

**Appendix for Safety Review of Original NDA  
Submission**

3877B2 - 07 - SAFETY REVIEW JUNE 2007

## 16.0 APPENDIX

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**Table 1A. Clinical Pharmacology Studies of Omapatrilat**

	Protocol	N	n	Dose (mg)	Exposure
<b>Tolerance/Biopharmaceutics</b>					
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 [ <sup>14</sup> 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 [ <sup>14</sup> C]BMS-186716	CV137-064	6	6	50	single dose
<b>Special Populations</b>					
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)

**Table 1A. (Cont'd)**

<b>Drug/Food Interactions</b>					
Interaction of Omapatrilat and Hydrochlorothiazide in Patients with Mild-to-Moderate Hypertension	CV137-008	36	18	10	multiple dose (21 days)
The Pharmacokinetic and pharmacodynamic Interaction Study of Omapatrilat and Digoxin in Healthy Subjects	CV137-011	18	9	25	multiple dose (10 days)
Evaluation of the Effect of Dosing Time Relative to the Intake of a Light Meal on Oral Bioavailability and Pharmacokinetics of BMS-186716 in Healthy Human Volunteers	CV137-014	28	28	25	crossover (x5)
Effect of Concomitant Administration of BMS-186716 on the Steady-State Pharmacodynamics of Warfarin	CV137-016	16	8	25	multiple dose (7 days)
The Pharmacokinetic and Pharmacodynamic Interaction of Omapatrilat (BMS-186716) and Furosemide	CV137-019	24	12	10, 25	multiple dose (10 days)
The Effect of Single-Dose Magnesium & Aluminum Hydroxides (Maalox®) on the Pharmacokinetics of a Single, Oral 25 mg Dose of omapatrilat	CV137-051	18	18	25	crossover (x3)
Evaluation of the Effect of Meal on Oral Bioavailability, Pharmacokinetics and Pharmacodynamics of Omapatrilat (BMS-186716) in Healthy Volunteers	CV137-055	22	22	80	crossover (x2)
The Pharmacodynamic Interaction of Omapatrilat and Viagra™ in Healthy Subjects	CV137-061	45	45	40	multiple dose (7 days)
Double-Blind Randomized Three-Way Crossover Interaction Study of the Pharmacodynamics and Pharmacokinetics of Single-Dose Omapatrilat and Atenolol in Healthy Volunteers	CV137-070	24	23	40	crossover (x3)
<b>Total</b>	<b>23 Studies</b>	<b>736</b>	<b>618</b>		

[Sponsor's analysis, adapted from NDA 21-188, Vol. 495, Table 18.1, pages 326 & 327. N = number of subjects randomized; n = number of subjects receiving omapatrilat.]

**Table 2A. Controlled Clinical Hypertension Studies of Omapatrilat**

<b>Protocol (Purpose)</b>	<b>Placebo (N)</b>	<b>Omapatrilat (N) Dosing</b>	<b>Active Control (N) Dosing</b>	<b>Duration of Rx</b>
CV137-006 (Dose-Ranging)	(121)	(337*) Fixed dose: 2.5, 5, 10 mg	(110) Fixed dose: Aml 10 mg	8 weeks
CV137-022 (Dose-Ranging)	(117)	(464) Parallel dose wk 1/wks 2-9: 5/5, 10/10, 10/20, 10/40 mg	(109) Parallel dose wk1/wks 2-9: Lis 10/20 mg	9 weeks
CV137-024 (Dose-Ranging)	(119)	(707) Parallel dose wk 1/wks 2-9: 10/20, 20/40, 30/60, 10/80, 20/80, 40/80mg	--	9 weeks
CV137-045 (Dose-Ranging)	(68)	(216) Forced titration wks 1/2/3-6: 20/80/120, 20/80/80 mg	--	6 weeks
CV137-030 (Comparative Efficacy)	(146)	(286) Forced titration wks 1-2/3-4/5-10 20/40/80 mg	(293) Forced titration wks 1-2/3-4/5-10: Aml 5/10/10 mg	10 weeks
CV137-031 (Comparative Efficacy-ABPM)	--	(173) Forced titration wks 1-2/3-4/5-10 20/40/80 mg	(174) Forced titration wks 1-2/3-4/5-10: Lis 10/20/40 mg	10 weeks
CV137-032 (Comparative Efficacy-ABPM)	--	(213) Forced titration wks 1-2/3-4/5-10 20/40/80 mg	(217) Forced titration wks 1-2/3-4/5-10: Aml 5/10/10 mg	10 weeks

**Table 2A. (Cont'd)**

CV137-037 (Comparative Efficacy)	(151)	(301) Forced titration wks 1-2/3-4/5-10: 20/40/80 mg	(295) Forced titration wks1-2/3-4/5-10: Lis 10/20/40 mg	10 weeks
CV137-029 (Special Population: Elderly)	(93)	(255) Parallel dose wk 1/wks 2-9: 10/10,20/20,20/40 mg <sup>b</sup>	--	13 weeks
CV137-038 (Special Population: Left Ventricular Hypertrophy)	--	(169) Forced titration wks 1-8/9-16/17-24 20/40/80 mg	(172) Forced titration wks 1-8/9-16/17-24: Los 50/100/100 mg	24 weeks
CV137-040 (Special Population: Hydrochlorothiazide Resistant)	(91)	(183) Elective titration wks 1-4/5-8: 10/20, 20/40	--	8 weeks
CV137-042 (Special Population: Isolated Systolic Hypertension)	(108)	(321) Parallel dose wk 1/wks 2-9: 10/10, 20/20, 20/40 mg <sup>b</sup>	--	13 weeks
CV137-049 (Special Population: Severe Hypertension)	--	(147) Titration: 20/40/80 mg	(67) Titration: Enal 10/20/40 mg	10 weeks
CV137-005 (Other/Pilot Dose- finding ABPM)	(49)	(125) Fixed dose: 1, 5, 12.5, 30 or 75 mg	--	2 weeks
CV137-036 (Other/ABPM)	(64)	(202) Fixed dose: 10 mg QD, 20 mg QD, 10 mg BID	--	8 weeks
CV137-054 (Other/Elective Titration)	(93)	(185) Elective titration wks 1-2/3-4/5-8: 10/40/80, 20/40/80 mg	--	8 weeks

[Sponsor's analysis, adapted from NDA 21-188, Vol. 494, Table 1.1.2.1A, page 79. Lis=Lisinopril; Aml=Amlodipine; Los=Losartan; Enal=Enalapril; HCTZ=Hydrochlorothiazide; ABPM=ambulatory blood pressure monitoring. <sup>a</sup> Treated number includes 3 subjects that were randomized to the 2 discontinued groups of omapatrilat 25 mg and 50 mg. <sup>b</sup> Dose may be doubled on Weeks 10-13.]

**Table 3A. Active-Controlled Studies in Hypertension**

Protocol	Omapatrilat N = 702	Active Comparator N = 630	Omapatrilat Dosing	Active Comparator Dosing	Adjunct Medication	Duration of Therapy
CV137-031	173	174 Lis	Forced titration wks 1-2/3-4/5-10 20/40/80 mg	Forced titration: Lis wks 1-2/3-4/5-10 10/20/40 mg	None	10 weeks
CV137-032	213	217 Aml	Forced titration wks 1-2/3-4/5-10 20/40/80 mg	Forced titration: Aml wks 1-2/3-4/5-10 5/10/10 mg	None	10 weeks
CV137-038	169	172 Los	Forced titration wks 1-8/9-16/17-24 20/40/80 mg	Forced titration: Los wks 1-8/9-16/17-24 50/100/100 mg	Amlodipine, HCTZ	24 weeks
CV137-049	147	67 Enal	Titration 20/40/80 mg	Titration Enalapril 10/20/40 mg	Amlodipine, HCTZ	10 weeks

[Sponsor's analysis, adapted from NDA 21-188, Vol. 494, Table 1.1.2.1B, page 81. Lis=Lisinopril; Aml=Amlodipine; Los=Losartan; Enal=Enalapril; HCTZ=Hydrochlorothiazide.]

**Table 4A. Ongoing Studies**

Study Type	Protocol Number
Long-Term, Open-Label, Extension Studies	CV137-009, -029, -042, -049
Long-Term Double-Blind Extension Study	CV137-037
Clinical Hypertension Studies	CV137-046, CV137-038 (months 7-12), CV137-066, CV137-072, CV137-073
Clinical Heart Failure Studies	CV137-013, -018, -028
Clinical Studies in Subjects with Coronary Artery Disease	CV137-050, CV137-071
Clinical Studies in Japan	201-101, 201-104, 201-105, 201-203, 201-204, 201-205, 201-206

[Sponsor's analysis, adapted from NDA 21-188, Vol. 494, Table 1.1.5, page 85.]

**Table 5A. Extent of Exposure to Double-Blind and Open-Label Omapatrilat for All Subjects, by Dose**

Dosage Mg	1-7 Days N	8-30 Days N	31-60 Days N	61-90 Days N	91-180 Days N	181-365 Days N	> 365 Days N	Total Subjects N
Oma 1	0	23	0	0	0	0	0	23
Oma 2.5	2	8	92	12	1	0	2	117
Oma 5	26	529	107	120	79	79	73	1013
Oma 7.5	1	2	1	1	0	0	0	5
Oma 10	316	604	343	217	201	228	175	2084
Oma 12.5	0	28	0	0	0	0	0	28
Oma 15	0	1	0	1	0	1	0	3
Oma 20	556	1550	624	207	214	225	150	3526
Oma 25	0	0	1	0	0	0	0	1
Oma 30	101	45	0	0	0	0	0	146
Oma 40	183	1153	580	212	165	105	9	2407
Oma 50	1	0	0	1	0	0	0	2
Oma 60	2	9	100	12	0	0	0	123
Oma 75	2	26	0	0	0	0	0	28
Oma 80	153	228	1316	127	160	110	7	2101
Oma 120	3	121	4	0	0	0	0	128
Oma 160 <sup>a</sup>	8	0	0	0	0	0	0	8

[Sponsor's analysis, adapted from NDA 21-188, Vol. 507, Appendix 2.1A, page 106. Protocols included: CV137-005, -006, -009, -022, -024, -029, -030, -031, -032, -036, -037, -038, -039, -40, -042, -045, -049, -054. Subjects discontinued prematurely are included in the table for days taking double-blind study drug. Days during documented interruptions of study drug are not included in exposure (except in -005, -006, -022). <sup>a</sup>Omapatrilat 160 mg was not a dose in any trial. All subjects in this category took extra doses of the prescribed 80 mg in error.]

## Narratives of Patients Who Died During Double-Blind Therapy

- **Subject ID 0083/010**, Age 68/Gender F/Weight 66.4 Kg, Dose 20 mg Omapatrilat x 4 days, Death/Cardiovascular/Cardiac Arrest. Significant medical history includes hypertension of one year, left ventricular hypertrophy, degenerative joint disease of the cervical spine, arthralgia, CVA, CAD, bursitis, insomnia, hypothyroidism, and rash (due to penicillin). Four days after beginning double-blind therapy, subject was found deceased at home after experiencing cardiac arrest. One day prior to receiving study drug, subject experienced upper chest tightness and did not inform the site of previous cardiac disease. Investigator considered the relationship of this event to study drug to be possible. Concomitant medications at onset of SAE: none. Additional concomitant medications during double-blind therapy: acetaminophen, codeine, flurazepam, levothyroxine. *Correction:* This subject was reported as having a history of CVA and CAD. However, she had a family history of CVA and CAD. One day prior to randomization, in addition to upper chest highness, the subject also experienced weakness, left shoulder pain, and pleuritic left upper back pain. Additionally, the dose of omapatrilat at the time of the event was reported as post-omapatrilat 20 mg, because the last known dose of drug was the day prior to her death.
- **Subject ID 0074/016**, Age 65/Gender M/Weight 90 Kg, Dose Placebo x 81 days, Death/Cardiovascular/Myocardial Infarction. Significant medical history includes hypertension of thirty years and arthritis. Eighty-one days after beginning double blind therapy, subject experienced myocardial infarction due to thrombotic occlusion of the circumflex coronary artery due to severe coronary artery disease and atherosclerosis. As a result, subject died. Investigator considered the relationship of this event to study drug to be unrelated. Concomitant medications at onset of SAE: acetaminophen. Additional concomitant medications during double-blind therapy: none.
- **Subject ID 0032/001**, Age 67/Gender M/Weight 90 Kg, Dose Omapatrilat 20/40/80 mg x 71 days (Level III), Death/Cardiovascular/Cardiac Arrest. Significant medical history includes hypertension of 33 years, systolic ejection murmur and led ventricular hypertrophy for three years, occasional PACs, cataracts, basal cell carcinoma, indigestion, leg cramps, tennis elbow, seasonal allergies, tension headaches, alcohol use of 2 beers per day. 71 days after beginning double-blind therapy, subject experienced shortness of breath and fatigue. Study medication was discontinued. After a positive stress test, the subject underwent a cardiac catheterization which showed severe three-vessel coronary disease, moderate left ventricular dysfunction, an elevated wedge pressure of 33, and a degree of left main coronary stenosis. He was scheduled for coronary artery bypass but, he collapsed and could not be resuscitated. The Investigator considered the relationship of this event to study drug to be not likely. Concomitant medications taken during double-blind therapy: acetylsalicylic acid, ascorbic acid, azelastine topical, beta carotene, calcium, cyanocobalamin, fexofenadine, potassium, pyridoxine, tocopherol. This subject's past medical history also includes hypercholesterolemia. Additionally, the subject also developed tachycardia 72 days after randomization.

## During Long-Term, Open-Label Therapy

- **Subject ID 0007/018**, Age 61/Gender M/Weight 77 Kg, Dose Omapatrilat 10 mg x 443 days, Death/Cardiovascular/Sudden Death. Significant medical history includes hypertension of 30 years, and precancerous lesions on the face and hands. This 61-year-old male, randomized to amlodipine 10 mg, completed 8 weeks of double-blind therapy and then entered the open-label phase. He had a basal cell carcinoma of the forehead and neck after 119 days of open-label therapy. He was treated with liquid nitrogen and the event resolved the same day. The investigator considered the event unrelated to study drug. He continued in the study until death, occurred after 381 days of open-label therapy. He had complained of indigestion prior to going to bed and later had an episode of vomiting. He returned to sleep and was found dead by his wife in the morning. The Investigator considered the event unrelated to study drug and due to a MI. The family refused an autopsy. Concomitant medications reported at onset of SAE: acetylsalicylic acid. Additionally, other medications received during open-label therapy: none.
- **Subject ID 0019/007**, Age 74/Gender M/Weight 71.1 Kg, Dose 10 mg Omapatrilat/ 5 mg Amlodipine x 527 days, Death/Consciousness Impair/Coma; Brain Dead. Significant medical history includes hypertension of 10 years, cardiac arrhythmias, benign prostatic hypertrophy, Type II diabetes mellitus and arthritis. This 74 year old male randomized to placebo, completed 8 weeks of double-blind therapy and then entered the open-label phase. After 464 days of open-label therapy, he was hospitalized due to black tarry stools and severe abdominal pain. While hospitalized, he was found unconscious (estimated 20 minutes). He was in a coma and died 5 days later. He was taking oxaprozin for a heel spur for approximately one month and the investigator considered this as a suspect drug. He was hospitalized in Japan so no further information was available. The investigator considered the event unrelated to study drug. Concomitant medications reported at onset of SAE: glyburide, nizatidine, oxaprozin. Additionally, other medications received during open-label therapy: acetaminophen, calcium carbonate, guaifensin, neomycin/polymyxin B, pirbuterol.

- **Subject ID 0081/002**, Age 60/Gender M/Weight 88.2 Kg, Dose Omapatrilat 20 mg x 218 days, Death/Cardiovascular/Sudden Cardiac Arrest. Significant medical history includes hypertension of 3 years, coronary artery disease, hyperlipidemia, smoking, and glucose intolerance. This 60-year-old male randomized to omapatrilat 10 mg completed 9 weeks of double-blind therapy and then entered the open-label phase. After 141 days of open-label therapy, he experienced sudden cardiac arrest. The Investigator felt the subject had a myocardial infarction following snow shoveling during a blizzard. The Investigator considered the event to be unrelated to study drug. Concomitant medications reported at onset of SAE: none. Additionally, other medications received during open-label therapy: acetylsalicylic acid, ascorbic acid, cyanocobalamin, tocopherol.
- **Subject ID 0006/001**, Age 56/Gender F/Weight 90.5 Kg, Dose Omapatrilat 10 mg/HCTZ 12.5 mg x 123 days, Death/Cardiovascular/Sudden Cardiac Arrest. Significant medical history includes hypertension of 10 years, hypercholesterolemia, hypertriglyceridemia, thyroidectomy, dyspnea and smoking for 30 years. This 56-year-old female, randomized to amlodipine 10 mg, completed 8 weeks of double-blind therapy and then entered the open-label phase. She has been experiencing dyspnea for many years, which worsened after 260 days of open-label therapy and requiring treatment with inhalers. She was under the care of her primary physician for a diagnostic work-up. A CT scan was performed approximately 7 months after open-label therapy, which revealed a mass in the right upper lobe. She was scheduled for a bronchoscopy, bone scan, and repeat CT scan. At the time of the study drug discontinuation, the event was ongoing. The investigator considered the event unrelated to study drug, but related to her heavy smoking. Post discontinuation follow up revealed a repeated CT scan, which was obtained 7 months after the initial scan, confirmed hilar adenopathy and a left adrenal mass due to metastatic disease. She died over one year due to respiratory arrest secondary to bronchogenic carcinoma after the initial cancer diagnosis. Concomitant medications reported at onset of SAE: triamcinolone inhaler, estrogens conjugated, levothyroxine. Additionally, other medications received during open-label therapy: terfenadine.
- **Subject ID 0017/011**, Age 50/Gender F/Weight 68.4 Kg, Dose Omapatrilat 20 mg x 944 days, Death/Cardiovascular/Myocardial Infarction. Significant medical history includes hypertension of 6 years and smoking. This 50-year-old female, randomized to placebo, completed 8 weeks of double-blind therapy and then entered the open-label phase. She had a myocardial infarction after 873 days of open-label therapy. She was treated with tPA and suffered an intraventricular hemorrhage. Her prognosis was poor at the time of the data lock. The Investigator considered the event to be unrelated to study drug. Post data lock note: The investigator reported the intraventricular hemorrhage as a separate event, which was also unrelated to study drug but related to the tPA. She had a craniotomy, duraplasty, cranioplasty, and ventriculostomy, tracheostomy and gastric tube placement. She stabilized and was transferred to a rehab facility where she experienced ventricular fibrillation. Resuscitation attempts were unsuccessful and she died presumably due to an acute MI, 25 days after onset of MI and hemorrhage. Subject was on omapatrilat at the time of the event. Concomitant medications reported at onset of SAE: None. Additionally, other medications received during open-label therapy: none.

### **In Ongoing Hypertension Study/Double-Blind Therapy**

- **Subject ID 0041/006**, Age 47/Gender M/Weight 84.2 Kg, Dose Blinded x 199 days, Death/Unwitnessed Sudden Death. Significant medical history includes hypertension for 15 years, osteochondrosis and ex-smoker. This 47-year-old male died suddenly after 199 days of double-blind therapy. No other information is available at this time. The investigator considered the event to be unrelated to study drug. Concomitant medications reported at the onset of the SAE: none. Additionally, other concomitant medications received during double-blind therapy: acetylsalicylic acid and erythromycin.
- **Subject ID 0090/002**, Age 76/Gender M/Weight 80.9 Kg, Dose Blinded x 10 days, Death/Cardiovascular/Acute Myocardial Infarction. Significant medical history includes hypertension of 15 years, hypercholesterolemia, posterior vitreous retina (separation of gel), cholecystectomy, kidney stone, right inguinal hernia repair, keratotic lesion right forearm removed and alcohol use. After 10 days of randomization, the subject experienced bilateral arm and shoulder pain not precipitated by exertion. EKG showed acute changes. Subject received acetylsalicylic acid and TPA and was admitted to the hospital. Subject was discontinued from the study at that time. Four days after admission, the subject underwent cardiac catheterization which showed extensive multi-vessel disease not amenable to angioplasty or stent placement. The subject was also judged not to be a surgical candidate. Five days after admission, the subject had a sudden episode of electro-mechanical dissociation, not preceded by evidence of arrhythmia. The subject expired. Investigator considered event to be unrelated to double-blind therapy. Concomitant medications reported at onset of SAE: none. Additionally, other concomitant medications received during double-blind therapy: none.

### **In Ongoing Coronary Artery Disease Study/Double-Blind Therapy (Protocol CV137-050)**

- **Subject ID 6020**, Age 67/Gender M/Weight 84 Kg, Dose Blinded x 0 days, Death/Sudden Cardiac Death. Subject 6020, a 67-year-old male with a history of more than one myocardial infarction complained of chest pain and collapsed 2 hours later. CPR was initiated. The subject was hospitalized however, he never regained consciousness and died 2 days later (sudden cardiac death). This event occurred after enrollment but prior to test dose. The Investigator considered the event unrelated to study medication. Concomitant medications received during double blind therapy: aspirin, pravastatin, sotalol.
- **Subject ID 14011**, Age 47/Gender M/Weight 115 Kg, Dose Blinded x 0 days, Death/Accidental Death. Subject 14011, a 47-year-old male with a history of non-insulin dependent diabetes mellitus and a history of more than one myocardial infarction died as a result of a motor vehicle accident. This event occurred after enrollment but prior to test dose. The investigator considered the event unrelated to study medication. Concomitant medications received during double blind therapy: aspirin, diamicon, metformin, orlistat.
- **Subject ID 13002**, Age 73/Gender F/Weight 73 Kg, Dose Blinded x 133 days, Death/Unwitnessed Death. Subject 13002, a 73-year-old female with a history of coronary artery bypass and graft, hypertension and tobacco use was found dead after 133 days on study treatment. An autopsy showed the subject's death resulted from ischemic heart disease due to severe coronary atherosclerosis. This event was considered by the Investigator as not likely/unrelated to study treatment. Concomitant medications received during double blind therapy: amitriptyline, aspirin, felodipine.
- **Subject ID 97004**, Age 72/Gender F/Weight 84 Kg, Dose Blinded x 195 days, Death/Unwitnessed Death. Subject 97004, a 72-year-old female with a history of non-insulin diabetes mellitus, a history of more than one myocardial infarction and hypertension was found dead in bed after 195 days of study treatment. The Investigator considered the event to be unrelated to study treatment. Concomitant medications received during double blind therapy: ditropan, metoprolol, moduretic, oscal-500, piroxicam, pravastatin.

**Table 6A. Accounting of Heart Failure Deaths**

Study	Omapatrilat Short-Term	Lisinopril Short-Term	Placebo Short-Term	Omapatrilat Open-Label Ongoing	Double-Blind Ongoing
CV137-003	-	-	1	1	-
CV137-012	12	-	-	-	-
CV137-013 <sup>c</sup>	2+1	2+1	-	-	-
CV137-028	7+1+1 <sup>c</sup>	10+1 <sup>d</sup>	-	-	18
CV137-018 <sup>b</sup>	13+15	20+18	-	7 <sup>a</sup>	-
<b>Total</b>	52	52	1	8	18

[Sponsor's analysis, NDA 21-188, Response on February 4, 2000, to request, dated 1/31/00, from Dr. Pelayo. <sup>a</sup>One subject (143/001) is reported in the -018 FSR, Table 12.2D. However, this subject is also listed as an 'ongoing' death in ISS Table 19.3, where 8 deaths appear; this latter number should thus be 7. <sup>b</sup>One subject died prior to randomization, and so is not listed in this table. The ST numbers represent double-blind deaths+post study drug discontinuation deaths. <sup>c</sup>Seven subjects as listed in ISS, plus one (105/104) post double-blind and one (114/007) after discontinuing for an AE; see FSR Section 12.2 for details. <sup>d</sup>Ten subjects as listed in ISS, plus one (26/001) post double-blind; see FSR Section 12.2 for details. <sup>e</sup>The ST numbers represent double-blind deaths+post study deaths; see FSR Section 12.2 for details.]

**Table 7A. Clinical Serious Adverse Events (Reported in Subjects in Any Treatment Group) in Placebo-Controlled Studies, by Body System**

Body System Primary Term	Placebo N = 1220 n(%)	Omapatrilat N = 3582 n(%)	Amlodipine N = 403 n(%)	Lisinopril N = 404 n(%)
<b>Cardiovascular</b>				
Hypotension	0	6 (0.2)	0	0
Atrial Rhythm Disturbance	1 (0.1)	3 (0.1)	0	0
Myocardial Infarction	2 (0.2)	3 (0.1)	0	4 (1.0)
Angina Pectoris	0	2 (0.1)	0	0
Cardiorespiratory Arrest	0	2 (0.1)	0	0
Orthostatic Hypotension	0	2 (0.1)	0	0
Peripheral Vascular Disease Venous	0	2 (0.1)	0	0
Pulmonary Embolism	0	2 (0.1)	0	0
Syncope	1 (0.1)	2 (0.1)	0	0
Conduction Disorder	0	1 (0.0)	0	0
Disturb Card Rhythm	0	1 (0.0)	0	0
Disturb Rhythm Subjective	0	1 (0.0)	0	0
Disturb Rhythm Ventricular	0	1 (0.0)	0	0
ECG Abnormality	0	1 (0.0)	0	0
Cardiac Murmur	1 (0.1)	0	0	0
Coronary Artery Disease	1 (0.1)	0	0	0
Disease Pericardium	1 (0.1)	0	0	0
Heart Failure	3 (0.2)	0	0	0
N-Angina Cardiac Chest Pain	1 (0.1)	0	0	0
<b>Dermatologic</b>				
Neoplasm Malignant Dermatologic	0	3 (0.1)	1 (0.2)	0
Rash	0	1 (0.0)	0	0
Infect Skin Bacteria	2 (0.2)	0	0	0
Ulcer Skin	1 (0.1)	0	0	0
<b>Gastrointestinal</b>				
Abdominal Pain	0	4 (0.1)	0	0
Diarrhea	0	2 (0.1)	0	0
Nausea/Vomiting	0	2 (0.1)	0	0
Neoplasm Malign GI	1 (0.1)	2 (0.1)	0	0
Dyspepsia/Heartburn	0	1 (0.0)	0	0
Epigastric Pain	0	1 (0.0)	0	0
Eructation	0	1 (0.0)	0	0
GI Surgery	0	1 (0.0)	0	0
Neoplasm Benign GI	0	1 (0.0)	0	0
Oral Surgery	0	1 (0.0)	0	0
Upper GI Bleeding	0	1 (0.0)	0	0
Abdominal Surgery	0	0	0	1 (0.2)
Diverticulosis	0	0	0	1 (0.2)
GI Bleeding	2 (0.2)	0	0	0
Hernia	0	0	0	3 (0.7)

**Table 7A. (Cont'd)**

<b>General</b>				
Chest Pain	0	6 (0.2)	0	0
Fatigue	0	1 (0.0)	0	0
Infection	1 (0.1)	1 (0.0)	0	0
Lymphedema	0	1 (0.0)	0	0
Surgical Complication	0	1 (0.0)	0	0
Trauma	0	1 (0.0)	0	0
Viral Infection	0	1 (0.0)	0	0
Volume Depletion	0	1 (0.0)	0	0
Septicemia	1 (0.1)	0	0	0
Wound	0	0	1 (0.2)	0
<b>Hepatic/Biliary</b>				
Gallbladder Disorder	0	1 (0.1)	0	2 (0.5)
Gallbladder Surgery	1 (0.1)	0	0	0
<b>Immunologic</b>				
Angioedema	0	16 <sup>a</sup> (0.4)	0	0
Allergic Reaction	0	2 (0.1)	0	0
Edema Head/Neck	0	1 (0.0)	0	0
<b>Musculoskeletal</b>				
Musculoskeletal Trauma	0	3 (0.1)	0	0
Orthopedic Surgery	0	2 (0.1)	0	0
Degenerative Arthritis	0	1 (0.0)	0	1 (0.2)
Epicondylitis	0	1 (0.0)	0	0
Muc/Skel Pain	0	1 (0.0)	0	0
Muscle Weakness	0	1 (0.0)	0	0
Fracture Bone	1 (0.1)	0	0	0
<b>Nervous</b>				
Dizziness	0	3 (0.1)	0	0
Intracranial Hemorrhage	0	2 (0.1)	1 (0.2)	0
TIA	0	2 (0.1)	0	0
Memory Impairment	1 (0.1)	0	0	0
Paralysis	0	0	1 (0.2)	0
Speech Disturbance	0	0	1 (0.2)	0
<b>Renal/Genitourinary</b>				
Procedure Urologic	0	1 (0.0)	0	0
<b>Respiratory</b>				
Dyspnea	1 (0.1)	2 (0.1)	0	0
Breathing Abnormality	0	1 (0.0)	0	0
Laryngitis	0	1 (0.0)	0	0
Pulmonary Infection	0	1 (0.0)	0	0
Tracheobronchitis	1 (0.1)	1 (0.0)	0	0
Neoplasm Malignant Pulmonary	0	0	1 (0.2)	0
Pleuritic Chest Pain	1 (0.1)	0	0	0
<b>Special Senses</b>				
Abnormality Retina	1 (0.1)	0	0	0
Vision Disturbance	1 (0.1)	0	0	0
Overall Total Events	28	106	6	12
Overall Total Subjects	23 (1.9)	81 (2.3)	4 (1.0)	11 (2.7)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 497, Supplemental Table S.6.1.1B, pages 140-145. *Note:* For each treatment regimen, the total of subjects experiencing at least one event is less than the sum of the subjects counted under each primary term. This is because some subjects experienced more than one event and are counted under each primary term in which they experienced events. <sup>a</sup>One additional event occurred in subject 037/034/040 per FSR Errata Table.]

**Table 8A. Clinical and Laboratory Adverse Events Leading to Discontinuation in Placebo-Controlled Studies, by Body System**

Body System Primary Term	Placebo N = 1220	Omapatrilat N = 3582	Amlodipine N = 403	Lisinopril N = 404
<b>Cardiovascular</b>				
Angina Pectoris	0	2 (0.1)	0	0
Atrial Rhythm Disturb	1 (0.1)	2 (0.1)	0	0
Cardiac Hypertrophy	1 (0.1)	0	0	0
Cardiac Respiratory Arrest	0	2 (0.1)	0	0
Coronary Artery Disease	2 (0.2)	0	0	0
Disease Pericardium	1 (0.1)	0	0	0
Disturb Cardiac Rhythm	0	1 (0.0)	0	0
Disturbance Rhythm Ventricular	0	1 (0.0)	0	0
Disturbance Rhythm Subjective	0	6 (0.2)	0	0
ECG Abnormality	1 (0.1)	5 (0.1)	0	0
Edema	2 (0.2)	2 (0.1)	14 (3.5)	0
Flushing	0	21 (0.6)	1 (0.2)	0
Heart Failure	3 (0.2)	0	0	0
Hypertension	3 (0.2)	1 (0.0)	0	0
Hypotension	0	30 (0.8)	0	0
Mitral Valve Disease	1 (0.1)	0	0	0
Myocardial Infarction	2 (0.2)	3 (0.1)	0	4 (1.0)
N-Ang Cardiac Chest Pain	1 (0.1)	0	0	0
Orthostatic Hypotension	1 (0.1)	8 (0.2)	1 (0.2)	0
Pulmonary Embolism	0	1 (0.0)	0	0
Syncope	1 (0.1)	4 (0.1)	0	0
Tachycardia	1 (0.1)	8 (0.2)	0	0
<b>Dermatologic</b>				
Dermatitis	0	2 (0.1)	0	1 (0.2)
Facial Redness	1 (0.1)	9 (0.3)	0	0
Induration Skin	1 (0.1)	1 (0.0)	0	0
Infection Skin Bacteria	2 (0.2)	0	0	0
Neoplasm Malignant Derm	0	1 (0.0)	0	0
Pruritis Rash	1 (0.1)	1 (0.0)	0	0
Pruritus	0	5 (0.1)	0	1 (0.2)
Rash	1 (0.1)	12 (0.3)	1 (0.2)	1 (0.2)
Skin Tightness	0	1 (0.0)	0	0
Urticaria	0	8 (0.2) <sup>a</sup>	0	1 (0.2)
<b>Endocrine/Metabolic</b>				
Gout	2 (0.2)	0	0	0
Hyperthyroidism	0 (0.1)	0	0	0
Hypothyroidism	0	1 (0.0)	0	0
Serum Glucose Increase	1 (0.1)	0	0	0
Serum Potassium Increase	0	1 (0.0)	0	0
Serum Sodium Decrease	0	1 (0.0)	0	0
Sexual Dysfunction	1 (0.1)	4 (0.1)	0	0

**Table 8A. (Cont'd)**

<b>Gastrointestinal</b>				
Abdominal Pain	1 (0.1)	5 (0.1)	0	0
Abnormality Mouth	0	1 (0.0)	0	0
Abnormality Tongue	0	1 (0.0)	0	0
Constipation	1 (0.1)	1 (0.0)	1 (0.2)	0
Decrease Appetite	0	2 (0.1)	0	0
Diarrhea	0	7 (0.2)	1 (0.2)	2 (0.5)
Disorder Salivary Gland	0	5 (0.1)	0	0
Diverticulosis	0	1 (0.0)	0	0
Dry Mouth	0	1 (0.0)	0	0
Dyspepsia/Heart Burn	0	2 (0.1)	1 (0.2)	0
Dysphagia	0	1 (0.0)	0	1 (0.2)
Epigastric Pain	0	1 (0.0)	0	0
Eructation	0	1 (0.0)	0	0
Flatulence	0	2 (0.1)	0	0
Gastroenteritis	0	1 (0.0)	0	0
Gastroesophageal Reflux	0	1 (0.0)	0	0
Nausea/Vomiting	1 (0.1)	23 (0.6)	0	3 (0.7)
Neoplasm Malignant GI	0	1 (0.0)	0	0
Upper GI Bleeding	0	1 (0.0)	0	0
<b>General</b>				
Chest Pain	3 (0.2)	10 (0.3) <sup>a</sup>	1 (0.2)	2 (0.5)
Chills	0	1 (0.0)	0	0
Cold Sensation	0	1 (0.0)	0	0
Fall	1 (0.1)	0	0	0
Fatigue	5 (0.4)	21 (0.6)	2 (0.5) <sup>a</sup>	3 (0.7)
Hyperhidrosis	1 (0.1)	1 (0.0)	0	0
Infection Herpes Simplex	0	1 (0.0)	0	0
Infection	1 (0.1)	0	0	0
Influenza	0	2 (0.1)	0	0
Malaise	0	1 (0.0)	1 (0.2)	0
Pain	0	2 (0.1)	0	1 (0.2)
Pallor	0	1 (0.0)	0	0
Sensation of Warmth	0	6 (0.2)	0	0
Viral Infection	0	1 (0.0)	0	0
Weakness	0	3 (0.1)	0	0
Weight Gain	0	0	1 (0.2)	0
<b>Hematopoietic</b>				
Lymphadenopathy	0	2 (0.1)	0	0
<b>Hepatic/Biliary</b>				
Abnormal Liver Function	0	1 (0.0)	0	0
ALAT Increased	0	1 (0.0)	0	0
Gallbladder Disorder	0	1 (0.0)	0	2 (0.5)
Gallbladder Surgery	1 (0.1)	0	0	0
<b>Immunologic</b>				
Allergic Reaction	0	5 (0.1) <sup>a</sup>	0	0
Angioedema	1 (0.1)	35 (1.0)	1 (0.2)	1 (0.2)
Edema Head/Neck	0	17 (0.5)	1 (0.2)	3 (0.7)
Edema Upper Extremity	0	1 (0.0)	1 (0.2)	0

**Table 8A. (Cont'd)**

<b>Musculoskeletal/Connective Tissue</b>				
Degenerative Arthritis	0	1 (0.0)	0	0
Joint Stiffness	0	0	1 (0.2)	0
Muscle/Skeletal pain	1 (0.1)	5 (0.1)	1 (0.2)	0
Muscle Cramp	0	1 (0.0)	0	1 (0.2)
Muscle Weakness	0	0	1 (0.2)	0
Muscle/Skeletal Trauma	0	2 (0.1)	0	0
Swelling Extremity	0	0	1 (0.2)	0
<b>Nervous</b>				
Anxiety/Nervousness	2 (0.2)	2 (0.1)	1 (0.2)	1 (0.2)
Behavior Change	0	1 (0.0)	0	0
Concentration Impaired	0	0	0	1 (0.2)
Coordination Disturb	0	1 (0.0)	0	0
Depression	0	1 (0.0)	1 (0.2)	1 (0.2)
Disorder Cranial Nerve	0	0	1 (0.2)	0
Disorder Stress Related	0	1 (0.0)	0	0
Disturb Sensation	0	1 (0.0)	0	0
Dizziness	3 (0.2)	33 (0.9)	0	1 (0.2)
Headache	14 (1.1)	28 (0.8)	3 (0.7)	4 (1.0)
Intracranial Hemorrhage	0	2 (0.1)	1 (0.2)	0
Memory Impairment	0	2 (0.1)	0	0
Numbness	0	6 (0.2)	0	0
Paralysis	0	0	1 (0.2)	0
Paresthesia	0	5 (0.1)	0	1 (0.2)
Sleep Disturbance	2 (0.2)	0	1 (0.2)	0
Somnolence	1 (0.1)	3 (0.1)	0	1 (0.2)
Speech Disturb	0	1 (0.0)	1 (0.2)	0
TIA	1 (0.1)	2 (0.1)	0	0
Tremor	0	1 (0.0)	0	0
Vertigo	1 (0.1)	2 (0.1)	1 (0.2)	0
<b>Renal/Genitourinary</b>				
Abnormal Urination	0	1 (0.0)	0	1 (0.2)
Increased BUN	0	2 (0.1)	0	0
Urine Protein Increase	0	1 (0.0)	0	0
<b>Respiratory</b>				
Abnormal Vocalization	1 (0.1)	0	0	0
Abnormality Throat	0	1 (0.0)	0	0
Asthma	0	1 (0.0)	0	0
Breathing Abnormal	0	4 (0.1)	0	0
Congestion	1 (0.1)	0	0	0
Constrict Upper-Airway	0	1 (0.0)	0	0
Cough	2 (0.2)	26 (0.7)	0	4 (1.0)
Disorder Airway Subjective	0	2 (0.1)	0	0
Dry Nasopharynx	0	1 (0.0)	0	0
Dyspnea	3 (0.2)	6 (0.2)	1 (0.2)	0
Epistaxis	0	1 (0.0)	0	1 (0.2)
Neoplasm Malignant Pulmonary	0	0	1 (0.2)	0
Rhinitis	0	2 (0.1)	0	1 (0.2)
Sinus Abnormality	0	1 (0.0)	0	0

**Table 8A. (Cont'd)**

<b>Special Senses</b>				
Abnormal Conjunctiva	0	1 (0.0)	0	0
Abnormal Visual Field	0	1 (0.0)	0	0
Abnormality Sclera	0	2 (0.1)	0	0
Disturbance Eye Other	0	3 (0.1)	0	0
Eyelid Abnormal	0	1 (0.0)	1 (0.2)	0
Hearing Abnormal	0	1 (0.0)	0	0
Pain Ear	0	2 (0.1)	0	0
Taste Disturbance	0	1 (0.0)	1 (0.2)	0
Vision Disturbance	1 (0.1)	2 (0.1)	0	0
Overall Total Events	82	481	47	44
Overall Total Subjects	53 (4.3)	262 (7.3)	26 (6.5)	27 (6.7)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 499, Supplemental Table S.7.1.1B, pages 046-053. Protocols included (Placebo Controlled Studies): CV137-005, -006, -022, -024, -029, -030, -036, -037, -040, -042, -045, -054. *Note:* For each treatment regimen, the total of subjects experiencing at least one event may be less than the sum of the subjects counted under each primary term. This is because some subjects experienced more than one event and are counted under each primary term in which they experienced events. <sup>a</sup>Two additional events (Subjects 089/013 and 034/040 in CV137-037) are not included in Table 7.1.1 and Supplemental Table S.7.1.1B due to incorrect information in the database, however, they are recorded in the Errata Table of the Final Study Report.]

**Table 9A. Discontinuations Due to Clinical and Laboratory Adverse Events in Protocol CV137-031**

Primary Term	Omapatrilat N = 173 n/%	Lisinopril N = 174 n/%
Hypotension	1 (0.6)	0
Tachycardia	1 (0.6)	0
Vasovagal Attack	1 (0.6)	0
Nausea/Vomiting	1 (0.6)	0
Sensation of Warmth	1 (0.6)	0
Jaundice	1 (0.6)	0
Dizziness	1 (0.6)	0
Headache	1 (0.6)	0
Entrapment Neuropathy	1 (0.6)	0
Rash	0	1 (0.6)
Diverticulosis	0	1 (0.6)
Overall Total Events	9	2
Overall Total Subjects	6 (3.5)	2 (1.1)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.1.2.1.]

**Table 10A. Discontinuations Due to Clinical and Laboratory Adverse Events in Protocol CV137-032**

Primary Term	Omapatrilat N = 213 n/%	Amlodipine N = 217 n/%
Rash	2 (0.9)	0
Depression	1 (0.5)	0
Sexual Dysfunction	1 (0.5)	0
Libido Change	1 (0.5)	0
Dizziness Orthostatic	1 (0.5)	0
Headache	1 (0.5)	1 (0.5)
Edema	0	10 (4.6)
Flushing	0	1 (0.5)
Facial Redness	0	1 (0.5)
Erythema Body	0	1 (0.5)
Nausea/Vomiting	0	2 (0.9)
Dysphagia	0	1 (0.5)
Pain	0	1 (0.5)
Fatigue	0	1 (0.5)
Swelling Extremity/Edema	0	1 (0.5)
Sleep Disturbance	0	1 (0.5)
Overall Total Events	7	21
Overall Total Subjects	6 (2.8)	14 (6.5)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.1.2.2.]

**Table 11A. Discontinuations Due to Clinical and Laboratory Adverse Events in Protocol CV137-038**

Primary Term	Omapatrilat N = 169 n/%	Losartan N = 172 n/%
Disturbance Rhythm Subjective	1 (0.6)	0
Angioedema	1 (0.6)	0
Dizziness	1 (0.6)	0
Hypertension	0	1 (0.6)
Serum Potassium Increased	0	1 (0.6)
Cushing's Syndrome	0	1 (0.6)
Diarrhea	0	1 (0.6)
Nausea/Vomiting	0	1 (0.6)
Pancreatitis	0	1 (0.6)
Musculoskeletal Trauma	0	1 (0.6)
Musculoskeletal Pain	0	1 (0.6)
Overall Total Events	3	8
Overall Total Subjects	3 (1.8)	5 (2.9)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.1.2.3.]

**Table 12A. Discontinuations Due to Clinical and Laboratory Adverse Events in Protocol CV137-049**

Primary Term	Omapatrilat N = 147 n/%	Enalapril N = 67 n/%
Cough	2 (1.4)	1 (1.5)
Angioedema	2 (1.4)	0
Rash	1 (0.7)	0
Facial Redness	1 (0.7)	0
Skin Tenderness	1 (0.7)	0
Atrial Rhythm Disturbance	1 (0.7)	0
Edema Head/Neck	1 (0.7)	0
Tachycardia	0	1 (1.5)
Dyspepsia/Heartburn	0	1 (1.5)
Constipation	0	1 (1.5)
Overall Total Events	9	4
Overall Total Subjects	6 (4.1)	3 (4.5)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.1.2.4.]

**Table 13A. Discontinuations Due to Clinical and Laboratory Adverse Events in Protocol CV137-039**

Primary Term	Omapatrilat N = 89 n/%
Headache	2 (2.2)
Hypertension	1 (1.1)
Hypotension	1 (1.1)
Facial Swelling	1 (1.1)
Serum Creatinine Increase	1 (1.1)
Weakness	2 (2.2)
Kidney Infection	1 (1.1)
Cerebral Vascular Accident	1 (1.1)
Dizziness	1 (1.1)
Deterioration of Renal Function	1 (1.1)
Overall Total Events	12
Overall Total Subjects	9 (10.1)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.2B.]

**Table 14A. Number (%) Of Subjects Who Discontinued Due to Adverse Events Beginning During Long-Term Open-Label Omapatrilat Treatment (Protocol CV137-009), By Primary Term and Treatment Subgroup**

AE Primary Term	Omapatrilat Mono Only N = 711 n/(%)	Omapatrilat + Adjunctive N = 387 n/(%)	Any Omapatrilat N = 1098 n/(%)
Cough	12 (1.7)	8 (2.1)	20 (1.8)
Fatigue	14 (2.0)	0	14 (1.3)
Dizziness	6 (0.8)	1 (0.3)	7 (0.6)
Angioedema	3 (0.4)	1 (0.3)	4 (0.4)
Chest Pain	4 (0.6)	0	4 (0.4)
Edema Head/Neck	2 (0.3)	2 (0.5)	4 (0.4)
Headache	4 (0.6)	0	4 (0.4)
Nausea/Vomiting	3 (0.4)	1 (0.3)	4 (0.4)
Diarrhea	2 (0.3)	1 (0.3)	3 (0.3)
Dyspnea	2 (0.3)	1 (0.3)	3 (0.3)
Edema	0	3 (0.8)	3 (0.3)
Libido Change	2 (0.3)	1 (0.3)	3 (0.3)
Malignant Neoplasm Reprod	3 (0.4)	0	3 (0.3)
Musculoskeletal Pain	3 (0.4)	0	3 (0.3)
Rash	1 (0.1)	2 (0.5)	3 (0.3)
Sleep Disturbance	3 (0.4)	0	3 (0.3)
ALAT Increased	0	2 (0.5)	2 (0.2)
Cerebrovascular Accident	1 (0.1)	1 (0.3)	2 (0.2)
Disturbance Rhythm Subjective	2 (0.3)	0	2 (0.2)
Dyspepsia/Heartburn	2 (0.3)	0	2 (0.2)
Epigastric Pain	2 (0.3)	0	2 (0.2)
Facial Redness	2 (0.3)	0	2 (0.2)
Hyperhidrosis	1 (0.1)	1 (0.3)	2 (0.2)
Hypotension	2 (0.3)	0	2 (0.2)
Liver Function Test Increased	2 (0.3)	0	2 (0.2)
Myocardial Infarct	2 (0.3)	0	2 (0.2)
Sexual Dysfunction	1 (0.1)	1 (0.3)	2 (0.2)

**Table 14A. (Cont'd)**

Abdominal Pain	1 (0.1)	0	1 (0.1)
Abnormal Urination	1 (0.1)	0	1 (0.1)
Abnormality GI	0	1 (0.3)	1 (0.1)
Anaphylaxis	1 (0.1)	0	1 (0.1)
Angina Pectoris	1 (0.1)	0	1 (0.1)
ASAT Increased	0	1 (0.3)	1 (0.1)
Atrial Rhythm Disturbance	1 (0.1)	0	1 (0.1)
Benign Neoplasm Urologic	1 (0.1)	0	1 (0.1)
Cold Sensation	1 (0.1)	0	1 (0.1)
Constipation	1 (0.1)	0	1 (0.1)
Coordination Disturbance	1 (0.1)	0	1 (0.1)
COPD	1 (0.1)	0	1 (0.1)
Coronary Artery Disease	0	1 (0.3)	1 (0.1)
Depression	1 (0.1)	0	1 (0.1)
Disturbance Rhythm Ventricular	0	1 (0.3)	1 (0.1)
Dizziness Orthostatic	1 (0.1)	0	1 (0.1)
Emotional Lability/Disturbance	1 (0.1)	0	1 (0.1)
Extrapyramidal Disorder	1 (0.1)	0	1 (0.1)
Flushing	1 (0.1)	0	1 (0.1)
Gastritis	1 (0.1)	0	1 (0.1)
Gastroesophageal Reflux	0	1 (0.3)	1 (0.1)
GI Bleeding	0	1 (0.3)	1 (0.1)
Gout	0	1 (0.3)	1 (0.1)
Heart Failure	1 (0.1)	0	1 (0.1)
Increased Hematocrit	0	1 (0.3)	1 (0.1)
Irritable Bowel Syndrome	1 (0.1)	0	1 (0.1)
Malaise	1 (0.1)	0	1 (0.1)
Mental Activity Disorder	1 (0.1)	0	1 (0.1)
Neop-Malignant Hemat/Lymph	0	1 (0.3)	1 (0.1)
Neoplasm Malignant GI	1 (0.1)	0	1 (0.1)
Neoplasm Malignant Breast	1 (0.1)	0	1 (0.1)
Neoplasm Malignant Pulmonary	0	1 (0.3)	1 (0.1)
Neoplasm Malignant Urological	1 (0.1)	0	1 (0.1)
Numbness	1 (0.1)	0	1 (0.1)
Orthostatic Hypotension	1 (0.1)	0	1 (0.1)
Pain Kidney	1 (0.1)	0	1 (0.1)
Pruritic Rash	1 (0.1)	0	1 (0.1)
Rhinitis	1 (0.1)	0	1 (0.1)
Scalp Hair Abnormality	0	1 (0.3)	1 (0.1)
Tremor	1 (0.1)	0	1 (0.1)
Upper Respiratory Infection	1 (0.1)	0	1 (0.1)
Urticaria	0	1 (0.3)	1 (0.1)
Vertigo	1 (0.1)	0	1 (0.1)
Vision Disturbance	0	1 (0.3)	1 (0.1)
Weakness	1 (0.1)	0	1 (0.1)
Weight Gain	1 (0.1)	0	1 (0.1)
Weight Loss	1 (0.1)	0	1 (0.1)
Wheezing	0	1 (0.3)	1 (0.1)
Overall Total Events	115	40	155
Overall Total Subjects (%)	76 (10.7)	32 (8.3)	108 (9.8)

[Sponsor's analysis, Study Report Data CV137-009, NDA 21-188, Vol. 499, Table S.73.1.1, pages 270-272. Note: Not included in this table are 5 discontinuations for Adverse Events that began in the preceding short term studies.]

**Table 15A. All Discontinuations Due to Adverse Events in the Open-Label Extension to Protocol CV137-029**

Primary Term	Omapatrilat Regimen
	N = 194 n/%
Hypotension	1 (0.5)
Atrial Rhythm Disturbance	1 (0.5)
Instable Vasomotor	1 (0.5)
Chest Pain	1 (0.5)
Weakness	1 (0.5)
Angioedema	1 (0.5)
Dizziness	1 (0.5)
Cough	1 (0.5)
Overall Total Events	8
Overall Total Subjects	5 (2.6)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.3.1.2A.]

**Table 16A. All Discontinuations Due to Clinical and Laboratory Adverse Events in the Open-Label Extension to Protocol CV137-042**

Primary Term	Omapatrilat Regimen
	N = 250 n/%
Cough	2 (0.8)
Angina Pectoris	1 (0.4)
Facial Redness	1 (0.4)
Serum Glucose Increase	1 (0.4)
Serum Potassium Increase	1 (0.4)
Neoplasm Malignant Breast	1 (0.4)
Abdominal Pain	1 (0.4)
Diarrhea	1 (0.4)
Fatigue	1 (0.4)
Weakness Extremity	1 (0.4)
Dizziness	1 (0.4)
Abnormal Urination	1 (0.4)
Abnormality Throat	1 (0.4)
Overall Total Events	14
Overall Total Subjects	12 (4.8)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.3.1.2B.]

Table 17A.

**Discontinuations Due to Clinical and Laboratory Adverse Events in  
the Long-Term, Double-Blind Extension to Protocol CV137-037**

<b>Primary Term</b>	<b>Omapatrilat N =254 n/%</b>	<b>Lisinopril N = 248 n/%</b>
Nausea/Vomiting	2 (0.8) <sup>a</sup>	1 (0.4)
Allergic Reaction	2 (0.8)	0
Flushing	1 (0.4)	0
Tachycardia	1 (0.4)	0
Pruritus	1 (0.4)	0
Pruritic Rash	1 (0.4)	0
Infection Skin Bacteria	1 (0.4)	0
Diarrhea	1 (0.4) <sup>a</sup>	0
Gastroenteritis	1 (0.4)	0
Chest Pain	1 (0.4)	1 (0.4)
Substance Abuse	1 (0.4)	0
Edema Head/Neck	1 (0.4)	1 (0.4)
Musculoskeletal Pain	1 (0.4)	0
Dizziness	1 (0.4)	2 (0.8)
Neuropsychiatric Syndrome	1 (0.4)	0
Urine Glucose Increased	1 (0.4)	0
Dyspnea	1 (0.4)	0
Cough	1 (0.4)	1 (0.4)
Conduction Disorder	0	1 (0.4)
Disturbance Cardiac Rhythm	0	1 (0.4)
Disturbance Rhythm Subjective	0	1 (0.4)
Edema	0	1 (0.4)
Urine RBC Increased	0	1 (0.4)
Malignant Neoplasm Reproductive	0	1 (0.4)
Overall Total Events	20	12
Overall Total Subjects	12 (4.7)	10 (4.0)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.3.2. <sup>a</sup>As described in the Final Study Report, site clarified that Subject 065/011 did not discontinue for an event of nausea/vomiting and an event of diarrhea. These events, however, are noted in this table.]

**Table 18A. Subjects Who Discontinued Due to Clinical and Laboratory Adverse Events in Ongoing Open-Label Studies**

<b>Protocol/Subject ID</b>	<b>Treatment Dose at AE Onset</b>	<b>Body System</b>	<b>Reason for Discontinuation</b>
CV137-009-0017-002	Omapatrilat 10 mg	Immunology/ Sensitivity Disorder	Angioedema
CV137-009-0031-008	Omapatrilat 20 mg	Endocrine/Metabolic/ Electrolyte Imbalance	Glucose Serum Increased
CV137-009-0079-008	Omapatrilat 80 mg	Cardiovascular	Disturbance Rhythm Atrial
CV137-009-0120-002	Omapatrilat 20 mg	Nervous System	Accident Cerebrovascular
CV137-042-0021-011	Omapatrilat 10 mg	Nervous System	Headache
CV137-042-0056-013	Omapatrilat 20 mg	Cardiovascular	Atrial Rhythm Disturbance
CV137-049-0001-010	Omapatrilat 20 mg	Hepatic/Biliary	Hepatitis
CV137-049-0013-001	Omapatrilat 80 mg/ HCTZ 50 mg	Gastrointestinal	Diarrhea
CV137-049-0035-004	Omapatrilat 40 mg/ Amlodipine 10 mg	Immunology/ Sensitivity Disorder	Edema Head/Neck
CV137-049-0036-007	Omapatrilat 80 mg/ Amlodipine 10 mg/ HCTZ 12.5 mg	Immunology Sensitivity Disorder	Edema Head/Neck
CV137-049-0045-004	Omapatrilat 80 mg HCTZ 25 mg	Hematopoietic Hepatic/Biliary  Musculoskeletal/ Connective Tissue	WBC Decreased Liver Function Tests Increased Creatine Phosphokinase Increased
Total Subjects = 11			Total Events = 13

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.4.]

**Table 19A. Subjects Who Discontinued Due to Clinical and Laboratory Adverse Events in the Ongoing, Double-Blind Studies**

<b>Protocol/Subject ID</b>	<b>Treatment Dose at AE Onset</b>	<b>Body System</b>	<b>Reason for Discontinuation</b>
CV137-038-0115-005	Blinded Treatment	Hepatic/Biliary	ALAT Increased
CV137-046-0004-003	Blinded Treatment	Cardiovascular	Disease Peripheral Vascular
CV137-046-0008-007	Blinded Treatment	Dermatologic	Rash Pruritic
CV137-046-0010-007	Blinded Treatment	Cardiovascular General Cardiovascular	Disturbance Rhythm Atrial Chest Pain Hypotension
CV137-046-0018-001	Blinded Treatment	Renal/Genitourinary Cardiovascular Endocrine/Metabolic/ Electrolyte Imbalance	Abnormality Kidney Hypertension Serum Glucose Increased
CV137-046-0018-004	Blinded Treatment	Cardiovascular	Disturbance Rhythm Atrial
CV137-046-0037-002	Blinded Treatment	Cardiovascular	Angina Pectoris
CV137-046-0037-009	Blinded Treatment	Gastrointestinal	Diarrhea
CV137-046-0038-006	Blinded Treatment	Cardiovascular	Hypotension
CV137-046-0041-043	Blinded Treatment	Nervous System	Disorder Cranial Nerve
CV137-046-0044-003	Blinded Treatment	Cardiovascular	Disturbance Cardiac Rhythm
CV137-046-0048-004	Blinded Treatment	Renal/Genitourinary	Neoplasm Malignant Reproductive
CV137-046-0051-010	Blinded Treatment	Cardiovascular Cardiovascular	Disturbance Rhythm Atrial Disturbance Rhythm Atrial
CV137-046-0070-002	Blinded Treatment	Cardiovascular Nervous System	Hypotension Dizziness
CV137-046-0074-011	Blinded Treatment	Respiratory Cardiovascular Dermatologic Dermatologic	Dyspnea Edema Pruritus Rash
CV137-046-0092-001	Blinded Treatment	General General Endocrine/Metabolic/ Electrolyte Imbalance	Abnormality Lab Abnormality Lab Hot Flashes
CV137-066-0012-020	Blinded Treatment	Cardiovascular	Edema
CV137-066-0028-021	Blinded Treatment	Dermatologic Gastrointestinal Cardiovascular Dermatologic	Rash Diarrhea Flushing Pruritus
CV137-066-0028-028	Blinded Treatment	Respiratory Musculoskeletal/ Connective Tissue Nervous System	Constriction Upper Airway Limitation Movement Headache
CV137-066-0030-006	Blinded Treatment	Immunology/ Sensitivity Disorder Cardiovascular	Edema Head/Neck Edema

**Table 19A. (Cont'd)**

CV137-066-0051-002	Blinded Treatment	Immunology/ Sensitivity Disorder	Angioedema
CV137-066-0061-001	Blinded Treatment	Nervous System	Dizziness
CV137-066-0073-001	Blinded Treatment	Nervous System	Dizziness
CV137-066-0084-002	Blinded Treatment	Respiratory Cardiovascular General Cardiovascular	Dyspnea Edema Fatigue Disturbance Rhythm Subjective
CV137-066-0090-002	Blinded Treatment	Cardiovascular	Myocardial Infarction
CV137-066-0092-004	Blinded Treatment	Immunology/ Sensitivity Disorder	Edema Head/Neck
CV137-066-0098-005	Blinded Treatment	Cardiovascular Immunology/ Sensitivity Disorder	Edema Edema- upper extremity
CV137-066-0105-001	Blinded Treatment	Immunology/ Sensitivity Disorder Dermatologic	Edema Head/Neck Pruritus
CV137-066-0105-002	Blinded Treatment	Immunology/ Sensitivity Disorder Dermatologic Gastrointestinal	Edema Head/Neck Rash Lesion Oral
CV137-066-0129-003	Blinded Treatment	Immunology/ Sensitivity Disorder	Angioedema
Total Subjects = 30			Total Events = 54

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.7.4.]

**Table 20A. Adverse Events Leading to Discontinuation in Clinical Pharmacology Studies (All Doses Oral Unless Otherwise Noted)**

Subject Number Age/Gender	Study Number	Treatment at AE Onset	AE by Primary Term
028 <sup>a</sup> -28/Male	CV137-002	Omapatrilat 125 mg	Fatigue, Pallor, Decreased Appetite
031 <sup>a</sup> -33/Male	CV137-002	Omapatrilat 125 mg	Nausea/Vomiting
034 <sup>a</sup> -29/Male	CV137-002	Omapatrilat 125 mg	Sleep Disturbance, Pallor, Disturbance Rhythm Subjective, Dyspnea
036 <sup>a</sup> -28/Male	CV137-002	Omapatrilat 125 mg	Rash
043 <sup>b</sup> -31/Female	CV137-025	Omapatrilat 40 mg	Decreased Appetite, Headache, Abdominal Pain
005-39/Male	CV137-026	Omapatrilat 10 mg	Abnormality Throat, Sensation Warmth
023-29/Male	CV137-026	Omapatrilat 10 mg	Dyspnea
026-32/Male	CV137-026	Omapatrilat 10 mg	Rash
005-26/Male	CV137-060	Predose	Urethral Abnormality
033-38/Male	CV137-060	Predose	Anemia
036-19/Male	CV137-060	Omapatrilat 80 mg	Pharyngitis, Fever, Chills, Cough
024-61/Female	CV137-017	Omapatrilat 40 mg	Edema Head/Neck
009-48/Female	CV137-020	Omapatrilat 10 mg	Edema Head/Neck

**Table 20A (Cont'd)**

005-73/Male	CV137-021	Omapatrilat IV 10 mg	Dyspnea <sup>d</sup>
014-46/Female	CV137-021	Omapatrilat 25 mg	Diarrhea, Chills, Edema Head/Neck
008-30/Male	CV137-014	Omapatrilat 25 mg	Diarrhea, Fatigue, Abdominal Pain
		Follow-up	Rectal Bleeding, Abdominal Pain, Fever, Diarrhea, Nausea/Vomiting
011-24/Male	CV137-014	Omapatrilat 25 mg	Orthopedic Surgery <sup>e</sup>
013-31/Male	CV137-014	Omapatrilat 25 mg	Pharyngitis, Diarrhea, Dizziness, Flushing
001-35/Male	CV137-019	Furosemide 20 mg	Constipation
		Omapatrilat 25 mg + Furosemide 20 mg	Fatigue, Headache, Chest Pain, Fever, Nausea/Vomiting
		Follow-up	Volume Depletion, Abdominal Pain
015-26/Male	CV137-019	Furosemide 20 mg	Chest Pain
003-28/Male	CV137-051	Omapatrilat 25 mg	Edema Head/Neck
006-28/Male	CV137-051	Omapatrilat 25 mg	Numbness, Edema Head/Neck
002-26/Male	CV137-055	Omapatrilat 80 mg	Ear Infection
005-27/Male	CV137-055	Omapatrilat 80 mg	Nausea/Vomiting, Abdominal Pain
012-44/Male	CV137-055	Omapatrilat 80 mg	Disorder Salivary Gland
001-23/Male	CV137-061	Omapatrilat 40 mg	Headache, Musc/Skel Pain, Chest Pain, Nausea/Vomiting, Abdominal Pain
006-25/Female	CV137-070	50 mg Atenolol	Pregnancy

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.18.7B. <sup>a</sup>Events reflect tabular listing in Appendix 7.5.1 of Final Study Report CV137-002. The report text was inadvertently incorrect. <sup>b</sup>Subject requested to be discontinued after experiencing adverse events, but was not discontinued by Investigator. <sup>c</sup>Not applicable. <sup>d</sup>Event was classified as a Serious Adverse Event. <sup>e</sup>Event occurred during washout between Treatment Periods 1 and 2 and was omitted from counted events in database in error.]

**Table 21A. Clinical Adverse Events (Reported in  $\geq 1\%$  of Subjects in Any Treatment Group) in Protocol CV137-031**

<b>Primary Term</b>	<b>Omapatrilat N = 173 n(%)</b>	<b>Lisinopril N = 174 n(%)</b>
Tracheobronchitis	10 (5.8)	4 (2.3)
Cough	9 (5.2)	7 (4.0)
Headache	6 (3.5)	8 (4.6)
Dizziness	5 (2.9)	0 (0.0)
Weakness	4 (2.3)	2 (1.1)
Flushing	3 (1.7)	0
Erythema Face	3 (1.7)	0
Diarrhea	3 (1.7)	3 (1.7)
Fatigue	3 (1.7)	3 (1.7)
Abnormal Urination	3 (1.7)	1 (0.6)
Pharyngitis	3 (1.7)	5 (2.9)
Rhinitis	2 (1.2)	4 (2.3)
Influenza	2 (1.2)	3 (1.7)
Vertigo	2 (1.2)	3 (1.7)
Sleep Disturbance	2 (1.2)	1 (0.6)
Tremor	2 (1.2)	0
Taste Disturbance	2 (1.2)	0
Musculoskeletal Pain	2 (1.2)	7 (4.0)
Orthostatic Hypotension	1 (0.6)	2 (1.1)
Tachycardia	1 (0.6)	2 (1.1)
Abdominal Pain	1 (0.6)	2 (1.1)
Arthritis	1 (0.6)	2 (1.1)
Upper Respiratory Infection	1 (1.2)	0
Abnormal Visual Field	1 (0.6)	2 (1.1)
Superficial Fungal Infection	0	2 (1.1)
Flatulence	0	2 (1.1)
Gastroenteritis	0	2 (1.1)
Abnormality Retina	0	2 (1.1)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.1.2.1, pages 25-30.]

**Table 22A. Clinical Adverse Events (Reported in  $\geq 1\%$  of Subjects in Any Treatment Group) in Protocol CV137-032**

<b>Primary Term</b>	<b>Omapatrilat N = 213 n/%</b>	<b>Amlodipine N = 217 n/%</b>
Headache	16 (7.5)	16 (7.4)
Dizziness	13 (6.1)	4 (1.8)
Facial Redness	12 (5.6)	5 (2.3)
Tracheobronchitis	9 (4.2)	5 (2.3)
Influenza	8 (3.8)	9 (4.1)
Cough	7 (3.3)	3 (1.4)
Nausea/Vomiting	6 (2.8)	2 (0.9)
Fatigue	6 (2.8)	10 (4.6)
Flushing	5 (2.3)	10 (4.6)
Musculoskeletal Pain	5 (2.3)	12 (5.5)
Rhinitis	5 (2.3)	7 (3.2)
Upper Respiratory Infection	4 (1.9)	7 (3.2)
Sexual Dysfunction	4 (1.9)	5 (2.3)
Vertigo	4 (1.9)	5 (2.3)
Somnolence	4 (1.9)	4 (1.8)
Edema	3 (1.4)	54 (24.9)
Pruritus	3 (1.4)	4 (1.8)
Epigastric pain	3 (1.4)	1 (0.5)
Diarrhea	3 (1.4)	0
Weakness	3 (1.4)	4 (1.8)
Musculoskeletal Trauma	3 (1.4)	0
Pharyngitis	3 (1.4)	3 (1.4)
Dyspepsia/Heartburn	2 (0.9)	3 (1.4)
Abnormal Urination	2 (0.9)	5 (2.3)
Disturbance Rhythm Subjective	2 (0.9)	6 (2.8)
Gastroenteritis	0	4 (1.8)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.1.2.2, pages 31-36.]

**Table 23A. Clinical Adverse Events (Reported in  $\geq 1\%$  of Subjects in Any Treatment Group) in Protocol CV137-038**

Primary Term	Omapatrilat N = 169 n(%)	Losartan N = 172 n(%)
Dizziness	20 (11.8)	8 (4.7)
Headache	12 (7.1)	20 (11.6)
Cough	8 (4.7)	4 (2.3)
Musculoskeletal Pain	8 (4.7)	8 (4.7)
Influenza	7 (4.1)	4 (2.3)
Somnolence	7 (4.1)	3 (1.7)
Pharyngitis	6 (3.6)	6 (3.5)
Upper Respiratory Infection	6 (3.6)	9 (5.2)
Abnormal Urination	5 (3.0)	1 (0.6)
Disturbance Rhythm Subjective	5 (3.0)	3 (1.7)
Tracheobronchitis	5 (3.0)	9 (5.2)
Viral Infection	5 (3.0)	1 (0.6)
Fatigue	4 (2.4)	9 (5.2)
Hypotension	4 (2.4)	2 (1.2)
Hypertension	3 (1.8)	7 (4.1)
Flushing	3 (1.8)	5 (2.9)
Sleep Disturbance	3 (1.8)	5 (2.9)
Chest Pain	3 (1.8)	2 (1.2)
Abdominal Pain	2 (1.2)	6 (3.5)
Weakness	2 (1.2)	4 (2.3)
Atrial Rhythm Disturbance	2 (1.2)	1 (0.6)
Edema	2 (1.2)	1 (0.6)
Disturbance Rhythm Ventricular	2 (1.2)	0
Erythema Face	2 (1.2)	0
Dyspepsia/Heartburn	2 (1.2)	2 (1.2)
Cold Sensation	2 (1.2)	1 (0.6)
Hyperhidrosis	2 (1.2)	0
Infection	2 (1.2)	0
Musculoskeletal Trauma	2 (1.2)	3 (1.7)
Degenerative Arthritis	2 (1.2)	0
Numbness	2 (1.2)	2 (1.2)
Disorder Tonsil	2 (1.2)	2 (1.2)
Sinus Abnormality	2 (1.2)	0
Rhinitis	2 (1.2)	5 (2.9)
Rash	1 (0.6)	2 (1.2)
Nausea/Vomiting	1 (0.6)	3 (1.7)
Dental Abnormality	1 (0.6)	4 (2.3)
Diarrhea	1 (0.6)	5 (2.9)
Bradycardia	0	3 (1.7)
Pruritus	0	2 (1.2)
Fever	0	2 (1.2)
Urinary Tract Infection	0	3 (1.7)
Pulmonary Infection	0	2 (1.2)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.1.2.3, pages 37-43.]

**Table 24A. Clinical Adverse Events (Reported in  $\geq 1\%$  of Subjects in Any Treatment Group) in Protocol CV137-049**

<b>Primary Term</b>	<b>Omapatrilat Regimen N = 147 n (%)</b>	<b>Enalapril Regimen N = 67 n (%)</b>
Headache	21 (14.3)	11 (16.4)
Upper Respiratory Infection	21 (14.3)	6 (9.0)
Dizziness	17 (11.6)	9 (13.4)
Cough	15 (10.2)	8 (11.9)
Musculoskeletal Pain	12 (8.2)	3 (4.5)
Fatigue	11 (7.5)	6 (9.0)
Facial Redness	9 (6.1)	0 (0)
Diarrhea	8 (5.4)	1 (1.5)
Flushing	8 (5.4)	6 (9.0)
Nausea/Vomiting	7 (4.8)	1 (1.5)
Somnolence	7 (4.8)	2 (3.0)
Influenza	6 (4.1)	1 (1.5)
Edema	5 (3.4)	5 (7.5)
Disturbance Rhythm Subjective	4 (2.7)	0 (0)
Weakness	4 (2.7)	1 (1.5)
Constipation	4 (2.7)	2 (3.0)
Dental Abscess	3 (2.0)	0 (0)
Edema Head/Neck	3 (2.0)	0 (0)
Muscle Ache	3 (2.0)	0 (0)
Musculoskeletal Trauma	3 (2.0)	1 (1.5)
Urinary Tract Infection	3 (2.0)	1 (1.5)
Dyspepsia/Heartburn	3 (2.0)	1 (1.5)
Disturbance Eye Other	3 (2.0)	1 (1.5)
Dental Abnormality	3 (2.0)	2 (3.0)
Abdominal Pain	3 (2.0)	2 (3.0)
Erythema Extremities	2 (1.4)	0
Pruritus	2 (1.4)	1 (1.5)
Urticaria	2 (1.4)	0
Hyperhidrosis	2 (1.4)	0
Pallor	2 (1.4)	0
Angioedema	2 (1.4)	0
Numbness	2 (1.4)	0
Paresthesia	2 (1.4)	0
Abnormal Urination	2 (1.4)	0
Abnormal Vocalization	2 (1.4)	0
Dyspnea	2 (1.4)	1 (1.5)
Pharyngitis	2 (1.4)	2 (3.0)
Chest Pain	2 (1.4)	2 (3.0)
Tachycardia	1 (0.7)	1 (1.5)
Dermatitis	1 (0.7)	1 (1.5)
Infection Skin Bacteria	1 (0.7)	1 (1.5)
Flatulence	1 (0.7)	1 (1.5)
Rash	1 (0.7)	2 (3.0)
Hypertension	0	1 (1.5)
Increase Appetite	0	1 (1.5)
Body Odor	0	1 (1.5)
Fungal Infection	0	1 (1.5)
Lymphadenopathy	0	1 (1.5)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.1.2.4, pages 44-48.]

**Table 25A. Most Common Clinical Adverse Events (Reported in  $\geq 2\%$  of Subjects) in Protocol CV137-039**

<b>Primary Term</b>	<b>Omapatrilat N = 89 n(%)</b>
Dizziness	16 (18.0)
Upper Respiratory Infection	12 (13.5)
Headache	10 (11.2)
Weakness	10 (11.2)
Flushing	9 (10.1)
Influenza	8 (9.0)
Dyspepsia/Heartburn	6 (6.7)
Musculoskeletal Pain	6 (6.7)
Diarrhea	5 (5.6)
Fatigue	4 (4.5)
Nausea/Vomiting	4 (4.5)
Tracheobronchitis	4 (4.5)
Cough	3 (3.4)
Edema Head and Neck	3 (3.4)
Facial Redness	3 (3.4)
Hypertension	3 (3.4)
Anxiety Nervousness	2 (2.2)
Dental Abnormality	2 (2.2)
Gastroenteritis	2 (2.2)
Muscle Ache	2 (2.2)
Muscle Cramp	2 (2.2)
Paresthesia	2 (2.2)
Pharyngitis	2 (2.2)
Sleep Disturbance	2 (2.2)
Urinary Tract Infection	2 (2.2)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.2, pages 70-74.]

Table 26A.

**Most Common Clinical Adverse Events (Reported in  $\geq 2\%$  of Subjects) in the Long-Term Open-Label Extension Protocol CV137-009**

<b>Primary Term</b>	<b>Omapatrilat Mono Only N = 711 n/%</b>	<b>Omapatrilat + Any Adjunctive N = 387 n/%</b>	<b>Any Omapatrilat N = 1098 n/%</b>
Upper Respiratory Infection	165 (23.2)	116 (30.0)	281 (25.6)
Musculoskeletal Pain	118 (16.6)	89 (23.0)	207 (18.9)
Cough	71 (10.0)	65 (16.8)	136 (12.4)
Headache	74 (10.4)	59 (15.2)	133 (12.1)
Dizziness	66 (9.3)	59 (15.2)	125 (11.4)
Fatigue	55 (7.7)	49 (12.7)	104 (9.5)
Sinus Abnormality	51 (7.2)	43 (11.1)	94 (8.6)
Influenza	51 (7.2)	42 (10.9)	93 (8.5)
Tracheobronchitis	51 (7.2)	34 (8.8)	85 (7.7)
Musculoskeletal Trauma	52 (7.3)	30 (7.8)	82 (7.5)
Edema	31 (4.4)	46 (11.9)	77 (7.0)
Rhinitis	44 (6.2)	29 (7.5)	73 (6.6)
Diarrhea	30 (4.2)	33 (8.5)	63 (5.7)
Rash	23 (3.2)	32 (8.3)	55 (5.0)
Dyspepsia/Heartburn	32 (4.5)	22 (5.7)	54 (4.9)
Nausea/Vomiting	33 (4.6)	21 (5.4)	54 (4.9)
UTI	34 (4.8)	20 (5.2)	54 (4.9)
Pharyngitis	30 (4.2)	19 (4.9)	49 (4.5)
Allergy	27 (3.8)	17 (4.4)	44 (4.0)
Chest Pain	22 (3.1)	21 (5.4)	43 (3.9)
Dental Abnormality	25 (3.5)	16 (4.1)	41 (3.7)
Abdominal Pain	22 (3.1)	18 (4.7)	40 (3.6)
Abnormal Urination	18 (2.5)	22 (5.7)	40 (3.6)
Sleep Disturbance	28 (3.9)	12 (3.1)	40 (3.6)
Flushing	20 (2.8)	9 (2.3)	29 (2.6)
Muscle Cramp	16 (2.3)	12 (3.1)	28 (2.6)
Paresthesia	18 (2.5)	11 (2.8)	29 (2.6)
Depression	13 (1.8)	15 (3.9)	28 (2.6)
Anxiety/Nervousness	16 (2.3)	11 (2.8)	27 (2.5)
Viral Infection	19 (2.7)	8 (2.1)	27 (2.5)
Ear Infection	22 (3.1)	5 (1.3)	27 (2.5)
Sexual Dysfunction	9 (1.3)	17 (4.4)	26 (2.4)
Muscle Ache	14 (2.0)	12 (3.1)	26 (2.4)
Gastroenteritis	21 (3.0)	4 (1.0)	25 (2.3)
Superficial Fungal Infection	14 (2.0)	10 (2.6)	24 (2.2)
Dermatitis	14 (2.0)	9 (2.3)	23 (2.1)
Pain	15 (2.1)	8 (2.1)	23 (2.1)
Ecchymosis	13 (1.8)	9 (2.3)	22 (2.0)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.3.1.1, pages 75-89.]

**Table 27A. Clinical Adverse Events (Reported in  $\geq 2\%$  of Subjects) in the Open-Label Extension to Study CV137-029**

<b>Primary Term</b>	<b>Omapatrilat N = 194 n(%)</b>
Cough	11 (5.7)
Dizziness	10 (5.2)
Upper Respiratory Infection	9 (4.6)
Edema	7 (3.6)
Fatigue	6 (3.1)
Sinus Abnormality	6 (3.1)
Abnormal Urination	5 (2.6)
Diarrhea	4 (2.1)
Nausea/Vomiting	4 (2.1)
Musculoskeletal Pain	4 (2.1)
UTI	4 (2.1)
Vision Disturbance	4 (2.1)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.3.1.2A, pages 90-95.]

**Table 28A. Clinical Adverse Events (Reported in  $\geq 2\%$  of Subjects) in the Open-Label Extension to Study CV137-042**

<b>Primary Term</b>	<b>Omapatrilat N = 250 n(%)</b>
Upper Respiratory Infection	13 (5.2)
Headache	10 (4.0)
Musculoskeletal Pain	9 (3.6)
Diarrhea	8 (3.2)
Nausea/Vomiting	8 (3.2)
Edema	7 (2.8)
Cough	7 (2.8)
Dizziness	6 (2.4)
Facial Redness	5 (2.0)
Abdominal Pain	5 (2.0)
Abnormal Urination	5 (2.0)
Urinary Tract Infection	5 (2.0)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.3.1.2B, pages 96-102.]

**Table 29A. Most Common Clinical Adverse Events (Reported in  $\geq 2\%$  of Subjects) in the Open-Label Extension to Study CV137-049**

<b>Primary Term</b>	<b>Omapatrilat N = 157 n(%)</b>
Upper Respiratory Infection	10 (6.4)
Dizziness	7 (4.5)
Musculoskeletal Pain	6 (3.8)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.3.1.2C, pages 103-106.]

**Table 30A. Most Common Clinical Adverse Events (Reported in  $\geq 2\%$  of Subjects) in the Double-Blind Extension to Protocol CV137-037**

Primary Term	Omapatrilat Regimen N = 254 n(%)	Lisinopril Regimen N = 248 n(%)
Upper Respiratory Infection	31 (12.2)	17 (6.9)
Cough	15 (5.9)	22 (8.9)
Musculoskeletal Pain	13 (5.1)	12 (4.8)
Influenza	12 (4.7)	8 (3.2)
Headache	11 (4.3)	19 (7.7)
Sinus Abnormality	10 (3.9)	10 (4.0)
Nausea/Vomiting	10 (3.9)	5 (2.0)
Pharyngitis	7 (2.8)	4 (1.6)
Chest Pain	7 (2.8)	2 (0.8)
Dizziness	6 (2.4)	12 (4.8)
Diarrhea	4 (1.6)	5 (2.0)
Musculoskeletal Trauma	2 (0.8)	7 (2.8)
Fatigue	1 (0.4)	7 (2.8)

[Sponsor's analysis, adapted from NDA 21-188, Vol. 496, Supplemental Table S.4.3.2A, pages 107-114.]

**Table 31A. Most Common (Occurring in 1% or More of the Omapatrilat-Treated Population) Treatment-Emergent Adverse Events Occurring in All Subjects Enrolled in Clinical Pharmacology Studies, by Primary Term**

Primary Term	Omapatrilat (N = 618) n(%)	Placebo (N = 107) n(%)
Headache	141 (22.8)	5 (4.7)
Dizziness	66 (10.7)	0
Flushing	38 (6.1)	0
Nausea/vomiting	37 (6.0)	0
Diarrhea	36 (5.8)	1 (0.9)
Tachycardia	26 (4.2)	2 (1.9)
Abdominal Pain	19 (3.1)	0
Fatigue	16 (2.6)	0
Musculoskeletal Pain	15 (2.4)	1 (0.9)
Rash	15 (2.4)	0
Chest Pain	14 (2.3)	0
Edema Head/Neck	13 (2.1)	0
Hypotension	13 (2.1)	0
Pharyngitis	13 (2.1)	0
Sensation Warmth	13 (2.1)	0
Dizziness Orthostatic	12 (1.9)	0
Rhinitis	10 (1.6)	1 (0.9)
Disturbance Eye Other	10 (1.6)	0
Taste Disturbance	9 (1.5)	0
Vision Disturbance	8 (1.3)	0
Numbness	7 (1.1)	0
Cough	6 (1.0)	0
Dyspnea	6 (1.0)	0
Hyperhidrosis	6 (1.0)	0

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.18.4.2C.]

## Laboratory Data Collection

Complete laboratory panels were obtained at baseline, at predetermined intervals during therapy and at the end of the study therapy period for evaluation of the following analytes:

- Hematology: hemoglobin, hematocrit, red blood cell count, white blood cell count and differential, and platelet count.
- Serum Chemistry: creatinine, blood urea nitrogen or urea, glucose, total protein, albumin, aspartate aminotransferase (AST, ASAT), alanine aminotransferase (ALT, ALAT), alkaline phosphatase (ALP), total bilirubin, total cholesterol, sodium, potassium, chloride, phosphorus, calcium, uric acid, magnesium, serum bicarbonate, and creatine kinase (CK), plus creatine kinase-MB if total CK was > 2x upper limit of normal (selected studies) and lactate dehydrogenase (LD) (selected studies).
- Urinalysis: dipstick evaluation for pH, protein, glucose, and blood. (Microscopy for red and white blood cells and casts was to be performed if dipstick was positive for blood. A 24-hour urine quantification was to be obtained if 2 + or greater protein was found on urine dipstick. In practice, very few subjects had these abnormalities and thus very few samples were collected for these latter assays.)

**Table 32A. Laboratory Adverse Events In Placebo-Controlled Studies, by Body System, Primary Term and Treatment Group**

Body System (Primary Term)	Number (%) of Subjects			
	Placebo N = 1220	Any Omapatrilat N=3582	Any Amlodipine N = 403	Any Lisinopril N = 404
<b>Cardiovascular</b>				
CPK Isoenzyme MB Increased	0	1 (0.0)	0	0
<b>Endocrine/Metabolic/Electrolyte Imbalance</b>				
Serum Glucose Increased	11 (0.9)	24 (0.7)	4 (1.0)	1 (0.2)
Serum Cholesterol Increased	2 (0.2)	11 (0.3)	0	3 (0.7)
Serum Potassium Increased	1 (0.1)	9 (0.3)	1 (0.2)	1 (0.2)
Serum Glucose Decreased	1 (0.1)	5 (0.1)	0	0
Serum Triglycerides Increased	1 (0.1)	4 (0.1)	0	0
Serum Potassium Decreased	1 (0.1)	2 (0.1)	5 (1.2)	0
Serum Sodium Decreased	0	2 (0.1)	0	0
Serum Phosphorus Decreased	0	1 (0.0)	0	0
Serum Calcium Decreased	0	1 (0.0)	0	0
Serum Lipids Increased	0	1 (0.0)	0	0
Serum Uric Acid Increased	2 (0.2)	1 (0.0)	0	1 (0.2)
Serum Phosphorus Increased	0	1 (0.0)	0	0
Serum Sodium Increased	0	1 (0.0)	0	1 (0.2)
Serum HDL Decreased	0	0 (0.0)	0	1 (0.2)
Serum Magnesium Decreased	0	0 (0.0)	1 (0.2)	0
Serum Magnesium Increased	0	0 (0.0)	0	1 (0.2)
<b>Hematopoietic</b>				
Decreased Platelets	0	7 (0.2)	1 (0.2)	0
Decreased Hemoglobin	0	3 (0.1)	1 (0.2)	0
Lymphopenia	0	3 (0.1)	1 (0.2)	0
Decreased Hematocrit	0	2 (0.1)	1 (0.2)	0
Decreased RBC	0	2 (0.1)	0	0
Eosinophils Increased	0	2 (0.1)	1 (0.2)	0
WBC Blood Decreased	1 (0.1)	2 (0.1)	1 (0.2)	0
WBC Increased	0	2 (0.1)	0	0
Erythocytosis	0	1 (0.0)	0	0
Increased Hematocrit	0	1 (0.0)	0	0
Increased Hemoglobin	0	1 (0.0)	0	0
Lymphocytes Abnormal	0	1 (0.0)	0	0
RBC Indices Increased	0	1 (0.0)	0	0
RBC Indices Decreased	0	0	1 (0.2)	0
RBC Morphology Abnormal	0	0	1 (0.2)	0
<b>Hepatic/Biliary</b>				
ALAT Increased	4 (0.3)	8 (0.2)	1 (0.2)	4 (1.0)
Liver Function Test Increased	2 (0.2)	8 (0.2)	1 (0.2)	2 (0.5)
ASAT Increased	2 (0.2)	2 (0.1)	1 (0.2)	1 (0.2)
Alkaline Phosphatase Increased	1 (0.1)	2 (0.1)	0	0
Serum Bilirubin Increased	2 (0.2)	1 (0.0)	0	0
Serum LDH Increased	0	1 (0.0)	0	1 (0.2)
<b>Musculoskeletal/Connective Tissue</b>				
CPK Increased	5 (0.4)	14 (0.4)	3 (0.7)	1 (0.2)

**Table 32A. (Cont'd)**

<b>Renal/Genitourinary</b>				
Urine RBC Increased	7 (6.0)	14 (0.4)	3 (0.7)	0
Urine Protein Increased	4 (0.3)	7 (0.2)	1 (0.2)	2 (0.5)
BUN Increased	1 (0.1)	6 (0.2)	0	0
Urine Glucose Increased	0	3 (0.1)	0	0
WBC Urine Increased	2 (0.2)	3 (0.1)	0	0
Serum Creatinine Increased	0	2 (0.1)	1 (0.2)	0
Abnormal Urinalysis	1 (0.1)	0	2 (0.5)	0
Bacteria Urine	1 (0.1)	0	0	0
PSA Increased	1 (0.1)	0	1 (0.2)	0
Overall Total Events	53	163	33	20
Overall Total Subjects	37 (3.0)	125 (3.5)	23 (5.7)	15 (3.7)

[Sponsor's analysis, adapted from NDA 21-188, Supplemental Table S.8.1.1.2, Vol. 500, pages 12-15. Protocols included: CV137-005, -006, -022, -024, -029, -030, -036, -037, -040, -042, -045, -054.]

## Narratives for Patients Who Developed Laboratory Adverse Events

### Decreased Platelets

- Subject 030/003 from study CV137-006, a 69-year-old male, with a history of occasional palpitations, hypercholesterolemia, hypothyroidism, allergies to penicillin and adhesive tape, and prostatectomy developed decreased platelets while on omapatrilat 2.5 mg. The platelet count fell from 190,000 cells/mm<sup>3</sup> at baseline and 192,000 cells/mm<sup>3</sup> at Day B29 to 71,000 cells/mm<sup>3</sup> at the last double-blind visit. Thirteen (13) days after completion of double-blind therapy, his platelet count fell further to 16,000 cells/mm<sup>3</sup>, and he complained of hemoptysis, low grade fever, sore throat and aches and pains. The subject was hospitalized with a platelet count of 29,000 cells/mm<sup>3</sup> and WBC count of 3,400 cells/mm<sup>3</sup>. Bone marrow biopsy was normal and he was treated with corticosteroids for presumed autoimmune or drug-induced thrombocytopenia, with prompt response. This event was also reported as a SAE. Concomitant therapy included levothyroxine and aspirin.
- Subject 005/014 from study CV137-022, a 48-year-old male, developed a decrease in platelet count from 268,000 cells/mm<sup>3</sup> at baseline to 104,000 cells/mm<sup>3</sup> after 65 days of 5 mg omapatrilat treatment. This event was also reported as a non-serious AE and did not lead to discontinuation. The follow up value on Day 72, after the subject completed the study, returned to normal (305,000 cells/mm<sup>3</sup>).
- Subject 037/019 from study CV137-024, a 55-year-old male, had a decrease in platelet count from 169,000 cells/mm<sup>3</sup> at baseline to 67,000 cells/mm<sup>3</sup> at the last double-blind assessment after treatment with omapatrilat 80 mg. This event was reported as a non-serious AE and did not lead to discontinuation. No follow up values are available.
- Subject 014/006 from study CV137-024, a 37 year-old male, had decreased platelets after 65 days of omapatrilat treatment. The Investigator judged the event to be possibly related to therapy. The subject completed the study.
- Subject 015/001 from study CV137-030 a 58 year-old male, had decreased platelets after 41 days of omapatrilat treatment. The Investigator judged the event to be unrelated to therapy and the subject completed the study.
- Subject 026/019 from study CV137-054, a 46 year-old male, had decreased platelets after 57 days of omapatrilat treatment. The Investigator judged the event to be not likely related to therapy and the subject completed the study.
- Subject 149/001 from study CV137-042, a 52 year-old male, had decreased platelets after 36 days of omapatrilat treatment. The Investigator judged the event to be possibly related to therapy but study medication was continued and the subject completed the study.
- Subject 091/016 from study CV137-024, a 63-year-old male, had a decrease in platelet count from 177,000 cells/mm<sup>3</sup> at baseline to 103,000 cells/mm<sup>3</sup> at the last double blind assessment. No follow-up values are available.
- Subject 014/038 from study CV137-030, a 46-year-old female, had a decrease in platelet count from 142,000 cells/mm<sup>3</sup> at baseline to 68,000 cells/mm<sup>3</sup> at the last double-blind assessment. This subject had been referred to a hematologist due to low platelet count prior to study enrollment. Her thrombocytopenia was considered chronic and not representing a disease. At the initial visit, the subject's platelet count was 71,000 cells/mm<sup>3</sup>. The investigator did not consider the abnormal values to be related to therapy.

## Liver Enzyme Abnormalities

- Subject 031/011 from study CV137-024, a 51-year-old female, presented with ALT elevation after 64 days of omapatrilat treatment. Her ALT levels went from 37 U/L at baseline to 175 U/L. The subject completed the study. No further information is available for this subject.
- Subject 052/001 from CV137-036, a 48 year-old white woman, had elevated ALT and AST levels after 29 days of omapatrilat treatment: AST 334 U/L, ALT 636 U/L. One week after discontinuation of therapy, AST was 111 U/L and ALT 312 U/L. The liver enzymes subsequently progressively returned to normal, and were 42 U/L for AST and 146 U/L for ALT 2 weeks after discontinuation of therapy.
- Subject 003/016 from study CV137-040, a 25 year-old Hispanic female, had an elevated AST level of 213 U/L at the end of double blind. The baseline AST was 36 U/L (ALT was 27 U/L). Re-evaluation a week later showed values had returned to normal (AST 32 U/L and ALT 46 U/L).
- Subject 025/017 from study CV137-040, a 47 year-old black male, entered the study with normal liver enzymes (baseline AST 41 U/L and ALT 40 U/L), then developed elevations of AST (148-244 U/L) and ALT (147-275 U/L). No clinical AEs were reported in conjunction with these laboratory abnormalities. On the last day of therapy, Hepatitis C antibodies were confirmed. Both AST and ALT returned to normal after 2 months post study.
- Subject 035/001 from study CV137-045, a 56 year-old female, discontinued after 17 days of omapatrilat treatment for facial flushing, headache and joint pain. In addition to these clinical events she was also noted to have elevations of ALT (294 U/L) and AST (248 U/L). Eighteen days later these values returned to normal.

Figure 1. HR

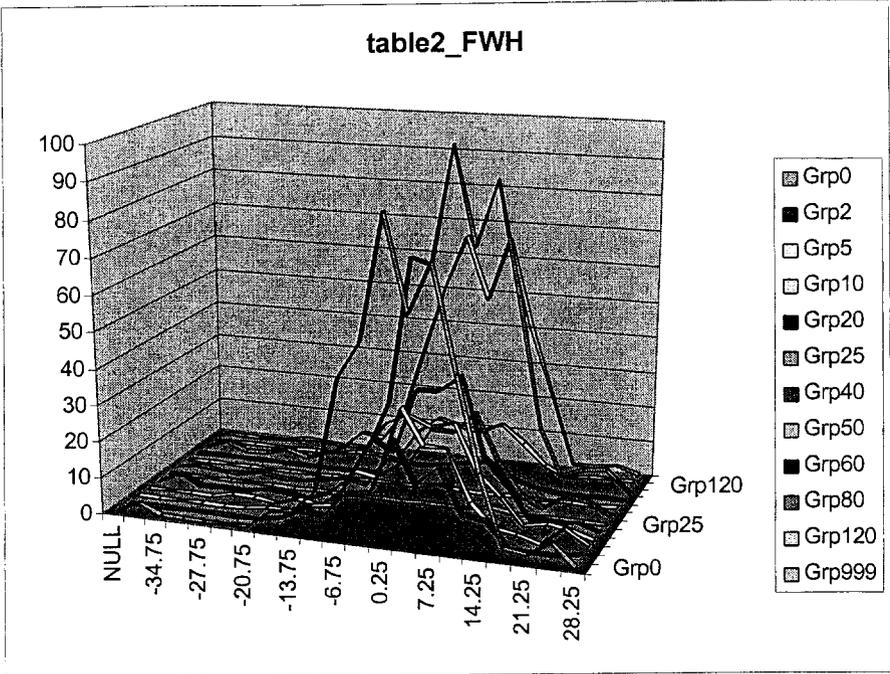
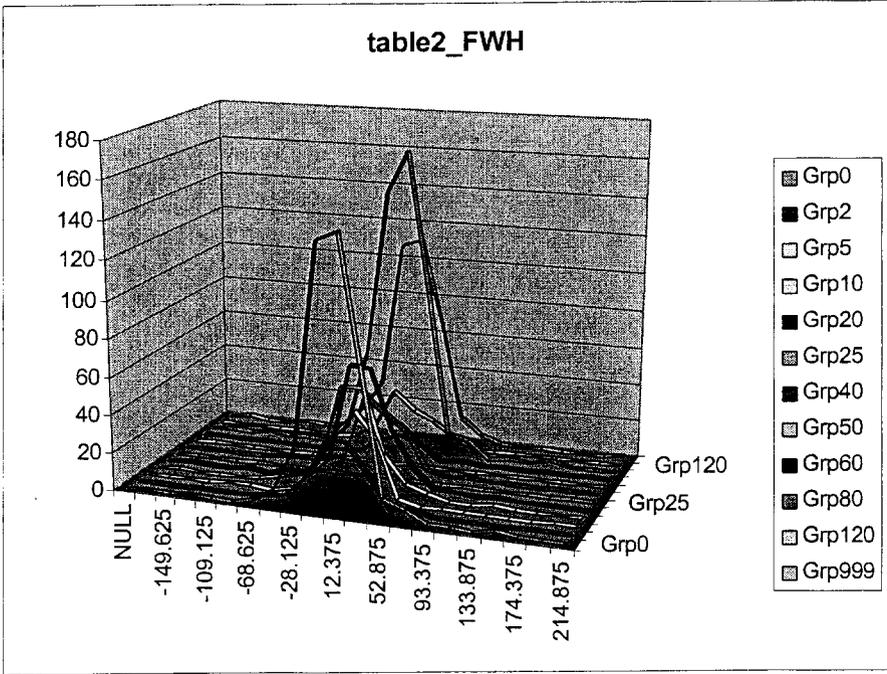


Figure 2. QTc



# ANGIOEDEMA-CLINICAL NARRATIVES<sup>1</sup>

## Subjects who Experienced Serious Adverse Events

### Protocol CV137-005 (Double-Blind Therapy)

- Subject ID: 016/003

Age/Gender: 46/F

Dose (mg) 75

Treatment Duration (days): 1 day

This subject's significant medical history includes hypertension, tubal ligation, obesity, hand ligament repair, cigarette smoking and sinus congestion. The subject completed 4 weeks of placebo lead-in and entered the 2-week double-blind period randomized to 75 mg/day. 45 minutes after receiving the first dose of study drug, subject experienced swelling in the face, throat, and tongue. Symptoms were accompanied by burning over the face, upper chest and arms. Subject felt chilled and noted a flushing sensation in the head with eye swelling and tearing. She also developed extreme nausea without vomiting or abdominal pain. Blood pressure was 190/110 mmHg and pulse was too rapid to count. Subject was treated with diphenhydramine hydrochloride and oxygen. The symptoms subsided without sequelae. Study medication was discontinued. The investigator considered the event to be possibly related to study medication.

Concomitant medication: estradiol, medroxy-progesterone acetate

### Protocol CV137-009 (Double-Blind Therapy)

- Subject ID: 0108/016

Age/Gender: 43/M

Dose (mg)/Adjunctive Med: Oma 20 mg

Study Duration (days)/Days from starting LT: 614/544

Significant medical history includes hypertension of 10 years, pneumonia and smoking. This 43 year old male, randomized to omapatrilat 10 mg titrated to 40 mg, completed 9 weeks of double-blind therapy and then entered the open-label phase. After 544 days of open-label therapy, he experienced angioneurotic edema. He had been on the omapatrilat 20 mg dose for about 3 months. He awoke with a flushing sensation, itching and progressive swelling of both lips. He did not have any shortness of breath or difficulty swallowing. His tongue, throat and lungs were normal on physical examination. He was treated with prednisone and fexofenadine and the event resolved the following day. He discontinued study medication. The only other adverse event reported during open-label therapy was the flu about three months prior to this event. He did not experience any adverse events during the double-blind study. The Investigator considered the event to be of probable relationship to study drug.

Concomitant medications reported at onset of SAE: none

Additionally, other medications received during open-label therapy: none

### Protocol CV137-022 (Double-Blind Therapy)

- Subject ID: 0047/008

Age/Gender: 50/F

Dose (mg)/ Omapatrilat 5 mg Level I

Treatment Duration (days): 1

Significant medical history includes hypertension of seven years, rash (due to lanolin), and anemia. Subject experienced angioedema 55 minutes after initial dose of double-blind therapy. No specific symptoms were reported. Treatment of the event included epinephrine, intravenous methylprednisolone, sodium succinate, and prednisone. The angioedema resolved after approximately four hours. Investigator considered the event was certainly related to double-blind therapy and study drug was discontinued

Concomitant medications: none

Additionally, other medications received during double-blind therapy: multivitamin with minerals, estradiol topical.

Subject 047/008, a 50 year old white female with no previous allergy to ACE inhibitors, developed angioedema 55 minutes after administration of the initial dose of omapatrilat 5 mg. She was treated with epinephrine 0.3 mg subcutaneous and solu-medrol (methylprednisolone sodium succinate) 125 mg intravenous with satisfactory recovery. The event was considered life

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<sup>1</sup> Clinical narratives were provided by the Sponsor.

threatening, but did not require hospitalization. Oral prednisone was prescribed for the next four days. The investigator indicated the relationship of the event to study treatment was certain and study treatment was discontinued.

#### **Protocol CV137-024 (Double-Blind Therapy)**

- Subject ID: 0020/001

Age/Gender: 53/M

Dose (mg): Omapatrilat 20.0

Duration (days): 1

Significant medical history includes hypertension of nine years and psoriasis. Two hours after receiving initial dose of double-blind therapy, subject experienced facial flushing and angioedema which required hospitalization. Subject was discontinued from the study. Tracheostomy was performed and both events resolved within five days of onset. Investigator considered the relationship of these events to study drug to be certain.

Concomitant medications at onset of SAE: none.

Additional concomitant medications during double-blind therapy: none.

Subject 020/001, a 53-year old caucasian male, developed life-threatening angioedema within two hours of receiving omapatrilat 20 mg. After initial therapy with oral diphenhydramine, intravenous methylprednisolone, and subcutaneous epinephrine, intravenous epinephrine was administered, then discontinued because of ventricular arrhythmia and chest pain. An emergent cricothyrotomy was then performed for worsening airway obstruction, with subsequent conversion to a tracheostomy. The tracheostomy tube was removed and the subject discharged to home after three days. There was no evidence of myocardial infarction. The relationship of the event to study drug was classified by the investigator as "certain".

#### **Protocol CV137-029 (Double-Blind Therapy)**

- Subject ID: 0010/014

Age/Gender: 66/F

Dose (mg): Oma 10

Duration (days): 50

Significant medical history includes hypertension for 3 years, Type II diabetes mellitus, and arthritis. After 50 days of double-blind therapy, the subject developed severe swelling of the face, lips and hands which resolved in 3 days. The subject was hospitalized and admitted to the Intensive Care Unit. Treatment of this event was not specified. Study drug was discontinued. The investigator considered the event to be certainly related to study drug.

Concomitant medications received during double-blind therapy: glyburide, ibuprofen.

- Subject ID: 0015/002

Age/Gender: 73/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 22 years, hernias, multiple fractures, amputated digits, impotence, tobacco use, currently drinks 4-5 drinks per day. Approximately 6 hours after receiving the first dose of double-blind medication, the subject developed edema of the upper lip, and of the bilateral cheeks. The subject was also found to have atrial fibrillation.

Shortness of breath and wheezing were not present. These events were treated with methylprednisolone, diphenhydramine, and prednisone. Study medication was discontinued. The atrial fibrillation was resolved at the time of discontinuation. The angioedema resolved 7 days after discontinuation. The investigator considered these events to be probably related to study drug. Concomitant medications taken during double-blind therapy: None.

Subject 015/002, a 73 year old white male with a 22-year history of hypertension, began experiencing edema of bilateral upper lip to the base of the nose and cheeks, approximately 6 hours after initiation of omapatrilat 20/20-40 mg which was diagnosed as angioedema. He was also found to have atrial fibrillation. Treatment of these events included methylprednisolone, diphenhydramine hydrochloride, and prednisone. Study medication was discontinued. The atrial fibrillation resolved in 1 day, but the angioedema did not resolve for 8 days. The Investigator considered these events to be probably related to study drug. Prior to enrollment, this subject had been treated with atenolol/chlorthalidone. The subject also took sildenafil as a concomitant medication during Period A.

#### **Protocol CV137-029 (Open-Label Therapy)**

- Subject ID: 0041/014

Age/Gender: 65/F

Dose (mg): Oma 10

Duration (days): 78

Significant medical history includes hypertension for 9 years, Type II Diabetes Mellitus, endometrial hyperplasia, degenerative joint disease, and chronic sinus problems. Approximately 18 days after starting treatment with 10 mg per day of open-label omapatrilat, the subject was titrated to the 20 mg per day dose. A few hours after titration, the subject developed swelling of her face and tongue. She was treated with diphen-hydramine, epinephrine and methylprednisolone sodium succinate and oxygen via nasal canula. After stabilization, she was transported to the hospital via ambulance, and admitted into the ICU for observation and treatment with undetermined IV steroids, diphenhydramine, and undetermined H2 blockers. After receiving a fiberoptic laryngoscopy and a physical exam, it was determined that the subject's airway was not compromised. Further history obtained from the subject at this time revealed that she had experienced a similar reaction when she was taking the ace inhibitor, enalapril maleate. She had not mentioned this to any of her physicians during the pre-study evaluation. Study drug was discontinued. The angioedema resolved 11 days after discontinuation. The Investigator considered this event probably related to study medication. Concomitant medications received during open-label therapy: Ascorbic acid, tocopherol, lecithin, magnesium, acetaminophen, acetylsalicylic acid, and multivitamin.

#### **Protocol CV137-030 (Double-Blind Therapy)**

- Subject ID: 0031/005

Age/Gender: 45/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 4 years, left eye injury, cornea transplant, occasional headaches, myopia, urolithiasis, and tobacco use. On the first day of double-blind therapy subject experienced angioedema and study drug was discontinued. Symptoms presented were: facial flushing, swelling of neck, difficulty swallowing, difficulty breathing, nasal congestion, headache, lips swelling and tingling. The event resolved within one hour. Investigator considered the event to be certainly related to double-blind therapy. Treatment of the event included epinephrine, diphenhydramine, and prednisone.

Medically important concomitant medications reported at onset of SAE: omeprazole and loteprednol etabonate

Concomitant medications received during double-blind therapy: omeprazole and loteprednol etabonate eye drops.

#### **Protocol CV137-037 (Double-Blind Therapy)**

- Subject ID: 004/009

Age/Gender: 42/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 10 years and an allergy to non-steroidal pain medication which caused facial swelling. At the time of the screening physical exam the subject had a rash on his upper chest. The subject's baseline ECG showed left ventricular hypertrophy, sinus bradycardia, ST elevation and first degree A-V Block. After one day of double-blind therapy the subject experienced severe nausea, vomiting, angioedema (tingling and swelling of the lips, tongue and throat.) The study drug was discontinued. Treatment for the event was diphenhydramine. All 3 events were resolved at the time of discontinuation. The Investigator considered the relationship to double-blind therapy to be certain.

Concomitant medications taken during double-blind therapy: None

Subject 004/009, a 42 year old male with a history of hypertension for 10 years, smoked one pack of cigarettes per day, and had an allergy to non-steroidal pain medication which caused facial swelling. After 2½ hours of receiving omapatrilat 20 mg, the subject developed angioedema (tingling and swelling of the lips, tongue and throat) along with severe nausea and vomiting. He was treated in the office with one dose of diphenhydramine and the angioedema gradually improved. The nausea and vomiting resolved after 30 minutes. Study drug was discontinued at this time. All events had resolved by the time the subject left the office. The relationship to double-blind therapy was considered to be certain. Prior to participating in this trial, the subject was taking an ACEI.

- Subject ID: 0006/006

Age/Gender: 49/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 3 years, allergies to penicillin which resulted in hives and seafood which resulted in hives and shortness of breath and seasonal allergies. The subject's baseline ECG showed left atrial hypertrophy. Fifty (50) minutes post first dose of double-blind therapy the subject experienced symptoms of angioedema while in the office. The

symptoms included swelling of the throat, and bilateral tingling of the hands. The subject did not complain of shortness of breath or chest pain. The study drug was discontinued. The subject was sent to the emergency unit by the investigator. She was treated with hydroxyzine hydrochloride, diphenhydramine, and adrenaline. The event was resolved at the time of discontinuation. The Investigator considered the relationship to double-blind therapy to be certain and life-threatening. Concomitant medications taken during double-blind therapy were: hydroxyzine hydrochloride, diphenhydramine, adrenaline, nifedipine, vitamins C,E,A,D,B12, and B complex.

- Subject ID: 0034/029

Age/Gender: 55/F

Dose (mg): Oma 40

Duration (days): 11

Significant medical history included hypertension for 3 years. Baseline ECG showed a left axis deviation. After 11 days on double-blind therapy the subject experienced symptoms of angioedema such as facial edema, glossopharyngeal edema and difficulty breathing which occurred approximately 2 to 3 hours post dose. The subject went to the emergency unit where she was intubated, transferred to the medical intensive care unit and placed on a ventilator. She was extubated 2 days later. The treatment of the event included epinephrine, diphenhydramine, intravenous methylprednisolone sodium succinate and diltiazem. The study drug was discontinued the day of the event. The subject was released from the hospital 3 days after the onset with no symptoms of angioedema. Upon discharge from the hospital, subject was placed on prednisone for 10 days. The Investigator considered the relationship to double-blind therapy to be probable and the event to be life threatening. Prior to participating in this trial, the subject was taking quinapril hydrochloride.

Concomitant medications taken during the double-blind therapy were: conjugated estrogens and medroxyprogesterone acetate.

- Subject ID: 0034/040

Age/Gender: 37/F

Dose (mg): Lead-in

Duration (days): 1

Significant medical history included hypertension for 5 years and no known allergies, experienced presumptive angioedema with laryngeal fullness, conjunctivitis and tachycardia 1 hour after taking omapatrilat 20 mg. She was treated in the office with diphenhydramine. Study drug was discontinued at that time. The event resolved within 2 hours and the subject discontinued. The relationship to double-blind therapy was considered to be probable.

Concomitant medications taken during double-blind therapy were: fexofenadine hydrochloride.

- Subject ID: 0039/006

Age/Gender: 42/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 8 years, Intermittent neck rash due to nerves, an allergy to mold dust and cats and a smoking history of 10 cigarettes per day. After the first dose of double-blind therapy the subject experienced submandibular swelling. The treatment of the event included prednisone and diphenhydramine. The study drug was discontinued. The event was resolved at the time of discontinuation. The Investigator considered the relationship to double-blind therapy to be certain.

Concomitant medications taken during the double-blind therapy: None

Subject 039/006, a 42 year old female with a history of hypertension for 8 years, smoked 10 cigarettes per day and had an allergy to dust from molds and cats. Forty-five (45) minutes after receiving the first dose of omapatrilat 20 mg, she began to feel lightheaded and her submandibular glands were enlarged. She also had redness of the face and her pupils were dilated. A few minutes later she developed a rash from her waist upward and complained of right abdominal pain. She was give epinephrine intramuscularly and all symptoms began to improve. Her blood pressure was 205/110 mmHg. She was taken to the emergency unit via an ambulance a ½ hour after onset of symptoms. She arrived at the hospital 20 minutes later and all symptoms, other than neck swelling, had resolved. She never experienced any difficulty breathing. Treatment in the emergency unit included prednisone and diphenhydramine. She was released from the hospital after 3 hours with instructions to continue on these medications, at home, for 3 more days. The site spoke to the subject 2½ hours later and she was fine. She was seen 2 days later in the office and the neck swelling had totally resolved. She was withdrawn from the study at this time. Study drug was discontinued after the first dose. The relationship to double-blind therapy was considered to be certain.

- Subject ID: 0089/017

Age/Gender: 34/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 1 year, asthma, allergies to animals, dust, pollen and smoked 10 cigarettes per day. Baseline ECG showed other nonspecific ST/T waves. Within the first hour of receiving the first dose of double-blind therapy, the subject experienced symptoms of angioedema (swelling of lips and throat, nausea, dyspnea and “egg size lumps around her throat”). She was sent to the emergency unit, treated with diphenhydramine and albuterol and released after approximately 4 ½ hours. That evening she was again having difficulty breathing and had swollen lips. She was hospitalized, intubated and was put on a ventilator for 3 days. The study drug was discontinued. Her symptoms resolved but the subject remained hospitalized for migraine headaches. The event of angioedema resolved after 11 days. Treatment for the event included: acetaminophen, methylprednisolone, famotidine, albuterol, midazolam, prednisone, diphenhydramine, and percocet. The Investigator considered the relationship to double-blind therapy to be probable.

Concomitant medications taken during double-blind therapy: None

Subject 089/017, a 34 year old female with a history of hypertension for 1 year, and asthma, smoked 10 cigarettes per day, and had allergies to animals, dust and pollen. She experienced symptoms of angioedema (swelling of lips and throat, nausea, dyspnea and egg size lumps around her throat) within the first hour of receiving the first dose of omapatrilat 20 mg. She was sent to the emergency unit, treated with diphenhydramine, methylprednisolone, acetaminophen and albuterol nebulizer treatments. After an hour and forty-five minutes she stated she felt better but an hour later she complained that her throat was still swelling and was given more diphenhydramine. Approximately 1 hour later she stated she felt fine although her neck and face were still swollen. Two and a half hours (2½) after going to the hospital she was released with instructions to take the diphenhydramine every 6 - 8 hours and the albuterol inhaler every 3-4 hours. Three (3) hours later, after experiencing difficulty breathing and lip swelling, she was admitted to the hospital with a diagnosis of angioedema, bronchial asthma, pneumonia and acute right maxillary and right sphenoid sinusitis. Because of acute respiratory distress she was intubated and placed on a ventilator for 3 days. She was treated with intravenous methylprednisolone, diphenhydramine, famotidine, subcutaneous epinephrine, acetaminophen, albuterol, midazolam, prednisone and percocet. The subject remained in the hospital for 10 days and it is not known exactly when the symptoms resolved but it is known that they were gone by the time she was discharged. Study drug was discontinued after the first dose and the randomization visit was the last. The relationship to double-blind therapy was considered to be probable.

- Subject ID: 0073/007

Age/Gender: 43/F

Dose (mg): Oma 80

Duration (days): 35

Significant medical history included hypertension for 23 years, watery eyes and rhinitis in the mornings, and smoking ½ pack of cigarettes per day. After 35 days on double-blind therapy, the subject experienced angioedema with lip swelling. Subject went to the emergency unit. Following treatment there, the subject was admitted to the hospital. Treatment of the event included prednisone, intravenous metho-prednisolone, intravenous and oral diphenhydramine and ranitidine. The study drug was discontinued. The event resolved the next day after onset. The Investigator considered the relationship to double-blind therapy to be certain.

Concomitant medications taken during double-blind therapy were: ibuprofen, acetaminophen with codeine, triamcinolone cream, acetaminophen-pseudoephedrine hydrochloride-dextromethorphan-doxylamine succinate and an unknown throat spray.

Subject 073/007, a 43-year-old female with a history of hypertension for 23 years, had a history of watery eyes and rhinitis in the mornings and smoked a ½ pack of cigarettes per day. After 35 days while an omapatrilat 80 mg she experienced angioedema. She took her morning dose at 0930 and around 1800-1830 began to experience lip swelling. The swelling increased over the evening and at 0220 the next day she went to the emergency unit and was admitted to the hospital. While there she was treated with prednisone, intravenous methylprednisolone, intravenous and oral diphenhydramine and ranitidine. Study drug was not resumed. The event resolved the day after onset. The relationship to double-blind therapy was considered to be certain.

#### **Protocol CV137-038 (Double-Blind Therapy)**

- Subject ID: 0124/027

Age/Gender: 62/F

Dose (mg): Oma 20.0

Duration (days): 14

Subject's significant medical history included hypertension for 9 years. Subject experienced mild swelling of left side of face and lip 14 days after start of omapatrilat double-blind therapy; vital signs were stable. Airway was not compromised. The Investigator diagnosed the event to be angioedema and considered the event to be probably related to study medication. No treatment was given for the event. The subject was discontinued from the study. Concomitant medications during double-blind therapy: none.

#### **Protocol CV137-042 (Double-Blind Therapy)**

- Subject ID: 0025/003

Age/Gender: 75/M

Dose (mg): Oma 20

Duration (days): 1

Subjects medical history includes hypertension of 5 years, diabetes mellitus type II, anemia, cataract surgery, gout, hot flashes, hydrocele repair and vagotomy-gastrojejunostomy. Subject is a 75 year old male who experienced angioedema approximately five and one-half hours after receiving first dose of double-blind therapy. Subject presented with tongue, lip and nose swelling and was sent to the ER. Subject was treated with IV methylprednisone sodium succinate, diphenhydramine HCL, and instructed to take methylprednisolone for 7 days. The duration of the angioedema was 3 days and investigator considered the relationship of this event to study drug to be certain.

Subject was discontinued from the study. Concomitant medications: diphenhydramine, methylprednisolone.

- Subject ID: 0091/013

Age/Gender: 59/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history of hypertension of 6 years, cardiac arrhythmia's, coronary artery disease, arthritis knees, fingers and hands, exposed to tuberculosis 1980, Grade I Fundi, heart burn, numbness in feet and hands, slight impotence 1997 and nocturia. Subject is a 59 year old male who experienced angioedema one hour after the first dose of double-blind therapy and was discontinued from study. During the event the subject experienced swelling of right salivary gland, right lower gum pain and swelling of lips. Subject was treated with diphenhydramine HCL, solucortef, and prednisone. The event resolved within one day of onset. Investigator considered the relationship of this event to study drug to be certain.

Concomitant medication during double-blind therapy: none

- Subject ID: 0094/009

Age/Gender: 78/M

Dose (mg): Oma 20

Duration (days): 6

Significant medical history includes hypertension for 2 years, peripheral vascular disease, constipation, convulsive crisis (not diagnosed as epilepsy), osteoarthritis, prostate adenoma surgery, renal failure, sepsis for staphylococcus aureus. After 6 days of double-blind therapy, the subject was hospitalized for loss of consciousness. While under observation, patient developed glottis and larynx edema which obstructed the airway. Patient underwent a cricothyrotomy with a subsequent tracheotomy and was treated with methylprednisolone and amoxicillin/clavulanic acid. Double-blind therapy was discontinued. The glottis and larynx edema was ongoing at the time of discontinuation, but resolved subsequently. Investigator considered the event to be possibly related to double-blind therapy.

Concomitant medications received during double-blind therapy: acetylsalicylic acid.

#### **Protocol CV137-045 (Double-Blind Therapy)**

- Subject ID: 0028/004

Age/Gender: 41/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 5 years, dilation and curettage, intermittent headaches secondary to hypertension, left foot surgery repair. Subject experienced hypotension two hours after initial dose of double-blind therapy and angioedema 4 ½ hours after initial dose of double-blind therapy. Blood pressure values dropped as low as 90 mmHg systolic and 50 mmHg diastolic. After also developing angioedema, swollen upper lip, and tingling in the throat the subject was hospitalized. Treatment of the events included oxygen, prednisone, and IV fluids. The hypotension lasted only a few minutes; blood pressure at time of hospitalization was 150/90 mmHg. The angioedema (swollen lips) resolved after approximately 7 days.

Investigator considered the events to be certainly related to double-blind therapy and study drug was discontinued.

Concomitant medications reported at onset of SAE: prednisone, Procordia and cortisone.

Additional other therapies received during double-blind therapy: None.

#### **Protocol CV137-049 (Double-Blind Therapy)**

- Subject ID: 0034/005

Age/Gender: 45/M

Dose (mg): Oma 80

Duration (days): 16

Significant medical history includes hypertension of 2 years, bronchitis, hives, stress headaches, seasonal allergic rhinitis, use of alcohol, tobacco, and marijuana. After 5 days of omapatrilat 80 mg therapy, the subject developed angioedema and presented to the emergency room with symptoms of swollen lips, swollen uvula, and itching. He was treated with methylprednisolone, prednisone, and hydroxyzine, and then released from the emergency room. The event resolved within 3 days of onset. Study drug was discontinued. The Investigator considered the relationship to be probably related to double-blind therapy.

Medically important concomitant medications reported at onset of SAE: none.

Additional concomitant medications received during double-blind therapy: famotidine, diphenhydramine, and naproxen.

#### **Protocol CV137-054 (Double-Blind Therapy)**

- Subject ID: 0032/002

Age/Gender: 38/F

Dose (mg): Oma 80

Duration (days): 36

Significant medical history includes hypertension diagnosed 2 weeks prior to study enrollment, cholecystectomy, degenerative joint disease, sleep disturbance, and use of tobacco. After 36 days of double-blind therapy (subject had been titrated to Level III), subject developed angioedema of the upper lip with a symptom described as "buzzing of the upper lip". Subject went to a hospital emergency room and was treated with methylprednisolone, diphenhydramine, and epinephrine. Subject was discharged from the emergency room with prednisone, cefadroxil and diphenhydramine. The event resolved completely within 3 days. Double-blind therapy was discontinued. Investigator considered the event possibly related to double-blind therapy.

Medically important concomitant medications reported at onset of SAE: none reported.

Additional concomitant medications received during double-blind therapy: amitriptyline, and nortriptylene.

Subject 032/002, a 38-year-old black female, experienced angioedema of the upper lip after 36 days of double-blind therapy with omapatrilat 20/40/80 mg regimen and 6 days after being titrated to Level III, 80 mg. The subject went to the emergency room and was treated with methylprednisone, diphenhydramine, and epinephrine. The subject was discharged from the emergency room and the event resolved within 3 days. The Investigator considered the event possibly related to double-blind therapy.

#### **Protocol CV137-009 (Ongoing Long-Term Hypertension Study)**

- Subject ID: 0017/002

Age/Gender: 50/F

Dose (mg): Oma 10

Duration (days): 981/

Significant medical history includes hypertension of 9 years and hypercholesterolemia. This 66 year old female completed 8 weeks of double-blind therapy and then entered the open-label phase. She started on omapatrilat 5 mg and remained on this dose for over a year. Then, after 981 days of open-label therapy, she was hospitalized due to tongue swelling which was diagnosed as angioedema. She had reported lip swelling for 2 weeks prior to the event. She was treated with diphenhydramine and fexofenadine and the event resolved after 3 days. She discontinued study medication. The Investigator considered the event to be of certain relationship to study drug. (See Supplemental Table S.7.4 for Discontinuation Summary)

Concomitant medications reported at onset of SAE: none

Additionally, other medications received during open-label therapy: lovastatin, conjugated estrogens

#### **Protocol CV137-066 (Ongoing Hypertension Study Double-Blind Therapy)**

- Subject ID: 0051/002

Age/Gender: 43/F

Dose (mg): Blinded

Duration (days): 1

Significant medical history includes hypertension for 7 months, hypercholesterolemia, G.E.R.D., back and neck pain, arthritis, migraines, depression and allergies to decaffeinated tea (with the symptom of facial swelling) and

ranitidine (with the symptom of vomiting). One and a half hours after the first dose of double-blind therapy, she experienced nausea, vomiting, facial redness, tachycardia, throat, face and tongue swelling. This was also termed very severe angioedema. Study drug was discontinued the same day. Treatment for these events included methylpredisolone and loratidine. The events resolved the next day. The investigator considered the relationship to double-blind study drug to be certain. (See Supplemental Table S.7.4 for Discontinuation Summary)  
Concomitant medications reported at the onset of SAE: omeprazole, fluoxetine, medroxyprogesterone, hydrocodone  
Additionally, other concomitant medications received during double-blind therapy: none

- Subject ID: 0129/003

Age/Gender: 57/M

Dose (mg): Blinded

Duration (days): 26

Significant medical history includes hypertension for 3 years, impotence while on antihypertensive medication and occasional tobacco use. After 26 days of study medication, the subject experienced an episode of angioneurotic edema involving right cheek and lips but not causing respiratory obstruction which began 2 hours prior to taking his dose of study medication. Study drug was discontinued. Treatment for this event included fexofenadine. The event resolved 2 days after onset. The investigator considered the relationship to double-blind study drug to be possible. (See Supplemental Table S.7.4 for Discontinuation Summary)

Concomitant medications reported at the onset of the SAE: none

Additionally, other concomitant medications taken during double-blind therapy: none

#### **Protocol CV137-012 (Heart Failure Studies)**

- Subject ID: 0027/006

Age/Gender: 51/M

Dose (mg): Ome 40

Treatment Duration (days): 1

Patient's significant history includes: myocardial infarction, percutaneous transluminal coronary angioplasty, unstable angina, hypercholesterolemia.

This subject experienced angioedema 45 minutes after the first dose of study medication was administered. At 0955 hours the patient was dosed. At 1030, the patient began to complain of nausea, throat discomfort and experienced diaphoresis. The throat swelling increased swiftly with the patient becoming unable to swallow and control oral secretions. He also experienced mild difficulty in speaking. With the increase of symptoms, the patient was given 50 mg of intravenous benadryl (diphenhydramine hydrochloride) and monitored until he became stable. The event resolved and the patient was withdrawn from the study. The event was considered to be related to the study drug.

Concomitant medications: acetylsalicylic acid, atenolol, clarithromycin, fluvastatin, furosemide, metolazone, nabumetone, nitroglycerin topical, potassium, quinine

## Subjects Who Discontinued Because of Omapatrilat-Induced Angioedema

### Protocol CV137-005 (Double-Blind Therapy)

- Subject ID: 016/003

Age/Gender: 46/F

Dose (mg): Oma 75

Treatment Duration (days): 1

This subject's significant medical history includes hypertension, tubal ligation, obesity, hand ligament repair, cigarette smoking and sinus congestion. The subject completed 4 weeks of placebo lead-in and entered the 2-week double-blind period randomized to 75 mg/day. 45 minutes after receiving the first dose of study drug, subject experienced swelling in the face, throat, and tongue. Symptoms were accompanied by burning over the face, upper chest and arms. Subject felt chilled and noted a flushing sensation in the head with eye swelling and tearing. She also developed extreme nausea without vomiting or abdominal pain. Blood pressure was 190/110 mmHg and pulse was too rapid to count. Subject was treated with diphenhydramine hydrochloride and oxygen. The symptoms subsided without sequelae. Study medication was discontinued. The investigator considered the event to be possibly related to study medication.

Concomitant medication: estradiol, medroxy-progesterone acetate

### Protocol CV137-006 (Double-Blind Therapy)

- Subject ID: 010/007

Age/Gender: 55/M

Dose (mg): Oma 5

Treatment Duration (days): 1

Significant medical history includes hypertension of 9 years hypertriglyceridemia, hypercholesterolemia and an allergy to penicillin. The subject experienced angioneurotic edema (symptoms: bilateral parotid swelling) 1 hour after ingestion of first dose of omapatrilat. He did not experience any dizziness, wheezing or hoarseness. The swelling improved by 50% within 1 hour after treatment with diphenhydramine. Five and one half hours post dose, the swelling improved to the point the subject could return to work. Additionally, he was treated with cetirizine. The swelling completely resolved the following day. Study medication was discontinued the same day. The event resolved the following day. The investigator considered the event to be of probable relationship to study drug. This event was reported to the FDA in Safety Addendum #1 (revised).

Concomitant medications: cetirizine, diphenhydramine

- Subject ID: 053/013

Age/Gender: 57/F

Dose (mg): Oma 5.0

Treatment Duration (days): 11

Significant medical history includes hypertension of 10 months, migraines, peptic ulcers, hiatal hernia and hayfever. The subject experienced angioedema after 11 days of omapatrilat therapy. Study medication was discontinued the next day, no treatment was reported and the event resolved 5 days after onset. The investigator considered the event to be of probable relationship to study drug. The subject started on diltiazem for hypertension.

Concomitant medications: beclomethasone, cyclobenzaprine, diltiazem, estrogens conjugated

- Subject ID: 010/011

Age/Gender: 52/F

Dose (mg): Oma 50

Treatment Duration (days): 1

Significant medical history includes hypertension of 4 years, hypertriglyceridemia, hypercholesterolemia and an allergy to sulfa. One and a half hours after the first dose of omapatrilat, the subject experienced a mild headache, which resolved. Two hours after the initial dose, the subject experienced angioneurotic edema and postural hypotension (symptoms: neck swelling, dizziness and excessive eye tearing without wheezing, hoarseness or tongue swelling). Her BPs 2 hours post dose were: standing (not mean) 100/60 mmHg, mean supine BP: 115/59 mmHg and mean SeBP:

125/67 mmHg. Her baseline mean BPs were: seated: 165/101 mmHg, supine: 164/100 mmHg, and standing BP: 149/99 mmHg.

She was initially treated with intravenous normal saline and diphenhydramine. A second dose of diphenhydramine was administered. The subject discontinued study medication. She was sent home six hours post dose. The edema resolved after 2 days and the hypotension resolved after one hour. The investigator considered the events to be of probable relationship to study drug. This event was reported to the FDA in Safety Addendum #1 (revised).

Concomitant medications: diphenhydramine, sodium chloride

### Protocol CV137-009 (Long-Term, Open-Label Therapy)

- Subject ID: 0031/002

Age/Gender: 70/M

Dose (mg): Oma 20

Study Duration (days)/Days from starting LT: 165/96

Significant medical history includes hypertension of 9 years and an allergy to aspirin. This 70 year old male randomized to omapatrilat 10 mg titrated to 40 mg, completed 9 weeks of double-blind therapy and then entered the open-label phase. He experienced angioedema after 96 days of open-label therapy. He had been on omapatrilat 20 mg for approximately 2 months prior to the event. He was randomized to amlodipine 5 mg one month prior to the event but the site could not confirm whether the subject actually took the adjunctive medication. He initially presented with lip edema and later was diagnosed with angioedema. Omapatrilat was discontinued and he was treated with loratidine. The event resolved the day after discontinuation. He did not present with any other adverse events during double-blind or open-label periods. The Investigator considered the event of possible relationship to study drug.

Concomitant medications: moexipril

- Subject ID: 0108/016

Age/Gender: 43/M

Dose (mg): Oma 20

Study Duration (days)/Days from starting LT: 614/544

Significant medical history includes hypertension of 10 years, pneumonia and smoking. This 43 year old male, randomized to omapatrilat 10 mg titrated to 40 mg, completed 9 weeks of double-blind therapy and then entered the open-label phase. After 544 days of open-label therapy, he experienced angioneurotic edema. He had been on the omapatrilat 20 mg dose for about 3 months. He awoke with a flushing sensation, itching and progressive swelling of both lips. He did not have any shortness of breath or difficulty swallowing. His tongue, throat and lungs were normal on physical examination. He was treated with prednisone and fexofenadine and the event resolved the following day. He discontinued study medication. The only other adverse event reported during open-label therapy was the flu about three months prior to this event. He did not experience any adverse events during the double-blind study. The Investigator considered the event to be of probable relationship to study drug.

Concomitant medications: none

- Subject ID: 0086/005

Age/Gender: 74/M

Dose (mg): Oma 20 mg/Aten 50 mg + Aml 10 mg

Study Duration (days)/Days from starting LT: 277/207

Significant medical history includes hypertension of 4 years, angina pectoris, CABG, coronary artery disease, hypercholesterolemia, PTCA, benign bladder tumor, Legionnaire's disease and basal cell cancer lip. This 74 year old male, randomized to omapatrilat 5 mg, completed 9 weeks of double-blind therapy and then entered the open-label phase. Angioedema was first reported after 187 days of open-label therapy and resolved the same day without treatment. Then, he experienced angioedema and a truncal rash after 207 and 208 days of open-label omapatrilat therapy, respectively. Open-label therapy was discontinued the next day. He was treated with fexofenadine and the rash and angioedema resolved 8 and 9 days after event onset. He had been on omapatrilat 20 mg for over 5 months and stable doses of the adjunctive medications for about one month prior to onset of both angioedemas. He also experienced leg edema, which was attributed to amlodipine. The Investigator considered the event of probable relationship to study drug.

Concomitant medications: acetyl salicylic acid, fexofenadine, ibuprofen, ranitidine, simvastatin

- Subject ID: 0079/014

Age/Gender: 63/M

Dose (mg): Oma 40

Study Duration (days)/Days from starting LT: 124/58

Significant medical history includes hypertension of 14 years, hypercholesterolemia, hypertriglyceridemia, cholelithiasis, degenerative arthritis, GERD, depression and panic attacks. This 63 year old male, randomized to omapatrilat 20 mg titrated to 40 mg, completed 9 weeks of double-blind therapy and then entered open-label therapy. He first experienced lip swelling after 15 days of omapatrilat 5 mg open-label therapy, which resolved after 3 days. He was treated with diphenhydramine. He then experienced dizziness, tingling in his hands, facial numbness and nausea after 50 days (on the first day of omapatrilat 20 mg and two days after a capped tooth dental procedure). The tingling and numbness decreased in severity and he continued in the trial. He again experienced lip swelling after 58 days of open-label therapy. The Investigator reported that the acute swelling of the left upper lip extended to the left maxillary region and was consistent with angioedema. There was no shortness of breath or chest tightness. He had titrated to the 40 mg dose of omapatrilat 5 days prior to the event. He again required treatment with

diphenhydramine. The swelling resolved one week after discontinuation of open-label therapy. The Investigator considered the event of probable relationship to study drug.

Concomitant medications: acetaminophen, ciprofloxacin, diclofenac, diphenhydramine, nabumetone, ranitidine.

#### **Protocol CV137-022 (Double-Blind Therapy)**

- Subject ID: 0047/008

Age/Gender: 50/F

Dose (mg): Oma 5

Treatment Duration (days): 1

Significant medical history includes hypertension of seven years, rash (due to lanolin), and anemia. Subject experienced angioedema 55 minutes after initial dose of double-blind therapy. No specific symptoms were reported. Treatment of the event included epinephrine, intravenous methylprednisolone, sodium succinate and prednisone. The angioedema resolved after approximately four hours. Investigator considered the event to be related to double-blind therapy.

Concomitant medications reported at onset of SAE: none

Additionally, other medications received during double-blind therapy: multivitamin with minerals, estradiol topical.

Subject 047/008, a 50 year old white female with no previous allergy to ACE inhibitors, developed angioedema 55 minutes after administration of the initial dose of omapatrilat 5 mg. She was treated with epinephrine 0.3 mg subcutaneous and solu-medrol (methylprednisolone sodium succinate) 125 mg intravenous with satisfactory recovery. The event was considered life threatening, but did not require hospitalization. Oral prednisone was prescribed for the next four days. The investigator indicated the relationship of the event to study treatment was certain and study treatment was discontinued.

- Subject ID: 0073/012

Age/Gender: 40/M

Dose (mg): Oma 40

Treatment Duration (days): 19

Significant medical history includes hypertension of two years. After 19 days of double-blind therapy, the subject experienced angioedema and urticaria. Treatment included epinephrine and cetirizine with satisfactory recovery. Investigator considered both events to be probably related to study drug and discontinued double-blind therapy.

Concomitant medications during double-blind therapy: epinephrine, methylprednisolone, prednisone, and cetirizine.

#### **Protocol CV137-024 (Double-Blind Therapy)**

- Subject ID: 0020/005

Age/Gender: 51/M

Dose (mg): Oma 10

Duration (days): 1

Significant medical history includes hypertension of eight years, hypercholesterolemia, and hypertriglyceridemia. Ninety minutes after receiving initial dose of double-blind therapy, subject experienced left ear ache, tingling in arms and legs, flushing of arms, face, and neck, difficulty in swallowing, angioedema, and hypotension which resulted in discontinuation of study drug. Mean SeBP and HR 30 minutes prior to the time of event were 124/90 mmHg and 60 bpm (baseline: 140/96 mmHg and 64 bpm). All events resolved the same day. Except for left ear ache and tingling of arms and legs, investigator considered the relationship of these events to study drug to be certain. Relationship of left ear ache and tingling of arms and legs to study drug were considered to be probable.

Concomitant medications during double-blind therapy: simvastatin.

- Subject ID: 0019/007

Age/Gender: 60/M/

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension of sixteen years and hypercholesterolemia. Subject experienced angioedema on the same day as the beginning of double-blind therapy, therefore, was discontinued from the study. No specific symptoms were reported. With treatment of diphenhydramine and prednisone, angioedema resolved within five days of onset. Investigator considered the relationship of the event to study drug to be certain.

Additional concomitant medications during double-blind therapy: acetylsalicylic acid.

- Subject ID: 020/001

Age/Gender: 53/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension of nine years and psoriasis. Two hours after receiving initial dose of double-blind therapy, subject experienced facial flushing and angioedema which required hospitalization. Subject was discontinued from the study. Tracheostomy was performed and both events resolved within five days of onset. Investigator considered the relationship of these events to study drug to be certain.

Concomitant medications during double-blind therapy: none.

Subject 020/001, a 53-year old caucasian male, developed life-threatening angioedema within two hours of receiving omapatrilat 20 mg. After initial therapy with oral diphenhydramine, intravenous methylprednisolone, and subcutaneous epinephrine, intravenous epinephrine was administered, then discontinued because of ventricular arrhythmia and chest pain. An emergent cricothyrotomy was then performed for worsening airway obstruction, with subsequent conversion to a tracheostomy. The tracheostomy tube was removed and the subject discharged to home after three days. There was no evidence of myocardial infarction. The relationship of the event to study drug was classified by the investigator as "certain".

- Subject ID: 0053/012

Age/Gender: 60/F

Dose (mg): Oma 20

Duration (days): 5

Significant medical history includes hypertension of eight years, myopia, infections, sweating (due to tylenol), and rare bladder infections. Subject experienced angioedema five days after beginning double-blind therapy and was discontinued from the study. No specific symptoms were reported. Angioedema resolved within three days of onset with diphenhydramine. Subject was discontinued from the study and investigator considered the relationship of the event to study drug to be certain.

Additional concomitant medications during double-blind therapy: amlodipine.

- Subject ID: 0062/004

Age/Gender: 58/M

Dose (mg): Oma 30

Duration (days): 2

Significant medical history includes hypertension of six years and arthritis. Two days after beginning double-blind therapy, subject experienced angioneurotic edema and was discontinued from the study. The event resolved within eight days of onset. Investigator considered the relationship of this event to study drug to be probable.

Concomitant medications during double-blind therapy: amlodipine.

#### **Protocol CV137-029 (Double-Blind Therapy)**

- Subject ID: 0010/014

Age/Gender: 66/F

Dose (mg): Oma 10

Duration (days): 50

Significant medical history includes hypertension for three years, Type II diabetes mellitus, and arthritis. After 50 days of double-blind therapy, the subject developed severe swelling of the face, lips and hands. She was admitted to the hospital and placed in ICU. The event which resolved in 2 days. Treatment of this event was not specified. Study drug was discontinued. The Investigator considered the event to be certainly related to study drug.

Concomitant medications received during double-blind therapy: glyburide, ibuprofen.

- Subject ID: 0039/012

Age/Gender: 78/F

Dose (mg): Oma 10

Duration (days): 39 & 46

Significant medical history includes hypertension for 33 years, urinary incontinence, and osteoporosis. Thirty-nine (39) days after starting treatment with double-blind therapy, the subject developed a headache and throat swelling. Fioricet was given for treatment of the headache. Nothing was initially given for the throat swelling. Study drug was discontinued. Seven days after discontinuing study medication the subject developed angioedema and was treated for this event with prednisone. The throat swelling resolved in 3 days, however the headache was still continuing. The angioedema resolved 8 days after onset. The Investigator considered the throat swelling and headache to possibly be related to study medication, and the angioedema to probably be related.

Concomitant medications received during double-blind therapy: None.

Subject 039/012, a 78 year old white female with a 33 year history of hypertension, developed a headache and throat swelling 39 days after beginning double-blind therapy with omapatrilat 10/10-20 mg. The headache was considered to be severe in intensity, and the throat swelling was considered to be moderate in intensity. Acetaminophen/butalbital was given for the headache. Nothing was initially given for the throat swelling. Study drug was discontinued. In addition, 7 days after discontinuation of the study medication (and 46 days after starting double-blind therapy), the subject developed angioedema of the face and was treated for this event with prednisone. The angioedema resolved in 8 days. The headache was still ongoing after discontinuation. The Investigator considered the headache and throat swelling to be possibly related to study medication, and the angioedema to be probably related.

- Subject ID: 0015/002

Age/Gender: 73/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 22 years, hernias, multiple fractures, amputated digits, and impotence.

Approximately 6 hours after receiving the first dose of double-blind medication, the subject developed angioedema of the upper lip, and of the bilateral cheeks. The subject was also found to have atrial fibrillation, however, shortness of breath and wheezing were not present. These events were treated with diphenhydramine, prednisone and methylprednisolone. Study medication was discontinued. The atrial fibrillation resolved in 1 day. The angioedema resolved in 8 days. The investigator considered these events to be probably related to study drug.

Concomitant medications taken during double-blind therapy: None.

Subject 015/002, a 73 year old white male with a 22-year history of hypertension, began experiencing edema of bilateral upper lip to the base of the nose and cheeks, approximately 6 hours after initiation of omapatrilat 20/20-40 mg which was diagnosed as angioedema. He was also found to have atrial fibrillation. Treatment of these events included methylprednisolone, diphenhydramine hydrochloride, and prednisone. Study medication was discontinued. The atrial fibrillation resolved in 1 day, but the angioedema did not resolve for 8 days. The Investigator considered these events to be probably related to study drug. Prior to enrollment, this subject had been treated with atenolol/chlorthalidone. The subject also took sildenafil as a concomitant medication during Period A.

#### **Protocol CV137-029 (Open-Label Therapy)**

- Subject ID: 0041/014

Age/Gender: 65/F

Dose (mg): Oma 10

Duration (days): 78

Significant medical history includes hypertension for 9 years, Type II Diabetes Mellitus, endometrial hyperplasia, degenerative joint disease, and chronic sinus problems. Approximately 18 days after starting treatment with 10 mg per day of open-label omapatrilat, the subject was titrated to the 20 mg per day dose. A few hours after titration, the subject developed angioedema.

The subject was treated with diphenhydramine, epinephrine and methylprednisolone sodium succinate and was given oxygen via nasal canula. She was transported to the ER after stabilization, and admitted into the ICU for observation. She was subsequently treated with undetermined IV steroids, diphenhydramine, and undetermined H2 blockers. After receiving a fiberoptic laryngoscopy and a physical exam, it was determined that the subject's airway was not compromised. Further history obtained from the subject at this time revealed that she had experienced a similar reaction when she was taking the ace inhibitor, enalapril maleate. She had not mentioned this to any of her physicians during the pre-study evaluation. Study drug was discontinued. The angioedema resolved 11 days after discontinuation. The Investigator considered this event to probably be related to study medication.

Concomitant medications received during open-label therapy: None.

#### **Protocol CV137-030 (Double-Blind Therapy)**

- Subject ID: 0027/013

Age/Gender: 35/F

Dose (mg): Placebo

Duration (days): 5

Significant medical history includes hypertension for 6 years, allergy to novocaine, occasional headaches, alcohol and tobacco use. After 5 days of double-blind therapy subject experienced angioedema of the tongue and left eye area. No treatment was required. Investigator considered event to be certainly related to double-blind therapy. Subject was discontinued from the study and angioedema resolved after 4 days.

Concomitant medication received during double-blind therapy was acetaminophen.

- Subject ID: 0023/002

Age/Gender: 65/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 14 years, tobacco use, chronic obstructive pulmonary disease and pneumonia, hypothyroidism and shingles. Within a half hour of the first dose of double-blind therapy the subject experienced angioedema. Treatment for the event was diphenhydramine. Angioedema resolved after 6 hours. Investigator considered the event certainly related to double-blind therapy. Subject was discontinued from the study at this time.

Concomitant medication received during double-blind therapy was levothyroxine sodium

- Subject ID: 0031/005

Age/Gender: 45/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 4 years, injury left eye, cornea transplant, occasional headaches, myopia, urolithiasis, and tobacco use. On the first day of double-blind therapy subject experienced angioedema and study drug was discontinued. Symptoms presented were: facial flushing, swelling of neck, difficulty swallowing, difficulty breathing, nasal congestion, headache, lips swelling and tingling. The event resolved within one hour. Investigator considered the event to be certainly related to double-blind therapy. Treatment of the event included epinephrine, diphenhydramine, and prednisone.

Concomitant medications received during double-blind therapy: omeprazole and loteprednol etabonate eye drops.

- Subject ID: 0087/001

Age/Gender: 60/M

Dose (mg): Oma 20

Duration (days): 22

Significant medical history includes hypertension for 2 months, and alcohol use. After 22 days of double-blind therapy subject developed angioedema. Subject was treated with diphenhydramine, prednisone, and triamcinolone. Investigator considered the event certainly related to double-blind therapy. Subject was discontinued, and the event resolved after 9 days.

Concomitant medications received during double-blind therapy: None

- Subject ID: 0075/012

Age/Gender: 51/F

Dose (mg): Aml 5

Duration (days): 5

Significant medical history includes hypertension for 6 years, migraines, asthma, gastric ulcer, seasonal allergies, and alcohol use. After 5 days of double-blind therapy subject experienced angioedema. Specific symptoms reported were: shortness of breath, feeling of something lodged in throat, flushed face, voice deepened like laryngitis, cough, and "funny feeling in nose". No treatment was required. Subject was discontinued from the study. All events resolved after 6 days. Investigator considered event probably related to double-blind therapy.

Concomitant medications received during double-blind therapy. None

#### **Protocol CV137-036 (Double-Blind Therapy)**

- Subject ID: 0016/009

Age/Gender: 32/F

Dose (mg): Oma 10 (BID)

Duration (days): 1

Significant medical history includes hypertension for two years, seasonal allergies with occasional bronchospasms and use of tobacco. Subject experienced angioedema 45 minutes after initial dose of double-blind therapy. Symptoms included swelling in the lip and jawline areas and lip numbness. Treatment of the event included loratadine and prednisone. The event resolved within approximately four hours. Investigator considered the event to be related to double-blind therapy.

Concomitant medications received during double-blind therapy: none reported.

#### **Protocol CV137-037 (Double-Blind Therapy)**

- Subject ID: 0004/009

Age/Gender: 42/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 10 years, smoked one pack of cigarettes per day, and had an allergy to non-steroidal pain medication which caused facial swelling. After 2½ hours of receiving omapatrilat 20 mg, the subject developed angioedema (tingling and swelling of the lips, tongue and throat) along with severe nausea, vomiting. He was treated in the office with one dose of diphenhydramine and the angioedema gradually improved. The nausea and vomiting resolved after 30 minutes. Study drug was discontinued at this time. All events had resolved by the time the subject left the office. The relationship to double-blind therapy was considered to be certain. Prior to participating in this trial, the subject was taking an ACEI. Concomitant medications taken during double-blind therapy: None

Subject 004/009, a 42 year old male with a history of hypertension for 10 years, smoked one pack of cigarettes per day, and had an allergy to non-steroidal pain medication which caused facial swelling. After 2½ hours of receiving omapatrilat 20 mg, the subject developed angioedema (tingling and swelling of the lips, tongue and throat) along with severe nausea and vomiting. He was treated in the office with one dose of diphenhydramine and the angioedema gradually improved. The nausea and vomiting resolved after 30 minutes. Study drug was discontinued at this time. All events had resolved by the time the subject left the office. The relationship to double-blind therapy was considered to be certain. Prior to participating in this trial, the subject was taking an ACEI.

- Subject ID: 0006/006

Age/Gender: 49/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 3 years, smoked ½ pack of cigarettes per day and reported a history of seasonal allergies and allergies to penicillin, causing hives and to seafood, causing hives and shortness of breath. Fifty (50) minutes after receiving the first dose of omapatrilat 20 mg, the subject experienced angioedema with mild swelling of the throat and some difficulty swallowing but denied any difficulty breathing or other symptoms. Treatment given in the office included hydroxyzine hydrochloride, diphenhydramine, and adrenaline. She was then taken to the emergency unit by ambulance. At the hospital she informed the doctors that she was also allergic to aspirin. She was found to have a mildly congested pharynx with mild swelling of the uvula and lymphoid hyperplasia with a copious amount of green purulent drainage. Treatment given in the hospital included intravenous ranitidine and diphenhydramine with minimal resolution. She was reevaluated an hour later (approximately 4 hours after the onset of the event) and continued to have large submandibular nodes with purulent drainage at the posterior pharynx. She was sent home and instructed to take azithromycin and to continue to take diphenhydramine for 72 hours. The event resolved within 24 hours and study drug was discontinued. The relationship to double-blind therapy was considered to be certain.

Concomitant medications taken during double-blind therapy were: hydroxyzine hydrochloride, diphenhydramine, adrenaline, nifedipine, vitamins C,E,A,D,B12, and B complex.

- Subject ID: 0034/029

Age/Gender: 55/F

Dose (mg): Oma 20

Duration (days): 11

Significant medical history included hypertension for 3 years and no known allergies experienced angioedema after 11 days on omapatrilat 20 mg. Approximately 2 to 3 hours after taking her dose for the day, she began to experience facial and glossopharyngeal edema and difficulty breathing. She was driven to the emergency unit by family. The subject failed to respond to epinephrine and steroids and required intubation. She was transferred to the medical intensive care unit and placed on a ventilator. She was extubated 2 days later. Treatment of the event included epinephrine, diphenhydramine, intravenous methylprednisolone sodium succinate and diltiazem. Study drug was discontinued as of the day of the event. The subject was released from the hospital 3 days after the onset with no symptoms of angioedema. Upon discharge from the hospital, she was placed on prednisone for 10 days. Discontinuation from the study was 6 days later and there were no signs of angioedema. The relationship to double-blind therapy was considered to be probable. Prior to participating in this trial, the subject was taking an ACEI.

Concomitant medications taken during the double-blind therapy were: conjugated estrogens and medroxyprogesterone acetate.

- Subject ID: 006/006

Age/Gender: 49/F

Dose (mg): Oma 20

Duration (days): 1

Subject 006/006, a 49 year old female with a history of hypertension for 3 years, smoked ½ pack of cigarettes per day and

reported a history of seasonal allergies and allergies to penicillin, causing hives, and to seafood, causing hives and shortness of breath. Fifty (50) minutes after receiving the first dose of omapatrilat 20 mg, the subject experienced angioedema with mild swelling of the throat and some difficulty swallowing but denied any difficulty breathing or other symptoms. Treatment given in the office included hydroxyzine hydrochloride, diphenhydramine, and adrenaline. She was then taken to the emergency unit by ambulance. At the hospital she informed the doctors that she was also allergic to aspirin. She was found to have a mildly congested pharynx with mild swelling of the uvula and lymphoid hyperplasia with a copious amount of green purulent drainage. Treatment given in the hospital included intravenous ranitidine and diphenhydramine with minimal resolution. She was reevaluated an hour later (approximately 4 hours after the onset of the event) and continued to have large submandibular nodes with purulent drainage at the posterior pharynx. She was sent home and instructed to take azithromycin and to continue to take diphenhydramine for 72 hours. The event resolved within 24 hours and study drug was discontinued. The relationship to double-blind therapy was considered to be certain. Prior to participating in this trial the subject was taking an ACEI.

- Subject ID: 0039/006

Age/Gender: 42/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 8 years, smoked 10 cigarettes per day and had an allergy to dust from molds and cats. Forty-five (45) minutes after receiving the first dose of omapatrilat 20 mg, she began to feel lightheaded and her submandibular glands were enlarged. She also had redness of the face and her pupils were dilated. A few minutes later she developed a rash from her waist upward and complained of right abdominal pain. She was given epinephrine intramuscularly and all symptoms began to improve. Her blood pressure was 205/110 mmHg. She was taken to the emergency unit via an ambulance a ½ hour after onset of symptoms. She arrived at the hospital 20 minutes later and all symptoms, other than neck swelling, had resolved. She never experienced any difficulty breathing. Treatment in the emergency unit included prednisone and diphenhydramine. She was released from the hospital after 3 hours with instructions to continue on these medications, at home, for 3 more days. The site spoke to the subject 2½ hours later and she was fine. She was seen 2 days later in the office and the neck swelling had totally resolved. She was withdrawn from the study at this time. Study drug was discontinued after the first dose. The relationship to double-blind therapy was considered to be certain.

Concomitant medications taken during the double-blind therapy: None

Subject 039/006, a 42 year old female with a history of hypertension for 8 years, smoked 10 cigarettes per day and had an allergy to dust from molds and cats. Forty-five (45) minutes after receiving the first dose of omapatrilat 20 mg, she began to feel lightheaded and her submandibular glands were enlarged. She also had redness of the face and her pupils were dilated. A few minutes later she developed a rash from her waist upward and complained of right abdominal pain. She was given epinephrine intramuscularly and all symptoms began to improve. Her blood pressure was 205/110 mmHg. She was taken to the emergency unit via an ambulance a ½ hour after onset of symptoms. She arrived at the hospital 20 minutes later and all symptoms, other than neck swelling, had resolved. She never experienced any difficulty breathing. Treatment in the emergency unit included prednisone and diphenhydramine. She was released from the hospital after 3 hours with instructions to continue on these medications, at home, for 3 more days. The site spoke to the subject 2½ hours later and she was fine. She was seen 2 days later in the office and the neck swelling had totally resolved. She was withdrawn from the study at this time. Study drug was discontinued after the first dose. The relationship to double-blind therapy was considered to be certain.

- Subject ID: 0068/030

Age/Gender: 53/F

Dose (mg): Oma 20

Duration (days): 4

The subject's significant medical history included hypertension for 10 years, first degree A-V block. The subject also has an allergy to codeine where she develops a skin rash and a history of seasonal allergies. After 4 days of double-blind therapy, the subject experienced angioedema of the lips. The study drug was discontinued. The treatment for the event included hydroxyzine pamoate and diphenhydramine. The event resolved 6 days after the last dose of study medication. The Investigator considered the relationship to double-blind therapy to be certain.

Concomitant medications taken during double-blind therapy were: conjugated estrogen and ibuprofen.

- Subject ID: 0077/009

Age/Gender: 56/M

Dose (mg): Oma 20

Duration (days): 5

The subject's significant medical history included hypertension for 17 years, hepatitis B, pancreatitis and tobacco use (1 pack per day). The subject developed angioedema after 5 days of double-blind therapy. The symptom was a severely swollen lower lip. Treatment of the event included intravenous diphenhydramine and prednisone. The study drug was discontinued. The event resolved 4 days after onset. The Investigator considered the relationship to double-blind therapy to be possible.

Concomitant medications taken during double-blind therapy were: pancrelipase and ranitidine

- Subject ID: 0089/017

Age/Gender: 34/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history included hypertension for 1 year and asthma, smoked 10 cigarettes per day, and had allergies to animals, dust and pollen. She experienced symptoms of angioedema (swelling of lips and throat, nausea, dyspnea and egg size lumps around her throat) within the first hour of receiving the first dose of omapatrilat 20 mg. She was sent to the emergency unit, treated with diphenhydramine, methylprednisolone, acetaminophen and albuterol nebulizer treatments. After an hour and forty-five minutes she stated she felt better but an hour later she complained that her throat was still swelling and was given more diphenhydramine. Approximately 1 hour later she stated she felt fine although her neck and face were still swollen. Two and a half (2½) hours after going to the hospital she was released with the instructions to take the diphenhydramine every 6 - 8 hours and the albuterol inhaler every 3-4 hours. Three (3) hours later, after experiencing difficulty breathing and lip swelling, she was admitted to the hospital with a diagnosis of angioedema, bronchial asthma, pneumonia and acute right maxillary and right sphenoid sinusitis. Because of acute respiratory distress she was intubated and placed on a ventilator for 3 days. She was treated with intravenous methylprednisolone, diphenhydramine, famotidine, subcutaneous epinephrine, acetaminophen, albuterol, midazolam, prednisone, and percocet. The subject remained in the hospital for 10 days and it is not known exactly when the symptoms resolved but it is known that they were gone by the time she was discharged. Study drug was discontinued after the first dose and the randomization visit was the last. The relationship to double-blind therapy was considered to be probable.

Concomitant medications taken during double-blind therapy: None.

Subject 089/017, a 34 year old female with a history of hypertension for 1 year, and asthma, smoked 10 cigarettes per day, and had allergies to animals, dust and pollen. She experienced symptoms of angioedema (swelling of lips and throat, nausea, dyspnea and egg size lumps around her throat) within the first hour of receiving the first dose of omapatrilat 20 mg. She was sent to the emergency unit, treated with diphenhydramine, methylprednisolone, acetaminophen and albuterol nebulizer treatments. After an hour and forty-five minutes she stated she felt better but an hour later she complained that her throat was still swelling and was given more diphenhydramine. Approximately 1 hour later she stated she felt fine although her neck and face were still swollen. Two and a half hours (2½) after going to the hospital she was released with instructions to take the diphenhydramine every 6 - 8 hours and the albuterol inhaler every 3-4 hours. Three (3) hours later, after experiencing difficulty breathing and lip swelling, she was admitted to the hospital with a diagnosis of angioedema, bronchial asthma, pneumonia and acute right maxillary and right sphenoid sinusitis. Because of acute respiratory distress she was intubated and placed on a ventilator for 3 days. She was treated with intravenous methylprednisolone, diphenhydramine, famotidine, subcutaneous epinephrine, acetaminophen, albuterol, midazolam, prednisone and percocet. The subject remained in the hospital for 10 days and it is not known exactly when the symptoms resolved but it is known that they were gone by the time she was discharged. Study drug was discontinued after the first dose and the randomization visit was the last. The relationship to double-blind therapy was considered to be probable.

- Subject ID: 0034/040

Age/Gender: 37/F

Dose (mg): Lead-in

Duration (days): 1

Significant medical history included hypertension for 5 years and no known allergies, experienced presumptive angioedema with laryngeal fullness, conjunctivitis and tachycardia 1 hour after taking omapatrilat 20 mg. She was treated in the office with diphenhydramine. Study drug was discontinued at that time. The event resolved within 2 hours and the subject discontinued. The relationship to double-blind therapy was considered to be probable.

Concomitant medications taken during double-blind therapy were: fexofenadine hydrochloride.

- Subject ID: 0005/006

Age/Gender: 57/M

Dose (mg): Oma 80

Duration (days): 31

The subject's significant medical history included hypertension for 3 years and an allergy to penicillin which caused a rash. The subject's baseline ECG showed left ventricular hypertrophy and sinus bradycardia. After 31 days of double-blind therapy the subject experienced angioedema with symptoms of swollen face, lips and tongue. The study drug was discontinued and the event resolved by the next day. There was no treatment for the event. The Investigator considered the relationship to double-blind therapy to be possible.

Concomitant medications taken during double-blind therapy: None

- Subject ID: 0073/007

Age/Gender: 43/F

Dose (mg): Oma 80

Duration (days): 35

Significant medical history included hypertension for 23 years, had a history of watery eyes and rhinitis in the mornings, and smoked a ½ pack of cigarettes per day. After 35 days while on omapatrilat 80 mg, she experienced angioedema. She took her morning dose around 0930 and around 1800-1830 began to experience lip swelling. The swelling increased over the evening and at 0220 the next day she went to the emergency unit and was admitted to the hospital. While there she was treated with prednisone, intravenous methylprednisolone, intravenous and oral diphenhydramine and ranitidine. Study drug was not resumed. The event resolved the day after onset. The relationship to double-blind therapy was considered to be certain.

Concomitant medications taken during double-blind therapy were: ibuprofen, acetaminophen with codeine, triamcinolone cream, acetaminophen-pseudoephedrine hydrochloride-dextromethorphan-doxylamine succinate and an unknown throat spray.

Subject 073/007, a 43-year-old female with a history of hypertension for 23 years, had a history of watery eyes and rhinitis in the mornings and smoked a ½ pack of cigarettes per day. After 35 days while an omapatrilat 80 mg she experienced angioedema. She took her morning dose at 0930 and around 1800-1830 began to experience lip swelling. The swelling increased over the evening and at 0220 the next day she went to the emergency unit and was admitted to the hospital. While there she was treated with prednisone, intravenous methylprednisolone, intravenous and oral diphenhydramine and ranitidine. Study drug was not resumed. The event resolved the day after onset. The relationship to double-blind therapy was considered to be certain.

- Subject ID: 0090/021

Age/Gender: 62/F

Dose (mg): Oma 80

Duration (days): 65

The subject's significant medical history included hypertension for 16 years, coronary artery disease, cardiac arrhythmia's, cerebral vascular accident, shortness of breath, and an allergy to codeine with the reaction of itching. The subject also has a history of shortness of breath on and off. After 65 days of double-blind therapy, the subject experienced angioneurotic edema. After 66 days of double-blind therapy the study drug was discontinued. Treatment for the event included prednisone and diphenhydramine. The event resolved 3 days after onset and the day after the last dose of study medication. The Investigator considered the relationship to study drug to be possible. Prior to participating in this trial the subject was taking atenolol and hydrochlorothiazide.

Concomitant medications taken during the double-blind therapy were: methocarbamol, ranitidine, ibuprofen, nitroglycerin, aspirin and diphenhydramine.

- Subject ID: 0098/023

Age/Gender: 61/F

Dose (mg): Lis 10

Duration (days): 2

The subject's significant medical history included hypertension for 39 years, arthritis and occasional headaches. The subject's initial dose of double-blind therapy was at 0845 AM and during the night the subject awoke with swelling of the lower lip. The subject returned to the clinic in the morning for an evaluation and was diagnosed with angioedema. No other doses of study drug were taken after the initial dose. Treatment of the event included diphenhydramine and methylprednisolone dose pack. The event resolved 4 days after onset. The Investigator considered the relationship to double-blind therapy to be certain. Felodipine and hydrochlorothiazide were started after study drug was discontinued.

Concomitant medications taken during double-blind therapy: None

#### **Protocol CV137-038 (Double-Blind Therapy)**

- Subject ID: 0124/027

Age/Gender: 62/F

Dose (mg): Oma 20

Duration (days): 14

Subject's significant medical history included hypertension for 9 years. Subject experienced mild swelling of the left side of face and lip 14 days after start of omapatrilat double-blind therapy; vital signs were stable. Airway was not compromised. The Investigator diagnosed the event to be angioedema and considered the event to be probably related to study medication. No treatment was given for the event. The subject was discontinued from the study. Concomitant medications during double-blind therapy: none.

#### **Protocol CV137-042 (Double-Blind Therapy)**

- Subject ID: 0025/003

Age/Gender: 75/M

Dose (mg): Oma 20

Duration (days): 1

Subjects medical history includes hypertension of 5 years, diabetes mellitus type II, anemia, cataract surgery, gout, hot flashes, hydrocele repair and vagotomy-gastrojejunostomy. Subject is a 75 year old male who experienced angioedema approximately 5 ½ hours after receiving first dose of double-blind therapy. Subject presented with tongue, lip and nose swelling and was sent to the ER. Subject was treated with IV methylprednisolone sodium succinate, diphenhydramine HCL, and instructed to take methylprednisolone for 7 days. The duration of the angioedema was 3 days and investigator considered the relationship of this event to study drug to be certain. Subject was discontinued from the study. Concomitant medications: diphenhydramine, methylprednisolone.

- Subject ID: 0091/013

Age/Gender: 59/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history of hypertension of 6 years, cardiac arrhythmia's, coronary artery disease, arthritis knees, fingers and hands, exposed to tuberculosis 1980, Grade I Fundi, heart burn, numbness in feet and hands, slight impotence 1997 and nocturia. Subject is a 59 year old male who experienced angioedema one hour after the first dose of double-blind therapy and was discontinued from study. During the event the subject experienced swelling of right salivary gland, right lower gum pain and swelling of lips. Subject was treated with diphenhydramine HCL, solucortef, and prednisone. The event resolved within one day of onset. Investigator considered the relationship of this event to study drug to be certain.

Concomitant medication during double-blind therapy: none

- Subject ID: 0094/009

Age/Gender: 78/M

Dose (mg): Oma 20

Duration (days): 6

Significant medical history includes hypertension for 2 years, peripheral vascular disease, constipation, convulsive crisis (not diagnosed as epilepsy), osteoarthritis, prostate adenoma surgery, renal failure, sepsis for staphylococcus aureus. After 6 days of double-blind therapy, the subject was hospitalized for loss of consciousness. While under observation, patient developed glottis and larynx edema which obstructed the airway. Patient underwent a cricothyrotomy with a subsequent tracheotomy and was treated with methylprednisolone and amoxicillin/clavulanic acid. Double-blind therapy was discontinued. The glottis and larynx edema was ongoing at the time of discontinuation, but resolved subsequently. Investigator considered the event to be possibly related to double-blind therapy.

Concomitant medications received during double-blind therapy: acetylsalicylic acid.

- Subject ID: 0056/020

Age/Gender: 74/F

Dose (mg): Oma 40

Duration (days): 14

Significant medical history includes hypertension of 9 years, hypertriglyceridemia, viral pericarditis and anxiety. Subject is a 74 year old female who after fourteen days of beginning double-blind therapy presented with edema of the left side of face and numbness of the upper left lip which was diagnosed as angioedema. The angioedema resolved within 4 days and subject was discontinued from the study. No treatment was required. Investigator considered the relationship of this event to study drug to be probable. Concomitant medications taken during double-blind therapy: calcium, diazepam, ethinyl estradiol.

#### **Protocol CV137-045 (Double-Blind Therapy)**

- Subject ID: 0005/004

Age/Gender: 56/M

Dose (mg): Oma 20

Duration (days): 1

Significant history includes hypertension for four years, appendectomy, fatty benign tumor removed from right side of neck, hole in septum-etiology unknown, allergy to penicillin which results in swelling, tobacco use. Approximately 50 minutes after the subject received their initial dose of double-blind therapy the subject developed angioedema with mild distress, developing swelling of submandibular glands, throat tightness, and stuffy sensation in nose. Subject was discontinued from study drug and treated with diphenhydramine; the event resolved in 5 days.

Investigator considered the event to be certainly related to double-blind therapy.

Concomitant medications during double-blind therapy: acetaminophen, diphenhydramine, multivitamin w/minerals, nifedipine (Procardia), and prednisolone.

- Subject ID: 0028/004

Age/Gender: 41/F

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension for 5 years, dilation and curettage, intermittent headaches secondary to hypertension, left foot surgery repair. Subject experienced hypotension two hours after initial dose of double-blind therapy and angioedema 4 ½ hours after initial dose of double-blind therapy. Blood pressure values dropped as low as 90 mmHg systolic and 50 mmHg diastolic. After also developing angioedema, swollen upper lip, and tingling in the throat the subject was hospitalized. Treatment of the events included oxygen, prednisone, and IV fluids. The hypotension lasted only a few minutes; blood pressure at time of hospitalization was 150/90 mmHg. The angioedema (swollen lips) resolved after approximately seven days.

Investigator considered the events to be certainly related to double-blind therapy and study drug was discontinued.

Concomitant medications during double-blind therapy: prednisone, Procardia and cortisone.

- Subject ID: 0056/007

Age/Gender: 54/M

Dose (mg): Oma 20

Duration (days): 1

Significant history includes recently diagnosed hypertension, appendectomy, sebaceous cyst on the back, alcohol use, tobacco use. On day one of double-blind therapy the subject developed angioedema, complaining of throat tightness. Subject was discontinued from study drug and treated with diphenhydramine; the event resolved in one day.

Investigator considered the event to be certainly related to double-blind therapy and study drug was discontinued.

Concomitant medications during double-blind therapy: diphenhydramine.

#### **Protocol CV137-049 (Double-Blind Therapy)**

- Subject ID: 0012/002

Age/Gender: 53/M

Dose (mg): Oma 20

Duration (days): 1

Significant medical history includes hypertension of 29 years, hypertriglyceridemia, cardiomegaly, heart murmur, intermittent chest pain, intermittent swelling of feet and hands, gout, and use of alcohol and tobacco. Thirty minutes after initial dose of double-blind therapy, subject developed angioedema, erythema of the face, and tenderness to facial and throat areas that resulted in study drug discontinuation. After treatment with diphenhydramine and hydrocortisone, the erythema and angioedema were resolved the same day. Tenderness to facial and throat areas resolved within 10 days of onset. Investigator considered the relationship of these events to be certainly related to double-blind therapy.

Concomitant medications received during double-blind therapy: none.

- Subject ID: 0034/005

Age/Gender: 45/M

Dose (mg): Oma 80

Duration (days): 16

Significant medical history includes hypertension of 2 years, bronchitis, hives, stress headaches, seasonal allergic rhinitis, use of alcohol, tobacco, and marijuana. After 16 days on double-blind therapy, while receiving omapatrilat 80 mg, the subject developed angioedema and presented to the emergency room with symptoms of swollen lips, swollen uvula, and itching. He was treated with methylprednisolone, prednisone, and hydroxyzine, and released from the emergency room. The event resolved within 3 days of onset. Study drug was discontinued. The investigator considered the relationship to be probably related to double-blind therapy.

Medically important concomitant medications reported at onset of SAE: none.

Additional concomitant medications received during double-blind therapy: famotidine, diphenhydramine, and naproxen.

#### **Protocol CV137-054 (Double-Blind Therapy)**

- Subject ID: 0032/002

Age/Gender: 38/F

Dose (mg): Oma 80

Duration (days): 36

Significant medical history includes hypertension diagnosed 2 weeks prior to study enrollment, cholecystectomy, degenerative joint disease, sleep disturbance, and use of tobacco. After 36 days of double-blind therapy (subject had been titrated to Level III), subject developed angioedema of the upper lip with a symptom described as “buzzing of the upper lip”. Subject went to a hospital emergency room and was treated with methylprednisolone, diphenhydramine, and epinephrine. Subject was discharged from the emergency room with prednisone, cefadroxil and diphenhydramine. The event resolved completely within 3 days. Double-blind therapy was discontinued. Investigator considered the event possibly related to double-blind therapy.

Medically important concomitant medications reported at onset of SAE: none reported.

Additional concomitant medications received during double-blind therapy: amitriptyline, and nortriptylene.

Subject 032/002, a 38-year-old black female, experienced angioedema of the upper lip after 36 days of double-blind therapy with omapatrilat 20/40/80 mg regimen and 6 days after being titrated to Level III, 80 mg. The subject went to the emergency room and was treated with methylprednisone, diphenhydramine, and epinephrine. The subject was discharged from the emergency room and the event resolved within 3 days. The Investigator considered the event possibly related to double-blind therapy.

#### **Protocol CV137-009 (Ongoing Long-Term Hypertension Study Open Label)**

- Subject ID: 0017/002

Age/Gender: 50/F

Dose (mg): Oma 10

Duration (days): 981

Significant medical history includes hypertension of 9 years and hypercholesterolemia. This 66 year old female, completed 8 weeks of double-blind therapy and then entered the open-label phase. She started on omapatrilat 5 mg and remained on this dose for over a year. Then, after 981 days of open-label therapy, she was hospitalized due to tongue swelling which was diagnosed as angioedema. She had reported lip swelling for 2 weeks prior to the event. She was treated with diphenhydramine and fexofenadine and the event resolved after 3 days. She discontinued study medication. The investigator considered the event to be of certain relationship to study drug. (See Supplemental Table S.6.4 for Serious Adverse Event summary)

Concomitant medications: lovastatin, conjugated estrogens

#### **Protocol CV137-066 (Ongoing Hypertension Study Double-Blind Therapy)**

- Subject ID: 0051/002

Age/Gender: 43/F

Dose (mg): Blinded

Duration (days): 1

Significant medical history includes hypertension for 7 months, hypercholesterolemia, G.E.R.D., back and neck pain, arthritis, migraines, depression and allergies to decaffeinated tea (with the symptom of facial swelling) and ranitidine (with the symptom of vomiting). One and a half hours after the first dose of double-blind therapy, she experienced nausea, vomiting, facial redness, tachycardia, throat, face and tongue swelling. This was also termed very severe angioedema. Study drug was discontinued the same day. Treatment for these events included methylprednisolone and loratidine. The events resolved the next day. The investigator considered the relationship to double-blind study drug to be certain. (See Supplemental Table S.6.4 for Serious Adverse Event Summary)

Concomitant medications reported at the onset of SAE: omeprazole, fluoxetine, medroxyprogesterone, hydrocodone

Additionally, other concomitant medications received during double-blind therapy: none

- Subject ID: 0129/003

Age/Gender: 57/M

Dose (mg): Blinded

Duration (days): 26

Significant medical history includes hypertension for 3 years, impotence while on antihypertensive medication and occasional tobacco use. After 26 days of study medication, the subject experienced an episode of angioneurotic edema involving right

cheek and lips but not causing respiratory obstruction, which began 2 hours prior to taking his dose of study medication. Study drug was discontinued. Treatment for this event included fexofenadine. The event resolved 2 days after onset. The investigator considered the relationship to double-blind study drug to be possible. (See Supplemental Table S.6.4 for Serious Adverse Event Summary)

Concomitant medications: none

#### **Protocol CV137-012 (Heart Failure Study Double-Blind Therapy)**

- Subject ID: 0027/006

Age/Gender: 51/M

Dose (mg): Oma 40

Treatment Duration (days): 1

Patient's significant history includes: myocardial infarction, percutaneous transluminal coronary angioplasty, unstable angina, hypercholesterolemia

This subject experienced angioedema 45 minutes after the first dose of study medication was administered. At 0955 hours the patient was dosed. At 1030, the patient began to complain of nausea, throat discomfort and experienced diaphoresis. The throat swelling increased swiftly with the patient becoming unable to swallow and control oral secretions. He also experienced mild difficulty in speaking. With the increase of symptoms, the patient was given 50 mg of intravenous benadryl (diphenhydramine hydrochloride) and monitored until he became stable. The event resolved and the patient was withdrawn from the study. The event was probably/likely related to the study drug.

Concomitant medications: acetylsalicylic acid, atenolol, clarithromycin, fluvastatin, furosemide, metolazone, nabumetone, nitroglycerin topical, potassium, quinine.

#### **Protocol CV137-013 (Heart Failure Study Double-Blind Therapy)**

- Subject ID: 0040/005

Age/Gender: 71/M

Dose (mg): Oma 10

Duration (days): 20

Patient's significant history includes angina, MI, carotid stenosis bilateral diagnosed 1996, GI bleed 4/96, hypertension 4/96, allergy to iodine, mild renal insufficiency (creatinine stable), psoriasis (elbows & knees), questionable TIA's 3/92, remote pulmonary edema 4/96, COPD.

The subject had been receiving captopril prior to the study and during period A. The subject developed angioedema (lip swelling and urticaria on forearms) after 20 days of double-blind therapy. This persisted for 5 days at which time the subject was discontinued from the study. The symptoms resolved without treatment. The investigator stated that this adverse event was probably related to study drug administration.

Concomitant medications: acetylsalicylic acid, amiodarone, digoxin, doxazosin, furosemide, hydralazine, iron, isosorbide, nitroglycerin, potassium, tocopherol.

**Table 33A. Incidence of Angioedema in Heart Failure Studies, by Treatment Group and Race**

Race	Omapatrilat		Lisinopril	
	N	n (%)	N	n (%)
Black	55	0 (0.0)	34	1 (3.0)
White	532	1 (0.2)	422	0 (0.0)
Other	49	0 (0.0)	32	0 (0.0)
<b>Total</b>	<b>636</b>	<b>1 (0.2)</b>	<b>488</b>	<b>1 (0.2)</b>

[Sponsor's analysis, adapted from NDA 21-188, Amendment dated March 6, 2000. Includes Protocol CV137-013, -018 (Trial naïve subjects only), & -028.]