	(-5.2, -0.8)	(-6.2, -1.7)	(-6.6, -2.1)	(-8.9, -4.3)	(-7.8, -3.4)
p value	--	0.004	<0.001	<0.001	<0.001	<0.001
Week 4: N	83	91	79	83	81	83
* Mean ± SD	-5.2 (7)	-9.3 (6.9)	-10.0 (6.4)	-11.0 (7.7)	-12.2 (7.6)	-12.3 (8.2)
95% CI (vs. PBO):	--	(-6.5, -1.6)	(-7.6, -2.4)	(-8.6, -3.5)	(-9.3, -4.0)	(-10.2, -5.1)
p value	--	<0.001	<0.001	<0.001	<0.001	<0.001

Source: Tables 17a, 19a.*LS Means were not meaningfully different from the raw means.

Table 67: Mean change from baseline siSBP: Wks1, 2, 4, 8 (ITT: All Sites) 866-305

		CS-866				
	Placebo	**2.5 mg**	**5 mg**	**10 mg**	**20 mg**	**40 mg**
Week 1: N	88	90	80	85	85	87
Mean ± SD	-4.8 (10.4)	-8 (10.4)	-7.2 (11.1)	-11.4 (11.9)	-9.2 (12.2)	-10.6 (14)
LS Mean	-4.6	-7.1	-7.9	-11.8	-9.0	-9.7
95% CI (vs. PBO):	--	(-6.4, 1.5)	(-7.4, 0.9)	(-11.3, -3.1)	(-8.4,-0.3)	(-9.1, -1.1)
p value	--	.11	.06	<.001	.017	.007
Week 2: N	86	91	80	83	82	85
Mean ± SD	-5.3 (11.2)	-10.1(10.8)	-8.6 (12.9)	-12.8 (11.0)	-12.7 (12.7)	-14.8 (12.7)
LS Mean		-9.5	-9.2	-12.5	-11.7	-14.0
95% CI (vs. PBO):	--	(-8.5, -0.7)	(-8.4, -0.3)	(-11.6, -3.6)	(-10.9, -2.9)	(-13.1, -5.2)
p value	--	0.011	0.018	<0.001	<0.001	<0.001
Week 4: N	83	91	79	83	81	83
Mean ± SD	-3.7 (11.6)	-11.6 (9.9)	-9.8 (12.2)	-13.7 (12.5)	-13.6 (14.7)	-14.7 (13.4)
LS Mean	-2.8	-11.5	-10.9	-13.3	-11.9	-14.5
95% CI (vs. PBO):	--	(-12.7, -4.7)	(-12.2, -3.9)	(-14.7, -6.4)	(-13.2, -5)	(-15.9, -7.6)
p value	--	<0.001	<0.001	<0.001	<0.001	<0.001
Week 8: N	79	87	78	81	80	80
Mean * ± SD	-4.3 (12.2)	-9.5 (12.0)	-9.9 (12.9)	-14.7 (12.2)	-14.2 (12.5)	-16.8 (14.4)
95% CI (vs. PBO):	--	(-10, -1.5)	(-11.1, -2.4)	(-16.2, -7.5)	(-15.3, -6.7)	(-18.1, -9.3)
p value	--	0.005	0.002	<0.001	<0.001	<0.001

Source: Tables 17b, 19b: Weekly values *LS Means were not meaningfully different from the raw means and are therefore not presented here.

For standing DBP and standing SBP (ITT, all sites, LOCF), the change from baseline to Week 8 was significantly different compared to that of placebo (p <. 02) at all doses studied (Table 7.4.1c).

Responders

Table 68: Responders for Week 8 Completers (ITT) Study #866-305

	Placebo	**CS-866 (mg)**				
	N (%)	**2.5 N (%)**	**5 N (%)**	**10 N (%)**	**20† N (%)**	**40 N (%)**
N	88	91	80	85	85	88
Completers*	78 (89)	87 (96)	78 (98)	81 (95)	80 (94)	79 (90)
Responders	27 (35)	43 (49)	37 (47)	51 (63)	54 (68)	50 (63)
95% CI**	--	(.99, 3.5)	(.90, 3.3)	(1.7, 6.1)	(2.0, 7.6)	(1.7, 6.3)

*Week 8 or usable early termination data measured at least 54 days after the first randomized dose.
** Based on odds ratio (percent responders divided by percent non-responders) of each dose group relative to placebo.
Source: NDA 21-286: 866-305: Volume 2: Table 21 (page 298)
†2 patients in the 20-mg treatment group were discontinued because of uncontrolled blood pressure. It is unclear whether these patients were included in this analysis. .

7.7 Subgroup analyses: Race

There appeared too few Black/Hispanic patients to permit further analysis by race.

Age: A breakdown of the elderly population revealed the following:

Figure 26: Treatment group by age-866-305

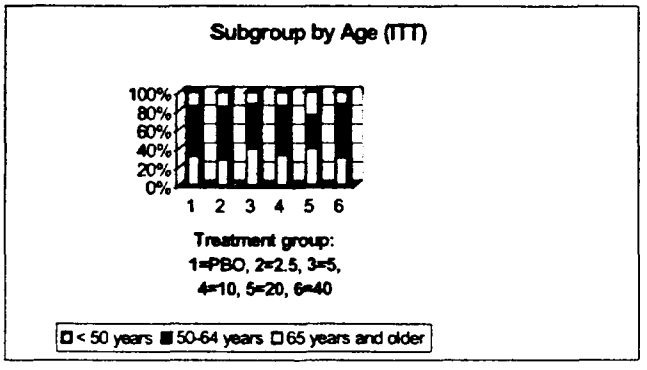


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Figure 27: Efficacy by age-866-305

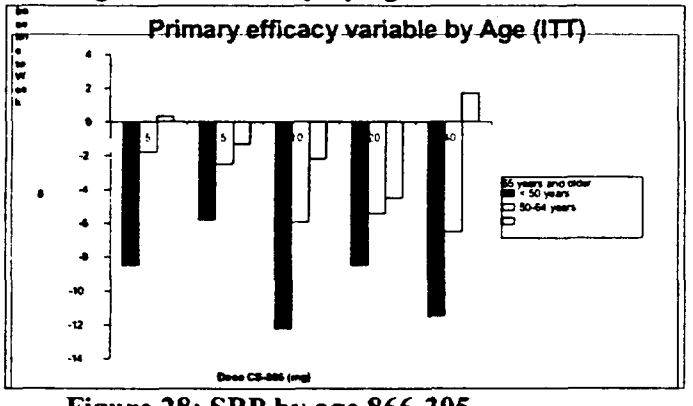

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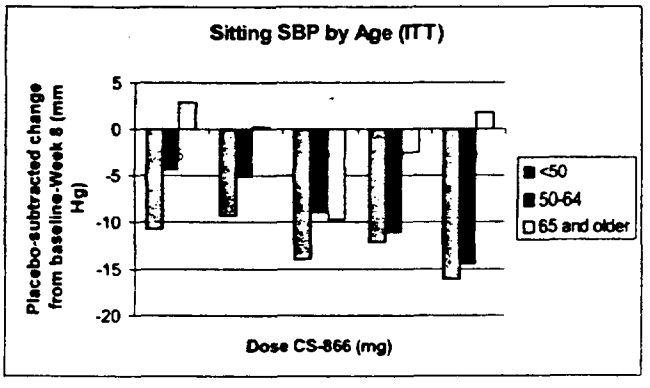
Figure 28: SBP by age 866-305



It should be noted that in the > 65 population, larger placebo effects were noted in both mean sitting DBP and SBP changes from baseline. This might explain the diminished placebo-subtracted effect. (Source: Sponsor's Table 27a, 27b)

For subgroup analysis by gender, there were no meaningful patterns in placebo-subtracted drug effects on sitting systolic or diastolic blood pressure.

7.8 Other endpoints

Heart rate: There were slight, insignificant decreases in heart rate (1-2 bpm) between baseline and Week 8 (Volume 2; Table 17c, 19c).

7.9 Long-term phase

The objective of the long-term phase was to evaluate the safety of olmesartan. The following table lists, by treatment arm, discontinuations from the entire study.

Table 69: Patient discontinuations from entire study - #866-305

	Placebo	CS-866 (mg)				
	N (%)	2.5 N (%)	5 N (%)	10 N (%)	20 N (%)	40 N (%)
Randomized	91	91	84	86	86	88
Discontinued*	43 (47)	33 (36)	28 (33)	15 (17)	17 (20)	20 (23)
Reasons: Did not meet entry criteria	1	0	0	0	0	0
Patient request	12	9	11	5	5	9
Uncontrolled BP	20	12	4	4	3	1
Adverse Event	2	2	3	1	1	4
Investigator judgement	3	5	2	1	2	2
Lost to follow-up	2	2	2	1	1	2
Noncompliance	2	2	5	2	4	1
Protocol violation	1	1	1	0	1	0
Other	0	0	0	1	0	1

*Day 1 to Month 12: All Randomized Patients

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Figure 29: Sitting DBP by treatment group (Long-term) #866-305

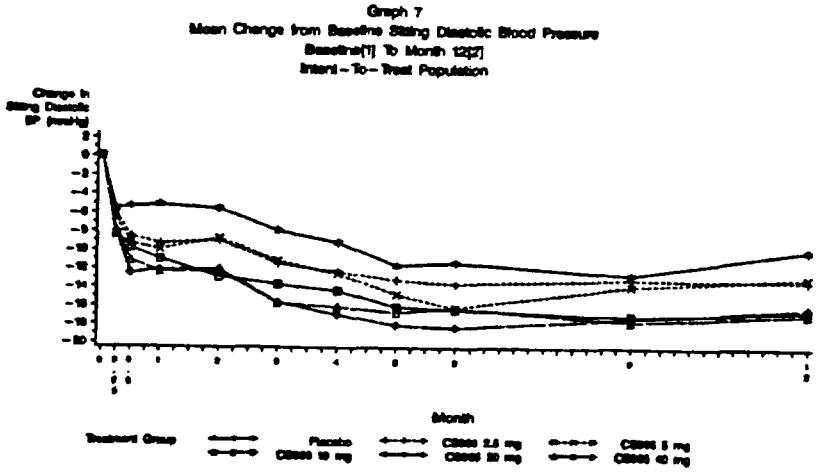
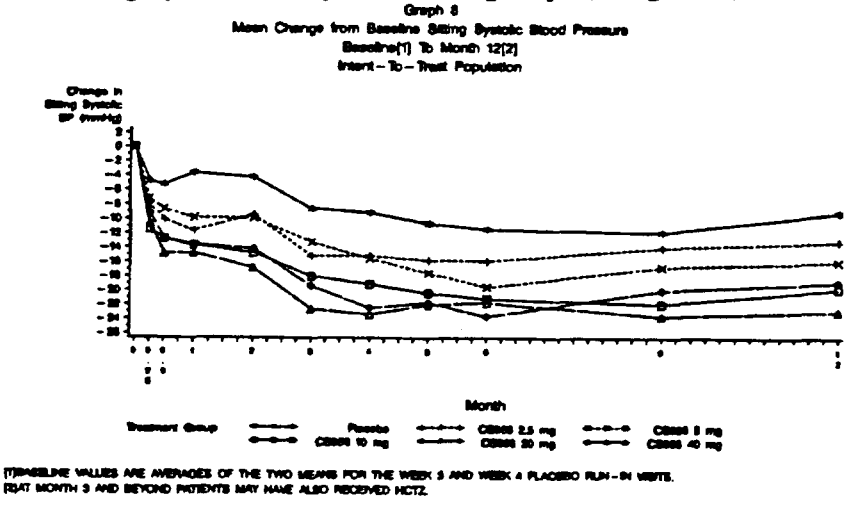


Figure 30: Sitting Systolic BP by treatment groups (Long term) 866-305



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These graphs do not take into account the numbers of patients on concomitant HCTZ or the dose of HCTZ used.

7.10 Safety

There were no deaths during the study.

For further safety discussion please see the Integrated Summary of Safety.

Conclusions

The decrease from baseline in sitting DBP and SBP at Week 8 was significantly different from placebo in the CS-866 treatment groups at all doses studied (2.5 to 40 mg daily).

The decrease from baseline in sitting DBP and SBP at all doses was significantly greater than placebo beginning at Week 2.

There was a flattening in placebo-subtracted effect at once daily doses of CS-866 10 mg and above.

In this study, CS-866 appears to be less effective in lowering sitting DBP in the elderly population. This finding may be explained by the larger placebo effect in this subgroup.

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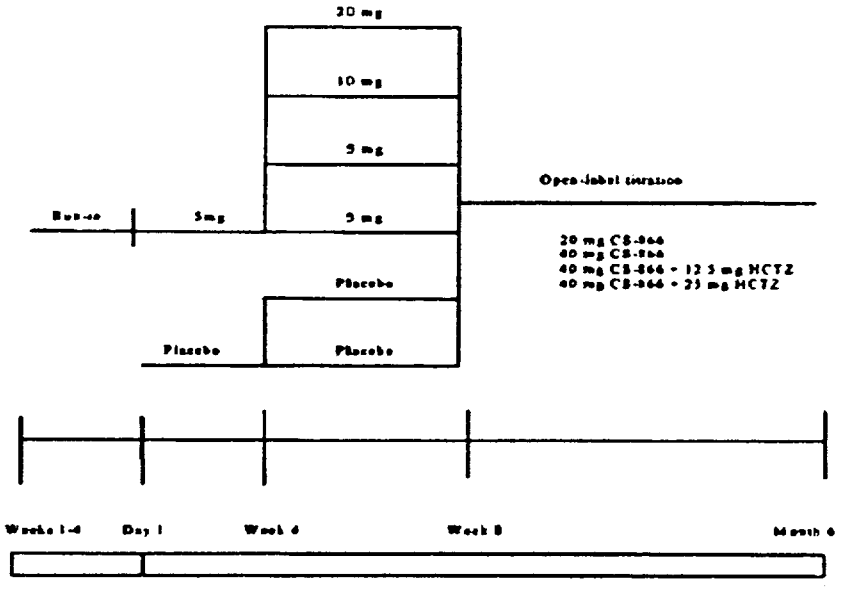
8.0 –10.0 Study SE #866-306
Materials used in review Volumes 305-308
Investigator/Monitor Donald Hinman Ph.D
8.01 Title: "A randomized placebo-controlled dose titration study of CS-866 with long-term safety evaluation in patients with essential Hypertension"

Related reviews from other disciplines
Clinical Pharmacology and Biopharmaceutics
See Dr Sayed Al-Habet's review
Biostatistics
See Dr Hung's review
Chemistry and Manufacturing controls
See Dr Zielinski's review
Pre-clinical pharmacology and toxicology
See Dr Jagadeesh's review

8.1 Description of Clinical data sources
The study design is shown in Figure 31 and described below.
Figure 31: Study design 866-306



8.2 Study Objectives
To assess the efficacy and safety of CS-866 after 8 weeks of treatment in patients with essential hypertension.
To study the effect of dose titration in such patients with uncontrolled blood pressure after therapy with 5mg CS-866, and

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To assess the safety and tolerance of long-term (up to 6 months) treatment with CS-866, alone or in combination with HCTZ, in patients with essential hypertension.

8.3 Rationale
This study was conducted to assess the antihypertensive effect of olmesartan at various doses and the effect of adding HCTZ in patients who did not adequately respond as defined in the protocol. The primary efficacy analysis is performed on the ITT basis using the final on-therapy changes from baseline value on trough SiDBP.

8.4 Study design
This was an 8-week, randomized, double-blind, placebo controlled, parallel-group, dose-titration study followed by a 4-month open label extension. After an initial 4-week placebo run-in period, eligible patients were randomly assigned to treatment of 5mg CS-866 or placebo. After 4 weeks of treatment, patients with a mean sitting Diastolic Blood Pressure (SiDBP) <90mm Hg continued receiving their initial dosage of 5 mg, and those with SiDBP >90mmHg were titrated upwards in a randomized, double-blind fashion receiving up to 20 mg CS-866. Patients who completed the 8-week phase of the study continued in the open-label period. All patients who entered the open label period initially received 20mg CS-866. Subsequent titration was based on blood pressure response and modified in a stepwise fashion if: (1) the daily average SiDBP was >95mmHg at 2 consecutive visits, or (2) the daily average SiDBP was >105mmHg at any one visit (Figure 31).

8.5 Inclusion criteria
Male and female adult outpatient above 18 years old with essential hypertension (mean SiDBP >100mmHg and < 115mmHg). No studies were carried out on patients under the age of 18 years (Appendix 1)

8.6 The drug supply for this study is presented below (Table 70).
Table 70: Drug Supply Study #866-306

Study Drug	Batch Number
Placebo	295
5mg	291
10mg	292
20mg	293
40mg	294
12.5 mg HCTZ	706602

8.7 Statistical analyses - Primary hypothesis
There is no difference in treatment effect between CS-866 combined and placebo when the effect is measured by the change from baseline at week 8 in SiDBP.

Secondary hypothesis
There is no effect in titrating the daily dose of CS-866 upward.
There is no difference in treatment effect between CS-866 combined and placebo when the effect is measured by:

(a) the change from baseline at weeks 1, 2, 4, and 6 in SiDBP;
(b) the change from baseline at weeks 1, 2, 4, 6, and 8 in SiSBP ;
(c) the change from baseline at weeks 1, 2, 4, 6 and 8 in StDBP and ,
(d) change from baseline at weeks 1, 2, 4, 6, and 8 in StSBP.

ANCOVA with baseline SiDBP as covariate was proposed in the protocol to test the overall treatment differences. Pairwise comparison of each dose versus placebo was also proposed to test significance of overall treatment differences or trends. Secondary variables include proportion of responders defined as patients who achieved a mean SiDBP of < 90mmHg or a drop from baseline >10mmHg with or without HCTZ. The same ANCOVA was proposed to analyze all the secondary variables. Trough to Peak ratio was calculated using the ABPM data obtained on the final visit of the double-blind period.

8.8 Definition of primary efficacy

A regimen was considered effective if it resulted in clinically significant ($p<0.05$) greater mean reduction from baseline in mean trough SiDBP as compared to the effect of placebo at week 8.

9.0 Results of Study SE #866-306

9.1 Patient disposition

The disposition of patients is summarized in Tables 71-74. Out of seven hundred and fifty-eight subjects screened, 650 were enrolled, 457(60.3%) were randomized, 451 (98.7 %) were classified as intent-to-treat (ITT), 384 (84.0%) were evaluable, and 407 (89.1%) went into the open label period (Table 72). Table 72 presents the disposition of all subjects including the open-label period. The reasons for the 108/758 (14.2%) screening failures are presented in Table 73. The distribution of patients after week 4 of the 8-week double-blind period by dosing regimen is presented in Table 74. Of 442 subjects who received CS-866 between Day 1 and 6 months, 76 (17.2 %) were discontinued for a variety of reasons (Table 75). The distribution of completers during the 8-week double-blind period is presented in Table 74 and Figure 32.

Table 71: Enumeration of subjects 866-306

Population	N	%[1]
Screened	758	100.0
Enrolled	650	85.8
Randomized	457	60.3
Placebo	116	25.4
Olmesartan 5mg	341	74.6
Intent-To-Treat (ITT)	451	98.7
Evaluable	384	84.0
Open Label	407	89.1

[1] Percent of patients in the ITT, evaluable and open label populations are calculated as % of patients randomized.

Table 72: Overall disposition of ITT patients-866-306

	Number of Patients			
	Screening	**Placebo Run-in**	**Double-Blind**	**Open Label**
Entered	758	650	457	407
Withdrawn	108	193	50	41
Completed	650	457	407	366

The disposition of titrated ITT patients after week 4 is presented in Table 74.

Table 73: Reasons for screening failures - 866-306

Population	**N**	**%[1]**
Number of patients screened	758	100.0
Number of screening failures	108	14.2
Reasons for screening failures are as follows:		
Did not meet laboratory criteria	36	33.3
Did not meet other entry criteria	22	20.4
Patient request	21	19.4
Uncontrolled BP as defined in protocol	4	3.7
Investigator Judgement	13	12.0
Lost to follow – up	2	1.9
Non-compliance/Lack of cooperation	2	1.9
Termination of study by sponsor	0	0.0
Others	8	7.4

[1]% for reason calculated as % of screening failures

Table 74: Disposition of ITT Titrated Patients after week 4 - 866-306

Entered (Discontinued before wk 4)	**Placebo 116 (8)**		**Active 341 (19)**			
	NT	T	NT	NT	T	T
			5mg	5mg	10mg	20mg
Continued at wk 4	17	91	93	75	75	79
Discontinued-wk 4	0	6	3	4	0	6
Completed	17	85	90	71	75	73

T=Titrated; NT=Not Titrated

Eight out of 116 (6.9%) and 19/341(5.6 %) were discontinued before week 4 in the placebo and CS-866 treated groups, respectively (Table 5).

9.2 Adequacy of Clinical Experience and Quality of Data

There is adequate clinical experience for a drug of this class, based on the overall size of patients in all the pivotal clinical trials in this NDA. The quality of data in this study is considered adequate particularly in respect of comparability of groups and statistical analyses. Only 2 (1.9%) out of 108 withdrawn patients were lost to follow up (Table 73). The main reasons for discontinuations are listed in Table 75. Most patients (81% and

77%, placebo and drug, respectively) were 100% compliant during the randomized double-blind period of the trial.

The percentages of non-completers in the placebo and treated groups show no significant imbalance in demographic characteristics and baseline variables. No statistically significant differences in baseline characteristics, age and race of patients were seen among the randomized patients (Tables 76-77). Analysis of previous anti-hypertensive and concomitant medications revealed no differences between placebo and treatment groups.

Table 75: Discontinuation Day 1 – 6 month by last active treatment - ITT 866-306

	CS-866 N (%)	CS-866 +HCTZ N (%)
Number of patients received active treatment	342(100)	100 (100)
Number of patients discontinued during active treatment	66 (19.3)	10 (10)
Reasons for discontinuation		
Did not meet lab. entry criteria	0(0.0)	0(0.0)
Did not meet blood pressure entry criteria	0(0.0)	0(0.0)
Did not meet other entry criteria	0(0.0)	0(0.0)
Patient request	20(30.3)	4(40.0)
Uncontrolled BP	7(10.6)	3(30.0)
Adverse event	13(19.7)	1(10.0)
Investigator judgement	4(6.1)	1(10.0)
Lost to follow-up	6(9.1)	0(0.0)
Non-compliance/Lack of cooperation	7(10.6)	0(0.0)
Protocol Violation	6(9.1)	0(0.0)
Termination of study by sponsor	3(4.5)	0(0.0)
Others	0(0.)	1(10.0)

9.3 Demographics and treatment group comparability

Out of 650 hypertensive patients enrolled in this study, 457 (70.3%) were intent-to-treat (ITT). Of these, 258 (57%) were men and 193 (43%) were women. Among the 457 randomized patients, 347 patients initially received CS 866 and 116 received placebo. The mean ages of the subjects in the 2 treatment groups were 55.1 and 54.0 years, respectively. Essentially, no differences were seen between treatment groups with respect to baseline values, age, concomitant medication or previous intake of anti-hypertensive agents, drug exposure, weight, and duration of hypertension (Tables 76-78). Of 457 ITT subjects, 317 (70%) were Caucasians, 61 (13%) blacks, 7(1.5%) were Asians, 62 (13.5%) were Hispanics, and 4 (0.9%) others (Table 77). A total of 451 (98.7%) out of 457 randomized patients completed the study. Fifteen patients (6 in double-blind period, 7 in open label and 2 non-treatment emergent) discontinued treatment due to adverse events. The reasons for early withdrawal from the study and the number of patients withdrawn before the end of study were evenly distributed among treatment groups.

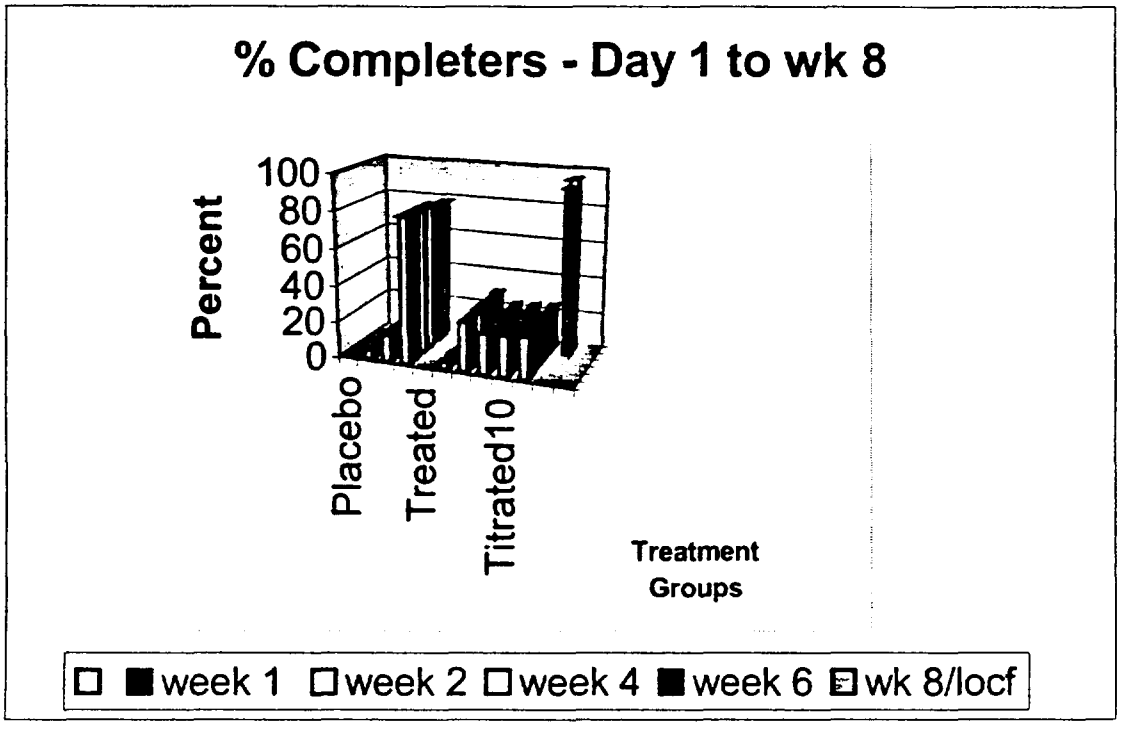
Table 76: Baseline BP values and heart rates - ITT - 866-306

Baseline value	Initial Treatment Placebo (N=114)	Initial Treatment CS-866 5mg (N=337)	p-value
SiDBP N			0.087
Mean	114	337	
Median	104.4	103.7	
SD	103.0	102.5	
	3.75	3.43	
SiSBP N			0.141
Mean	114	337	
Median	158.4	156.3	
SD	158.5	156.0	
	13.63	13.15	
HR(bpm)			0.031
N	114	337	
Mean	73.4	75.1	
Median	73.0	75.0	
SD	7.47	7.56	
Baseline values are averages of the means for wk 3 and 4 placebo run-in visits			

Table 77: Baseline characteristics - ITT - 866-306

	Initial Treatment Placebo (N=116)	Initial Treatment CS-866 5mg N=341	p-value
Age(yrs)			0.294
N	114	337	
Mean	55.1(24-78)	54.0(26-84)	
Median	55.5	54.0	
SD	10.37	10.12	
Race N (%)			0.597
Caucasian	84(73.7)	233(69.1)	
Black	14(12.3)	47(13.9)	
Asian	1(0.9)	6(1.8)	
Hispanic	13(11.4)	4914.5)	
Others	2(1.8)	2(0.6)	
Gender N (%)			0.696
Male	67(58.8)	191(56.7)	
Female	47(41.2)	146(43.3)	
Weight (lbs)	185	188	NS
Mean duration Hptn	9.4	8.5	NS
Family History Hptn	67.5%	60.5%	NS

Figure 32: Percent completers - ITT – Comparability - 866- 306



9.31 Drug Exposure is presented in Tables 78 to 80 below

Table 78: Duration of drug exposure-Day 1- 6month - ITT 866-306

Duration (days)	CS-866 only(N=340)	CS-866 and HCTZ(N=102)	
	CS-866 N (%)	CS-866 N (%)	HCTZ N (%)
Unknown	0(0.0%)	0(0.0%)	2(2%)
1-20	15(4.4%)	0(0.0%)	7(6.9%)
21-40	10(2.9%)	0(0.0%)	25(24.5%)
41-60	16(4.7%)	1(1.0%)	21(20.6%)
61-80	4(1.2%)	1(1.0%)	32(31.4%)
81-100	11(3.2%)	3(2.9%)	14(13.7%)
101-120	22(6.5%)	6(5.9%)	1(1.0%)
121-140	49(14.4%)	22(21.6%)	0(0.0%)
141-160	2(0.6%)	2(2.0%)	0(0.0%)
161-180	94(27.6%)	30(29.4%)	0(0.0%)
>180	117(34.4%)	37(36.3%)	0(0.0%)

Table 79: Estimated average drug exposure - double-blind period –ITT 866-306

EXPOSURE (MG)	CS-866		
	5mg	10mg	20mg
Before Titration (N=304/341)	304/341(89.1%)	-	-
Total (mg drug) wk 1-4	44372.5	44372.5	44372.5
After Titration (%)	151/168(89.9%)	67/75(89.3%)	69/79(87.3%)
Total (mg CS-866)wk 5-8	66379.5	64182.5	85782.5
*Average (mg)	194.7	188.2	251.6
*Not adjusted for missing subjects before and after titration (wks 1- 8 duration of drug exposure is between 24 and 31 days)			

Source: Reviewer

Table 80: Active Drug Exposure -All Randomized Patients -866-306 -Day 1-Mth. 6

Duration of Exposure	Placebo					CS 866				
	CS866	CS+12.5HCTZ		CS+25HCTZ		CS866	CS+12.5HCTZ		CS+25HCTZ	
	CS866	CS866	HCTZ	CS866	HCTZ	CS866	CS866	HCTZ	CS866	HCTZ
Unknown	0	0	2	0	0	0	0	0	0	0
1-20	0	0	0	0	0	15	0	6	0	1
21-40	3	0	7	0	1	7	0	16	0	1
41-60	1	0	3	1	3	15	0	7	0	8
61-80	1	1	5	0	3	3	0	16	0	8
81-100	4	1	3	0	0	7	1	5	1	6
101-120	20	3	0	1	0	2	2	1	0	0
121-140	45	15	0	5	0	4	1	0	1	0
141-160	0	0	0	0	0	2	1	0	1	0
161-180	0	0	0	0	0	94	22	0	8	0
>180	0	0	0	0	0	117	24	0	13	0

9.4 Analysis of Efficacy

Primary efficacy endpoint is the change from baseline in sitting diastolic blood pressure (SiDBP) at week 8 for the ITT population. This review of primary efficacy endpoint is based on analyses of data at the end of the 8-week, double-blind period or LOCF values where applicable. For primary and secondary efficacy evaluation at week 8, reviewer analyzed data for ITT patients. All patients receiving CS-866 were included in the analysis regardless of the dose received and referred to as the "combined group" during the double-blind period. Although there was no significant imbalance in demographic characteristics and baseline characteristics, the sponsor provided least square means to indicate possible post-treatment effects (i.e. means adjusted by the factors in the statistical ANCOVA model. The baseline means, however, were not adjusted).

Of the 407 patients who completed the 8 week, double-blind period, those with uncontrollable hypertension at week 4, 148 on active treatment were titrated upwards after week 4 and efficacy was evaluated between weeks 6 and 8 (Table 74). Efficacy results are presented in Figs. 33-38 &Tables 81-82.

Figure 33: Lowering of standing diastolic and systolic-BP-866-306

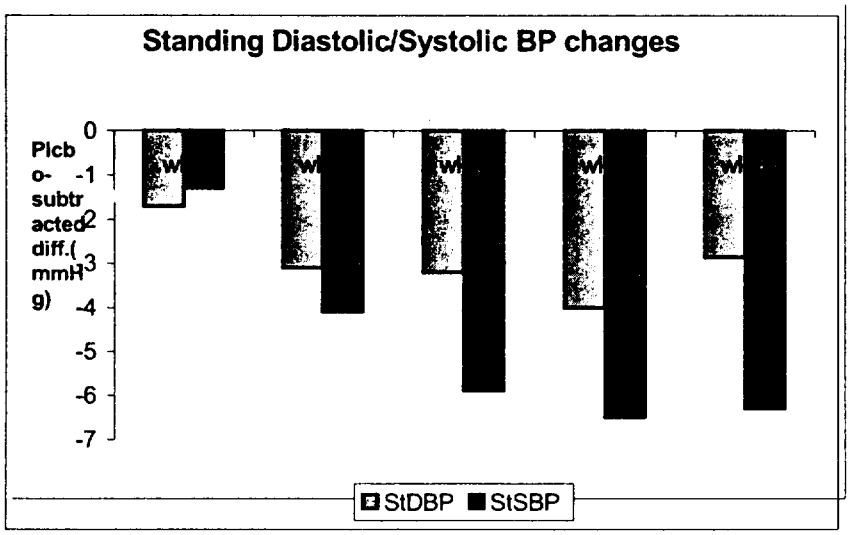
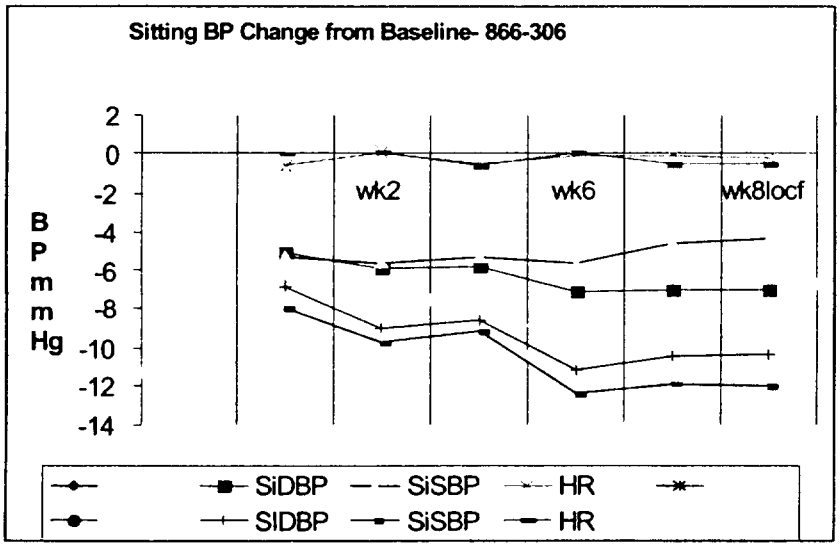


Figure 34: Timecourse of SiDBP SiSBP and HR by reviewer –Study866-306



9.5 Summary of primary efficacy

The results from this study evaluated the effect of 3 doses (5mg, 10mg and 20mg daily) of olmesartan compared to placebo on the magnitude and duration of blood pressure response in patients with essential hypertension, and an appropriate dose range was established.

The final on-therapy changes from baseline in trough SiDBP are presented in Figures 35 –38; Tables 81-83). In this 8-week study, data from the first 4 weeks confirmed 5 mg of olmesartan to have suboptimal antihypertensive effect. Subsequent titration of uncontrolled hypertensive subjects with 10mg and 20 mg of olmesartan showed some

effect and with addition of HCTZ the antihypertensive effect was increasedcompared to placebo. Both the week 8 and week 8/LOCF show a statistically significant difference between the treated and placebo groups (p=0.005 and p=0.004 respectively) Tables 81-82.

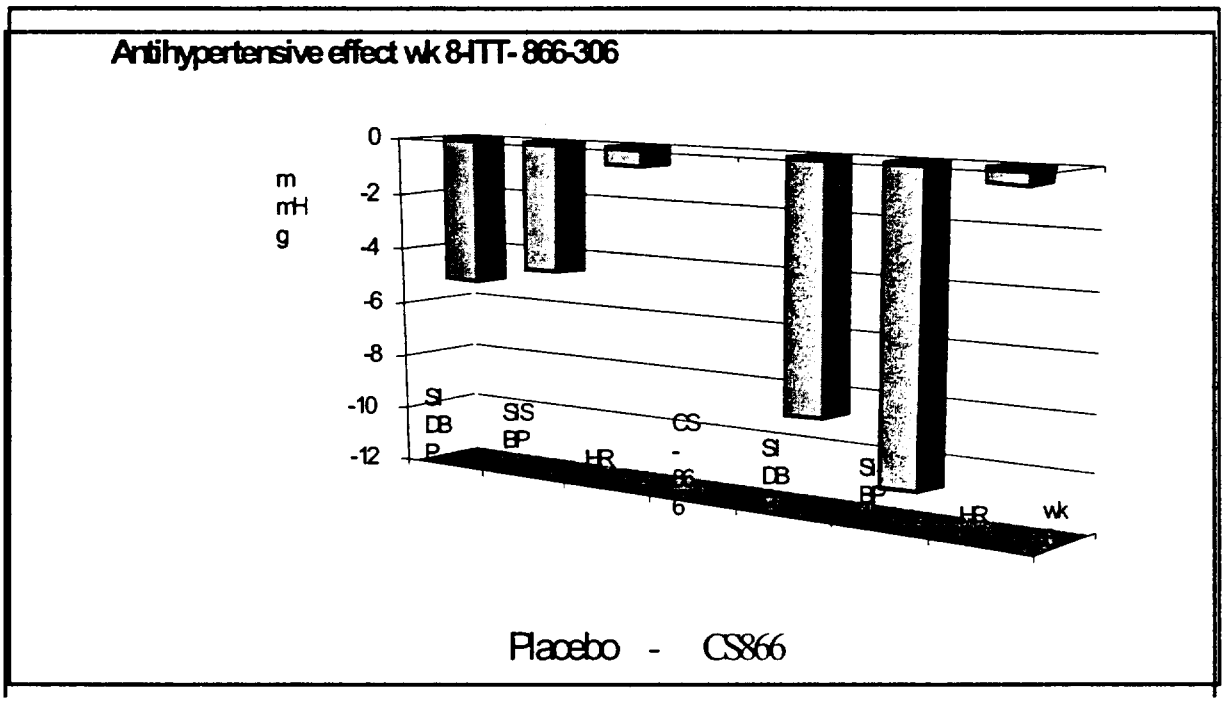
Table 81: Changes in Trough SiDBP at week 8 and LOCF- Study #860-306 -ITT

Sitting Diastolic Blood Pressure (SiDBP)	**Placebo**	**CS-866**	**p-value Placebo vs CS-866**
Change from Baseline-week 8 N Mean LS-mean	102 -7.0±8.54 -6.674	309 - 10.5±8.42 -9.713	**0.005**
Change from Baseline-week 8(LOCF) N Mean LS-mean	105* -7.0±8.48 -6.589	319* - 10.4±8.49 -9.703	**0.004**
±=Standard deviation; L.S. mean=least squares mean.	*There were 3 placebo and 10 treated patients whose week 8 measurements were missing and were imputed using the LOCF values. Source:Reviewer.		

Table 82: Mean SiDBP and SiSBP changes from baseline over time –ITT - 866-306

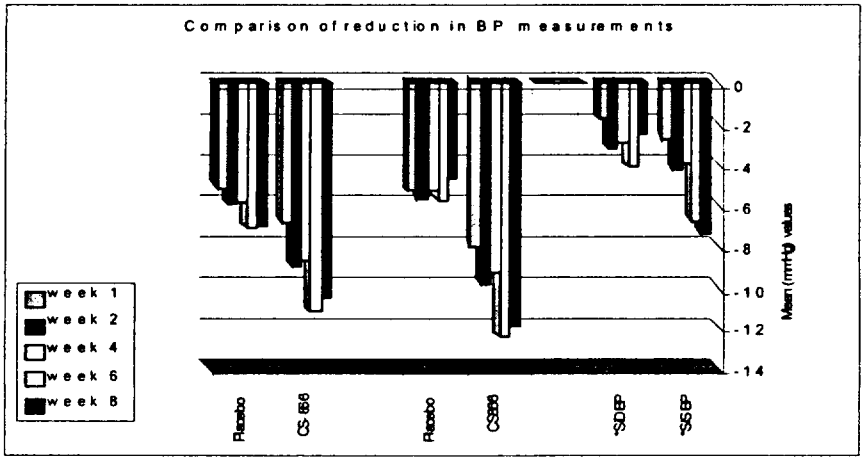
	Placebo			**CS-866**			**p-value**
	N	**Mean**	**LS-mean**	**N**	**Mean**	**LS-mean**	**Plcbo vs CS-866**
Sitting Diastolic BP	114	104.4		337	103.7		
Baseline	114	-5.1	-4.272	336	-6.8	-6.429	0.006
Week 1	111	-5.9	-4.658	333	-9.0	-8.544	<0.001
Week 2	108	-5.8	-5.600	326	-8.6	-7.807	0.016
Week 4	104	-7.1	-6.281	314	-11.2	-10.850	<0.001
Week 6	102	-7.0	-6.674	309	-10.5	-9.713	**0.005**
Week 8	105	-7.0	-6.589	319	-10.4	-9.703	**0.004**
Week 8/LOCF							
Sitting Systolic BP	114	158.4		337	156.3		
Baseline	114	-5.3	-3.586	336	-8.0	-7.29	0.007
Week 1	111	-5.6	-3.412	333	-9.8	-9.19	<0.001
Week 2	108	-5.3	-4.828	326	-9.2	-8.59	0.016
Week 4	104	-5.7	-4.991	314	-12.4	-12.46	<0.001
Week 6	102	-4.6	-3.817	309	-11.9	-11.24	<0.001
Week 8	105	-4.4	-3.527	319	-12.0	-11.47	<0.001
Week 8/LOCF							

Figure 35: Antihypertensive effect at week 8 – ITT combined group - 866-306



9.6 From the present study, the treatment effect of 3 doses (5mg, 10mg and 20mg daily) of olmesartan was evaluated and compared to placebo, the magnitude and duration of blood pressure lowering in patients with essential hypertension were also established. No significant difference was observed in heart rates between treatment groups (Figs 36-37). Figure 36 below shows the reduction in blood pressure measurement over time among ITT patients in study #866-306. The columns to the left are sitting diastolic BP, middle columns are sitting systolic BP and the columns to the far right are placebo subtracted values for both SiDBP and SiSBP over time. Heart rate shows no difference and is presented in between the middle columns and the far right columns

Figure 36: Summary Graph showing Reduction in BP over time 866-306



9.7 Secondary efficacy analyses

For secondary efficacy evaluation all randomized patients receiving CS-866 were included in the analysis regardless of the dose received and referred to as the "combined group" during the double-blind period. The data are presented as follows:
Hypothesis: There is no effect in titrating the daily dose of CS-866 upward.
4.7 Result: There was an effect in titrating the daily dose upward. Data on efficacy of titration after week 4 – by dose, are presented in Table 83 and Figure 34.

In the group of patients with DBP >90 at week, there is a significant difference between the 5 mg group versus 20mg group at week 8 (p=0.03 and LOCF p=0.021), whereas the data failed to show a significant difference between the 10 mg versus 20 mg group on the reduction of sitting diastolic and systolic BP measurements (Table 84). This would suggest that with the uncontrollable group, the data indicate that 20 mg dose shows a greater reduction in BP compared to the 5mg and 10mg dose groups. These significant differences are also achieved in the StDBP and StSBP pressure measurements between the 5 mg versus 20 mg groups (StDBP: p=0.009 and 0.004; StSBP, p=0.003). The overall effect changes due to titration suggest that there is a significant difference (Tables 83-84) and this trend is confirmed during the open label period up to 6 months (Fig. 39).

Table 83: Titrated Patients with Diastolic>90mmHg-wk4 by dose-ITT - 866-306

	CS-866 (N=75) 5MG		**CS-866(N=75) 10MG**		**CS-866(N=79) 20MG**		**P-VALUE (MG.VERSUS)**		
	Mean	LS-mean	Mean	LS-mean	Mean	LS-mean	5v10	5 v20	10v20
Sitting Diastolic BP	103.9		104.9		104.4				
Baseline	-5.2	-4.91		-5.107	-5.6	-5.903	0.850	0.340	0.440
Week 4	-7.9	-7.864	-5.1	-9.359	-9.5	-10.392	0.259	0.058	0.421
Week 6	-7.2	-6.41	-9.2	-7.90	-9.2	-10.108	0.319	0.016	0.131
Week 8	-6.8	-6.28	-8.3	-7.90	-9.1	-10.040	0.260	0.010	0.128
Week 8/LOCF			-8.3						
Sitting Systolic BP	158.0		157.3		160.0				
Baseline	-5.8	-5.79		-7.369	-7.5	-6.381	0.490	0.794	0.662
Week 4	-7.3	-7.879	-7.5	-10.650	-13.5	-13.911	0.221	0.008	0.140
Week 6	-6.1	-6.584	-10.4	-9.182	-13.7	-13.487	0.304	0.008	0.083
Week 8	-5.9	-6.307	-10.3	-9.205	-13.8	-12.799	0.245	0.010	0.141
Week 8/LOCF			-10.3						

Table 84: Effect changes on Titrated ITT patients by dose 866-306

MEASURE	p-value (mg versus)			
	N	5v10	5 v20	10v20
Sitting Diastolic BP	75			
Week 4	72	0.356	0.163	0.620
Week 6	71	0.330	0.031	0.205
Week 8	73	0.299	0.021	0.184
Week 8/LOCF				
Sitting Systolic BP	75			
Week 4	72	0.257	0.022	0.225
Week 6	71	0.346	0.010	0.084
Week 8	73	0.282	0.012	0.137
Week 8/LOCF				

9.8 Statistics

Hypothesis: There is no difference in the treatment effect between CS-866 combined and placebo when the effect is measured by:

Change from baseline at weeks 1, 2, 4, 6 and 8 in StDBP

Change from baseline at weeks 1, 2, 4, 6, and 8 in StSBP

There is no difference in the treatment effect between CS-866 combined and placebo when the effect is measured by:

Change from baseline at weeks 1, 2, 4, and 6 in SiDBP;

Change from baseline at weeks 1, 2, 4, and 6 in SiDBP;

the change from baseline at weeks 1, 2, 4, 6, and 8 in SiSBP;

The change from baseline at weeks 1, 2, 4, 6, and 8 in SiSBP;

The change from baseline at weeks 1, 2, 4, 6 and 8 in StDBP

Change from baseline at weeks 1, 2, 4, 6, and 8 in StSBP.

9.9 Results: At week 8 time point prespecified for evaluation of efficacy, the decrease in blood pressure from baseline was statistically significantly greater in CS 866-treated patients compared to placebo and this decrease was observed from as early as week 1. Data for these secondary efficacy changes relating to both standing and sitting diastolic and systolic blood pressure over time are presented in reviewer's graphs (Figures 33, 34, 366 & 38, and Tables 82 & 85) and supported by sponsor's data and graphs (Figsu41 and 42). The blood pressure lowering effects are also observed during the open label period at 3 and 6 months (Figures 38-40). In conclusion, there is a change from baseline in the treatment effect between CS866 treated hypertensive patients compared to placebo from weeks 1 to 8 as measured by SiDBP, SiSBP, StDBP, and StSBP.

Figure 37: StDBP, StSBP and HR: change from baseline 866-306. Source: Reviewer

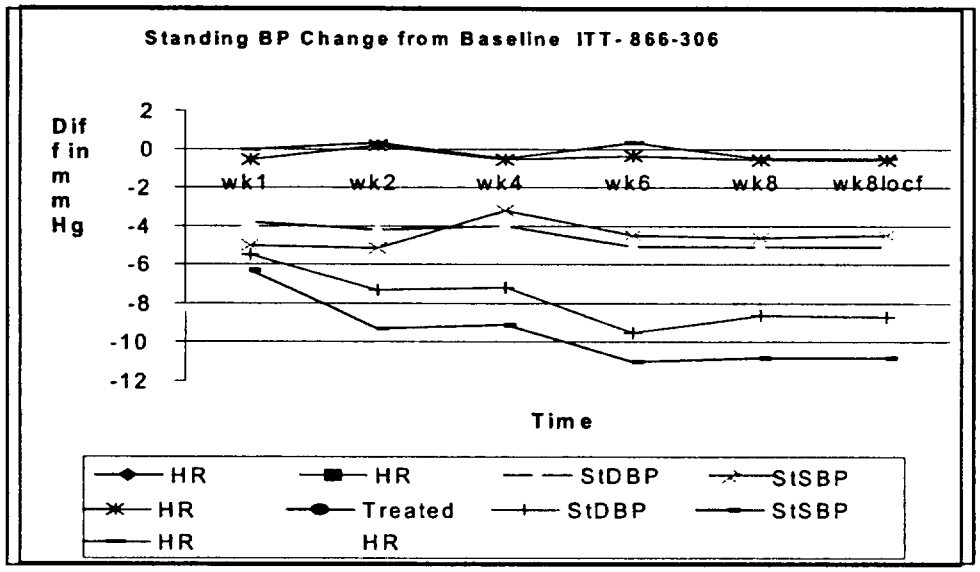


Figure 38: SiDBP of Titrated Patients 3-6months open label –866-306

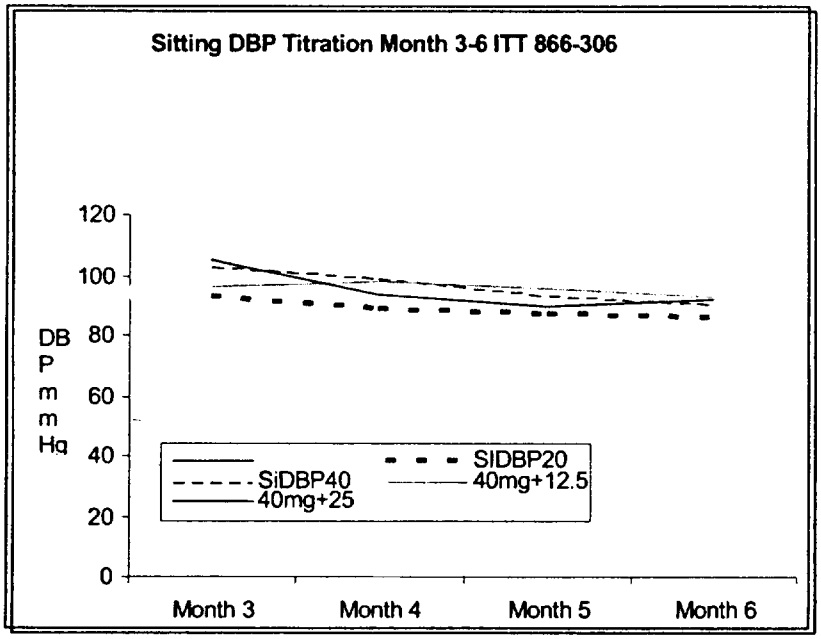
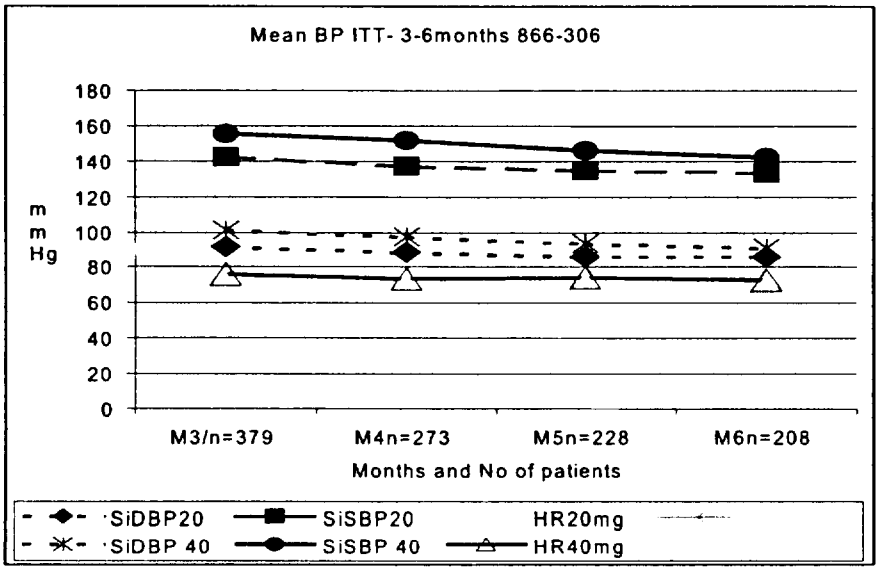


Figure 39: SiDBP, SiSBP and HR 3-6 months-Titrated patients - 866-306

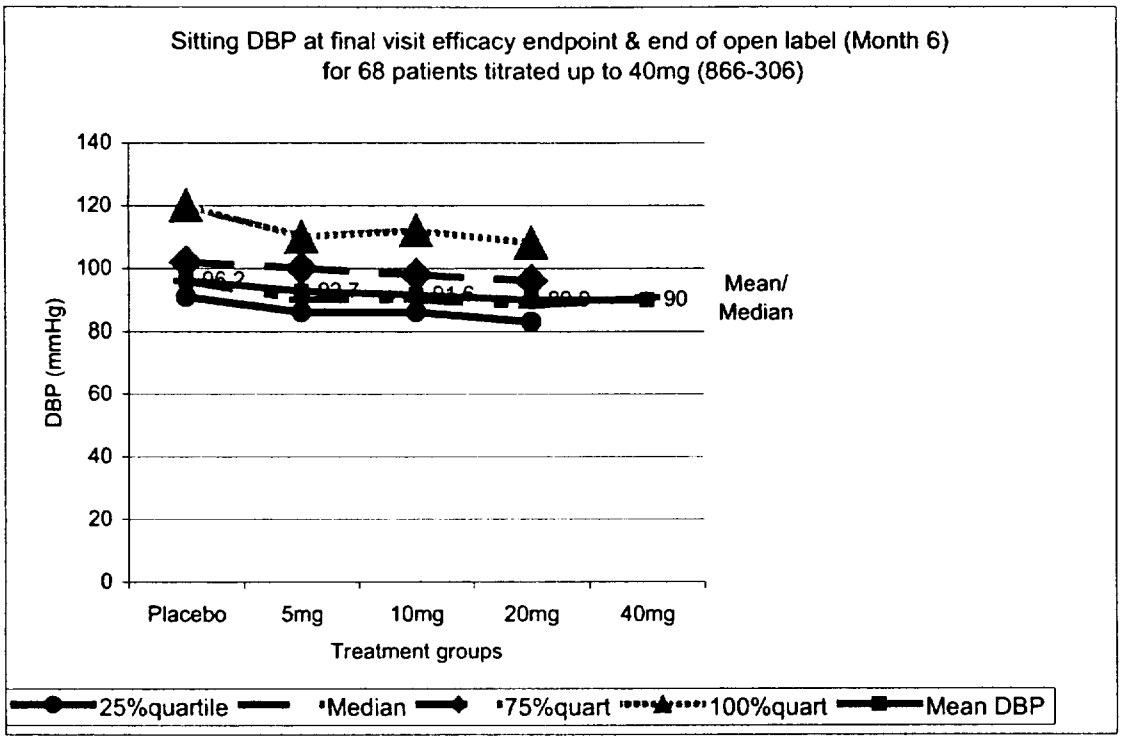


Source Reviewer

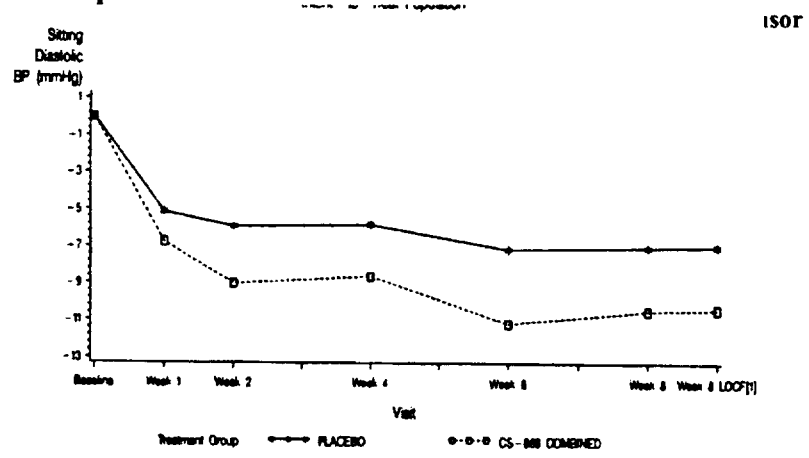
Table 85: Mean StDBP decreases from baseline – ITT 866-306

	PLACEBO			CS-866			P-VALUE
BP(MMHG)	N	Mean	LS-mean	N	Mean	LS-mean	Plcbo vs CS-866
Standing Diastolic BP							
Baseline	114	104.2		337	103.9		
Week 1	114	-3.8	-3.168	336	-5.5	-5.215	0.008
Week 2	111	-4.2	-2.965	333	-7.3	-7.256	<0.001
Week 4	108	-4.0	-3.193	326	-7.2	-6.696	<0.001
Week 6	104	-5.1	-4.178	314	-9.5	-9.047	<0.001
Week 8	102	-5.1	-4.351	309	-8.6	-7.964	<0.001
Week 8/LOCF	105	-5.1	-4.402	319	-8.7	-8.088	<0.001
Standing Systolic BP							
Baseline	114	158.1		337	155.5		
Week 1	114	-5.0	-3.982	336	-6.3	-6.191	0.111
Week 2	111	-5.2	-2.598	333	-9.3	-9.005	<0.001
Week 4	108	-3.2	-2.663	326	-9.1	-8.649	<0.001
Week 6	104	-4.5	-3.762	314	-11.0	-10.981	<0.001
Week 8	102	-4.6	-3.916	309	-10.8	-10.141	<0.001
Week 8/LOCF	105	-4.5	-3.747	319	-10.8	-10.283	<0.001

Figure 40: Sitting diastolic BP at efficacy end point –ITT- 866-306 - Reviewer



Figures 41 and 42 below Submitted by sponsor 866-306 SiDBP Titrated and non-titrated patients.



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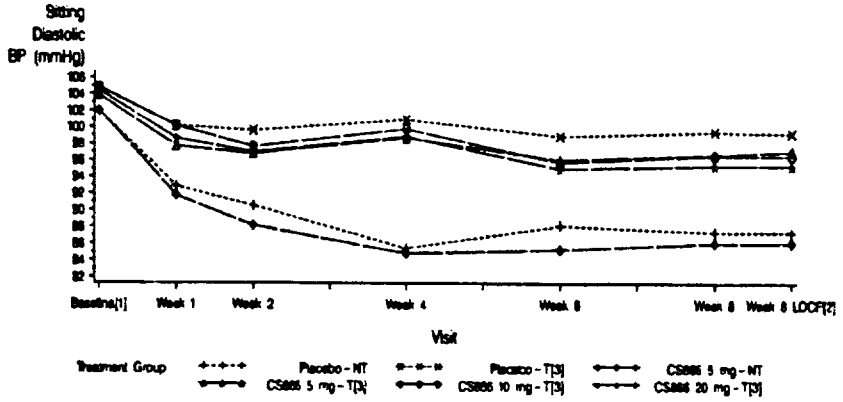
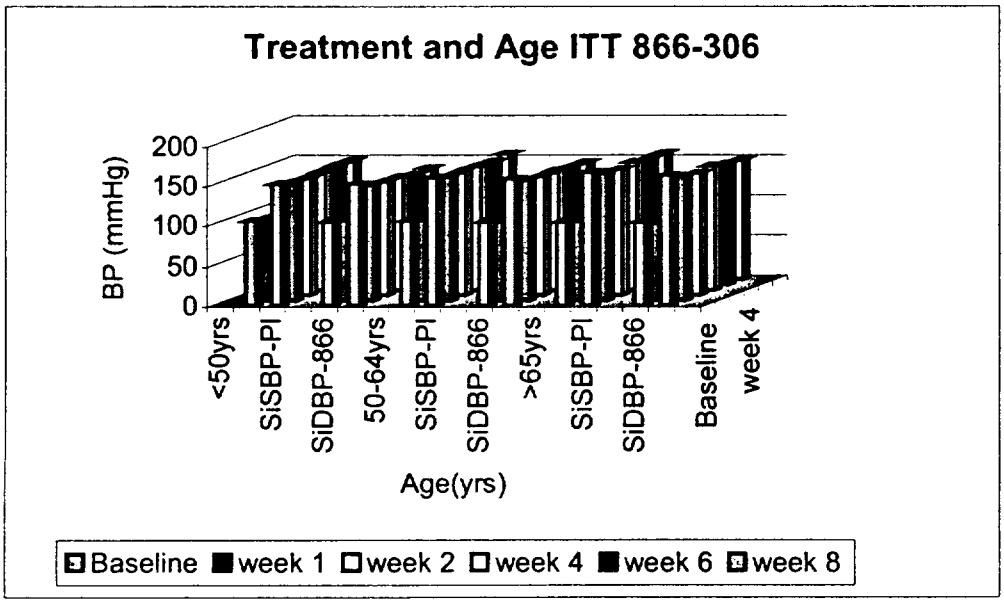


9.10 Efficacy and Age

The mean sitting BP at baseline and at weeks 1-8 are similar among placebo-treated and CS866-treated patients (Figure 43). The SiDBP was slightly lower among the >65year olds compared to <50 year old patients. The mean SiDBP at week 8 was lower in the group of patients >65(89.9) compared to those <50, and 50-64; 93.7 and 93.8mm Hg, respectively. Older patients had a larger placebo response compared to younger patients suggesting that CS866 in not a more effective agent in lowering diastolic blood pressure in older patients as previously postulated.

Figure 43: Effect of treatment on Age by time – 860-306 (Reviewer)

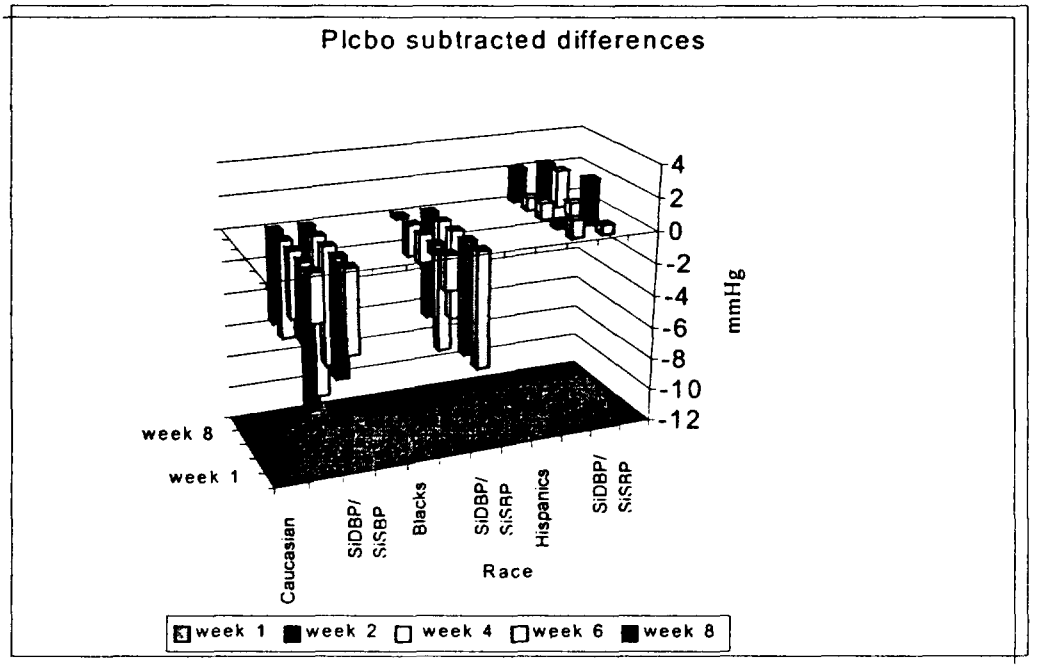


9.11 Efficacy and Race

Mean SiDBP at baseline through week 8 was similar among the racial groups in both treatment groups. The placebo-subtracted differences in Caucasians were the largest compared to blacks and there was no difference in Hispanics (Figure 44). Regardless of concomitant HCTZ, the antihypertensive effect in blacks was less than in Caucasians and similarly on Hispanics who constituted the same percentage as blacks. The reasons for the reduced antihypertensive effect on the black and Hispanic populations is not known.

The relatively reduced effect on blacks is consistent with other sartans that have been reviewed by this division (See stastistical review). The sponsor claims that due to small numbers no conclusions can be drawn from the data.

Figure 44: Effect of race on BP change over time wk 1-8 ITT- 860-306



9.12 Efficacy and Sex

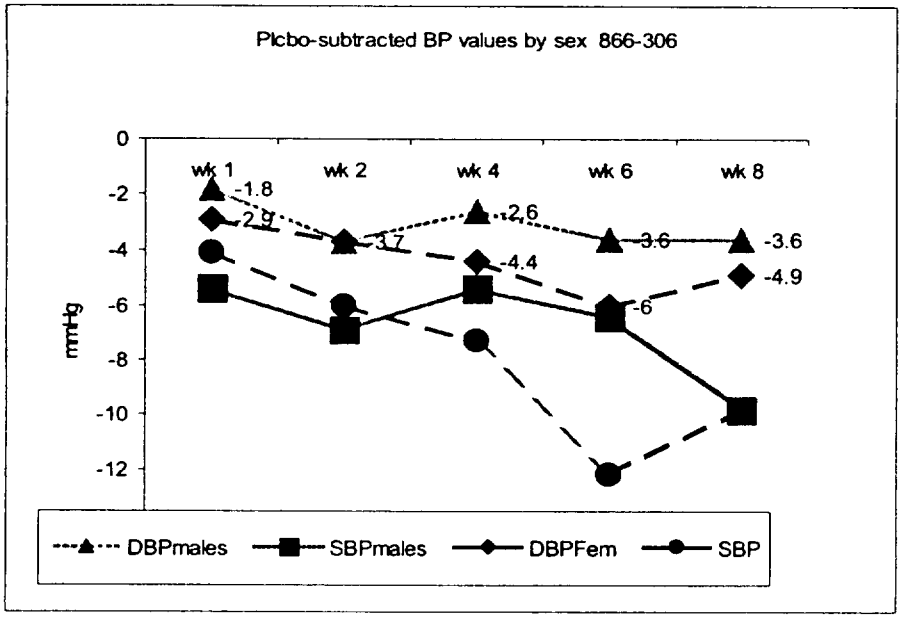
Baseline SiDBP was similar among males and females in both treatment groups. The mean reduction in both DBP and SBP from baseline to week 8 was slightly higher in females than males particularly after week 4. (Figure 45). Table 86a shows increased percentage of non-titrated females normalized between weeks 6 and 8 compared to males: 83.3% versus 68.8% and 78.6% versus 78.6%, respectively. However, there was no significant difference in the response rates between the sexes (Table 86a).

Table 86a: Antihypertensive effect of CS 866 only by sex-double-blind period - ITT -

COMBINED N	WEEK 1		WEEK 2		WEEK 4		WEEK 6		WEEK 8	
(N) 114 placebo (N) Treated 337	M	F	M	F	M	F	M	F	M	F
SiDBP	-1.8	-2.9	-3.7	-3.7	-2.6	-4.4	-3.6	-6.0	-3.6	-4.9
SiSBP	-5.4	-4.1	-6.9	-6.0	-5.4	-7.3	-6.4	-12.2	-9.8	-9.8
Normalized(%) 1-4wks	15.3	21.2	24.5	29	27.2	31.7				
*Normalized(%) 6-8wks							**68.8**	**83.3**	**58.3**	**78.6**
Responders(%)1-4wks	32.6	34.9	44.7	46.9	40.2	43.7				
*Responders(%) 6-8wks							**91.7**	**92.9**	**77.1**	**83.3**

Source for BP data - Reviewer See Figure * and Bold figures refer to non titrated subjects with optimal response at 4 weeks. Excludes patients with suboptimal response at four weeks and required titration. No data given for StDBP and StSBP. M=Male; F=Female.

Figure 45: Antihypertensive effect and sex over time -866-306



Source Reviewer. Note values for diastolic blood pressure lowering in graph shows a greater response in females than males after week 2. Similar pattern for systolic blood pressure lowering.

9.13 Response rate

The proportion of responders to placebo and to CS 866 at week 8 for week 8 completers (ITT) was 35.6% and 52.3% respectively. The proportion of non-responders to placebo and to CS 866 at week 8 for week 8 completers (ITT) was 64.4% and 47.7%, respectively. The 95% CI for the odds ratio of 1.978 (95% CI 1.243, 3.147), which does not include 1, and a p-value = 0.004 suggest a treatment effect that was statistically significant (Table 86b)

The proportions of non-responders for placebo and to 5, 10 and 20 mg CS 866 respectively, after 4 weeks are presented in Table 86b. These data show no difference even in the 20 mg group where the non-responders were 68.8% compared to placebo of 72.3%.

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Responders before 4 weeks to 5 mg dose and then up to 8 weeks-866-306

Table 86b: Response rates before and after week 4 showing effect of titration -ITT-

	Placebo			CS-866				
	NT	T	Total	NT	NT	T	T	Total
	N=117	N=91	N=208	5mg N=93	5mg N=75	10mg N=75	20mg N=79	N=322
Completers at wk 8 N (%)	**16 (94.1%)**	**85 (93.4 %)**	**101 (93.5 %)**	**90 (96.8%)**	**71 (94.7%)**	**74 (98.7%)**	**73 (92.4%)**	**308 (95.7%)**
Change from baseline (N)	11 (68.8%)	25 (29.4%)	36 (35.6%)	72 (80.0%)	27 (38.0%)	28 (37.8%)	34 (46.6%)	161 (52.3%)
Respond-ers	5 (31.2%)	50 (70.6%)	65 (64.4%)	18 (20.0%)	44 (62.0%)	46 (62.2%)	39 (53.4%)	147 (47.7%)
Non-responders								
Change from wk 4								
Change from baseline (N)	11 (68.8%)	17 (20.0%)	28 (27.7%)	62 68.9%)	19 (26.8%)	18 (24.3%)	23 (31.5%)	122 (39.6%)
Responders	5 (31.2%)	68 (80.0%)	73 (72.3%)	28 (31.1%)	52 (73.2%)	56 (75.7%)	50 (68.5%)	186 (60.4%)
Non-responders								

9.14 There was no center by dose interaction for SiDBP or SiSBP. ANOVA analysis showed a significant positive dose response relationship (See statistical review). All doses of olmesartan yielded significant differences from placebo for SiDBP, whereas all doses showed significant differences from placebo for SiSBP.

10.0 Review of safety – study SE- #866-306

All the 457 ITT patients were included in the safety analysis. There was a mean exposure of the study drug for approximately 28 days during week 1 to 8 ([redacted]) (Table 79). Tables 78 and 79 summarize the duration and estimates of total amount of drug exposure. Most subjects (90% of 168 on 5mg, 89.5% of 75 on 10mg and 87.3% of 79 on 20mg) were on drugs compared to 86.1% of 108 on placebo. At the end of week 8, SiDBP was >90mmHg in 153 (108 placebo) subjects 75 on 10mg and 79 on 20 mg and these subjects received additional hydrochlorothiazide (12.5 mg) for 4 weeks (Table 80). Of the 10 patients receiving additional HCTZ, 3 (30%) had uncontrolled hypertension and were discontinued, and 4 (40%) requested to be withdrawn from the study.

Table 87: Frequency of Adverse events by dose - ITT - 866-306

	Placebo	CS-866		
	(N=116)	5mg-5mg(N=187)	5mg-10mg(N=75)	5mg-20mg(N=79)
At least one AE	71(61.2%)	103(55.1)	50(66.7%)	41(51.9%)
At least one D-R-AE	13(11.2%)	20(10.7%)	6(8.0%)	9(11.4%)
At least one severe AE	5(4.3%)	3(1.6%)	2(2.7%)	3(3.8%)
At least one serious AE	1(0.9%)	0	0	1(1.3%)
Discontinued for AE	1(0.9%)	4(2.1%)	0	3(3.7%)

There were 76 discontinuations throughout the 6 month study [(66 (19.3%) on CS-866 alone and 10 (10%) on CS866+HCTZ)]. Of those, 13 were as a result of adverse events in the monotherapy group and 1 in the combined group. Table 87 presents the frequencies of adverse events by dose during the double-blind period.

10.1 Treatment emergent adverse events can be discussed under 2 periods, namely; 1) during the first 4 weeks of the double-blind period that subjects received 5mg CS-866 versus placebo, and 2) titrated subjects who received 5mg, 10mg or 20mg CS-866 or placebo during weeks 5 to 8. Safety data were collected at each clinic visit as per protocol including early termination if withdrawn early.
Discontinuations for adverse events are presented in Tables 88-89 below. The most frequent AEs are in Table 90.

Table 88: Discontinuations for AEs - double-blind and open label periods - 866-306

Group	Day	Adverse event	Dose	Group	Days	Adverse Evt	Dose
CS-866 (DBp)	?	Dysphasia;CVA	Pl	Pl	37	Peripheral edema	Plcbo
	Preexisting	CHF	Pl	CS-866	30	Orthostatic dizziness	5
	Preexisting	Headache Headache	Pl	CS-866	9	Impotence	5
	Preexisting	Lightheadedness	Pl	CS-866	3	Nausea, Flatulence	5
	Preexisting	Hypokalemia		CS-866	17	Dizziness	5
	Day 1	Increased CPK		CS-866	55	CVA	20
Open Label				Open Label			
	95	Non-Q wave MI, sepsis, Mitral Endocarditis	20		57	Dizziness	20
	61	Ca. Esophagus	20		113	Ca. Breast	40
	27	Increased CPK	20		121	CVA	40
	85	Chest pain	20				

Dbp=double-blind period.

Table 89: Discontinuations for SAEs 866-306 - double-blind and open label periods

GROUP	ADVERSE EVENT	DOSE	GROUP	ADVERSE EVENT	DOSE
Plcbo-run-in period	Myocardial Infarction	Pl	8 wk d.-blind.		
	Myocardial Infarction	Pl		Bilateral pneumonia	Plcbo
	Rectal bleeding	Pl		CVA	20
	Pneumonia, A.Fib.	Pl			
Open Label			Open Label		
	Non-Q MI	20		Chest pain ? MI	20
	Ca Esophagus	20		Chest pain	20
	Unstable angina	20		Blurred vision	40
	Chest pain	20		Ca Breast	40
				CVA	40/12.5
Post Treatment	Renal failure			Left parietal mass	

PRIP=Placebo run in period; Pl=placebo; db=double-blind period.

Table 90: Relatively frequent Treatment-Emergent AEs Day 1 - week 8 866-306

	PLACEBO N=116	CS-866 COMBINED N=341	P-VALUE
At least 1 adverse event	13(11.2%)	35(10.3%)	
Dizziness	1(0.9%)	11(3.2%)	0.31
Headache	5(4.3%)	3(0.9%)	0.03*
Dyspepsia	2(1.7%)	0(0.0%)	0.06*
Tachycardia/Arrhythmia	0(0.0%)	3(0.9%)	0.57
Fatigue	0	4(1.2%)	0.58
Impotence-male	0(0.0%)	3(0.9%)	0.57

Headache and dizziness appear to be more common in those patients that received CS-866 compared to placebo.

10.2 Deaths and discontinuations will be presented in the integrated summary for safety.

10.3 Adverse events

Of the total 1627 adverse events reported by 371 patients during this study, a total of 150 patients complained of headache. Eighty-six patients had no adverse events. The

commonest adverse events are presented in Table 90. Headache and dyspepsia are statistically more frequent in the patients on active treatment compared to placebo (p=0.03; p=0.06 respectively,). Adverse events by race are presented in Table 91below. The observed increase in frequency of cough among the blacks may not be related to olmesartan.

Table 91: Relatively frequent AEs by race Day 1 -week 8 - 866-306

	CS-866*					
	Caucasian N=86		Black N=14		Hispanics N=13	
Event	Pl	CS	Pl	CS	Pl	CS
Headache	12(14.0%)	21(8.9%)	2(14.3%)	11(23.4 %)	1(7.7%)	1(2.0%)
Dizziness	4(4.7%)	11(4.7%)		0		5(10.0%)
Edema	8	10(4.2%)	0	0	0	0
Rhythm disorders	0	5(2.1%)	0	1	0	1
Insomnia	0	5(2.1%)	0	1	0	1
Coughing	1	3	0	4(8.5%)	0	0

10.4 Discontinuations due to laboratory events during the double blind period will be included in the integrated summary of safety. However the tables submitted by the sponsor summarizes the abnormal laboratory findings in this study and none of these appear to be dose related.

Efficacy Conclusions

This study shows that CS-866 treated patients had a statistically significant greater reduction in their mean blood pressure measurements (SiDBP) at week 8, being the protocol-defined primary efficacy variable (p=0.004). This was true not only for the SiDBP but also for SiSBP. This confirmed the primary objective of the study that CS-866 was more effective than placebo in lowering blood pressure in patients with essential hypertension. Because of the design of this study a definitive dose-response cannot be established. However, there is evidence that patients whose hypertension is uncontrolled by 5 mg CS-866 may benefit from upward titration to 20mg. Patients treated with 5mg CS-866 and whose diastolic blood pressure was not reduced below 90mm Hg after 4 weeks of treatment and received 20 mg showed a greater diastolic blood pressure reduction compared to those that continued with 5mg CS-866. From these data CS-866 is an effective antihypertensive agent in patients with essential hypertension. For patients with suboptimal response to 5mg CS-866, upward titration of the dose provided added antihypertensive effect.

Comparisons of efficacy of 5mg dose versus 10mg dose and 10mg dose versus 20mg dose show no statistically significant difference in effect change for lowering of blood pressure, whereas 5mg versus 20 mg showed a statistically significant difference suggesting that 20 mg may be an effective starting dose (p=0.03).

Patients administered 20mg without or with HCTZ during the double blind and or during the open label period achieved a statistically significant difference in change of SiDBP from baseline compared to placebo ($p < 0.05$). Addition of HCTZ resulted in greater antihypertensive effect in uncontrolled patients. Even though there is a difference in treatment effect between placebo and all the 3 doses given, the present data suggest that 20mg olmesartan is a reasonable starting dose for mild to moderate hypertensive patients and if the blood pressure remains uncontrolled, addition of HCTZ may be appropriate. There is no significant benefit in the observed antihypertensive effect on blood pressure when 40 mg dose CS-866 is given except in blacks and in uncontrolled hypertensives HCTZ is often required. Comparing peak to trough responses, olmesartan resulted in trough SiDBP values that ranged between approximately 96 to100% of peak, suggesting that once daily dosing is adequate.

Olmesartan at 20mg with or without additional HCTZ showed less change in SiDBP from baseline in blacks and virtually no effect in Hispanics compared to Caucasians. This may be due to small numbers of blacks or Hispanics or to other biological factors hitherto unknown in these 2 ethnic groups. This observation will be evaluated further in the integrated summary of efficacy. There is a gender difference, though not significant, in treatment effect. The antihypertensive effect of CS-866 is greater in females compared to males.

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11.0 Study SE-#866-10
Source documents: Study Report NDA 21-286, volumes 242-267 reviewed.
Investigators: This study was conducted at 47 sites in Europe.
Study Dates: September 1997 to July 1999

11.01 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"
Duration of study: 52 weeks (12 weeks plus 40 weeks extension study)

11.1 Study Objectives: Primary
To determine the diastolic blood pressure lowering effect at trough level of CS-866 at doses of 5, 10, 20 mg o.d. under placebo-controlled conditions, after 12 weeks compared to baseline in patients with mild-to-moderate hypertension.
11.2 Secondary Objectives
To determine the blood pressure lowering effect and the effect on pulse rate of CS-866 at dose levels of 5, 10, 20 mg o.d at the trough level after 2, 4, 6, 8, 12, (SiDBP and PR only), 16, 20, 36, 44, 52 weeks of treatment compared to baseline.
To evaluate the responder rate at each dose level of 5,10, and 20mg o.d. of CS-866 after 2, 4, 8, and 12 weeks of treatment.
To evaluate the rate of patients currently in treatment compared to the randomized patients after 16, 20, 28, 36, 44, and 52 weeks of treatment.
To assess the long-term safety and tolerability of CS-866 at doses of 5, 10, and 20 mg o.d. in terms of adverse events and laboratory data.
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.

11.3 Rationale of study
This Phase III study was conducted to assess the antihypertensive effect and safety of olmesartan administered to hypertensive patients once daily over a relatively long time and also the effect of adding HCTZ to CS-866 in uncontrolled hypertensive patients.
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.

11.4 Study design
This was a 12 week, randomized, double-blind, placebo-controlled, multi-center study conducted in 47 sites in patients with mild-to-moderate hypertension (95<SiDBP <110mmHg). The 12 week, double blind period (Period I) was preceded by a 3-week placebo run-in period (Period 0), and followed by a 40 week extension treatment period (Period II). Patients on previous antihypertensive therapy were tapered off their medication for about one week before the 3-week placebo run-in period. After the placebo run-in period, eligible patients were randomized to receive 5, 10 or 20 mg CS-866 or placebo once daily for 12 weeks. After 12 weeks of treatment, completers with a mean sitting diastolic blood pressure (SiDBP) <90mm Hg entered the 40 week extension phase and still remained on their previous treatment. Completing patients with SiDBP>90 mmHg received HCTZ in doses of 12.5mg or 25 mg once daily in addition to CS-866 for

about 2 weeks. This addition of HCTZ was neither in the protocol nor submitted as an amendment. Uncontrolled patients (patients whose SiDBP >95 mm Hg after 12 weeks of treatment) were excluded from the study only after they had received up to the maximum of 25mg of HCTZ.

The total duration of the trial for each ITT patient was 55 weeks (inclusive of a 3-week placebo run-in phase) plus a pre-run in taper-off period. A safety follow-up examination was carried out about 2 weeks after the last administration of the trial medication. Of the patients who completed the 12 week double blind period, those with uncontrollable hypertension (SiDBP > 95 at 12 weeks were either titrated upwards to 40mg CS-866 and given HCTZ 12.5 or 25mg or were excluded from the study. All the patients who completed the 12 week period continued in the double blind period for a further period of 40 weeks where subsequent dosing was based on BP response and titration of drug was effected (Figures 46 and 47).

11.5 Inclusion criteria

The patients were more than 18 years old and were taken from a healthy non-obese population. Inclusion and exclusion criteria were applied to determine eligibility of randomized patients. In addition to administrative changes, there were some amendments made after the start of the enrollment that did not affect reliability of the study.

11.6 Primary efficacy

Statistical analyses: Hypothesis - 866-10

There is no difference in the treatment effect between CS-866 (at doses 5, 10, and 20 mg) and placebo when the effect is measured by the change from baseline at week 12 in trough SiDBP.

For primary efficacy variables, there are 3 comparisons of interest corresponding to each active treatment group compared to placebo. Adjusting tests for multiple comparisons using Dunnett's test and Sidak's adjustment will decrease any chance of false positive results. A statistical model with additional term for the treatmentxpooled center interaction was fitted to check that the results were consistent across all centers. The study was powered accordingly to detect a difference of 5 mmHg between each active group and placebo.

11.61 Secondary efficacy: Hypotheses - 866-10

There is no effect on trough SiDBP and pulse rate at daily dose of CS-866 (5, 10, 20 mg) at 2, 4, 6, 12 weeks.

There is no difference at each dose level of 5, 10, 20 mg o.d. compared to placebo when the effect is measured by:

(a) The response rate at 2, 4, 8, & 12 weeks after treatment

(b) The change from baseline and age

Dose selection

The dose levels of 5mg, 10mg and 20 mg adopted for us in this study are based on previously published pre-clinical animal studies and human experience. In the past,

different doses of CS-866 had been given to healthy volunteers (N=235) or hypertensive patients (N=1200) in Europe, Japan and the US. The oral dose given in previous published studies ranged from a single dose of up to 320 mg to multiple doses of 80 mg for 14 days and exposure in those studies ranged from 2-12 weeks.

Patients on previous antihypertensive treatment

At screening, patients on previous antihypertensive medication had to undergo a tapering off period (Table 92). The patients who took concomitant medication either before or during the trial may have had an effect on the outcome of the study. Most patients took agents acting on RAS (190), followed by 150 patients on ASA type drugs, and 135 patients took antidiabetic agents, while another 100 patients took beta-blocking agents. Some of the agents taken as concomitant medication belonged to the antihypertensive group and some belonged to the prohibited group of concomitant medication. Several patients on these prohibited medications were not withdrawn from the trial constituting protocol violations.

Table 92: Taper-off period - ITT - 866-10

Taper-off	Placebo	5mg	10mg	20mg
Yes	42	75	68	70
No	47	97	103	96
Total	89	172	171	166

Patients with < 7 days tapering-off period were excluded from the PP sample

11.7 Results

Patient disposition: Disposition of patients during the double-blind period and after 12 weeks of trial is presented in Tables 93-99. Out of 645 patients that the 47 centers enrolled, 26 (4.03%) dropped out prior to randomization leaving 619 randomized patients. Another 19 were removed from the study (10 from center No. 37 and 9 patients withdrew after receiving one dose of medication. Completers in each group are shown in Table 94. Table 99 shows reasons for exclusion prior to randomization and also at study completion. A total of 557 and 518 ITT patients completed Periods I and II of the study, respectively (Figures 46 and 47).

Table 93: Enumeration of patients –ITT- 866-10

Population	N	%[1]
Enrolled	645	
Randomized	600	100.0
Placebo	89	14.8
CS-866 5, 10, 20 mg	511	85.2
ITT (Total)	600	100.0
Per Protocol (PP)	418	69.7
ITT completed	486	
ITT withdrawn	82	
ITT completed & PP	518	86.3

[1] Percent of patients in the ITT, PP and open label populations are calculated as % of patients randomized.

11.71 Patient disposition

Out of 645 patients with mild-to-moderate hypertension enrolled in this study, 619 (93.0%) were randomized to one of four treatment arms (Tables 94-100). Nineteen patients withdrew without post randomization data leaving 600 patients as ITT. Six hundered (600) patients were therefore treated as intent-to-treat (ITT). Of the 600 randomized patients, 258 (43%) were men and 342 (57 %) were women (Table 101). Among the 600 randomized patients, 511 (85.1%) patients initially received CS-866 and 89 (14.8%) received placebo. Of the 511 patients administered CSS-866, 486 (95.1%) completed Period 1 of the study whereas 71 out of the 89 (79.8%) randomized to placebo completed the study.

Table 94: Disposition of patients by treatment group (Periods I &II) Study # 866-10

No. of patients	Placebo	CS-866 5mg	CS-866 10mg	CS-866 20mg	Total
Placebo run-in					645(26)*
Randomized	93(100%)	178(100%)	177(100%)	171(100%)	619(19)**
ITT	89(14.8%)	172(28.7%)	171(28.5%)	168(28.0%)	600(100.0%)
Withdrawn(%ITT)	33(35%)	19(11%)	18(10.5%)	12(7.2%)	82(13.7%)
Completed	56(65%)	153(89%)	153(89.5%)	156(92.8%)	518(86.3%)
Of the 619 randomized, 9** were withdrawn after dose 1 of drug, 10** were excluded from efficacy analysis from center 37, leaving 600 randomized patients for efficacy analysis. 26* out of 645 entering placebo run in period dropped out. See Table 99					

Figure 46: ITT Patients completing 12 weeks of Period I - 866-10-above

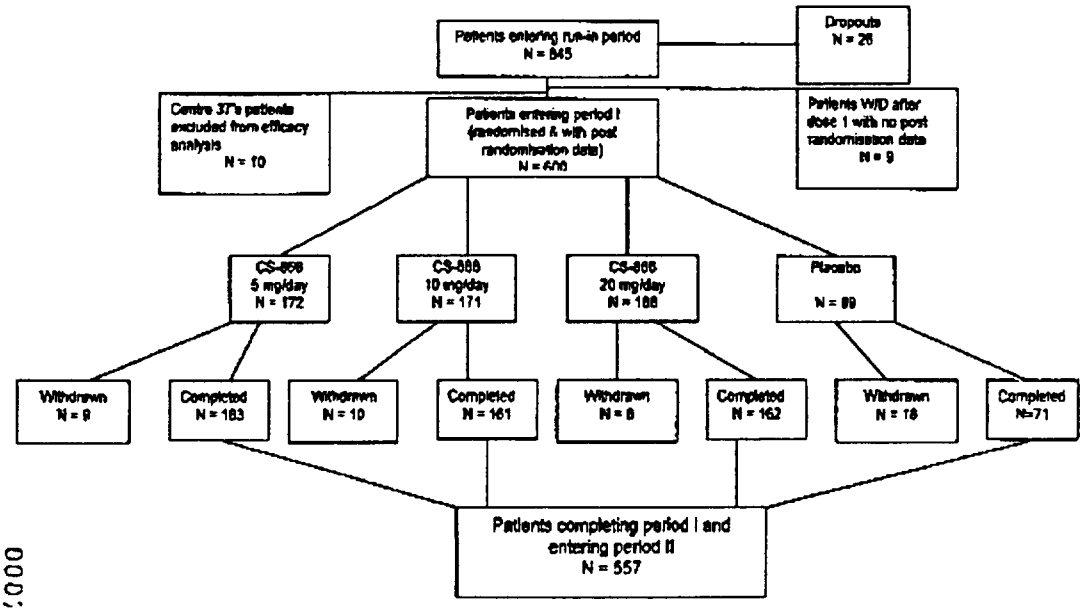

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Figure 47: ITT Patients completing 55 weeks of Period II – 866-10- below

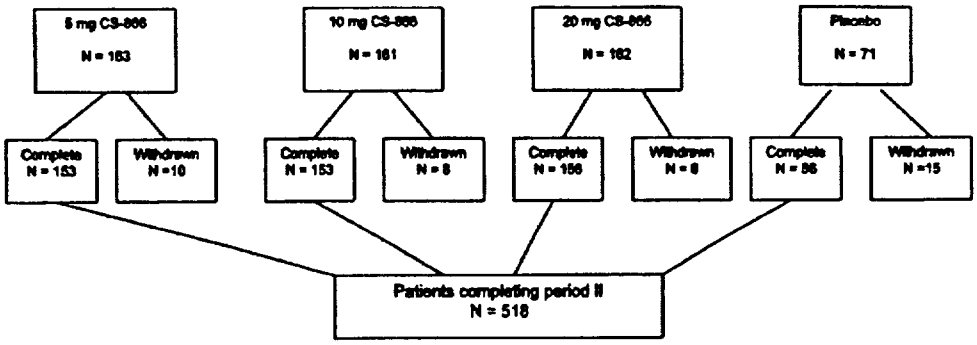

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Table 95: Overall disposition of ITT patients at end of Period II - study 866-10

	Period I		Period II	
	Placebo	Active	Placebo	Active
Randomized	89	511	71	486
Withdrawn	18	27	15	24
Completed	71	486	56	462*
Missing	0	?18	0	0

*Out of 462 patients, 8 were excluded from the efficacy analysis but included in the safety analyses.

Table 96: Disposition of ITT patients after wk 12 in 866-10- and extension

	Placebo		CS-866						
			5mg		10mg		20mg		Total
Patients for evaluation	N	%	N	%	N	%	N	%	N (%)
ITT Total for Safety	53	11.49	136	29.43	137	29.45	136	29.43	462
ITT Total for Efficacy	50	11.01	136	29.96	134	29.5	134	29.5	*454 (100)
HTCZ recipients>12 wks.*	23	46	46	33.8	42	31.3	27	20.1	138 (30.4)
HCTZ/CS 866	23/ 27	54	46/ 90	66.2	42/ 92	68.7	27/ 107	79.9	138 (30.4)
Total HCTZ +HCTZ/CS-		100		100		100		100	

*454 patients completed SE 866-10 and proceeded to study .

Table 97: Disposition of ITT and Per Protocol (PP) populations - 866-10

	Placebo		CS-866						
			5mg		10mg		20mg		Total
Pts. evaluated	N	%	N	%	N	%	N	%	N (%)
ITT	89	14.8	172	28.7	171	28.5	168	28.0	600(100)
Per Proto. (PP)	44	10.5	113	27	126	30.1	135	32.3	418(100)

Cumulative withdrawals by treatment groups are shown in Table 99 below.

Table 98: Cumulative withdrawals by treatment groups - Periods I and II.

	Visit 8*	Visit 10	Visit 12	Final visit**
Not randomized	26	26	26	26
CS-866 5mg	8	10	10	12
CS-866 5mg +12.5mg HCTZ	0	2	2	2
CS-866 5mg +25mg HCTZ	0	4	7	7
CS-866 10mg	10	10	13	13
CS-866 10 mg +12.5 mg HCTZ	0	0	0	1
CS-866 10mg +25 mg HCTZ	0	3	3	4
CS-866 20 mg	6	7	9	9
CS-866 20 mg +12.5 mg HCTZ	0	0	2	2
CS-866 20 mg +25 mg HCTZ	0	0	1	1
Placebo 0 mg	26	30	31	31
Placebo 0 mg +12.5mg HCTZ	0	0	10	10
Placebo 0 mg +25mg HCTZ	0	8	10	10
Total ITT (600)	76	103	115	119 (19.8%)

*End of Period I; (866-10), **End of Period II (

11.72 Screening failures and withdrawals are presented in Tables 99 and 100. Of the 93 withdrawn patients (no post randomization data was available on 9), 22 were due to AEs (8, 7, 3, and 4, were randomized to the 5, 10, 20 mg, and placebo groups, respectively. Eighteen (18) patients withdrew their consent, 43 due to a lack of efficacy 1 due to concomitant medication and 11 others due to multiple or other reasons (Table 101).

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