DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

STATISTICAL REVIEW AND EVALUATION

NDA #: 20-838

SERIAL #: SE4-S015

DRUG NAME: ATACAND (candesartan cilexetil) Tablets

INDICATION: Hypertension

SPONSOR: AstraZeneca LP

DOCUMENT REVIEWED:

1. Vols. 1.1, 1.5, 1.37, 1.52, 1.71 (CDER REC'D Date: September 27, 2001), Supplemental new correspondence (CDER REC'D Date: 4/16/02)
2. SAS database in EDR

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STATISTICAL KEY WORDS: ANCOVA, LOCF, Least square mean

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0. SUMMARY

This NDA provides three main clinical trials (two CLAIM studies and one CANDLE study) for comparison of the candesartan 16 mg to 32 qd mg regimen with the losartan 50 mg to 100 mg qd regimen. The two CLAIM studies showed that the candesartan regimen gave a statistically significantly greater reduction in blood pressures than the losartan regimen when given by forced titration. The difference was 1 to 2.2 mm Hg in trough sitting DBP and about 3.5 mm Hg in trough sitting SBP. When given by optional titration, the candesartan regimen also gave a statistically significantly greater reduction in trough sitting diastolic blood pressure. The difference was 2.2 mm Hg in trough sitting DBP. The difference in trough sitting SBP was < 2 mm Hg, not statistically significant.

Over the course of each study, the candesartan group appeared to have lower mean blood pressures than the losartan group. In all the studies, the mean blood pressures in both treatment groups were greatly reduced in the first two weeks and then seemed to stabilize afterwards.

Candesartan had a favorable trend in gender, race and age subgroups, except small subgroups.

1. INTRODUCTION

This statistical review pertains to the three clinical studies, CLAIM (Studies 230 and 231) and CANDLE (Study 175). Most of the sponsor's main results were confirmed by the reviewer's analyses and reported in this review unless stated otherwise.

2. OVERVIEW OF THREE CLINICAL TRIALS

2.1 Study 230

This was a multicenter, double-blind, randomized, parallel-group, forced-titration study to evaluate the anti-hypertensive efficacy of candesartan 16 mg forced titrated to 32 mg in comparison to losaran 50 mg forced titrated to 100 mg in the patients with mild-to-moderate essential hypertension (sitting DBP of 95 mm Hg to 114 mm Hg inclusive). The doses were selected to represent the labeled maximum doses of candesartan and losartan. All treatments were given once daily.

Following a 4 to 5 week placebo run-in period, qualified study patients were randomized in 1:1 ratio to candesartan 16 mg or losartan 50 mg. After two weeks of randomized treatment, all patients doubled their current dose of candesartan or losartan and continued treatment for an additional 6 weeks. Patients were also seen 48 hours following their last dose of study medication and 2 weeks after they discontinued therapy with the study medication for follow-up visits.

The primary efficacy measure was the mean change in trough sitting DBP from baseline to the double-blind week 8 visit. Secondary measures include sitting systolic pressures and peak blood

pressures at week 1, week 2 and week 8, and proportion of responders and controlled patients based on trough sitting DBP and SBP at week 8. The primary analysis is based on ITT principle and the last value carried forward strategy for incompleters.

The sample size of 735 patients to be enrolled from 75 investigative sites was planned to detect a difference in mean change from baseline in trough sitting DBP of 2.0 mm Hg between the two treatment groups at 2-sided alpha level of 0.05 and power of 95%, assuming a standard deviation of 7.5 mm Hg.

Efficacy results

A total of 613 patients out of 926 patients screened were randomized at 72 sites. Of these patients, 12.1% patients in the candesartan group and 12.4% patients in the losartan group discontinued treatment during the double-blind phase of the study. The distribution of patients discontinuing treatment by reason was similar in the two treatment groups (Table 230-1). Numerically, the losartan group appeared to have a bit larger proportion of discontinuation due to lack of response whereas the candesartan group appeared to have a bit larger proportion of discontinuation due to adverse event.

Table 230-1. Disposition of patients entering trial

	Candesartan	Losartan
Randomized to double-blind	307	304
Discontinued*	37 (12.1%)	37 (12.2%)
Lost to follow-up	5 (1.6%)	4 (1.3%)
Lack of response	8 (2.6%)	13 (4.3%)
Adverse event	9 (2.9%)	6 (2.0%)
Consent withdrawal	10 (3.3%)	8 (2.6%)
Sponsor/Investigator decision	5 (1.6%)	6 (2.0%)
Completed study	268 (87.3%)	267 (87.8%)

Sponsor's results confirmed by reviewer's analysis

* 2 additional patients in the candesartan group due to an adverse event while in the follow-up phase and thus not during the double-blind period.

The two treatment groups appeared to be comparable with respect to baseline characteristics (Sponsor's Table 4 of study report for Study 230) and treatment compliance (Sponsor's Table 14.1.1.03,14.1.1.05, 14.1.1.06). The mean age was 55 years and the average duration of hypertension is 10+ years. Fifty nine percent of patients were male an 20% were blacks. The mean sitting DBP/SBP was 100/153 mm Hg.

Treatment differences in BP at last visit

The primary efficacy variable, change from baseline to double-blind week 8 in trough sitting DBP, showed a greater reduction with candesartan (Table 230-2). Statistical significance is borderline. The statistical analysis was based on the model containing center where centers with at least one treatment arm having less than two patients were pooled using a prespecified pooling algorithm according to the sponsor's clarification. Since it was borderline significance, this reviewer did analysis without adjusting for centers and analysis by pooling all centers with less than two patients in a treatment arm into one center. Both analyses gave a smaller p-value and an estimated treatment difference very similar to the estimate reported in Table 230-2. Excluding baseline sitting DBP from the model made little change in the result. Candesartan also gave a statistically significantly greater reduction in trough sitting SBP and peak sitting DBP/SBP. However, the differences in all blood pressures were small.

Table 230-2. Least square mean change from baseline to double-blind week 8 (ITT population)

	Candesartan (N=306)	Losartan (N=303)	Difference# (95% CI)	p-value
Trough BP	N=306	N=303		
sitting DBP*	-10.5	-9.1	-1.5 (-2.9, -0.06)	0.041
sitting SBP	-13.4	-10.1	-3.4 (-5.7, -1.0)	0.005
Peak BP	N=274	N=266		
sitting DBP	-12.9	-9.5	-3.4 (-5.0, -1.9)	<0.0001
sitting SBP	-15.5	-12.0	-3.5 (-5.8, -1.2)	0.0032

Sponsor's results confirmed by reviewer's analysis
* primary endpoint #difference: candesartan minus losartan

Blood pressures over time

Blood pressures seemed to trend favorably to candesartan over time (Table 230-3). The

Table 230-3. Mean trough sitting blood pressures over time

	Trough sitting DBP				Trough sitting SBP			
	Candesartan		Losartan		Candesartan		Losartan	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	307	100.4	303	100.2	307	153.6	303	152.2
DB Wk1	304	93.1	302	93.2	304	144.0	302	143.9
DBWK2	300	91.4	297	92.5	300	141.1	297	142.2
DBWK4	292	89.5	292	90.4	292	139.0	292	140.4
DBWK8	284	89.8	280	90.9	284	139.6	280	141.2
DBWK8 (LOCF)	306	90.2	303	91.5	306	140.4	303	142.2
48hr FU	246	91.0	247	93.1	246	142.9	247	146
WK2 FU	269	89.5	271	89.9	269	140.6	271	141.1

Sponsor's results confirmed by reviewer's analysis

favorable difference in blood pressures seemed to remain at 48 hours after the last dose. Two weeks after the last dose, the mean blood pressures were similar between the two treatment groups. In both treatment groups, blood pressures were greatly reduced in the first two weeks and then seemed to stabilize afterwards.

Subgroup results

Candesartan appeared to have a favorable trend in change from baseline in trough sitting blood pressures in most of the subgroups, except blacks or small subgroups.

Table 230-5. Mean difference (Δ) and 95% CI of BPs by subgroups

	N	Trough sitting DBP	Trough sitting SBP
	C / L	Δ (95% CI)	Δ (95% CI)
Male	178/178	-1.6 (-3.4, 0.2)	-3.0 (-5.7, -0.3)
Female	128/125	-1.2 (-3.1, 0.7)	-3.0 (-6.5, 0.4)
Caucasian	211/213	-2.6 (-4.1, -1.0)	-4.1 (-6.5, -1.6)
Black	61/59	1.3 (-1.6, 4.3)	-1.4 (-6.9, 4.1)
Asian	4/8	0 (-9.1, 9.1)	6.6 (-2.0, 15.2)
Other	30/23	0.2 (-3.8, 4.3)	0.2 (-6.8, 7.2)
< 65 yrs old	244/247	-1.7 (-3.2, -0.2)	-3.1 (-5.5, -0.8)
≥ 65 yrs old	62/56	-0.6 (-3.5, 2.3)	-2.7 (-7.9, 2.4)

Reviewer's analysis Δ: candesartan minus losartan C: candesartan L: losartan

2.2 Study 231

The trial design of this study is identical to that of Study 230.

Efficacy results

A total of 655 patients out of 921 patients screened were randomized. 654 patients has at least

Table 231-1. Disposition of patients entering trial

	Candesartan	Losartan
Randomized to double-blind	332	322
Discontinued	15 (4.5%)	20 (6.2%)
Lost to follow-up	2 (0.6%)	3 (0.9%)
Lack of response	2 (0.6%)	5 (1.6%)
Adverse event	6 (1.8%)	5 (1.6%)
Consent withdrawal	2 (0.6%)	3 (0.9%)
Sponsor/Investigator decision	3 (0.9%)	4 (1.2%)
Completed study	317 (95.5%)	302 (93.8%)

Sponsor's results confirmed by reviewer's analysis

one post-baseline site contact. These patients constituted the intent-to-treat population. Of these patients, 4.5% patients in the candesartan group and 6.2% patients in the losartan group

discontinued treatment during the double-blind portion of the study. The distribution of patients discontinuing treatment by reason was similar in the two treatment groups (Table 231-1).

The two treatment groups appeared to be comparable with respect to baseline characteristics (Sponsor's Table 4 of study report for Study 231) and treatment compliance (Sponsor's Table 14.1.1.05,14.1.1.06, 14.1.1.03). The mean age was 54 years and the average duration of hypertension was 9 years. Fifty eight percent of patients were male and 17 percent were blacks. The mean sitting DBP/SBP was 100/152 mm Hg.

Treatment differences in BP at last visit

The primary efficacy variable, change from baseline to double-blind week 8 in trough sitting DBP, showed a significantly greater reduction with candesartan (Table 231-2).

Table 231-2. Least square mean change from baseline to double-blind week 8 (ITT population)

	Candesartan (N=332)	Losartan (N=322)	Difference# (95% CI)	p-value
Trough BP	N=332	N=322		
sitting DBP*	-10.9	-8.7	-2.2 (-3.4, -1.0)	0.0005
sitting SBP	-13.3	-9.8	-3.5 (-5.5, -1.5)	0.0007
Peak BP	N=312	N=294		
sitting DBP	-11.6	-10.1	-1.5 (-2.9, -0.1)	0.038
sitting SBP	-15.2	-12.6	-2.6 (-4.8, -0.5)	0.017

Sponsor's results confirmed by reviewer's analysis
* primary endpoint #difference: candesartan minus losartan

Blood pressures over time

Blood pressures seemed to trend favorably to candesartan over time (Table 230-3). The favorable difference in blood pressures seemed to remain at 48 hours after the last dose. Two weeks after the last dose, the mean blood pressures were similar between the two treatment groups. As in Study 230, In both treatment groups, blood pressures were greatly reduced in the first two weeks and then seemed to stabilize afterwards.

Table 231-3. Mean trough sitting blood pressures over time

	Trough sitting DBP				Trough sitting SBP			
	Candesartan		Losartan		Candesartan		Losartan	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	332	100.1	322	99.9	332	152.6	322	152.0
DB Wk1	332	92.5	319	93.3	332	142.8	319	144.2
DBWK2	330	91.7	319	93.0	330	141.2	319	143.2
DBWK4	328	89.0	317	90.3	328	139.2	317	141.1
DBWK8	321	89.1	306	90.7	321	138.9	306	141.7
DBWK8 (LOCF)	332	89.2	322	91.2	332	139.2	322	142.3
48hr FU	298	90.6	280	93.9	298	141.6	280	146.7
WK2 FU	318	88.6	308	88.5	318	138.2	308	139.4

Sponsor's results confirmed by reviewer's analysis

Subgroup results

In this study, candesartan had a favorable trend in gender, race and age subgroups (Table 231-4).

Table 231-4. Mean difference (Δ) and 95% CI in BPs by subgroups

	N	Trough sitting DBP	Trough sitting SBP
	C / L	Δ (95% CI)	Δ (95% CI)
Male	192/188	-2.3 (-3.8, -0.8)	-3.6 (-6.0, -1.1)
Female	140/134	-2.0 (-3.9, -0.0)	-3.6 (-7.0, -0.3)
Caucasian	246/236	-2.2 (-3.6, -0.8)	-3.7 (-6.1, -1.4)
Black	59/54	-1.7 (-4.6, 1.2)	-4.0 (-8.6, 0.7)
Asian	3/4	-7.4 (-17.4, 2.6)	1.3 (-21.8, 24.3)
Other	24/28	-2.9 (-6.9, 1.2)	-3.0 (-8.8, 2.7)
< 65 yrs old	278/273	-1.9 (-3.3, -0.6)	-3.5 (-5.7, -1.3)
≥ 65 yrs old	54/49	-3.5 (-6.3, -0.6)	-4.1 (-8.7, 0.5)

Reviewer's analysis Δ: candesartan minus losartan C: candesartan L: losartan

2.3 Study 175

This was a multicenter, double-blind, randomized, parallel-group, optional-titration (titration-to-effect) study to evaluate the anti-hypertensive efficacy of candesartan 16 mg titrated to 32 mg in comparison to losaran 50 mg titrated to 100 mg in the patients with mild-to-moderate essential hypertension (sitting DBP of 95 mm Hg to 114 mm Hg inclusive). Patients with a mean of sitting DBP ≥ 90 mm Hg after 4 weeks of treatment were up-titrated to candesartan 32 mg or losartan 100 mg for the remaining 4 weeks of the study. Patients with a mean of sitting DBP < 90 mm Hg after 4 weeks of treatment continued on candesartan 16 mg or losartan 50 mg. All treatments were given once daily.

Following a 4 to 5 week placebo run-in period, qualified study patients were randomized in 1:1 ratio to candesartan 16 mg or losartan 50 mg. After four weeks of randomized treatment, all patients either continued on the same dose or up-titrated according to the criterion described above for an additional 4 weeks. Patients were also seen 2 weeks after they discontinued therapy with the study medication for follow-up visits.

The primary efficacy measure was the mean change in trough sitting DBP from baseline to the double-blind week 8 visit. Secondary measures include sitting systolic pressures and peak blood pressures, standing blood pressures, and proportion of responders and controlled patients based on trough sitting DBP and SBP at week 8. The primary analysis is based on ITT principle and the last value carried forward strategy for incompleters.

The sample size of 330 patients to be enrolled from 45 investigative sites was planned to detect a difference in mean change from baseline in trough sitting DBP of 3.0 mm Hg between the two treatment groups at 2-sided alpha level of 0.05 and power of 95%, assuming a standard deviation of 7.5 mm Hg.

Efficacy results

A total of 332 patients out of 460 patients screened were randomized at 40 sites. 329 patients has at least one post-baseline site contact. These patients constituted the intent-to-treat population. Of these patients, 4.3% patients in the candesartan group and 9.4% patients in the losartan group discontinued treatment during the double-blind portion of the study. The distribution of patients discontinuing treatment by reason was summarized (Table 175-1). The losartan group appeared to have more discontinuations due to lack of response or adverse event.

Table 175-1. Disposition of patients entering trial

	Candesartan	Losartan
Randomized to double-blind	162	170
Discontinued	7 (4.3%)	16 (9.4%)
Lost to follow-up	2 (1.2%)	2 (1.2%)
Lack of response	1 (0.6%)	5 (2.9%)
Adverse event	2 (1.2%)	6 (3.5%)
Consent withdrawal	2 (1.2%)	3 (1.8%)
Completed study	155 (95.7%)	154 (90.6%)

Sponsor's results confirmed by reviewer's analysis

The two treatment groups appeared to be comparable with respect to baseline characteristics (Sponsor's Table 4 of study report for Study 175) and treatment compliance (Sponsor's Table 10.1.1.05,10.1.1.06, 10.1.1.03). The mean age was 55 years and the average duration of hypertension was 9+ years. Fifty eight percent of the patients were male and 12% blacks. The mean sitting DBP/SBP was 100/154 mm Hg.

Treatment differences in BP at last visit

The primary efficacy variable, change from baseline to double-blind week 8 in trough sitting DBP, showed a significantly greater reduction with candesartan (Table 175-2). Other blood pressures showed a numerically trend in favor of candesartan but only the reduction in peak sitting DBP showed a statistically significant treatment difference.

Table 175-2. Least square mean change from baseline to double-blind week 8 (ITT population)

	Candesartan (N=160)	Losartan (N=169)	Difference# (95% CI)	p-value
Trough BP	N=160	N=169		
sitting DBP*	-11.0	-8.9	-2.2 (-3.9, -0.4)	0.016
sitting SBP	-11.9	-10.0	-1.9 (-5.0, 1.3)	0.25
Standing DBP	-9.3	-7.9	-1.3 (-3.2, 0.5)	0.15
Standing SBP	-10.5	-9.4	-1.1 (-4.5, 2.2)	0.51
Peak BP	N=143	N=147		
sitting DBP	-12.6	-9.6	-2.9 (-5.0, -0.9)	0.005
sitting SBP	-16.5	-14.4	-2.0 (-5.4, 1.3)	0.24
Standing DBP	-11.5	-9.4	-2.2 (-4.2, -0.1)	0.038
Standing SBP	-15.2	-13.7	-1.5 (-4.8, 1.8)	0.38

Sponsor's results confirmed by the reviewer's analysis
* primary endpoint #difference: candesartan minus losartan

Blood pressures over time

Blood pressures seemed to trend favorably to candesartan over time (Table 175-3). This pattern was observed in the patients who did not have their doses up titrated and who had (Table 175-4).

Two weeks after the last dose, the mean blood pressures were similar between the two treatment

Table 175-3. Mean trough sitting blood pressures over time

	Trough sitting DBP				Trough sitting SBP			
	Candesartan		Losartan		Candesartan		Losartan	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	160	100.3	169	100.5	160	152.9	169	154.1
DB Wk2	160	91.5	168	93.5	160	142.1	168	146.1
DBWK4	157	90.8	165	92.0	157	141.3	165	144.9
DBWK6	157	88.0	161	90.0	157	139.3	161	141.6
DBWK8	155	89.2	157	90.9	155	140.3	157	143.2
DBWK8 (LOCF)	160	89.3	169	91.5	160	140.7	169	143.9
WK2 FU	158	88.9	165	89.0	158	140.3	165	140.5

Sponsor's results confirmed by the reviewer's analysis

Table 175-4. Mean trough sitting DBP over DB visits

	Not up-titrated group				Up-titrated group			
	Candesartan		Losartan		Candesartan		Losartan	
	N	Mean	N	Mean	N	Mean	N	Mean
Baseline	75	98.4	74	99.1	85	102.1	95	101.6
DB Wk2	75	87.0	73	89.7	85	95.5	95	96.4
DBWK4	72	83.9	70	84.2	85	96.8	95	97.7
DBWK6	73	84.1	66	84.4	84	91.5	95	93.8
DBWK8	71	85.6	64	86.2	84	92.3	93	94.2
DBWK8 (LOCF)	75	85.8	74	87.8	85	92.4	95	94.4

Sponsor's results confirmed by the reviewer's analysis

groups. Standing blood pressures showed a similar pattern (Sponsor's Tables 10.2.4.02, 10.2.4.05). Also, the mean blood pressures in both treatment groups were greatly reduced in the first two weeks and then seemed to stabilize afterwards.

Subgroup results

In this study, candesartan had a favorable trend in gender, race and age subgroups (Table 175-4), except in small subgroups.

Table 175-5. Mean difference (Δ) and 95% CI in BPs by subgroups

	N	Trough sitting DBP	Trough sitting SBP
	C / L	Δ (95% CI)	Δ (95% CI)
Male	90/99	-3.0 (-5.4, -0.6)	-2.6 (-6.0, -1.1)
Female	70/0	-0.9 (-3.2, 1.5)	-1.2 (-7.0, -0.3)
Caucasian	127/131	-2.5 (-4.3, -0.7)	-2.3 (-5.5, 0.9)
Black	18/22	-0.1 (-6.0, 5.9)	1.3 (-8.6, 11.5)
Asian	7/3	3.0 (-2.8, 8.7)	1.5 (-21.8, 18.6)
Other	8/13	2.2 (-4.6, 8.9)	0.2 (-8.8, 12.3)
< 65 yrs old	137/133	-2.6 (-4.4, -0.8)	-1.8 (-5.7, 1.4)
≥ 65 yrs old	23/36	-0.3 (-4.9, 4.2)	-2.6 (-8.7, 4.8)

Reviewer's analysis Δ: candesartan minus losartan C: candesartan L: losartan
Age = (date of randomization – date of birth)/365

3. CONCLUSIONS

Two CLAIM studies showed that the candesartan 16 mg to 32 mg regimen gave a statistically significantly greater reduction in blood pressures than the losartan 50 mg to 100 mg regimen when given via force-titration. The difference was 1 to 2.2 mm Hg in trough sitting DBP and about 3.5 mm Hg in trough sitting SBP. The CANDLE study showed that when given by optional titration, the candesartan regimen also gave a statistically significantly greater reduction in trough sitting diastolic blood pressure. The difference was 2.2 mm Hg in trough sitting DBP. The difference in trough sitting SBP was < 2 mm Hg, not statistically significant. Over the

course of each study, the candesartan group appeared to have lower mean blood pressures than the losartan group. In all the studies, the mean blood pressures in both treatment groups were greatly reduced in the first two weeks and then seemed to stabilize afterwards.