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Memorandum

DATE: 6.20.02

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SUBJECT: Summary of comparative anti-hypertensive trials submitted during initial review of omapatrilat.

DOCUMENTS USED FOR REVIEW: Previous combined Medical/ Statistical review of omapatrilat efficacy, dated 3.29.2000, by Douglas C. Throckmorton, M.D., and John Lawrence, Ph.D.

BACKGROUND

This document is intended to summarize the data on the comparative anti-hypertensive effects of omapatrilat that was submitted as part of the original NDA submission, and is based on the combined Medical/Statistical review conducted by myself and Dr. John Lawrence. It includes the efficacy reviews of trials comparing omapatrilat with other approved antihypertensives, conducted as part of an overall efficacy review, completed 3.29.2000. Several trials previously conducted in resistant populations (*e.g.*, hypertensive on HCTZ, patients with severe HTN) are summarized below as well. This document also includes the original overall summary of antihypertensive efficacy, which references other antihypertensive trials not included here as they do not address the relative antihypertensive efficacy of omapatrilat. This accounts for the differences in the numeration in the individual trial headings.

Overall, there were 6 trials in the original submission that compared omapatrilat to active drugs:

Comparison with Amlodipine

CV137-006

CV137-030

CV137-032

Comparison with Lisinopril

CV137-022

CV137-031

CV137-037

389732 - 05 - FDA - ANTI-HYPERTENSIVE

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a. A detailed table of contents appears at the start of each of the individual trials reviews.

0.0 Primary Medical Efficacy Summary (from original NDA submission)

Omapatrilat is a combined Angiotensin Converting-Enzyme (ACE) and Neutral Endopeptidase (NEP) inhibitor. In the NDA there were four long-term dose-ranging trials, and a total of 18 clinical trials that examined the anti-hypertensive efficacy of omapatrilat. Omapatrilat doses between 5 and 120 mg significantly lowered trough seated diastolic blood pressure (SeDBP), seated systolic blood pressure (SeSBP), seated pulse pressure (SePP) as well as other markers of anti-hypertensive efficacy. Omapatrilat doses between 60 and 120 mg had similar effects on placebo-subtracted trough SeDBP (-8.0 to -9.0 mmHg), SeSBP (-13.5 to -15.0 mmHg) and SePP (-6.0 to -6.5 mmHg).

Omapatrilat worked equally well in subjects grouped according to gender, and age. Omapatrilat was an effective anti-hypertensive in black subjects, although comparing the data from one trial that enrolled only black subjects (CV137-037) with three other trials that enrolled largely white subjects suggest that omapatrilat may work less well in black subjects. Omapatrilat was also effective in lowering blood pressure in several other groups of patients in single trials, including those with severe hypertension and those with isolated systolic hypertension.

Omapatrilat was effective at lowering blood pressures to pre-specified limits (*e.g.*, diastolic BP <90 mmHg) in 50-70% of the randomized subjects.

The duration of the anti-hypertensive effect of omapatrilat was examined in three ways. The trough:peak ratio for the changes in SeDBP averaged approximately 0.7. This ratio that is similar to agents that are currently approved for once a day use. In study CV137-036, the use of omapatrilat 10 BID caused a significantly greater reduction in trough SeDBP and SeSBP when compared with 20 mg once per day. This suggests that twice a day dosing may be superior to once a day dosing. Finally, in two studies examining 24-hour changes in blood pressure using ABPM, there was a significant rise (approximately 20-25 mmHg) in the average diastolic BP between hours 18 and 24 after last dose of omapatrilat. The curve of the average blood pressure over 24 hours for omapatrilat resembled that of lisinopril and amlodipine, two compounds approved for once per day dosing.

At the doses studied, omapatrilat has no significant effect on heart rate. There is no evidence for rebound hypertension following omapatrilat discontinuation, as assessed by changes in mean blood pressures and reported adverse events after drug discontinuation.

The anti-hypertensive efficacy omapatrilat was compared with lisinopril and amlodipine in several studies.

Lisinopril

Compared with lisinopril(40 mg), omapatrilat(80 mg) had a significantly greater effect on ABPM parameters of blood pressure control in one study (CV137-031). The difference in the 14-hour mean Ambulatory Diastolic BP (ADBP) between lisinopril and omapatrilat was -2.9 mmHg ($p<0.001$).

Significantly greater effects of omapatrilat on trough SeDBP (measured using BP cuff) were demonstrated in two trials (CV137-031, CV137-037). Study CV137-037 enrolled only black subjects. The difference between omapatrilat and lisinopril in these two studies was -2.1 ($p=0.013$) and -2.5 mmHg ($p<0.001$) respectively.

Amlodipine

Compared with amlodipine(10 mg), omapatrilat(80 mg) had a significantly greater effect on ABPM parameters of blood pressure control in one study (CV137-032). The difference in the 14-hour mean Ambulatory Diastolic BP (ADBP) between lisinopril and omapatrilat was -4.4 mmHg ($p<0.001$).

Significantly greater effects of omapatrilat on trough SeDBP (measured using BP cuff) were demonstrated in one trial (CV137-030), where the difference between amlodipine and omapatrilat was -2.1 mmHg, $p=0.002$. Measurement of trough SeDBP in CV137-032 failed to detect a significant difference between omapatrilat and amlodipine (-0.3 mmHg, $p=0.617$).

In conclusion, omapatrilat has a dose-dependent anti-hypertensive effect at doses ranging between 5 and 120 mg daily with a plateau of effect between 60 and 120 mg per day. Whether or not the data support a superior anti-hypertensive efficacy for omapatrilat when compared with either lisinopril or amlodipine when the change in trough SeDBP is used as the primary metric depends on the number of trials necessary to support such a claim and the metrics to be used in the comparison.

1.0 to 1.9 Summary Data on Omapatrilat Anti-Hypertensive Efficacy

This summary of the anti-hypertensive efficacy of omapatrilat is from the data obtained from the trials shown in the table below, which form the data used to formulate the resume above. Those trials attached as Appendices to this document are shaded. The remainder of the studies were reviewed by Dr. Norman Stockbridge, and the reader is referred to his review document for details.

Table 1.0.1 Overview of omapatrilat clinical development program^a.

Study #	Population	Control	Key Purposes
CV137-005 ^a	Mild/moderate hypertension	Placebo	Dose-finding/ABPM through 2 weeks
CV137-006	Mild/moderate hypertension	Placebo/amlodipine	Dose-ranging
CV137-022	Mild/moderate hypertension	Placebo/lisinopril	Dose-ranging
CV137-024	Mild/moderate hypertension	Placebo	Dose-ranging
CV137-029	Elderly (age ≥65 years)	Placebo	Special Population
CV137-030	Mild/moderate hypertension	Placebo/amlodipine	Comparative efficacy
CV137-031	Mild/moderate hypertension	Lisinopril	Comparative efficacy/ABPM
CV137-032	Mild/moderate hypertension	Amlodipine	Comparative efficacy/ABPM
CV137-036	Mild/moderate hypertension	Placebo	ABPM, once vs. twice daily evaluation
CV137-037	African-American	Placebo/lisinopril	Comparative efficacy and special population
CV137-038	Mild/moderate hypertension		
CV137-038	Left ventricular hypertrophy	Losartan	Special population
CV137-039	Renal insufficiency	None	Special population
CV137-040	HCTZ-resistant	Placebo	Special population/ use with HCTZ
CV137-042	Isolated systolic hypertension	Placebo	Special population
CV137-045	Mild/moderate hypertension	Placebo	Dose-ranging
CV137-049	Severe hypertension	Enalapril	Special population/ use with Amlodipine/HCTZ
CV137-054	Mild/moderate hypertension	Placebo	Elective-titration
CV137-009	Mild/moderate hypertension	None	Long-term effects/ use with Amlodipine/HCTZ/Atenolol

a. Trials not shaded were reviewed by Dr. Norman Stockbridge.

1.1 Effects on Placebo-Subtracted Trough Seated Diastolic Blood Pressure (SeDBP)

The first section of this review will focus on the anti-hypertensive effect of omapatrilat as measured by changes in placebo-subtracted trough SeDBP. Initially, the data from the effects of omapatrilat in the overall population using blood pressure measured using blood-pressure cuffs and mercury sphygmomanometers in physician's offices will be presented, followed by the blood pressure data obtained using Ambulatory Blood Pressure Monitoring (ABPM). Following this, changes reported in various relevant sub-populations will be summarized. Finally, the other aspects of the anti-hypertensive effect of omapatrilat will be summarized: time-course of effect, rebound hypertension, therapeutic response, and duration of anti-hypertensive effect.

The first table summarizes the effect of omapatrilat on placebo-subtracted, trough, SeDBP from placebo-controlled trials enrolling patients with mild-to-moderate hypertension lasting more than 2 weeks. The 95% confidence intervals associated with each of these points can be found in the NDA appendices.

Table 1.1.1 Placebo-subtracted, trough SeDBP in NDA 21-188^a.

Omapatrilat Dose (mg)	CV137-006 8 wks ^b	CV137-022 ^a 9 wks	CV137-024 ^a 9 wks	CV137-030 ^a 10 wks	CV137-045 ^a 6 wks
2.5	-2.3				
5	-3.3	-5.6			
10	-3.2	-5.3			
20		-6.5	-4.8		
40		-7.6	-6.7		
60			-8.0		
10/80 ^c			-10.0		
20/80 ^c			-7.8	-9.9	-10.0
40/80 ^c			-8.3		
20/120 ^c					-10.4

a. Data from individual study reviews.

b. Shown below the trial number is the duration of exposure to study drug when the measurement was obtained.

c. Numbers refer to the initial dose of omapatrilat as well as the final dose, following a forced-titration schedule.

1.2 Effects of Omapatrilat Effects on SeDBP in SubGroups

In the long-term trials, the effect of omapatrilat on SeDBP was examined in three specific sub-groups: Gender, Race, and Age. In addition, several smaller studies were performed that examined the effects of omapatrilat in other sub-groups of interest, such as subjects with isolated systolic hypertension and those with uncontrolled hypertension on diuretics. These results are summarized in the following section.

Gender

As shown in the demographics section below, between 33 and 56% of the subjects enrolled in the efficacy trials were women. Overall, no effect of gender on the anti-hypertensive efficacy of omapatrilat was discerned. The table below summarizes the effect of omapatrilat on SeDBP from three of the larger dose-ranging trials.

Table 1.2.1 Mean changes in SeDBP by Gender in NDA 21-288^a.

Omapatrilat Dose (mg)	CV137-022 9 Weeks		CV137-024 9 Weeks		CV137-030 10 Weeks	
	Males	Females	Males	Females	Males	Females
Placebo	-3.2 (n=74)	-4.0 (n=34)	-5.4 (n=70)	-5.5 (n=27)	-4.2 (n=58)	-4.5 (n=46)
5	-8.1 (n=63)	-10.8 (n=38)				
10	-8.7 (n=66)	-8.9 (n=37)				
20	-9.4 (n=82)	-11.7 (n=34)	-10.4 (n=77)	-10.1 (n=32)		
40	-10.3 (n=78)	-13.0 (n=32)	-11.8 (n=66)	-12.8 (n=36)		
60			-13.6 (n=71)	-13.3 (n=34)		
10/80			-14.7 (n=76)	-16.9 (n=29)		
20/80			-13.3 (n=62)	-13.6 (n=41)	-14.0 (n=139)	-15.0 (n=102)
40/80			-13.2 (n=49)	-15.0 (n=34)		

a. Data from individual study reports, shown for mean change from baseline for SeDBP, based on Randomized Subjects.

Race

In general, fewer than 15 'Non-white/Other' and 'Black' subjects were enrolled in each treatment group in the efficacy trials. This limits the conclusions about the anti-hypertensive effects of omapatrilat in such a small group, although the trend towards an anti-hypertensive effect of omapatrilat was evident in most trials. Some examples from the large efficacy trials are found below. Note the large placebo effect recorded in the Non-White subjects in CV137-024.

Table 1.2.2 Mean changes in SeDBP by Race in NDA 21-288^a.

Omapatrilat Dose (mg)	CV137-022 9 Weeks			CV137-024 9 Weeks		
	White	Black	Non-White	White	Black	Non-White
Placebo	-4.0 (n=83)	-2.8 (n=12)	-1.2 (n=13)	-4.5 (n=81)	-4.9 (n=5)	-11.9 (n=11)
5	-9.1 (n=76)	-10.6 (n=13)	-7.7 (n=12)			
10	-8.5 (n=82)	-9.9 (n=11)	-9.7 (n=10)			
20	-10.8 (n=91)	-6.5 (n=13)	-8.3 (n=12)	-10.3 (n=93)	-11.2 (n=7)	-9.2 (n=9)
40	-10.9 (n=89)	-11.4 (n=13)	-12.9 (n=8)	-12.2 (n=81)	-13.3 (n=9)	-11.2 (n=12)
60				-13.4 (n=86)	-15.3 (n=7)	-13.2 (n=12)
10/80				-15.7 (n=92)	-14.1 (n=8)	-8.5 (n=4)
20/80				-14.1 (n=74)	-11.9 (n=20)	-10.6 (n=9)
40/80				-14.2 (n=68)	-13.0 (n=9)	-12.4 (n=6)

a. Data from individual study reports, shown for mean change from baseline for SeDBP, based on Randomized Subjects.

The CV137-037 trial, however, enrolled only black subjects, and in that trial the anti-hypertensive effect of omapatrilat was clear.

Table 1.2.3 Summary of primary efficacy variable and other trough BP changes at 10 weeks in CV137-037^a.

Efficacy Variable	Placebo N = 108	Omapatrilat 20/40/80 mg N = 224
Trough SeDBP, mmHg Adjusted Mean Change (se)	-4.5 (0.8)	-10.0 (0.6) ^b
Trough SeSBP, mmHg Adjusted Mean Change (se)	-4.9 (1.3)	-14.2 (0.9)
Trough Pulse Pressure, mmHg Adjusted Mean Change (se)	-0.4 (1.0)	-4.3 (0.7)

a. Data from NDA vol. 2.331, study report summary. Adjusted mean change is relative to baseline.
b. p-Values per sponsor for omapatrilat vs. placebo <0.001.

However, the degree of placebo-subtracted trough SeDBP reduction in the omapatrilat group for the blacks in the CV137-037 study was less than was seen in the three other trials that enrolled a largely white population (5.5 mmHg in CV137-037, compared with 8-10 mmHg in the other three trials). The demographics of these four studies were not significantly different apart from the racial makeup of the enrolled subjects.

Table 1.2.4 Placebo-subtracted, trough SeDBP (with 95% C.I.) in NDA 21-188^a.

Omapatrilat Dose (mg)	CV137-024 9 wks	CV137-030 10 wks	CV137-037 ^c 10 wks	CV137-045 6 wks
20/80	-7.8 (-10.5, -5.2)	-9.9 (-11.6, -8.2)	-5.5 (-7.4, -3.5)	-10.0 (-12.5, -7.6)

a. Data from individual study reports.
c. Enrolled only black subjects.

Age (<65, ≥65 Years)

The effect of omapatrilat on SeDBP was also examined in the subjects grouped by age. The anti-hypertensive effect of omapatrilat was evident in the subjects < and ≥65 years of age.

Table 1.2.5 Mean changes in SeDBP by Age in NDA 21-288^a.

Omapatrilat Dose (mg)	CV137-022 9 Weeks		CV137-024 9 Weeks		CV137-045 6 Weeks	
	<65	≥65	<65	≥65	<65	≥65
Placebo	-3.3 (n=80)	-4.1 (n=28)	-5.4 (n=78)	-5.2 (n=19)	-2.4 (n=48)	-9.1 (n=10)
2.5						
5	-9.1 (n=83)	-9.1 (n=18)				
10	-8.6 (n=82)	-9.4 (n=21)				
20	-10.3 (n=90)	-9.2 (n=26)	-10.5 (n=88)	-9.2 (n=21)		
40	-11.2 (n=84)	-10.6 (n=26)	-12.3 (n=87)	-11.2 (n=15)		
60			-13.3 (n=86)	-14.5 (n=19)		
10/80			-15.0 (n=83)	-16.6 (n=21)		
20/80			-13.3 (n=89)	-13.7 (n=14)		
40/80					-13.5 (n=55)	-14.3 (n=7)
20/120					-13.9 (n=110)	-14.8 (n=10)

a. Data from individual study reports.

Study CV137-029

This study enrolled elderly subjects (≥ 65 years old) with mild-to-moderate HTN. The effects on placebo-subtracted SeDBP, from Dr. Stockbridge's review, are summarized below.

Table 1.2.6 Mean changes in SeDBP and SeSBP from CV137-029^a.

Omapatrilat Dose (mg)	CV137-029 9 Weeks	
	SeDBP ^b	SeSBP
10	-2.9	-5.2
20	-4.4	-10.7
40	-4.8	-13.0

a. Data from draft study report from Dr. Stockbridge, where the reader is referred for details.

b. Baseline- and placebo-subtracted trough effects at week 9.

Renal Insufficiency: CV137-039

The effect of omapatrilat in patients with an estimated GFR of < 60 ml/min was examined in an open-label, uncontrolled comparison of omapatrilat (at doses up to 80 mg). While the design of the trial precluded determination of true treatment size, Dr. Stockbridge concluded that 'the magnitude of the treatment effect (mean change from baseline through 16 weeks of 27/15 mmHg) was large enough that there was probably a true drug effect in this population.'

Hypertension on HCTZ (CV137-040)

The effect of omapatrilat in patients with hypertension despite treatment with HCTZ 25 mg (SeDBP 93-110 mmHg) was examined in one double-blind study comparing two doses of omapatrilat (20 and 40) to placebo. At the end of 8 weeks, mean change in the placebo-subtracted trough SeDBP was -4.4 and -5.4 mmHg for the 20 and 40 mg treatment groups respectively, results that were statistically significant.

Isolated Systolic Hypertension (CV137-042)

The effect of omapatrilat in patients with SeDBP < 90 mmHg and SeSBP 160-179 mmHg was examined in one double blind trial comparing three doses of omapatrilat (10, 20 and 40 mg) to placebo. At the end of week 9, mean change in the placebo-subtracted trough SeDBP was -1.3, -2.1 and -4.2 mmHg for the 10, 20, and 40 mg doses respectively. The changes for the 20 and 40 mg doses achieved statistical significance. The reductions in SeDBP and SeSBP are summarized below.

Table 1.2.7 Mean changes in SeDBP and SeSBP from CV137-042^a.

Omapatrilat Dose (mg)	CV137-022 9 Weeks	
	SeDBP	SeSBP
10	1.3	-1.7
20	-2.1	-8.8
40	-4.1	-11.8

a. Data from review by Norman Stockbridge, based on complete population.

Severe Hypertension: CV137-049

The effect of omapatrilat in subjects with severe hypertension (SeDBP 115-130 mmHg at the end of a one-week wash-out phase) was examined in one trial comparing omapatrilat (20-80 mgs) to enalapril (10-20 mg). Patients were also treated with amlodipine and HCTZ as needed for BP control. At the end of week 10, the change from baseline for SeDBP was similar in the two groups (-26 for omapatrilat and -29 mmHg for enalapril).

Elective Titration: CV137-054

The primary efficacy trials all utilized a forced-titration strategy for dose-escalation. The effect of omapatrilat used in an elective titration scheme was examined in one double-blind trial comparing two doses of omapatrilat (10 or 20 mg) to placebo. At the end of two weeks, subjects who had SeDBP > 90 mmHg had their medications increased again to 40 and then to 80 mg. The results at the end of week 8 are shown below.

Table 1.2.8 Mean changes in SeDBP and SeSBP from CV137-054^a.

Omapatrilat Dose (mg)	CV137-022 8 Weeks	
	SeDBP	SeSBP
10	10 mg	10 mg
	-7.0	-12.6
20	-8.0	-13.5

a. Data from review by Norman Stockbridge, based on complete population.

1.3 Other Measures of Anti-Hypertensive Efficacy (SeDBP)

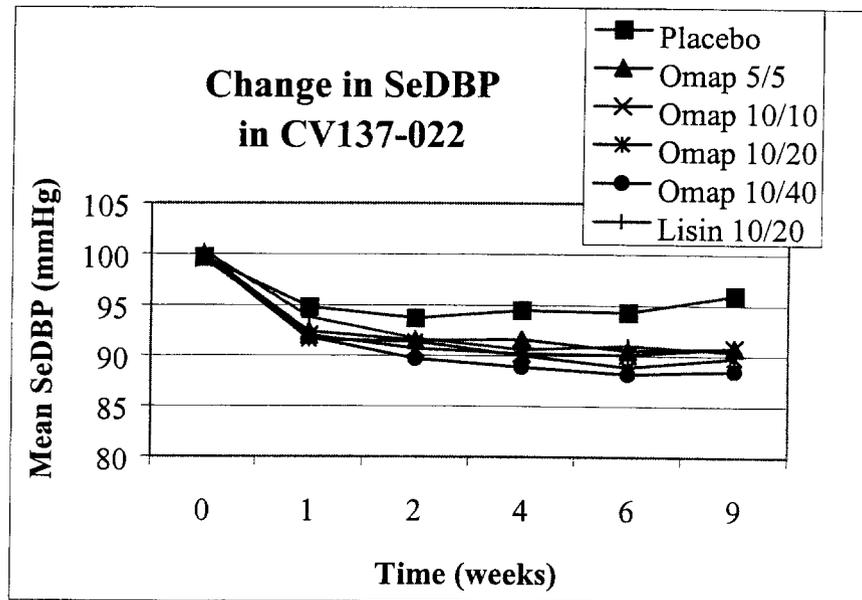
1.3a Time-Course of Anti-Hypertensive Effect

The reader is referred to the pharmacokinetics review for a description of the effects of omapatrilat on BP found in the first hours after drug administration.

In the efficacy trials summarized in this document, anti-hypertensive effect of omapatrilat was noted within one week after starting the drug, as seen from study CV137-022 below. In general, almost the entire effect of omapatrilat on SeDBP was seen by the end of week 2.

CV137-022

This study compared the anti-hypertensive efficacy of omapatrilat and lisinopril. The time-course for the anti-hypertensive effects of omapatrilat and lisinopril are summarized in the graph below. Trough SeDBP decreased relative to baseline by the end of the first week of therapy in all of the omapatrilat treatment groups, with almost all of the treatment effect seen by the end of the second week of therapy.



1.3b Duration of Anti-Hypertensive Effect

The duration of the anti-hypertensive effect of omapatrilat was examined in three ways in the efficacy trials. First, the trough:peak ratio was calculated from several of the trials. Second, study CV137-036 compared the effects of once- vs. twice-daily administration of omapatrilat. Finally, the 24-hour mean data from the ABPM trials were examined for evidence of a waning of anti-hypertensive activity at trough.

Trough:Peak Ratio

The table below summarizes the Trough:Peak ratios derived using the available subjects with both trough and peak data in the efficacy trials. The Trough:Peak ratio for lisinopril and amlodipine are shown for comparison from two trials where data were collected.

Table 1.3b.1 Trough:Peak from SeDBP in long-term placebo-controlled trials^a.

	CV137-006 8 wks	CV137-022 ^a 9 wks	CV137-024 ^a 9 wks	CV137-030 ^a 10 wks
Omapatrilat Dose (mg)				
2.5	0.85			
5	0.71	0.69		
10	0.62	0.69		
20		0.75	0.64	
40		0.70	0.63	
60			0.68	
10/80			0.72	
20/80			0.72	0.80
40/80			0.78	
Amlodipine 10				0.90
Lisinopril 20		0.74		

a. Data from individual study reviews. Trough:peak ratio calculated using SeDBP data.

CV137-036

This study compared the anti-hypertensive efficacy of omapatrilat in three groups (10 mg qd, 10 mg BID, and 20 mg qd) to placebo subjects with mild-to-moderate hypertension. The first table summarizes the placebo-subtracted mean changes in systolic and diastolic BP, obtained using ABPM. Note that the reduction in both diastolic and systolic BP was greatest in the 10 BID dose group.

Table 1.3b.2 Placebo-subtracted changes in mean BP at trough in CV137-036^a.

ABPM	Omapatrilat		
	10 mg qD	20 mg qD	10 mg BID
Diastolic (mmHg)	-7.6	-7.2	-11.7
Systolic (mmHg)	-12.4	-12.1	-18.0

a. Data from study review by Norman Stockbridge.

The next table summarizes the blood pressure derived from cuff-BP measurements.

Table 1.3b.3 Placebo-subtracted changes in mean BP at trough in CV137-036^a.

Cuff	Omapatrilat		
	10 mg qD	20 mg qD	10 mg BID
SeDBP	-6.1	-5.9	-10.6
SeSBP	-8.0	-6.3	-14.2
PP (SeSBP-SeDBP)	-1.9	-0.4	-3.6

a. Data from study review by Norman Stockbridge.

ABPM

In CV137-031 and CV137-032, plots of the 24-hour BP data (average diastolic or systolic) revealed a trend towards a decline in anti-hypertensive effect at trough levels of omapatrilat, as well as both of the comparator drugs (amlodipine and lisinopril). Graphs of representative data from these studies can be found in section 0.3b below (Comparative Anti-Hypertensive Efficacy Using Ambulatory Blood Pressure Measurements). Both amlodipine and lisinopril are labeled as once-daily medications, although the lisinopril label states... 'The antihypertensive effect may diminish toward the end of the dosing interval regardless of the administered dose, but most commonly with the 10 mg daily.'

1.3c Effect on Trough Seated SBP and Pulse Pressure

The first table below summarizes the effect of omapatrilat on placebo-subtracted SeSBP. This same table, with the associated 95% confidence intervals, can be found in NDA appendices.

Table 1.3c.1 Change in placebo-subtracted SeSBP (95% C.I.) in long-term placebo-controlled trials.

Omapatrilat Dose (mg)	CV137-006 8 wks	CV137-022 ^a 9 wks	CV137-024 ^a 9 wks	CV137-030 ^a 10 wks	CV137-045 ^a 6 wks
2.5	-6.4				
5	-5.6	-8.3			
10	-7.8	-7.7			
20		-11.5	-8.6		
40		-13.2	-13.5		
60			-13.7		
10/80			-17.9		
20/80			-13.6	-17.8	-15.1
40/80			-14.6		
20/120					-18.2

a. Dose shown is the starting and the final dose used after forced dose-titration. Subjects unable to tolerate the forced-titration were discontinued. Shown as mean placebo-subtracted SeSBP (95% C.I.).

Next, the effect of omapatrilat on Pulse Pressure (PP), derived by subtracting the mean change in SeDBP from the change in SeSBP, is summarized for the same trials.

Table 1.3c.2 Omapatrilat effect on SePP from NDA 21-188^{a, b}.

Omapatrilat Dose (mg)	CV137-006 8 wks	CV137-022 ^a 9 wks	CV137-024 ^a 9 wks	CV137-030 ^a 10 wks	CV137-045 ^a 6 wks
2.5	-4.4				
5	-2.3	-2.7			
10	-4.6	-2.4			
20		-5.0	-3.8		
40		-5.6	-6.8		
60			-5.7		
10/80			-7.9		
20/80			-5.8	-8.2	-5.1
40/80			-6.3		
20/120					-7.7

a. Data from individual studies. Dose shown is the starting and the final dose used after forced dose-titration. Subjects unable to tolerate the forced-titration were discontinued. Shown as mean placebo-subtracted PP.

b. Mean trough placebo-subtracted SeSBP minus SeDBP.

These data, along with the data for the change in SeDBP, are presented graphically below.

1.3d Effects on Supine, Standing, and Peak Blood Pressures

The effects of omapatrilat on supine, standing and peak blood pressure parameters were examined in all of the trials that collected information on the seated BP parameters (summarized above). No substantial differences between the trends summarized above for the SeDBP and SeSBP were apparent. The reader is referred to the individual trials for details. The blood pressure reductions at peak were appreciably larger than those at trough, as shown for the two large dose-ranging trials below. The first table shows the peak SeDBP and SeSBP from CV137-022 (compare with the summary tables of trough BP above).

Table 1.3d.1 Effect of omapatrilat and lisinopril on peak seated DBP (SeDBP) and peak seated SBP (SeSBP) at the end of week 9 in CV137-022^a.

Efficacy Variable	Placebo N=101	Omap 5/5 mg N=95	Omap 10/10 mg N=97	Omap 10/20 mg N=106	Omap 10/40 mg N=101
Peak SeDBP mmHg Change from Placebo	--	-8.0	-8.3	-8.5	-10.6
Peak SeSBP mmHg Change from Placebo	--	-14.3	-14.9	-16.9	-20.8

a. Data from NDA vol. 2.296, table S.10.1.3A. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

The next table shows the same data from CV137-024.

Table 1.3d.2 Treatment comparisons of change from baseline in peak measures for SeSBP and SeDBP for 'evaluable' subjects in CV137-024^a.

Efficacy Variable	Placebo N=89	10/20 mg Omap N=98	20/40 mg Omap N=95	30/60 mg Omap N=98	10/80 mg Omap N=96	20/80 mg Omap N=92	40/80 mg Omap N=73
Peak SeDBP mmHg Difference from Placebo	--	-8.0	-9.9	-11.9	-13.8	-10.5	-9.7
Peak SeSBP mmHg Difference from Placebo	--	-13.8	-18.3	-19.8	-23.4	-20.8	-18.4

a. Data from NDA vol. 2.304, table S.10.1.3A. Evaluable patients had valid peak and trough data available.

1.3e Rebound Hypertension

The effect of withdrawal of omapatrilat on BP was examined primarily in two placebo-controlled trials (CV137-006, CV137-022) where 801 patients who received relatively low doses of omapatrilat (2.5 to 40 mg per day) were followed for 7 days after drug withdrawal. After discontinuation of omapatrilat, blood pressure rose towards but did not return to pre-treatment levels within one weeks. Rebound increases in mean blood pressure to above baseline were not observed among the population as a whole. Similarly, no adverse events related to rebound hypertension were reported by the investigators.

1.3f Therapeutic Response

Therapeutic Response, defined by the sponsor to be the percentage of subjects who stayed on study drug and achieved a pre-specified level of blood pressure lowering (either DBP or the combination of SBP and DBP) was examined in all of the placebo-controlled trials in the database. The table below summarizes the results for the 'Therapeutic Response' defined as an improvement in DBP for the larger placebo-controlled trials. Note the smaller percentage of 'responders' at the 80-mg dose in CV137-037, which enrolled only black subjects.

Table 1.3f.1 'Therapeutic Response' based on decreases in DBP in NDA 21-188^{a,b}.

Omapatrilat Dose (mg) ^c	CV137-022 ^a 9 wks	CV137-024 9 wks	CV137-030 10 wks	CV137-037 10 wks	CV137-045 6 wks
Placebo	18%	27%	24%	22%	14%
5	50%				
10	45%				
20	53%	53%			
40	53%	65%			
60		64%			
10/80		78%			
20/80		61%	67%	42%	68%
40/80		67%			
20/120					73%

a. Data from individual study reviews.

b. Numbers shown as percentage of randomized subjects with normalized DBP at time of measurement (SeDBP <90 mmHg). See individual trials for details.

c. Refers to the initial and final doses administered to the patient under forced-titration trial design.

1.3g Ambulatory Measures of Anti-Hypertensive Efficacy

The anti-hypertensive effects of omapatrilat were measured using ABPM in two large studies. Neither study was submitted to the IND, and both trials found a significant anti-hypertensive effects of omapatrilat.

CV137-031

This study compared the anti-hypertensive efficacy of omapatrilat and lisinopril using the change from baseline to 10 weeks 24hr-average ambulatory systolic blood pressure (ASBP) as the primary efficacy analysis. The table below summarizes the effects of omapatrilat on ABPM parameters in the study after 10 weeks on drug. The comparison with lisinopril will be performed in a later section.

Table 1.3g.1 Efficacy analyses from CV137-031 at 10 weeks^a.

Efficacy Variable	Omapatrilat 20/40/80 n=160
24-hour ASBP, mm Hg Adjusted Mean Change (se)	-19.0 (0.9)
24-hour ADBP, mm Hg Adjusted Mean Change (se)	-10.5 (0.5)
24-hour APP^b Adjusted Mean Change (se)	-8.5 (0.5)
24-hour AMBP^b Adjusted Mean Change (se)	-13.3 (0.6)

a. Data from NDA vol. 2.392, table 10.1.1.

b. APP = ambulatory pulse pressure. AMBP = ambulatory mean blood pressure.

CV137-032

This study compared the anti-hypertensive efficacy of omapatrilat and amlodipine using the change from baseline to 10 weeks 24hr-average ambulatory mean blood pressure (AMBP) as the primary efficacy analysis. The table below summarizes the effects of omapatrilat on ABPM parameters in the study after 10 weeks on drug. The comparison with lisinopril will be performed in a later section.

Table 1.3g.2 Changes in ABPM parameters at week 10 in CV137-032^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 192
24hr-average AMBP, mmHg^b Adjusted Mean Change (se)	-15.9 (0.5)
24hr-average ASBP, mmHg Adjusted Mean Change (se)	-20.4 (0.6)
24hr-average ADBP, mmHg Adjusted Mean Change (se)	-13.6 (0.4)
24hr-average APP, mmHg Adjusted Mean Change (se)	-6.7 (0.4)

a. Data from NDA vol. 2.385 table 10.1.1.

b. Pre-specified primary efficacy parameter.

1.4 Other Physiologic/ Pharmacodynamic Effects of Omapatrilat

The next section will deal with effects of omapatrilat other than its anti-hypertensive effects.

1.4a Changes in Heart Rate

In the efficacy trials summarized above, no significant effect of omapatrilat on heart rate was detected, when compared with placebo. See individual study summaries for details.

1.4b Changes in Urinary ANP Levels

ANP excretion was measured as a marker for the inhibition of Neutral Endopeptidase (NEP).

Study CV137-030

In this study, omapatrilat use was associated with an increase in ANP excretion relative to placebo, while no significant change was detected in the amlodipine group. Note the broad standard deviations.

Table 1.4b.1 Peak and Trough changes in urinary ANP excretion in CV137-030^a.

Urinary ANP, pg/mg Crt	Placebo	Omapatrilat 20/40/80 mg	Amlodipine 5/10/10 mg
Trough (Week 10)	N = 31	N = 92	N = 91
Mean Change (sd)	0.0 (4.7)	7.4 (17)	0.3 (7.4)
Peak (Week 8)	N = 32	N = 91	N = 93
Mean Change (sd)	1.1 (7.1)	41.4 (29)	-0.2 (4.3)

a. Data from NDA vol. 2.331, table 11.2.1.

CV137-054

Urinary ANP levels, along with several other hormone levels, were assessed in patients randomized to receive one of two doses of omapatrilat (10 or 20 mg) compared with placebo. These results, illustrating an increase in urinary ANP at week 8, are summarized below.

Table 1.4b.2 Pharmacodynamic data in CV137-054^a.

Change from Baseline to Week 8	Placebo	Omapatrilat	
		10 mg	20 mg
Urinary ANP (pg/mg Crt)	1	54	63
Plasma ANP 2 hrs post-dose	9	24	21
Plasma ANP trough	13	-3	1
Plasma ACE activity	0.2	-5.2	-4.6
Plasma renin activity	0.1	5.1	4.8
Plasma catecholamines	32	44	53

a. Data from review by Norman Stockbridge.

1.4c Changes in Serum Endothelin Levels

Study CV137-037

The sponsor measured endothelin levels at baseline and again at 10 weeks, and the changes in mean endothelin levels are summarized below. Treatment with omapatrilat was associated with a 0.12 pmol/liter decrease from baseline (approximately 9% decrease from baseline). Note the broad standard deviations for each mean value and the differences in the baseline means for the three treatment groups.

Table 1.4c.1 Plasma endothelin levels (pmol/L) at baseline and week 10 in CV137-037^a.

Endothelin Levels	Placebo N = 17	Omapatrilat 20/40/80 mg N = 28	Lisinopril 10/20/40 mg N = 28
Baseline Mean (sd)	0.78 (0.96)	1.08 (1.12)	1.02 (1.60)
Week 10			
Mean on Treatment (sd)	0.83 (0.86)	0.96 (1.06)	0.99 (1.18)
Mean Change (sd)	0.05 (0.28)	-0.12 (0.30)	-0.04 (0.75)

a. Data from NDA vol. 2.332, table S.11.

1.5 Comparative Anti-Hypertensive Efficacy (vs. Lisinopril and Amlodipine)

The final section in the Integrated Summary of Efficacy will focus on the trials comparing omapatrilat anti-hypertensive efficacy with other anti-hypertensives (amlodipine and lisinopril). As in the first section, two types of blood pressure data were obtained (cuff and ABPM), and these will be summarized in turn.

1.5a.1 Comparative Anti-Hypertensive Efficacy (vs. Lisinopril and Amlodipine) Using Cuff BP Measures

Two types of trials were submitted to the NDA in support of superior efficacy for omapatrilat relative to two active comparators:

1) two trials (CV137-031, CV137-032) that used ABPM measurements as primary efficacy markers. These also measured changes in cuff BP. Neither trial was conducted under the IND.

2) four trials (CV137-006, CV137-022, CV137-030, CV137-037) following cuff measurements of BP, comparing the anti-hypertensive effects of omapatrilat to both an active comparator and placebo. All four were conducted under the IND.

These trials are summarized in the following section.

**1.5a.1 Non-IND Trials Comparing Omapatrilat With Active Controls (Cuff BP Measurements)
CV137-031**

This trial compared omapatrilat with amlodipine or lisinopril using ABPM measurements as the primary efficacy analyses, but also collected cuff BP measurements. The cuff BP results are summarized below. At 10 weeks the difference between omapatrilat (force-titrated to 80 mg) and lisinopril (force-titrated to 40 mg) on placebo-subtracted SeDBP was -2.1 mmHg, a value which achieved nominal statistical significance.

Table 1.5a.1.1 Mean changes in trough SeSBP and SeDBP at 10 weeks in CV137-031^a.

Efficacy Variable	Omapatrilat 20/40/80 N=166	Lisinopril 10/20/40 N=168
Trough SeDBP, mmHg		
Adjusted Mean Change (se)	-12.1 (0.6)	-10.1 (0.6)
Difference from Lisinopril (95% CI)	-2.1 (-3.7, -0.4)	--
p-Value ^a	0.013	--
Trough SeSBP, mmHg		
Adjusted Mean Change (se)	-23.5 (1.0)	-19.2 (1.0)
Difference from Lisinopril (95% CI)	-4.3 (-7.2, -1.4)	--
p-Value c/w Lisinopril ^a	0.004	
Trough PP^b		
Adjusted Mean Change (se)	-11.6 (0.8)	-8.9 (0.8)
Difference from Lisinopril (95% CI)	-2.7 (-5.0, -0.5)	--
p-Value c/w Lisinopril ^a	0.019	

a. Data from NDA vol. 2.392, table 10.2.1. p-Value using ANCOVA per sponsor, unadjusted for multiple comparisons.

b. PP = pulse pressure.

CV137-032

This trial compared omapatrilat with amlodipine or lisinopril using ABPM measurements as the primary efficacy analyses, but also collected BP measurements. The cuff BP results are summarized below. The difference between omapatrilat (force-titrated to 80 mg) and amlodipine (force-titrated to 10 mg) at 10 weeks was -0.3 mmHg which was not statistically significant.

Changes in blood pressure as measured using blood-pressure cuffs in the office were also analyzed, and the results are summarized below. No significant difference in the SeDBP was demonstrated between the two treatment groups.

Table 1.5a.1.2 Mean changes in trough seated BPs at week 10 in CV137-032^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 194	Amlodipine 5/10/10 mg N = 194
Trough SeDBP, mmHg		
Adjusted Mean Change	-13.5	-13.1
Difference from Amlodipine	-0.3	--
p-Value	0.617	--
Trough SeSBP, mmHg		
Baseline Mean	157.0	156.3
Adjusted Mean Change	-20.4	-17.5
Difference from Amlodipine	-2.9	--
p-Value	0.014	--
Trough PP, mmHg		
Adjusted Mean Change (se)	-6.9	-4.4
Difference from Amlodipine	-2.6	--
p-Value	0.005	--

a. Data from NDA vol. 2.385, table 10.2.1

1.5a.2 IND Trials Comparing Omapatrilat With Active Controls (Cuff BP Measurements)

There were four trials that used cuff BP to compare omapatrilat with lisinopril or amlodipine. Of these, two the trials utilized either low doses of omapatrilat (CV137-006) or of lisinopril (CV137-022), and so are of limited interest with regard to comparison of efficacy.

CV137-006

This trial compared the effects of omapatrilat (2.5, 5, or 10 mg) with amlodipine 10 mg and placebo. After 8 weeks, amlodipine had a greater effect on cuff BP parameters than any of the three doses of omapatrilat.

Table 1.5a.2.1 Mean changes from baseline in trough SeDBP and SeSBP at week 8 for 'as randomized' population from CV137-006^a.

Efficacy Variable	Omapatrilat 2.5 mg N=96	Omapatrilat 5 mg N=100	Omapatrilat 10 mg N=106	Amlodipine 10 mg N=96
Trough SeDBP mmHg Difference from Placebo	-2.3	-3.3	-3.2	-6.8
Trough SeSBP mmHg Difference from Placebo	-6.4	-5.6	-7.8	-12.6

a. Data from NDA vol. 2.286, table 10.1.1. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

CV137-022

This trial compared four doses of omapatrilat to lisinopril 20 mg or placebo. Note that the lisinopril dose is not the maximum dose recommended in the approved label (40 mg). The results, summarized below, found no significant difference between these doses of omapatrilat and lisinopril on the placebo-subtracted trough SeDBP after 9 weeks

Table 1.5a.2.2 Effect of omapatrilat and lisinopril on trough seated blood pressures at the end of week 9^a.

Efficacy Variable	Omap 5/5 mg N=101	Omap 10/10 mg N=103	Omap 10/20 mg N=116	Omap 10/40 mg N=110	Lisinopril 10/20 mg N=99
Trough SeDBP mmHg Difference from Placebo	-5.6	-5.3	-6.5	-7.6	-6.2
Difference from Lisinopril	+0.6	+0.9	-0.4	-1.4	--
Trough SeSBP mmHg Difference from Placebo	-8.3	-7.7	-11.5	-13.2	-7.7

a. Data from NDA vol. 2.296, table S.10.1.1A1.

Two trials measured cuff BP as their primary efficacy parameter, utilized higher doses of omapatrilat and the highest approved dose of either amlodipine or lisinopril.

CV137-030.

This trial compared omapatrilat with amlodipine and placebo using cuff BP measurements, which are summarized below. The difference between omapatrilat (20 mg force-titrated to 80 mg) and amlodipine (5 mg force-titrated to 10 mg) was -2.1 mmHg, which reached statistical significance (p=0.002). A larger effect of omapatrilat on pulse pressure was not demonstrated.

Table 1.5a.2.3 Mean change from baseline in trough BP measures at week 10 in CV137-030^a.

EFFICACY VARIABLE	Omapatrilat 20/40/80 mg N=241	Amlodipine 5/10/10 mg N=251
Trough SeDBP, mmHg		
Diff. From Amlodipine	-2.1	N/A
p-value c/w Amlodipine	0.002	--
Diff. From Placebo (95% CI)	-9.9	-7.8
p-Value c/w Placebo	<0.001	<0.001
Trough SeSBP, mmHg		
Diff. From Amlodipine (95% CI)	-3.1	N/A
p-value c/w Amlodipine	0.005	--
Diff. From Placebo (95% CI)	-17.8	-14.4
p-Value c/w Placebo	<0.001	--
Pulse Pressure, mmHg		
Diff. From Amlodipine (95% CI)	-1.0	--
p-value c/w Amlodipine	0.219	--
Diff. From Placebo (95% CI)	-8.2	-7.2
p-Value c/w Placebo	0.387	N/A

a. Data from NDA vol. 3.321, table 10.1.1. P-value using ANCOVA per the sponsor. Excludes site 55.

CV137-037

This trial compared omapatrilat with lisinopril and placebo using cuff BP measurements, which are summarized below. The difference in trough, placebo-subtracted SeDBP between omapatrilat (20 mg force-titrated to 80 mg) and lisinopril (10 mg force-titrated to 40 mg) was -2.5 mmHg, which was statistically significant. Similarly, the differences between omapatrilat and lisinopril for the other measures of trough BP change also achieved nominal significance.

Table 1.5a.2.4 Summary of trough BP changes at 10 weeks in CV137-037^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 224	Lisinopril 10/20/40 mg N = 213
Trough SeDBP, mmHg		
Difference from Lisinopril	-2.5	
p-Value ^a	0.002	
Difference from Placebo	-5.5	-2.9
p-Value ^a	<0.001	(0.003)
Trough SeSBP, mmHg		
Difference from Lisinopril	-5.2	
p-Value ^a	<0.001	
Difference from Placebo	-9.3	-5.1
p-Value ^a	<0.001	
Trough Pulse Pressure, mmHg		
Difference from Lisinopril	-2.8	
p-Value ^a	0.004	
Difference from Placebo	-3.8	-2.2
p-Value ^a	0.001	

a. Data from NDA vol. 2.331, study report summary. p-Values per sponsor.

1.5a.3 Summary of Placebo- and Active-Comparator Trials (Cuff BP Measurements)

These tables summarize mean changes in SeDBP and SeSBP from trials with placebo- and active-controls.

Table 1.5a.3.1 Placebo-subtracted changes in trough SeDBP in placebo- and active-control trials^a.

Daily Dose of Omapatrilat (mg)	CV137-006 8 wks	CV137-022 ^a 9 wks	CV137-030 ^a 10 wks	CV137-037 ^{a,c} 10 wks
2.5	-2.3			
5	-3.3	-5.6		
10	-3.2	-5.3		
20		-6.5		
40		-7.6		
20/80			-9.9	-5.5
Daily Dose of Amlodipine (mg) 10 or 5/10	-6.8		-7.8	
Daily Dose of Lisinopril (mg) 10/20 10/40		-6.2		-2.9

a. Dose shown is the starting and the final dose used after forced dose-titration.

c. This trial was conducted in blacks only.

The next table summarizes the changes in the placebo-subtracted trough SeSBP in the trials that compared omapatrilat to an active control as well as a placebo group.

Table 1.5a.3.2 Placebo-subtracted trough SeSBP changes in the active- and placebo-controlled trials.

Dose of Omapatrilat (mg)	CV137-006 8 wks	CV137-022 ^a 9 wks	CV137-030 ^a 10 wks	CV137-037 ^{a,c} 10 wks
2.5	-6.4			
5	-5.6	-8.3		
10	-7.8	-7.7		
20		-11.5		
40		-13.2		
20/80			-17.8	-9.3
Dose of Amlodipine 10 or 5/10	-12.6		-14.4	
Dose of Lisinopril 10/20 10/40		-7.7		-5.1

a. Dose shown is the starting and the final dose used after forced dose-titration. Subjects unable to tolerate the forced-titration were discontinued. This trial was conducted in blacks only.

The table below summarizes the peak placebo-subtracted SeDBP and peak placebo-subtracted SeSBP changes in two trials where this was measured that contained an active control. The two ABPM trials (CV137-031, CV137-032) did not measure peak BP effects as part of their cuff BP measurements.

Table 1.5a.3.3 Placebo-subtracted peak SeDBP and SeSBP in the active- and placebo-controlled trials.

	CV137-030 10 wks	CV137-031 9 wks	CV137-032 10 wks	CV137-037 ^{a,b} 10 wks
Peak SeDBP		Not Measured	Not Measured	
Omapatrilat 20/80 mg	-10.5			-8.4
Amlodipine 5/10 mg	-7.9			--
Lisinopril 10/40 mg	--			-5.3
Omap vs. Active Control	-2.6 (-4.0, -1.2), p<0.001			-3.1 (-4.8, -1.4), p<0.001
Peak SeSBP		Not Measured	Not Measured	
Omapatrilat 20/80 mg	-23.4			-15.4
Amlodipine 5/10 mg	-16.9			--
Lisinopril 10/40 mg	--			-8.0
Omap vs. Active Control	-6.5 (-8.9, -4.1), p<0.001			-7.4 (-10.0, -4.7), p<0.001

a. Dose shown is the starting and the final dose used after forced dose-titration. Subjects unable to tolerate the forced-titration were discontinued.

b. This trial was conducted in blacks only.

1.5b Comparative Anti-Hypertensive Efficacy Using Ambulatory Blood Pressure Measurements

Two trials used ABPM methodology as their primary method to compare one dose of omapatrilat with either amlodipine or lisinopril. For both trials, there was a significantly greater anti-hypertensive effect of omapatrilat 80 mg compared with lisinopril 40 mg (CV137-031) or amlodipine 10 mg (CV137-032) when ABPM parameters of mean changes in BP were examined.

Study CV137-031

The primary efficacy outcome in the study was the mean change from baseline in 24hr-average ambulatory systolic blood pressure (ASBP) following 10 weeks of once-daily treatment with omapatrilat versus lisinopril as presented in the following table, along with other efficacy markers (including ambulatory DBP, ADBP).

Table 1.5b.1 ABPM Efficacy analyses from CV137-031 at 10 weeks^a.

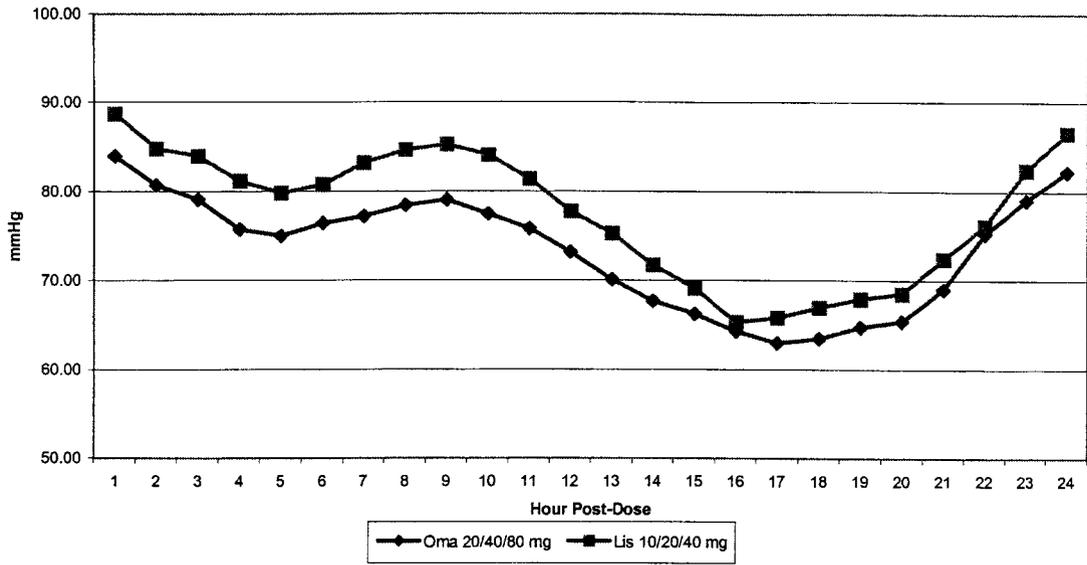
Efficacy Variable	Omapatrilat 20/40/80 n=160	Lisinopril 10/20/40 n=157
24-hour ASBP, mm Hg		
Adjusted Mean Change (se)	-19.0 (0.9)	-12.2 (0.9)
Difference from Lisinopril	-6.8	--
p-Value ^a	<0.001	--
24-hour ADBP, mm Hg		
Adjusted Mean Change (se)	-10.5 (0.5)	-7.5 (0.5)
Difference from Lisinopril	-2.9	--
p-Value ^a	<0.001	--
24-hour APP^b		
Adjusted Mean Change (se)	-8.5 (0.5%)	-4.8 (0.5)
Difference from Lisinopril	-3.7	--
p-Value ^a	<0.001	--
24-hour AMBP^b		
Adjusted Mean Change (se)	-13.3 (0.6)	-9.1 (0.6)
Difference from Lisinopril	-4.3	--
p-Value	<0.001	--

a. Data from NDA vol. 2.392, table 10.1.1. p-Value per sponsor using ANCOVA.

b. APP = ambulatory pulse pressure. AMBP = ambulatory mean blood pressure.

The hourly means for the ADBP at week 10 are summarized below. The upper curve is for lisinopril and the lower curve for omapatrilat. Subjects in the lisinopril group started with a higher mean blood pressure. Both drugs show a decrease in anti-hypertensive efficacy between 20 and 24 hours after the last dose.

Diastolic



Study CV137-032

This trial compared omapatrilat with amlodipine using ABPM methodology. The first table summarizes the changes in various ABPM parameters, including the primary efficacy analysis: the change from baseline to 10 weeks in the 24-hour average AMBP.

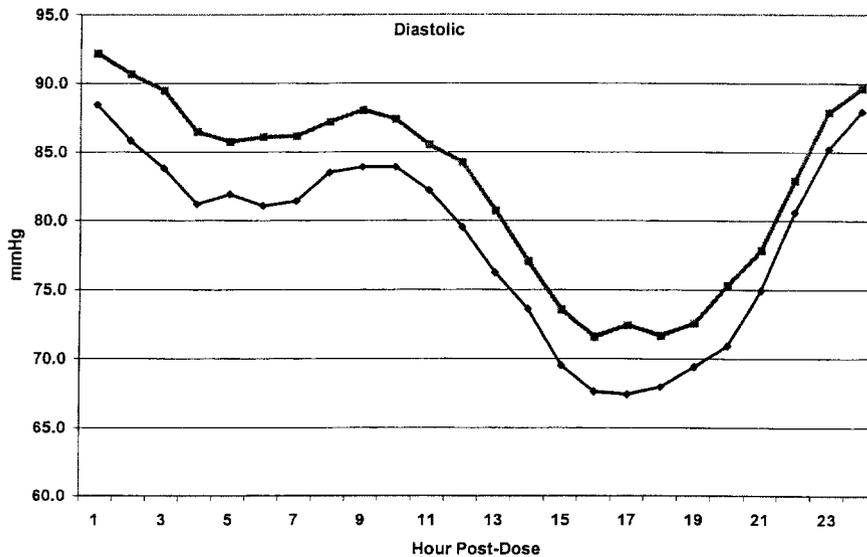
Table 1.5b.2 Changes in ABPM parameters at week 10 in CV137-032^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 192	Amlodipine 5/10/10 mg N = 187
24hr-average AMBP, mmHg^b		
Adjusted Mean Change (se)	-15.9 (0.5)	-11.0 (0.5)
Difference from Amlodipine	-4.9	
p-Value	< 0.001	
24hr-average ASBP, mmHg		
Adjusted Mean Change (se)	-20.4 (0.6)	-14.5 (0.6)
Difference from Amlodipine	-5.9	
p-Value	< 0.001	
24hr-average ADBP, mmHg		
Adjusted Mean Change (se)	-13.6 (0.4)	-9.3 (0.4)
Difference from Amlodipine	-4.4	
p-Value	< 0.001	
24hr-average APP, mmHg		
Adjusted Mean Change (se)	-6.7 (0.4)	-5.2 (0.4)
Difference from Amlodipine	-1.5	
p-Value	0.003	

a. Data from NDA vol. 2.385 table 10.1.1.

b. Pre-specified primary efficacy parameter.

The hourly means for ABPM at week 10 are shown below. The next two figures (from the sponsor) show the hourly means for the SBP and DBP at 10 weeks. The upper curve is the amlodipine group, which started with a slightly higher mean BP. Both drug demonstrate some decrease in anti-hypertensive efficacy at 18-24 hours after last dose.



In data not shown, similar changes were seen in the mean daytime 12-hour ABPM measurements: Daytime Average AMBP, ASBP, ABP, and PP (see NDA vol. 2.385 table 10.1.2 for summary).

4.0 to 4.14 Review of Protocol CV137-006

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4.1 Title of Study

A Multicenter, Randomized, Double-Blind, Placebo and Active-Controlled, Parallel 8-Week Dose-Ranging Study of the Vasopeptidase Inhibitor, Omapatrilat (BMS-186716), in the Treatment of Mild-to-Moderate Hypertension (CV137-006).

4.2 Sites of Investigation and Investigators

The list of investigators can be found in NDA vol. 2.287, table S.4. Fifty-eight investigators and sites participated (50 sites in the United States, 5 in Canada, 3 in France).

4.3 Background

Initial protocol submission to FDA: 7.12.96 (serial #024).

First protocol amendment: September 12, 1996

Eliminated 25 mg and 50 mg omapatrilat treatment groups after 2 patients were enrolled in the 25 mg group and 1 patient in the 50 mg group.

Subject entry: 7.30.96 to 3.31.97

4.4 Study Design

This multicenter study was conducted under a randomized, double-blind, placebo and active-controlled, parallel design. Antihypertensive efficacy and safety were compared among the omapatrilat, amlodipine besylate, and placebo regimens in subjects with mild-to-moderate hypertension. After withdrawal of antihypertensive therapy (if applicable) and a 4-week single-blind placebo lead-in period (Period A), eligible subjects were randomized to one of 7 treatment groups (omapatrilat 2.5, 5, 10, 25, 50 mg, amlodipine besylate 10 mg, placebo) to receive study medication for a total of 8 weeks (Period B). Subjects were also followed for one week after discontinuation of study drug to assess the impact of drug withdrawal on BP (Period C).

Blood Pressure Measurement

Blood pressure assessments were performed in a uniform fashion in this and all subsequent trials in this review. For blood pressure assessment using a sphygmomanometer (cuff blood pressures), 3 initial measurements were taken at each visit in each position (seated, supine and standing). For each position, if the range of the 3 diastolic measurements was greater than 8 mmHg then 2 additional blood pressure measurements were taken.

Blood Pressure Measurement (cont)

The average of these 3 or 5 measurements was used in the analyses. If measurements were missing, then the average was calculated from the available measurements. The methods used for the Ambulatory Blood Pressure Monitoring (ABPM) will be described in the review of protocol CV137-031, where it was used for the first time among the studies in this review.

Baseline Blood Pressure Determination

Similar to blood pressure assessments, baseline assessments were performed in a uniform fashion throughout the trials. Baseline trough assessments were the last taken during the qualifying visits, before the start of Period B treatment (or on or before the randomization date for subjects randomized but never treated). These were generally assessments taken at the last Period A (wash-out period) visit. For most subjects this occurred just prior to taking the first dose of double-blind medication at the B1 portion of the visit at the end of the placebo run-in phase (Period A).

Baseline peak assessments were the assessments taken during placebo lead-in at the estimated time of peak effect (7 ± 1 hour post-dose) at the last visit prior to the double-blind treatment phase.

Baseline assessments for trough-to-peak ratio were both taken at the last visit prior to the double-blind treatment phase. Baseline trough was the morning assessment just prior to dose (0 hour); baseline peak was the assessment at estimated time of peak (7 ± 1 hour post-dose).

4.5 Primary and Secondary Endpoints

Primary Objective

To compare the change from baseline in trough (24 ± 3 hours post dose) seated diastolic blood pressure (SeDBP), relative to placebo at the end of 8 weeks for omapatrilat and amlodipine. In the Statistical section, a preference for the 'as randomized' population was specified for the primary analyses.

Secondary Objectives

1) To compare the change from baseline, relative to placebo, in trough (24 ± 3 hours post dose) seated systolic and supine and standing systolic and diastolic BP and heart rate (seated, supine and standing) after 1, 2, 4, 6, and 8 weeks for omapatrilat and amlodipine.

2) To compare the change from baseline in seated blood pressure and seated heart rate at estimated peak (7 ± 1 hours post dose), relative to placebo, following 8 weeks of once-daily administration of omapatrilat at doses ranging from 2.5 to 10 mg;

3) To assess the trough to peak ratio of omapatrilat at doses of 2.5 to 10 mg and amlodipine besylate 10mg with respect to SeBP after 8 weeks of once daily administration.

4) To assess blood pressure changes and clinical symptomatology following the withdrawal of omapatrilat.

5) To assess therapeutic response at Weeks 4 and 8.

4.6 Number of subjects/ randomization

A total of 817 subjects was enrolled, 769 entered the placebo lead-in phase, and 569 randomized into the study. Of these, 512 completed the double-blind portion of the study, and 505 entered the placebo-withdrawal phase. A total of 495 patients completed the trial.

Table 4.6.1 Subjects randomized in study CV137-006^a.

Placebo	Omapatrilat	Amlodipine
122	336	108

a. Data from NDA volume 2.286.

4.7 Inclusion/ Exclusion Criteria

For full list of inclusion/exclusion criteria see NDA vol. 2.286, section 5.2. In general, consenting males and females who were not nursing, not pregnant and of non-childbearing potential (surgically sterile or post-menopausal); age 18 years or greater, with mild-to-moderate hypertension (SeDBP of 95-110 mmHg) were eligible.

Exclusion criteria include the presence of bronchospastic lung disease requiring medication, heart failure (LVEF $\leq 45\%$), AODM or Secondary Hypertension.

4.8 Dosage/ Administration

Patient who qualified for the double-blind portion of the trial were randomized to one of the following treatment groups:

Omapatrilat: 2.5, 5, 10, 25, 50 mg

25 and 50 mg doses were discontinued after 1 and 2 patients were enrolled respectively.

Amlodipine: 10 mg

Placebo

4.9 Duration/ Adjustment of Therapy

13 weeks (4 weeks of placebo lead-in, 8 weeks of double-blind treatment, and one week of placebo withdrawal).

4.10 Safety and Efficacy Endpoints Measured

The table below summarizes the efficacy and safety measurements performed during the trial, along with their time of measurement. Serum bicarbonate was not measured.

Table 4.10.1 Timetable for clinical observations and lab measurements in CV137-006^a.

Day	Enroll	A1	Lead-in Period A	Double-Blind Period B						Withdrawal Period C	
				B1	B8	B15	B29	B43	B57	C3	C7
Consent	X										
Full Hx and PE	X								X		
Brief Physical Exam		X	A29				X			X	X
BP, Heart rate	X	X	A15, A22, A29	X	X	X	X	X	X	X	X
Adverse Events		X	A15, A22, A29	X	X	X	X	X	X	X	X
Review Medications	X	X	A15, A22, A29	X	X	X	X	X	X	X	X
12-lead ECG		X	A22 or A29						X		X
Chest X-ray ^c		X									
Laboratory Tests		X	A22 or A29				X		X		
Pregnancy test			A29								
Randomize				X							
Extended Visit				X							
Peak BP Measurement			A22				X		X		
Medication Dispensing		X	A15, A22	X	X	X	X	X	X		
Medication Count			A15, A22, A29		X	X	X	X	X	X	X

a. Data from NDA volume 2.286.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, total cholesterol, creatine kinase); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis).

c. If not done in previous 6 months.

4.11 Statistical Considerations

Sponsor's Statistical Plan

Power

A total of 94 subjects randomized to each treatment would have been sufficient to provide 90% power to detect true differences of 4.2 mmHg between any omapatrilat group and placebo.

Multiplicity

No adjustment of p-Values was proposed to adjust for multiplicity of analyses.

Interim Analyses

An 'administrative analysis' was carried out after 290 subjects had completed the double-blind phase and had Week 8 efficacy data. The purpose of this analysis (per the sponsor) was to define the dose range for subsequent studies. Results were not to be divulged to any of the investigator sites. No adjustment of p-Values or confidence intervals was made in the final analyses for this 'administrative analysis.'

Statistical Analyses

1) Study Populations

Randomized Subjects

This dataset includes all subjects randomized into the study, excluding subjects from site number 59. In addition, subjects who did not have both a baseline and post-randomization assessment available for a given analysis were also excluded from the analysis of that variable.

Evaluable Subjects with Valid Peaks and Troughs

These subject having both valid peak and trough measurements BP measurements at week 8. Subjects from site number 59 were excluded from the dataset. For this dataset, the 13 subjects who were randomized but given a treatment kit different from the one intended were also excluded.

This dataset was used to analyze peak assessments and to obtain estimates of trough-to-peak ratio.

Treated Subjects

This dataset consists of safety data from all randomized subjects who received at least one dose of study medication, including the subjects from site number 59. For safety, subjects are grouped as treated. All safety listings were based on this dataset. Safety summaries and analyses excluded any data collected more than 14 days after the last dose of double-blind medication.

2) Efficacy Analyses

Analysis of covariance (ANCOVA) was used to compare the omapatrilat regimens to placebo with respect to changes from baseline in trough seated, supine, and standing measures and peak seated measures of blood pressure and heart rate. The ANCOVA model included terms for treatment regimen and for baseline value as covariate. The typical sample sizes obtained at individual sites too small to use of study site as an additional term in this model.

Therapeutic Response: the proportion of subjects normalized (trough SeDBP < 90 mmHg) and the proportion with favorable response (trough SeDBP normalized or decreased at least 10 mmHg from baseline) were summarized using Cochran-Mantel-Haenszel tests stratified by baseline SeDBP (strata were ≤ 99 mmHg; $> 99 - \leq 104$ mmHg; > 104 mmHg).

Pharmacokinetics

No pharmacokinetic data were collected in the trial.

Safety

Safety parameters included spontaneously reported adverse events and vital signs, which are summarized descriptively. Several important lab measurements as detailed above were also analyzed.

FDA Statistical Analysis

Unless noted, all p-Values and treatment effects in this review are from the sponsor's analysis. In many cases, the sponsor's analysis excluded particular individuals and/or sites, largely for protocol violations. In addition, only observed values were used in the sponsor's analyses (that is, missing values were not imputed). The FDA preferred the intent-to-treat population for efficacy. Missing values were imputed using Last Observation Carried Forward (LOCF) methods, including all randomized patients. The FDA analyses were done using ANOVA without adjustment for baseline covariates, based on concerns for the uniformity of the relationship between baseline and change from baseline across the treatment groups (a requisite for use of ANCOVA). Using these methods, important efficacy variables were reanalyzed. Unless otherwise noted, this approach yielded qualitatively similar results to those obtained by the sponsor.

4.12 Efficacy Outcomes

4.12a Disposition of Subjects

A total of 817 subjects was enrolled, 769 entered the placebo lead-in phase, and 569 randomized into the study. Of these, 512 completed the double-blind portion of the study, and 505 entered the placebo-withdrawal phase. A total of 495 patients completed the trial (87.0% of the patients who entered the double-blind portion of the trial).

The first table summarizes the reasons for discontinuation in the trial prior to randomization into the double-blind portion of the trial. The majority of the discontinuations were due to failure of the BP to qualify for the study (106/248 patients).

Table 4.12a.1 Reasons for discontinuation prior to entry into the double-blind portion of CV137-006^a.

Reason for Exclusion/Discontinuation	Number of Subjects
Adverse event	23
Concomitant medication	8
BP did not qualify per protocol	106
Investigator request	10
Laboratory abnormality	44
Lost to follow-up	12
Other	19
Subject request	26
Total	248

a. Data from NDA vol. 2.286, table 8.1A.

The next table summarizes the discontinuations during the double-blind phase of the trial.

Table 4.12a.2 Reasons for discontinuation during double-blind therapy in CV137-006^a.

	Placebo	Omapatrilat					Amlodipine 10 mg
		2.5 mg	5 mg	10 mg	25 mg	50 mg	
No. of subjects randomized	122	109	111	116	1	2	108
No. of subjects discontinued	13 (10.6%)	13 (11.9%)	11 (9.9%)	7 (6.0%)	0	1 (50%)	11 (10.2%)
Adverse Event	2	5	7	5	0	1	7
Concomitant medication	0	1	0	0	0	0	0
Investigator request	5	4	1	0	0	0	1
Lost to follow-up	0	2	0	0	0	0	2
Other reasons	0	0	0	1	0	0	0
Subject request	2	0	3	1	0	0	1
BP above limit as per protocol	4	1	0	0	0	0	0
Number of subjects completing double-blind period	109 (89.3%)	96 (88.1%)	100 (90.1%)	109 (94.0%)	1 (100%)	1 (50%)	97 (89.8%)

a. Data from NDA vol. 2.286, table 8.1B.

4.12b Protocol Violations & Deviations

Thirteen subjects in all were randomized to a different drug than the one they received, although only 12 actually received an unintended treatment.

During the trial analysis, the sponsor determined that '(b)ecause of the questionable accuracy of the blood pressure readings at this site, it was decided to include the 9 randomized subjects from Site 59 in the safety analysis only and not in the analysis of efficacy for this study.'

4.12c Subject Demographics & Baseline Characteristics

The demographics of the treatment groups are shown below.

Table 4.12c.1 Demographics of subjects enrolled in CV137-006^a.

Baseline Characteristic	Placebo	OMAPATRILAT			Amlodipine
	N = 122	2.5 mg N = 109	5 mg N = 111	10 mg N = 116	10 mg N = 108
Age, yr					
Mean	54.6	55.2	54.4	55.3	55.3
SD	10.9	10.6	8.4	9.8	9.9
Age Group, n (%)					
< 65 yr	99 (81%)	89 (82%)	99 (89%)	95 (82%)	89 (82%)
65 - 74 yr	23 (19%)	17 (16%)	10 (9%)	20 (17%)	17 (16%)
≥ 75 yr	0 (0%)	3 (3%)	2 (2%)	1 (1%)	2 (2%)
Gender, n (%)					
Male	67 (55%)	69 (63%)	66 (59%)	72 (62%)	69 (64%)
Female	55 (45%)	40 (37%)	45 (41%)	44 (38%)	39 (36%)
Race, n (%)					
White	98 (80%)	91 (83%)	92 (83%)	95 (82%)	92 (85%)
Black	16 (13%)	10 (9%)	10 (9%)	18 (16%)	11 (10%)
Other	8 (7%)	8 (7%)	9 (8%)	3 (3%)	5 (5%)
Weight, kg					
Mean	83.8	87.3	85.2	88.9	86.7
SD	17.1	16.9	16.2	16.2	16.9
Duration of HTN, yr					
Mean	9.6	11.2	9.3	10.6	12.3
SD	8.1	8.6	7.6	9.8	10.2

a. Data from NDA vol. 2.286, table 8.3A.

Baseline values for seated trough systolic and diastolic BP were similar in the three drug groups, and among the three doses of omapatrilat (see NDA vol. 2.287, tables 8.3B and 8.3C for details). The five treatment groups had mean SeDBP that ranged between 99.7 and 100.8. Overall, 75-85% of the patients had a seated trough diastolic BP (SeDBP) of <104 mm Hg).

The occurrence of cardiovascular conditions in randomized subjects were hypercholesterolemia and hypertriglyceridemia, that occurred in 30.6 to 41.0% and 13.9 to 19.7% of the subjects respectively. Diabetes was reported in 3.3. to 9.2% of the treatment groups. Prior antihypertensive therapy was used by 492 (86.5%) of the 569 randomized subjects, and was balanced among the treatment groups.

4.12d Concomitant Therapies used after Trial Initiation

Concomitant medications were used by 95-100% of the subjects in the three drug treatment groups. Use of these medications was similar in incidence among the treatment groups (see NDA vol. 2.287, table S.9.4A for details). A total of 492 (86.5%) of the patients had previously received antihypertensive therapy.

4.12e Extent of Exposure to Study Drug in CV137-006

The mean duration of exposure to study drug was 54-56 days in all treatment groups (see NDA vol. 2.286, table 9.1 for details).

4.12f Primary Efficacy Analyses of CV137-006

The primary efficacy analysis was the trough SeDBP, relative to placebo at the end of 8 weeks for omapatrilat and amlodipine. These results, along with other significant endpoints, are summarized below. Note that all doses of omapatrilat had a smaller effect on both placebo-subtracted SeDBP and SeSBP than amlodipine.

Table 4.12f.1 Mean changes from baseline in trough SeDBP and SeSBP at week 8 for 'as randomized' population^a.

Efficacy Variable	Placebo N=107	Omapatrilat 2.5 mg N=96	Omapatrilat 5 mg N=100	Omapatrilat 10 mg N=106	Amlodipine 10 mg N=96
Trough SeDBP mmHg					
Baseline Mean (SD)	100.3 (3.8)	100.0 (3.7)	99.8 (3.4)	99.8 (4.1)	99.6 (3.8)
Adjusted Mean Change (SE)	-4.9 (0.6)	-7.2 (0.7)	-8.2 (0.7)	-8.1 (0.6)	-11.7 (0.7)
Difference from Placebo (95% CI)	--	-2.3 (-4.5, -0.2)	-3.3 (-5.4, -1.1)	-3.2 (-5.3, -1.1)	-6.8 (-8.6, -5.0)
p-Value: comparison with placebo ^a	--	0.011	< 0.001	< 0.001	--
Difference from Amlodipine (95% CI)	--	+4.5 (2.6, 6.3)	+3.6 (1.7, 5.4)	+3.6 (1.8, 5.4)	--
Trough SeSBP mmHg					
Baseline Mean (SD)	150.6 (12.8)	154.0 (14.2)	150.5 (14.7)	152.9 (14.9)	151.1 (13.5)
Adjusted Mean Change (SE)	-4.3 (1.1)	-10.7 (1.2)	-9.9 (1.2)	-12.1 (1.1)	-16.9 (1.2)
Difference from Placebo (95% CI)	--	-6.4 (-9.6, -3.2)	-5.6 (-8.7, -2.4)	-7.8 (-10.9, -4.7)	-12.6
p-Value: comparison with placebo ^b	--	< 0.001	< 0.001	< 0.001	< 0.001

a. Data from NDA vol. 2.286, table 10.1.1. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

Similar changes were seen for the 'as treated' population (shown below) and for the population with available peak and trough data ('evaluable' population, data not shown).

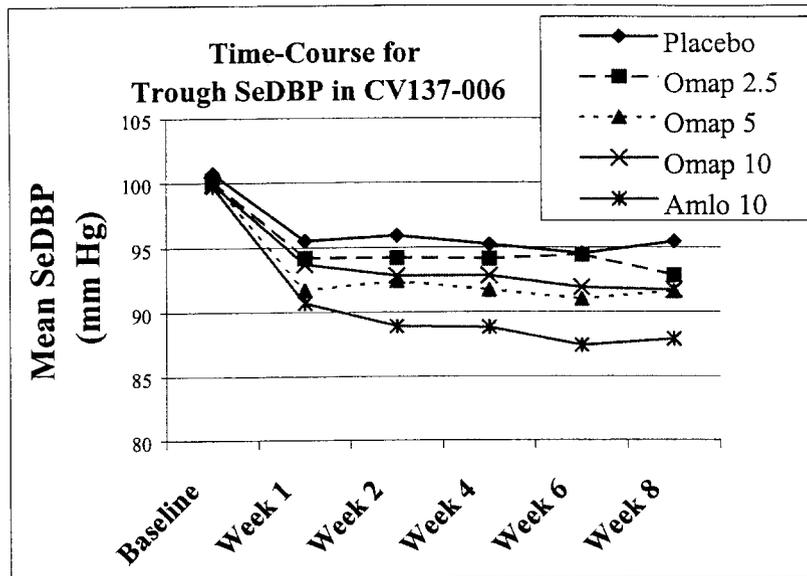
Table 4.12f.2 Mean changes from baseline in trough SeDBP and SeSBP at week 8 for 'as treated' population^a.

Efficacy Variable	Placebo N=106	2.5 mg Omapatrilat N=99	5 mg Omapatrilat N=99	10 mg Omapatrilat N=103	10 mg Amlodipine N=98
Trough SeDBP mmHg					
Baseline Mean	100.4	100.0	99.9	99.6	99.7
Adjusted Mean Change (SE)	-4.7	-7.2 (0.7)	-8.2 (0.7)	-8.2 (0.6)	-11.9 (0.7)
Difference from Placebo (95% CI)	--	-2.5 (-4.6, -0.4)	-3.5 (-5.7, -1.4)	-3.6 (-5.7, -1.5)	-7.2 (-9.0, -5.4)
p-Value: comparison with placebo ^a	--	0.006	< 0.001	< 0.001	--
Difference from Amlodipine (95% CI)	--	4.7 (2.9, 6.5)	3.6 (1.7, 5.4)	3.6 (1.8, 5.4)	--
Trough SeSBP mmHg					
Baseline Mean (SD)	150.9	153.3	150.8	152.4	151.7
Adjusted Mean Change (SE)	-4.1 (1.1)	-10.5 (1.2)	-9.5 (1.2)	-12.3 (1.1)	-17.3 (1.2)
Difference from Placebo (95% CI)	--	-6.4 (-9.5, -3.2)	-5.4 (-8.6, -2.3)	-8.2 (-11.3, -5.1)	--
p-Value: comparison with placebo ^a	--	< 0.001	< 0.001	< 0.001	--

a. Data from NDA vol. 2.287, tables S.10.1.1B3, S.10.1.1A4, S.10.1.1A5. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

In data not shown here, similar differences were seen for trough standing DBP (StDBP) and trough standing SBP (StSBP): see data table S.10.1.1C1, vol. 2.287 for details.

A reduction in blood pressure (SeDBP) occurred within the first week of treatment for all groups, including placebo.



4.12g Additional Efficacy Analyses of CV137-006

Sub-Group Analyses of Primary Endpoint

Changes from baseline in trough SeDBP and SeSBP at Week 8 grouped by gender, age group (< 65 years old, at least 65 years old), and race (White, Black, Other) were analyzed. The overall trends were similar to those seen in the primary efficacy analysis, although relatively few patients >65 or non-white were included in the trial (<20 for those >65, <10 for those non-white). See NDA vol. 2.287, tables S.10.S.1 to S.10.S.3 for details.

Trough:Peak Ratio

Peak SeDBP and peak SeSBP were also examined, first alone and then as part of an assessment of the peak/trough ratio. Only those patients with valid peak and trough data are included in the table below. Peak values were measured 7±1 hour after dosing.

Table 4.12g.1 Treatment comparisons of change from baseline in peak measures for SeSBP and SeDBP for 'evaluable' subjects.

Efficacy Variable	Placebo N=97	2.5 mg Omapatrilat N=88	5 mg Omapatrilat N=92	10 mg Omapatrilat N=93	10 mg Amlodipine N=90
Peak SeDBP mmHg					
Baseline Mean (SD)	97.9	97.8	97.1	97.4	97.8
Adjusted Mean Change (SE)	-4.7 (0.8)	-8.0 (0.8)	-10.2 (0.8)	-10.7 (0.8)	-13.5 (0.8)
Difference from Placebo (95% CI)	--	-3.3 (-5.6, -1.1)	-5.5 (-7.8, -3.3)	-6.0 (-8.3, -3.8)	-8.8
p-Value: comparison with placebo ^a	--	0.004	< 0.001	< 0.001	--
Peak SeSBP mmHg					
Baseline Mean (SD)	148.7	151.1	148.5	148.6	151.1
Adjusted Mean Change (SE)	-3.5 (1.2)	-11.7 (1.3)	-14.1 (1.2)	-15.9 (1.2)	-17.9 (1.2)
Difference from Placebo (95% CI)	--	-8.2 (-11.6, -4.8)	-10.6 (-14.0, 7.3)	-12.5 (-15.8, -9.1)	-14.4
p-Value: comparison with placebo ^b	--	< 0.001	< 0.001	< 0.001	--

a. Data from NDA vol. 2.287, table S.10.1.3A. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

Using these data, then sponsor then determined the peak:trough ratio for the treated patients with evaluable data at week 8 (calculated for DBP). These data are summarized below.

Table 4.12g.2 Summary statistics for trough and peak measures of SeDBP after 8 weeks for ‘evaluable’ subjects^a.

Efficacy Variable	Placebo N=97	2.5 mg Omapatrilat N=88	5 mg Omapatrilat N=92	10 mg Omapatrilat N=93	10 mg Amlodipine N=90
Peak SeDBP mmHg					
Baseline Mean (SD)	97.9	97.8	97.1	97.4	97.8
Adjusted Mean Change (SE)	-4.7 (0.8)	-8.0 (0.8)	-10.2 (0.8)	-10.7 (0.8)	-13.5 (0.8)
Relative Change from Placebo	--	-3.3	-5.5* ^c	-6.0*	-8.8*
Trough SeDBP mmHg					
Baseline Mean (SD)	100.2	100.1	99.6	99.7	99.8
Adjusted Mean Change (SE)	-4.5 (0.7)	-7.4 (0.7)	-8.5 (0.7)	-8.3 (0.7)	-12.2 (0.7)
Relative Change from Placebo	--	-2.8	-4.0	-3.8	-7.7
Trough:Peak Ratio^b	--	0.85	0.71	0.62	0.87

a. Data from NDA vol. 2.287, table S.10.1.3A. Statistical analysis done using ANCOVA. Dunnett’s method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

b. Calculated from ratio of relative changes from placebo.

c. Starred values significantly different from baseline at <0.017 per the sponsor.

Therapeutic Response

The sponsor also examined the anti-hypertensive effects of omapatrilat using a categorical analysis of ‘Therapeutic Response.’ Therapeutic response was defined as a normalized BP (SeDBP < 90 mmHg) or a favorable BP response (BP normalized or SeDBP ≥ 10mmHg decrease from baseline) at Week 10.

Table 4.12g.3 Subjects with normalization or favorable trend in BP at 10 weeks in CV137-006^a.

Therapeutic Response	Placebo N = 107	Omapatrilat 2.5 mg N = 96	Omapatrilat 5 mg N = 100	Omapatrilat 10 mg N = 106	Amlodipine 10 mg N = 96
Normalized n (%)	24 (22%)	31 (32%)	42 (42%)	42 (40%)	59 (61%)
Favorable n (%)	31 (29%)	37 (39%)	52 (52%)	52 (49%)	70 (73%)

a. Data from NDA vol. 2.332, table 10.2.1.2A2, based on Randomized Subjects.

b. Normalized: Trough SeDBP <90 mmHg

Favorable: Trough SeDBP <90 or decrease from baseline ≥10 mmHg.

Heart Rate

The effect of omapatrilat and amlodipine on trough supine heart rate at the end of 8 weeks is summarized below. No significant trends were discernable.

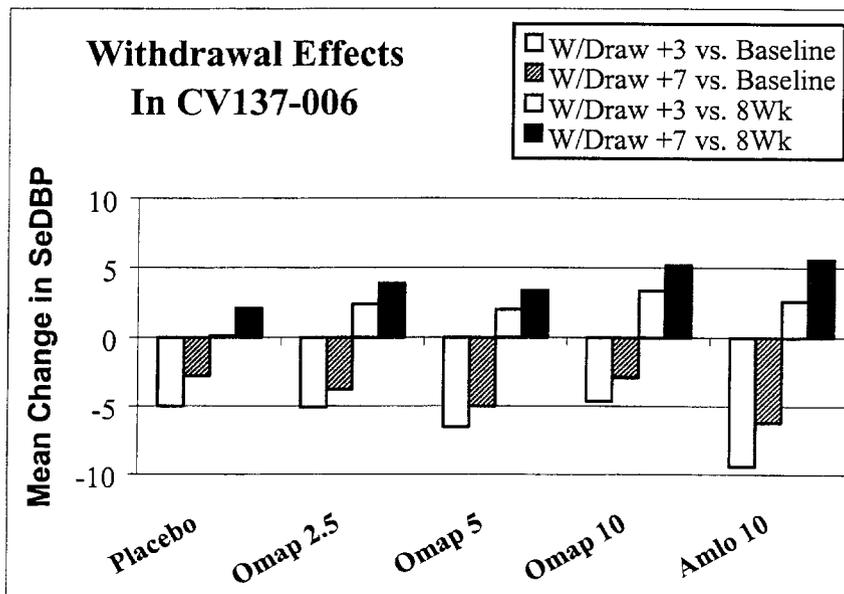
Table 4.12g.4 Treatment comparisons of change from baseline in trough measures for trough seated heart rate (Se HR), supine heart rate (SuHR), and standing heart rate (StHR) at the end of week 8^a.

Efficacy Variable	Placebo N=107	2.5 mg Omapatrilat N=96	5 mg Omapatrilat N=100	10 mg Omapatrilat N=106	10 mg Amlodipine N=96
Trough SeHR					
Baseline Mean (SD)	72.6	73.6	72.7	73.9	71.4
Adjusted Mean Change (SE)	+0.4 (0.7)	-0.4 (0.8)	-0.3 (0.8)	+0.1 (0.7)	+0.3 (0.8)
Difference from Placebo (95% CI)	--	-0.8 (-2.8, 1.2)	-0.7 (-2.7, 1.3)	-0.3 (-2.3, 1.7)	-0.3
p-Value: comparison with placebo ^a	--	NS	NS	NS	NS
Trough StHR:					
Baseline Mean (SD)	75.9	76.0	74.8	76.4	74.2
Adjusted Mean Change (SE)	-0.3 (0.7)	-1.0 (0.8)	-0.2 (0.7)	+0.6 (0.7)	+0.4 (0.8)
Difference from Placebo (95% CI)	--	-0.7 (-2.7, 1.4)	+0.5 (-1.6, 2.5)	+0.9 (-1.1, 2.9)	+0.7
p-Value: comparison with placebo ^b	--	NS	NS	NS	NS
Trough SuHR					
Baseline Mean (SD)	71.4	72.4	70.5	72.1	70.1
Adjusted Mean Change (SE)	-0.4 (0.7)	-0.7 (0.7)	-0.3 (0.7)	-0.2 (0.7)	-0.6 (0.7)
Difference from Placebo (95% CI)	--	-0.3 (-2.7, 1.7)	+0.1 (-1.9, 2.1)	+0.2 (-1.8, 2.1)	-0.2
p-Value: comparison with placebo ^b	--	NS	NS	NS	NS

a. Data from NDA vol. 2.287, table S.10.1.1D1, from as randomized population. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.

Withdrawal Effect

The sponsor measured blood pressure 3 and 7 days after withdrawal of study drug, and the available data are summarized below as mean changes from the baseline and from week 8. In short, at both 3 and 7 days after stopping study drug, subjects taking either omapatrilat or amlodipine had lower mean blood pressures than they did at baseline, but higher mean blood pressure than then they did at the end of 8 weeks of therapy.



4.13 Safety Outcomes

The adverse events, serious adverse events, deaths and subject discontinuations are discussed in Dr. Pelayo's integrated review of safety. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 4.13.1 Summary of subject outcomes in CV137-006 through 14 days after drug cessation^a.

Event	Placebo N=121	Omap 2.5 mg N=112	Omap 5.0 mg N=109	Omap 10 mg N=113	Omap 25 mg N=1	Omap 50 mg N=2	Any Omap N=337	Amlodipine 10 mg N=110
AE, total (%)	83 (68.6%)	64 (57.1%)	69 (63.3%)	75 (66.4%)	0 (0%)	2 (100%)	210 (62.3%)	74 (67.3%)
SAE	0	0	0	0	0	0	0	0
Death	0	0	0	0	0	0	0	0
D/Cs due to AE	2 (1.7%)	5 (4.5%)	7 (6.4%)	5 (4.4%)	0 (0%)	1 (50%)	18 (5.3%)	7 (6.4%)

a. Data from NDA volume 2.286.

4.14 CV137-006 Efficacy Summary

Study CV137-006 compared the antihypertensive effects of three doses of omapatrilat to amlodipine and placebo in a randomized, double-blind trial. Along with assessing antihypertensive effects, the changes in blood pressure following discontinuation of omapatrilat were monitored for one week.

1. Omapatrilat at doses of 2.5, 5, and 10 mg per day lowered blood pressure in patients with mild-to-moderate hypertension. Effects on placebo-subtracted, trough seated diastolic BP (Se DBP) ranged between -2.3 mmHg at the 2.5 mg dose of omapatrilat to -3.2 mmHg at the 10 mg dose ($p < 0.001$ for all three treatment groups).

2. Withdrawal of omapatrilat at the end of 8 weeks resulted in a rise in SeDBP at days 3 and 7, which did not return to the baseline level prior to starting omapatrilat.

3. The highest dose of omapatrilat used in the trial (10 mg) exerted less of an antihypertensive effect than did amlodipine 10 mg.

4. The doses of omapatrilat used in this trial led to a 'normalization' or 'favorable response' of Se DBP in less than 50% of the subjects.

5. Once a day omapatrilat had a peak:trough ratio that ranged between 0.62 and 0.85 at the end of 8 weeks.

6. No significant effect of omapatrilat on mean heart rate at the end of 8 weeks was detected.

7.0 to 7.14 Review of Protocol CV137-030

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7.1 Title of Study

A Multicenter, Randomized, Double-blind, Amlodipine an Placebo-Controlled, 10-week Study of Omapatrilat in the Treatment of Mild-to-Moderate Hypertension (CV137-030).

7.2 Sites of Investigation and Investigators

There were 77 investigators at 77 sites: 70 in the United States, 4 in Argentina, and 3 in Brazil. For a list, see NDA vol. 3.321, table S.4.

7.3 Background

Initial Protocol: submitted 3.11.98 (serial 124).

Protocol amendments: all amendments were administrative or related to minor changes in protocol.

Subject entry: 5.12.98 to 5.12.99.

7.4 Study Design

This multicenter, randomized, double-blind, active- and placebo-controlled, parallel group forced dose-titration study was designed to compare omapatrilat to a standard antihypertensive therapy, amlodipine. Another objective was to evaluate the tolerability and efficacy of omapatrilat when increased stepwise from a starting dose of 20 mg to a maintenance dose of 80 mg daily in subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg).

After a 4-week single-blind, placebo lead-in period (Period A) subjects were randomized to a 10-week, double-blind treatment period (Period B), and received once-daily treatment with a regimen of omapatrilat, amlodipine or placebo. The regimen of omapatrilat consisted of 20 mg force-titrated to 40 mg at Week 2 and to 80 mg at Week 4. The regimen of amlodipine consisted of 5 mg force-titrated to 10 mg at Week 2 and maintained at 10 mg at Week 4. Placebo was mock-titrated at the same visits.

See previous review of CV137-006 for details of the methods used for blood pressure measurement and baseline determination.

7.5 Primary and Secondary Objectives

Primary Objective

The primary objective was to compare the change from baseline in trough seated diastolic blood pressure (SeDBP), following 10 weeks of once-daily oral administration of omapatrilat to amlodipine in subjects with mild to moderate hypertension.

Secondary Objectives

1) To compare the change from baseline, relative to amlodipine, in trough seated systolic blood pressure (SeSBP) and pulse pressure (PP, SeSBP minus SeDBP) after 10 weeks of once-daily administration of a regimen of omapatrilat.

2) To compare the change from baseline, relative to amlodipine, in trough seated blood pressure (SeBP) after 2 and 4 weeks of once-daily administration of a regimen of omapatrilat.

3) To compare the change from baseline, relative to placebo, in trough seated blood pressure (SeBP) after 2, 4 and 10 weeks and in trough seated heart rate (HR) and PP at Week 10, after 10 weeks of once-daily administration of a regimen of omapatrilat.

4) To compare the response to omapatrilat, relative to placebo, based on the percentage of subjects normalized (SeDBP < 90 mmHg) at Week 10.

5) To compare the change from baseline, relative to amlodipine, in seated blood pressure at 7 ± 1 hours post dose after 8 weeks of once-daily administration of a regimen of omapatrilat.

6) To assess the safety and tolerability of a regimen of omapatrilat relative to amlodipine and placebo when administered over the 10 week treatment period.

7) To compare the incidence, relative to amlodipine, of treatment-emergent edema occurring during the 10 week treatment period.

8) To describe changes in BP and HR in other positions and at other time points.

9) To assess the trough-to-peak ratio.

Additional assessments included the changes from baseline in urinary ANP, a marker of neutral endopeptidase (NEP) inhibition, as assessed at peak and trough.

7.6 Number of subjects/ randomization

A total of 1232 subjects were enrolled and 725 were randomized into the study.

Table 7.6.1 Subjects enrolled in CV137-030^a.

Placebo	Omapatrilat	Amlodipine
146	286	293

a. Data from NDA volume 3.322, table S.7.1.

7.7 Inclusion/ Exclusion Criteria

Consenting males and females who were not nursing, not pregnant and of non-childbearing potential (surgically sterile or post-menopausal); age 18 years or greater, with mild-to-moderate hypertension SeDBP of 95-110 mmHg). Per the sponsor, 'each center was encourage to enroll at least 30% subjects with SeDBP >104 mm Hg and no more than 30% black subjects.' For full list of inclusion/exclusion criteria see Final Report for CV137-030, section 5.2, NDA vol. 2.321.

7.8 Dosage/ Administration

Following the single-blind placebo run-in period, lasting one week, patients were randomized to one of three treatment groups (1:2:2): placebo, omapatrilat or amlodipine. After 2 weeks of double-blind therapy doses of study medications were force-titrated from the level I to the level II shown below (placebo was sham-increased). After 4 weeks, the dose of medication was again increased to level III.

Table 7.8.1 Titration visits and dose levels in trial CV137-030^a.

Study Drug	Day	Omapatrilat	Amlodipine	Placebo
Level I	B1	20 mg	5 mg	Placebo
Level II	B15	40 mg	10 mg	Placebo
Level III	B29	80 mg	10 mg	Placebo

a. Data from NDA vol. 2.321, table 5.5.1B.

7.9 Duration/ Adjustment of Therapy

See section above for details of duration and mandated adjustment of therapy. Subjects who were unable to tolerate each new dose-titration were discontinued from the study. Reduction in dose was not permitted.

7.10 Safety and Efficacy Endpoints Measured

The table below summarizes the efficacy and safety measurements performed during the trial, along with their time of measurement.

Table 7.10.1 Timetable for clinical observations and lab measurements in CV137-030^a.

	Enroll	A1	Lead-in Period A	Double-Blind Period B						
				1	2	4	6	8	10	
Week:			A1-A4							
Day:		A1	A15 – A29	B1	B8	B15	B29	B43	B57	B71
Consent	X									
Medical Hx	X									
Full Physical Exam	X									X
Brief Physical Exam		X	A29			X	X	X		
Trough BP, Heart Rate	X	X	A15, A22, A29	X	X	X	X	X	X	X
Adverse Events		X	A15, A22, A29	X	X	X	X	X	X	X
Concomitant Medication	X	X	A15, A22, A29	X	X	X	X	X	X	X
12-lead ECG		X	A22							X
CXR		X								
Laboratory Tests ^b		X	A22					X		X
Trough Urinary ANP			A22							X
Pregnancy Test	X		A29			X		X		X
Randomization				X						
Study Drug Titration						X	X			
Extended Visit				X		X	X			
BP, Heart Rate ^d			A22						X	
Urinary ANP ^{d, e}			A22						X	
Plasma Drug Levels ^c										X
Medication Dispensing		X	A15, A22	X	X	X	X	X	X	
Medication Count			A15, A22, A29		X	X	X	X	X	X

a. Data from NDA volume 2.321, table 5.8.

b. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); and (3) Urinalysis (specific gravity, pH, protein, microscopic analysis). A 24-hour urine was to be obtained if the dipstick was >2+.

c. Stored for later analysis as needed.

d. Measured at 7 plus or minus one hour after last dose.

e. Urinary ANP levels measured using a radioimmunoassay after solid phase extraction of ANP from urine.

7.11 Statistical Considerations

Sponsor's Statistical Plan

Power

The trial size resulted in a 90% power to detect differences of 2.2 mmHg between treatment groups. This assumed a 10% drop-out rate and a standard deviation of 7.5 mmHg for change between baseline in trough SeDBP.

Multiplicity

Dunnnett's procedure was used to adjust for multiple comparisons between four treatment groups and still maintain the overall significance level of 0.05 for the primary analysis.

Exploratory Analyses

None.

Interim Analyses

None.

Statistical Analysis

1) Populations for Analysis

Randomized Subjects

This set was used for the primary efficacy analyses. It did not include those subjects who did not have both a baseline and post-randomization assessment. Subsets of this population included the 'Evaluable patients with valid troughs.' Missing values were not imputed.

Treated Subjects

This population included those subjects who received at least one dose of medication, according to the actual study drug administered. A subset of this population included 'Subjects with Available Urinary ANP,' which was drawn from the first 217 subjects.

2) Statistical Methods for protocol CV137-030

ANCOVA was used to compare the omapatrilat regimens to placebo with respect to changes in BP. The ANCOVA model included a term for treatment regimen and baseline BP as covariates.

For each comparison of omapatrilat dose to placebo and omapatrilat to amlodipine, the estimated difference in adjusted mean and the associated 95% confidence interval and p-Value for the t-test of the between-group difference was calculated. Statistical significance was evaluated at alpha=0.05.

a) Safety

Standard analyses of reported AEs and changes in lab values were to be performed. See vol. 2.321, section 6.3.5 for details.

FDA Statistical Analysis

Unless noted, all p-Values and treatment effects in this review are from the sponsor's analysis. In many cases, the sponsor's analysis excluded particular individuals and/or sites, largely for protocol violations. In addition, only observed values were used in the sponsor's analyses (that is, missing values were not imputed). The FDA preferred the intent-to-treat population for efficacy. Missing values were imputed using Last Observation Carried Forward (LOCF) methods, including all randomized patients. The FDA analyses were done using ANOVA without adjustment for baseline covariates, based on concerns for the uniformity of the relationship between baseline and change from baseline across the treatment groups (a requisite for use of ANCOVA). Using these methods, important efficacy variables were reanalyzed. Unless otherwise noted, this approach yielded qualitatively similar results to those obtained by the sponsor.

7.12 Efficacy Outcomes

7.12a Disposition of Subjects

As presented below, 1232 subjects were enrolled and 725 were randomized to receive double-blind therapy. Reasons for discontinuation prior to entry into the double-blind phase (primarily failure to meet inclusion/exclusion criteria) are shown below.

Table 7.12a.1 Reasons for discontinuation prior to randomization^a.

Reason for Exclusion/Discontinuation	Number of Subjects
Inclusion/Exclusion Criteria Not Met	338
Withdrawal of Subject Consent	82
Lost to Follow-up	34
Adverse event	25
Investigator Request	11
Uncontrolled Disease State	8
Other	3
Prohibited Medication	3
Administrative Reason	1
Non-Compliance	1
Protocol Violation	1
Total	507

a. Data from NDA vol. 2.321, table 8.1A.

After randomization, 606 subjects (83.6%) completed the 10-week double-blind treatment period, and 119 (16.4%) discontinued prematurely. The discontinuation rate was highest in the placebo group (27.4%) and was lower with omapatrilat (14.7%) and amlodipine (12.6%) regimens.

Table 7.12a.2 Summary of subjects discontinued in CV137-030^a.

	Placebo N = 146	Omapatrilat 20/40/80 mg N = 286	Amlodipine 5/10/10 mg N = 293
Reason for Discontinuation			
Subjects Discontinued	40	42	37
Adverse Event	9 (6.2%)	23 (8.0%)	19 (6.5%)
Subject Request	12	8	11
Uncontrolled Disease State	3	0	0
Prohibited Medication	1	1	0
Lost to Follow-up	2	3	5
Poor or Non-Compliance	0	1	0
Investigator Request	11	5	1
Inclusion/Exclusion Criteria Not Met	0	1	0
Other	2	0	1
Subjects Completing The Double-blind Period	106 (72.6%)	244 (85.3%)	256 (87.4%)

a. Data from NDA volume 3.321, table 8.1B.

7.12b Protocol Violations & Deviations

Because of 'questionable accuracy,' efficacy results from site #055 (9 subjects) were excluded from the efficacy analyses. The list of protocol violations can be found in vol. 3.321, table 7.3B. There were 30 patients so identified, the most common cause for violation being use of prohibited medications (e.g., anti-arrhythmics, decongestants).

7.12c Subject Demographics & Baseline Characteristics

The demographics of the randomized treatment groups are shown below. The groups were well-balanced demographically at the time of randomization.

Table 7.12c.1 Demographics of subjects randomized into double-blind part of CV137-030^a.

Baseline Characteristic	Placebo N = 146	Omapatrilat 20/40/80 mg N = 286	Amlodipine 5/10/10 mg N = 293
Age, years			
Mean (sd)	51.1 (8.4)	51.4 (8.2)	51.4 (8.6)
Range	23 - 65	24 - 74	19 - 68
Age Group, n (%)			
< 65 years	145 (99%)	283 (99%)	289 (99%)
≥ 65 years	1 (1%)	3 (1%)	4 (1%)
Gender, n (%)			
Male	83 (57%)	170 (59%)	171 (58%)
Female	63 (43%)	116 (41%)	122 (42%)
Race, n (%)			
White	110 (75%)	226 (79%)	235 (80%)
Black	17 (12%)	33 (12%)	32 (11%)
Other	19 (13%)	27 (9%)	26 (9%)
Weight, kg			
Mean (sd)	90.9 (19.8)	91.4 (20.4)	88.4 (17.6)
Range	45.5 - 142.7	47.9 - 173.7	49.6 - 137.7
Duration of HTN (yrs),			
Mean (sd)	8.9 (7.8)	8.2 (8.6)	9.2 (8.6)
Range	0 - 32	0 - 42	0 - 45

a. Data from NDA volume 2.321, table 8.3A.

Baseline trough SeDBP was similar in all of the treatment groups, averaging 100.2 mm Hg in the omapatrilat and placebo groups and 100.6 mm Hg in the amlodipine group. Baseline trough SeSBP was between 151.8 and 152.9 mm Hg for the 3 treatment groups.

Other baseline measures of blood pressure (e.g., peak SBP and DBP) and heart rate were also similar among the treatment groups (see NDA vol. 2.321, Tables 8.3B and 8.3C for details).

The occurrence of other medical conditions, when grouped by body system, was similar across the treatment groups, occurring in an average of 48.3 to 50.6% of the treatment groups. The most common cardiovascular conditions present were hypertriglyceridemia and hypercholesterolemia, present in 32.5 to 35.6% and 8.7 to 12.3% of the subjects respectively. Prior anti-hypertensive medications were used by 67.8 to 74.0% of the treatment groups. Diabetes occurred in 34.5 to 7.5% of the patients. See NDA tables S.6.4A and S.8.4A for details.

7.12d Concomitant Therapies used after Trial Initiation

Concomitant medications were used by 70.5 to 73.7% of the subjects during the double-blind portion of the study. The use of concomitant medications used (see NDA volume 3.322, table S.9.4A) was balanced across the 3 treatment groups.

7.12e Extent of Exposure to Study Drug in CV137-030

Subjects in the trial received study drug for a mean of 60-65 days.

Table 7.12e.1 Exposure to study drug in CV137-030^a.

Duration	Placebo N = 146	Omapatrilat N = 286	Amlodipine N = 293
≤ 7 days	5 (3.4)	9 (3.1)	6 (2.0)
8-30 days	20 (13.7)	20 (7.0)	14 (4.8)
31-60 days	13 (8.9)	15 (5.2)	17 (5.8)
61-90 days	108 (74.0)	242 (84.6)	256 (87.4)
Mean Duration of Exposure (days)	60	63	65

a. Data from NDA vol. 3.321, table 9.1.

7.12f Primary Analyses of the Study CV137-030 Results

The first table summarizes the results of the primary efficacy analysis: the change from baseline in trough seated diastolic blood pressure (SeDBP) following 10 weeks of once-daily oral administration of omapatrilat or amlodipine. As shown, the omapatrilat group had a significantly greater fall in SeDBP at 10 weeks than amlodipine (-14.4 vs. -12.3 mmHg, a difference of 2.1 mm Hg, p=0.002). A comparison to placebo-treated subjects is included as well.

The table also summarizes two of the secondary analyses of interest: the effect of omapatrilat on SeSBP and on the pulse pressure, compared with amlodipine.

Table 7.12f.1 Mean change from baseline in trough SeDBP, SeSBP, and pulse pressure at week 10 in CV137-030^a.

Efficacy Variable	Placebo N=104	Omapatrilat 20/40/80 mg N=241	Amlodipine 5/10/10 mg N=251
Trough SeDBP, mmHg			
Baseline Mean (sd)	99.4 (3.5)	100.2 (4.1)	100.5 (4.3)
Adjusted Mean Change (se)	-4.5 (0.7)	-14.4 (0.5)	-12.3 (0.5)
Diff. From Amlodipine (95% CI)	+7.8	-2.1 (-3.4, -0.8)	N/A
p-Value c/w Amlodipine	--	0.002	--
Diff. From Placebo (95% CI)	N/A	-9.9 (-11.6, -8.2)	-7.8 (-9.5, -6.1)
p-Value c/w Placebo	--	<0.001	<0.001
Trough SeSBP, mmHg			
Baseline Mean (sd)	151.8 (15.5)	151.6 (14.4)	152.8 (14.8)
Adjusted Mean Change (se)	-3.0 (1.2)	-20.8 (0.8)	-17.7 (0.8)
Diff. From Amlodipine (95% CI)	+14.7	-3.1 (-5.2, -0.9)	N/A
p-Value c/w Amlodipine	--	0.005	--
Diff. From Placebo (95% CI)	N/A	-17.8 (-21.0, -14.6)	-14.4 (N/A)
p-Value c/w Placebo	--	<0.001	--
Pulse Pressure, mmHg			
Baseline Mean (sd)	52.5 (14.3)	51.4 (13.1)	52.3 (13.2)
Adjusted Mean Change (se)	+1.8 (0.9)	-6.4 (0.6)	-5.4 (0.6)
Diff. From Amlodipine (95% CI)	+7.2	-1.0 (-2.5, 0.6)	--
p-Value c/w Amlodipine	N/A	0.219	--
Diff. From Placebo (95% CI)	--	-8.2 (-10.2, -6.2)	-7.2
p-Value c/w Placebo	--	0.387	N/A

a. Data from NDA vol. 3.321, table 10.1.1. P-value using ANCOVA per the sponsor. Excludes site 55.

The results of the FDA statistician, John Lawrence, are summarized in the table below. His modeling did not exclude site 55, and used last observation carried forward to account for missing data. He reported a nominally significant greater effect of omapatrilat on the placebo-subtracted trough SeDBP (the primary efficacy endpoint). Other relevant changes from his analysis are also summarized. Note the relatively larger difference in the peak SeSBP between the two groups, relative to the difference at trough.

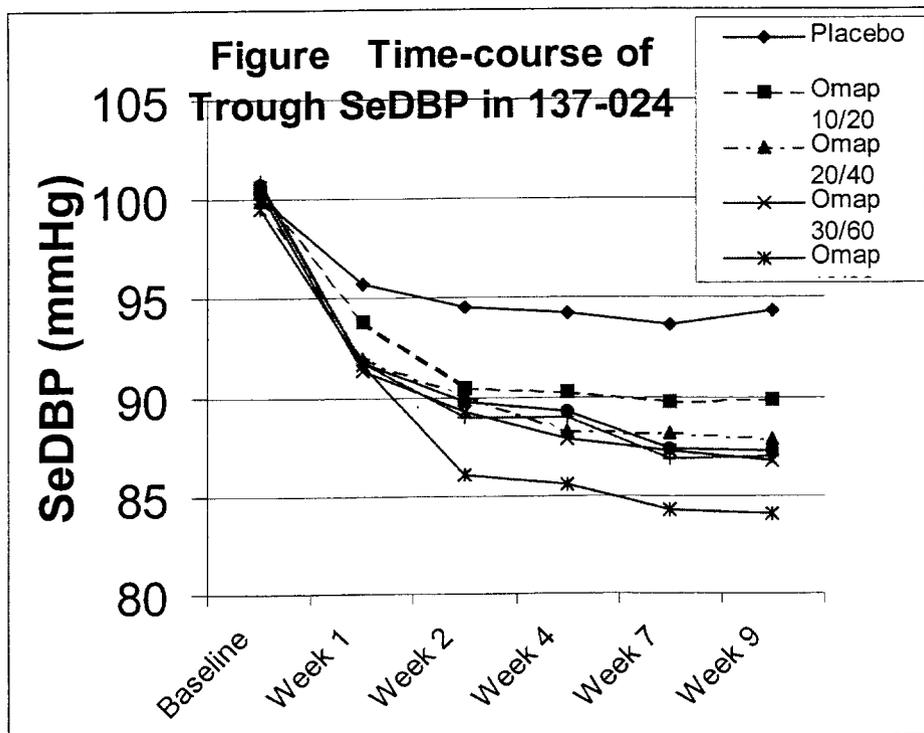
Table 7.12f.2 Mean change from baseline in trough and peak SeDBP and SeSBP at week 10 in CV137-030 per the FDA statistical analysis^a.

Efficacy Variable	Omapatrilat N=241	Amlodipine N=251
Trough SeDBP, mmHg		
Diff. From Amlodipine	-1.73	--
p-Value c/w Amlodipine	0.0079	--
Diff. From Placebo	-10.02	-8.29
p-Value c/w Placebo	<0.001	<0.001
Trough SeSBP, mmHg		
Diff. From Amlodipine	-2.17	--
p-Value c/w Amlodipine	0.063	--
Diff. From Placebo	-17.20	-15.03
p-Value c/w Placebo	<0.001	<0.001
Peak SeDBP, mmHg		
Diff. From Amlodipine	-2.42	--
p-Value c/w Amlodipine	0.0012	--
Diff. From Placebo	-10.45	-8.03
p-Value c/w Placebo	<0.001	<0.001
Peak SeSBP, mmHg		
Diff. From Amlodipine	-6.82	--
p-Value c/w Amlodipine	<0.001	--
Diff. From Placebo	-23.4	-16.6
p-Value c/w Placebo	<0.001	<0.001

a. Analysis per Dr. John Lawrence, FDA statistician.

In data not shown, similar changes were reported by the sponsor for the population with available peak and trough data ('evaluable' population). See NDA vol. 2.322, tables S.10.1.4A and S.10.1.4B for details.

A reduction in blood pressure occurred within the first week of treatment for all groups, including placebo.



7.12g Additional Efficacy Analyses of the Study CV137-030

Sub-Group Analyses

Too few individuals >65 years of age were included in the trial to allow meaningful analysis of sub-grouping by age. No disparity of effect was detected when the patients were analyzed according to gender.

Table 7.12g.1 Effects of omapatrilat on trough SeDBP in subjects grouped by gender from CV137-030^a.

Gender Effects on SeDBP	Placebo	Omapatrilat 20/40/80 mg	Amlodipine 5/10/10 mg
Male	N=58	N=139	N=143
Mean change in SeDBP (mm Hg)	-4.2	-14.0	-11.1
Female	N=46	N=102	N=108
Mean change in SeDBP (mm Hg)	-4.5	-15.0	-14.0

a. Data from NDA vol. 2.322, table S.10.4A, and excludes site #55.

Omapatrilat had a similar effect on placebo-subtracted SeDBP in blacks (8.4 mmHg) when compared with either white (10.8 mmHg) or 'other' (6.9 mmHg) racial groups, although the numbers of subjects in the black and non-white groups were small. For the black population, no difference between omapatrilat and amlodipine are evident.

Table 7.12g.2 Effects of omapatrilat on trough SeDBP in subjects grouped by race from CV137-030^a.

Racial Effects on Mean Changes in Trough SeDBP	Placebo	Omapatrilat 20/40/80 mg	Amlodipine 5/10/10 mg
White	N=80	N=195	N=204
Mean change in SeDBP (mm Hg)	-3.8	-14.6	-12.3
Black	N=10	N=15	N=24
Mean change in SeDBP (mm Hg)	-4.7	-13.1	-13.0
Other	N=14	N=22	N=23
Mean change in SeDBP (mm Hg)	-7.2	-14.1	-12.3

a. Data from NDA vol. 2.322, table S.10.4B, and excludes site #55.

The FDA also performed an analysis looking at the effects of race and gender combined. These results, shown below, suggest that the effects of omapatrilat are significantly diminished in the black populations of both genders, relative to amlodipine. For black females, amlodipine was nominally significantly more effective at lowering SeDBP.

Table 7.12g.3 FDA analysis of trough SeDBP in subjects grouped by race and gender^a.

Difference between Amlop and Ompa for Trough SeDBP	Omap vs. Amlodipine	p-Value
White Males (n=328)		
Mean change in SeDBP (mm Hg)	-2.5	0.008
White Females (n=225)		
Mean change in SeDBP (mm Hg)	-2.3	0.04
Black Males (n=43)		
Mean change in SeDBP (mm Hg)	+1.0	0.8
Black Females (n=36)		
Mean change in SeDBP (mm Hg)	+7.9	0.01

a. Analysis per Dr. John Lawrence, FDA statistician.

Amlodipine was also more effective at lowering the SeSBP in black females in this analysis (-18.1 for amlodipine, -5.7 for omapatrilat, difference +12.4 mmHg, p=0.018).

Therapeutic Response

The sponsor calculated the percentage of the subjects who had their blood pressures improve to pre-specified levels in the three treatment groups at 10 weeks, and these results are summarized below. First, improvement in SeDBP alone is summarized, where both omapatrilat and amlodipine use was associated with a >50% of the subjects who either normalized or improved their SeDBP. Next, improvement in both SeDBP and SeSBP is examined. Subjects taking either amlodipine or omapatrilat had a higher rate of improvement relative to placebo.

Table 7.12g.4 Therapeutic response at week 10 in CV137-030^{a, b}.

Therapeutic Response ^b	Placebo N= 104	Omapatrilat 20/40/80 mg N = 241	Amlodipine 5/10/10 mg N = 251
SeDBP			
Normalized, n (%)	25 (24.0%)	161 (66.8%)	149 (59.4%)
Favorable, n (%)	27 (26.0%)	185 (76.8%)	181 (72.1%)
Both SeDBP and SeSBP			
Normalized, n (%)	15 (14.4%)	141 (58.5%)	122 (48.6%)
Favorable, n (%)	18 (17.3%)	170 (70.5%)	159 (63.3%)

a. Data from NDA vol. 2.321, table 10.1.2, based on Randomized Subjects with available trough SeDBP at week 10.

b. Normalized: Trough SeDBP <90 mmHg
Trough SeSBP <140 mmHg.

Favorable: Trough SeDBP <90 or decrease from baseline ≥10 mmHg.
Trough Se SBP <140 mmHg or decrease from baseline ≥20 mmHg.

Trough:Peak Ratio

Peak SeDBP and peak SeSBP were also examined, first alone, and then as part of an assessment of the peak/trough ratio. Due to the use of peak data for peak/trough determination, only those patients with valid peak and trough data are included in the table below. Peak values were measured 7±1 hour after dosing.

Table 7.12g.5 Treatment comparisons of change from baseline in peak measures for SeSBP and SeDBP for 'evaluable' subjects, from CV137-030 excluding site #55^a.

Efficacy Variable	Placebo N=96	Omapatrilat 20/40/80 mg N=231	Amlodipine 5/10/10 mg N=236
Peak SeDBP mmHg			
Baseline Mean	97.5	98.4	98.8
Mean Change from Baseline (SE)	-5.5 (0.8)	-16.0 (0.5)	-13.4 (0.5)
Difference from Placebo	--	-10.5	-7.9
p-Value: c/w placebo ^a	--	<0.001	N/A
Difference from Amlodipine	+7.9	-2.6	--
p-Value: c/w amlodipine ^a	N/A	<0.001	--
Peak SeSBP mmHg			
Baseline Mean (SD)	150.4	152.2	151.8
Adjusted Mean Change (SE)	-1.2 (1.4)	-24.6 (0.9)	-18.1 (0.9)
Difference from Placebo	--	-23.4	-16.9
p-Value: c/w placebo	--	<0.001	N/A
Difference from Amlodipine	+16.9	-6.5	--
p-Value: c/w amlodipine ^a	N/A	<0.001	--

a. Data from NDA vol. 2.322, table S.10.1.3A. Evaluable patients had valid peak and trough data available.

Using these data, then sponsor then determined the trough:peak ratio for the treated patients with evaluable data at the end of week 8. These data are summarized below for the SeDBP measurements. Similar results were obtained for the systolic BP.

Table 7.12g.6 Summary statistics for trough and peak measures of SeDBP after 8 weeks for 'evaluable' subjects in CV137-030^a.

Efficacy Variable	Placebo N=104	Omapatrilat 20/40/80 mg N=241	Amlodipine 5/10/10 mg N=251
Peak SeDBP mmHg			
Baseline Mean	97.5	98.4	98.8
Mean Change from Baseline (SE)	-5.5 (0.8)	-16.0 (0.5)	-13.4 (0.5)
Difference from Placebo	--	-10.5	-7.9
Trough SeDBP mmHg			
Baseline Mean	99.3	100.4	100.4
Adjusted Mean Change (SE)	-5.6 (0.7)	-13.9 (0.5)	-12.7 (0.5)
Difference from Placebo	--	-8.4	-7.2
Trough:Peak Ratio^a	--	0.80	0.90

a. Data from NDA vol. 2.322 table S.10.1.4A. Trough:peak calculated from ratio of relative changes from placebo.

Withdrawal Effects

Changes in blood pressure following drug withdrawal were not measured in this trial.

Pharmacokinetic Effects

Pharmacokinetic effects were not studied in this trial.

Heart Rate

The effect of omapatrilat and amlodipine on trough supine heart rate at the end of 8 weeks is summarized below. No significant trends were discernable in the trough data (shown below) or in the changes in mean peak heart rate (not shown).

Table 7.12g.7 Treatment comparisons of change from baseline in trough measures for trough seated heart rate (SeHR), supine heart rate (SuHR), and standing heart rate (StHR) at week 10^a.

Efficacy Variable	Placebo N=104	Omapatrilat 20/40/80 mg N=241	Amlodipine 5/10/10 mg N=251
Trough SeHR			
Baseline Mean (SD)	72.4	73.6	73.2
Adjusted Mean Change (SE)	0.9 (0.8)	0.1 (0.5)	1.3 (0.5)
Difference from Placebo (95% CI)	--	-0.9	0.4
p-Value: comparison with placebo	--	0.387	N/A
Trough StHR			
Baseline Mean (SD)	75.8	76.4	76.5
Adjusted Mean Change (SE)	2.1 (9.4)	0.6 (10.0)	1.2 (9.7)
Difference from Placebo (95% CI)	--	-1.5	-0.9
p-Value: comparison with placebo	--	N/A	N/A

a. Data from NDA vol. 2.306, table S.10.1.1D3 and D5, from as randomized population excluding site #55.

Urinary ANP Excretion

ANP excretion has been taken as a marker of neutral endopeptidase (NEP) activity, as in the absence of NEP there is a reduction in the metabolism of ANP. The sponsor looked at ANP excretion at trough and peak in the three treatment groups, as summarized below. Omapatrilat use was associated with an increase in ANP excretion of approximately 4-fold over baseline, while no significant change was detected in the amlodipine group.

Table 7.12g.8 Peak and Trough changes in urinary ANP excretion in CV137-030^a.

Urinary ANP, pg/mg Creatinine	Placebo	Omapatrilat 20/40/80 mg	Amlodipine 5/10/10 mg
Trough (Week 10)	N = 31	N = 92	N = 91
Mean Change (sd)	0.0 (4.7)	7.4 (17)	0.3 (7.4)
95% Confidence Limits	(-1.8, 1.7)	(4.0, 10.9)	(-1.3, 1.8)
Peak (Week 8)	n = 32	n = 91	n = 93
Mean Change (sd)	1.1 (7.1)	41.4 (29)	-0.2 (4.3)
95% Confidence Limits	(-1.5, 3.6)	(35.3, 47.5)	(-1.1, 0.7)

a. Data from NDA vol. 2.331, table 11.2.1.

7.13 Safety Outcomes

The adverse events, serious adverse events, and subject discontinuations are discussed in Dr. Pelayo's review. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 7.13.1 Clinical adverse experience summary from CV137-030^a.

Event	Placebo N = 146	Omapatrilat N = 286	Amlodipine N = 293
AE, total (% of subjects)	90 (61.6)	192 (67.1)	198 (67.6)
SAE	1 (0.7)	3 (1.0)	2 (0.7)
Death	0	0	0
Discontinuations due to AE	9 (6.2)	23 (8.0)	19 (6.5)

a. Data from NDA volume 3.321, table 12.0.

7.14 Study CV137-030 Efficacy Summary

In CV137-030, eligible patients were randomized to receive placebo, omapatrilat or amlodipine. Doses of omapatrilat and amlodipine were force-titrated to achieve final doses by the end of 4 week: omapatrilat 80 mg per day, amlodipine 40 mg per day. Patients were then followed through week 10. The primary endpoint of the trial was the comparison of the change from baseline in trough SeDBP for omapatrilat and amlodipine at 10 weeks.

1. Omapatrilat, at the dose used in this trial, had a larger anti-hypertensive effect than amlodipine (used as a forced-titration 5 to 10 mg per day), as measured by the change in SeDBP. After 10 weeks, the sponsor reported a difference in the placebo-subtracted SeDBP between the two groups was 2.1 mm Hg (omapatrilat -9.9 mm Hg, amlodipine -7.8 mmHg, $p < 0.001$). Similar effects were seen for the placebo-subtracted SeSBP (omapatrilat -17.8 mmHg, amlodipine -14.4 mmHg, $p < 0.001$), but not the placebo-subtracted changes in pulse pressure (omapatrilat -8.2 mmHg, amlodipine -7.2 mm Hg, p-Value NS). The FDA confirmed that omapatrilat had a significantly larger effect on SeDBP using a separate analysis.

2. Omapatrilat, used in a forced titration scheme (20 to 40 to 80 mg per day) for 10 weeks, lowered blood pressure in patients with mild-to-moderate hypertension, including effects on placebo-subtracted trough and peak seated diastolic BP (Se DBP) as well as placebo-subtracted trough and peak seated systolic BP (SeSBP).

1) Placebo-subtracted SeDBP: -9.9 mmHg (95% C.I. -11/6 to 8.2, $p < 0.001$).

2) Placebo-subtracted SeSBP: -17.8 mmHg (95% C.I. -21.0 to -14.6, $p < 0.001$).

3) Placebo-subtracted PP: -8.2 mmHg (95% C.I. -10.2 to -6.2).

3. Omapatrilat and amlodipine had similar effects on SeDBP and SeSBP were seen when the population was examined by subgroups according to gender and race. Too few subjects ≥ 65 years old were enrolled to assess efficacy in that sub-groups.

4. Amlodipine had a greater effect than omapatrilat on SeDBP and SeSBP in black females, per an FDA analysis. These data suggest a racial component to the anti-hypertensive effect of omapatrilat.

5. Once a day omapatrilat had a peak:trough ratio of 0.80 after 10 weeks.

6. After 10 weeks, a higher percentage of patients in both the amlodipine and omapatrilat groups had a 'Therapeutic Response' as defined by the sponsor (50-70%), when compared with placebo (15-25%).

7. No clinically-significant effect of omapatrilat on mean heart rate after 10 weeks was detected.

8. Omapatrilat use for 10 weeks was associated with an increase in ANP excretion when compared with placebo, while no significant change was detected in the amlodipine group.

9.0 to 9.14 Review of CV137-032

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9.1 Title of Study

A Multicenter, Randomized, Double-Blind Study of Omapatrilat Versus Amlodipine As Assessed by 24-Hour Ambulatory Blood Pressure Monitoring (ABPM) Technique (CV137-032).

9.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA volume 2.386, table S.4. CV137-032 was conducted at 93 sites in France, U.K., Spain, Germany, Italy, Switzerland, Belgium, and Israel.

9.3 Background

Initial protocol submitted to the FDA: Non-IND study, protocol not submitted to FDA

First protocol amendment submitted: Not applicable for non-IND study

Subject entry: 6.22.98 to 5.19.99

9.4 Study Design

This was a multicenter, randomized, double-blind, active-controlled, parallel group, forced titration study comparing the anti-hypertensive effects of omapatrilat and amlodipine in subjects with mild-to-moderate hypertension. Following a 4-week single-blind placebo lead-in period, qualifying subjects were randomized in a 1:1 ratio to a regimen of omapatrilat or amlodipine for 10 weeks. The regimen of omapatrilat consisted of 20 mg initially (Level I), titrated to 40 mg at Week 2 (to Level II) and to 80 mg at Week 4 (to Level III). The regimen of amlodipine consisted of 5 mg initially (Level I) titrated to 10 mg at Week 2 (Level II) and maintained at 10 mg at Week 4 (Level III).

For details on the collection of ABPM blood pressures, see my review of CV137-030. For details of the methods used in the collection of cuff BP, including the determination of baseline values, see my review of CV137-006.

9.5 Primary and Secondary Objectives

Primary Objective

Primary objective was to compare the change from baseline in 24hour(hr)-average ambulatory mean blood pressure following 10 weeks of once-daily oral administration of omapatrilat to that of amlodipine in subjects with mild-to-moderate hypertension.

Secondary objectives:

- 1) To compare the change from baseline in 24hr-average ambulatory diastolic blood pressure (ADBP), ambulatory systolic blood pressure (ASBP) and ambulatory pulse pressure APP) after 10 weeks of once-daily administration of omapatrilat and amlodipine.
- 2) To compare the change from baseline in 12hr-average daytime AMBP, ADBP, ASBP and APP after 10 weeks of once-daily administration of omapatrilat to amlodipine.
- 3) To assess the change from baseline in trough seated office blood pressure (SeBP) and pulse pressure (PP) after 10 weeks of once-daily administration of omapatrilat and amlodipine.
- 4) To compare the response to therapy based on the percentage of subjects normalized (trough SeDBP < 90 mmHg) after 10 weeks of once-daily administration of omapatrilat and amlodipine.
- 5) To assess the safety and tolerability of omapatrilat and amlodipine administered for 10 weeks
- 6) To compare the incidence, relative to amlodipine, of treatment-emergent edema occurring during the 10-week treatment period.
- 7) To describe changes in blood pressure (BP) and heart rate (HR) in other positions and at other timepoints.

9.6 Number of subjects/ randomization

A total of 644 subjects were enrolled, of whom 430 were randomized and 397 completed 10 weeks of double-blind therapy.

9.7 Inclusion/ Exclusion Criteria

Consenting males, or females of non-childbearing potential, age 18 years or greater, with mild-to-moderate hypertension (SeDBP 95-110 mmHg). For full list of inclusion and exclusion criteria see NDA vol. 2.385.

9.8 Dosage/ Administration

Following a 4-week single-blind placebo lead-in period, qualifying subjects were randomized in a 1:1 ratio to a regimen of omapatrilat or amlodipine for 10 weeks. The regimen of omapatrilat consisted of 20 mg titrated to 40 mg at Week 2 (to Level II) and to 80 mg at Week 4 (to Level III). The regimen of amlodipine consisted of 5 mg titrated to 10 mg at Week 2 (Level II) and maintained at 10 mg at Week 4 (Level III).

9.9 Duration/ Adjustment of Therapy

For sites in France, because of the central Ethics Committee request, subjects with SeSBP ≤ 100 mmHg prior to titration at Week 2 (Level II) or Week 4 (Level III) were not to be titrated to the next dose level of study medication and were to be discontinued.

9.10 Safety and Efficacy Endpoints Measured

Table 9.10.1 Timetable for clinical observations and lab measurements in the CV137-032^a.

	Enroll	A1	Lead-In Period (A)	Double-Blind Period (B)							
Week			A1-A4		1	2	4	6	8		10
Day			A15- A29	B1	B8	B15	B29	B43	B57	B70	B71
Consent	X										
Medical History	X										
Full Physical Exam	X										X
Brief Physical Exam		X	A29			X	X	X			
BP, Heart rate	X	X	A15, A22, A29	X	X	X	X	X	X	X	X
Adverse Events		X	A15, A22, A29	X	X	X	X	X	X	X	X
12-lead ECG		X	A22								X
Chest X-ray ^b		X									
Laboratory Tests ^c		X	A23					X			X
Randomization				X							
Extended Visit				X		X	X				
Titration Study Visit						X	X				
ABPM Measurements			A22, A23							X	X

a. Data from NDA volume 2.385, table 5.8.

b. If not done in previous 6 months.

c. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis).

9.11 Statistical Considerations

Sponsor's Statistical Plan

Power

The sample size was based on the single comparison between omapatrilat and amlodipine with respect to change from baseline to Week 10 in 24hr-average AMBP. A sample size of 165 subjects randomized to each group, including a 15% dropout rate, would provide at least 90% power to detect a 2.7 mmHg difference between the treatment regimens if such a difference truly existed. The sample size assumed a standard deviation of 7.0 mmHg, with two-sided testing at a significance level of $\alpha = 0.05$.

Multiplicity

No adjustment for multiplicity was made in the overall level of alpha necessary for significance.

Interim Analyses

There were no interim analyses.

Statistical Analysis

1) Study Populations

Randomized Subjects

This dataset included all efficacy data from the scheduled visits for all subjects randomized into the study. In this dataset, all subjects are included in the group to which they were randomized. For efficacy analyses, data from Site #069 were excluded.

This dataset was used for the summaries of subject disposition, demographic characteristics and baseline office efficacy measures as well as summaries and analyses of changes from baseline in the trough office measures.

For analysis of each efficacy variable at each analysis timepoint, any subjects who did not have both a baseline and post-randomization assessment were not represented in the analysis of that variable. Thus, analyses of individual efficacy variables could be based on a subset of the subjects in the Randomized Subject dataset (e.g., those with Week 10 data), rather than all randomized subjects.

One subset of the Randomized Subjects dataset was used for some analyses.

Randomized Subjects with Acceptable ABPM

This subset was used for analysis of the primary efficacy variable, 24hr-average AMBP at Week 10, and for the analysis of all secondary efficacy measures based on ABPM recordings and summaries of baseline ambulatory measures. This dataset contains assessments from all available acceptable ABPM recordings. A recording was considered acceptable for statistical analysis if at least 75% of the anticipated programmed readings remained after completion of machine editing, and if there were no more than 2 hours with missing or invalid readings within the first 12 hours and no more than 2 within the last 12 hours (with a total of no more than 3 missing hours during the entire 24 hour post-dosing period).

Treated Subjects

The dataset consisted of safety data from all subjects who received at least one dose of double-blind study medication. In this dataset, subjects are grouped according to the treatment actually received.

2) Statistical Methods for CV137-032

Change from baseline to Week 10 in 24hr-average AMBP was analyzed using analysis of covariance (ANCOVA) to compare the anti-hypertensive effects of omapatrilat and amlodipine. The model contained treatment as the main factor, with baseline as the covariate. The treatment comparison was carried out at the two-sided $\alpha=0.05$ level; the associated 95% confidence interval was calculated for the estimated difference.

Comparisons were done between the omapatrilat and amlodipine regimens for changes from baseline in trough SeBP measures and pulse pressure at Week 10, trough SeBP at Weeks 2 and 4, and peak SeBP at Week 8. These used the estimated difference in adjusted means between the omapatrilat and amlodipine together with the associated 95% confidence interval and the p-Value for the t-test of the between-group difference.

Therapeutic Response, defined as the proportions of subjects with normalized DBP (trough SeDBP < 90 mmHg) and favorable DBP (trough SeDBP normalized, or decreased at least 10 mmHg from baseline), and with normalized SBP (trough SeSBP < 140 mmHg) and favorable SBP (trough SeSBP normalized, or decreased at least 20 mmHg from baseline) were summarized by treatment regimen for each timepoint, as were the proportion of subjects with normalized systolic and diastolic BP and the proportion with favorable response in both trough diastolic and systolic BP .

Pharmacokinetics

There were no pharmacokinetic data collected or analyzed.

Safety

Safety analyses were descriptive in nature, and no formal statistical analyses were performed.

FDA Statistical Analysis

Unless noted, all p-Values and treatment effects in this review are from the sponsor’s analysis. In many cases, the sponsor’s analysis excluded particular individuals and/or sites, largely for protocol violations. In addition, only observed values were used in the sponsor’s analyses (that is, missing values were not imputed). The FDA preferred the intent-to-treat population for efficacy. Missing values were imputed using Last Observation Carried Forward (LOCF) methods, including all randomized patients. The FDA analyses were done using ANOVA without adjustment for baseline covariates, based on concerns for the uniformity of the relationship between baseline and change from baseline across the treatment groups (a requisite for use of ANCOVA). Using these methods, important efficacy variables were reanalyzed. Unless otherwise noted, this approach yielded qualitatively similar results to those obtained by the sponsor.

9.12 Efficacy Outcomes for CV137-032

9.12a Disposition of Subjects

A total of 644 subjects were enrolled into CV137-032, of which 430 subjects were randomized to receive double-blind therapy. After randomization, 397 (92.3%) subjects completed the 10 week double-blind period. The reasons for discontinuation prior to randomization for the double-blind portion of the trial are summarized below.

Table 9.12a.1 Reasons for discontinuation prior to randomization in CV137-032^a.

Reasons for Exclusion/Discontinuation	Number of Subjects
Adverse event	11
Inclusion/Exclusion Criteria not met	160
Withdrawal of subject consent	17
Investigator request	10
Other	7
Prohibited medication	4
Lost to follow-up	3
Uncontrolled disease state	2
Total	214

a. Data from NDA volume 2.385, Table 8.1A.

The next table summarizes the discontinuations during the double-blind portion of CV137-032.

Table 9.12a.2 Discontinuations during double-blind therapy in CV137-032^a.

Reason for Discontinuation	Omapatrilat 20/40/80 mg	Amlodipine 5/10/10 mg
Number of subjects randomized	213	217
Number of subjects discontinued	15 (7.0%)	18 (8.3%)
Adverse event	6	14
Withdrawal of subject consent	3	1
Uncontrolled disease state	2	0
Prohibited medication	2	1
Investigator request	1	0
Other	1	2
Number of subjects completing double-blind period	198 (93%)	199 (91.7%)

a. Table from NDA vol. 2.385, table 8.1B.

9.12b Protocol Violations & Deviations

Because of possible improprieties in the recording of blood pressure results in source documents, blood pressure and heart rate data from Site #069 (Principal Investigator J. Mey, M.D.) were excluded from all efficacy analyses.

A listing of the 34 subjects identified with significant protocol violations is presented in Supplemental Table S.7.3B in NDA vol. 2.386. The most common protocol violations included use of restricted medications and entry into the trial despite the presence of exclusion criteria (e.g., proteinuria) at baseline.

9.12c Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the subjects enrolled in the double-blind portion of the study are summarized below.

Table 9.12c.1 Demographics of CV137-032^a.

Baseline Characteristics	Omapatrilat 20/40/80 mg N = 213	Amlodipine 5/10/10 mg N = 217
Age, years		
Mean (sd)	53.9 (9.7)	53.5 (10.4)
Range	26 - 78	23 - 76
Age Group, n(%)		
< 65 years	176 (83%)	181 (83%)
65 - 74 years	32 (15%)	34 (16%)
≥ 75 years	5 (2%)	2 (1%)
Gender, n (%)		
Male	155 (73%)	156 (72%)
Female	58 (27%)	61 (28%)
Race, n (%)		
White	211 (99%)	216 (100%)
Black	2 (1%)	1 (0%)
Other	0	0
Weight, kg		
Mean (sd)	84.5 (15.0)	82.8 (12.4)
Range	45 - 135	55 - 120
Duration of HTN, years		
Mean (sd)	6.5 (6.7)	6.3 (7.1)
Range	0 - 32	0 - 40

a. Data from NDA volume 2.385, table 8.3A.

The baseline ambulatory and office (manual-cuff) blood pressures are summarized in the two tables below. Overall, the two treatment groups were balanced with regard to their mean blood pressures at the time of entry into the double-blind portion of the study.

Table 9.12c.2 Ambulatory blood pressure measurements at baseline in CV137-032^a.

Baseline Characteristic	Omapatrilat 20/40/80 mg N = 208	Amlodipine 5/10/10 mg N = 211
24hr-Averages		
24hr-Average AMBP, mmHg		
Mean (sd)	110.1 (9.1)	109.1 (9.1)
Range	86.4 - 135.2	79.6 - 133.5
24hr-Average ASBP, mmHg		
Mean (sd)	145.8 (13.2)	144.8 (13.4)
Range	116.5 - 194.1	111.0 - 174.2
24hr-Average ADBP, mmHg		
Mean (sd)	92.3 (8.4)	91.2 (8.2)
Range	69.6 - 116.5	60.4 - 117.0
24hr-Average APP, mmHg		
Mean (sd)	53.5 (9.8)	53.5 (9.7)
Range	36.9 - 88.9	33.6 - 82.4

Table 9.12c.2 Ambulatory blood pressure measurements at baseline in CV137-032 (cont)^a.

Baseline Characteristic	Omapatrilat 20/40/80 mg N = 208	Amlodipine 5/10/10 mg N = 211
Daytime (12hr)Averages		
12hr-Average AMBP, mmHg		
Mean (sd)	115.8 (9.5)	114.4 (10.0)
Range	89.7 - 143.1	81.7 - 142.5
12hr-Average ASBP, mmHg		
Mean (sd)	152.2 (13.5)	150.7 (14.2)
Range	120.3 - 195.8	110.6 - 185.9
12hr-Average ADBP, mmHg		
Mean (sd)	97.6 (8.8)	96.3 (9.2)
Range	72.2 - 123.5	65.9 - 121.3
12hr-Average APP, mmHg		
Mean (sd)	54.6 (10.2)	54.4 (10.2)
Range	37.1 - 89.1	32.0 - 83.6

a. Data from NDA vol. 2.385, table 8.3B.

Table 9.12c.3 Office blood pressure readings at baseline prior to randomization in CV137-032^a.

Baseline Characteristic	Omapatrilat 20/40/80 mg N = 209	Amlodipine 5/10/10 mg N = 213
SeSBP, mmHg		
Mean (sd)	157.0 (14.5)	156.6 (14.1)
Range	116.7 - 198.0	122.0 - 203.3
SeDBP, mmHg		
Mean (sd)	101.3 (5.1)	101.1 (4.4)
Range	82.0 - 114.7	94.7 - 110.8
SeDBP Group, n (%)		
SeDBP < 104 mmHg	136 (65.1%)	151 (70.9%)
SeDBP ≥ 104 mmHg	73 (34.9%)	62 (29.1%)
Pulse Press (PP), mmHg		
Mean (sd)	55.7 (12.9)	55.5 (12.8)
Range	21.3 - 98.7	26.7 - 98.7
SeHR, beats/min ^a		
Mean (sd)	74.0 (9.4)	73.3 (9.3)
Range	48 - 102	52 - 120

a. Data from NDA vol. 2.385, table 8.3C.

Past Medical History

Of the 430 randomized subjects, 192 subjects had a history of cardiovascular or other related diseases (other than hypertension). The most common of these were hypercholesterolemia (34.0%), hypertriglyceridemia (14.2%), and diabetes mellitus (8.6%).

Prior Antihypertensive Medications

A total of 289 (67.2%) of the 430 randomized subjects were reported to have previously received antihypertensive therapy. There were no important imbalances between groups related to the use of antihypertensive medications.

9.12d Concomitant Therapies used after Trial Initiation

Concomitant antihypertensive medications were not allowed. Other prohibited medications are listed in section 5.6.3 of the NDA study report, and included ergotamine tartrate, chronic bronchodilators, digitalis and other anti-arrhythmic agents, anticonvulsant medications, anti-psychotic or chronic tricyclic or tetracyclic anti-depressant medications, and lithium. In addition, immunosuppressive drugs or cytotoxic drugs within 12 months prior to enrollment, anabolic steroids, monoamine oxidase inhibitors, venlafaxine and bile acid-binding resins (e.g., cholestyramine and colestipol) were prohibited.

9.12e Extent of Exposure to Study Drug

Patient exposure to study drug is summarized below. Patients received study drug for a mean of 67-68 days.

Table 9.12e.1 Extent of exposure to double-blind study drug in CV137-032^a.

Duration	Omapatrilat 20/40/80 mg N = 213	Amlodipine 5/10/10 mg N = 217
≤ 7 days	3 (1.4%)	1 (0.5%)
8-30 days	7 (3.3%)	11 (5.1%)
31-60 days	3 (1.4%)	6 (2.8%)
61-90 days	200 (93.9%)	199 (91.7%)
Mean Exposure (days)	68	67

a. Data from NDA vol. 2.385, table 9.1.

9.12f Primary Efficacy Analysis for CV137-032

The primary efficacy analyses focused on the data at 10 weeks in the two treatment groups, using the randomized subjects population with acceptable ABPM data at baseline and at 10 weeks. In all analyses, the data from study site #069 was excluded from the analysis.

Ambulatory Blood Pressure Monitoring Results

The first table summarizes the changes in various ABPM parameters, including the primary efficacy analysis: the change from baseline to 10 weeks in the 24-hour average AMBP. For each of these points, the subjects in the omapatrilat group had a lower adjusted mean blood pressure.

Table 9.12f.1 Changes in ABPM parameters at week 10 in CV137-032^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 192	Amlodipine 5/10/10 mg N = 187
24hr-average AMBP, mmHg^b		
Baseline Mean (sd)	110.2 (8.9)	109.5 (9.0)
Adjusted Mean Change (se)	-15.9 (0.5)	-11.0 (0.5)
Difference from Amlodipine	-4.9	
(95 % CI)	(-6.2, -3.5)	
p-Value	< 0.001	
24hr-average ASBP, mmHg		
Baseline Mean (sd)	145.7 (12.7)	145.1 (13.2)
Adjusted Mean Change (se)	-20.4 (0.6)	-14.5 (0.6)
Difference from Amlodipine	-5.9	
(95 % CI)	(-7.7, -4.1)	
p-Value	< 0.001	
24hr-average ADBP, mmHg		
Baseline Mean (sd)	92.5 (8.2)	91.7 (8.0)
Adjusted Mean Change (se)	-13.6 (0.4)	-9.3 (0.4)
Difference from Amlodipine	-4.4	
(95 % CI)	(-5.6, -3.2)	
p-Value	< 0.001	
24hr-average APP, mmHg		
Baseline Mean (sd)	53.2 (9.2)	53.4 (9.7)
Adjusted Mean Change (se)	-6.7 (0.4)	-5.2 (0.4)
Difference from Amlodipine	-1.5	
(95 % CI)	(-2.5, -0.5)	
p-Value	0.003	

a. Data from NDA vol. 2.385 table 10.1.1.

b. Pre-specified primary efficacy parameter.

These data can also be shown as hourly means for ABPM at week 10. The next two figures (from the sponsor) show the hourly means for the SBP and DBP at 10 weeks. The upper curve in both cases is the amlodipine curve.

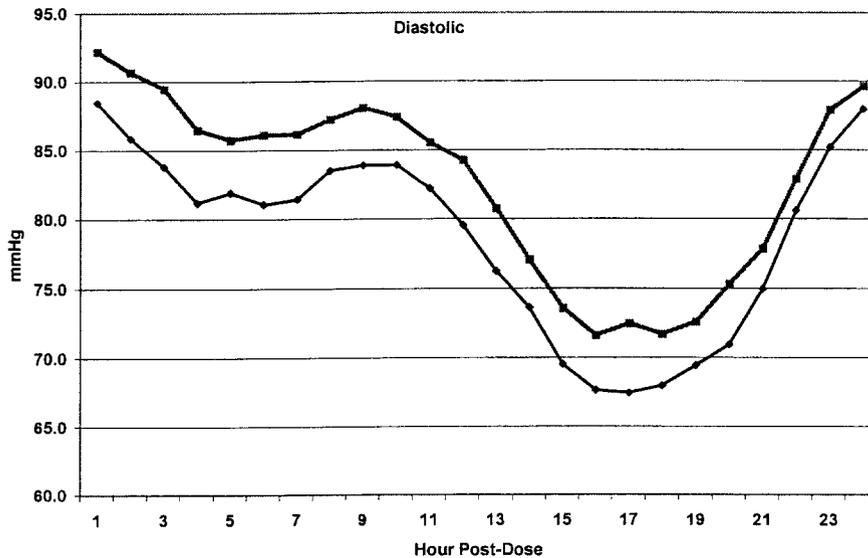
The results of the FDA statistician, John Lawrence, are summarized in the table below. He confirmed the absence of a significantly greater effect of omapatrilat on the primary efficacy endpoint of the trial.

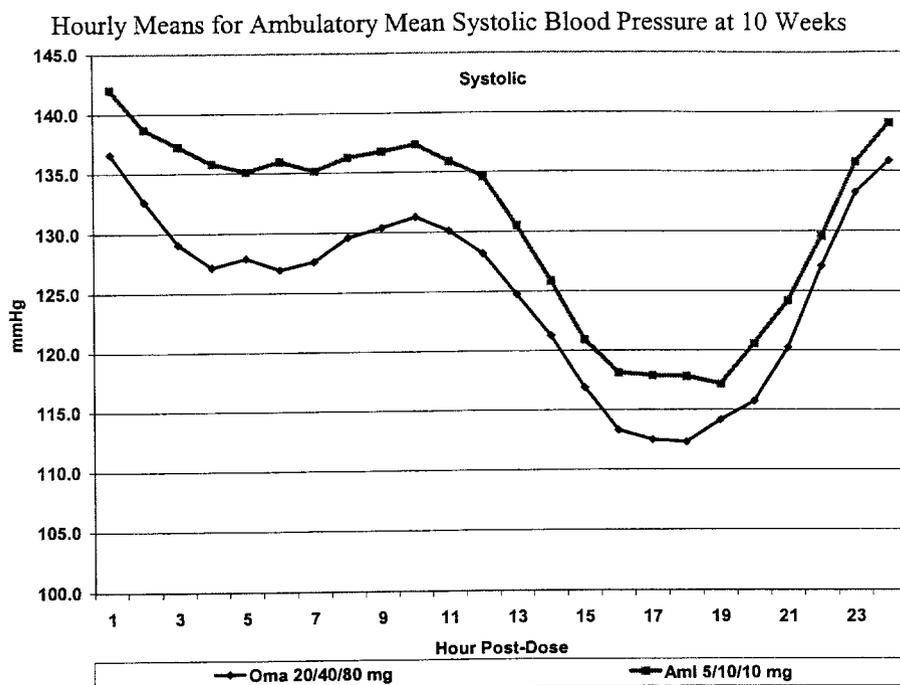
Table 9.12f.2 Mean change from baseline in ABPM measures at week 10 per the FDA statistical analysis^a.

EFFICACY VARIABLE	Omapatrilat c/w Amlodipine
24-Hour Mean ABP^b	
Diff. From Amlodipine	-6.10
p-Value c/w Amlodipine	<0.001
24-Hour Mean DBP	
Diff. From Amlodipine	-5.25
p-Value c/w Amlodipine	<0.001
24-Hour Mean SBP	
Diff. From Amlodipine	-7.78
p-Value c/w Amlodipine	<0.001

a. Analysis per Dr. John Lawrence, FDA statistician.
 b. Primary efficacy variable for this trial.

Hourly Means for Ambulatory Mean Diastolic Blood Pressure at 10 Weeks





In data not shown, similar changes were seen in the mean daytime 12-hour ABPM measurements: Daytime Average AMBP, ASBP, ABP, and PP (see NDA vol. 2.385 table 10.1.2 for summary).

9.12g Additional Analyses for CV137-032
Office (Cuff) Measurements of Blood Pressure

Changes in blood pressure as measured using blood-pressure cuffs in the office were also analyzed, and the results are summarized below. No significant difference in the SeDBP was demonstrated between the two treatment groups.

Table 9.12g.1 Mean changes in trough seated BPs at week 10 in CV137-032^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 194	Amlodipine 5/10/10 mg N = 194
Trough SeDBP, mmHg		
Baseline Mean (sd)	101.3 (5.1)	101.1 (4.5)
Adjusted Mean Change (se)	-13.5 (0.5)	-13.1 (0.5)
Difference from Amlodipine	-0.3	
95 % CI	(-1.7, +1.0)	
p-Value	0.617	
Trough SeSBP, mmHg		
Baseline Mean (sd)	157.0 (14.1)	156.3 (14.5)
Adjusted Mean Change (se)	-20.4 (0.8)	-17.5 (0.8)
Difference from Amlodipine	-2.9	
95 % CI	(-5.1, -0.6)	
p-Value	0.014	
Trough PP, mmHg		
Baseline Mean (sd)	55.6 (12.6)	55.2 (13.0)
Adjusted Mean Change (se)	-6.9 (0.6)	-4.4 (0.6)
Difference from Amlodipine	-2.6	
95 % CI	(-4.3, -0.8)	
p-Value	0.005	

a. Data from NDA vol. 2.385, table 10.2.1

The results of the FDA statistician, John Lawrence, are summarized in the table below. His modeling used last observation carried forward to account for missing data. He confirmed the absence of a significantly greater effect of omapatrilat on SeDBP. Other relevant changes from his analysis are also summarized.

Table 9.12g.2 Mean change from baseline in ABPM measures at week 10 per the FDA statistical analysis^a.

Efficacy Variable	Omapatrilat c/w Amlodipine
Trough SeDBP, mmHg	
Diff. From Amlodipine	-0.85
p-Value c/w Amlodipine	0.226
Trough SeSBP, mmHg	
Diff. From Amlodipine	-3.11
p-Value c/w Amlodipine	0.018

a. Analysis per Dr. John Lawrence, FDA statistician.

Therapeutic Response

The sponsor also evaluated the percentage of patients with evaluable data at 10 weeks who had a 'therapeutic response,' either normalized or favorable, to omapatrilat and amlodipine. The percentages were similar between the two treatment groups.

Table 9.12g.3 Therapeutic response at 10 weeks in CV137-032^a.

Therapeutic Response	Omapatrilat 20/40/80 mg N = 194	Amlodipine 5/10/10 mg N = 194
Trough SeDBP		
Normalized ^b , n (%)	117 (60.3%)	115 (59.3%)
Favorable ^b , n (%)	150 (77.3%)	152 (78.4%)
Both Trough SeDBP and Trough SeSBP		
Normalized, n (%)	90 (46.4%)	81 (41.8%)
Favorable, n (%)	125 (64.4%)	119 (61.3%)

a. Data from NDA vol. 2.385, table 10.2.2, based on Randomized Subjects.

b. Normalized: Trough SeDBP <90 mmHg

Trough SeSBP <140 mmHg.

Favorable: Trough SeDBP <90 or decrease from baseline ≥10 mmHg.

Trough Se SBP <140 mmHg or decrease from baseline ≥20 mmHg.

Sub –Group Analyses

Randomized Subjects with Baseline ADBP ≥ 85 mmHg

Results of the analyses of the 24hr-average AMBP, ASBP, and ADBP in the subset of subjects with baseline ADBP ≥ 85 mmHg were similar to the 24hr averages as above. This analysis was performed after a review of the blinded baseline ABPM data revealed that a significant number of subjects had baseline ADBP < 85 mmHg, in spite of elevated office cuff SeDBP > 95 mmHg.

Table 9.12g.4 Mean changes at 10 weeks in ABPM efficacy variables for subjects with baseline ADBP ≥ 85 mmHg in CV137-032^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 161	Amlodipine 5/10/10 mg N = 153
24hr-average AMBP, mmHg		
Baseline Mean (sd)	112.4 (7.6)	112.0 (7.6)
Adjusted Mean Change (se)	-16.6 (0.5)	-12.4 (0.5)
Difference from Amlodipine (95 % CI)	-4.2 (-5.7, -2.8)	
p-Value	< 0.001	
24hr-average ASBP, mmHg		
Baseline Mean (sd)	147.9 (11.5)	147.8 (12.1)
Adjusted Mean Change (se)	-21.1 (0.7)	-16.2 (0.7)
Difference from Amlodipine (95 % CI)	-4.9 (-6.9, -3.0)	
p-Value	< 0.001	
24hr-average ADBP, mmHg		
Baseline Mean (sd)	94.7 (6.8)	94.1 (6.5)
Adjusted Mean Change (se)	-14.4 (0.5)	-10.5 (0.5)
Difference from Amlodipine (95 % CI)	-3.9 (-5.2, -2.6)	
p-Value	< 0.001	

a. Data from NDA vol. 2.385, table 10.1.3.

Analyses According to Race, Gender and Age

Too few non-white individuals were included in the trial to allow meaningful analysis of sub-grouping by race (3 total subjects). As summarized below, no disparity of effect was detected using ABPM when the patients were analyzed according to gender or age (< 65 , ≥ 65).

Table 9.12g.5 Effect of omapatrilat and amlodipine on changes from baseline in 24-hour average ABPM analyzed by age group^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 34	Amlodipine 5/10/10/mg N = 27	Omapatrilat 20/40/80 mg N = 158	Amlodipine 5/10/10/mg N = 160
	Age ≥ 65		Age < 65	
24hr-average AMBP, mmHg				
Baseline Mean (sd)	110.2 (7.9)	109.8 (7.2)	110.2 (9.2)	109.4 (9.3)
Mean Change (sd)	-17.2 (7.0)	-11.7 (8.8)	-15.8 (8.1)	-10.7 (7.4)
24hr-average ASBP, mmHg				
Baseline Mean (sd)	150.4 (13.3)	150.7 (11.2)	144.7 (12.4)	144.1 (13.4)
Mean Change (sd)	-23.8 (10.0)	-16.5 (11.0)	-19.8 (10.2)	-14.0 (10.7)
24hr-average ADBP, mmHg				
Baseline Mean (sd)	90.1 (6.6)	89.4 (6.3)	93.0 (8.4)	92.1 (8.2)
Mean Change (sd)	-13.9 (6.3)	-9.3 (7.9)	-13.8 (7.4)	-9.0 (6.2)

a. Data from NDA vol. 2.385, table 10.4.

Table 9.12g.6 Effect of omapatrilat and amlodipine on changes from baseline in 24-hour average ABPM analyzed by gender^a.

Efficacy Variable	Omapatrilat 20/40/80 mg N = 34	Amlodipine 5/10/10/mg N = 27	Omapatrilat 20/40/80 mg N = 158	Amlodipine 5/10/10/mg N = 160
	Male		Female	
24hr-average AMBP, mmHg Mean Change (sd)	-15.5 (7.7)	-10.5 (6.9)	-17.7 (8.4)	-11.7 (9.5)
24hr-average ADBP, mmHg Mean Change (sd)	-13.5 (6.9)	-9.0 (6.0)	-14.8 (7.9)	-9.2 (7.8)
24hr-average ASBP, mmHg Mean Change (sd)	-19.4 (10.1)	-13.6 (9.4)	-23.5 (10.2)	-16.7 (14.0)

a. Data from NDA vol. 2.386, table S.10.4A.

The FDA analysis likewise found significantly greater effects of omapatrilat on the following BP parameters for white males and females: 24-hour average DBP and SBP, and 24-hour average mean BP.

9.13 Safety Outcomes for CV137-032

The evaluation of safety includes the 420 subjects who received at least one dose of study medication. The reader is referred to the Integrated Summary of Safety by Dr. Pelayo for more details. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 9.13.1 Clinical adverse experience (AE) summary from CV137-032^a.

Event	Omapatrilat 20/40/80 mg N = 213	Amlodipine 5/10/10 mg N = 217
AE, total (% of subjects)	98 (46.0%)	116 (53.5%)
SAE	3 (1.4%)	1 (0.5%)
Death	0	0
Discontinuations due to AE	6 (2.8%)	14 (6.5%)

a. Table from NDA vol. 2.385, table 12.0. AEs reported through 14 days after last dose shown.

9.14 CV137-032 Efficacy Summary

Study CV137-032 was a randomized, double-blind trial that compared the anti-hypertensive effects of omapatrilat (force-titrated up to 80 mg per day) with amlodipine (force-titrated up to 10 mg per day) through 10 weeks using both ABPM and cuff measurements of BP.

1. The primary efficacy endpoint in this trial was the a comparison of the change in the 24-hour average ambulatory mean blood pressure in the omapatrilat and amlodipine-treated patients. After 10 weeks, AMBP was reduced by 15.9 mm Hg in the omapatrilat group and by 11.0 mm Hg in the lisinopril group (a difference of 4.8 mm Hg, $P < 0.001$) per the sponsor. The FDA statistician, John Lawrence, confirmed a significantly greater effect of omapatrilat on the primary efficacy endpoint of the trial. In his analysis, omapatrilat reduced the AMBP by 6.10 mmHg more than amlodipine ($p < 0.001$).

2. Omapatrilat, used in a forced titration scheme (20 to 40 to 80 mg per day) for 10 weeks, lowered blood pressure in patients with mild-to-moderate hypertension, assessed either by ABPM or by cuff measurements of BP. This includes effects on the following parameters:

- 24-hour ASBP.
- 24-hour ADBP.
- 24-hour Mean BP (MBP).
- 24-hour Mean Pulse Pressure (MPP).
- Daytime (12-hour) averages for both ASBP and ADBP

3. When the anti-hypertensive effect of omapatrilat and amlodipine were compared using office-based cuff BP measurements, there was no significant difference in the mean change in SeDBP at 10 weeks compared with baseline: omapatrilat -13.5 mmHg, amlodipine -13.1 mmHg, p -Value 0.62. This result was confirmed by a separate FDA analysis.

4. Similar effects to those seen in the primary efficacy analysis (changes in average ABP) were seen when the population was examined by subgroups according to gender and age. Too few non-white subjects were enrolled to assess efficacy in racial sub-groups.

5.0 to 5.14 Review of Protocol CV137-022

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5.1 Title of Study

A Multicenter, Randomized, Double-blind, Placebo and Active-controlled, Parallel Dose-ranging Study of Omapatrilat (BMS-186716), in the Treatment of Mild-to-Moderate Hypertension (CV137-022).

5.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA volume 2.296, Table S-4. A total of 66 sites in the U.S. were used in the trial, although not all sites enrolled any subjects.

5.3 Background

Initial protocol submitted: 3.24.97 (serial #056)

First protocol amendment submitted: No protocol amendments

Subject entry: 4.8.97 to 1.9.98

5.4 Study Design

This multicenter study was conducted under a randomized, double-blind, active and placebo-controlled, parallel design. Antihypertensive efficacy and safety were compared among the omapatrilat, lisinopril, and placebo regimens in subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg). After withdrawal of antihypertensive therapy (if applicable) and a four week single-blind placebo lead-in period, eligible subjects were randomized to one of six treatment groups for nine weeks. The first dose of study medication (Level I) was given for one week followed by the second dose of study medication (Level II) for eight weeks.

The six treatment groups (Level I dose/Level II dose) were:

- 1) Omapatrilat 5 mg/omapatrilat 5 mg;
- 2) Omapatrilat 10 mg/ omapatrilat 10 mg;
- 3) Omapatrilat 10 mg/omapatrilat 20mg;
- 4) Omapatrilat 10 mg/omapatrilat 40 mg;
- 5) Placebo/placebo; and
- 6) Lisinopril 10 mg/lisinopril 20mg.

Subjects completing the double-blind phase then entered a one-week single-blind placebo-withdrawal phase.

For details of BP measurement and baseline BP determination see protocol CV137-006.

5.5 Primary and Secondary Objectives

Primary Objectives

The primary objective was to compare the change from baseline in trough (24 ± 3 hours post dose) seated diastolic blood pressure (SeDBP), relative to placebo, following nine weeks of once-daily oral administration of four dose regimens of omapatrilat in subjects with mild to moderate hypertension.

Secondary Objectives

Secondary objectives were:

- 1) To assess the safety and tolerability of four dose regimens of omapatrilat and lisinopril when administered over nine weeks,
- 2) To characterize the dose-response relationship between the dose of omapatrilat and change from baseline in trough (24 ± 3 hours post dose) SeDBP following nine weeks of once-daily oral administration of four dose regimens of omapatrilat,
- 3) To compare the change from baseline, relative to placebo, in trough (24 ± 3 hours post dose) seated systolic and supine and standing systolic and diastolic BP and heart rate (seated, supine, and standing) after nine weeks of once-daily administration of four dose regimens of omapatrilat,
- 4) To compare the change from baseline in trough (24 ± 3 hours post dose) seated blood pressure (systolic and diastolic), relative to placebo, following four and six weeks of once-daily administration of four dose regimens of omapatrilat,
- 5) To estimate the change from baseline in trough (24 ± 3 hours post dose) SeDBP between lisinopril and each of the four doses of omapatrilat following four, six and nine weeks of treatment,
- 6) To compare the change from baseline in SeBP (systolic and diastolic) and seated heart rate at estimated peak (7 ± 1 hours post dose), relative to placebo, following nine weeks of once-daily administration of each of the four dose regimens of omapatrilat,
- 7) To assess the trough to peak ratio of omapatrilat doses and lisinopril with respect to SeBP (systolic and diastolic) after nine weeks of once-daily administration, and
- 8) To compare the degree of therapeutic response between each of the four dose regimens of omapatrilat and placebo based on the proportion of subjects with a normalized BP (SeDBP < 90 mmHg) at week 9.

5.6 Number of subjects/ randomization

A total of 1120 subjects were enrolled in the trial, and 690 randomized, as summarized below.

Table 5.6.1 Summary of subjects entered into each dose group in protocol CV137-022^a.

Placebo	Omapatrilat 5/5 mg	Omapatrilat 10/10 mg	Omapatrilat 10/20 mg	Omapatrilat 10/40 mg	Lisinopril 10/20 mg
117	111	109	123	122	108

a. Data from NDA volume 2.296, table S-4.

5.7 Inclusion/ Exclusion Criteria

For full list of inclusion/exclusion criteria see NDA vol. 2.295, section 5.2. In general, consenting males and females who were not nursing, not pregnant and of non-childbearing potential (surgically sterile or post-menopausal); age 18 years or greater, with mild-to-moderate hypertension (SeDBP of 95-110 mmHg) were eligible for enrollment.

Exclusion criteria include the presence of bronchospastic lung disease requiring medication, heart failure (LVEF $\leq 45\%$), AODM or Secondary Hypertension.

5.8 Dosage/ Administration

As listed above, patients received one of three treatment doses for the first week of therapy (placebo, omapatrilat 5 or 10 mg, or lisinopril 10 mg). At the end of the first treatment week the doses were force-titrated in the omapatrilat groups to 5, 10, 20 or 40 mg, and the lisinopril group was increased to 20 mg for the remaining 8 weeks of therapy.

5.9 Duration/ Adjustment of Therapy

Total trial duration was 14 weeks: 4 weeks of placebo lead-in, 9 weeks of double-blind treatment, and one week of placebo withdrawal.

5.10 Safety and Efficacy Endpoints Measured

The table below summarizes the safety and efficacy measurements performed during the trial. Note that serum bicarbonate was not measured.

Table 5.10.1 Timetable for clinical observations and lab measurements in study CV137-022^a.

	Enroll	A1	Lead-in Period 'A'		Double- Blind Period 'B'							Period 'C'
Day			A15 - A29	B1	B8	B15	B29	B43	B64	C3	C7	
Consent	X											
Full Medical Hx, PE	X								X			
Brief PE		X	A29		X		X			X	X	
BP, Heart rate	X	X	A15, A22, A29	X	X	X	X	X	X	X	X	X
Adverse Events		X	A15, A22, A29	X	X	X	X	X	X	X	X	X
Review Concomitant Meds	X	X	A15, A22, A29	X	X	X	X	X	X	X	X	X
12-lead ECG		X	A22 or A29						X			X
CXR		X										
Standard Labs (fasting) ^a		X	A22 or A29				X		X			
Randomize				X								
Extended Visit				X	X							
Peak BP			A22						X			
Medication Dispensing		X	A15, A22	X	X	X	X	X	X			
Medication Count			A15, A22 and A29		X	X	X	X	X	X	X	X

a. Data from NDA vol. 2.295, table 5.8. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, total protein, albumin, calcium, phosphorus, total cholesterol, creatine kinase); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis). Bicarbonate was not measured.

5.11 Statistical Considerations

Sponsor's Statistical Plan

Power

The trial size resulted in a 90% power to detect differences of 4.2 mmHg between treatment groups. This assumed a 10% drop-out rate and a standard deviation of 7.5 mmHg for change between baseline in trough SeDBP.

Multiplicity

Dunnett's procedure was used to adjust for multiple comparisons between four treatment groups and still maintain the overall significance level of 0.05 for the primary analysis.

Exploratory Analyses

None.

Interim Analyses

None.

Statistical Analysis

1) Study Populations

Randomized Subjects

This set was used for the primary efficacy analyses. It did not include those subjects who did not have both a baseline and post-randomization assessment. Subsets of this population included the 'Evaluable patients with valid troughs' and 'Evaluable patients with valid peaks and troughs.'

Treated Subjects

This population included those subjects who received at least one dose of medication, according to the actual study drug administered. One patient was randomized to receive omapatrilat 10/20 but instead received lisinopril 10/20.

Table 1A. Clinical Pharmacology Studies of Omapatrilat

	Protocol	N	n	Dose (mg)	Exposure
Tolerance/Biopharmaceutics					
An Oral Single-Dose Tolerance Study of BMS-186716 in Healthy Male Subjects	CV137-001	63	42	2.5, 7.5, 25, 50, 125, 250, 500	single dose
An Oral Multiple-Dose Tolerance Study of BMS-186716 in Healthy Subjects	CV137-002	46	30	10, 25, 50, 75, 125	multiple dose (10 days)
Evaluation of the Effect of Particle Size of BMS-186716 on the Oral Bioavailability of BMS-186716 in Normal Healthy Male Volunteers	CV137-004	24	24	25	crossover (4x)
Disposition and Bioavailability of BMS-186716 in Healthy Male Subjects After Intravenous and Oral Administration of [¹⁴ C]BMS-186716 in Solution	CV137-007	12	12	50 PO, 20 IV	crossover (2x)
Comparative Oral Bioavailability of a 40-mg Dose of BMS-186716 in Healthy Human Volunteers when Given as one 40-mg Tablet (10% W/W Granulation) vs. Two 20-mg Capsules	CV137-025	54	54	40	crossover (2x)
Comparative Oral Bioavailability of a 10-mg Dose of BMS-186716 in Healthy Human Volunteers when Given as one 10-mg Tablet (10% W/W Granulation) or Four 2.5-mg Tablets (2.5% W/W Granulation) vs. One 10-mg Capsule	CV137-026	51	51	10	crossover (3x)
Pharmacokinetic Single-Dose Proportionality Study of Omapatrilat (BMS-186716) in Healthy Volunteers	CV137-060	44	44	10, 20, 40, 80	crossover (4x)
Disposition of Omapatrilat in Healthy Subjects After Administration of Triple-Labeled [¹⁴ C]BMS-186716	CV137-064	6	6	50	single dose
Special Populations					
Comparison of the Biochemical and Hemodynamic Effects of a Dual Metalloprotease Inhibitor (BMS-186716) and an Angiotensin-Converting Enzyme Inhibitor (Fosinopril) in Healthy Male Volunteers	CV137-015	9	9	10	crossover (3x)
The Effect of Omapatrilat (BMS-186716) and Lisinopril in the Treatment of Mild-to-Moderate Hypertension in Salt-Sensitive Subjects	CV137-017	61	28	10, 40	multiple dose (28 days)
The Safety, Pharmacokinetics and Pharmacodynamics of Daily Doses of Omapatrilat in Subjects with Normal Renal Function, Mild-to-Moderate Renal Impairment, Severe Renal Impairment and In Hemodialysis Subjects	CV137-020	30	30	10	multiple dose (8-9 days)
The Pharmacokinetics and Pharmacodynamics of Omapatrilat (BMS-186716) in Congestive Heart Failure Patients and Matching Controls	CV137-021	36	36	10(IV), 25 (PO)	crossover (x 2 single doses)
The Effects of Age and Gender on the Single Dose Pharmacokinetics of Omapatrilat (BMS-186716) Administered to Healthy Volunteers	CV137-027	49	49	40	single dose
Single- and Multiple-Dose Pharmacokinetics and Pharmacodynamics of Omapatrilat in Subjects with Hepatic Cirrhosis Compared to Normal, Healthy Subjects	CV137-052	20	20	25	multiple dose (14 days)

2) Efficacy Analyses

Analysis of covariance (ANCOVA) was used to compare the omapatrilat regimens to placebo with respect to changes from baseline in trough seated, supine, and standing measures and peak seated measures of blood pressure and heart rate. The ANCOVA model included terms for treatment regimen and for baseline value as covariate. The typical sample sizes obtained at individual sites too small to use of study site as an additional term in this model.

Therapeutic Response: the proportion of subjects normalized (trough SeDBP < 90 mmHg) and the proportion with favorable response (trough SeDBP normalized or decreased at least 10 mmHg from baseline) used Cochran-Mantel-Haenszel stratified by baseline SeDBP (strata were ≤ 99 mmHg; $> 99 - \leq 104$ mmHg; > 104 mmHg).

Safety

Standard analyses of reported AEs and changes in lab values were to be performed. See vol. 2.295, section 6.3.5 for details.

FDA Statistical Analysis

Unless noted, all p-Values and treatment effects in this review are from the sponsor's analysis. In many cases, the sponsor's analysis excluded particular individuals and/or sites, largely for protocol violations. In addition, only observed values were used in the sponsor's analyses (that is, missing values were not imputed). The FDA preferred the intent-to-treat population for efficacy. Missing values were imputed using Last Observation Carried Forward (LOCF) methods, including all randomized patients. The FDA analyses were done using ANOVA without adjustment for baseline covariates, based on concerns for the uniformity of the relationship between baseline and change from baseline across the treatment groups (a requisite for use of ANCOVA). Using these methods, important efficacy variables were reanalyzed. Unless otherwise noted, this approach yielded qualitatively similar results to those obtained by the sponsor.

5.12 Efficacy Outcomes for CV137-022

5.12a Disposition of Subjects

A total of 1120 subjects were enrolled in CV137-022. Of the 690 subjects who were randomized, 632 completed the double-blind portion of the study and 620 (89.9%) completed the placebo-withdrawal phase. The first table summarizes the reasons for subject drop-out prior to randomization.

Table 5.12a.1 Subjects who discontinued prior to randomization^a.

Reason for Discontinuation	# of Subjects
Administrative reason	1
Adverse event	22
Concomitant Medication	21
BP did not qualify per protocol	184
Investigator request	9
Laboratory Abnormality	53
Lost to follow-up	16
Other	52
Subject request	65
Poor compliance	5
Total	428

a. Data from NDA vol. 2.295, table 8.1A.

The next table summarizes the discontinuations during the double-blind therapy.

Table 5.12a.2 Summary of subjects entered into each dose group in protocol #CV137-022^a.

Reason for Discontinuation	Placebo	Omapatrilat				Lisinopril
		5/5 mg	10/10 mg	10/20 mg	10/40 mg	
No. of subjects randomized	117	111	109	123	122	108
No. of subjects discontinued	9 (7.7)	10 (9.0)	6 (5.5)	10 (8.1)	12 (9.8)	11 (10.2)
Adverse Event	4 (3.4)	3 (2.7)	4 (3.7)	5 (4.1)	9 (7.4)	4 (3.7)
Concomitant medication	1 (0.9)	0	0	0	0	0
Investigator request	4 (3.4)	3 (2.7)	1 (0.9)	2 (1.6)	0	2 (1.9)
Other reasons	0	1 (0.9)	1 (0.9)	0	1 (0.8)	1 (0.9)
Subject request	0	1 (0.9)	0	1 (0.8)	2 (1.6)	3 (2.8)
BP above limit as per protocol	0	1 (0.9)	0	1 (0.8)	0	1 (0.9)
Poor or non-compliance	0	1 (0.9)	0	1 (0.8)	0	0
Number of subjects completing double-blind period	108 (92.3)	101 (91.0)	103 (94.5)	113 (91.9)	110 (90.2)	97 (89.8)

a. Data from NDA volume 2.295, table 8.1B.

5.12b Protocol Violations & Deviations

The most common protocol violations were insufficient adherence to taking study medication (34 subjects) and the use of contraindicated medications (15 patients). One patient was randomized to one treatment group (omapatrilat 10/20) and instead received lisinopril 10/20.

5.12c Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 690 subjects enrolled in the double-blind portion of CV137-022 are summarized below.

Table 5.12c.1 Demographics of CV137-022^a.

Baseline Characteristic	Placebo N = 117	Omap 5/5 mg N = 111	Omap 10/10 mg N = 109	Omap 10/20 mg N = 123	Omap 10/40 mg N = 122	Lisinopril 10/20 mg N = 108
Age, years						
Mean (sd)	57.4 (10.6)	54.5 (10.6)	56.2 (10.3)	55.4 (10.9)	55.9 (10.1)	55.0 (9.5)
Range	22-89	31-82	29-75	24-77	33-77	31-79
Age Group, n(%)						
< 65 years	88 (75%)	91 (82%)	86 (79%)	95 (77%)	95 (78%)	91 (84%)
65 - 74 years	25 (21%)	18 (16%)	21 (19%)	24 (20%)	26 (21%)	15 (14%)
≥ 75 years	4 (3%)	2 (2%)	2 (2%)	4 (3%)	1 (1%)	2 (2%)
Gender, n (%)						
Male	82 (70%)	70 (63%)	68 (62%)	87 (71%)	88 (72%)	67 (62%)
Female	35 (30%)	41 (37%)	41 (38%)	36 (29%)	34 (28%)	41 (38%)
Race, n (%)						
White	90 (77%)	85 (77%)	86 (79%)	96 (78%)	99 (81%)	82 (76%)
Black	12 (10%)	14 (13%)	12 (11%)	14 (11%)	13 (11%)	16 (15%)
Other	15 (13%)	12 (11%)	11 (10%)	13 (11%)	10 (8%)	10 (9%)
Weight, kg						
Mean (sd)	89.4 (18.2)	89.5 (17.0)	90.5 (19.9)	90.4 (17.4)	89.6 (18.5)	91.0 (19.2)
Range	48-141	55-146	46-149	45-151	50-158	42-163
Duration of HTN (Years)						
Mean (sd)	9.6 (9.9)	9.6 (8.5)	10.7 (9.5)	9.1 (9.1)	9.7 (8.6)	9.6 (9.6)
Range	0-57	0-47	0-56	0-40	0-42	0-57

a. Data from NDA volume 2.295, Table 8.3A.

Baseline trough mean seated DBP (SeDBP) was similar in all of the treatment groups, averaging 99.6 to 100.3 mm Hg. Baseline trough mean seated SBP (SeSBP) was between 151.6 and 154.7 mm Hg for the 6 treatment groups.

Other baseline measures of blood pressure and heart rate were also similar among the treatment groups (see NDA vol. 2.295, Tables 8.3B and 8.3C for details).

The occurrence of other medical conditions, when grouped by body system, was similar across the treatment groups. The most common cardiovascular conditions present were hypertriglyceridemia and

hypercholesterolemia, present in 10 to 20% and 30 to 40% of the subjects respectively. Among the treatment groups, diabetes occurred in 5.6 to 11.1% of the patients.

5.12d Concomitant Therapies used after Trial Initiation

Concomitant medication use was common during the trial (62.4 to 71.2% of patients in the treatment groups). See NDA table S.9.4A for details.

5.12e Extent of Exposure to Study Drug in CV137-022

The mean period of drug exposure averaged 60 days. Overall, between 85 and 92% of the patients in each treatment group received study drug for >60 days (Study Report, table 9.1).

5.12f Primary Analyses of CV137-022 Results

The primary objective of the trial was to compare the change in trough SeDBP with placebo in the active treatment groups (4 doses of omapatrilat or lisinopril). The first table summarizes the primary efficacy results, measuring the placebo-subtracted effects of omapatrilat (4 doses) and lisinopril on trough SeDBP and SeSBP at the end of 8 weeks. The placebo-subtracted trough BP changes are shaded.

Table 5.12f.1 Effect of omapatrilat and lisinopril on trough seated blood pressures at the end of week 9 in CV137-022^a.

Efficacy Variable	Placebo N=108	Omap 5/5 mg N=101	Omap 10/10 mg N=103	Omap 10/20 mg N=116	Omap 10/40 mg N=110	Lisinopril 10/20 mg N=99
Trough SeDBP mmHg						
Baseline Mean (SD)	99.5 (3.2)	99.9 (3.9)	99.6 (3.7)	99.9 (3.7)	99.6 (3.6)	100.2 (3.7)
Adjusted Mean Change (SE)	-3.5 (0.7)	-9.1 (0.7)	-8.8 (0.7)	-10.1 (0.7)	-11.1 (0.7)	-9.7 (0.7)
Difference from Placebo	--	-5.6	-5.3	-6.5	-7.6	-6.2
95% CI	--	(-8.0, -3.2)	(-7.6, -2.9)	(-8.4, -4.2)	(-9.9, -5.3)	(-8.1, -4.2)
p-Value: c/w placebo ^a	--	<0.001	<0.001	<0.001	<0.001	<0.001
Difference from Lisinopril	--	+0.6	+0.9	-0.4	-1.4	--
95% CI	--	(-1.4, 2.5)	(-1.1, +2.8)	(-2.3, +1.5)	(-3.3, +0.5)	--
Trough SeSBP mmHg						
Baseline Mean (SD)	153.8 (12.4)	152.5 (14.7)	152.5 (14.1)	151.3 (11.9)	153.8 (13.8)	152.7 (14.1)
Adjusted Mean Change (SE)	-2.8 (1.2)	-11.1 (1.2)	-10.5 (1.2)	-14.3 (1.1)	-16.0 (1.1)	-10.5 (1.2)
Difference from Placebo	--	-8.3	-7.7	-11.5	-13.2	-7.7
95% CI	--	(-11.6, -5.1)	(-10.9, -4.4)	(-14.7, -8.4)	(-16.4, -10.0)	(-11.0, -4.5)
p-Value: c/w placebo	--	<0.001	<0.001	<0.001	<0.001	<0.001

a. Data from NDA vol. 2.296, table S.10.1.1A1. p-Values per sponsor and verified by FDA statistician.

Similar changes were seen for the population with available peak and trough data ('evaluable' population). See NDA vol. 2.296, table S.10.1.3A for details.

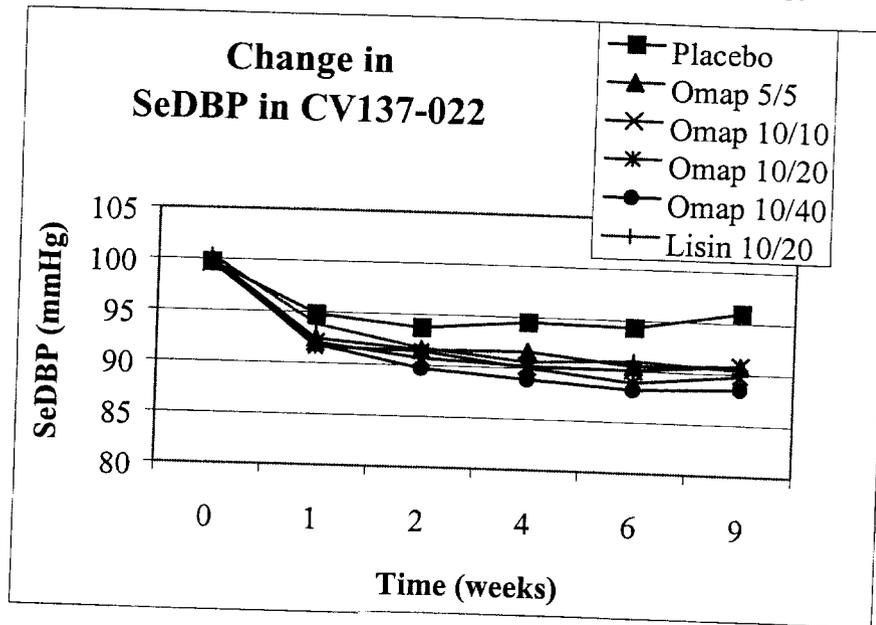
Similarly, trough standing and supine blood pressures showed a significant effect of omapatrilat to lower blood pressure. The data below are for the DBP; effects on SBP were similar in trend.

Table 5.12f.2 Effect of omapatrilat and lisinopril on trough standing DBP (StDBP) and supine DBP (SuDBP) at the end of week 9 in CV137-022^a.

Efficacy Variable	Placebo N=108	Omap 5/5 mg N=101	Omap 10/10 mg N=103	Omap 10/20 mg N=116	Omap 10/40 mg N=110	Lisinopril 10/20 mg N=99
Trough StDBP mmHg						
Baseline Mean (SD)	99.4 (4.7)	98.9 (4.9)	99.2 (5.0)	99.3 (5.4)	99.2 (5.8)	100.0 (5.5)
Adjusted Mean Change (SD)	-3.5 (6.4)	-7.0 (7.2)	-7.0 (7.6)	-9.1 (8.5)	-9.8 (7.5)	-8.9 (7.3)
Difference from Placebo	--	-3.5	-3.5	-5.6	-6.3	-5.4
Trough SuSBP mmHg						
Baseline Mean (SD)	97.9 (4.7)	97.6 (5.0)	97.4 (5.9)	97.7 (5.2)	97.7 (5.2)	98.4 (5.6)
Adjusted Mean Change (SD)	-3.1 (7.2)	-7.5 (7.1)	7.0 (7.4)	-9.2 (8.7)	-9.8	-7.9 (7.0)
Difference from Placebo	--	-4.4	-3.9	-6.1	-6.7	-4.8

a. Data from NDA vol. 2.296, table S.10.1.1A1.

The time-course for the anti-hypertensive effects of omapatrilat and lisinopril are summarized in the graph below. Trough SeDBP decreased relative to baseline by the end of the first week of therapy.



5.12g Additional Efficacy Analyses of CV137-022

Sub-Group Analyses of Primary Efficacy Endpoint

Regarding gender effects, approximately 1/3 of the patients in each group were female. In data not shown, the placebo-subtracted effect of omapatrilat on trough SeDBP was similar in trend and magnitude for males (-7.1 mm Hg for the 10/40 dose) and females (-9.0 mm Hg). See NDA vol. 2.295, table S.10.5A for details. Data for SeSBP were similar.

Regarding the effect of advanced age, between 25 and 30% of the subjects were >65 years old. The placebo-subtracted effect of omapatrilat on SeDBP was similar in trend and magnitude for ≤65 (-7.9 mm Hg for the 10/40 dose) and >65 (-6.5 mm Hg). See NDA vol. 2.295, table S.10.5B for details. Data for SeSBP were similar.

Regarding the effect of race, 'Black' and 'Other' categories each had approximately 10-15 patient in each treatment group (20-30% of the total enrollment). These small numbers limit data interpretation, but the trend towards an effect of omapatrilat on placebo-subtracted SeDBP (shown below) and SeSBP is evident.

Table 5.12g.1 Effect of omapatrilat and lisinopril on trough seated DBP at the end of week 9 according to race in CV137-022^a.

Race/ Change in SeSBP	Placebo	Omap 5/5 mg	Omap 10/10 mg	Omap 10/20 mg	Omap 10/40 mg	Lisinopril 10/20 mg
Trough SeDBP mmHg:						
White (n=76 to 91)						
Mean Change (SE)	-4.0 (5.8)	-9.1 (6.8)	-8.5 (7.0)	-10.8 (8.8)	-10.9 (6.4)	-11.1 (7.3)
Difference from Placebo	--	-5.1	-4.5	-5.8	-5.9	-7.1
Black (n=11 to 14)						
Mean Change (SE)	-2.8 (6.5)	-10.6 (9.9)	-9.9 (6.7)	-6.5 (5.8)	-11.4 (7.6)	-5.1 (6.8)
Difference from Placebo	--	-7.8	-7.1	-4.3	-8.6	-2.3
Other (n=8 to 12)						
Mean Change (SE)	-1.2 (5.6)	-7.7 (7.3)	-9.7 (4.2)	-8.3 (6.8)	-12.9 (5.6)	-5.8 (4.7)
Difference from Placebo	--	-6.5	-8.5	-7.1	-11.7	-4.6

a. Data from NDA vol. 2.296, table S.10.5C.

Trough:Peak Ratio

Peak SeDBP and peak SeSBP were also examined. Then, the peak and trough SeDBP was used to calculate Trough:Peak Ratio. The first table shows the peak SeDBP and SeSBP from this subset of patients with valid peak and trough data.

Table 5.12g.2 Effect of omapatrilat and lisinopril on peak SeDBP SeSBP at the end of week 9 in CV137-022^a.

Efficacy Variable	Placebo N=101	Omap 5/5 mg N=95	Omap 10/10 mg N=97	Omap 10/20 mg N=106	Omap 10/40 mg N=101	Lisinopril 10/20 mg N=93
Peak SeDBP mmHg						
Baseline Mean (SD)	97.6	97.6	97.3	97.7	97.0	97.8
Adjusted Mean Change (SE)	-3.8	-11.9	-12.0	-12.3	-14.0	-11.1
Relative Change from Placebo	--	-8.0	-8.3	-8.5	-10.6	-7.7
p-Value	--	<0.001	<0.001	<0.001	<0.001	N/A
Peak SeSBP mmHg						
Baseline Mean (SD)	152.4	151.5	151.7	150.9	152.2	152.0
Adjusted Mean Change (SE)	-3.0	-16.9	-17.7	-19.7	-23.6	-15.2
Relative Change from Placebo	--	-14.3	-14.9	-16.9	-20.8	-12.3
p-Value	--	<0.001	<0.001	<0.001	<0.001	N/A

a. Data from NDA vol. 2.296, table S.10.1.3A. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.
b. Calculated from ratio of relative changes from placebo.

Next, the peak and trough SeDBP are used to calculate the trough:peak ratio, which average $\geq 69\%$ in all treatment groups.

Table 5.12g.3 Effect of omapatrilat and lisinopril on peak and trough SeDBP at the end of week 9 in CV137-022^a.

Efficacy Variable	Placebo N=101	Omap 5/5 mg N=95	Omap 10/10 mg N=97	Omap 10/20 mg N=106	Omap 10/40 mg N=101	Lisinopril 10/20 mg N=93
Peak SeDBP mmHg						
Baseline Mean (SD)	97.6	97.6	97.3	97.7	97.0	97.8
Adjusted Mean Change (SE)	-3.8	-11.9	-12.0	-12.3	-14.0	-11.1
Relative Change from Placebo	--	-8.0* ^c	-8.3*	-8.5*	-10.6*	-7.7**
Trough SeDBP mmHg						
Baseline Mean (SD)	99.7	99.7	99.9	99.7	99.5	99.8
Adjusted Mean Change (SE)	-3.7	-9.1	-9.3	-10.1	-11.0	-9.4
Relative Change from Placebo	--	-5.5	-5.7	-6.4	-7.4	-5.7
Trough:Peak Ratio^b	--	0.69	0.69	0.75	0.70	0.74

a. Data from NDA vol. 2.296, table S.10.1.3A. Statistical analysis done using ANCOVA. Dunnett's method of multiple comparison was used to determine the statistical significance of the difference in adjusted means and associated confidence intervals.
b. Calculated from ratio of relative changes from placebo.
c. Starred values significant relative to baseline per the sponsor at <0.001. Double-starred p-Values were not reported by the sponsor.

Therapeutic Response

The sponsor also examined the anti-hypertensive effects of omapatrilat using a categorical analysis of 'Therapeutic Response.' Therapeutic response was defined as a normalized BP (SeDBP < 90 mmHg) or a favorable BP response (BP normalized or SeDBP ≥ 10 mmHg decrease from baseline) at Week 10.

Table 5.12g.4 Subjects with normalization or favorable trend in trough SeDBP at week 9 in CV137-022^a.

	Placebo N = 108	5/5 mg Omapatrilat N = 101	10/10 mg Omapatrilat N = 103	10/20 mg Omapatrilat N = 116	10/40 mg Omapatrilat N = 110	10/20 mg Lisinopril N = 99
Therapeutic Response						
Normalized n (%)	19 (18%)	50 (50%)	46 (45%)	61 (53%)	58 (53%)	45 (45%)
Favorable n (%)	24 (22%)	55 (54%)	52 (50%)	74 (64%)	69 (63%)	56 (57%)

a. Data from NDA vol. 2.296, table 10.2.1.2A2, based on Randomized Subjects.
b. Normalized: Trough SeDBP <90 mmHg
Favorable: Trough SeDBP <90 or decrease from baseline ≥ 10 mmHg.

Heart Rate

The effect of omapatrilat and amlodipine on trough heart rate at the end of 9 weeks is summarized below. At the highest doses there was a trend towards a very small decrease in heart rate.

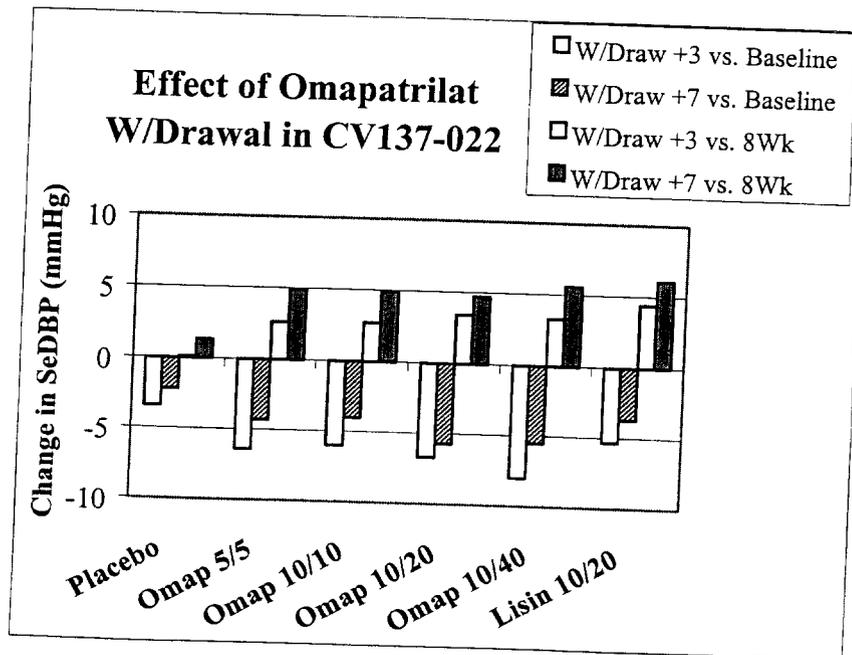
Table 5.12g.5 Change from baseline in trough measures for trough seated heart rate (Se HR), supine heart rate (SuHR), and standing heart rate (StHR) at the end of week 8 in CV137-022^a.

Efficacy Variable	Placebo N=101	Omap 5/5 mg N=95	Omap 10/10 mg N=96	Omap 10/20 mg N=105	Omap 10/40 mg N=101	Lisinopril 10/20 mg N=93
Trough SeHR:						
Baseline Mean	72.3	70.9	72.0	72.0	71.8	73.1
Adjusted Mean Change (SE)	0.7 (0.7)	0.0 (0.7)	-0.6 (0.7)	-1.1 (0.7)	-1.4 (0.7)	-0.6 (0.7)
Difference from Placebo (95% CI)	--	-0.7	-1.2	-1.8	-2.1	-1.3
p-Value: c/w with placebo	--	NS	NS	0.073	0.039	NS
Trough StHR:						
Baseline Mean (SD)	74.2	72.9	73.6	74.2	74.4	74.5
Adjusted Mean Change (SE)	1.2 (0.7)	0.1 (0.7)	-0.2 (0.7)	-1.6 (0.7)	-1.1 (0.7)	-0.3 (0.7)
Difference from Placebo (95% CI)	--	-1.0	-1.4	-2.7	-2.3	-1.5
p-Value: comparison with placebo	--	NS	NS	0.005	0.019	NS
Trough SuHR						
Baseline Mean (SD)	70.8	70.2	70.4	70.3	70.0	71.2
Adjusted Mean Change (SE)	0.6 (0.6)	0.1 (0.7)	-0.4 (0.7)	-0.9 (0.6)	-0.9 (0.6)	-0.2 (0.7)
Difference from Placebo (95% CI)	--	-0.5	-1.1	-1.6	-1.5	-0.8
p-Value: comparison with placebo	--	NS	NS	0.08	0.1	NS

a. Data from NDA vol. 2.296, table S.10.1.1D1, from as randomized population. Statistical analysis done using ANCOVA.

Withdrawal Effect

The sponsor measured blood pressure 3 and 7 days after withdrawal of study drug, and the available data are summarized below as mean changes from the baseline and from week 8. In short, at both 3 and 7 days subjects taking either omapatrilat or amlodipine had lower mean blood pressures than they did at baseline, but higher mean blood pressure than then they did at the end of 8 weeks of therapy.



5.13 Safety Outcomes in CV137-022

The adverse events, serious adverse events, and subject discontinuations are discussed in Dr. Pelayo's review. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 5.13.1 Clinical adverse experience (AE) summary from protocol CV137-022^a.

Clinical event n (% of total)	Placebo N = 117	Omap 5/5 mg N = 111	Omap 10/10 mg N = 109	Omap 10/20 mg N = 123	Omap 10/40 mg N = 122	Lisinopril 10/20 mg N = 108
With Any AE	67 (57.3%)	72 (64.9%)	66 (60.6%)	84 (68.9%)	85 (69.7%)	68 (62.4%)
With Serious AE	2 (1.7%)	2 (1.8%)	2 (1.8%)	3 (2.5%)	1 (0.8%)	3 (2.8%)
Discontinued due to an AE	4 (3.4%)	3 (2.7%)	4 (3.7%)	5 (4.1%)	9 (7.4%)	4 (3.7%)
Deaths	0	0	0	0	0	0

a. Data from NDA volume 2.295, summary.

5.14 Study CV137-022 Efficacy Summary

CV137-022 compared the antihypertensive effects of four doses of omapatrilat and one dose of lisinopril to placebo in a double-blind, randomized trial. Following 8 weeks of therapy in one of the six treatment groups, patients were followed for one week off of study drug to assess the effects of drug withdrawal on BP.

1. Omapatrilat at doses of 5mg for 9 weeks, and 10mg for one week followed by either 10, 20, or 40 mg per day lowered blood pressure significantly in patients with mild-to-moderate hypertension. Omapatrilat had significant effects on trough and peak seated diastolic BP (Se DBP) as well as trough and peak seated systolic BP (SeSBP).

The size of the placebo-subtracted SeDBP effect varied from -5.6 mmHg for the lowest dose of omapatrilat (5/5 mg) up to -7.6 mmHg in the highest dose of omapatrilat (40 mg). Lisinopril lowered the SeDBP by an average of 6.2 mmHg.

2. Similar effects on SeDBP and SeSBP were seen when the population was examined by subgroups according to race (black, white, other), gender and age (≤ 65 , > 65).

3. Withdrawal of omapatrilat at the end of 8 weeks resulted in a rise in SeDBP at days 3 and 8, which did not return to the baseline level prior to starting omapatrilat.

4. The highest dose of omapatrilat used in the trial (10/40 mg) had a similar antihypertensive effect to that of the highest approved dose of lisinopril (10/20 mg).

5. Once a day omapatrilat had a peak:trough ratio that ranged between 0.69 and 0.75 at the end of 8 weeks.

6. No clinically-significant effect of omapatrilat on mean heart rate at the end of 9 weeks was detected, although there was a nominally-significant decrease in mean heart rate (1-2 BPM) at the two higher doses of omapatrilat.

8.0 to 8.14 Review of Protocol CV137-031

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8.1 Title of Study

A Randomized, Double-Blind Study of Omapatrilat Versus Lisinopril as Assessed by 24-Hour Ambulatory Blood Pressure Monitoring (CV137-031).

8.2 Sites of Investigation and Investigators

This non-IND study was conducted by 58 investigators in 58 centers (41 in France and 17 in Germany). See NDA vol. 2.393, table S.4 for listing of investigators and sites.

8.3 Background

Initial protocol submitted: Non-IND study. Protocol was not submitted to the FDA.

Protocol amendment(s): Amendment I, dated June 8, 1998, specified that subjects with SeSBP \leq 100 mmHg prior to completing the schedule of titration up to Level II or Level III, were to be discontinued from the study.

Subject entry: 6.17.98 to 5.19.99

8.4 Study Design

This multicenter, randomized, double-blind, active-controlled, parallel group, forced-titration study was designed to evaluate the safety and antihypertensive efficacy of omapatrilat and assess the relative blood pressure lowering effects of omapatrilat compared to lisinopril in subjects with mild-to-moderate hypertension.

The study consisted of 2 periods. Following a 4 week single-blind placebo lead-in period (Period A), qualifying subjects were randomized in a 1:1 ratio to a regimen of omapatrilat or lisinopril for 10 weeks (Period B). Subjects with SeSBP of \leq 100 mmHg before either titration were not to be titrated to the next dose level of study medication and were to be discontinued.

Ambulatory Blood Pressure Assessments

For ABPM recordings, after an initial one-hour acclimatization period, all measurements within each hour after dosing were averaged to provide individual hourly measures. The 24hr-average ASBP and ADBP are the average of the first 24 hourly measures immediately following the morning's dose. The 12hr (daytime) averages are the averages of the first 12 hourly measures immediately following the morning's dose.

For ABPM data, missing hours were not imputed for any hour during which there was no valid data, but for the ABPM to be considered acceptable there was a limit on the total number of hours that could be completely missing.

Office Blood Pressure Assessments

See CV137-006 for a description of the methods used for measurement of BP using office cuffs.

8.5 Primary and Secondary Endpoints

Primary Objective

The primary objective was to compare the change from baseline in 24hr-average ambulatory systolic blood pressure (ASBP) following 10 weeks of once-daily oral administration of omapatrilat versus lisinopril in subjects with mild-to-moderate hypertension. ASBP was derived from analysis of ambulatory blood pressure monitoring.

Secondary Objectives

- 1) To compare the change from baseline in daytime 12hr-average ASBP after 10 weeks of once-daily administration of omapatrilat vs. lisinopril.
- 2) To compare the change from baseline in 24hr-average and daytime 12hr-average ambulatory diastolic blood pressure (ADBP) after 10 weeks of once-daily administration of omapatrilat vs. lisinopril.
- 3) To compare the change from baseline in 24hr-average, and daytime 12hr-average ambulatory pulse pressure (APP = ASBP - ADBP) after 10 weeks of once-daily administration of omapatrilat vs. lisinopril.
- 4) To compare the change from baseline in 24hr-average ambulatory mean blood pressure (AMBP) following 10 weeks of once-daily administration of omapatrilat vs. lisinopril.
- 5) To compare the change from baseline in trough office seated blood pressure (SeBP) and pulse pressure (PP) after 10 weeks of once-daily administration of omapatrilat vs. lisinopril.
- 6) To assess the response to therapy based on the percentage of subjects normalized (SeSBP <140 mmHg) at Week 10.
- 7) To assess the relative safety and tolerability of omapatrilat and lisinopril after 10 weeks of once-daily administration.
- 8) To describe the changes in blood pressure (BP) and heart rate (HR) in other positions at other timepoints.

8.6 Number of subjects/ randomization

Subjects were randomized to omapatrilat or lisinopril. The randomization was balanced within each site in a 1:1 ratio, across the treatments in blocks of 4.

Table 8.6.1 Subjects entered into each dose group in CV137-031^a.

	Omapatrilat 20/40/80	Lisinopril 10/20/40
Entered	173	174

a. Data from NDA volume 2.392.

8.7 Inclusion/ Exclusion Criteria

Consenting males and females who were not nursing, not pregnant and of non-childbearing potential (surgically sterile or post-menopausal); age 18 years or greater, with mild-to-moderate hypertension SeDBP of 95-110 mmHg). For full list of inclusion/exclusion criteria see Final Report, NDA vol. 2.392 section 5.2 for details. Subjects had to have an acceptable baseline ABPM measurement, and demonstrate compliance of >80 and <120% with medications during the last 2 weeks of the single-blind placebo period.

8.8 Dosage/ Administration

After entry into the double-blind period, patients were randomized to receive either omapatrilat 20 mg or lisinopril 10 mg. At the end of 2 and 4 weeks of therapy patients were force-titrated to receive higher doses of either drug (omapatrilat 20 to 40 and then to 80 mg, lisinopril 10 mg to 20 and then to 40 mg). Patients then remained on the same dose through 10 weeks.

8.9 Duration/ Adjustment of Therapy

Dose modifications outside the protocol were prohibited. Doses of study medication were adjusted as detailed above. Subjects who were unable to tolerate the new higher doses of medication were to be discontinued from the study.

8.10 Safety and Efficacy Endpoints Measured

Table 8.10.1 Timetable for clinical observations and lab measurements in CV137-031^a.

Week	Enroll	A1	Lead-in Period A	Double-Blind Period							
				Period A		Period B					
Day			A1-A4		1	2	4	6	8		10
			A15- A29	B1	B8	B15	B29	B43	B57	B70	B71
Consent	X										
Medical History	X										
Full Physical Exam	X										
Brief Physical Exam		X	A29			X	X	X			X
BP, Heart rate	X	X	A15, A22, A29	X	X	X	X	X	X	X	X
Adverse Events		X	A15, A22, A29	X	X	X	X	X	X	X	X
Review Concomitant Meds	X	X	A15, A22, A29	X	X	X	X	X	X		X
12-lead ECG		X	A22								X
Chest X-ray ^c		X									X
Safety Lab Tests ^e		X	A23					X			X
Randomization				X							
Extended Visit ^d				X		X	X				
Titration Study Visit						X	X				
ABPM Measurements			A22, A23							X	X
Med Dispensing		X	A15, A22	X	X	X	X	X	X		
Medication Count			A15, A22, A29		X	X	X	X	X		X

a. Data from NDA volume 2.392, table 5.8.

c. If not done in the previous 6 months.

d. Additional BP monitoring performed for 4 hours after drug administration.

e. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); and (3) Urinalysis (specific gravity, pH, protein, microscopic analysis).

8.11 Statistical Considerations

Sponsor's Statistical Plan

Power

The sample size determination was based on a single comparison between omapatrilat and lisinopril with respect to the primary efficacy parameter, change from baseline in 24hr-average ASBP following 10 weeks of once-daily treatment of double-blind study medication.

With 135 subjects randomized to each group, there would have been at least 90% power to detect a difference of 4.5 mmHg between the treatment regimens, if such a difference truly existed. This planned calculated sample size included allowance for a 15% dropout rate (10% discontinuation rate and further 5% loss through invalid ABPM recordings), and assumed a standard deviation of 10.5 mm Hg for changes from baseline to Week 10 in 24hr-average ASBP, and two-sided testing at a significance level of 0.05.

Multiplicity

There was no adjustment for multiplicity.

Interim Analyses

There were no interim analyses.

Statistical Analysis

1) Study Populations

Two major patient populations were examined: 'Randomized Subjects' (all subjects randomized) and 'Treated Subjects' (all subjects who received at least one dose of study medication).

The Randomized Subjects were further divided into those with acceptable ABPM data (Randomized Subjects with Acceptable ABPMs), which was the population used for the primary efficacy analysis, and 'Evaluable Subjects with Valid ABPMs', which included only ABPM data from subjects who did not exhibit significant departures from important protocol-specified procedures that may have affected the assessment. See study report, NDA vol 3.393 section 6.2 for details.

2) Statistical Methods for Analyses

FINAL ANCOVA MODEL

Analysis of covariance (ANCOV) was used to compare the omapatrilat regimen with the lisinopril regimen for the majority of the efficacy variables, including the primary efficacy analysis. The ANCOVA model included a term for treatment regimen, with the baseline value as covariate. The typical sample sizes obtained at individual sites were too small to use study site as an additional term in this model. Statistical significance was evaluated at $\alpha=0.05$.

COMPARISONS OF OMAPATRILAT AND LISINOPRIL

The estimated difference in adjusted means between omapatrilat and lisinopril regimens was calculated together with the associated 95% confidence interval and the p-Value for the t-test of the between-group difference, for each of the following variables: change from baseline to Week 10 in 24hr-average mean ASBP, ADBP, AMBP and APP; daytime (12hr-average) ASBP, ADBP, and APP; 24hr-average ASBP, ADBP and AMBP in subjects with baseline ASBP ≥ 135 mmHg; and trough seated BP and PP.

Pharmacokinetics

No pharmacokinetic measurements were included in this trial.

Safety

Safety evaluation was primarily descriptive, and no statistical tests were used to assess AEs or incidence of marked abnormal laboratory values.

Statistical Analysis

Unless noted, all p-Values and treatment effects in this review are from the sponsor's analysis. In many cases, the sponsor's analysis excluded particular individuals and/or sites, largely for protocol violations. In addition, only observed values were used in the sponsor's analyses (that is, missing values were not imputed). The FDA preferred the intent-to-treat population for efficacy. Missing values were imputed using Last Observation Carried Forward (LOCF) methods, including all randomized patients. The FDA analyses were done using ANOVA without adjustment for baseline covariates, based on concerns for the uniformity of the relationship between baseline and change from baseline across the treatment groups (a requisite for use of ANCOVA). Using these methods, important efficacy variables were reanalyzed. Unless otherwise noted, this approach yielded qualitatively similar results to those obtained by the sponsor.

8.12 Efficacy Outcomes for protocol

8.12a Disposition of Subjects

Over an 8 month period, a total of 463 subjects were enrolled at 58 study sites located in France and Germany, and a total of 347 subjects were randomized. After randomization, 334 (96.3%) subjects completed the 10 week double-blind treatment. The reasons for discontinuation prior to entry into the double-blind period are summarized in the table below.

Table 8.12a.1 Reasons for discontinuation prior to randomization in CV137-031^a.

Reasons for Discontinuation	Number of Subjects
Adverse event	4
Inclusion/Exclusion Criteria not met	86
Withdrawal of subject consent	22
Prohibited medication	1
Uncontrolled disease state	1
Investigator request	1
Other	1
Total	116

a. Data from NDA vol. 2.392, table 8.1B.

During the early course of the study, a review of the blinded baseline ABPM data revealed that a significant number of subjects had baseline ASBP < 135 mmHg, in spite of elevated office cuff SBP > 150 mmHg. Accordingly, investigators were requested to review each subject's baseline ABP as well as office BP and to randomize only those subjects in whom BP was elevated by both methods of measurements.

The table below summarizes the disposition of the individuals entered into the double-blind portion of the study.

Table 8.12a.2 Summary of subjects entered into each dose group in CV137-031^a.

Reason for Discontinuation	Omapatrilat 20/40/80 mg	Lisinopril 10/20/40 mg
No. of subjects randomized	173	174
No. of subjects discontinued	7	6
Adverse event	6 (3.5%)	2 (1.1%)
Other	1	4
Subjects completing double-blind period	166	168

a. Data from NDA volume 2.392, table 8.1A.

8.12b Protocol Violations & Deviations

The most common protocol violations involved the use of proscribed medications and failure to meet entry criteria, especially those specifying acceptable lab parameters at baseline. A list of these violation can be found in supplemental table S.7.3B, but were not considered of sufficient significance to exclude individuals or sites from the primary analysis.

8.12c Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the 347 subjects enrolled in CV137-031 are summarized in the tables below.

Table 8.12c.1 Demographics of CV137-031^a.

Baseline Characteristics	Omapatrilat 20/40/80 mg N = 173	Lisinopril 10/20/40 mg N = 174
Age, years		
Mean (sd)	60.0 (10.7)	61.1 (10.1)
Range	29-79	35-85
Age Group, n(%)		
< 65 years	106 (61%)	110 (63%)
65 - 74 years	59 (34%)	48 (28%)
>74 years	8 (5%)	16 (9%)
Gender, n (%)		
Male	73 (42%)	78 (45%)
Female	100 (58%)	96 (55%)
Race, n (%)		
White	170 (98%)	174 (100%)
Black	0	0
Other	3 (2%)	0
Weight, kg		
Mean (sd)	78.8 (13.3)	77.4 (13.7)
Range	51-115	42-115
Duration of Hypertension, years		
Mean (sd)	6.6 (5.5)	7.5 (8.9)
Range	0-26	0-88 ^a

a. Data from NDA volume 2.392, table 8.3.

Table 8.12c.2 Baseline ABPM data from study CV137-031^a.

Baseline Characteristic	Omapatrilat 20/40/80 mg N = 173	Lisinopril 10/20/40 mg N = 171
24-Hour Averages		
24hr-Average ASBP, mmHg		
Mean (sd)	141.3 (14.6)	144.7 (14.2)
Range	107.7 - 191.7	105.1 - 176.3
24hr-Average ADBP, mmHg		
Mean (sd)	83.5 (10.4)	85.5 (10.3)
Range	56.1 - 112.2	59.5 - 118.2
24hr-Average APP, mmHg		
Mean (sd)	57.9 (10.2)	59.2 (10.9)
Range	39.4 - 86.7	31.3 - 88.7
24hr-Average AMBP, mmHg		
Mean (sd)	102.7 (10.9)	105.2 (10.5)
Range	76.3 - 133.9	75.4 - 136.6
Daytime (12hr)Averages		
12hr-Average ASBP, mmHg		
Mean (sd)	146.8 (14.8)	150.0 (15.0)
Range	114.7 - 193.3	108.7 - 185.1
12hr-Average ADBP, mmHg		
Mean (sd)	88.1 (11.0)	90.2 (11.0)
Range	58.0 - 117.3	62.4 - 122.4
12hr-Average APP, mmHg		
Mean (sd)	58.6 (10.6)	59.8 (11.6)
Range	40.0 - 84.8	31.9 - 91.0

a. From NDA vol. 2.392, table 8.3B.

The next table summarizes the baseline blood pressure data obtained using office cuff measurements. The baseline SeDBP was lower in this trial than in the other trials reviewed (which averaged a SeDBP of 100 mmHg-plus).

Table 8.12c.3 Baseline office blood pressure measurements from study CV137-031^a.

Baseline Characteristic	Omapatrilat 20/40/80 mg N = 173	Lisinopril 10/20/40 mg N = 174
SeSBP, mmHg		
Mean (sd)	161.5 (8.0)	163.3 (7.9)
Range	150.7-182.0	150.0-179.3
SeDBP, mmHg		
Mean (sd)	95.8 (8.2)	96.0 (8.5)
Range	75.3-112.7	69.3-118.7
Pulse Press., mmHg		
Mean (sd)	65.8 (8.6)	67.4 (9.3)
Range	49.3-93.3	46.0-92.7
SeHR, beats/min		
Mean (sd)	74.3 (8.2)	73.4 (8.6)
Range	56-112	56-96

a. Data from NDA vol. 2.392, table 8.3C.

Past Medical History

Of the 347 randomized subjects, 223 subjects had a history of cardiovascular or other related diseases (other than hypertension). The most common were hypercholesterolemia (43.2%), peripheral vascular disease (23.6%), hypertriglyceridemia (16.4%), and diabetes mellitus Type II (13.8%). The most common general medical history findings involved the musculoskeletal system (51.3%), genitourinary system (31.7%), gastrointestinal system (26.5%), endocrine/metabolic system (24.8%), and head/ear/eye/nose/throat (20.5%). Frequency of these conditions was overall balanced among the treatment groups.

Prior Antihypertensive Medications

A total of 240 (69.2%) of the 347 randomized subjects were reported to have received antihypertensive therapy within one month of study start. The most frequent prior antihypertensive drug classes were angiotensin converting enzyme inhibitors, beta-blocking agents, angiotensin II receptor inhibitors, and diuretics. There were no important imbalances between groups.

8.12d Concomitant Therapies used after Trial Initiation

The percentage of subjects who received concomitant medications in each treatment regimen was similar between the two treatment groups (data not shown, see NDA vol. 2.393, table S.9.4B for details).

8.12e Extent of Exposure to Study Drug in CV37-031

The sponsor summarized the extent of subject exposure to study, and those results are shown below. Subjects received study drug for a mean of 69 days in both groups.

Table 8.12e.1 Extent of exposure to study drug in CV137-031^a.

Duration	Omapatrilat 20/40/80 mg N = 173	Lisinopril 10/20/40 mg N = 174
≤ 7 days	2 (1.2)	1 (0.6)
8-30 days	4 (2.3)	5 (2.9)
31-60 days	1 (0.6)	1 (0.6)
61-90 days	166 (96.0%)	167 (96.0%)
Mean duration of Exposure (days)	69	69

a. Data from NDA vol. 2.392, table 9.1.

8.12f Primary Analyses of CV137-031

The primary efficacy outcome was the mean change from baseline in 24hr-average ambulatory systolic blood pressure (ASBP) following 10 weeks of once-daily treatment with omapatrilat versus lisinopril as presented in the following table, along with other efficacy markers (including ambulatory DBP, ADBP). These results were independently confirmed by the FDA statistician, John Lawrence, whose findings agree with the overall trend and nominal statistical significance of the results below.

Table 8.12f.1 Efficacy analyses from CV137-031 at 10 weeks^a.

Efficacy Variable	Omapatrilat 20/40/80 n=160	Lisinopril 10/20/40 n=157
24-hour ASBP, mm Hg^c		
Baseline Mean (sd)	141.1 (14.6)	144.7 (14.4)
Adjusted Mean Change (se)	-19.0 (0.9)	-12.2 (0.9)
Difference from Lisinopril (95% CI)	-6.8 (-9.2, -4.4)	--
p-Value ^a	<0.001	--
24-hour ADBP, mm Hg		
Baseline Mean (sd)	83.6 (10.6)	85.5 (10.4)
Adjusted Mean Change (se)	-10.5 (0.5)	-7.5 (0.5)
Difference from Lisinopril	-2.9 (-4.4, -1.5)	--
p-Value ^a	<0.001	--
24-hour APP^b		
Baseline mean (sd)	57.5 (10.0)	59.2 (11.2)
Adjusted Mean Change (se)	-8.5 (0.5%)	-4.8 (0.5)
Difference from Lisinopril	-3.7 (-5.0, -2.4)	--
p-Value ^a	<0.001	--
24-hour AMBP^b		
Baseline Mean (sd)	102.8 (11.1)	105.2 (10.7)
Adjusted Mean Change (se)	-13.3 (0.6)	-9.1 (0.6)
Difference from Lisinopril (95% CI)	-4.3 (-6.0, -2.6)	--
p-Value	<0.001	--

a. Data from NDA vol. 2.392, table 10.1.1. p-Value per sponsor using ANCOVA.

b. APP = ambulatory pulse pressure. AMBP = ambulatory mean blood pressure.

c. The primary efficacy variable.

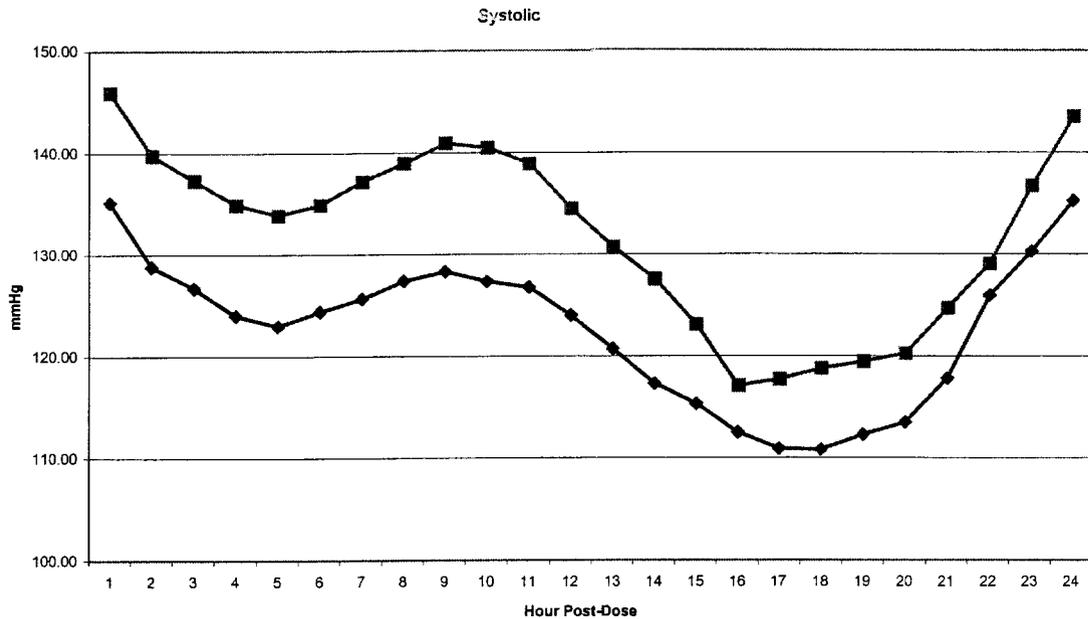
The results of the FDA statistician, John Lawrence, are summarized in the table below. His modeling used last observation carried forward to account for missing data. He confirmed the a significantly larger effect of omapatrilat on the ABPM measures of blood pressure, relative to lisinopril. Other relevant changes from his analysis are also summarized.

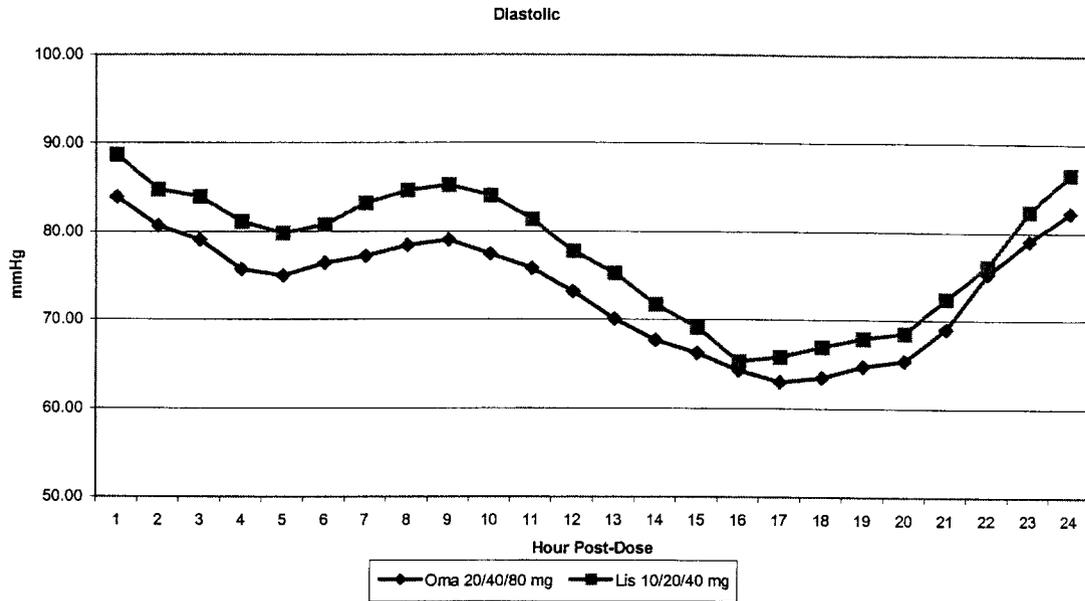
Table 8.12f.2 Mean change from baseline in trough and peak SeDBP and SeSBP at week 10 in CV137-031 per the FDA statistical analysis^a.

Efficacy Variable	Omapatrilat c/w Lisinopril
24-Hour Mean ABP^b	
Diff. From Lisinopril	-4.71
p-Value c/w Lisinopril	<0.001
24-Hour Mean DBP	
Diff. From Lisinopril	-3.33
p-Value c/w Lisinopril	0.0003
24-Hour Mean SBP	
Diff. From Lisinopril	-7.46
p-Value c/w Lisinopril	<0.001

a. Analysis per Dr. John Lawrence, FDA statistician.
 b. Primary efficacy variable for this trial.

The hourly means for the ASBP and SDBP at week 10, per the sponsor, are summarized below. In both plots, the upper curve is for lisinopril and the lower curve for omapatrilat. Recall that the lisinopril group started with a higher mean blood pressure.





8.12g Additional Efficacy Analyses from CV137-031
Sub-Group Analyses

Too few non-white subjects were enrolled to allow an analysis according to race. The overall results were similar to the results described above in the patients sub-grouped according to gender or age (<65, ≥65). The results grouped according to gender are summarized below.

Table 8.12g.1 Effects of omapatrilat on ADBP in subjects grouped by gender from CV137-031^a.

Gender Effects on ADBP	Omapatrilat 20/40/80 mg	Lisinopril 10/20/40 mg
Male	N=70	N=70
Mean change in ADBP (mm Hg)	-9.5	-7.8
Female	N=90	N=87
Mean change in ADBP (mm Hg)	-10.7	-7.8

a. Data from NDA vol. 2.393, table S.10.4A.

The FDA analysis likewise found significantly greater effects of omapatrilat on the following BP parameters for white males and females: 24-hour average DBP and SBP, and 24-hour average mean BP.

Other Ambulatory Measures of BP Effect

Similarly, omapatrilat had a greater effect than lisinopril on the following efficacy variables:

- 1) the daytime (12-hour) averages for both ASBP and ADBP (data not shown, see NDA vol. 2.392 table 10.1.2 for details).
- 2) the 24-hour average ASBP and ADBP from patients with a baseline ASBP >135 mmHg (data not shown, see NDA vol. 2.392 table 10.1.3 for details).
- 3) the trough ASBP and ADBP (data not shown, see NDA vol. 2.393 tables S.10.1.1A4 and S.10.1.1B1 for details).

BP Efficacy Analyses from Office Cuff BP Measurements

The effects on trough SeSBP, SeDBP and PP were similar to those for ABPM, in that the reductions from baseline were larger for omapatrilat than for lisinopril.

Table 8.12g.2 Mean changes in trough SeSBP and SeDBP at 10 weeks in CV137-031^a.

Efficacy Variable	Omapatrilat 20/40/80 N=166	Lisinopril 10/20/40 N=168
Trough SeDBP, mmHg		
Baseline Mean (sd)	95.7 (8.3)	96.1 (8.5)
Adjusted Mean Change (se)	-12.1 (0.6)	-10.1 (0.6)
Difference from Lisinopril (95% CI)	-2.1 (-3.7, -0.4)	--
p-Value ^a	0.013	--
Trough SeSBP, mmHg		
Baseline Mean (sd)	161.7 (8.1)	163.4 (7.8)
Adjusted Mean Change (se)	-23.5 (1.0)	-19.2 (1.0)
Difference from Lisinopril (95% CI)	-4.3 (-7.2, -1.4)	--
p-Value c/w Lisinopril ^a	0.004	--
Trough PP^b		
Baseline Mean (sd)	66.0 (8.6)	67.4 (9.4)
Adjusted Mean Change (se)	-11.6 (0.8)	-8.9 (0.8)
Difference from Lisinopril (95% CI)	-2.7 (-5.0, -0.5)	--
p-Value c/w Lisinopril ^a	0.019	--

a. Data from NDA vol. 2.392, table 10.2.1. p-Value using ANCOVA per sponsor.

b. PP = pulse pressure.

The results of the FDA statistician, John Lawrence, are summarized in the table below. His modeling used last observation carried forward to account for missing data. His analysis found no significant effect of omapatrilat on SeDBP or SeSBP relative to lisinopril.

Table 8.12g.3 Mean change from baseline in trough and peak SeDBP and SeSBP at week 10 in CV137-031 per the FDA statistical analysis^a.

EFFICACY VARIABLE	Omapatrilat c/w Lisinopril
Trough SeDBP, mmHg	
Diff. From Lisinopril	-1.51
p-Value c/w Lisinopril	0.085
Trough SeSBP, mmHg	
Diff. From Lisinopril	-2.57
p-Value c/w Lisinopril	0.074

a. Analysis per Dr. John Lawrence, FDA statistician.

b. Primary efficacy variable for this trial.

Therapeutic Response

The sponsor also looked at the percentage of patients who achieved arbitrary levels of blood pressure reduction at 10 weeks. For both measures shown below, the numerical trend favors omapatrilat.

Table 8.12g.4 Therapeutic response at week 10 in CV137-031^a.

Therapeutic Response	Omapatrilat 20/40/80 mg N = 166	Lisinopril 10/20/40 mg N = 168
Normalized (Trough SeSBP) n (%)	93 (56%)	66 (39%)
Favorable (Trough SeSBP) n (%)	115 (69%)	88 (52%)

a. Data from NDA vol. 2.392, table 10.2.2.

b. Definitions

Normalized: Trough SeSBP <140 mmHg at 10 weeks.

Favorable: Trough SeSBP <140 or a reduction from baseline ≥20 mmHg.

8.13 Safety Outcomes

The evaluation of safety includes all 347 treated subjects who received at least one dose of study medication. The reader is referred to the Integrated Summary of Safety by Dr. Pelayo for more details. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 8.13.1 Clinical adverse experience (AE) summary from CV137-031^a.

Event	Omapatrilat 20/40/80 mg N = 173	Lisinopril 10/20/40 mg N = 174
AE, total (% of subjects)	57 (32.9)	59 (33.9)
SAE	1 (0.6)	3 (1.7)
Death	0	0
Discontinuations due to AE	6 (3.5)	2 (1.1)

a. Data from NDA volume 2.392, table 12.0.

8.14 Study CV137-031 Efficacy Summary

Study CV137-031 was a randomized, double-blind trial that compared the anti-hypertensive effects of omapatrilat (force-titrated up to 80 mg per day) with lisinopril (force-titrated up to 40 mg per day) through 10 weeks using both ABPM and cuff measurements of BP.

1. The primary efficacy endpoint in this trial was a comparison of the change in the 24-hour average SBP (ASBP) in the omapatrilat and lisinopril-treated patients. After 10 weeks, the sponsor reported that ASBP reduced by 19.0 mm Hg in the omapatrilat group and by 12.2 mm Hg in the lisinopril group (a difference of 6.8 mm Hg, $p < 0.001$). The FDA statistician confirmed the a significantly larger effect of omapatrilat on the ABPM measures of blood pressure, relative to lisinopril.

2. Omapatrilat, used in a forced titration scheme (20 to 40 to 80 mg per day) for 10 weeks, lowered blood pressure in patients with mild-to-moderate hypertension, assessed either by ABPM or by cuff measurements of BP. This includes effects on the following parameters:

- a. 24-hour ASBP.
- b. 24-hour ADBP.
- c. 24-hour Mean BP (MBP).
- d. 24-hour Mean Pulse Pressure (MPP).
- e. daytime (12-hour) averages for both ASBP and ADBP.
- f. 24-hour average ASBP and ADBP from patients with a baseline ASBP > 135 mmHg.
- g. trough ASBP and ADBP.
- e. placebo-subtracted trough and peak seated diastolic BP (Se DBP).
- f. placebo-subtracted trough and peak seated systolic BP (SeSBP).

3. Similar effects on the measures of blood pressure change were seen when the population was examined by subgroups according to gender and age. Too few non-white subjects were enrolled to assess efficacy in racial subgroups.

4. Omapatrilat had a larger effect on cuff measurements of blood pressure than lisinopril, including trough SeSBP, SeDBP and PP. For the trough SeDBP, this difference amounted to 2.1 mmHg ($p = 0.013$) per the sponsor and 1.51 mmHg ($p = 0.085$) per the FDA statistician.

10.0 to 10.14 Review of CV137-037

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10.1 Title of Study

A Multicenter, Randomized, Double-Blind, Lisinopril and Placebo Controlled Trial of the Antihypertensive Efficacy and Safety of Omapatrilat in Black Subjects with Mild-to-Moderate Hypertension (Including Double-Blind Extension) (CV137-037).

10.2 Sites of Investigation and Investigators

The list of investigators and sites is found in NDA volume 2.332, table S.4.

The trial was conducted by 102 investigators at 102 outpatient clinics in the United States.

10.3 Background

Initial protocol submitted to FDA: 5.14.98 (serial #127)

First protocol amendment submitted: 12.14.98 (serial #176)

Shortened the time of observation after the titration visits to 2 hours (from 4 hours).

Subject entry: 5.26.98 to 7.1.99

10.4 Study Design

Initial Double-Blind Study

This multi-center, randomized, double-blind, placebo and active-controlled, parallel group forced dose titration study evaluated the antihypertensive effects and tolerability of titrated doses of omapatrilat (up to 80 mg daily) compared to titrated doses of lisinopril (up to 40 mg daily) and placebo in black subjects with mild-to-moderate hypertension.

Following withdrawal of previous antihypertensive medications (if any) subjects entered into a single-blind placebo lead-in period lasting 4 weeks. If the mean trough SeDBP at both Week 3 (Day A22) and Week 4 (Day A29) of the single-blind placebo lead-in period was 95-110 mmHg and the difference between the 2 blood pressure measurements was no more than 8 mmHg, qualified subjects were randomized in a 2:2:1 ratio to a regimen of omapatrilat 20 mg force titrated to 40 mg at Week 2, and to 80 mg at Week 4, or a regimen of lisinopril 10 mg force titrated to 20 mg at Week 2 and to 40 mg at Week 4, or placebo for 10 weeks (Period B). Concomitant antihypertensive therapies were not allowed and subjects who could not tolerate the higher dose level of study medication were discontinued.

Double-Blind Long-Term Extension

Subjects who completed 10 weeks of Period B continued into a 4-month long-term double-blind extension (Period C). Subjects randomized to placebo in Period B were reallocated in a 1:1 fashion to omapatrilat or lisinopril in Period C. Subjects randomized to active treatment (omapatrilat or lisinopril) in Period B would remain on the same drug in Period C. All subjects started Period C on Level I study medication. Study medication was force titrated to Level II at Week 1 or sooner if necessary. Titration to Level III was elective and could occur any time after Week 2 in subjects with SeDBP ≥ 90 mmHg. Down titration from Level III to Level II was allowed for intolerance. Subjects who did not reach target SeDBP (<90 mmHg) on Level III could have adjunctive antihypertensive medications added and titrated as needed starting with amlodipine (2.5 or 5 mg titrated to 10 mg daily) followed by the addition of hydrochlorothiazide (HCTZ, 12.5 mg titrated to 25 and then 50 mg daily). If amlodipine was contraindicated, adjunctive therapy with HCTZ could be initiated first. Subjects who were down-titrated from Level III to Level II for intolerance could have adjunctive therapy added in the same sequence noted above. Subjects who could not tolerate Level II study medication were discontinued.

10.5 Primary and Secondary Endpoints

Short-Term Double-Blind

The primary objective was to compare the change from baseline in trough (24 ± 3 hours post dose) seated diastolic blood pressure (SeDBP) following 10 weeks of once-daily oral administration of a regimen of omapatrilat (20 mg force titrated to 40 mg at Week 2 and to 80 mg at Week 4) to a regimen of lisinopril (10 mg force titrated to 20 mg at Week 2 and to 40 mg at Week 4) in black subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg).

The secondary objectives of the initial double-blind portion of CV137-037 were:

- 1) To compare the change from baseline, relative to lisinopril, in trough seated systolic BP (SeSBP) and pulse pressure (PP, SeSBP minus SeDBP) after 10 weeks of once-daily administration of omapatrilat.
- 2) To compare the change from baseline, relative to lisinopril, in trough seated blood pressure (SeBP) following 2 and 4 weeks of once-daily administration of omapatrilat.
- 3) To compare the change from baseline, relative to placebo, in trough SeBP (diastolic and systolic), pulse pressure and heart rate (HR) following 10 weeks of once-daily administration of omapatrilat.
- 4) To compare the change from baseline, relative to placebo, based on trough seated blood pressure (SeBP) after 2 and 4 weeks of once-daily administration of a regimen of omapatrilat.
- 5) To compare the response to therapy, relative to placebo, based on the percentage of subjects normalized (SeDBP < 90 mmHg) at Week 10.
- 6) To compare the change from baseline relative to lisinopril, in estimated omapatrilat peak (7 ± 1 hours post dose) blood pressure after 8 weeks of once-daily administration of a regimen of omapatrilat.
- 7) To assess the safety and tolerability of a regimen of omapatrilat relative to lisinopril and placebo when administered over the 10-week treatment period.
- 8) To describe changes in blood pressure and heart rate in other positions and at other time points.
- 9) To assess plasma endothelin levels at baseline and following 10 weeks of double-blind therapy in a subset of subjects.

Long-Term Double-Blind Extension

The primary objective of the double-blind extension was to assess the safety, tolerability and antihypertensive activity of once-daily omapatrilat during long-term administration in black subjects with mild-to-moderate hypertension.

Blood Pressure Measurement and Baseline Determination

See my review of CV137-006.

10.5 Primary and Secondary Objectives

Short-Term Double-Blind:

Primary Objective

The primary objective was to compare the change from baseline in trough SeDBP following 10 weeks of once-daily oral administration of omapatrilat and lisinopril in black subjects with mild-to-moderate hypertension.

Secondary Objectives

- 1) To compare the change from baseline, relative to lisinopril, in trough SeSBP and pulse pressure (PP, SeSBP minus SeDBP) after 10 weeks of once-daily administration of omapatrilat.
- 2) To compare the change from baseline, relative to lisinopril, in trough SeBP following 2 and 4 weeks of once-daily administration of omapatrilat.
- 3) To compare the change from baseline, relative to placebo, in trough SeBP (diastolic and systolic), pulse pressure and heart rate (HR) following 10 weeks of once-daily administration of omapatrilat.
- 4) To compare the change from baseline, relative to placebo, based on trough seated blood pressure (SeBP) after 2 and 4 weeks of once-daily administration of a regimen of omapatrilat.
- 5) To compare the response to therapy, relative to placebo, based on the percentage of subjects normalized (SeDBP < 90 mmHg) at Week 10.
- 6) To compare the change from baseline relative to lisinopril, in estimated omapatrilat peak (7 ± 1 hours post dose) blood pressure after 8 weeks of once-daily administration of a regimen of omapatrilat.
- 7) To assess the safety and tolerability of a regimen of omapatrilat relative to lisinopril and placebo when administered over the 10-week treatment period.
- 8) To describe changes in blood pressure and heart rate in other positions and at other time points.
- 9) To assess plasma endothelin levels at baseline and following 10 weeks of double-blind therapy in a subset of subjects.

Long-Term Double-Blind Extension:

The primary objective of the double-blind extension was to assess the safety, tolerability and antihypertensive activity of once-daily omapatrilat during long-term administration in black subjects with mild-to-moderate hypertension.

10.6 Number of subjects/ randomization

A total of 1503 subjects were enrolled of which 747 were randomized into the study and 548 completed 10 weeks of double-blind drug therapy (Period B). A total of 502 subjects entered the double-blind, long-term extension (Period C) of the study. Of these, 445 have completed or were ongoing at the time of the study report completion.

10.7 Inclusion/ Exclusion Criteria

Consenting black males, or females of non-childbearing potential, age 18 years or greater, with mild-to-moderate hypertension (SeDBP 95-110 mmHg). For full list of inclusion and exclusion criteria see NDA vol. 2.331, section 5.2.

10.8 Dosage/ Administration

Double-Blind Therapy (Period B)

Subjects who completed the placebo wash-out period successfully were eligible for randomization into the double-blind portion of the trial. During the first 2 weeks of double-blind therapy, subjects received treatment with Level I study medication, as shown in the table below.

At Week 2 (Day B15), following completion of trough BP measurements, the dose of study medication was increased to Level II.

At Week 4 (Day B29), following completion of trough BP measurements, the dose of study medication was increased to Level III.

Table 10.8.1 Period B dosing levels in CV137-037^a.

Study Drug	Treatment Interval	Omapatrilat	Lisinopril	Placebo
Level I	B1-B14	20 mg	10 mg	placebo
Level II	B15-B28	40 mg	20 mg	placebo
Level III	B29-B71	80 mg	40 mg	placebo

a. Data from NDA vol. 2.331, Table 5.5.3B.

The initial dose of each level of medication was dispensed in the clinic. Subjects who were unable to tolerate the new dose of medication were withdrawn from the study, as reduction in dose was not permitted in the short-term period.

Long-term Double-Blind Therapy (Period C)

During the long-term double-blind extension period (Period C), all subjects began treatment with Level I study medication. Subjects randomized to placebo in Period B were reallocated in a 1:1 fashion to omapatrilat or lisinopril, while those who had taken omapatrilat or lisinopril continued their same medications. At Week 1, the dose of study medication was increased to Level II and electively titrated at Week 2 to Level III (titration could have been accomplished sooner based on SeDBP \geq 90 mmHg). Following Level III titration, adjunctive antihypertensive therapy starting with amlodipine, followed by the addition of HCTZ could be added if needed for further BP control. If amlodipine was contraindicated, HCTZ could be initiated first. Subjects who could not tolerate Level II study medication were to be discontinued. Subjects that remained on Level II study medication because of intolerance to Level III could have adjunctive medications added as outlined above to ensure optimal control of BP. The following table outlines long-term extension dose, (Period C) and dose levels.

Table 10.8.2 Dosing during the long-term double-blind portion of CV137-037^a.

Study Drug	Treatment Interval	Omapatrilat	Lisinopril
Level I	Day 1 – Week 1	20 mg	10 mg
Level IIa	Week 1 – Week 2	40 mg	20 mg
Level IIIb,	Week 2- Month 4	80 mg	40 mg
Level III + adjunctive	Week 4 – Month 4	80 mg + adj	40 mg + adj
Adjunctive sequence: amlodipine 2.5 or 5.0 to 10 mg then HCTZ 12.5 to 25.0 to 50.0 mg	Open Label Adjunctive therapy to be added only after Level III for BP control (if SeDBP \geq 90 mmHg) or at Level II if down-titrated for intolerance at Level III.		

a. Data from NDA vol. 2.331, table 5.5.3B.

10.9 Duration/ Adjustment of Therapy

Treatment with study drug lasted 30 weeks (4 weeks of placebo lead-in, 10 weeks of double-blind treatment and 4 months of double-blind long-term extension treatment). Subjects who could not tolerate the amount of Level II study medication were discontinued.

10.10 Safety and Efficacy Endpoints Measured

The tables below summarize the timing of the clinical data collected in CV137-037, first for the trial through the end of the first double-blind portion (Period B). The second table summarizes the data collection for the long-term extension (Period C).

Table 10.10.1 Timetable for clinical observations and lab measurements in CV137-037^a.

Day	Enroll	A1	Lead-in	Double-Blind Period (B)							
			Period A	B1	B8	B15	B29	B43	B57	B71 /C1	
Consent	X		A15-A29								
Full Medical Hx and Physical Exam	X										X
Brief Physical Exam		X	A29			X		X			
Trough BP, HR	X	X	A15, A22, A29	X	X	X	X	X	X	X	X
Adverse Events		X	A15, A22, A29	X	X	X	X	X	X	X	X
Review Con. Meds	X	X	A15, A22, A29	X	X	X	X	X	X	X	X
12-Lead ECG		X	A22 or A29								X
Chest X-ray ^b		X									
Laboratory Tests		X	A22 or A29					X			X
Plasma endothelin Level (at selected sites)			A22 or A29								X
Pregnancy Test	X		A29			X		X			X
Randomization				X							
Extended Visit				X		X	X				
Peak BP/HR			A22							X	
Medication Ct/Review			A15, A22, A29		X	X	X	X	X	X	X

a. Data from NDA volume 2.331, table 5.8A.

b. If not performed in the previous six months.

c. Lab work included: (1) A complete blood count (hemoglobin, hematocrit, white blood count and differential, platelet count); (2) Serum chemistries (blood urea nitrogen, creatinine, total bilirubin, SGOT (AST), SGPT (ALT), glucose, LDH, uric acid, sodium, potassium, magnesium, chloride, alkaline phosphatase, bicarbonate, total protein, albumin, calcium, phosphorus, total cholesterol); (3) Urinalysis (specific gravity, pH, protein, microscopic analysis) and (4) Stool for occult blood (as available).

Table 10.10.2 Timetable for clinical observations and lab measurements in CV137-037 (long-term extension)^a.

Day:	B71/ C1	Week 1b	Week 2	Week 4	Month 2	Month 3	Month 4
Physical Exam	Full	Brief		Brief	Brief		Full
BP, Heart rate	(X)	X	X	X	X	X	X
12-lead ECG	(X)						X
Labs	(X)				X		X
Pregnancy Test	(X)			X	X	X	X
Adverse Events	(X)	X	X	X	X	X	X
Review Concom Meds	(X)	X	X	X	X	X	X
Plasma Endothelin	(X)						
Extended Visit	X	X	X				
Medication Dispensing	X	X	X	X	X	X	
Medication Count		X	X	X	X	X	X

a. Data from NDA vol. 2.331, table 5.8B.

b. At this visit items in parentheses were part of final short-term visit (B71).

10.11 Statistical Considerations

Sponsor's Statistical Plan

Power

Sample size was based on the comparison of omapatrilat and lisinopril with respect to changes from baseline in trough SeDBP at Week 10. With 270 subjects per active treatment group (270 omapatrilat, 270 lisinopril, 135 placebo) there was 90% power to detect differences of at least 2.5 mmHg between active treatments, assuming a standard deviation = 8.5 mmHg, with 2-sided testing, significance level of alpha= 0.05, and dropout rate of 10%.

Multiplicity

No statistical adjustments for multiplicity were performed.

Exploratory Analyses

There were no exploratory analyses.

Interim Analyses

There were no interim analyses

Statistical Analysis

1) Study Populations

Randomized Subjects

This dataset included all efficacy data from the scheduled visits for all subjects randomized into the study. In this dataset, all subjects are included in the group to which they were randomized.

This dataset was used for the summaries of subject disposition, demographic characteristics and baseline office efficacy measures as well as summaries and analyses of changes from baseline in the trough office measures.

For analysis of each efficacy variable at each analysis timepoint, any subjects who did not have both a baseline and post-randomization assessment were not represented in the analysis of that variable. Thus, analyses of individual efficacy variables could be based on a subset of the subjects in the Randomized Subject dataset (e.g., those with Week 10 data), rather than all randomized subjects.

Treated Subjects

The dataset consists of safety data from all subjects who received at least one dose of double-blind study medication, was used for all safety summaries, but truncated for the short-term double-blind analysis to exclude events or measurements occurring more than 14 days into an extended interruption or more than 14 days after the last dose of short-term double-blind medication. For subjects entering the long-term extension (Period C), the 14-day period was cut off at the start of Period C.

Subjects with Available Plasma Endothelin

This population included plasma endothelin data from those sites performing this test. Samples were collected at selected sites for endothelin determinations at A22 or A29 and at Week 10. This dataset was used to summarize change from baseline to Week 10 in endothelin plasma concentration.

2) Statistical Methods for CV137-037

Efficacy Analyses

Analysis of covariance (ANCOVA) was used to compare the omapatrilat and lisinopril regimens with respect to changes from baseline in the primary variable, trough SeDBP, at the primary timepoint, Week 10. This was the protocol-defined primary comparison for the study. The ANCOVA model used data from all 3 randomized groups and included terms for treatment regimen and baseline value as covariate. The typical sample sizes obtained at individual sites were too small to use study site as an additional term in this model.

Comparisons were done between the omapatrilat, placebo and lisinopril regimens for changes from baseline in trough SeBP measures and pulse pressure at Week 10, trough SeBP at Weeks 2 and 4, and peak SeBP at Week 8. These used the estimated difference in adjusted means between the omapatrilat and lisinopril or placebo together with the associated 95% confidence interval and the p-Value for the t-test of the between-group difference.

Therapeutic Response, defined as the proportions of subjects with normalized DBP (trough SeDBP < 90 mmHg) and favorable DBP (trough SeDBP normalized, or decreased at least 10 mmHg from baseline), and with normalized SBP (trough SeSBP < 140 mmHg) and favorable SBP (trough SeSBP normalized, or decreased at least 20 mmHg from baseline) were summarized by treatment regimen for each timepoint, as were the proportion of subjects with normalized systolic and diastolic BP and the proportion with favorable response in both trough diastolic and systolic BP.

For the primary analysis, and all other comparisons listed above, the statistical significance of the difference in adjusted means was evaluated at $\alpha = 0.05$ (2-sided) and 95% confidence intervals are presented.

Pharmacokinetics

No pharmacokinetic measurements were performed in CV137-037. The effects of the study drugs on endothelin levels were examined at week 10.

Safety

Safety analyses were descriptive in nature.

FDA Statistical Analysis

Unless noted, all p-Values and treatment effects in this review are from the sponsor's analysis. In many cases, the sponsor's analysis excluded particular individuals and/or sites, largely for protocol violations. In addition, only observed values were used in the sponsor's analyses (that is, missing values were not imputed). The FDA preferred the intent-to-treat population for efficacy. Missing values were imputed using Last Observation Carried Forward (LOCF) methods, including all randomized patients. The FDA analyses were done using ANOVA without adjustment for baseline covariates, based on concerns for the uniformity of the relationship between baseline and change from baseline across the treatment groups (a requisite for use of ANCOVA). Using these methods, important efficacy variables were reanalyzed. Unless otherwise noted, this approach yielded qualitatively similar results to those obtained by the sponsor.

10.12 Efficacy Outcomes for CV137-037

10.12a Disposition of Subjects

A total of 1503 subjects were enrolled of which 747 were randomized into the study and 548 (73.4%) completed 10 weeks of Period B.

Out of the 502 subjects who entered double-blind extension (Period C) 262 have completed and 183 are ongoing at the time of CRF lock.

The reasons for discontinuation prior to randomization into the double-blind portion of CV137-037 are summarized below.

Table 10.12a.1 Reasons for discontinuation prior to randomization into CV137-037^a.

Reason for Discontinuation	Number of Subjects
Inclusion/Exclusion Not Met	408
Withdrawal of Subject Consent	101
Lost to follow-up	98
Other	40
Adverse event	37
Uncontrolled Disease State	25
Investigator Request	23
Prohibited Medication	13
Non-Compliance	9
Pregnancy	2
Total	756

a. Data from NDA volume 2.331, table 8.1A.

The reasons for discontinuations during the double-blind portion of CV137-037 are summarized below.

Table 10.12a.2 Discontinuations during double-blind portion of CV137-037^a.

Reason for discontinuation	Placebo N = 151	Omapatrilat 20/40/80 mg N = 301	Lisinopril 10/20/40 mg N = 295
Number of subjects discontinued	42 (27.8%)	76 (25.2%)	81 (27.5%)
Adverse Event	11 (7.3%)	38 (12.6%)	21 (7.1%)
Withdrawal of Subject Consent	9	11	26
Lost to Follow-up	2	9	13
Uncontrolled Disease State	10	6	8
Other	1	4	4
Investigator Request	7	3	4
Non-Compliance	1	3	3
Prohibited Medication	1	1	2
Pregnancy	0	1	0
Subjects completing double-blind period	109 (72.2%)	225 (74.8%)	214 (72.5)

a. Data from NDA vol. 2.331, table 8.1B.

10.12b Protocol Violations & Deviations

Two patients who were white were inadvertently enrolled, but not randomized. One other individual was unblinded at the insistence of an emergency room physician when they presented with angioedema (patient 34/029).

The list of protocol violations can be found in vol. 2.332, table S.7.3B. There were 56 patients so identified, the most common cause for violation being use of prohibited medications, dosing errors or collection of data outside the allowed time interval.

10.12c Subject Demographics & Baseline Characteristics

The demographic and clinical background data for the subjects enrolled in CV137-037 are summarized below. Recall that all patients who received study drug were black.

Table 10.12c.1 Demographics of CV137-037^a.

Baseline Characteristic	Placebo N = 151	Omapatrilat 20/40/80 mg N = 301	Lisinopril 10/20/40 mg N = 295
Age, years			
Mean (sd)	49.9 (9.6)	50.3 (10.0)	50.1 (10.7)
Range	28 - 76	21 - 85	23 - 85
Age Group, n (%)			
< 65 years	137 (91%)	273 (91%)	265 (90%)
65 - 75 years	12 (8%)	23 (8%)	25 (8%)
≥ 75 years	2 (1%)	5 (2%)	5 (2%)
Gender, n (%)			
Male	66 (44%)	138 (46%)	136 (46%)
Female	85 (56%)	163 (54%)	159 (54%)
Weight, kg			
Mean (sd)	87.6 (18.4)	91.5 (20.1)	92.2 (19.8)
Range	49.1 - 162.0	48.2 - 176.8	50.9 - 162.9
Duration of HTN, years			
Mean (sd)	8.9 (9.6)	9.4 (8.6)	9.4 (9.1)
Range	0 - 51	0 - 48	0 - 50

a. Data from NDA volume 2.331, study report.

Baseline trough mean seated DBP (SeDBP) was similar in all of the treatment groups, averaging 101.1 mmHg in the omapatrilat group, 101.4 in the placebo group and 101.0 mmHg in the lisinopril group. Baseline mean seated SBP (SeSBP) was between 154.0 and 154.9 mmHg for the 3 treatment groups.

Other baseline measures of blood pressure (e.g., peak SBP and DBP) and heart rate were also similar among the treatment groups (see NDA vol. 2.331, Tables 8.3B for details).

The occurrence of other medical conditions, when grouped by body system, was similar across the treatment groups, occurring in an average of 44.4 to 48.5% of the treatment groups. The most common cardiovascular conditions present was hypercholesterolemia, present in 17.2 to 24.1% of the subjects grouped by treatment. Prior anti-hypertensive medications were used by 75.5 to 77.4% of the treatment groups, with use of specific agents fairly well-balanced across the treatment groups. Diabetes occurred in 9.9 to 13.1% of the patients. See NDA tables S.6.4A and S.8.4A for details.

10.12d Concomitant Therapies used after Trial Initiation

Concomitant antihypertensive medications were not allowed. Other prohibited medications are listed in section 5.6.3 of the NDA study report, and included ergotamine tartrate, chronic bronchodilators, digitalis and other anti-arrhythmic agents, anticonvulsant medications, anti-psychotic or chronic tricyclic or tetracyclic anti-depressant medications, and lithium. In addition, immunosuppressive drugs or cytotoxic drugs within 12 months prior to enrollment, anabolic steroids, monoamine oxidase inhibitors, venlafaxine and bile acid-binding resins (e.g., cholestyramine and colestipol) were prohibited.

Use of concomitant medications during the trial were balanced across the treatment groups.

10.12e Extent of Exposure to Study Drug

Patient exposure to study drug is summarized below. Patients received study drug for a mean of 59 days.

Table 10.12e.1 Extent of exposure to study drug during double-blind period in CV137-037^a.

	Placebo N = 151	Omapatrilat 20/40/80 mg N = 301	Lisinopril 10/20/40 mg N = 295
Duration			
≤ 7 days	7 (4.6)	23 (7.6)	16 (5.4)
8-30 days	20 (13.2)	24 (8.0)	39 (13.2)
31-60 days	13 (8.6)	25 (8.3)	18 (6.1)
61-90 days	111 (73.5)	229 (76.1)	222 (75.3)
Mean Duration of Exposure (days)	59	59	59

a. Data from NDA vol. 2.331, table 9.1A.

10.12f Primary Efficacy Analyses of CV137-037

The primary objective was to compare the change from baseline in trough seated diastolic blood pressure (SeDBP) following 10 weeks of treatment between omapatrilat and lisinopril. The first table summarizes this comparison along with other trough seated BP changes.

Table 10.12f.1 Summary of primary efficacy variable and other trough BP changes at 10 weeks in CV137-037^a.

	Placebo N = 108	Omapatrilat 20/40/80 mg N = 224	Lisinopril 10/20/40 mg N = 213
Efficacy Variable			
Trough SeDBP, mmHg			
Baseline Mean (sd)	100.8 (4.0)	100.9 (4.2)	100.7 (4.4)
Adjusted Mean Change (se)	-4.5 (0.8)	-10.0 (0.6)	-7.4 (0.6)
Difference from Lisinopril (95% CI)		-2.5 (-4.1, -1.0)	
p-Value ^a		0.002	
Difference from Placebo (95% CI)		-5.5 (-7.4, -3.5)	-2.9 (-4.9, -1.0)
p-Value ^a		<0.001	(0.003)
Trough SeSBP, mmHg			
Baseline Mean (sd)	154.0 (15.6)	153.7 (14.7)	154.5 (14.9)
Adjusted Mean Change (se)	-4.9 (1.3)	-14.2 (0.9)	-9.0 (0.9)
Difference from Lisinopril (95% CI)		-5.2 (-7.8, -2.7)	
p-Value ^a		<0.001	
Difference from Placebo (95% CI)		-9.3 (-12.4, -6.2)	-5.1
p-Value ^a		<0.001	
Trough Pulse Pressure, mmHg			
Baseline Mean (sd)	53.2 (14.8)	52.7 (13.3)	53.9 (14.2)
Adjusted Mean Change (se)	-0.4 (1.0)	-4.3 (0.7)	-1.5 (0.7)
Difference from Lisinopril (95% CI)		-2.8 (-4.7, -0.9)	
p-Value ^a		0.004	
Difference from Placebo (95% CI)		-3.8 (-6.2, -1.5)	-2.2
p-Value ^a		0.001	

a. Data from NDA vol. 2.331, study report summary. p-Values per sponsor.

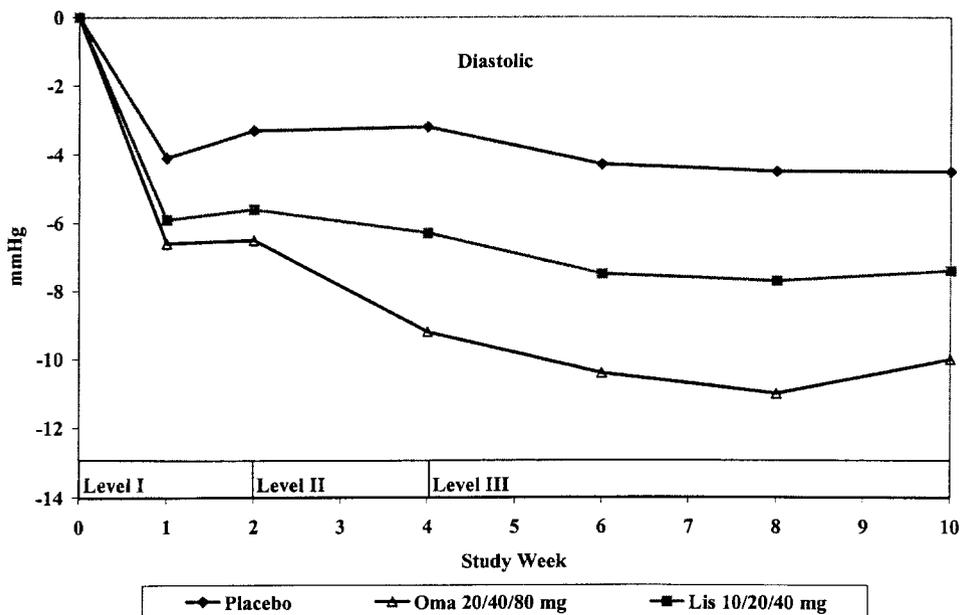
The presence of a significant difference between lisinopril and omapatrilat for SeDBP, SeSBP, and SePP was confirmed by FDA statistical analysis by John Lawrence. His modeling used last observation carried forward to account for missing data. His analyses are also summarized.

Table 10.12f.2 Mean change from baseline in cuff BP measures in CV137-037 per the FDA statistical analysis^a.

Efficacy Variable	Omapatrilat c/w Amlodipine
Trough SeDBP, mmHg	
Diff. From Lisinopril	-2.84
p-Value c/w Amlodipine	<0.001
Trough SeSBP, mmHg	
Diff. From Amlodipine	-6.13
p-Value c/w Amlodipine	<0.001

a. Analysis per Dr. John Lawrence, FDA statistician.

The majority of the mean change from baseline occurred by the end of week one in all treatment groups (shown for the mean change from baseline in trough SeDBP).



10.12g Additional Efficacy Analyses of CV137-037 Sub-Group Analyses

As all of the randomized subjects were black, no sub-set analysis by race is informative. No disparity of effect was detected when the patients were analyzed according to gender. In the small number of enrolled patients ≥ 65 years old, no effect of either omapatrilat or lisinopril was seen on SeDBP.

Table 10.12g.1 Effects of study drugs on trough SeDBP at 10 weeks in subjects grouped by gender from CV137-037^a.

Gender Effects on SeDBP	Placebo	Omapatrilat 20/40/80 mg	Lisinopril 10/20/40 mg
Male	N=45	N=107	N=107
Mean change in SeDBP (mm Hg)	-3.7	-10.6	-6.4
Female	N=63	N=117	N=106
Mean change in SeDBP (mm Hg)	-5.0	-9.4	-8.4

a. Data from NDA vol. 2.332, table S.10.4A. Based on randomized subjects population.

According to an FDA analysis, there was no significant effect of lisinopril on SeDBP demonstrated in the trial among black males, consistent with the prevailing view that ACE inhibitors have weak anti-hypertensive effect in this population.

Table 10.12g.2 FDA analysis of trough SeDBP in subjects grouped by gender from CV137-037^a.

Gender Effects on Placebo-subtracted trough SeDBP	Omapatrilat 20/40/80 mg	Lisinopril 10/20/40 mg
Male		
SeDBP (mm Hg) c/w placebo	-6.35	-2.17
p-Value	<0.001	0.13
SeDBP Omap c/w Lis	-4.18	--
p-Value	0.0003	--
Female		
SeDBP (mm Hg) c/w placebo	-4.42	-2.72
p-Value	<0.001	0.017
SeDBP Omap c/w Lis	-1.70	--
p-Value	<0.001	--

a. Data from NDA vol. 2.332, table S.10.4A. Based on randomized subjects population.

Table 10.12g.3 Effect of study drugs on trough SeDBP at 10 weeks in subjects grouped according to age in CV137-037^a.

Age Effects on SeDBP	Placebo	Omapatrilat 20/40/80 mg	Lisinopril 10/20/40 mg
<65	N=99	N=202	N=190
Mean change in SeDBP (mm Hg)	-3.9	-9.9	-7.2
≥65	N=9	N=22	N=23
Mean change in SeDBP (mm Hg)	-10.5	-10.4	-9.0

Changes in Standing BP Measures

The changes in standing BP were similar to those seen for the seated BP changes summarized above.

Table 10.12g.4 Summary of standing SBP and DBP changes at 10 weeks in CV137-037^a.

Efficacy Variable	Placebo N = 108	Omapatrilat 20/40/80 mg N = 224	Lisinopril 10/20/40 mg N = 213
Trough Standing DBP, mmHg			
Adjusted Mean Change	-2.8	-9.3	-6.0
Trough Standing SBP, mmHg			
Adjusted Mean Change	-3.8	-14.0	-8.3

a. Data from NDA vol. 2.332, table S.10.1.1D1 and .1D2.

BP Effects at Peak

The effect of omapatrilat on peak BP (collected 7±1 hour after dose) was assessed after 8 weeks of double-blind therapy, and the results are summarized below. The numerical and (nominally) significant difference between omapatrilat and lisinopril on SeDBP persists at the peak measurement.

Table 10.12g.5 Peak changes in mean BP at 10 weeks in CV137-037^a.

Efficacy Variable	Placebo N = 94	Omapatrilat 20/40/80 mg N = 200	Lisinopril 10/20/40 mg N = 187
Peak SeDBP, mmHg			
Baseline Mean (sd)	98.3 (5.8)	98.5 (6.0)	98.4 (6.0)
Adjusted Mean Change (se)	-3.3 (0.9)	-11.7 (0.6)	-8.6 (0.6)
Difference from Lisinopril (95% CI)		-3.1 (-4.8, -1.4)	
p-Value ^a		(< 0.001)	
Peak SeSBP, mmHg			
Baseline Mean (sd)	152.4 (13.8)	153.3 (14.2)	154.1 (14.8)
Adjusted Mean Change (se)	-3.0 (1.4)	-18.4 (0.9)	-11.0 (1.0)
Difference from Lisinopril (95% CI)		-7.4 (-10.0, -4.7)	
p-Value ^a		(< 0.001)	

Therapeutic Response

The sponsor also examined the anti-hypertensive effects of omapatrilat using a categorical analysis of 'Therapeutic Response.' Therapeutic response was defined as a normalized BP (SeDBP < 90 mmHg) or a favorable BP response (BP normalized or SeDBP ≥ 10mmHg decrease from baseline) at Week 10.

Table 10.12g.6 Subjects with normalization or favorable trend in BP at 10 weeks in CV137-037^a.

Therapeutic Response	Placebo N = 108	Omapatrilat 20/40/80 mg N = 224	Lisinopril 10/20/40 mg N = 213
SeDBP^b			
Normalized, n (%)	24 (22.2%)	95 (42.4%)	71 (33.3%)
Favorable, n (%)	31 (28.7%)	115 (51.3%)	92 (43.2%)
SeSBP and SeDBP^b			
Normalized, n (%)	10 (9.3%)	75 (33.5%)	53 (24.9%)
Favorable, n (%)	14 (13.0%)	97 (43.4%)	71 (33.3%)

a. Data from NDA vol. 2.332, table 10.2.1.2A2, based on Randomized Subjects.

b. Normalized: Trough SeDBP <90 mmHg

Trough SeSBP <140 mmHg.

Favorable: Trough SeDBP <90 or decrease from baseline ≥10 mmHg.

Trough Se SBP <140 mmHg or decrease from baseline ≥20 mmHg.

Heart Rate

No effect of omapatrilat or lisinopril on the change in mean trough heart rate at 10 weeks (summarized below). In data not shown, trough seated and standing heart rates were similarly unchanged at week 10 in the omapatrilat and lisinopril groups, relative to placebo (see NDA vol. 2.332, tables S.10.1.1D4 and 5).

Table 10.12g.7 Mean changes in trough seated heart rate at 10 weeks in CV137-037^a.

Efficacy Variable	Placebo N = 108	Omapatrilat 20/40/80 mg N = 224	Lisinopril 10/20/40 mg N = 213
Trough Heart Rate, beats/min			
Baseline Mean (sd)	73.4 (9.3)	74.6 (9.4)	74.0 (9.2)
Adjusted Mean Change (se)	-0.2 (0.7)	-1.4 (0.5)	-0.5 (0.5)
Difference from Placebo (95% CI)		-1.2 (-2.9, 0.6)	-0.3
p-Value		(0.195)	NS

a. Data from NDA vol. 2.331, table 10.1.1.

Plasma Endothelin Levels

The sponsor measured endothelin levels at baseline and again at 10 weeks, and the changes in mean endothelin levels are summarized below. Treatment with omapatrilat was associated with a 0.12 pmol/liter decrease from baseline (approximately 9% decrease from baseline). Note the broad standard deviations for each mean value.

Table 10.12g.8 Plasma endothelin levels (pmol/L) at baseline and week 10^a.

Endothelin Levels at Baseline	Placebo N = 17	Omapatrilat N = 28	Lisinopril N = 28
Baseline, Mean (sd)	0.78 (0.96)	1.08 (1.12)	1.02 (1.60)
Week 10			
Mean on Treatment (sd)	0.83 (0.86)	0.96 (1.06)	0.99 (1.18)
Mean Change (sd)	0.05 (0.28)	-0.12 (0.30)	-0.04 (0.75)

a. Data from NDA vol. 2.332, table S.11.

Efficacy Parameters During Period C (Double-Blind Long-Term Extension)

During the long-term extension period of CV137-037 (4 months), subjects were initially started on the lowest doses of study drug (omapatrilat 20 mg, lisinopril 10 mg). These doses were increased as needed at the end of week one and again at the end of week two, to achieve the final study drug doses (omapatrilat 80 mg, lisinopril 40 mg). If these levels of medications were insufficient to control BP, subjects were to receive concomitant anti-hypertensive medications, beginning with amlodipine and then HCTZ. The following table summarizes the use of adjunctive therapy in the long-term, double-blind extension period. Use of adjunctive therapy was higher in the lisinopril group.

Table 10.12g.9 Summary of Adjunctive use of anti-hypertensives in CV137-037 long-term extension^a.

Timepoint	Treatment	N	Any Adjunctive ^a N (%)
LT Week 1	Oma 20/40/80 mg	209	0
	Lis 10/20/40 mg	201	0
LT Week 2	Oma 20/40/80 mg	215	0
	Lis 10/20/40 mg	206	0
LT Month 1	Oma 20/40/80 mg	214	7 (3.3%)
	Lis 10/20/40 mg	203	3 (1.5%)
LT Month 2	Oma 20/40/80 mg	168	43 (25.6%)
	Lis 10/20/40 mg	165	82 (49.7%)
LT Month 3	Oma 20/40/80 mg	150	47 (31.3%)
	Lis 10/20/40 mg	143	82 (57.3%)
LT Month 4	Oma 20/40/80 mg	127	42 (33.1%)
	Lis 10/20/40 mg	133	78 (58.6%)

a. Data from NDA vol. 2.331, table 13.3.1. Any adjunctive therapy is amlodipine, HCTZ, or both. LT= Long-term.

Next, the sponsor analyzed the changes in BP through the 4 months of therapy, and compared them to a baseline value taken before the start of the initial double-blind portion (Period B). The sponsor ascribed the similar effects seen with both treatment groups to the increased use of adjunctive medications in the lisinopril group.

Table 10.12g.10 Changes in trough SeDBP and Se SBP during long-term extension of CV137-037^a.

Variable/Time	Omapatrilat			Lisinopril		
	N	Mean	Mean Change	N	Mean	Mean Change
Trough SeDBP						
Baseline ^b	254	100.8		248	100.8	
Month 1 (Week 4)	214	88.7	-12.0	203	92.2	-8.6
Month 2	168	86.4	-14.0	165	88.3	-12.4
Month 3	150	85.3	-15.2	143	87.2	-13.5
Month 4	127	85.2	-15.4	133	86.4	-14.5
Trough SeSBP						
Baseline ^b	254	153.3		248	154.7	
Month 1 (Week 4)	214	137.9	-15.5	203	144.4	-10.6
Month 2	168	134.1	-18.6	165	137.0	-17.8
Month 3	150	132.8	-20.2	143	136.9	-18.8
Month 4	127	132.0	-21.4	133	136.1	-19.5

a. Data from NDA vol. 2.331, table 13.3.2.

b. Baseline value taken from start of short-term double-blind period (B).

10.13 Safety Outcomes

The evaluation of safety includes the 747 subjects who received at least one dose of study medication. The reader is referred to the Integrated Summary of Safety by Dr. Pelayo for more details. The overall event rates for adverse events, serious adverse events, discontinuations, and deaths are shown below.

Table 10.13.1 Clinical adverse experience (AE) summary from CV137-037 during initial double-blind period^a.

Event	Placebo N = 151	Omapatrilat 20/40/80mg N = 301	Lisinopril 10/20/40mg N =295
AE, total (% of subjects)	94 (62.3)	174 (57.8)	182 (61.7)
SAE	4 (2.6)	16 (5.3)	8 (2.7)
Death	0	0	0
Discontinuations due to AE	11 (7.3)	38 (12.6) ^c	21 (7.1) ^c

a. Data from NDA volume 2.331, report summary table.

10.14 Study CV137-037 Efficacy Summary

Study CV137-037 was a randomized, double-blind trial in black subjects that compared the anti-hypertensive effects of placebo, omapatrilat (force-titrated up to 80 mg per day), and lisinopril (force-titrated up to 40 mg per day) through 10 weeks. After that time, the patients on omapatrilat and lisinopril continued their medications for an additional four months, during which time additional anti-hypertensive medications could be used as needed. Patients initially randomized to placebo were re-randomized to receive omapatrilat or lisinopril at the start of the long-term extension portion of the trial.

Initial Double-Blind Phase (Period B)

1. The primary objective was to compare the change from baseline in trough seated diastolic blood pressure (SeDBP) following 10 weeks of once-daily oral administration of a regimen of omapatrilat and lisinopril in black subjects with mild-to-moderate hypertension (SeDBP 95-110 mmHg). After 10 weeks, the omapatrilat group had a mean trough SeDBP that was 2.5 mmHg less than the group receiving lisinopril (95% C.I., -4.1 to -1.0, p=0.002) per the sponsor's analysis. A separate analysis by the FDA confirmed that omapatrilat had a significantly larger effect on SeDBP. In his model, the omapatrilat group had a mean trough SeDBP that was 2.84 mmHg less than lisinopril (p<0.001).

2. Omapatrilat, used in a forced titration scheme up to 80 mg per day for 10 weeks, lowered blood pressure measured by the following parameters in patients with mild-to-moderate hypertension, when compared with placebo,:

- 1) Placebo-subtracted Trough SeDBP: -5.5 mmHg (95% C.I. -7.4 to -3.5, p<0.001)
- 2) Placebo-subtracted Trough SeSBP: -9.3 mmHg (95% C.I. -12.4 to -6.2, p<0.001)
- 3) Placebo-subtracted Trough SePP: -3.8 mmHg (95% C.I. -6.2 to -1.5, p=0.001)

3. The following differences were found comparing omapatrilat and lisinopril in this study (per the sponsor):

- 1) Trough SeDBP: -2.5 mmHg (95% C.I. -4.1 to -1.0, p=0.002)
- 2) Trough SeSBP: -5.2 mmHg (95% C.I. -7.8 to -2.7, p<0.001)
- 3) Trough SePP: -2.8 mmHg (95% C.I. -4.7 to -0.9, p<0.001)

4. Omapatrilat and lisinopril had similar effects on the primary efficacy analysis (changes in trough SeDBP) when the population was examined by subgroups according to gender. Too few non-white subjects were enrolled to assess efficacy in racial sub-groups, but no effect of lisinopril on SeDBP was found in the black male population. In a small number of patients >65 years of age, no effect of either omapatrilat or lisinopril on BP was detected.

5. Like the measurements taken at trough, omapatrilat and lisinopril had significant effects to lower the placebo-subtracted BP measurements taken at the time of peak drug effect.

6. A significant fraction of the anti-hypertensive effects of omapatrilat and lisinopril were seen within the first week after starting study drug.

7. Both omapatrilat and lisinopril increased the percentage of subjects who had a complete or favorable improvement in their blood pressure control at 10 weeks. For both SeDBP and the combination of SeDBP plus SeSBP, the percentage of patients whose BP improved was numerically larger in the omapatrilat group compared with lisinopril.

8. Omapatrilat and lisinopril had no clinically-significant effects on mean heart rate.
9. Omapatrilat use for 10 weeks was associated with a decrease in the baseline endothelin level of approximately 9% from baseline, with broad inter-patient variability.

Extension Double-Blind Phase (Period C)

1. No significant differences between omapatrilat and lisinopril were detected in the changes in trough SeDBP and Se SBP through 4 months.
2. A higher percentage of subjects in the lisinopril group used adjunctive anti-hypertensive therapy for BP control during Period C.