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PHARMACEUTICAL RESEARCH INSTITUTE

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Briefing Book  
For OMAPATRILAT Tablets  
NDA 21-188**

**Cardiovascular and Renal Drugs FDA Advisory Committee Meeting  
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**AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACTION**

Bristol-Myers Squibb Pharmaceutical Research Institute  
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## **1 BACKGROUND**

In December 1999, the Sponsor filed a New Drug Application (NDA) for omapatrilat for the treatment of hypertension.

In April 2000, the Sponsor voluntarily withdrew its NDA for omapatrilat in response to questions raised by the FDA regarding the comparative incidence and severity of angioedema.

In August 2000, the Sponsor initiated the OCTAVE (Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril) hypertension study. OCTAVE was designed to compare the efficacy and safety of omapatrilat and enalapril in a broad range of approximately 25,000 uncontrolled hypertensive patients, including untreated patients and patients already being treated with antihypertensive therapy. The OCTAVE study protocol closely resembled a clinical practice setting, enrolling untreated as well as treated but uncontrolled patients. To fully assess the potential benefits of omapatrilat, adjunctive therapy was added to patients uncontrolled by elective titration of monotherapy. The incidence and severity of angioedema were carefully assessed by active collection of potential angioedema events for adjudication by a blinded expert committee.

On December 14, 2001, based upon review and analysis of the results of OCTAVE, the Sponsor resubmitted the NDA for omapatrilat for the treatment of hypertension.

Since that time, as the result of numerous additional statistical analyses of OCTAVE data and extensive consultation with medical and regulatory experts, the Sponsor has identified the types of hypertension patients that would be expected to obtain the highest relative benefit from treatment with omapatrilat. This patient population would have hypertension that is difficult to control with currently available therapies and would be at a higher than average risk of having a cardiovascular event.

Omapatrilat is not marketed in any country. Aside from the US NDA, there are no active marketing authorization applications for omapatrilat pending.

## **2 INTRODUCTION**

Effective antihypertensive therapy can prevent death and disability, but fewer than half of those treated for hypertension reach recommended blood pressure targets. Lack of awareness of hypertension, limited access to care, and insufficiently aggressive treatment all contribute to failure to reach blood pressure target. A growing body of evidence suggests that existing medications, even used optimally, are inadequate to control blood pressure in those most at risk of cardiovascular events – those with marked elevations in systolic blood pressure, those with diabetes, and those with established end-organ damage or cardiovascular disease. More effective antihypertensive agents are needed for these difficult to control patients.

This briefing book summarizes data in support of the use of omapatrilat for treatment of hypertension in difficult to control patients. Omapatrilat is a vasopeptidase inhibitor – a new class of drugs that simultaneously inhibit angiotensin converting enzyme (ACE) and neutral endopeptidase (NEP). Omapatrilat is the first agent in this class to seek marketing authorization.

Through an extensive development program, omapatrilat has been shown to be more effective than many commonly used antihypertensive agents, including enalapril, lisinopril, amlodipine, and losartan. By allowing more patients to reach blood pressure targets, omapatrilat offers the potential for important benefits. Omapatrilat has also been shown to cause angioedema more frequently than enalapril, and to cause life-threatening angioedema at a rate of approximately 2-3 per 10,000 treated. This risk must also be carefully evaluated in selecting the most appropriate hypertensive population to treat.

Consideration of benefit and risk suggests that omapatrilat may offer significant benefit in patients whose hypertension is difficult to control with existing medications. In these patients, omapatrilat offers the potential for a benefit, through blood pressure reduction and prevention of cardiovascular events, that is not otherwise available. Given the potential risk of angioedema, omapatrilat should not generally be used in patients who can readily achieve comparable blood pressure reduction using existing drugs.

The evaluation of risk and benefit further suggests that in patients with difficult to control hypertension omapatrilat may prevent a substantial number of cardiovascular events.

These patients typically have characteristics that increase their risk of cardiovascular events, such as severe hypertension, older age, diabetes, target organ damage, or established cardiovascular disease. With increasing cardiovascular risk, the absolute number of cardiovascular events potentially preventable by further blood pressure reduction also increases. It is estimated that treatment with omapatrilat in high CV risk patients has the potential to prevent at least 20-30 more major CV events per year per 10,000 treated than enalapril or comparable existing agents. These benefits strongly outweigh the risk of angioedema. The relationship between potential benefit and risk is therefore most favorable in these patients with difficult to control hypertension.

Organization of this Briefing Book: The FDA has indicated that there are no apparent barriers to approval of omapatrilat related to the chemistry, pharmacology, toxicology, or biopharmaceutics of the drug. This briefing document will therefore focus on the following issues:

- Unmet medical need in hypertension
- Antihypertensive efficacy of omapatrilat compared to existing antihypertensives, at the maximum recommended doses of each;
- Antihypertensive efficacy of omapatrilat compared to enalapril, with both drugs titrated electively and supplemented with other antihypertensives as necessary;
- Effectiveness of omapatrilat in difficult to control populations;
- Safety of omapatrilat, including angioedema;
- Benefit and risk of treatment with omapatrilat relative to existing therapy.

The presentation is organized as follows:

1) Unmet Medical Need in Hypertension

Section 2 summarizes data from clinical trials and hypertension referral clinics, indicating that adequate control of blood pressure is difficult to achieve in many patients with diabetes, target organ damage, or cardiovascular disease.

2) Pharmacology and Toxicology

The pharmacology and toxicology of omapatrilat are outlined in Section 3. A detailed summary of these topics is provided in Appendix 1.

### 3) Overview of the Clinical Development Program

Section 4 summarizes the clinical development program, which included almost 35,000 hypertensive subjects, of whom approximately 18,700 were exposed to omapatrilat. The study population was demographically diverse and includes large numbers of patients with relevant comorbid conditions. This includes many patients with relevant comorbid conditions that are associated with elevated CV risk.

### 4) Clinical Efficacy

Section 5 includes data that show omapatrilat is an efficacious antihypertensive. Used at maximum recommended doses, omapatrilat reduces blood pressure significantly more than lisinopril, amlodipine, or losartan. Used under conditions similar to those of clinical practice (titrated electively, with additional antihypertensives as needed), a regimen based on omapatrilat provides greater mean blood pressure reduction than one based on enalapril. The efficacy advantage of omapatrilat is preserved in difficult to control patients (those with phenotypic characteristics associated with resistance to antihypertensive treatment and those who have not reached target on other antihypertensives).

### 5) Clinical Safety and Risk of Angioedema

Section 6 includes data on the safety of omapatrilat, which has been clearly defined through an unusually extensive clinical development program, involving almost 35,000 hypertensive subjects of whom approximately 18,700 were exposed to omapatrilat. There are no significant differences in safety or tolerability between omapatrilat and enalapril, aside from the risk of angioedema. Omapatrilat produces angioedema roughly three times as frequently as enalapril. Life-threatening angioedema occurred in approximately 2-3 patients per 10,000 treated, is highly symptomatic, and appears to be manageable with appropriate medical attention. The clinical manifestations and risk factors for angioedema will be discussed in this section.

### 6) Consideration of Risk and Benefit

Section 7 presents the benefit and risk of omapatrilat therapy. The relationship between blood pressure reduction and cardiovascular event rate reduction with omapatrilat is assessed. Based on well-described relationships between blood pressure and

cardiovascular events, treatment with omapatrilat in high cardiovascular (CV) risk patients has the potential to prevent at least 20-30 more major cardiovascular events per year per 10,000 treated than enalapril or comparable existing agents.

Cardiovascular event data from OCTAVE and OVERTURE, a morbidity and mortality trial in heart failure, are summarized.

Lastly, consideration is given to strategies to maximize the benefit and minimize the risk of omapatrilat treatment. Benefit can be maximized by targeted use in patients with hypertension that is difficult to control. Risk of omapatrilat treatment can be minimized through an effective Risk Management Program (see Appendix 3). The sponsor is working with the FDA to develop such a program prior to product launch.

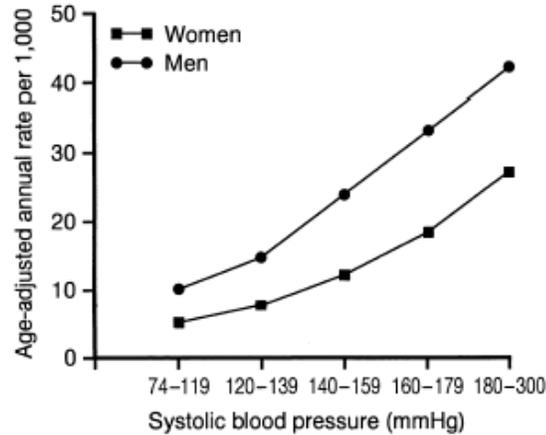
## **2.1 Hypertension Epidemiology and Burden of Illness**

Hypertension affects 600 million people worldwide.<sup>1</sup> It is estimated that 43 million adults in the United States (24% of the adult population) are affected.<sup>2</sup> Because the prevalence, incidence, and complications of hypertension increase with advancing age, the impact of hypertension is likely to increase as the US population ages.<sup>3,4</sup>

Hypertension is a major risk factor for coronary heart disease (CHD), stroke, heart failure and renal disease. It is estimated that 35% of atherosclerotic CV events may be attributable to hypertension.<sup>5</sup> CHD and stroke are the first and third leading causes of death in the US, collectively accounting for 700,000 deaths in 1999.<sup>6</sup>

Data from numerous large prospective cohort studies and clinical trials provide clear evidence of the continuous, graded relationship between increased blood pressure and increased CV risk. Within the range of blood pressures studied, there is no evidence of a blood pressure threshold below which this relationship does not exist.<sup>7</sup> Results from 38-year follow-up of persons initially free from CV disease in the Framingham Heart Study are depicted in Figure 2.1, showing correlation of systolic blood pressure and risk of subsequent CV events. An analogous relationship occurs for diastolic blood pressure.<sup>8</sup>

**Figure 2.1: Risk of CV Events by Systolic Blood Pressure Observed in 38-year Follow-Up from the Framingham Heart Study**



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Source: Kannel *et al*, Am J Cardiol 2000<sup>8</sup>

The benefit of pharmacologic reduction in blood pressure has been shown in a large number of clinical trials using a variety of drug classes and agents. The magnitude of the reduction in cardiovascular outcomes that can be achieved with pharmacologic reduction in blood pressure is largely consistent with what would be predicted from observational data. In a meta-analysis of older trials using primarily diuretic-based regimens, a reduction of 5-6 mmHg in diastolic blood pressure was shown to result in a reduction of 42% in stroke and 14% in coronary heart disease.<sup>9</sup>

A more recent meta-analysis of contemporary trials revealed 30-39% reduction in stroke and 21-28% reduction in major cardiovascular events relative to placebo with ACE inhibitors and calcium channel blockers<sup>10</sup>. In trials comparing more intensive and less intensive blood pressure lowering strategies, an incremental reduction in systolic blood pressure of 3 mmHg was associated with a 15% reduction in major cardiovascular events.

In a meta-regression of 27 randomized controlled trials of patients with hypertension and follow-up of 2 years or longer, Staessen *et al* modeled the predicted benefit associated with observed differences in systolic blood pressure.<sup>11</sup> This analysis suggested that small

differences in achieved systolic blood pressure lowering are associated with significant and clinically meaningful reductions in the risk of CV death and CV events.

Hypertensive patients with comorbidities including diabetes and history of CV disease are at heightened CV risk. Given the increased baseline absolute risk, modest blood pressure reduction translates into large clinical benefits.

## **2.2 Blood Pressure Control**

Despite knowledge of the risks of hypertension and the benefits of antihypertensive therapy, blood pressure control remains unsatisfactory. Based on Phase 2 data from NHANES III (National Health and Nutrition Examination Survey) (1991-1994), only 27% of adults aged 18-74 with hypertension achieved the recommended target blood pressure of < 140 mmHg systolic and < 90 mmHg diastolic.<sup>12</sup> Only 45% of treated hypertensive patients reached the same blood pressure level.<sup>13</sup>

NHANES III also indicates that blood pressure control is particularly difficult to achieve in those with increased risk of cardiovascular events, including older persons and those with diabetes. With increasing age, the gap between observed systolic blood pressures and systolic blood pressure target widens.<sup>13</sup> Only 12% of patients with diabetes and hypertension reach the blood pressure target of 130/85 mmHg established by the Joint National Commission (JNC)-VI.<sup>14</sup>

While lack of awareness of hypertension, limited access to care, and insufficient aggressiveness of treatment all contribute to failure to reach blood pressure target, a growing body of evidence suggests that existing medications, even used optimally, are inadequate to control blood pressure in those most at risk of cardiovascular events - those with predominant elevations in systolic blood pressure, those with diabetes, and those with established end-organ damage or cardiovascular disease.

In the Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), patients over the age of 55 with at least one CV risk factor aside from hypertension were randomized to one of four different blinded antihypertensive medications.<sup>15</sup> Patients typically returned at monthly intervals; for those not reaching the target blood pressure of < 140/90, open-label antihypertensive agents were provided.

Despite these efforts, only 53% of patients were controlled to < 140/90 mmHg at 1 year.<sup>16</sup> Inability to control patients to JNC VI goal was largely the result of uncontrolled systolic blood pressure; only 55.2% of patients had systolic blood pressure < 140 mmHg while 86.4% had diastolic blood pressure < 90 mmHg (Table 2.2).

**Table 2.2: Blood Pressure Control at Baseline and 1-Year from the ALLHAT Trial**

blood pressure, mmHg	Systolic		Diastolic	Systolic and Diastolic	
	< 140	< 150	< 90	< 140/90	< 150/90
Screening	31.6%	58.2%	69.4%	28.1%	46.8%
All, 12 mo	55.2%	76.5%	86.4%	53.0%	71.1%

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Source: Cushman *et al*, Am J Hypertension 1998<sup>16</sup>

The challenge in controlling systolic blood pressure as compared with diastolic blood pressure was similarly observed in the Controlled Onset Verapamil Investigation of Cardiovascular Endpoints (CONVINCE) trial.<sup>17,18</sup> Hypertensive patients over the age of 55 with at least one CV risk factor aside from hypertension were randomized to either: 1) a physician-directed choice of hydrochlorothiazide or atenolol; or 2) extended release verapamil. After randomization, patients were force-titrated to achieve systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg. Open-label adjunctive medications were allowed to achieve target. At thirty months, control rates were 68% and 91% for systolic blood pressure and diastolic blood pressure, respectively. As with ALLHAT, a significant percentage of patients were difficult to bring under control in spite of the ability to use multiple medications in a setting where physicians were instructed to lower blood pressure to pre-specified targets. Systolic blood pressure, in particular, was difficult to control.

In the Irbesartan Diabetic Nephropathy Trial (IDNT), hypertensive patients with type 2 diabetes and nephropathy were randomized to treatment with irbesartan, amlodipine, or placebo.<sup>19</sup> The protocol instructed physicians to add adjunctive antihypertensive medications in order to reach target blood pressure levels of 135/85 mmHg or to decrease systolic blood pressure at least 10 mmHg in patients with systolic blood pressure > 145 mmHg at screening. In addition, a Clinical Management Committee was chartered

to oversee individual blood pressure measurements from each patient in the trial and to make management recommendations to the Investigator. Patients received an average of 3 open-label antihypertensive medications in addition to double-blind irbesartan or amlodipine. The mean systolic BP at visits after baseline was 140-141 mmHg in these groups. These blood pressure values were 5-6 mmHg above the pre-specified treatment target, and at least 10 mmHg above the current JNC-VI target of < 130 mmHg for diabetic patients. These findings are consistent with the notion that pathophysiologic factors lead to additional difficulties in achieving blood pressure control in diabetic patients with hypertension even under stringent treatment conditions with multiple existing agents.<sup>20</sup>

In the Losartan Intervention for Endpoints (LIFE) trial, hypertensive patients with left ventricular hypertrophy were randomized to receive losartan or atenolol.<sup>21</sup> Mean baseline blood pressure was 174.4/97.8 mmHg, resulting in a large gap to reach goal in this difficult to control population with target organ damage. Despite the ability to add open-label medications to achieve a target blood pressure of < 140/90 mmHg, only 25.8% of patients had systolic blood pressure < 140 mmHg at 1-year.

Data from hypertension specialty clinics suggest that even expert clinicians may be unable to control blood pressure in more than 50 to 65% of referral patients. Singer *et al* commented on control rates for patients with refractory hypertension referred to the Rush University Hypertension Service.<sup>22</sup> A target blood pressure of < 140/90 mmHg was attained in only 65% of patients. In addition, in order to achieve this level of control, multiple agents were used in approximately 71% of patients. Graves *et al* described hypertension control rates in patients managed in the Mayo Clinic Division of Hypertension.<sup>23</sup> Only 47% of patients aged 60 to 79 years were controlled to blood pressure < 140/90 mmHg. Control rates reported in a hypertension clinic in Milan, Italy were 50%, with 67% of patients on multiple medications.<sup>24</sup> Blood pressure control rates were 51.9%, 53.3%, 52.0%, and 31.8% among patients receiving 1, 2, 3, or 4 or more antihypertensive medications, respectively.

Recent data suggest that the ability to achieve blood pressure control by adding antihypertensive medications decreases in older patients and in those already on more than 2 medications. Bailey *et al* showed that the conditional probability of achieving blood pressure control with each additional antihypertensive agent added decreased for

patients on 3 or more medications, based on results from the Mayo Clinic Hypertension Continuity Clinic.<sup>25</sup> In addition, the efficacy of adding additional medications was 50% greater in patients aged < 60 years as compared with those aged ≥ 60 years.

These findings confirm the existence of a population of hypertensive patients that is difficult to control, even with optimal therapy. Such patients typically have more marked elevations in systolic blood pressure and tend to be older. They often have diabetes, target organ damage, or established cardiovascular disease.

Difficult to control patients are widely perceived to have a less satisfactory response to antihypertensive therapy than other hypertensive patients, but difficult to control patients have other features as well. The gap between pre-treatment blood pressure and goal blood pressure in these individuals may be relatively great. Their treatment options may be limited by comorbid conditions which create contraindications or severe intolerance to particular classes of antihypertensive agents. The same comorbid conditions often require therapies which further complicate their medical management and aggravate the difficulties inherent in management of a chronic, asymptomatic condition such as hypertension with multi-drug regimens. Lastly, these patients are at greater than average risk of cardiovascular (CV) events and may achieve a significant clinical benefit from more effective antihypertensive therapy.

### **2.3 Importance of Systolic Blood Pressure**

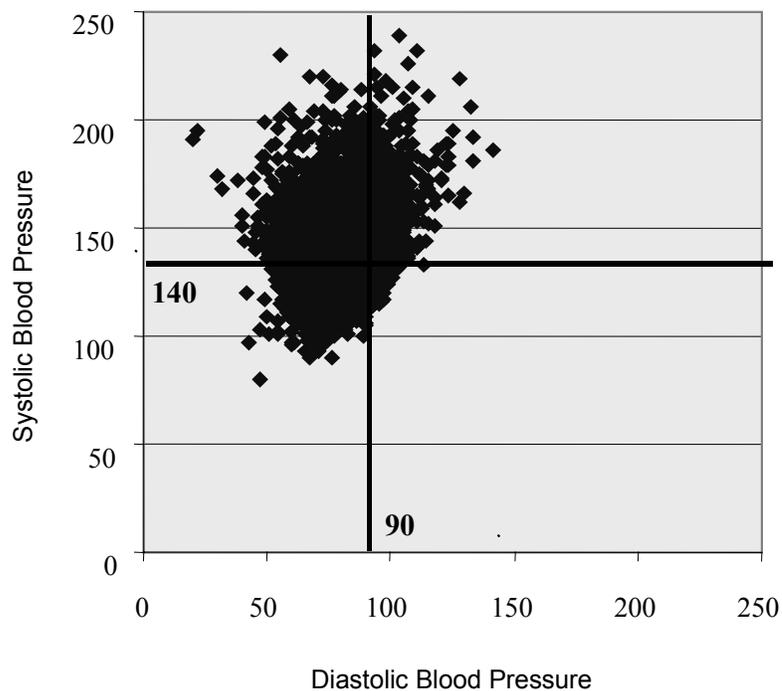
Systolic blood pressure is a better predictor of subsequent CV events than diastolic blood pressure.<sup>26</sup> Data from the Framingham study, published in the late 1960s and 1970s, suggested that systolic blood pressure has a greater impact than diastolic blood pressure on CV events.<sup>27</sup> Data from the Multiple Risk Factor Intervention Trial (MRFIT), based on a subset of 347,978 men aged 35 to 57 years, showed systolic blood pressure to be more strongly related than diastolic blood pressure to the risk of CHD death and stroke.<sup>28</sup> The greater importance of systolic blood pressure has been further demonstrated in other studies conducted in diverse settings.<sup>29,30</sup>

The benefits of lowering systolic blood pressure in reducing CV events have been confirmed in a number of randomized, controlled trials in patients with isolated systolic hypertension.<sup>31,32,33</sup> The importance of controlling systolic blood pressure was noted in a

Clinical Advisory Statement from the Coordinating Committee of the National High Blood Pressure Education Program.<sup>34</sup> The Committee’s first recommendation was that “systolic blood pressure should become the principal clinical end point for the detection, evaluation, and treatment of hypertension, especially in middle-aged and older Americans.”

Moreover, failure to reach recommended blood pressure target results largely from its systolic component. Among hypertensive adult patients in NHANES III, 73% reached the diastolic goal of < 90 mmHg, but only 34% reached the systolic goal of < 140 mmHg (Figure 2.3).<sup>35</sup>

**Figure 2.3: Systolic Versus Diastolic Blood Pressure for Hypertensive Adults in NHANES III**



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Source: Whyte JL, *et al*, J Clin Hypertension 2001<sup>35</sup>

Data will be presented to show that omapatrilat produces greater reductions in both systolic and diastolic blood pressure than enalapril, lisinopril, amlodipine, or losartan.

Because the need for better control of systolic blood pressure is particularly great, presentations of antihypertensive efficacy in the briefing book will emphasize effects on systolic blood pressure.

### **3 PHARMACOLOGY AND TOXICOLOGY**

Omapatrilat is a potent, orally active, long-acting, selective competitive inhibitor of both neutral endopeptidase (NEP) (enkephalinase, neprilysin, EC 3.4.24.11) and angiotensin converting enzyme (ACE) (EC 3.4.15.1). Omapatrilat has been shown to selectively inhibit NEP and ACE *in vivo*, thereby decreasing the formation of the vasoconstrictor peptide angiotensin II and slowing the degradation of the vasodilatory peptides ANP, adrenomedullin, and bradykinin. Beneficial effects of combined NEP and ACE inhibition have been demonstrated in a variety of preclinical models of hypertension, heart failure and myocardial ischemia.

Omapatrilat reduces blood pressure dose-dependently in normotensive man, and in low and high-renin states of hypertension, without affecting heart rate. Omapatrilat is a potent ACE inhibitor, with doses of 10-125 mg once daily producing > 80% inhibition of plasma ACE activity. The extent of NEP inhibition appears to be modest with the 10 mg dose, and is significantly higher at doses of 25-125 mg.

Omapatrilat is generally well tolerated in animals at doses yielding drug exposures several-fold greater than humans administered omapatrilat at 80 mg/day. Omapatrilat has no mutagenic or clastogenic potential and does not induce drug-related neoplasms when given at maximum tolerated doses in bioassay studies.

An extensive clinical pharmacology program was undertaken consisting of ~700 subjects in single and multiple ascending-dose tolerance studies, radio-labeled drug disposition studies, food effect, formulation and pharmacokinetic studies including 4 special-population studies and 8 drug-drug interaction studies.

Omapatrilat is an orally active agent that does not require biotransformation for activity. Omapatrilat does not demonstrate diuretic, natriuretic or kaliuretic effects in healthy subjects, hypertensive patients with preserved renal function, and/or patients with renal impairment.

The pharmacokinetics and pharmacodynamics of omapatrilat, following doses of omapatrilat given alone or along with other drugs or food to a diverse population of healthy subjects and patients, support a once daily regimen, without adjustments in dose.

No significant drug interactions have been found in specific clinical studies with warfarin, digoxin, atenolol, hydrochlorothiazide, and furosemide.

In summary, the efficacy and safety evaluations in the Pharmacology and Toxicology studies of omapatrilat adequately support the omapatrilat hypertension clinical program. Please refer to Appendix 1 for a more detailed review of pharmacology and toxicology.

Several pharmacodynamic studies have been completed in patients with hypertension and related cardiovascular disorders (see Appendix 2).

Study CV137-071 was designed to assess the anti-anginal and anti-ischemic efficacy of omapatrilat in patients with coronary artery disease and chronic stable angina pectoris. Following a single-blind placebo lead-in period, 348 patients were randomized to receive either omapatrilat or placebo for four weeks. Concomitant beta-blocker therapy was allowed. At 2 hours post dose (estimated time at peak plasma activity) at Week 4, the omapatrilat group had a larger mean increase from baseline in maximal treadmill exercise time than did the placebo group (76.6 seconds vs. 28.7 seconds,  $p < 0.001$ ).

Study CV137-038 was a 52 week double-blind study comparing the effects of omapatrilat and losartan on left ventricular mass index (LVMI) in hypertensive patients with left ventricular hypertrophy. At Week 24 (the primary timepoint), LVMI was significantly reduced in omapatrilat-treated patients ( $-7.2 \text{ g/m}^2$ ,  $p < 0.001$ ) and losartan-treated patients ( $-3.4 \text{ g/m}^2$ ,  $P = 0.04$ ), compared with baseline, with a trend favoring omapatrilat-treated patients ( $P = 0.11$ ). Greater reductions in systolic and diastolic blood pressure were observed with omapatrilat than losartan.

Study CV137-046 was designed to evaluate the antiproteinuric effects of omapatrilat and amlodipine in type 2 diabetics with hypertension, preserved renal function, and microalbuminuria or overt nephropathy. Three hundred nineteen (319) subjects were randomized to treatment with omapatrilat (20 mg starting dose, with elective titration up to 80 mg) or amlodipine (2.5 mg starting dose, with elective titration up to 10 mg) for 12 weeks. Open-label adjunctive antihypertensive therapy with alpha blockers, beta blockers, or diuretics was permitted for subjects receiving the maximum tolerated dose of double-blind study medication. At Week 12, omapatrilat-treated subjects had a greater reduction in 24 hour urine albumin excretion rate (the primary outcome measure)

compared to amlodipine-treated subjects. The reduction was 28.7% for omapatrilat versus 4.5% for amlodipine ( $p < 0.001$ ).

## **4 CLINICAL DEVELOPMENT PROGRAM FOR OMAPATRILAT IN HYPERTENSION**

### **4.1 Clinical Development Program in Hypertension: Overall Description**

The clinical development program for omapatrilat in hypertension includes data reported from ~35,000 hypertensive patients, of whom ~19,000 were exposed to omapatrilat, ~15,000 were exposed to active comparator agents, and ~1000 were exposed to placebo.

A total of 23 randomized, controlled hypertension studies, one uncontrolled study, and 5 long-term extension studies involving 34,780 patients worldwide, were conducted in support of the omapatrilat hypertension application. The controlled hypertension studies included up to 52 weeks of dosing, while the uncontrolled experience with omapatrilat exceeded 4 years for some patients in open-label studies.

The majority of patients were treated in one large controlled study of ~25,000 patients, OCTAVE. Accordingly, special emphasis has been placed on OCTAVE in this briefing book, as it represents the most comprehensive evaluation of omapatrilat. OCTAVE (CV137-120) was a ~25,000 patient, 24-week, double-blind, randomized, active controlled (versus enalapril) trial that assessed omapatrilat efficacy and safety using clinically relevant treatment strategies (i.e., omapatrilat as initial therapy, replacement therapy, and add-on therapy). Key objectives included assessment of efficacy and safety in a variety of sub-groups, including patients with subtypes of hypertension (isolated systolic hypertension or severe hypertension) or comorbid conditions (diabetes, atherosclerotic disease, or renal disease). Among the ~13,000 patients exposed to omapatrilat in this study, 1300 were African-American, ~3600 were elderly (age  $\geq$  65 years), and ~1000 were very elderly (age  $\geq$  75 years). The incidence and severity of angioedema were carefully assessed by active collection of potential angioedema events for adjudication by a blinded expert committee. The OCTAVE study design and procedures are described in detail in Section 5.2.1 and 6.4.1.2 for efficacy and safety, respectively.

## 4.2 Exposure

Exposure to omapatrilat in hypertension trials is presented in Table 4.2 (by dose and duration) and Supplemental Table S.4.2 (by age and duration).

Overall, 12,995 patients received omapatrilat for over 3 months, 2,186 patients received omapatrilat for over 6 months, and 1,478 patients received omapatrilat for over one year. A total of 5,053 omapatrilat-exposed patients were  $\geq 65$  years of age; 646 of these patients received omapatrilat for  $> 6$  months and 488 for  $> 1$  year. A total of 1,350 omapatrilat-exposed patients were  $\geq 75$  years of age; 129 of these patients received omapatrilat for  $> 6$  months. A total of 6,922 patients were exposed to omapatrilat 80 mg.

**Table 4.2: Exposure to Omapatrilat in Hypertension Studies, by Dose and Duration**

	OCTAVE N = 12,609	All Hypertension Studies Including OCTAVE N = 18,723
All Doses	12609	18723
for > 90 days	10755	12995
for > 180 days	290	2186
for > 365 days	0	1478
10 mg	12609	15058
for > 90 days	0	708
for > 180 days	0	543
for > 365 days	0	380
20 mg	11899	16655
for > 90 days	3813	4594
for > 180 days	17	576
for > 365 days	0	342
40 mg	7596	11317
for > 90 days	3339	3873
for > 180 days	0	331
for > 365 days	0	198
80 mg	3769	6922
for > 90 days	3310	4133
for > 180 days	0	625
for > 365 days	0	363

### 4.3 Demographics

Patients exposed to omapatrilat were demographically diverse, as summarized in Table 4.3. Substantial numbers of patients had demographic or clinical characteristics often associated with difficult to control hypertension, including older age and diabetes.

**Table 4.3: Demographic Characteristics of Patients Exposed to Omapatrilat in Hypertension Studies**

	Hypertension Studies other than OCTAVE	OCTAVE <sup>a</sup>
	N = 6,114 n (%)	N = 12,609 n (%)
Age, years		
Mean (SD)	55.9 (11.3)	56.9 (12.5)
Range	18-90	18-95
< 65	4630 (75.7)	9040 (71.7)
65-74	1192 (19.5)	2511 (19.9)
≥ 75	292 (4.8)	1058 (8.4)
Gender		
Male	3542 (57.9)	6570 (52.1)
Female	2572 (42.1)	6039 (47.9)
Race		
White	4664 (76.3)	11101 (88.0)
African-American	956 (15.6)	1300 (10.3)
Asian/Pacific Islander	78 (1.3)	184 (1.5)
Hispanic	360 (5.9)	-- <sup>b</sup>
Other	56 (0.9)	24 (0.2)
Diabetes <sup>c</sup>		
Yes	643 (10.5)	1712 (13.6)
No	5471 (89.5)	10897 (86.4)

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- <sup>a</sup> Percentages may not add up to 100% in subgroups due to incomplete collection of demographic data.
- <sup>b</sup> In the OCTAVE study, investigators were asked to identify race using one of four categories (white, African-American, Asian/Pacific Islander, or other). Therefore patients are counted in these 4 race categories. Investigators were asked separately whether a patient was Hispanic; 541 patients (4.3%), treated with omapatrilat, were noted as being Hispanic.
- <sup>c</sup> For hypertension studies other than OCTAVE, diabetes is limited to type 2.

Those exposed to omapatrilat in OCTAVE also included substantial numbers with a history of cardiovascular disease, including chronic stable angina (599 patients), myocardial infarction (371 patients), and stroke/TIA (343 patients).

## **5 CLINICAL EFFICACY**

Efficacy results of controlled clinical hypertension studies with omapatrilat are discussed in Section 5. The order of presentation is as follows:

- 1) Fixed Dose Comparisons (Dose-Ranging Studies and Top-Dose, Active-Comparator Studies) are presented to illustrate dose-response and peak-antihypertensive efficacy relative to maximum doses of widely used antihypertensive agents.
- 2) Elective Titration Study (OCTAVE) is presented to illustrate efficacy in settings that resemble clinical practice.
- 3) Efficacy in Difficult to Control Patients (OCTAVE and other studies) is presented to inform decisions about use of omapatrilat in these patients.

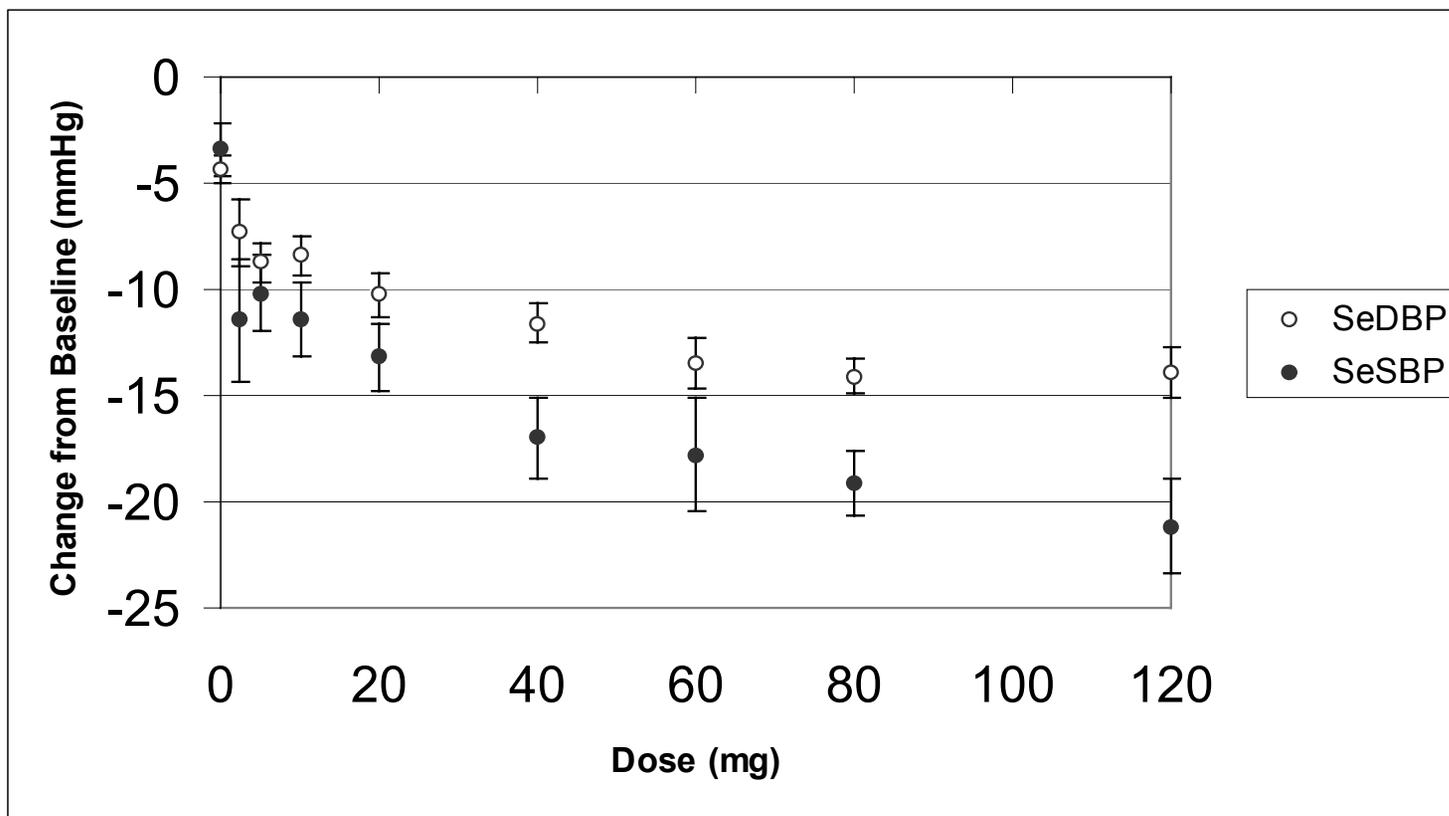
### **5.1 Fixed Dose Comparisons**

#### **5.1.1 Dose Ranging Studies**

Four placebo-controlled, parallel group, 6-9 week dose-ranging studies (CV137-006, -022, -024 and -045) examined the antihypertensive efficacy of omapatrilat at doses from 2.5 mg to 120 mg once daily. A total of 2369 subjects with trough seated diastolic blood pressure 95-110 mmHg were randomized in these studies. Blood pressure was measured in the office using traditional cuff methodology at trough ( $24 \pm 3$  hours following the previous dose).

Pooled data from these studies demonstrate a dose-response relationship for both diastolic blood pressure and systolic blood pressure at doses of 10 to 80 mg (Figure 5.1.1). At 80 mg, the proposed maximum dose, office trough systolic blood pressure was reduced by 15.7 mmHg and diastolic blood pressure was reduced by 9.7 mmHg relative to placebo.

**Figure 5.1.1: Mean Reductions [95% Confidence Interval] from Baseline in Trough Seated Blood Pressure at the Primary Timepoint in Dose Ranging Studies**



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## **5.1.2 Top Dose, Active-Comparator Studies**

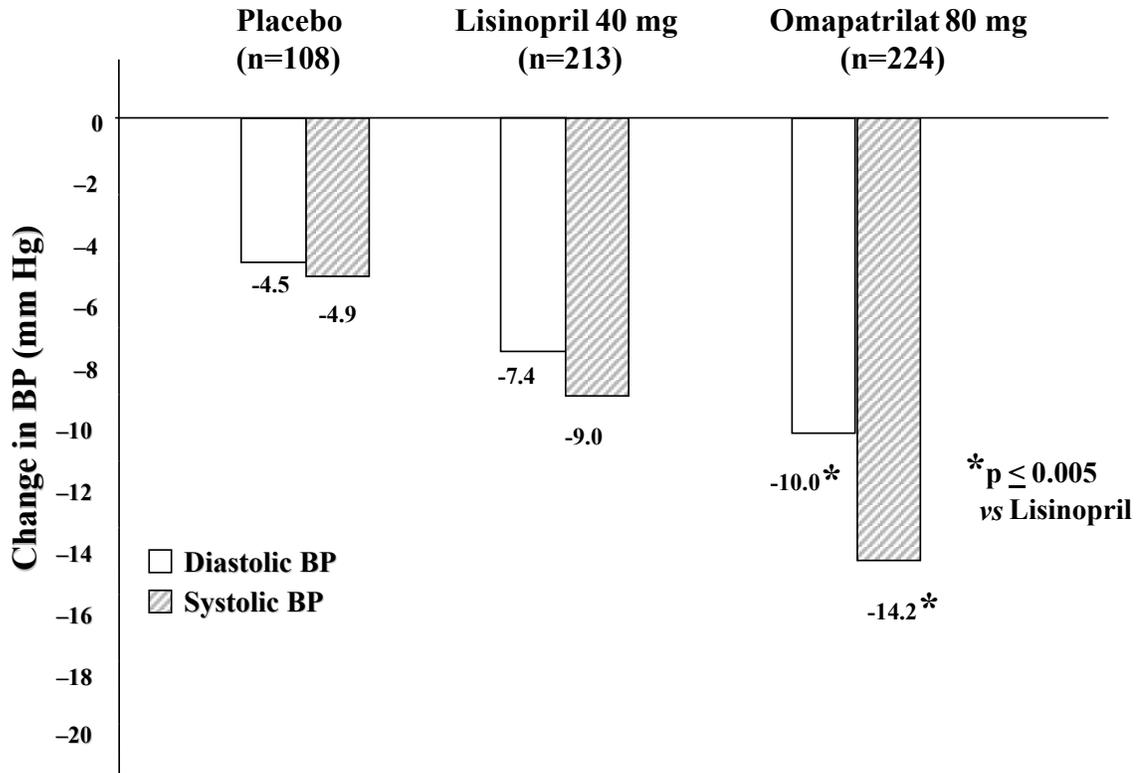
This section presents the results of all studies in general hypertensive populations comparing the maximum proposed dose of omapatrilat (80 mg) with other commonly used antihypertensive medications at their maximum doses.

### **5.1.2.1 Efficacy Comparisons Versus Lisinopril**

Two studies (CV137-031 and -037) compared maximum doses of omapatrilat (80 mg) and lisinopril (40 mg).

Study CV137-037 randomized 747 African-American patients with diastolic blood pressure of 95-110 mmHg to once daily treatment with placebo, lisinopril (10 mg for 2 weeks, 20 mg for 2 weeks, and 40 mg for the final 6 weeks) or omapatrilat (20 mg for 2 weeks, 40 mg for 2 weeks and 80 mg for the final 6 weeks). At Week 10, omapatrilat 80 mg produced greater reductions than lisinopril 40 mg in trough seated systolic blood pressure and diastolic blood pressure ( $p \leq 0.005$ ; Figure 5.1.2.1A).

**Figure 5.1.2.1A: Changes in Office Trough Blood Pressure at Week 10, Lisinopril Comparison (CV137-037)**

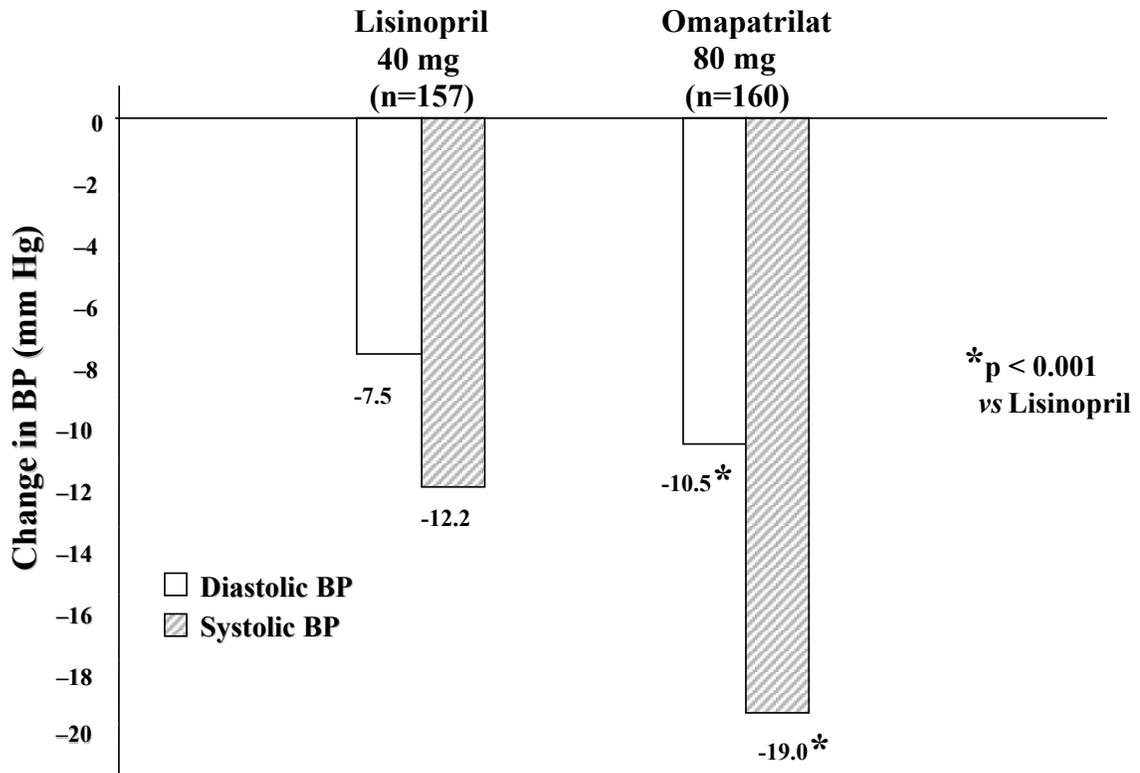


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Study CV137-031 randomized 347 patients with office trough systolic blood pressure of 150-180 mmHg to once daily treatment with lisinopril or omapatrilat for 10 weeks. The overall study design is similar to Study CV137-037 (described above). However, the study population was primarily Caucasian, there was no placebo arm, and antihypertensive efficacy was assessed using ambulatory blood pressure monitoring.

At Week 10, omapatrilat 80 mg produced greater reductions than lisinopril 40 mg in systolic (primary endpoint) and diastolic ambulatory blood pressure ( $p < 0.001$ ; Figure 5.1.2.1B).

**Figure 5.1.2.1B: Changes in 24-Hour Average Ambulatory Blood Pressure at Week 10, Lisinopril Comparison (CV137-031)**



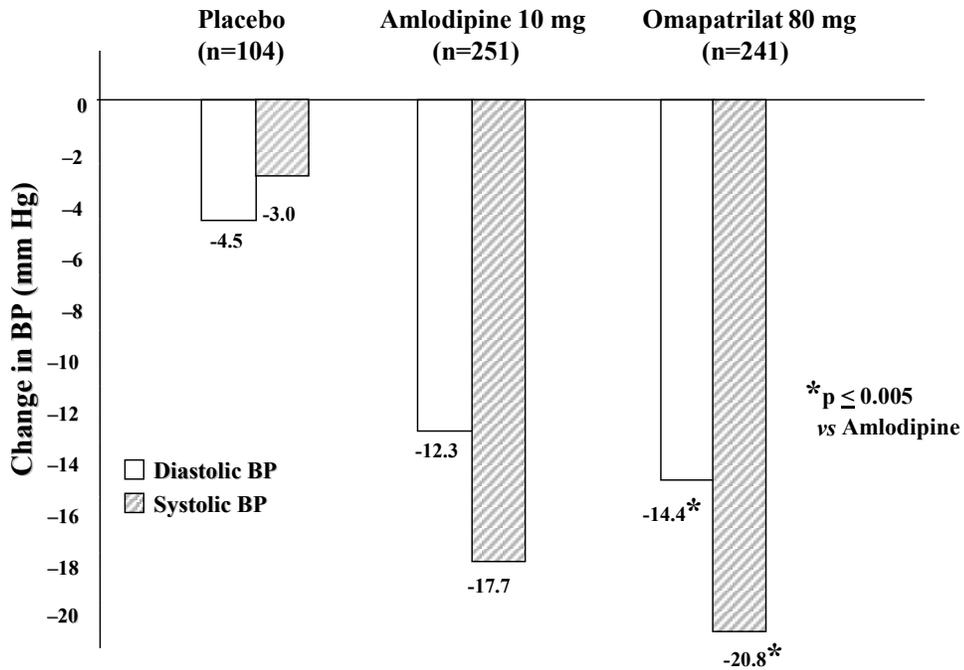
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### 5.1.2.2 Efficacy Comparisons Versus Amlodipine

Three studies (CV137-030, -032, and -066) compared top doses of omapatrilat (80 mg) and amlodipine (10 mg).

Study CV137-030 randomized 725 subjects with diastolic blood pressure of 95-110 mmHg to once daily treatment with omapatrilat (20 mg for 2 weeks, 40 mg for 2 weeks and 80 mg for the final 6 weeks), amlodipine (5 mg for 2 weeks and 10 mg for 8 weeks), or placebo. At Week 10, omapatrilat 80 mg produced greater reduction than amlodipine 10 mg in trough seated diastolic and systolic blood pressure ( $p \leq 0.005$ ; Figure 5.1.2.2A).

**Figure 5.1.2.2A: Adjusted Mean Change in Office Trough Blood Pressure at Week 10, Amlodipine Comparison (CV137-030)**

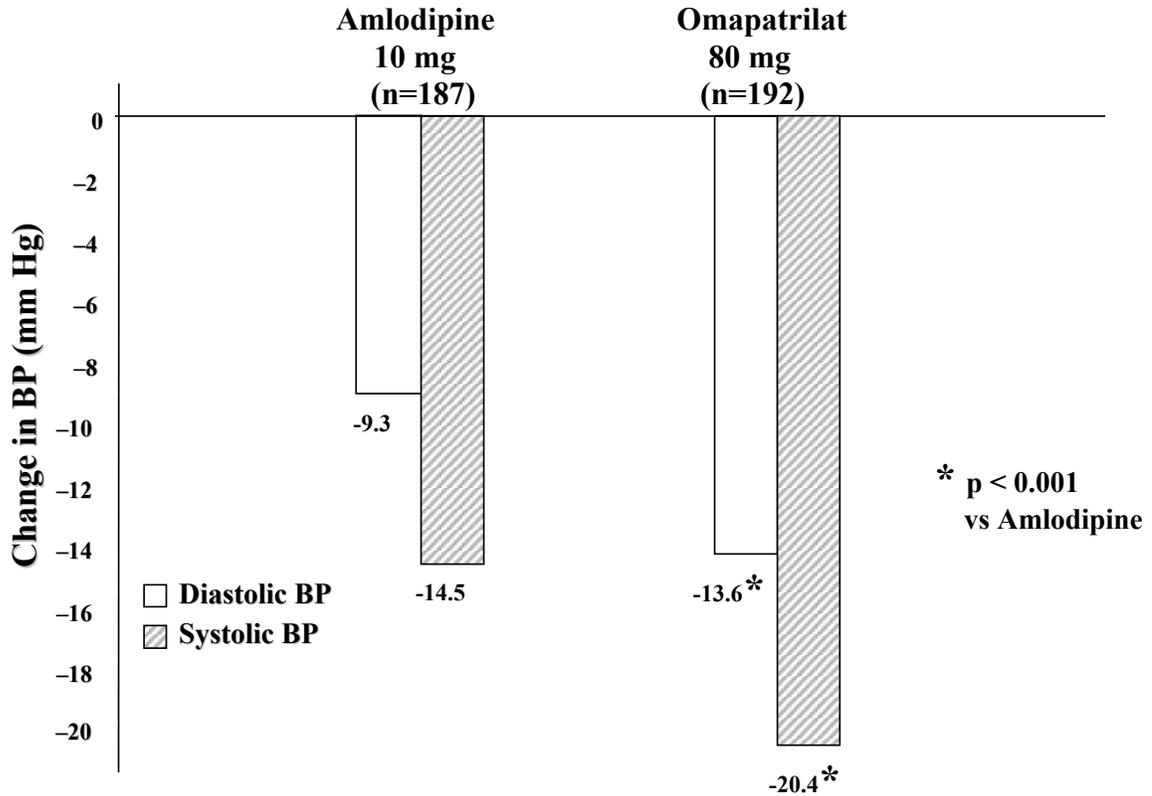


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Study CV137-032 randomized 430 patients with diastolic blood pressure of 95-110 mmHg to treatment with omapatrilat or amlodipine for 10 weeks. The overall design for study CV137-032 was similar to study CV137-030 described above except that there was no placebo arm and antihypertensive efficacy in this study was assessed using ambulatory blood pressure measurements.

At Week 10, omapatrilat 80 mg produced greater reductions than amlodipine 10 mg in systolic and diastolic ambulatory blood pressure (Figure 5.1.2.2B).

**Figure 5.1.2.2B: Adjusted Mean Change in 24-Hour Average Ambulatory Blood Pressure at Week 10, Amlodipine Comparison (CV137-032)**



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Study CV137-066 randomized 812 patients with diastolic blood pressure 95-110 mmHg in a 3:3:1 ratio to 10 weeks treatment with omapatrilat (20 mg for 2 weeks, 40 mg for 2 weeks, and 80 mg for the final 6 weeks), amlodipine (2.5 mg for 2 weeks, 5 mg for 2 weeks, and 10 mg for the final 6 weeks), or losartan (placebo for 2 weeks, losartan 50 mg for 2 weeks, and 100 mg for the final 6 weeks). At Week 10, omapatrilat 80 mg produced greater reductions than amlodipine 10 mg in ambulatory systolic (-18.9 vs. -13.5 mmHg; difference -5.4 mmHg, p < 0.001) and diastolic blood pressure (-12.7 vs. -8.7 mmHg; difference -4.0 mmHg, p < 0.001). The comparison of omapatrilat with losartan is discussed in Section 5.1.2.3 (below).

### **5.1.2.3 Efficacy Comparisons Versus Losartan**

In CV137-066 (described above), omapatrilat 80 mg produced greater reductions than losartan 100 mg in ambulatory systolic blood pressure (-18.9 vs. -10.0 mmHg; difference -8.9 mmHg,  $p < 0.001$ ) and ambulatory diastolic blood pressure (-12.7 vs. -7.3 mmHg; difference -5.4 mmHg,  $p < 0.001$ ).

In CV137-077, 288 patients with diastolic blood pressure 95-110 mmHg were randomized in a 3:3:1 ratio to treatment with omapatrilat (20 mg for 2 weeks, 40 mg for 2 weeks, and 80 mg for the final 6 weeks), losartan (50 mg for 2 weeks and 100 mg for the remaining 8 weeks), or placebo. Omapatrilat 80 mg produced greater reductions than losartan 100 mg in office trough seated systolic (-20.9 vs. -13.7 mmHg; difference -7.2 mmHg,  $p < 0.001$ ) and diastolic blood pressure (-15.0 vs. -10.5 mmHg; difference -4.5 mmHg,  $p < 0.001$ ).

### **5.1.2.4 Summary of Top Dose Comparisons**

In summary, omapatrilat exhibits a strong dose-response relationship for both systolic and diastolic blood pressure from 10 to 80 mg. In head-to-head, monotherapy comparisons, omapatrilat 80 mg consistently produced significantly greater reductions in systolic and diastolic blood pressure than maximum doses of lisinopril, amlodipine, or losartan.

Whether these results could be duplicated under clinically relevant conditions – with elective titration to target, and use of combination therapy if needed -- was studied in OCTAVE, which is described below.

## **5.2 Elective Titration (OCTAVE Study)**

### **5.2.1 Design of the OCTAVE Study (CV137-120)**

#### **5.2.1.1 Study Objectives**

OCTAVE evaluated the safety and efficacy of omapatrilat in comparison with enalapril in a broad range of hypertensive patients.<sup>36</sup> OCTAVE trial utilized elective titration and permitted the use of adjunctive antihypertensive therapy as needed to reach target blood

pressure. Thus the OCTAVE study tested whether the antihypertensive advantage of omapatrilat would be preserved in a setting resembling actual clinical use.

A 10 mg starting dose of omapatrilat is proposed in the current application. OCTAVE used a 10 mg starting dose of omapatrilat, with forced-titration to 20 mg and subsequent elective titration up to 80 mg as needed to achieve blood pressure control. OCTAVE therefore provides extensive clinical experience with the proposed 10 mg starting dose of omapatrilat. For enalapril, a starting dose of 5 mg and a target dose of 40 mg, in accordance with the product label, were chosen.

OCTAVE was conducted under the auspices of an independent Steering Committee. Study data were periodically reviewed by an independent Data and Safety Monitoring Committee charged to protect patient safety. An Event Adjudication Committee (EAC) assessed all potential events of angioedema and head/neck swelling without knowledge of patient treatment assignment (see Section 6.4).

The primary objectives of the OCTAVE study were:

- 1) To compare the reduction in systolic blood pressure at the completion of 8 weeks administration (end of titration phase) of omapatrilat or enalapril in three groups of hypertensive patients:
  - untreated hypertensives;
  - treated hypertensives with persistent mild elevation in blood pressure (JNC-VI Stage I)
  - treated hypertensives with persistent moderate/severe elevation in blood pressure (JNC-VI Stage II)
- 2) To compare the percentage of patients who had received new adjunctive antihypertensive medication at the completion of 24 weeks administration (end of maintenance phase) of omapatrilat or enalapril in the three groups of hypertensive patients mentioned above.

Other key objectives included assessment of angioedema, characterization of blood pressure changes and at Week 24 (study end), and evaluation of efficacy and safety in patients with different demographic characteristics, subtypes of hypertension (isolated

systolic hypertension or severe hypertension), and comorbid conditions (diabetes, atherosclerotic disease, or renal disease).

### **5.2.1.2 Selection of Study Population**

The study enrolled a broad range of uncontrolled hypertensive patients, including untreated patients as well as patients on current antihypertensive therapy. The study population consisted of 3 groups of hypertensive patients, defined in terms of treatment status and blood pressure at randomization.

Group 1 (Initial Therapy): Untreated hypertensive patients (systolic blood pressure  $\geq 140$  mmHg or diastolic blood pressure  $\geq 90$  mmHg on no antihypertensive therapy). These patients initiated antihypertensive therapy at randomization with double-blind omapatrilat or enalapril. There was no restriction with regard to severity of hypertension (any JNC-VI Stage, as illustrated in Table 5.2.1.2).

Group 2 (Replacement Therapy): Treated hypertensive patients with persistent mild hypertension (blood pressure at randomization corresponds to JNC-VI Stage I, as illustrated in the Table 5.2.1.2). These patients received double-blind omapatrilat or enalapril as replacement for prior antihypertensive therapy at randomization, i.e., antihypertensive therapy received at enrollment was discontinued at randomization.

Group 3 (Add-on Therapy): Treated hypertensive patients with persistent moderate/severe hypertension (blood pressure at randomization corresponds to JNC-VI Stage II, as illustrated in Table 5.2.1.2). These patients added double-blind omapatrilat or enalapril to antihypertensive therapy received prior to randomization.

**Table 5.2.1.2: Blood Pressure Stages as Defined in JNC-VI**

<b>Blood Pressure Stage</b>	<b>Systolic Blood Pressure (mmHg)</b>	<b>Diastolic Blood Pressure (mmHg)</b>
I	140-159	90-99
II	160-179	100-109
III	$\geq 180$	$\geq 110$

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Note: If systolic blood pressure and diastolic blood pressure are in different stages, the higher of the two is used to determine blood pressure stage.

### **5.2.1.3 Study Treatment**

The 24 week double-blind treatment period included 2 phases:

- 1) Titration phase (Weeks 1-8), in which the antihypertensive effect of omapatrilat and enalapril, titrated to reach target blood pressure, was evaluated, and
- 2) Maintenance phase (Weeks 9-24), in which the need for additional adjunctive antihypertensive therapy to reach target blood pressure was evaluated.

Prior antihypertensive medications were documented at enrollment. Patients in Group 2 who were receiving antihypertensive medication at the enrollment visit were required to have their current treatment withdrawn at randomization. Patients randomized to Group 3 were to continue prior antihypertensive medications following randomization.

Omapatrilat was administered starting at 10 mg once daily. All patients were force titrated to 20 mg once daily at Week 2, and then electively titrated to 40 mg at Week 4 and 80 mg at Week 6 as needed to achieve blood pressure control (systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg). A similar titration scheme was used for enalapril. Enalapril was administered starting at 5 mg once daily. All patients were force titrated to 10 mg once daily at Week 2, and then electively titrated to 20 mg at Week 4 and 40 mg at Week 6 as needed to achieve blood pressure control.

Investigators were free to add any antihypertensive medication, with the exception of ACE inhibitors, as needed to reach blood pressure target following the completion of the 8 week titration phase. Investigators were asked to consider using a thiazide diuretic as the first adjunctive agent because of the synergy between these medications and drugs which act on the renin angiotensin system (RAS).

### **5.2.2 Summary of Overall OCTAVE Efficacy Results**

The OCTAVE study results demonstrated that in all patient types, regardless of severity of hypertension, demographics, or comorbid conditions, treatment with omapatrilat consistently resulted in significantly greater systolic and diastolic blood pressure reductions, less need for adjunctive therapy, and improved blood pressure control rates compared to enalapril (Table 5.2.2). Further, the greater antihypertensive efficacy of omapatrilat was demonstrated regardless of whether omapatrilat or enalapril were used as

monotherapy or in combination with other antihypertensive treatments. The results of the study are described in detail by treatment group below (Sections 5.2.3, 5.2.4, 5.2.5).

**Table 5.2.2: Summary of Primary Efficacy Results in the OCTAVE Study**

Efficacy variable	Group 1 Initial Therapy		Group 2 Replacement Therapy		Group 3 Add-On Therapy	
	Omapatrilat N=4478	Enalapril N=4542	Omapatrilat N=5383	Enalapril N=5461	Omapatrilat N=2335	Enalapril N=2256
Baseline Mean Systolic Blood Pressure	156.3	156.0	149.8	149.9	166.5	166.1
Mean change from Baseline in Systolic Blood Pressure at Week 8	-21.5 <sup>a</sup>	-18.3	-11.4 <sup>a</sup>	-7.6	-23.2 <sup>a</sup>	-19.6
% Subjects reaching blood pressure goal at Week 24	65.7% <sup>a</sup>	57.3% <sup>b</sup>	57.4%	48.3%	45.6%	37.1%
% Subjects with adjuncts added at Week 24 <sup>c</sup>	12.7% <sup>a</sup>	19.3%	25.5% <sup>a</sup>	35.5%	17.1% <sup>a</sup>	22.3%

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<sup>a</sup> All p value < 0.001 versus enalapril

<sup>b</sup> N = 4543 for Week 8 LOCF

<sup>c</sup> Only subjects entering the maintenance phase of the trial (Weeks 9-24) are considered in these calculations.

### 5.2.3 Initial Therapy (OCTAVE Group 1): Overall and by Severity (JNC-VI Stage I-III)

In OCTAVE Study Group 1, omapatrilat was evaluated as initial therapy for hypertension. A total of 9292 patients were randomized to OCTAVE Study Group 1.

#### Demographics

Baseline demographics in Group 1 were comparable for omapatrilat and enalapril. The planned target of approximately 10% African-American patients randomized was achieved (9% omapatrilat, 8% enalapril). 45% of subjects were female. Large numbers of patients ≥ 65 and ≥ 75 years of age were randomized (1,831 and 535, respectively). The mean baseline blood pressure was 156/96 mmHg.

Blood Pressure Reduction

Reductions in blood pressure at Week 8 in OCTAVE study Group 1 are displayed in Table 5.2.3A.

At Week 8, omapatrilat reduced both systolic blood pressure and diastolic blood pressure to a greater extent than enalapril (Table 5.2.3A). Mean reductions in systolic and diastolic blood pressure at Week 8 were 3.2 mmHg and 1.9 mmHg greater, respectively, with omapatrilat than with enalapril. This occurred despite fewer patients receiving top dose of study drug in the omapatrilat (25%) treatment group than in the enalapril (33%) treatment group.

**Table 5.2.3A: Mean Blood Pressure Changes from Baseline at Week 8 (or LOCF) in OCTAVE Study Group 1**

Week/Efficacy Variable	Omapatrilat N = 4478	Enalapril N = 4542
<b>Week 8</b>		
<b>Systolic Blood Pressure mmHg</b>		
Baseline Mean	156.3	156.0
Mean change from baseline (se)	-21.5 (0.2)	-18.3 (0.2)
Difference from Enalapril (95%CI)	-3.2 (-3.9,-2.6)	
p-value: comparison with Ena	< 0.001	
<b>Diastolic Blood Pressure mmHg</b>		
Baseline Mean	95.7	95.5
Mean change from baseline (se)	-12.4 (0.1)	-10.5 (0.1)
Difference from Enalapril (95%CI)	-1.9 (-2.3,-1.5)	
p-value: comparison with Ena	< 0.001	

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Note: N = number of patients with baseline and at least one on-treatment efficacy measure by Week 8. Last on-treatment blood pressure measure was used for analysis if Week 8 measure not obtained. For co-primary analysis (comparison of systolic blood pressure at Week 8), statistical significance declared if  $p < 0.0083$ .

At Week 24, fewer omapatrilat-treated patients than enalapril-treated patients received new adjunctive antihypertensive medications (12.7% versus 19.3%;  $p < 0.001$ ). With the addition of adjunctive antihypertensive therapy, greater mean reductions from baseline in blood pressure were achieved at Week 24 than at Week 8 for study Group 1 in both

treatment groups (Table 5.2.3B). Nevertheless, the difference in blood pressure reduction between omapatrilat and enalapril observed at Week 8 was largely unchanged at Week 24. The mean reduction in systolic blood pressure and diastolic blood pressure at Week 24 was 3.1 mmHg and 1.6 mmHg greater with omapatrilat than with enalapril. In addition, more patients in the omapatrilat group (65.7%) compared with the enalapril group (57.3%) achieved blood pressure control to target level.

**Table 5.2.3B: Mean Blood Pressure Changes from Baseline and Percentage of Patients Reaching Goal Blood Pressure at Week 24 (or LOCF) in OCTAVE Study Group 1**

<b>Week/Efficacy Variable</b>	<b>Omapatrilat N = 4478</b>	<b>Enalapril N = 4542</b>
<b>Week 24</b>		
<b>Systolic Blood Pressure mmHg</b>		
Baseline Mean	156.3	156.0
Mean change from baseline (se)	-23.6 (0.2)	-20.5 (0.2)
Difference from Enalapril (95%CI)	-3.1 (-3.8, -2.4)	
p-value: comparison with Ena	< 0.001	
<b>Diastolic Blood Pressure mmHg</b>		
Baseline Mean	95.7	95.5
Mean change from baseline (se)	-13.7 (0.1)	-12.1 (0.1)
Difference from Enalapril (95%CI)	-1.6 (-2.0, -1.2)	
p-value: comparison with Ena	< 0.001	
<b>Controlled<sup>a</sup> (%)</b>	2944 (65.7%)	2605 (57.3%)
95% CI	(64.4%,67.1%)	(55.9%,58.8%)
p-value: comparison with Ena	< 0.001	

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Note: N = number of patients with baseline and at least one on-treatment efficacy measure by Week 8. For co-primary analysis (comparison of systolic blood pressure at Week 8), statistical significance declared if  $p < 0.0083$ .

<sup>a</sup> Controlled = systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg.

### Efficacy by Baseline JNC-VI Stage

The effects of omapatrilat and enalapril as initial therapy are presented by baseline JNC-VI blood pressure stage in Table 5.2.3C.

Blood pressure was significantly reduced by both enalapril and omapatrilat in patients with JNC-VI Stage I, II, and III hypertension. Within each JNC-VI Stage, patients randomized to omapatrilat experienced greater mean reductions in systolic blood pressure at Week 8 and were more likely to reach target BP at Week 24 than patients randomized to enalapril, despite receiving fewer new adjunctive antihypertensive medications.

The magnitude of difference between omapatrilat and enalapril was greatest in the most severely hypertensive patients. Among patients with JNC-VI Stage III hypertension, the mean reduction in systolic blood pressure at Week 8 was 6.6 mmHg greater with omapatrilat than with enalapril, and at Week 24 was 4.6 mmHg greater with omapatrilat than enalapril (36.6 vs. 32.0 mmHg). 41.6% of patients reached blood pressure target with omapatrilat vs. 32.0% with enalapril.

**Table 5.2.3C: Efficacy by Baseline JNC-VI Stage in OCTAVE Study Group 1**

JNC-VI Stage	Mean Change in Systolic Blood Pressure at Week 8 (95% CI)	% New Adjuncts by Week 24	% Controlled at Week 24
Stage I			
Omapatrilat (n = 2029)	-16.5 (-17.0, -16.0)	6.3%	76.2%
Enalapril (n = 2132)	-14.3 (-14.9, -13.8)	10.9%	68.2%
Stage II			
Omapatrilat (n = 1947)	-24.1 (-24.8, -23.5)	14.4%	61.0%
Enalapril (n = 1917)	-20.9 (-21.5, -20.2)	21.8%	51.7%
Stage III			
Omapatrilat (n = 493)	-32.1 (-33.8, -30.4)	32.4%	41.6%
Enalapril (n = 490)	-25.5 (-27.2, -23.7)	46.4%	32.0%

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Note: Subject numbers include all randomized subjects with at least one on-treatment blood pressure measurement. Only those entering maintenance phase of study (Weeks 9-16) are considered in calculation of % receiving new adjunct.

In summary, as initial therapy in untreated hypertensive patients omapatrilat produced greater reductions than enalapril in systolic and diastolic blood pressure at Week 8, the end of study drug titration, despite an elective titration design and greater use of top-dose enalapril. Omapatrilat also produced greater reductions than enalapril in systolic and diastolic blood pressure at Week 24, the end of the study, despite greater use of adjunctive antihypertensive therapy with enalapril. More patients reached blood pressure target with omapatrilat than enalapril. Omapatrilat was more effective than enalapril in

patients with all levels of severity of hypertension (JNC-VI Stages I, II, and III). The magnitude of the difference in blood pressure reduction between omapatrilat and enalapril was greatest in those with severe (JNC-VI Stage III) hypertension.

#### **5.2.4 Replacement Therapy in Patients Not at Target on Antihypertensive Therapy at Baseline (OCTAVE Group 2)**

In OCTAVE Study Group 2, omapatrilat was evaluated as replacement therapy for hypertension. A total of 11,224 patients were randomized to OCTAVE Study Group 2. Approximately two-thirds of patients (64%) were receiving only a single antihypertensive medication at baseline, despite mild elevations in blood pressure (mean systolic blood pressure approximately 150 mmHg)

##### Demographics

Within each study group, baseline demographics, blood pressure, and antihypertensive medication at enrollment were comparable for omapatrilat and enalapril.

##### Blood Pressure Reductions

The blood pressure reductions at Weeks 8 and 24 are displayed in Tables 5.2.4A and B, respectively. A greater reduction in both systolic and diastolic blood pressure was observed with omapatrilat than with enalapril.

At Week 24, fewer omapatrilat than enalapril treated patients received new adjunctive antihypertensive medications (25.5% vs 35.5%, respectively,  $p < 0.0001$ ). Despite more frequent use of adjunctive therapy in the enalapril group, omapatrilat-treated patients experienced greater reductions in both systolic and diastolic blood pressure and higher blood pressure control rates.

**Table 5.2.4A: Mean Blood Pressure Changes from Baseline at Week 8 (or LOCF) in OCTAVE Study Group 2**

Efficacy variable	Study Group 2 (replacement therapy)	
	Oma N = 5383	Ena N = 5461
<b>Week 8</b>		
<b>Systolic Blood Pressure mmHg</b>		
Baseline Mean	149.8	149.9
Mean change from baseline (se)	-11.4 (0.2)	-7.6 (0.2)
Difference from Enalapril (95%CI)	-3.9 (-4.5,-3.3)	
p-value: comparison with Ena	< 0.001	
<b>Diastolic Blood Pressure mmHg</b>		
Baseline Mean	90.9	90.9
Mean change from baseline (se)	-7.0 (0.1)	-4.7 (0.1)
Difference from Enalapril (95%CI)	-2.3 (-2.6,-1.9)	
p-value: comparison with Ena	< 0.001	

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Note: N = number of patients with baseline and at least one on-treatment efficacy measure by Week 8 or 24. For co-primary analysis (comparison of systolic blood pressure at Week 8), statistical significance declared if  $p < 0.0083$ .

**Table 5.2.4B: Mean Blood Pressure Changes from Baseline and Percentage of Patients Reaching Goal Blood Pressure at Week 24 (or LOCF) in OCTAVE Study Group 2**

Efficacy variable	Study Group 2 (replacement therapy)	
	Oma N = 5383	Ena N = 5461
<b>Week 24</b>		
<b>Systolic Blood Pressure mmHg</b>		
Baseline Mean	149.8	149.9
Mean change from baseline (se)	-14.0 (0.2)	-10.9 (0.2)
Difference from Enalapril (95%CI)	-3.1 (-3.7, -2.5)	
p-value: comparison with Ena	< 0.001	
<b>Diastolic Blood Pressure mmHg</b>		
Baseline Mean	90.9	90.9
Mean change from baseline (se)	-8.7 (0.1)	-6.8 (0.1)
Difference from Enalapril (95%CI)	-1.9 (-2.2, -1.5)	
p-value: comparison with Ena	< 0.001	
<b>Controlled<sup>a</sup> (%)</b>	3092 (57.4%)	2639 (48.3%)
95% CI	(56.1%, 58.8%)	(47.0%, 49.6%)
p-value: comparison with Ena	< 0.001	

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Note: N = number of patients with baseline and at least one on-treatment efficacy measure by Week 8 or 24. For co-primary analysis (comparison of systolic blood pressure at Week 8), statistical significance declared if  $p < 0.0083$ .

<sup>a</sup> Controlled = systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg.

### 5.2.5 Add-on Therapy in Patients Not at Target on Antihypertensive Therapy at Baseline (OCTAVE Group 3)

In OCTAVE Study Group 3, omapatrilat was evaluated as add-on therapy for hypertension. A total of 4,751 patients were randomized to OCTAVE Study Group 3.

Approximately one-half of the patients (50%) were receiving only a single antihypertensive medication at baseline, despite moderate/severe elevations in blood pressure (mean systolic blood pressure 166 mmHg), while 35% were receiving two

antihypertensive medications, and only 15% were receiving 3 or more antihypertensive medications.

### Demographics

Within each study group, baseline demographics, blood pressure, and antihypertensive medication at enrollment were comparable for omapatrilat and enalapril.

### Blood Pressure Reductions

The blood pressure reductions at Weeks 8 and 24 are displayed in Tables 5.2.5A and B, respectively. Omapatrilat-treated patients experienced greater reductions in both systolic and diastolic blood pressure at Week 8. At Week 24, fewer omapatrilat than enalapril treated patients received new adjunctive antihypertensive medications (17.1% vs 22.3%,  $p < 0.0001$ , respectively). Despite more frequent use of adjunctive therapy in the enalapril group, omapatrilat-treated patients experienced greater reductions in blood pressure and higher control rate at Week 24. These data are consistent with findings in other treatment groups.

**Table 5.2.5A: Mean Blood Pressure Changes from Baseline at Week 8 (or LOCF) in OCTAVE Study Group 3**

Efficacy variable	Study Group 3 (add-on therapy)	
	Oma N = 2335	Ena N = 2256
<b>Week 8</b>		
<b>Systolic Blood Pressure mmHg</b>		
Baseline Mean	166.5	166.1
Mean change from baseline (se)	-23.2 (0.3)	-19.6 (0.4)
Difference from Enalapril (95%CI)	-3.6 (-4.6,-2.6)	
p-value: comparison with Ena	< 0.001	
<b>Diastolic Blood Pressure mmHg</b>		
Baseline Mean	96.6	96.7
Mean change from baseline (se)	-11.8 (0.2)	-10.1 (0.2)
Difference from Enalapril (95%CI)	-1.7 (-2.3,-1.1)	
p-value: comparison with Ena	< 0.001	

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Note: N = number of patients with baseline and at least one on-treatment efficacy measure by Week 8 or 24. For co-primary analysis (comparison of systolic blood pressure at Week 8), statistical significance declared if  $p < 0.0083$ .

**Table 5.2.5B: Mean Blood Pressure Changes from Baseline and Percentage of Patients Reaching Goal Blood Pressure at Week 24 (or LOCF) in OCTAVE Study Group 3**

Efficacy variable	Study Group 3 (add-on therapy)	
	Oma N = 2335	Ena N = 2256
<b>Week 24</b>		
<b>Systolic Blood Pressure</b> mmHg		
Baseline Mean	166.5	166.1
Mean change from baseline (se)	-25.6 (0.4)	-22.8 (0.4)
Difference from Enalapril (95%CI)	-2.8 (-3.8, -1.8)	
p-value: comparison with Ena	< 0.001	
<b>Diastolic Blood Pressure</b> mmHg		
Baseline Mean	96.6	96.7
Mean change from baseline (se)	-13.3 (0.2)	-12.2 (0.2)
Difference from Enalapril (95%CI)	-1.2 (-1.8, -0.5)	
p-value: comparison with Ena	< 0.001	
<b>Controlled<sup>a</sup></b> (%)	1065 (45.6%)	837 (37.1%)
95% CI	(43.6%, 47.6%)	(35.1%, 39.1%)
p-value: comparison with Ena	< 0.001	

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Note: N = number of patients with baseline and at least one on-treatment efficacy measure by Week 8 or 24. For co-primary analysis (comparison of systolic blood pressure at Week 8), statistical significance declared if  $p < 0.0083$ .

<sup>a</sup> Controlled = systolic blood pressure < 140 mmHg and diastolic blood pressure < 90 mmHg.

### Summary of OCTAVE Findings

In sum, OCTAVE demonstrated that omapatrilat lowers blood pressure more than enalapril in clinical trial populations treated in a manner consistent with actual clinical practice. A potential role for omapatrilat in patients with hypertension that is difficult to control with other medications was supported by the demonstration of superior efficacy regardless of baseline severity of hypertension or failure to reach blood pressure target with existing medications. Further examination of data from OCTAVE and other trials, presented in the next section, confirms that additional blood pressure reduction with

omapatrilat can be obtained in patients who are difficult to control with existing antihypertensive medications.

### **5.3 Difficult to Control Patients**

In this section, data are presented to demonstrate the efficacy of omapatrilat in patients with difficult to control hypertension.

Data are presented first for patients with characteristics typically associated with difficult to control hypertension, including diabetes, isolated systolic hypertension, severe hypertension, renal disease, or pre-existing ischemic coronary or cerebrovascular disease. Omapatrilat is shown to be effective in each of these groups of patients, who are widely perceived to have a less satisfactory response to antihypertensive therapy than other patients. They share other features as well: a relatively large gap between pre-treatment blood pressure and goal, limited treatment options, need for simultaneous management of several chronic diseases, and increased risk of cardiovascular events.

Data are presented next for patients who have not reached target with existing antihypertensive agents, thus demonstrating resistance to antihypertensive therapy. The efficacy of omapatrilat in patients not reaching target with an ACE inhibitor or ACE inhibitor containing regimen is described in detail. Omapatrilat and ACE inhibitors both inhibit the renin-angiotensin system, but omapatrilat has an additional mechanism of action (NEP inhibition) which might provide additional antihypertensive efficacy in patients not responding to an ACE inhibitor. ACE inhibitors have also been broadly studied, and found to be generally effective, in the difficult to control, high cardiovascular risk patients. If omapatrilat were found to reduce blood pressure in ACE inhibitor resistant patients, it might provide an alternative to ACE inhibitors in patients with an indication for ACE inhibition who require additional blood pressure reduction.

Efficacy is also described in patients resistant to combination therapy not including an ACE inhibitor. Many of these patients had failed to reach target with three or more drugs prior to treatment with omapatrilat. Particular emphasis is placed on the OCTAVE subgroup in whom prior antihypertensive therapy was most carefully characterized – those on amlodipine and HCTZ on baseline. Omapatrilat is shown to be effective in patients not at target on prior therapy, regardless of the intensity of prior therapy.

### **5.3.1 Patients with Clinical Characteristics Associated with Difficult to Control Hypertension**

#### **5.3.1.1 *Patients with Severe Hypertension or Isolated Systolic Hypertension***

About 9000 patients in OCTAVE were not receiving antihypertensive treatment at the time of enrollment, allowing classification of their type and severity of hypertension. Of these, ~1000 had severe hypertension (JNC-VI Stage III: systolic blood pressure  $\geq 180$  mmHg or diastolic blood pressure  $\geq 110$  mmHg), and ~1200 had isolated systolic hypertension (systolic blood pressure  $\geq 140$  mmHg and diastolic blood pressure  $< 90$  mmHg). In both these groups, omapatrilat produced significantly greater reductions in blood pressure, with less subsequent use of adjunctive antihypertensive therapy, and was more likely to provide blood pressure control to target than enalapril (Table 5.3.1.1).

Despite greater use of adjunctive therapy with enalapril, blood pressure changes remained significantly greater at the end of the study (Week 24) with omapatrilat than enalapril. At Week 24 omapatrilat reduced systolic blood pressure 4.6 mmHg more than enalapril in patients with severe hypertension and 4.5 mmHg more than enalapril in subjects with isolated systolic hypertension.

**Table 5.3.1.1: Effectiveness of Omapatrilat in OCTAVE Patients with Severe Hypertension or Isolated Systolic Hypertension**

Subgroup	Systolic Blood Pressure (mmHg)				
	n	Mean Baseline	Adjusted Mean Change at Week 8	Adjuncts added by Week 24 <sup>a</sup> (%)	Controlled <sup>b</sup> at Week 24 (%)
<b>Severe Hypertension</b>					
Oma	493	178.4	-32.1	148/457 (32.4%)	205/493 (41.6%)
Ena	490	178.0	-25.5	206/444 (46.4%)	157/490 (32.0%)
Difference (Oma-Ena)			-6.6		
p-value			< 0.001		
<b>Isolated Systolic Hypertension</b>					
Oma	666	155.7	-20.7 <sup>c</sup>	73 / 611 (11.9%)	447 / 666 (67.1%)
Ena	666	155.5	-17.3 <sup>c</sup>	97 / 611 (15.9%)	369 / 666 (55.4%)
Difference (Oma-Ena)			-3.4		
p-value			< 0.001		

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<sup>a</sup> Includes only subjects who entered maintenance phase of the study

<sup>b</sup> Controlled = Systolic Blood Pressure < 140 mmHg and Diastolic Blood Pressure < 90 mmHg

<sup>c</sup> Not an adjusted change

Two smaller studies were conducted prior to OCTAVE in patients with severe hypertension or isolated systolic hypertension. These studies are presented for completeness. Compared to OCTAVE, the treatment durations were shorter and the number of subjects treated much smaller. A 10 week, descriptive study (CV137-049) was conducted in 214 subjects with severe diastolic hypertension (trough seated diastolic blood pressure 115-130 mmHg) to gain experience with omapatrilat in this population. Patients were randomized to omapatrilat (20/40/80 mg, n = 147) or enalapril (10/20/40 mg, n = 67) and adjunctive therapy as needed. Omapatrilat and enalapril-based regimens both produced significant reductions in blood pressure of 36-37 mmHg systolic at the end of 10 weeks. No statistical comparison was planned or performed. A 13 week

study (CV137-042) was performed in 429 subjects with isolated systolic hypertension (systolic blood pressure 160-199 mmHg and diastolic blood pressure < 90 mmHg). At 9 weeks, the primary timepoint, systolic blood pressure was reduced 8.8 mmHg relative to placebo with omapatrilat 20 mg and 11.8 mmHg relative to placebo with omapatrilat 40 mg ( $p < 0.001$  for both comparisons).

**5.3.1.2 Patients with Comorbid Conditions and Elevated CV Risk (Diabetes, Atherosclerotic Disease, or Renal Disease)**

Approximately 3,000 patients with diabetes, 2,000 patients with atherosclerotic disease (prior MI, angina, stroke, or TIA) and 500 patients with renal disease were treated in OCTAVE. As shown in Table 5.3.1.2, these patients experienced significantly greater mean reductions in systolic blood pressure with omapatrilat than with enalapril, were less likely to receive adjunctive antihypertensive medication, and more likely to reach blood pressure target. The magnitude of the difference between omapatrilat and enalapril for these measures was similar in each patient subgroup. Changes in diastolic blood pressure were similar to those observed for systolic blood pressure.

**Table 5.3.1.2: Effectiveness of Omapatrilat in OCTAVE Patients with Comorbid Conditions**

Subgroup	Systolic Blood Pressure (mmHg)				
	n	Mean Baseline	Adjusted Mean Change at Week 8	Adjuncts added by Week 24 <sup>a</sup> (%)	Controlled <sup>b</sup> at Week 24 (%)
<b>Diabetes Mellitus</b>					
Oma	1658	156.5	-15.2	384 / 1518 (25.3%)	855 / 1658 (51.6%)
Ena	1617	156.0	-10.5	447 / 1465 (30.5%)	682 / 1617 (42.2%)
Difference (Oma-Ena)			-4.7		
p-value			< 0.001		
<b>Atherosclerotic Disease</b>					
Oma	1141	158.2	-17.4	229 / 1043 (22.0%)	635 / 1141 (55.7%)
Ena	1142	158.0	-14.4	300 / 1040 (28.8%)	517 / 1142 (45.3%)
Difference (Oma-Ena)			-3.1		
p-value			< 0.001		

**Table 5.3.1.2: Effectiveness of Omapatrilat in OCTAVE Patients with Comorbid Conditions**

Subgroup	Systolic Blood Pressure (mmHg)				
	n	Mean Baseline	Adjusted Mean Change at Week 8	Adjuncts added by Week 24 <sup>a</sup> (%)	Controlled <sup>b</sup> at Week 24 (%)
Renal Disease					
Oma	290	157.4	-13.8	83 / 258 (32.2%)	141 / 290 (48.6%)
Ena	311	156.9	-9.5	93 / 248 (37.5%)	121 / 311 (41.4%)
Difference (Oma-Ena)			-4.3		
p-value			0.004		

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Dataset: Randomized Patients

<sup>a</sup> Includes only subjects who entered maintenance phase of the study

<sup>b</sup> Controlled = Systolic Blood Pressure < 140 mmHg and Diastolic Blood Pressure < 90 mmHg

Thus, the benefit of omapatrilat over enalapril is evident in patients with severe hypertension and isolated systolic hypertension, and in those with comorbid conditions and elevated CV risk, in whom hypertension is often difficult to control.

### 5.3.2 Patients Not at Target Blood Pressure on Existing Antihypertensive Therapy at Enrollment

Omapatrilat is effective in patients who have failed to reach blood pressure target with other therapies. In this section, patients who were not controlled on ACE inhibitors (alone or in combination with other agents) at randomization are discussed first, followed by patients who were not controlled with agents other than ACE inhibitors at randomization.

#### 5.3.2.1 Patients Not at Target on ACE Inhibitors

Overall, data from CV137-073 and OCTAVE treatment Group 2 demonstrate that omapatrilat provided significant additional blood pressure lowering in patients uncontrolled on ACE inhibitors. The greatest benefit was observed in the most resistant patients, those who failed to reach target blood pressure on an ACE inhibitor plus one or

more additional antihypertensives. The antihypertensive efficacy of omapatrilat relative to enalapril in diabetic patients not controlled on ACE inhibitors is also presented.

CV137-073: Patients Resistant to Maximal ACE Inhibitor Therapy

Study CV137-073 was conducted in patients who had not reached blood pressure target despite therapy for at least one month with maximal customary doses of an ACE inhibitor (e.g., enalapril 20 mg or lisinopril 20 mg). Potential patients entered a two-week lead-in in which ACE inhibitor therapy was continued and failure to reach blood pressure target was verified at consecutive visits. Eligible patients were then switched directly from prior ACE inhibitor therapy to omapatrilat or lisinopril and titrated to top-dose (omapatrilat 80 mg or lisinopril 40 mg) for four weeks. Any other antihypertensive medication(s) used prior to randomization were continued at established dose(s).

As shown in Table 5.3.2.1A, reductions in trough systolic blood pressure and diastolic blood pressure were 7.0 and 4.3 mmHg, respectively, greater with omapatrilat than lisinopril. Reduction in ambulatory systolic blood pressure was 8.8 mmHg greater with omapatrilat than with lisinopril.

**Table 5.3.2.1A: Effectiveness of Omapatrilat in Patients Not Reaching Target Blood Pressure with Maximal ACE Inhibitor Therapy (CV137-073)**

Efficacy Variable	<b>Omapatrilat 20/40/80 mg N = 127</b>	<b>Lisinopril 20/20/40 mg N = 126</b>
Trough Seated Diastolic Blood Pressure, mmHg		
Baseline Mean (sd)	91.6 (8.5)	92.5 (9.9)
Mean change from baseline (95% CI)	-7.1 (-8.5, -5.8)	-2.8 (-4.2, -1.4)
Difference from Lisinopril	-4.3	
Trough Seated Systolic Blood Pressure, mmHg		
Baseline Mean (sd)	151.8 (14.9)	151.5 (13.2)
Mean change from baseline (sd)	-10.9 (-13.5, -8.4)	-3.9 (-6.3, -1.6)
Difference from Lisinopril	-7.0	
	<b>Omapatrilat 20/40/80 mg N = 124</b>	<b>Lisinopril 20/20/40 mg N = 122</b>
24hr-average Ambulatory Systolic Blood Pressure, mmHg		
Baseline Mean (sd)	142.4 (13.6)	141.6 (12.0)
Adjusted Mean Change (95% CI)	-10.8 (0.8)	-1.9 (0.8)
Difference from Lisinopril	-8.8	-
(95 % CI)	(-10.9, -6.7)	-
p-value	<0.001	-

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Seventy-five (75) patients in CV137-073 were receiving an ACE inhibitor in combination with at least one other antihypertensive medication prior to randomization. In these patients, omapatrilat reduced ambulatory systolic blood pressure about 12 mmHg more than lisinopril (Table 5.3.2.1B), a highly clinically meaningful difference.

**Table 5.3.2.1B: Effectiveness of Omapatrilat in Patients Not Reaching Target Blood Pressure with Maximal ACE Inhibitor Therapy (CV137-073), by Number of Baseline Antihypertensives**

	<b>Mean Baseline Office Systolic Blood Pressure (sd)</b>	<b>Mean Baseline Ambulatory Systolic Blood Pressure (mmHg) (sd)</b>	<b>Mean Change in Ambulatory Systolic Blood Pressure (mmHg)</b>	<b>Absolute Difference (mmHg)</b>
ACE-I Monotherapy at Randomization				
Oma (n = 87)	151.4 (14.0)	142.9 (13.4)	-10.7	-7.6
Lis (n = 84)	150.7 (12.4)	142.6 (12.7)	-3.1	
ACE-I as part of Combination Therapy at Randomization				
Oma (n = 37)	152.8 (17.0)	141.2 (14.2)	-11.2	-12.1
Lis (n = 38)	153.4 (15.1)	139.3 (9.8)	0.9	

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OCTAVE: Patients Not at Target Prior to Randomization Despite ACE Inhibitor Therapy

A significant number of patients entered OCTAVE treatment Group 2 with uncontrolled blood pressure despite ACE inhibitor therapy. The reductions in blood pressure were significantly greater in those switched to omapatrilat than in those switched to enalapril (Table 5.3.2.1C). Numerically, the largest difference between omapatrilat and enalapril was observed in the most resistant patients, those not controlled on 3 or more drugs including an ACE inhibitor.

**Table 5.3.2.1C: Effectiveness of Omapatrilat in OCTAVE: Patients Not Reaching Target Blood Pressure with an ACE Inhibitor at Randomization**

	Mean Baseline Systolic Blood Pressure (mmHg)	Week 24	
		Mean Change in Systolic Blood Pressure (95% CI) (mmHg)	Absolute Difference (mmHg)
ACE Inhibitor Monotherapy at Randomization			
Oma (n = 1103)	149.7	-15.4 (-16.2, -14.5)	-3.5
Ena (n = 1175)	149.5	-11.9 (-12.8, -11.1)	
ACE Inhibitor + 1 Additional Antihypertensive at Randomization			
Oma (n = 677)	149.4	-10.8 (-12.0, -9.7)	-3.0
Ena (n = 691)	150.1	-7.8 (-9.0, -6.5)	
ACE Inhibitor + 2 or more Additional Antihypertensive at Randomization			
Oma (n = 282)	152.3	-9.6 (-12.0, -7.2)	-5.9
Ena (n = 264)	151.2	-3.7 (-6.2, -1.2)	

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OCTAVE Subgroup with Diabetes Resistant to ACE Inhibitors

As previously discussed, patients with diabetes often have refractory hypertension and elevated CV risk. The benefit of combined ACE/NEP inhibition with omapatrilat over ACE inhibition alone with enalapril in the overall diabetic population was shown in Table 5.3.1.2. The difference between omapatrilat and enalapril is even greater in diabetic patients not controlled by ACE inhibition. These patients are at high CV risk and may benefit significantly from more effective antihypertensive regimens.

As shown in Table 5.3.2.1D, omapatrilat produced blood pressure reductions at least 5 mmHg greater than enalapril in diabetic patients in whom blood pressure remained

above target despite treatment with ACE inhibitors or ACE inhibitor containing regimens. Among diabetic patients who had not reached target on regimens of 3 or more drugs, including an ACE inhibitor, omapatrilat produced blood pressure reduction about 9 mmHg greater than enalapril.

**Table 5.3.2.1D: Omapatrilat Efficacy in OCTAVE Patients with Diabetes Resistant to ACE Inhibitors (CV137-120)**

	Mean Baseline Systolic Blood Pressure (mmHg)	Week 24	
		Mean Change in Systolic Blood Pressure (95% CI) (mmHg)	Absolute Difference (mmHg)
ACE-I Monotherapy at Randomization			
Oma (n = 230)	150.4	-14.4 (-16.4, -12.5)	-4.7
Ena (n = 236)	150.7	-9.7 (-11.7, -7.6)	
ACE-I + 1 Additional Adjunct at Randomization			
Oma (n = 152)	150.7	-11.8 (-14.4, -9.2)	-6.8
Ena (n = 170)	150.8	-5.0 (-7.5, -2.4)	
ACE-I + 2 or more Additional Adjuncts at Randomization			
Oma (n = 90)	152.3	-9.3 (-13.6, -5.0)	-8.5
Ena (n = 79)	153.3	-0.8 (-6.2, 4.5)	

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These data demonstrate a significant benefit of omapatrilat beyond ACE inhibition in patients resistant to ACE inhibitor therapy.

**5.3.2.2 Patients Not Controlled by Other Drug Regimens**

OCTAVE Study Group 3: JNC-VI Stage II Blood Pressure Despite Treatment

The effectiveness of omapatrilat in patients not controlled by other multidrug regimens (i.e., those not including an ACE inhibitor) is supported by data from OCTAVE treatment Group 3. This treatment group included approximately 4500 patients who remained at JNC VI Stage II (systolic blood pressure 160-179 mmHg or diastolic blood pressure 100-109 mmHg) despite antihypertensive treatment. The baseline systolic blood pressure was approximately 166 mmHg and diastolic blood pressure 97 mmHg in these patients. Patients who remained above target despite therapy with an ACE inhibitor could not be randomized into this study group.

As shown in Table 5.3.2.2A, addition of omapatrilat provided consistently greater blood pressure reductions than addition of enalapril, overall and in patients receiving one, two, or three or more antihypertensive medications at baseline.

**Table 5.3.2.2A: Effectiveness of Omapatrilat in OCTAVE Group 3 Patients, by Number of Baseline Medications**

	Mean Baseline Systolic Blood Pressure (sd) (mmHg)	Week 24	
		Mean Change (95% CI) (mmHg)	Absolute Difference (mmHg)
<hr/>			
All Subjects in Group 3			
Oma (n = 2335)	166.5 (10.8)	-25.6 (-26.3, -24.9)	-2.8
Ena (n = 2256)	166.1 (10.9)	-22.8 (-23.5, -22.1)	
<hr/>			
Subjects on One Antihypertensive Medication at Randomization			
Oma (n = 1177)	166.3 (10.7)	-26.4 (-27.4, -25.4)	-3.3
Ena (n = 1105)	165.5 (10.9)	-23.1 (-24.0, -22.1)	
<hr/>			

**Table 5.3.2.2A: Effectiveness of Omapatrilat in OCTAVE Group 3 Patients, by Number of Baseline Medications**

	Mean Baseline Systolic Blood Pressure (sd) (mmHg)	Week 24	
		Mean Change (95% CI) (mmHg)	Absolute Difference (mmHg)
Subjects on Two Antihypertensive Medications at Randomization			
Oma (n = 802)	166.7 (11.0)	-25.5 (-26.7, -24.3)	-2.3
Ena (n = 804)	166.5 (10.5)	-23.2 (-24.4, -21.9)	
Subjects on Three or More Antihypertensive Medications at Randomization			
Oma (n = 356)	166.7 (11.1)	-23.4 (-25.2, -21.5)	-2.1
Ena (n = 347)	167.3 (11.4)	-21.3 (-23.2, -19.4)	

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A greater reduction in blood pressure was consistently observed with the addition of omapatrilat compared to enalapril, regardless of the number of antihypertensive medications used at baseline.

The patients with persistent JNC-VI Stage II hypertension, in spite of combination therapy with both a dihydropyridine calcium channel blocker and a diuretic, represent a patient group with strong medical need. In these patients, addition of a drug that blocks the renin-angiotensin system is a logical choice, with limited options thereafter. For amlodipine and HCTZ, Investigators reported the dose received at randomization, permitting precise characterization of the intensity of prior therapy.

One hundred and thirty-five patients in OCTAVE treatment Group 3 were receiving both amlodipine and HCTZ at baseline. The mean doses of amlodipine and HCTZ used in this subgroup were approximately 7 mg and 20 mg, respectively. Approximately 40% of patients also received a beta blocker and 11% also received a centrally acting alpha agonist at baseline.

As shown in Table 5.3.2.2B, addition of omapatrilat produced a 2.6 mmHg greater reduction in systolic blood pressure and a 3.7 mmHg greater reduction in diastolic blood pressure than enalapril in these patients with significant blood pressure elevation in spite of intensive antihypertensive treatment at baseline. These differences occurred even though more patients were titrated to top-dose enalapril than top-dose omapatrilat (63% vs. 41%), and more patients received additional antihypertensive therapy with enalapril than omapatrilat (15% vs. 13%). Thus, despite intensive therapy with multiple antihypertensives, including robust doses of HCTZ and amlodipine, an incremental benefit of omapatrilat over enalapril was maintained.

**Table 5.3.2.2B: Effectiveness of Omapatrilat at Week 24 in OCTAVE Group 3 Patients Receiving HCTZ and Amlodipine at Randomization**

<b>Efficacy variable</b>	<b>Oma N = 65</b>	<b>Ena N = 70</b>
Systolic Blood Pressure (mmHg):		
Baseline Mean	165.0	165.3
Mean change from baseline (95%CI)	-21.9 (-26.7, -17.1)	-19.3 (-23.4, -15.2)
Difference from Enalapril	-2.6	
Diastolic Blood Pressure:		
Baseline Mean	96.6	96.6
Mean change from baseline (95%CI)	-13.2 (-15.8, -10.6)	-9.5 (-11.9, -7.0)
Difference from Enalapril	-3.7	

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Overall, these data indicate that omapatrilat provides incremental blood pressure reduction in difficult to control patients. These patients have limited options for achieving additional blood pressure reduction and often remain above desired target blood pressure with currently available treatment. These patients also tend to be at greater than average risk of CV events, and thus stand to benefit the most from additional reduction in blood pressure. The incremental blood pressure reduction provided by omapatrilat may produce a very meaningful clinical benefit in these patients with significant medical need.

## **5.4 Efficacy Summary**

In fixed-dose, monotherapy studies, omapatrilat was shown to have a strong dose-response relationship and to produce greater blood pressure reductions than the widely

used antihypertensive agents lisinopril, amlodipine, and losartan. Whether these results could be duplicated under clinically relevant conditions – with elective titration to target, and use of combination therapy if needed -- was studied in OCTAVE. OCTAVE demonstrated that omapatrilat provides consistently greater blood pressure reduction than enalapril in variety of hypertensive populations, despite less use of top-dose therapy and adjunctive antihypertensive agents with omapatrilat.

Examination of data from OCTAVE and other studies provides evidence that the superior efficacy demonstrated for omapatrilat can result in additional blood pressure reduction in patients whose hypertension is difficult to control with existing agents. OCTAVE included large numbers of patients with characteristics associated with hypertension that is difficult to control, as well as large numbers of patients who had not achieved blood pressure control with existing antihypertensive treatment at baseline. In these patient subgroups, as in others, those who received omapatrilat had greater reductions in blood pressure and were more likely to reach blood pressure target than those who received enalapril.

While patients differ in their response to antihypertensive therapy, the efficacy of omapatrilat did not vary with the level of responsiveness to existing antihypertensive therapy. Efficacy in patients resistant to existing therapies was comparable to that observed overall. Amongst the most difficult to treat patients – diabetics uncontrolled on multiple drug regimens including high doses of ACE inhibitor, or those treated with high doses of hydrochlorothiazide, amlodipine, enalapril, and other drugs -- omapatrilat provided meaningful additional reductions in blood pressure.

Thus, efficacy results from a large clinical development program support the utility of omapatrilat in treating hypertension. The data also indicate that omapatrilat provides additional blood pressure reduction in patients with hypertension that is difficult to control with existing therapy.

## **6 CLINICAL SAFETY IN HYPERTENSION**

### **6.1 OVERVIEW**

The most extensive safety evaluation of omapatrilat is based on the 25,000 patient double-blind, randomized, enalapril-controlled OCTAVE study. The following discussion of clinical safety will thus focus on the OCTAVE trial. Data from placebo-controlled studies are also summarized. General safety will be discussed before review of angioedema findings.

The overall safety of omapatrilat is presented in the following order:

- 1) Safety data from placebo-controlled studies: Approximately 4900 hypertensive patients were treated with omapatrilat as part of the 1999 NDA. Of these, 3582 were treated in placebo-controlled trials. Data from these studies are presented to provide comparative safety information relative to placebo, which may be useful in identifying drug-related adverse events. It should be noted that these studies used a variety of starting doses, and most patients did not receive the starting dose of 10 mg omapatrilat that is currently proposed. These studies also used standard reporting and classification procedures for all adverse events, which created difficulties in accurate assessment of the incidence and severity of angioedema. These difficulties, and the procedures developed to address them in OCTAVE, are described below.
- 2) Safety data from OCTAVE; a 25,000 patient: 24 week trial. OCTAVE provides the bulk of exposure to omapatrilat overall and at the proposed dose regimen. OCTAVE also provides comparative safety data relative to enalapril, a representative of a widely used class of antihypertensive agent. Angioedema in OCTAVE is described in the following section.
- 3) Angioedema data from hypertension studies in current filing. Procedures for reporting and classification of angioedema, incidence, severity, clinical presentation, time-course, treatment, outcomes, and risk factors are described.
- 4) Safety in Difficult to Control Populations: Subgroup data from OCTAVE are presented. These represent the most extensive controlled exposure of patients with hypertension that is difficult to control to omapatrilat in the clinical development program.

## 6.2 Summary of Placebo-Controlled General Safety Data from 1999 NDA

A total of 3582 patients received omapatrilat in 12 placebo-controlled studies conducted primarily in the U.S. Four of these studies also included an active control arm (amlodipine or lisinopril).

The incidence of the most common clinical AEs in the 12 placebo-controlled studies is presented by treatment group in Table 6.2.

**Table 6.2: Most Common Clinical Adverse Events (Reported in Greater Than or Equal to 2 Percent of Patients in Any Treatment Group) in Placebo-Controlled Hypertension Studies, by Primary Term**

Primary Term	Number (%) of Patients			
	Placebo N = 1220	Omapatrilat N = 3582	Amlodipine N = 403	Lisinopril N = 404
Headache	203 (16.6)	481 (13.4)	50 (12.4)	63 (15.6)
Dizziness	81 (6.6)	349 (9.7)	23 (5.7)	30 (7.4)
Upper Respiratory Infection (URI)	97 (8.0)	322 (9.0)	46 (11.4)	43 (10.6)
Cough	37 (3.0)	247 (6.9)	16 (4.0)	26 (6.4)
Musculoskeletal Pain	93 (7.6)	246 (6.9)	37 (9.2)	30 (7.4)
Flushing	16 (1.3)	190 (5.3)	7 (1.7)	1 (0.2)
Fatigue	38 (3.1)	172 (4.8)	26 (6.5)	24 (5.9)
Nausea/Vomiting	25 (2.0)	155 (4.3)	12 (3.0)	21 (5.2)
Facial Redness	9 (0.7)	153 (4.3)	2 (0.5)	1 (0.2)
Diarrhea	27 (2.2)	143 (4.0)	6 (1.5)	18 (4.5)
Sinus Abnormality	45 (3.7)	142 (4.0)	10 (2.5)	15 (3.7)
Dyspepsia/Heartburn	24 (2.0)	94 (2.6)	12 (3.0)	10 (2.5)
Pharyngitis	21 (1.7)	87 (2.4)	11 (2.7)	7 (1.7)
Abnormal Urination	12 (1.0)	86 (2.4)	5 (1.2)	15 (3.7)
Influenza	20 (1.6)	86 (2.4)	12 (3.0)	14 (3.5)
Rash	19 (1.6)	76 (2.1)	8 (2.0)	3 (0.7)
Rhinitis	27 (2.2)	76 (2.1)	8 (2.0)	9 (2.2)
Chest Pain	17 (1.4)	71 (2.0)	5 (1.2)	8 (2.0)
Abdominal Pain	24 (2.0)	68 (1.9)	8 (2.0)	12 (3.0)
Edema	32 (2.6)	59 (1.6)	75 (18.6)	12 (3.0)
Musculoskeletal Trauma	17 (1.4)	55 (1.5)	9 (2.2)	7 (1.7)

**Table 6.2: Most Common Clinical Adverse Events (Reported in Greater Than or Equal to 2 Percent of Patients in Any Treatment Group) in Placebo-Controlled Hypertension Studies, by Primary Term**

Primary Term	Number (%) of Patients			
	Placebo N = 1220	Omapatrilat N = 3582	Amlodipine N = 403	Lisinopril N = 404
Sleep Disturbance	15 (1.2)	24 (0.7)	3 (0.7)	9 (2.2)
Swelling Extremity	4 (0.3)	23 (0.6)	15 (3.7)	3 (0.7)
Total Patients With At Least One Event	692 (56.7)	2256 (63.0)	272 (67.5)	250 (61.9)

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Dataset: Treated Patients in Group I (Placebo-Controlled Studies)

The most commonly reported clinical adverse events with omapatrilat were headache and dizziness. Headache occurred less commonly with omapatrilat than placebo. Most events of dizziness were not serious and did not result in discontinuation. Flushing and facial redness were also reported more commonly with omapatrilat than with placebo, amlodipine, and lisinopril. Flushing and facial redness were generally mild or moderate in intensity, self-limiting, and rarely resulted in discontinuation of treatment. In OCTAVE, which used a 10 mg starting dose of omapatrilat, dizziness, flushing, and facial redness occurred much less frequently (see Section 6.3.3, below) though still somewhat more commonly with omapatrilat than enalapril.

Cough is an AE associated with drugs that inhibit ACE. Cough was reported with a similar incidence in the omapatrilat-treatment group (6.9%) and lisinopril-treatment group (6.4%), both higher than placebo (3.0%).

A less frequent event also associated with drugs that inhibit ACE is angioedema. Angioedema was reported in 0.7% of non-African-Americans and 3.0% of African-Americans in these placebo-controlled studies. See Section 6.4 for further discussion of this event.

The frequencies of other common events were higher with either amlodipine or lisinopril than with omapatrilat.

## **6.3 Summary of OCTAVE General Safety Data**

### **6.3.1 General Safety: OCTAVE**

This section provides an overview of the safety data from the OCTAVE study, excluding potential angioedema events, which are discussed in the following section (Section 6.4).

Safety data from the OCTAVE study defines the safety profile for the omapatrilat regimen recommended in the current NDA. Except for angioedema, the overall incidence of adverse events, including serious adverse events and discontinuation for adverse events, was virtually the same for omapatrilat and enalapril in the OCTAVE study. Only flushing and dizziness occurred more frequently (by  $\geq 1\%$ ) in omapatrilat-exposed patients than in enalapril-exposed patients. Flushing and dizziness were generally well tolerated and infrequently resulted in discontinuation of omapatrilat. Headache occurred more frequently in enalapril-exposed patients than in omapatrilat-exposed patients.

### **6.3.2 Overall Summary of Adverse Events: OCTAVE**

The overall incidence of AEs in OCTAVE (excluding angioedema, which was reported separately) was comparable in omapatrilat-exposed patients (51.0%) and enalapril-exposed patients (50.4%). Similarly, the incidence of AEs - including SAEs, deaths, and AEs resulting in discontinuation - was virtually the same for omapatrilat and enalapril.

Table 6.3.2 presents the overall summary of clinical AEs, SAEs, deaths, and discontinuations due to AEs in the OCTAVE study.

**Table 6.3.2: Summary of Adverse Events During and Up to 14 Days Post Double-Blind Therapy**

Event	Number (%) of Patients	
	Omapatrilat N = 12,609	Enalapril N = 12,557
AE, total (% of patients)	6426 (51.0%)	6327 (50.4%)
SAE <sup>a</sup>	441 (3.5%)	470 (3.7%)
ADE <sup>a</sup>	3018 (23.9%)	2800 (22.3%)
Discontinuation Due to AE <sup>a</sup>	1007 (8.0%)	958 (7.6%)
Discontinuation Due to Non-serious AE <sup>a</sup>	891 (7.1%)	813 (6.5%)
Discontinuations Due to SAE <sup>a</sup>	125 (1.0%)	156 (1.2%)
Death <sup>a</sup>	19 (0.2%)	22 <sup>b</sup> (0.2%)

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Note: Special Events (potential angioedema) not included in this table.

<sup>a</sup> Subsets of total AEs: patients may be represented in more than one AE category.

<sup>b</sup> An additional enalapril-treated patient (8500/023) died within 14 days of the last dose of study drug, but was incorrectly noted in the database as discontinuing study drug more than 14 days prior to death, and therefore excluded from the table.

### 6.3.3 Most Common Adverse Events

Table 6.3.3 presents the most common clinical AEs (reported in  $\geq 2\%$  of patients in any treatment group) during and up to 14 days post double-blind therapy. Cough, the most common adverse event with omapatrilat, was reported in 8.7% of omapatrilat-exposed patients and 8.8% of enalapril-exposed patients. Flushing and dizziness occurred more frequently (by  $\geq 1\%$ ) in omapatrilat-exposed patients than in enalapril-exposed patients (flushing: 2.3% omapatrilat; 1.3% enalapril; dizziness: 6.8% omapatrilat; 5.4% enalapril). Flushing infrequently resulted in discontinuation of omapatrilat (0.3%). Dizziness was also generally well tolerated and caused discontinuation in only a small percentage of omapatrilat-exposed patients (1.0%, see Table 6.3.6).

No other adverse events were reported  $\geq 1\%$  more frequently with omapatrilat than enalapril. Headache was more common in enalapril-treated patients (8.9%) than in omapatrilat-treated patients (7.4%).

**Table 6.3.3: Most Common Adverse Events (Reported in Greater than or Equal to 2 Percent of Patients in Any Treatment Regimen) During and Up to 14 Days Post Double-Blind Treatment**

Primary Term	Number (%) of Patients	
	Omapatrilat N = 12609	Enalapril N = 12557
Cough	1099 (8.7%)	1108 (8.8%)
Headache	930 (7.4%)	1115 (8.9%)
Dizziness	856 (6.8%)	680 (5.4%)
Upper Respiratory Infection	852 (6.8%)	870 (6.9%)
Musculoskeletal Pain	661 (5.2%)	689 (5.5%)
Sinus Abnormality	404 (3.2%)	414 (3.3%)
Nausea/Vomiting	395 (3.1%)	379 (3.0%)
Fatigue	380 (3.0%)	381 (3.0%)
Tracheobronchitis	364 (2.9%)	353 (2.8%)
Diarrhea	353 (2.8%)	293 (2.3%)
Flushing	289 (2.3%)	164 (1.3%)
Rhinitis	266 (2.1%)	289 (2.3%)
Total Patients With at least One Event	6426 (51.0%)	6327 (50.4%)

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Note: Potential angioedema events are not included in this summary.

### 6.3.4 Deaths

During and up to 14 days following double-blind treatment, deaths occurred in 19 omapatrilat-treated patients and 23 enalapril-treated patients in OCTAVE. In each treatment group, 11 deaths were due to cardiovascular causes. The most common cause of death was myocardial infarction (4 omapatrilat-treated patients and 4 enalapril treated patients). For omapatrilat-treated patients, other common causes of death (reported in 2 patients each) were cardiorespiratory arrest, intracranial hemorrhage, and pulmonary infection. For enalapril-treated patients, other common causes of death (reported in two

or more patients) were heart failure (3 patients), and pulmonary infection, cerebral vascular accident (CVA), intestinal ischemic disease, and sudden death (2 patients each). There were no deaths which occurred as a result of angioedema in either treatment group.

### 6.3.5 Serious Adverse Events

There were no differences in the frequency of SAEs between omapatrilat and enalapril in OCTAVE. SAEs were reported in 3.5% of omapatrilat-treated patients and 3.7% of enalapril-treated patients. Table 6.3.5 presents the frequencies of the most common SAEs (reported in  $\geq 0.2\%$  of patients in any treatment group), by primary term. In both treatment groups, the most common SAEs were coronary artery disease, atrial rhythm disturbance, myocardial infarction, chest pain, and CVA. There were no SAEs that differed by more than 0.1% in incidence between treatment groups.

**Table 6.3.5: Most Common Serious Adverse Events Reported in Greater than or Equal to 0.2 Percent of Patients in Any Treatment Group, by Primary Term During and Up to 14 Days Post Double-Blind Treatment**

Primary Term	Number (%) of Patients	
	Omapatrilat N = 12609	Enalapril N = 12557
Chest pain	28 (0.2%)	25 (0.2%)
Coronary Artery Disease	25 (0.2%)	21 (0.2%)
Atrial rhythm disturbance	24 (0.2%)	35 (0.3%)
Myocardial infarction	21 (0.2%)	23 (0.2%)
CVA	17 (0.1%)	21 (0.2%)
Total Patients with at Least One Event	441 (3.5%)	470 (3.7%)

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Note: Potential angioedema events are not included in this summary.

### 6.3.6 Discontinuations Due to Adverse Events

Approximately 8.0% of omapatrilat-treated patients and 7.6% of enalapril-treated patients discontinued study drug due to an AE. The incidence of discontinuation for the most commonly ( $> 0.5\%$ ) reported AEs are shown in Table 6.3.6. Cough was the most

common AE that led to discontinuation of study drug (2.0% of omapatrilat-treated patients and 2.1% of enalapril-treated patients).

**Table 6.3.6: Most Common Adverse Events Resulting in Discontinuation (Reported by Greater than or Equal to 0.5 Percent of Patients in any Treatment Group), During and Up to 14 Days Post Double-Blind Treatment**

Primary Term	Number (%) of Patients	
	Omapatrilat N = 12609	Enalapril N = 12557
Cough	246 (2.0%)	260 (2.1%)
Dizziness	128 (1.0%)	94 (0.7%)
Headache	116 (0.9%)	103 (0.8%)
Nausea/vomiting	87 (0.7%)	62 (0.5%)
Fatigue	61 (0.5%)	53 (0.4%)
Total Patients With at Least One Event	1007 (8.0%)	958 (7.6%)

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Note: Discontinuations due to potential angioedema events are not included in this summary.

## 6.4 Angioedema

This section includes angioedema data from OCTAVE and other omapatrilat hypertension studies. Data regarding angioedema was collected and analyzed differently in OCTAVE and studies other than OCTAVE. Description of the specific procedures as well as the angioedema results are included in this section.

### 6.4.1 Assessment of Angioedema

#### 6.4.1.1 Studies Other than OCTAVE

In studies other than OCTAVE, potential episodes of angioedema were reported as adverse events by Investigators using language of their choosing and then coded in a blinded fashion by the sponsor using a coding system based on the International Classification of Disease-Ninth Revision (ICD-9). In general, only those adverse event reports that contained the terms “angioedema” or “angioneurotic edema” were coded as

angioedema. Some AEs coded as “edema head/neck” (head and neck edema) shared clinical features (i.e., lip edema, neck swelling, jaw swelling) with the events diagnosed as “angioedema” by the Investigators.

In this briefing book, for studies other than OCTAVE, both events coded as angioedema and events coded as head and neck edema are included to provide a complete representation of all potential angioedema events. This may result in overcounting of angioedema cases, since some events coded as head and neck edema were likely to have other causes.

#### **6.4.1.2 OCTAVE**

An important goal of OCTAVE was the evaluation of angioedema risk. To ensure accurate ascertainment and classification of angioedema, a special procedure was created, which included active reporting of potential angioedema events, comprehensive data collection using structure instruments, and adjudication by an expert panel without knowledge of treatment assignment for reporting and classification of potential episodes of angioedema.

If a patient experienced potential angioedema, including any swelling in the head and neck region, the Investigator was instructed to complete a special event (SE) Initial Report which included preliminary information regarding treatment, outcome, and suspected etiology of the event. The SE Initial Report was communicated to the Sponsor through a Contract Research Organization (CRO), which checked the form for completeness and entered available data into a database.

Subsequently the Sponsor completed a Follow-up Information Form for each event by contacting the Investigator by telephone. The Follow-up Form included more detailed information regarding the intensity, clinical features, treatment, outcome, etiology of the event as well as a description of diagnostic procedures, prodromal symptoms, concomitant medications, and a history of compliance with study drug. The Sponsor abstracted data from the Follow-up Form into a Narrative of the event and forwarded the Narrative as well as the completed Follow-up Form to the Investigator for review, editing, and signature. After sign off by the Investigator, data from the Follow-up Form were entered into a database.

The Sponsor forwarded the data from initial report, the Follow-up Form, and the Narrative for each event to the Event Adjudication Committee. Event Adjudication Committee members were selected by the Steering Committee on the basis of expertise in clinical allergy and immunology or cardiovascular medicine and experience in clinical trials. The three primary adjudicators for the Event Committee then reviewed each event and met to reach a consensus on presence/absence of angioedema, severity class, and etiology of the event. The determination of the Event Adjudication Committee was recorded on an Adjudication Case Report Form and was entered into a database by the Sponsor. The Sponsor was not present during the deliberations of the Event Adjudication Committee. The Event Adjudication Committee did not have any knowledge of treatment group assignment at anytime. The analyses of angioedema presented in this report are based on adjudicated outcomes of reported SEs.

All analyses in the OCTAVE study were based on events confirmed as angioedema by the Event Adjudication Committee. If patients had multiple events, only the first most severe event was counted. For most analyses (including summaries of incidence, timecourse, dose-response, and risk factors), the denominator for all presentations was the total number of patients treated. For analyses of the features of angioedema (including summaries of treatment, time to resolution, outcome, signs, and symptoms), the denominator for all presentations was the total number of patients experiencing an angioedema event.

#### **6.4.2 Angioedema Incidence in Randomized, Controlled Hypertension Studies Other than OCTAVE**

The incidence of angioedema in hypertension studies other than OCTAVE is summarized in Table 6.4.2A.

**Table 6.4.2A: Incidence of Angioedema in Studies Other than OCTAVE**

	<b>Number of Subjects Exposed to Omapatrilat</b>	<b>Angioedema N (%)</b>	<b>Head and Neck Edema N (%)</b>
1999 NDA database Randomized, Controlled Studies	4284	44 (1.03)	40 (0.93)
Controlled Hypertension Studies Since 1999 Submission (other than OCTAVE)	1226	13 (1.06)	19 (1.55)

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1999 NDA Submission

In the randomized, controlled hypertension studies included in the 1999 submission, a total of 44 episodes coded as angioedema and 40 episodes coded as head and neck edema were reported.

There were fewer cases of angioedema and head and neck edema in patients started on omapatrilat doses less than 20 mg than in patients started on doses of 20 mg or more (Table 6.4.2B). Because African-Americans have been noted to be at higher risk of angioedema from ACE inhibitors, the incidence of angioedema and head and neck edema was also analyzed by starting dose and race. African-Americans appeared to be at higher risk of angioedema and head and neck edema than others, regardless of starting dose.

**Table 6.4.2B: Angioedema and Head and Neck Edema in Omapatrilat-Treated Patients by Starting Dose and Race in Controlled Hypertension Trials (N = 4284), 1999 NDA**

	Overall		African-American		Non-African-American	
	< 20 mg (%) N = 1544	≥ 20 mg (%) N = 2740	< 20 mg (%) N = 148	≥ 20 mg (%) N = 540	< 20 mg (%) N = 1396	≥ 20 mg (%) N = 2200
Angioedema	7 (0.45) <sup>a</sup>	37 (1.35)	3 (2.03)	18 (3.33)	4 (0.29) <sup>a</sup>	19 (0.86)
Head and Neck Edema	11 (0.71) <sup>a</sup>	29 (1.06)	2 (1.35)	12 (2.22)	9 (0.64) <sup>a</sup>	17 (0.77)

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Note: Table includes events that occurred on the starting dose of omapatrilat and after titration to higher doses.

<sup>a</sup> One patient from study CV137-029 (039/012, 78 year old white female started on 10 mg omapatrilat) experienced both angioedema and head and neck edema. This patient is counted in the number of patients who experienced each event.

The incidence of life-threatening angioedema and head and neck edema (resulting in intubation/tracheostomy) is presented for starting doses of 10 and 20 mg by race and severity in Table 6.4.2C.

**Table 6.4.2C: Angioedema and Head and Neck Edema in Omapatrilat-Treated Patients for Starting Doses of 10 mg and 20 mg by Race and Severity in Controlled Hypertension Trials, 1999 NDA (N = 3586)**

Severity Class	Overall		African-American		Non-African-American	
	10 mg N = 1137	20 mg N = 2449	10 mg N = 103	20 mg N = 507	10 mg N = 1034	20 mg N = 1942
<b>Overall Incidence</b>						
Angioedema	4 (0.35%) <sup>a</sup>	33 (1.35%)	1 (0.97%)	18 (3.55%)	3 (0.29%)	15 (0.77%)
Head and Neck Edema	9 (0.79%) <sup>a</sup>	25 (1.02%)	2 (1.94%)	11 (2.17%)	7 (0.68%)	14 (0.72%)
<b>Incidence of Intubation/Tracheostomy</b>						
Angioedema	0 (0%)	4 (0.16%)	0 (0%)	2 (0.39%)	0 (0%)	2 (0.10%)
Head and Neck Edema	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)

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Note: Table includes events that occurred on the starting dose of omapatrilat and after titration to higher doses.

<sup>a</sup> One patient from study CV137-029 (039/012, 78 year old white female started on 10 mg omapatrilat) experienced both angioedema and head and neck edema. This patient is counted in the number of patients who experienced each event.

Four patients with angioedema (and none with head and neck edema) required mechanical airway protection with intubation or tracheostomy. All recovered without clinical sequelae. Two were African-American.

These four episodes occurred during the first two weeks of treatment, two on the first day. All occurred after initiation of therapy with a 20 mg starting dose. Narratives for these 4 patients are provided below.

Patient 020/001

Patient 020/001, in study CV137-024, 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 tracheotomy. The tracheotomy 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.”

#### Patient 034/029

Patient 034/029 in study CV137-037, a 55 year-old black female with a history of 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.

#### Patient 089/017

Patient 089/017 in study CV137-037, a 34 year-old black 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.

#### Patient 094/009

Patient 094/009 in study CV137-042, a 78 year-old white male with an 2-year history of hypertension, was hospitalized for syncope after 6 days of omapatrilat 20 mg. Double-blind therapy was discontinued. While under observation, the subject developed glottis and larynx edema which obstructed the airway. He underwent a cricothyrotomy with subsequent tracheotomy and was treated with methylprednisolone and amoxicillin/clavulanic acid with recovery. The Investigator classified the event as very severe and considered the event to be possibly related to double-blind therapy. Subsequent to database lock and unblinding, the investigator reviewed the final hospital records and now considers this event to be consistent with angioedema.

#### Controlled hypertension studies since 1999 NDA submission (other than OCTAVE)

One thousand two hundred twenty six (1226) patients were exposed to omapatrilat in 6 controlled hypertension studies (other than the OCTAVE study) that are newly reported in the NDA 2001. Among these 1226 patients (most started on omapatrilat 20 mg), 13 experienced angioedema and 19 experienced head and neck edema. After data lock, one additional omapatrilat-exposed patient (Patient 144/006 in study CV137-066) was reported to have head and neck edema. None of these events resulted in intubation or tracheostomy.

#### Summary

Combining the experience from all completed controlled hypertension studies (including studies newly reported in the NDA 2001), there were 3361 hypertensive patients who

started treatment with omapatrilat at a dose of 20 mg, 4 of whom experienced severe angioedema resulting in intubation or tracheostomy (including 2 cases of intubation or tracheostomy among the 645 African-American hypertensive patients started on omapatrilat 20 mg).

### 6.4.3 Incidence of Angioedema in the OCTAVE Study

The overall adjudicated incidence of angioedema over the 24 week treatment period was 2.17% (274 cases) with omapatrilat vs. 0.68% (86 cases) with enalapril (relative risk 3.17).

**Table 6.4.3: Incidence of Angioedema During and Up to 14 Days Post Double-Blind Therapy**

<b>Angioedema</b>	<b>Omapatrilat N = 12609</b>	<b>Enalapril N = 12557</b>
# of Patients with Angioedema (%)	274 (2.17%)	86 (0.68%)
Risk Ratio (LCL, UCL)	3.17 (2.52, 4.12)	
p-value <sup>a</sup> : testing for risk ratio >= 2	0.9999	

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<sup>a</sup> If p-value < 0.05 and relative risk < 2, the null hypothesis, overall event risk with omapatrilat relative to enalapril is 2 fold or greater, is rejected.

A total of 153 patients experienced potential angioedema which was not confirmed by the Event Adjudication Committee. This includes 84 omapatrilat-treated patients (0.67%) and 69 enalapril-treated patients (0.55%).

African-American patients in either treatment group had an incidence of omapatrilat almost 3 times higher than non-African-American patients. Similarly, current smokers exposed to omapatrilat had an incidence of angioedema almost 3 times higher than patients who never smoked. Two of 12,609 omapatrilat exposed patients (one African-American and one white smoker) experienced airway compromise associated with angioedema. One of these required mechanical airway protection. Both patients recovered. No enalapril-treated patients experienced airway compromise with angioedema. The risk factors, severity, signs and symptoms, timecourse and treatments received for the angioedema events observed in OCTAVE are discussed below.

#### **6.4.4 Severity of Angioedema in the OCTAVE study**

##### **6.4.4.1 Angioedema with Mechanical Airway Protection and/or Airway Compromise in the OCTAVE study**

Angioedema with mechanical airway protection and/or airway compromise was exceedingly rare. Of 12,609 omapatrilat-treated patients in OCTAVE, 2 developed angioedema with airway compromise (Table 6.4.4.1). No enalapril-treated patients developed angioedema with airway compromise. Summaries for the two patients with airway compromise are provided below.

###### Patient 00081/002

Patient 00081/002 was a 62 year old black female with a history of hypertension and hypercholesterolemia. She was a non-smoker and had never taken an ACE Inhibitor. Neither she nor her family had experienced angioedema in the past. She was randomized to Level I (10 mg) study medication on 06-Dec-2000 without incident and was titrated to Level II (20 mg) (20-Dec-2000), Level III (40 mg) (04-Jan-2001) and Level IV (80 mg) (17-Jan-2001) with no problems. She came in for her Week 8 visit on 31-Jan-2001, still on 80 mg, and was doing well. No AEs were reported at any time. Her blood pressure was 154/80 at the Week 8 visit. On 17-Feb-2001, the patient took her medication at 1600, rather than her normal time of 0800, and was feeling well until approximately 16:30 (30 minutes later) at which time she complained of her tongue feeling thick and numb, “like something bit her”, first only on the left side, and then on both sides. Her tongue continued to swell over the next 2 hours and she had her son take her to the emergency room. She presented to the emergency room with severe swelling of the tongue, and swelling of the lips eyelids, mucous membranes, pharynx, larynx, neck and face all symmetrical in nature. She had difficulty speaking and swallowing and her symptoms progressed to fully developed airway obstruction.

- 18:40 presented to emergency room (blood pressure 198/100, pulse oxygen 100%) tongue continuing to swell.
- 19:05 the patient treated with intra-venous Decadron and Benadryl, Versed shortly after.
- 19:15 to 19:26 attempted intubation but swelling of the throat and tongue made this impossible.
- 19:35 treated with 0.3 mg epinephrine and continued to try intubation.

- 19:37 cricothyroid tracheostomy performed.
- 19:53 respiratory therapy/ventilation performed.

The patient remained stable with tracheostomy in place through 20-Feb-2001 at which time she was sedated and orally intubated. Patient remained intubated until 22-Feb-2001 at which time she was extubated without incident. It was noted that angioedema had resolved at this time although some supraglottic edema remained, likely secondary to the cricothyroidotomy tube. She remained hospitalized until 09-Mar-01 for work-up of unrelated problems (atrial fibrillation, elevated pulmonary artery pressures, low ejection fraction, and bleeding gastric ulcers). She was released from the hospital on 09-Mar-2001 in good condition. The patient was contacted at home on 12-Mar-2001 and was feeling fine, although she still had some soreness from the tracheostomy site.

The Investigator reported all events as very severe in intensity and believed them to be an adverse reaction to double-blind study medication. Other causes for angioedema were extensively explored with the patient via interview by site personnel. No unusual foods were ingested and no other possible causes such as insect bite, etc were present. Concomitant medications at the time of the event were Norvasc 10 mg, Lipitor 10 mg and Naprosyn 375 mg as needed for osteoarthritis.

#### Patient 08215/016

Patient 08215/016 was a 56-year-old white female with a history of hypertension and hypercholesterolemia. She had received brief courses of an ACE inhibitor (ramipril) in 1998 and again in 1999 with no apparent adverse reaction. She had no other significant history. She was a current smoker. Concomitant medications at the time of the event were bendrofluazide 2.5 mg, diltiazem 240 mg, and atenolol 100 mg. She was randomized on 27-Nov-2000 and was administered Level I (10 mg) study drug at 1100. Fifteen (15) minutes after dosing, she reported an odd sensation in her neck and throat, hoarseness and difficulty speaking and swallowing. She was able to walk to the examination room, but began to deteriorate rapidly with apparent dyspnea, cyanosis and swelling of the eyelids, lips and neck. Swelling of the lips and eyes was noted to be symmetric. The patient then lost consciousness and was administered intra-muscular epinephrine. After 30 seconds she responded and was able to open her eyes. She still appeared cyanotic. After 5-7 minutes an additional dose of epinephrine was given. She improved with a

measurable blood pressure of 110/60 mmHg and started communicating with further improvement over the next 5 minutes. She was transferred by ambulance to the hospital for observation and treatment of the event and received additional doses of epinephrine as well as prednisolone and chlorpheniramine. She was discharged from the hospital in good condition on 28-Nov-2000. The discharge diagnosis was anaphylaxis. The Investigator reported the events as an adverse reaction to double-blind study medication. The patient was discontinued from the study.

Based on OCTAVE, the calculated incidence and accompanying 95% confidence intervals of angioedema with airway compromise, angioedema with mechanical airway protection, and angioedema resulting in death from airway compromise per 10,000 treated patients are summarized in Table 6.4.4.1.

**Table 6.4.4.1: Angioedema with Mechanical Airway Protection and/or Airway Compromise During and Up to 14 Days Post Double-Blind Therapy**

	<b>Oma</b> N = 12,609	<b>Ena</b> N = 12,557
<b>Mechanical Airway Protection and/or Airway Compromise</b>		
N	2 <sup>a</sup>	0
Rate per 10000 treated (95% CI)	1.6 (0.2 – 5.7)	0 (0 - 2.9)
<b>Mechanical Airway Protection</b>		
N	1	0
Rate per 10000 treated (95% CI)	0.8 (0.02 – 4.4)	0 (0 - 2.9)
<b>Resulting in Death</b>		
N	0	0
Rate per 10000 treated (95% CI)	0 (0 - 2.9)	0 (0 - 2.9)

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<sup>a</sup> One patient had airway compromise (without intubation/tracheostomy) due to angioedema associated with anaphylaxis.

**6.4.4.2 Pre-Specified Severity Scale Based on Treatment Administered and Location of Treatment in the OCTAVE Study**

Because angioedema with mechanical airway protection or airway compromise was very rarely observed in the OCTAVE study, an attempt was made to classify all angioedema events as to severity. Since no standardized or validated classification system for angioedema is currently available, a classification system was prospectively developed

for this purpose. This system utilized treatment variables including therapies received and location of treatment (outpatient versus inpatient) as the primary basis for classification, in the belief that the type of intervention (treatment provided) would reflect the severity and clinical importance of the signs and symptoms of angioedema. This information was routinely provided to the Data and Safety Monitoring Committee to assist in their safety monitoring while the study was ongoing.

In addition, a pre-specified analysis was described which tested for a significant association between treatment group (omapatrilat or enalapril) and severity classification. The results of this analysis are presented in Table 6.4.4.2. A significant association was noted between treatment group and severity class.

**Table 6.4.4.2: Confirmed Events, By Severity and Treatment Group**

Severity	Number (%) of Patients	
	Omapatrilat N = 12,609	Enalapril N = 12,557
I no treatment administered or antihistamines only	161 (1.28%)	65 (0.52%)
II treated with catecholamines or steroids	94 (0.75%)	19 (0.15%)
III hospitalized but no mechanical airway protection	18 (0.14%)	2 (0.02%)
IIIa hospitalized but no airway compromise	17	2
IIIb hospitalized with airway compromise	1	0
IV airway protection or death <sup>a</sup>	1 (0.01%)	0 (0.00%)
p-value (proportional odds model):	0.0045	
p-value (weighted least squares regression model):	0.0046	

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Note: Percentages were based on the number of treated patients with angioedema by treatment group. For patients with multiple events, the first most severe event was used.

<sup>a</sup> One omapatrilat-treated patient required mechanical airway protection. There were no deaths from angioedema in OCTAVE.

Although no attempt was made to formally validate this approach to classification of angioedema, patient narratives were reviewed in a blinded fashion to assess in a qualitative manner the extent to which hospitalization was associated with clinical signs and symptoms of angioedema. This review suggested that hospitalization may not be a reliable marker of the severity of angioedema in the absence of airway compromise. In 19 patients without airway compromise, hospitalizations were generally quite brief. Fifteen of these 19 patients were discharged from the hospital within one day of

admission, and three within two days of admission. None had progression of signs and symptoms of angioedema after hospital admission. Many had factors other than angioedema that may have contributed to the decision to hospitalize. These included late hour (i.e., treatment or observation required after 5 pm) in seven, social factors (advanced age, alcoholism, or mental illness) in three, and comorbid events (chest pain, syncope) in three. Hence, the results of this assessment should be interpreted with these observations in mind.

#### **6.4.5 Signs and Symptoms of Angioedema in the OCTAVE Study**

In OCTAVE, signs and symptoms of angioedema were similar for omapatrilat and enalapril. The most common physical signs were swelling of the lips or face. The most common symptoms were flushing/ facial redness. Difficulty swallowing and speaking were somewhat more common in omapatrilat-associated than enalapril-associated angioedema.

Most episodes of flushing and facial redness, however, occurred in patients without angioedema. Oropharyngeal involvement (swelling of the tongue, difficulty speaking, and difficulty swallowing) was somewhat more common with omapatrilat and may have triggered more active health-care seeking behavior on the part of patients and more aggressive treatment on the part of physicians.

#### **6.4.6 Timecourse of Onset of Angioedema in the OCTAVE Study**

The incidence of angioedema was not constant over time in the OCTAVE study (Table 6.4.6). The incidence of angioedema was highest on the first day of treatment, when 88 events occurred (0.70% of treated patients), versus 3 events with enalapril (0.02% of treated patients). Approximately two-thirds of first-dose events with omapatrilat occurred within 2 hours of dosing and over 80% within 4 hours of dosing.

**Table 6.4.6: Incidence of Confirmed Angioedema Events by Time Period**

Time Period	Omapatrilat		Enalapril	
	Total Patients at Risk	Number of Confirmed Events (Incidence)	Total Patients at Risk	Number of Confirmed Events (Incidence)
Day 1	12609	88 (0.70%)	12557	3 (0.02%)
Day 2 - Week 4	12521	83 (0.66%)	12554	43 (0.34%)
Week 5 - Week 8	11572	44 (0.38%)	11615	22 (0.19%)
Week 9 - Week 12	10952	25 (0.23%)	10972	3 (0.03%)
Week 13 - Week 16	10778	14 (0.13%)	10782	7 (0.06%)
Week 17 - Week 20	10581	10 (0.09%)	10597	4 (0.04%)
Week 21 - Week 24	10373	10 (0.10%)	10380	4 (0.04%)

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Note: For patients with multiple events, the first event is counted. After the first event patients are considered no longer at risk of an event.

## 6.4.7 Treatment, Time to Resolution, and Outcome of Angioedema in the OCTAVE Study

### 6.4.7.1 Treatment

Investigators were instructed to discontinue study drug in all patients with potential angioedema. As shown in Table 6.4.4.2, the majority of omapatrilat-treated patients in the OCTAVE study with angioedema either received no treatment, other than discontinuation of study drug, or were only treated with an antihistamine. The most common treatments provided to omapatrilat-treated patients who experienced angioedema were antihistamines (58.0%) and corticosteroids (38.7%); epinephrine was used less commonly (8.4%). Enalapril-treated patients who experienced angioedema were less likely to receive antihistamines, corticosteroids, or epinephrine (40.7%, 23.3% and 1.2%, respectively).

Swelling of the tongue, difficulty speaking, and difficulty swallowing, as well as extensive swelling ( $\geq 3$  sites) and lip swelling, were associated with treatment with

epinephrine/corticosteroids, consistent with customary clinical practice and instructions provided on the enalapril package insert, which was reproduced in the study protocol.

#### **6.4.7.2 Time to Resolution**

Approximately half of the events in the omapatrilat-treated patients in OCTAVE resolved within one day. Over 90% resolved within one week.

Angioedema associated with enalapril was slower to resolve. Only 24% of events resolved within one day versus 53% with omapatrilat. This difference in time to resolution may reflect the effects of treatment with epinephrine and corticosteroids, which were provided more frequently to patients experiencing angioedema with omapatrilat than those experiencing angioedema with enalapril.

#### **6.4.7.3 Outcome**

Almost all cases of angioedema resolved. For enalapril, two events were reported as unresolved (Patients 00190/019 and 08361/009) and two events were reported as resolved with sequelae (Patients 01080/027 and 06876/004) at the time of database lock. Information received subsequently indicates complete resolution of angioedema in these four patients.

One additional enalapril-treated patient (00646/014) had an angioedema event reported as unresolved at database lock. This patient had an earlier event of comparable intensity, which was reported as resolved. Because of programming conventions, which use the first most severe event in the case of multiple events, only the first event was counted. Information received after database lock indicates complete resolution of the second event.

For omapatrilat, two events (Patients 00233/028 and 08613/012) were reported as unresolved at the time of database lock. Both patients have been treated with ACE inhibitors since completion or discontinuation of study drug.

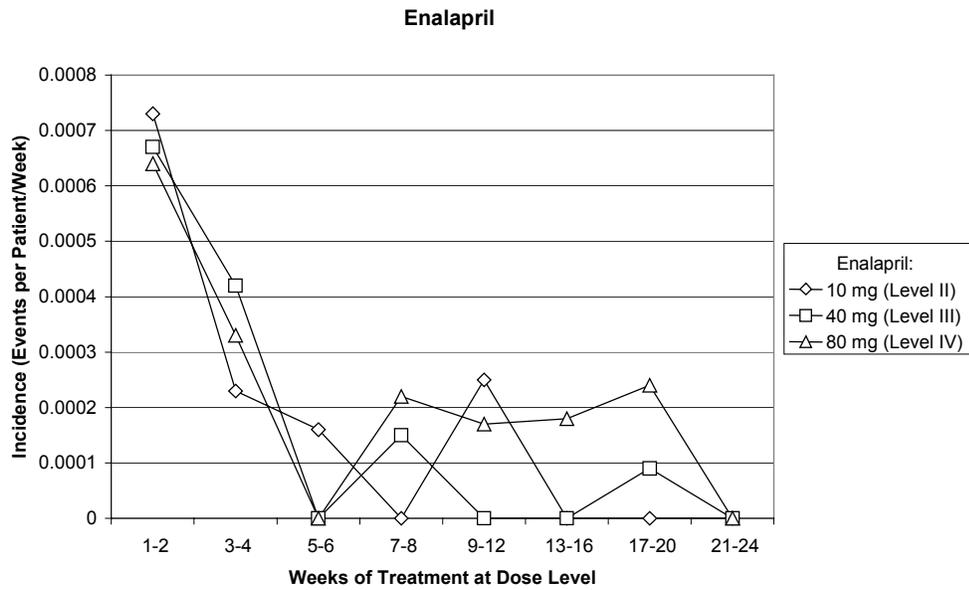
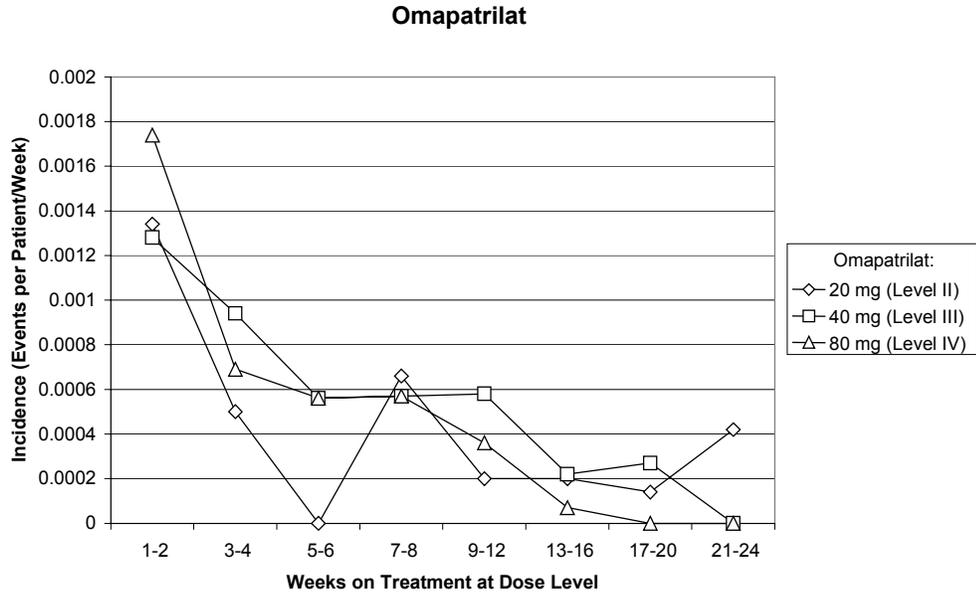
There were also 2 omapatrilat-treated patients with confirmed angioedema where the event was reported as resolved with sequelae. Neither were clinically significant (Patient 03662/007, sequelae of redness of cheek, and Patient 08883/007, sequelae of dry cough).

#### **6.4.8 Association of Angioedema with Starting Dose and Dose Titration**

Whereas the 1999 NDA database suggested the incidence of angioedema may be lower with an omapatrilat starting dose of 10 mg compared to 20 mg or higher, this observation was not confirmed by the results of OCTAVE. The overall incidence of angioedema with omapatrilat started at 10 mg in OCTAVE was 2.17%, comparable to the combined angioedema/head and neck edema incidence in prior studies using 20 mg starting dose. However, it should be noted that only 2 cases of airway compromise (one requiring intubation) were observed in 12,609 patients who received omapatrilat 10 mg as starting dose in OCTAVE compared to 4 cases observed in 2,449 patients who received omapatrilat 20 mg as starting dose in the 1999 NDA (see Table 6.4.2C). Given the low frequency of these severe events, the data should be interpreted with caution.

Approximately one-half of angioedema events with omapatrilat in OCTAVE occurred with 10 mg omapatrilat (Level I) with fewer events after dose increase to 20 mg (Level II), 40 mg (Level III) and 80 mg (Level IV) despite longer mean duration of exposure to higher doses (13.8 days, 60.1 days, 68.8 days, 115.0 days, respectively). As a function of time on treatment, the risk of angioedema was comparable with 20, 40, and 80 mg omapatrilat (Figure 6.4.8). While the risk of angioedema was somewhat higher during the first two weeks at each dose level than with subsequent treatment, the actual number of events associated with up-titration (occurring on the first day of treatment at a higher dose level) was very small (Table 6.4.8). These data demonstrate that upward dose titration was not associated with an increased risk of developing angioedema.

**Figure 6.4.8: Incidence of Angioedema on Dose Level II, III, and IV, as a Function of Time on Dose Level: OCTAVE Study**



**Table 6.4.8: Confirmed Events on First Day of Each Study Medication Dose Level**

First Day of Level	Omapatrilat		Enalapril	
	Total Patients Exposed	Number of Confirmed Events (Incidence)	Total Patients Exposed	Number of Confirmed Events (Incidence)
Level I	12609	88 (0.70%)	12557	3 (0.02%)
Level II	11899	3 (0.03%)	11946	2 (0.02%)
Level III	7596	3 (0.04%)	8429	1 (0.01%)
Level IV	3769	2 (0.05%)	4748	0 (0%)

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Note: Percentages were based on the number of treated patients exposed to particular dose level and time period. For patients with multiple events, the first most severe event was used.

#### **6.4.9 Risk Factors for Angioedema in the OCTAVE Study**

A detailed analysis of risk factors for angioedema with omapatrilat was conducted in the OCTAVE study including demographic characteristics, baseline severity/type of hypertension, clinical comorbidities, history of ACE inhibitor treatment, and other potential risk factors (allergy, rash and smoking history). Of these, only two, African-American race and current smoking, were associated with increased incidence of angioedema in omapatrilat-treated patients. A lower incidence of angioedema was observed in patients with diabetes, isolated systolic hypertension, heart failure, or a history of atherosclerotic disease than in the overall study population. Prior treatment with an ACE inhibitor was not associated with a lower risk of angioedema.

**6.4.9.1 Identification of Key Risk Factors in the OCTAVE study**

Stepwise logistic regression was used to identify key risk factors in the OCTAVE study for angioedema with omapatrilat. Candidate variables were derived from univariate analyses presented in Tables 6.4.9.1 - 6.4.9.4, and included major demographic variables, comorbid conditions, history of ACE inhibitor use, and history of seasonal allergy, rash, or smoking.

The results of this analysis are presented in Table 6.4.9.1. African-American race (2.97 times higher risk than non-African-American) and current smoking (2.49 times higher risk than non-smokers) were strongly associated with angioedema. Weaker associations were observed for female gender, a history of seasonal allergies, and former smoking. A history of diabetes reduced the risk for angioedema.

**Table 6.4.9.1: Risk Factors for Angioedema with Omapatrilat**

<b>Risk Factor</b>	<b>Odds Ratio (95% CI)</b>	<b>P value</b>
African-American Race	2.97 (2.24, 3.92)	< 0.0001
Current Smoker	2.49 (1.86, 3.34)	< 0.0001
Female Gender	1.49 (1.16, 1.91)	0.002
Seasonal Allergies	1.52 (1.12, 2.06)	0.008
Former Smoker	1.47 (1.09, 1.99)	0.013
History of diabetes	0.58 (0.38, 0.90)	0.014

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A detailed summary of the incidence of angioedema by demographic variables, comorbid conditions, history of ACE inhibitor use, and other characteristics is presented in the following sections.

**6.4.9.2 Demographic Characteristics**

The incidence of angioedema and relative risk in the OCTAVE study are displayed by demographic characteristic in Table 6.4.9.2.

The incidence of angioedema in the OCTAVE study was approximately three times higher in African-American patients than in white patients treated with omapatrilat.

Consistent with published literature for ACE inhibitors, the incidence of angioedema was also three times higher in African-American patients than in white patients treated with enalapril. The incidence of angioedema with both drugs was slightly higher for women than for men. In all other major demographic subgroups, the incidence of angioedema did not differ markedly from the incidence in the overall study population, and relative risks were comparable to that observed overall.

**Table 6.4.9.2: Incidence of Angioedema and Risk by Demographic Characteristic**

Demographic Characteristic	Omapatrilat		Enalapril		Relative Risk (LCL, UCL)
	No. of Confirmed Events/Total Number of Patients	Incidence	No. of Confirmed Events/Total Number of Patients	Incidence	
Age					
< 65 years	204 / 9040	2.26%	56 / 9045	0.62%	3.64 (2.77, 5.05)
≥ 65 years	70 / 3569	1.96%	30 / 3512	0.85%	2.30 (1.53, 3.73)
≥ 75 years	27 / 1058	2.55%	6 / 1044	0.57%	4.44
Gender					
Males	121 / 6570	1.84%	35 / 6510	0.54%	3.43 (2.42, 5.27)
Females	153 / 6039	2.53%	51 / 6047	0.84%	3.00 (2.23, 4.26)
Race					
White	198 / 11101	1.78%	61 / 11126	0.55%	3.25 (2.49, 4.46)
African-American	72 / 1300	5.54%	20 / 1237	1.62%	3.43 (2.20, 6.25)
Asian/Pacific Islander	4 / 184	2.17%	3 / 165	1.82%	1.20
Other	0 / 24	0.00%	2 / 29	6.90%	-

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Note: For patients with multiple events, the first event is counted.

Confidence limits are not calculated when there are fewer than 10 events per treatment group.

**6.4.9.3 Baseline Severity/Type of Hypertension and Clinical Comorbidities**

The incidence of angioedema and relative risk in the OCTAVE study are displayed by baseline severity/type of hypertension and clinical comorbidity in Table 6.4.9.3. The incidence of angioedema with omapatrilat was lower in a number of patient subgroups - isolated systolic hypertension, diabetes, heart failure, or a history of atherosclerotic disease - than in the overall study population. The incidence of angioedema with enalapril was decreased in diabetics, but not in other patient populations. As a result, the relative

risk of angioedema with omapatrilat versus enalapril was lower in patients with isolated systolic hypertension, heart failure, or atherosclerotic disease than in the overall study population. The relative risk (RR) of angioedema with omapatrilat versus enalapril was also slightly reduced in patients with renal disease.

**Table 6.4.9.3: Incidence of Angioedema and Relative Risk by Baseline Severity/Type of Hypertension and Clinical Comorbidities**

Characteristic	Omapatrilat		Enalapril		Relative Risk (LCL, UCL)
	No. of Events/Total Number of Patients	Incidence	No. of Events/Total Number of Patients	Incidence	
Severe Hypertension <sup>a</sup>	83 / 3774	2.20%	27 / 3680	0.73%	3.00 (2.01, 4.97)
Isolated Systolic Hypertension <sup>b</sup>	12 / 682	1.76%	8 / 677	1.18%	1.49
Diabetes	23 / 1712	1.34%	7 / 1646	0.43%	3.16
Heart Failure	1 / 116	0.86%	1 / 122	0.82%	1.05
Atherosclerotic Disease	14 / 1184	1.18%	7 / 1169	0.60%	1.97
Renal Disease <sup>c</sup>	11 / 302	3.64%	5 / 307	1.63%	2.24

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Note: Confidence limits are not calculated when there are fewer than 10 events in either treatment group.

For patients with multiple events, the first most severe event is counted.

<sup>a</sup> Defined as patients in study Group 1 (initial therapy) with JNC-VI Stage III hypertension at randomization or in study Group 2 (replacement therapy) or 3 (add-on therapy) receiving 2 or more antihypertensive medications at baseline.

<sup>b</sup> Defined as baseline systolic blood pressure  $\geq$  140 mmHg and diastolic blood pressure  $<$  90 mmHg in patients not treated at baseline.

<sup>c</sup> Defined as renal disease by medical history, or baseline serum creatinine  $>$  1.5 mg/dL.

#### 6.4.9.4 History of ACE Inhibitor Treatment

The incidence of angioedema in the OCTAVE study is summarized by history of ACE inhibitor use and treatment group in Table 6.4.9.4. For both omapatrilat and enalapril, the incidence of angioedema was generally similar for those with no history of ACE inhibitor use, those with a history of ACE inhibitor use in the remote past (> 6 months prior to enrollment) or recent past (48 hours - 6 months prior to enrollment), and those receiving an ACE inhibitor at enrollment.

**Table 6.4.9.4: Incidence of Angioedema and Relative Risk by History of ACE Inhibitor Use**

History of ACE-I Use <sup>a</sup>	Omapatrilat		Enalapril		Relative Risk (LCL, UCL)
	No. of Events/Total Number of Patients	Incidence	No. of Events/Total Number of Patients	Incidence	
Current	38 / 2176	1.75%	15 / 2253	0.67%	2.62 (1.50, 5.54)
Recent Past <sup>b</sup>	17 / 911	1.87%	8 / 905	0.88%	2.11
Remote Past <sup>c</sup>	35 / 1341	2.61%	13 / 1279	1.02%	2.57 (1.43, 5.83)
Never	184 / 8180	2.25%	50 / 8119	0.62%	3.65 (2.73, 5.17)

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Note: Confidence limits are not calculated when there are fewer than 10 events in each treatment group.

For patients with multiple events, the first most severe event is counted.

<sup>a</sup> For 2 patients (1 oma, 1 ena), the use of ACE-I was unknown.

<sup>b</sup> Defined as ACE-I use greater than 48 hours but less than 6 months prior to patient enrollment.

<sup>c</sup> Defined as ACE-I use greater than 6 months prior to patient enrollment.

#### 6.4.9.5 Other Potential Risk Factors: Allergy, Rash and Smoking History

The incidence of angioedema and relative risk in patients with other potential risk factors in the OCTAVE study (smoking or a history of seasonal allergies or drug rash) are displayed in Table 6.4.9.5. The incidence of angioedema with omapatrilat was increased in current smokers as compared with former smokers and those who had never smoked. Smoking was not, however, associated with an increased risk of angioedema with

enalapril. Thus, the relative risk of angioedema with omapatrilat versus enalapril was increased in current smokers.

The incidence of angioedema was modestly increased in patients with a history of seasonal allergy treated with either omapatrilat or enalapril. The relative risk for angioedema with omapatrilat versus enalapril in patients with seasonal allergies was comparable to the relative risk in the overall study population.

The incidence of angioedema was decreased with omapatrilat, and increased with enalapril, in patients with a history of drug rash, as compared to the overall study population. The relative risk (RR) in this small subgroup favored omapatrilat (RR = 0.42).

**Table 6.4.9.5: Incidence of Angioedema and Relative Risk by Other Potential Risk Factors**

Other Potential Risk Factors	Omapatrilat		Enalapril		Relative Risk (LCL, UCL)
	No. of Events/Total Number of Patients	Incidence	No. of Events/Total Number of Patients	Incidence	
History of Allergy	55 / 1644	3.35%	19 / 1614	1.18%	2.84 (1.76, 5.34)
History of Rash	3 / 286	1.05%	8 / 323	2.48%	0.42
Smoking Status <sup>a</sup>					
Never	107 / 6576	1.63%	40 / 6594	0.61%	2.68 (1.91, 4.02)
Former	78 / 3732	2.09%	28 / 3683	0.76%	2.75 (1.84, 4.52)
Current	89 / 2264	3.93%	18 / 2233	0.81%	4.88 (3.13, 9.25)

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Note: Confidence limits are not calculated when there are fewer than 10 events in each treatment group.

For patients with multiple events, the first most severe event is counted.

<sup>a</sup> Smoking status was unknown for a total of 84 patients.

#### 6.4.10 Angioedema in Long-Term Studies

Data from the 4 open-label long-term hypertension studies (i.e., CV137-009, -029LT, -042LT, -049LT) were pooled to assess the incidence of angioedema or head and neck edema as a function of duration of exposure to omapatrilat (see Supplemental

Table S.6.4.10). This analysis demonstrated that 0.9% of subjects experienced an episode of treatment-emergent angioedema or head and neck edema during the first 6 months of exposure to open-label omapatrilat; 0.6% during the second 6 months; 0.9% during the next 12 months; and 0.4% during the subsequent 12 months. None of these episodes required mechanical airway protection.

## **6.5 Safety in Difficult to Control Patients and Other Important Subgroups**

There were no meaningful differences in the frequency of adverse events between omapatrilat and enalapril in any demographic or clinical subgroups (Supplemental Tables S.6.5A, B, C and D).

## **6.6 Cardiovascular Safety of Omapatrilat**

### **6.6.1 Hypertension Findings from OCTAVE**

In OCTAVE, a planned summary was performed of the frequency of a pre-specified CV composite endpoint (including death from any cause, or hospitalization for MI, angina, stroke/TIA, heart failure, renal failure, or cardiorespiratory arrest) by treatment group.

As shown in Table 6.6.1, subjects treated with omapatrilat were less likely than subjects treated with enalapril to experience any of the pre-specified cardiovascular events while receiving double-blind treatment or up to 6 months following randomization.

**Table 6.6.1: Summary of Patients Experiencing a Cardiovascular Event in OCTAVE Up to 6 Months Post Randomization**

	Number (%) of Subjects	
	Omapatrilat N = 12,609	Enalapril N = 12,557
Any Endpoint	105 (0.83%)	121 (0.96%)
Death	26 (0.21%)	29 (0.23%)
Hospitalization for MI	18 (0.14%)	19 (0.15%)
Hospitalization for Unstable Angina	14 (0.11%)	16 (0.13%)
Hospitalization for Stroke/TIA	31 (0.25%)	38 (0.30%)
Hospitalization for Heart Failure	20 (0.16%)	24 (0.19%)
Hospitalization for Renal Failure	1 (0.01%)	3 (0.02%)
Hospitalization for Cardiopulmonary Arrest	0 (0.00%)	2 (0.02%)

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### 6.6.2 Heart Failure: Preliminary Findings from OVERTURE

In this section, preliminary cardiovascular event data from OVERTURE (Omapatrilat versus Enalapril Randomized Trial of Utility in Reducing Events) are presented. This study is complete but has not been submitted to the FDA.

OVERTURE was designed to compare the effects of omapatrilat and enalapril on morbidity and mortality in heart failure. A total of 5770 patients with moderate to severe heart failure (New York Heart Association Class II-IV and left ventricular ejection fraction  $\leq 30\%$ ) and a history of hospitalization for worsening heart failure within the previous 12 months were randomized to omapatrilat 40 mg once daily or enalapril 10 mg twice daily. ACE inhibitors and angiotensin receptor blockers were discontinued at randomization, but standard care was permitted. The trial continued until 850 deaths occurred, and all patients had been followed for a minimum of 8 months.

In general, all deaths and cardiovascular events were reported both as adverse events and as potential pre-specified study endpoints. Both types of reports are summarized below.

Demography

Baseline and demographic characteristics were equally distributed between treatments. The study population was predominantly white (89%) and male (79%), with an average age of 63.4 years. The mean left ventricular ejection fraction was 23.5%; 52% presented in NYHA functional class III/IV. Approximately 56% had an ischemic etiology of heart failure and 52% had a history of hypertension.

Blood Pressure

At baseline, 25.9% of patients were hypertensive (systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg). Changes in blood pressure from baseline were greater in those with hypertension at baseline than in others. Both overall and in patients with baseline hypertension, changes in blood pressure were similar for omapatrilat and enalapril. Similar changes in blood pressure were noted in the small number of subjects in OCTAVE with antecedent heart failure. The reason for this observation is not known.

**Table 6.6.2A: OVERTURE: Reduction in Systolic Blood Pressure at Month 12 (Mean Change From Baseline)**

	Omapatrilat	Enalapril
All patients	-3.5 mmHg (n = 1549)	-3.5 mmHg (n = 1539)
Hypertensive patients	-12.7 mmHg (n = 424)	-12.6 mmHg (n = 422)

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Cardiovascular Events Reported as Adverse Events

Overall, the incidence of clinical adverse events and serious adverse events was similar in the two treatment groups, although there were 34 fewer deaths in patients receiving omapatrilat. In patients with hypertension, AEs occurred less frequently, with similar incidence across treatments (Table 6.6.2B).

**Table 6.6.2B: OVERTURE: Number (Percent) of Patients with Clinical Adverse Events**

	Omapatrilat		Enalapril	
	All Patients N = 2888	Hypertensive N = 754	All Patients N = 2882	Hypertensive N = 743
AE, total (%) of patients	2337 (80.9)	556 (73.7)	2284 (79.3)	563 (75.8)
SAE <sup>a</sup>	1360 (47.1)	296 (39.3)	1401 (48.6)	338 (45.5)
DC due to AE <sup>a</sup>	505 (17.5)	104 (13.8)	488 (16.9)	108 (14.5)
Death	313 (10.8)	77 (10.2)	347 (12.0)	73 (9.8)

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Note: Hypertensive = baseline systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg

<sup>a</sup> Subsets of all AEs; patients may be represented in more than one category

Adverse events representing potential major cardiovascular events were also similar across treatment groups overall and in those who presented with hypertension (Table 6.6.2C).

**Table 6.6.2C: OVERTURE: Number (Percent) of Patients with Major CV Events Reported as Adverse Events**

	Omapatrilat		Enalapril	
	All Patients N = 2888	Hypertensive N = 754	All Patients N = 2882	Hypertensive N = 743
Angina Pectoris	238 (8.2)	55 (7.3)	256 (8.9)	52 (7.0)
Myocardial Infarction	84 (2.9)	25 (3.3)	84 (2.9)	23 (3.1)
Invasive Cardiovascular Procedure	64 (2.2)	15 (2.0)	70 (2.4)	15 (2.0)
Cerebrovascular Accident	43 (1.5)	10 (1.3)	38 (1.3)	8 (1.1)
Transient Ischemic Attack	19 (0.7)	2 (0.3)	22 (0.8)	7 (0.9)

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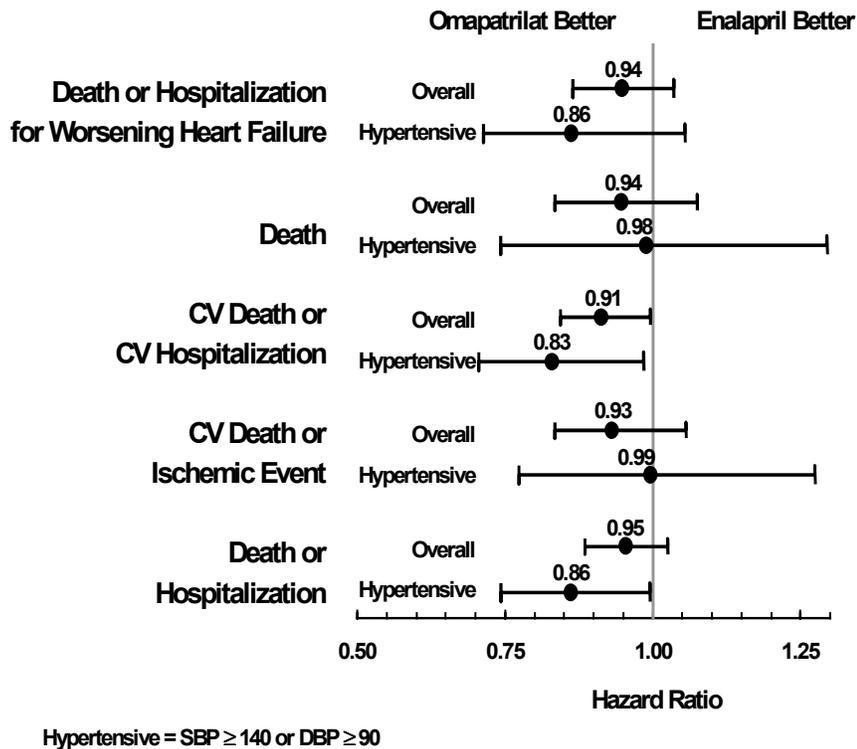
Note: Hypertensive = baseline systolic blood pressure  $\geq$  140 mmHg or diastolic blood pressure  $\geq$  90 mmHg

Cardiovascular Events Reported as Potential Pre-Specified Study Endpoints

All deaths and hospitalizations were also reported as potential pre-specified study endpoints. The hazard ratios and 95% CIs for time to first event (omapatrilat vs enalapril) for pre-specified adjudicated study endpoints that reflect cardiovascular event rates are summarized in Figure 6.6.2.

The hazard ratios for all comparisons favor omapatrilat, although the confidence intervals generally cross 1. Results in hypertensive patients were similar to those observed overall.

**Figure 6.6.2: Relative Risk with 95 Percent Confidence Intervals for Pre-Specified Study Endpoints**



## Summary

In patients with heart failure, omapatrilat and enalapril treatment were associated with similar rates of death and major cardiovascular events. Omapatrilat and enalapril also produced similar reductions in blood pressure. Therefore, in patients at high risk of cardiovascular events, omapatrilat does not appear to have any undesired cardiovascular effects that would offset the expected benefit of blood pressure reduction.

### **6.7 Safety Summary**

The safety of omapatrilat has been characterized in an extensive clinical development program. Overall, no significant safety issues other than angioedema were identified. Angioedema occurred roughly three times more frequently with omapatrilat than with enalapril. Angioedema was more common in black patients and current smokers, suggesting that omapatrilat should be used with particular care in these individuals.

Angioedema ranged in severity from mild, requiring no treatment other than discontinuation of study drug, to severe, requiring mechanical airway protection. About 60% of cases required no treatment or antihistamines only. Life-threatening angioedema occurred in 2/12,609 patients treated with omapatrilat in OCTAVE, and 6/18,723 patients treated with omapatrilat across the entire hypertension clinical development program.

The clinical manifestations of angioedema were similar for omapatrilat and enalapril. Severe cases of angioedema (those requiring epinephrine, corticosteroids, or mechanical airway protection) were likely to present with oropharyngeal symptoms (tongue swelling, difficulty speaking or swallowing), which may have prompted earlier or more aggressive treatment. With the exception of one case of anaphylaxis, angioedema had a rapid but not explosive onset, generally allowing time for medical attention to be sought. All cases were managed successfully using standard measures.

## **7 DISCUSSION**

### **7.1 Unmet Medical Need**

Hypertension affects more than 600 million people worldwide, including approximately 43 million adults in the United States. Uncontrolled hypertension is a major risk factor for cardiovascular disease and is directly implicated in the pathogenesis of its sequelae. The consequences of uncontrolled hypertension – coronary artery disease, heart failure, stroke, and renal disease – rank among the leading causes of death, disability, and health care expenditures.

Hypertension, however, is a modifiable risk factor. Randomized controlled studies using various classes of antihypertensive agents have consistently shown that reduction of blood pressure prevents cardiovascular events. But most individuals with hypertension are not treated adequately. In the US, only 27% of hypertensive patients have blood pressure below the minimally acceptable level of 140/90 mmHg.<sup>12</sup>

Lack of control of hypertension occurs across all racial, geographic, and socioeconomic categories. It occurs in those with health insurance and those without. Most cases occur in older adults, most of whom have health care access and relatively frequent physician contacts.<sup>37</sup> Even among those with free access to health care, control of blood pressure is suboptimal. In a study conducted in medical sites within the Department of Veterans Affairs, approximately 40% of patients had persistent elevation of blood pressure  $\geq 160/90$  mmHg over a 2-year period.<sup>38</sup> These patients had access to free medical care (averaging more than 6 hypertension-related visits per year) and either free or nominal cost antihypertensive medications. Non-compliance did not appear to be associated with lack of blood pressure control.

While lack of awareness of the importance of aggressively treating both systolic and diastolic blood pressure to target has been cited as a potential cause of poor control of blood pressure, failure to reach target blood pressure also commonly occurs even in clinical trials in hypertension. For example, in ALLHAT, a comparison of the effects of four blinded antihypertensive medications on the risk of heart attack in older individuals, only 53% of patients reached the blood pressure target of  $< 140/< 90$  mmHg at one year.<sup>16</sup> In the Irbesartan Diabetic Nephropathy Trial (IDNT) a Clinical Management

Committee (CMC) was chartered and met 3-4 times annually to oversee individual blood pressure values for each patient in the trial and make individualized recommendations to the Investigator to achieve a target blood pressure of < 135/85 mmHg. Patients received an average of 3 open-label antihypertensive medications in addition to double-blind irbesartan or amlodipine.<sup>19</sup> The mean systolic blood pressure at visits after baseline was 140-141 mmHg in these groups. These blood pressure values are 5-6 mmHg above the protocol-specified treatment target, and at least 10 mmHg above the current JNC-VI target of < 130 mmHg for diabetic patients. Thus, even in clinical trials, with investigators who are likely to be more motivated than physicians in the community, failure to reach target blood pressure is seen. Similar difficulty in controlling high blood pressure has been reported from various tertiary care hypertension specialty clinics, including Rush, Mayo Clinic, and Yale, with control of blood pressure ranging from 47-65%.<sup>22,23,39</sup>

The patients described in these publications typically have marked elevations in systolic blood pressure and tend to be older. They often have diabetes, target organ damage, or established cardiovascular disease. These types of patients are widely perceived to have a less satisfactory response to antihypertensive therapy than other patients. They share other features as well:

- 1) Large gap between pre-treatment blood pressure and goal: These patients often have more markedly elevated pretreatment blood pressure than other patients, and may also have more aggressive treatment goals (< 130 mmHg systolic and < 85 mmHg diastolic for those with diabetes, heart failure, or renal disease). Thus, the difference between pre-treatment blood pressure and target often exceeds 20-30 mmHg. Multiple-drug regimens are usually needed, and may not be successful at controlling blood pressure.
- 2) Limited treatment options: Diabetes, isolated systolic hypertension, severe hypertension, renal disease, or pre-existing ischemic coronary or cerebrovascular disease frequently occur in combination with each other, with other disorders such as hyperlipidemia or gout, or with other complications of hypertension such as peripheral arterial disease. These associated conditions may create contraindications or severe intolerance to treatment with particular classes of drugs, thus limiting treatment options.

- 3) Need for intensive management: Establishing and maintaining complicated therapeutic regimens for asymptomatic chronic diseases such as hypertension presents a significant challenge for physician and patient. The frequent co-occurrence of chronic diseases in these patients creates the need for other medications to treat diabetes and lipid disorders, or for secondary prevention of cardiovascular events. The need to simultaneously maintain multiple drug regimens for comorbid disorders aggravates the difficulties inherent in establishing and maintaining a complicated multi-drug regimen for hypertension.
  
- 4) Increased risk of cardiovascular events: The annual risk of major cardiovascular events is typically at least 2-3% per annum in these patients.<sup>40</sup> Because the baseline risk of cardiovascular events is so high, the number of cardiovascular events that might be prevented by blood pressure reduction is also high.

Thus, a growing body of evidence suggests that existing medications, even used optimally, are inadequate to control blood pressure in those most at risk of cardiovascular events - those with marked elevations in systolic blood pressure, those with diabetes, and those with established end-organ damage or cardiovascular disease. More effective antihypertensive agents are needed for these difficult to control patients.

## **7.2 Incremental Blood Pressure Reduction with Omapatrilat**

The efficacy of omapatrilat has been characterized in a large clinical development program. The program included four fixed-dose, forced-titration trials, placebo-controlled trials contributing information about the dose-response of omapatrilat, 6 forced-titration trials comparing the peak efficacy of omapatrilat, lisinopril, amlodipine, and losartan in patients with mild-to-moderate hypertension, and OCTAVE, a 25,000 patient elective-titration study comparing omapatrilat and enalapril in a broad range of hypertensive patients under conditions similar to clinical practice.

Omapatrilat produced dose-related reductions for both systolic and diastolic blood pressure. At 80 mg, the proposed maximum dose, office trough systolic blood pressure was reduced by 15.7 mmHg and diastolic blood pressure 9.7 mmHg relative to placebo. This compared favorably to reductions of 10-12 mmHg systolic and 5-6 mmHg diastolic historically observed in trials of antihypertensive therapy with primarily diuretic-based

regimens, and suggested that omapatrilat had the potential to lower blood pressure more than existing agents.<sup>9</sup>

In direct comparisons, omapatrilat was shown to reduce office trough systolic blood pressure by about 3-5 mmHg and diastolic blood pressure about 2-3 mmHg more than amlodipine and lisinopril. In studies using ambulatory measurements, omapatrilat was also shown to reduce 24 hour average ambulatory systolic blood pressure by 6-7 mmHg and diastolic blood pressure by 3-4 mmHg more than amlodipine and lisinopril. Overall, omapatrilat reduced both systolic and diastolic blood pressure more than amlodipine or lisinopril treatment.

The greater effectiveness of omapatrilat used in clinical practice settings was clearly demonstrated in OCTAVE, a randomized, double-blind comparison of omapatrilat and enalapril. In this large, simple trial, patients were treated much as they would be in clinical practice. Study drug was electively titrated to reach a common blood pressure target. Additional antihypertensive medications were added as needed in patients remaining above target after titration of study drug.

Several design features enhanced the validity and generalizability of OCTAVE. The broad eligibility criteria and large numbers of investigators and countries resulted in a demographically representative patient population. Important comorbid characteristics, such as diabetes and prior cardiovascular disease, were present in many patients. Three methods of use of study drug (initial therapy, replacement therapy, and add-on therapy) were evaluated. The sample size of roughly 25,000 patients was adequate to exclude random effects and permit determination of treatment effects in multiple subgroups.

In OCTAVE, omapatrilat was more effective in lowering blood pressure compared to enalapril, despite more frequent use of top-dose study drug and adjunctive antihypertensive therapy in patients randomized to enalapril than omapatrilat. Overall in the study, systolic blood pressure was reduced 3 mmHg, and diastolic blood pressure 2 mmHg, more with omapatrilat than enalapril. In all treatment groups and patient subgroups, more omapatrilat treated patients reached blood pressure target than those receiving enalapril. The differences observed between omapatrilat and enalapril were highly consistent in direction and magnitude, regardless of patient demographics, severity of hypertension, and comorbid conditions. The differences were also highly consistent

whether study drug was used as initial therapy in untreated patients, or replacement or add-on therapy in treated patients not at blood pressure target.

### **7.3 Projected Benefit of Omapatrilat**

#### Evidence from Observational Studies

Relative to the ACE inhibitors enalapril and lisinopril, omapatrilat has been shown to reduce diastolic blood pressure by 2-3 mmHg and systolic blood pressure by 3-5 mmHg. Observational data can be used to estimate the relationship between blood pressure differences of this magnitude and the incidence of coronary heart disease and stroke. In an analysis of 9 major prospective observational studies, including a total of 420,000 individuals, prolonged differences in diastolic blood pressure of 5 mmHg were associated with at least 34% less stroke and 21% less coronary heart disease.<sup>7</sup> This would suggest that differences of 2-3 mmHg in diastolic blood pressure would be associated with at least 14-20% less stroke and 8-13% less coronary heart disease. In a population where coronary heart disease is approximately twice as common as stroke (as in the US),<sup>6</sup> differences in diastolic blood pressure of 2-3 mmHg would be associated with at least 10-15% fewer major cardiovascular events (coronary heart disease + stroke). Differences in systolic blood pressure of 3-5 mmHg have been associated with reductions in cardiovascular events of similar magnitude.<sup>41</sup>

The reduction in absolute number of cardiovascular events associated with a given reduction in blood pressure will depend on the baseline risk of cardiovascular events. The WHO-ISH guidelines for the management of hypertension describe four categories of absolute cardiovascular disease risk and provide estimates of the future absolute risk of major cardiovascular events for each category (Table 7.3).<sup>40</sup>

**Table 7.3: World Health Organization – International Society of Hypertension Categories of Cardiovascular Risk and Estimates of Future Absolute Risk of Cardiovascular Events**

<b>Risk Category</b>	<b>Patient Population</b>	<b>Future Absolute Risk of Major CV Events Per Annum<sup>a</sup></b>
Low Risk	Stage I hypertension and no other CV risk factors	< 1.5%
Medium Risk	Stage 1 hypertension with 1-2 other CV risk factors or Stage 2 hypertension and 0-2 risk factors No DM, TOD, or CCD	1.5 -2%
High Risk	Stage 1 or 2 hypertension with 3 or more risk factors, diabetes mellitus, or TOD; Stage 3 hypertension without other risk factors	2-3%
Very High Risk	Stage 3 hypertension and $\geq 1$ risk factor and all patients with CCD disease	> 3%

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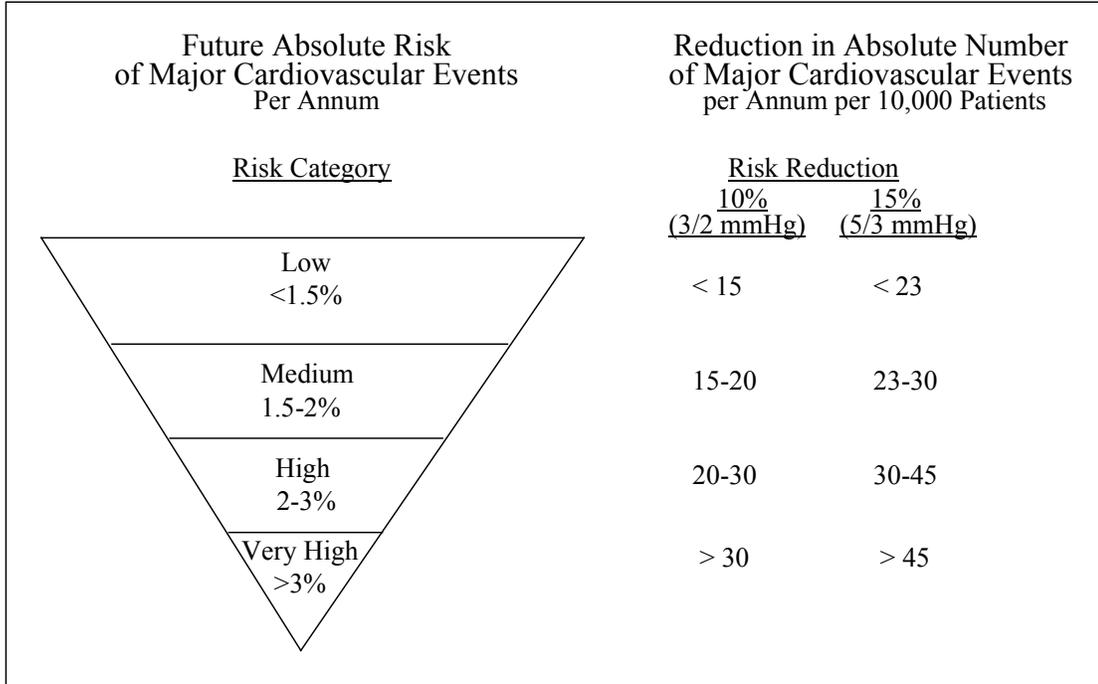
Source: World Health Organization-International Society for Hypertension Guidelines of Management of Hypertension<sup>40</sup>

TOD = target organ damage; CCD = Clinical Cardiovascular Disease

<sup>a</sup> Calculated from data on the average 10 year risk of cardiovascular death, non-fatal stroke, or non-fatal myocardial infarction among participants in the Framingham Study

Based on these categories of cardiovascular risk, it is possible to estimate the reduction in absolute number of cardiovascular events that would be associated with a reduction in systolic blood pressure of 3-5 mmHg (or diastolic blood pressure of 2-3 mmHg) (Figure 7.3).

**Figure 7.3: Categories of Cardiovascular Risk and Estimates of Future Absolute Risk of Cardiovascular Events Associated with 3-5 mmHg Systolic Blood Pressure Change**



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Evidence of Benefit with Pharmacologic Reduction in Blood Pressure

The benefit of pharmacologic reduction in blood pressure has been shown in a large number of clinical trials using a variety of drug classes and agents. The magnitude of the reduction in cardiovascular outcomes that can be achieved with pharmacologic reduction in blood pressure is largely consistent with what would be predicted from observational data.

In a meta-analysis of older trials using primarily diuretic-based regimens, a reduction of 5-6 mmHg in diastolic blood pressure was shown to result in a reduction of 42% in stroke and 14% in coronary heart disease.<sup>9</sup> A more recent meta-analysis of contemporary trials revealed 30-39% reduction in stroke and 21-28% reduction in major cardiovascular events with ACE inhibitors and calcium channel blockers.<sup>10</sup> In trials comparing more intensive and less intensive blood pressure lowering strategies, an incremental reduction

in systolic blood pressure of 3 mmHg was associated with a 15% reduction in major cardiovascular events.<sup>10</sup>

#### Data from Omapatrilat Development Program

Although OCTAVE was not designed to study the effect of omapatrilat on clinical outcomes, over two hundred patients reached a pre-specified cardiovascular composite endpoint of all-cause mortality or hospitalization for cardiovascular causes. This composite endpoint occurred about 15% less commonly in patients treated with omapatrilat than those treated with enalapril. The difference between treatments appeared about 3 months into the trial and persisted through 24 weeks. While not proof of outcomes benefit, these observations are quite consistent with what would be predicted from observational studies and outcomes trials with other agents.

Nevertheless, the possibility remains that any new antihypertensive agent may have untoward effects that offset the anticipated benefit of blood pressure reduction. This is a particular concern for agents that are the first in a new pharmacologic class, such as omapatrilat. Like other new antihypertensive agents, approval is sought for omapatrilat based on demonstration of efficacy in blood pressure reduction, rather than proven outcomes benefit in hypertensive patients.

The data presented for omapatrilat differ from those presented for other recently approved antihypertensives in several important respects. First, the number of patients exposed to omapatrilat is 5-10 times higher than the number of patients exposed to experimental therapy in a typical hypertension application. This provides assurance that infrequent but important adverse events have been identified. With a total of 18,723 exposed, one can exclude with 95% certainty the existence of any unknown adverse event with an underlying frequency of 2 per 10,000.

Second, an outcomes study has been completed (OVERTURE) comparing omapatrilat with a treatment of proven benefit in patients with heart failure. This population is at higher risk for cardiovascular events than a hypertensive population and more likely to manifest untoward cardiovascular effects of drug treatment. OVERTURE compared the effect of omapatrilat and enalapril on death or hospitalization for worsening heart failure in patients with NYHA Class II-IV heart failure and a history of heart failure hospitalization within the previous 12 months.

This population was at high risk for coronary heart disease and stroke. Over half had ischemia as their cause for heart failure. If omapatrilat produced cardiovascular harm, it might be expected to manifest itself here.

Comparable reductions in blood pressure were observed with omapatrilat and enalapril. The frequency of cardiovascular events, including coronary heart disease and cerebrovascular disease, was also almost identical in the two treatment groups. The results were similar in patients with hypertension at baseline (approximately 1/3rd of the cohort). These findings indicate that treatment with omapatrilat is not associated with any untoward cardiovascular effect in high risk patients that might blunt or offset the anticipated benefit of blood pressure reduction.

## **7.4 Defined Risk of Omapatrilat**

The risk of treatment with omapatrilat has been defined through an extensive clinical development program. Over 18,000 hypertensive patients have been exposed to omapatrilat in controlled trials. With the 10 mg starting dose of omapatrilat studied in OCTAVE, the only important difference in safety between omapatrilat and enalapril was the increased frequency of angioedema.

Angioedema ranges in severity from mild to severe and life-threatening. An angioedema classification system was created for OCTAVE which utilized measures of treatment intensity as proxies for severity. Using this system, approximately 60% of episodes of angioedema associated with omapatrilat treatment (161/274) were rated as Stage I (lowest severity). These episodes either received no treatment other than discontinuation of study drug, or were treated only with antihistamines, which are not thought to alter the course of severe angioedema.

Approximately 40% of episodes of angioedema associated with omapatrilat treatment (113/274) were rated as Stages II, III, or IV. These generally received treatment with epinephrine or corticosteroids. Two patients had airway compromise. One required mechanical airway protection. All recovered.

Angioedema was less frequent with enalapril, and no life-threatening episodes were observed. Life-threatening and fatal angioedema has been noted to occur with ACE inhibitors, but its precise frequency is unknown.

## 7.5 Assessment of Benefit and Risk

Weighing the incremental benefit and risk of treatment with omapatrilat requires identification of comparable benefits and risks. The cardiovascular events that may be prevented with omapatrilat treatment are life-threatening, so comparison with life-threatening angioedema is most appropriate. This comparison, while perhaps the best that can be made, nevertheless oversimplifies the assessment, in that non-fatal cardiovascular events carry significant long-term morbidity, while non-fatal angioedema typically has no comparable long-term consequences (Table 7.5).

**Table 7.5: Summary of Potential Incremental Benefits and Risks of Treatment with Omapatrilat**

	<b>Benefit (Risks Reduced)</b>	<b>Risks Incurred</b>
Event Types	Fatal and Non-Fatal MI, Stroke, Heart Failure, Renal Failure	Fatal <sup>a</sup> and non-fatal angioedema with airway compromise
Treatment required	Surgery, PCI, <sup>b</sup> Thrombolysis, Dialysis, Transplantation	Mechanical airway protection, steroids, epinephrine, antihistamines
Potential Long-Term Sequelae (if non-fatal)	Disability Discomfort  Increased risk for subsequent CV events  Need for surgery or other invasive interventions Chronic medical management	Psychologic Distress

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<sup>a</sup> None observed in OCTAVE or other omapatrilat trials

<sup>b</sup> Percutaneous coronary interventions

The potential benefit of omapatrilat treatment has been estimated above (Figure 7.3). The number of cardiovascular events that may be prevented by omapatrilat treatment varies from < 15 to > 45 per 10,000 patients treated per year, depending on the underlying risk of cardiovascular events.

The number of life-threatening angioedema events that may be caused by omapatrilat has been defined by the clinical development program. In OCTAVE, the number of

life-threatening angioedema events observed during 24 weeks of omapatrilat treatment was 2, yielding a rate of 1.6 per 10,000 treated. The upper bound of the 95% confidence interval for this rate is 5.7 per 10,000 treated.

Thus the number of cardiovascular events that may be prevented with omapatrilat treatment is substantially greater than the number of life-threatening angioedema events likely to be caused, even if the rate of life-threatening angioedema resembles the upper bound of the 95% CI rather than the point estimate. The comparison is most clearly favorable in those at medium, high, or very high underlying cardiovascular risk.

A similar conclusion is reached if one bases the estimate of the risk of life-threatening angioedema on the entire clinical omapatrilat development program, rather than OCTAVE alone. In earlier studies, using primarily a 20 mg starting dose of omapatrilat, four episodes of life-threatening angioedema were observed in roughly 6,000 treated. This rate was several fold-higher than that seen in OCTAVE, with its 10 mg starting dose, suggesting that a reduction in starting dose may reduce the risk of life-threatening angioedema. Pooling data from all hypertension studies, regardless of starting dose, yields a rate of life-threatening angioedema of 3.2 per 10,000 treated, compared to 1.6 per 10,000 treated for OCTAVE alone. The upper bound of the 95% confidence interval for this rate is 6.7 per 10,000 treated, similar to that derived from OCTAVE (5.7 per 10,000 treated). The comparison of projected benefit to risk is thus not substantially altered if the pooled rate is used.

This analysis does not take into account the effect of time on treatment. The estimates of life-threatening angioedema are based on the actual observations in OCTAVE and other controlled trials. With longer duration of treatment a greater number of life-threatening angioedema events might occur, and conversely a greater number of cardiovascular events might be prevented. In OCTAVE, the incidence of angioedema fell from 1.36% during the first four weeks of treatment to 0.10% during the last four weeks. The rate of angioedema observed during the last four weeks of OCTAVE is consistent with that observed during long-term open-label trials lasting several years (about 1% per year). If the ratio between all events and life-threatening events observed in OCTAVE – about one in one hundred – held true during long-term treatment, one would expect the incidence of life-threatening angioedema (below the initial exposure) to be perhaps one episode per 10,000 treated per year.

## **7.6 Potential Use of Omapatrilat to Meet Unmet Medical Need**

In general, safer alternatives, if available, should be considered before using a therapy that carries risk. Because of the risk of angioedema, omapatrilat should not generally be used as initial therapy or in patients who can be readily treated with existing medications. However, in patients who are difficult to control, omapatrilat may offer significant benefit as discussed previously.

Data from the published literature, and from OCTAVE, indicate that many patients cannot readily be treated with existing medications. These patients tend to be older and have predominant elevations in systolic blood pressure, are more likely to have more severe elevations in blood pressure, and often have diabetes, target organ damage, or established cardiovascular disease.

A true need for more effective antihypertensive therapy exists in these patients. It should be noted that the target blood pressure for these patients is often lower than the general population (< 130 mmHg for those with diabetes, heart failure, or renal disease). This lower blood pressure target, coupled with more severe elevations in blood pressure, create a significant distance to blood pressure goal that often exceeds 20-30 mmHg.

In theory, a blood pressure reduction of 20-30 mmHg could be achieved by use of 2-3 drugs in combination if their effects were additive. However, there is often physiologic resistance to antihypertensive therapy such that multiple-drug regimens produce increments in blood pressure control that are less than additive.<sup>25</sup>

Options for treatment are limited. Many patients with hypertension that is difficult to control have comorbid conditions that create absolute or relative contraindications to specific agents or classes of agents, while others have treatment-limiting intolerance. For example, those with gout may be unable to receive thiazide diuretics. Beta-blockers may exacerbate peripheral arterial disease and complicate the management of diabetes. A diabetic with proteinuria and peripheral edema may be unable to tolerate high-dose therapy with a dihydropyridine calcium channel blocker, which can exacerbate peripheral edema.

Lastly, management of complicated therapeutic regimens is difficult. In practice three drug regimens for treatment of hypertension are uncommon, and more complex regimens rare. Numerous physician visits are required to start, titrate, and maintain a complex multi-drug regimen, placing a substantial burden on both health care system and patient. As seen in OCTAVE, comorbid diastolic hyperlipidemia, and vascular disease are common in patients with difficult to treat hypertension. These conditions require their own treatments, increasing the burden of therapy.

For these reasons, blood pressure target is often not attainable for many patients with difficult to control blood pressure. A treatment regimen that includes omapatrilat has been shown to provide greater reductions in blood pressure, and a greater likelihood of reaching blood pressure target, thus meeting an important unmet medical need.

## **7.7 Managing the Risk of Angioedema**

Angioedema has readily recognizable clinical features which facilitate early identification and management.

Furthermore, the most serious cases of angioedema are generally highly symptomatic. The prominent signs and symptoms in the face and neck region prompt the affected patient to seek timely medical attention. The sponsor is committed to patient education programs to further assure that patients will seek medical attention at the earliest manifestation of any signs or symptoms of angioedema.

With the exception of one case of anaphylaxis, life-threatening angioedema observed in the omapatrilat development program did not have an explosive onset. All episodes evolved slowly enough to allow the patient time to seek medical attention.

The clinical presentation of omapatrilat-associated angioedema is similar to that of ACE inhibitor associated angioedema. ACE inhibitors are now the most common cause of angioedema in hospital emergency departments.<sup>42</sup> Thus, omapatrilat-associated angioedema should be easily recognized by medical personnel.

Treatment of life-threatening angioedema does not require specialized training. Angioedema associated with omapatrilat is managed in the same fashion as angioedema of any other cause. Treatment of serious allergic reactions is a core skill for physicians

and nurses. Airway protection is a routine procedure for emergency medical personnel. Timely treatment can prevent fatalities. With airway support, recovery is usually complete.

## **7.8 Conclusions**

In patients with hypertension that is difficult to control with existing medication, a true need exists for more efficacious therapy. Evidence has been presented that omapatrilat is effective in patients that are difficult to control with existing therapy.

Omapatrilat has also been shown to cause life-threatening angioedema in about 2-3 per 10,000 patients treated. Consideration of benefit and risk suggests that omapatrilat should not generally be used as initial therapy, and should not be used in patients who can readily achieve comparable blood pressure reduction using existing drugs. In patients whose hypertension is difficult to control with existing medications, however, omapatrilat offers the potential for a benefit, through blood pressure reduction and prevention of cardiovascular events, that is not otherwise available.

Because patients with difficult to control hypertension typically have characteristics that increase their risk of cardiovascular events, such as severe hypertension, older age, diabetes, target organ damage, or established cardiovascular disease, the absolute number of cardiovascular events potentially preventable by further blood pressure reduction in these patients is substantial. It is estimated that treatment with omapatrilat in high CV risk patients has the potential to prevent at least 20-30 more major CV events per year per 10,000 treated than enalapril or comparable existing agents. These benefits strongly outweigh the risk of angioedema.

African-American patients and current smokers have been shown to have a risk of angioedema that is about 3 times higher than in others. In these patients, the risk, benefit, and possible therapeutic alternatives should be carefully considered prior to use of omapatrilat.

## 8 LIST OF ABBREVIATIONS

<b>Term</b>	<b>Definition</b>
Abn	abnormal
ABP	ambulatory blood pressure
ABPM	ambulatory blood pressure monitoring
ACE	angiotensin-converting enzyme
ACEI	angiotensin-converting enzyme inhibitor
ADE	adverse drug experience
ADM	adrenomedullin
AE	adverse event
ALLHAT	Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial
AM	Latin ante meridiem, before noon
AMBP	ambulatory mean blood pressure
Aml	amlodipine
ANCOVA	analysis of covariance
ANP	atrial natriuretic peptide
AUC	area under the curve
beats/min	beats per minute
BK	bradykinin
BMS	Bristol-Myers Squibb
BMS-186716	The study drug: omapatrilat
BNP	brain natriuretic peptide
BP	blood pressure
CCB	calcium channel blocker
CCD	Clinical Cardiovascular Disease
CE	concomitant event
cGMP	cyclic guanine monophosphate

<b>Term</b>	<b>Definition</b>
CHD	coronary heart disease
CHF	congestive heart failure
CI	confidence interval
C <sub>max</sub>	maximum concentration
CMC	Clinical Management Committee
CNP	C-type natriuretic peptide
CONVINCE	Controlled Onset Verapamil Investigation of Cardiovascular Endpoints
CrCl	creatinine clearance
CRF	case report form
CRO	contract research organization
CSR	clinical study report
CV	cardiovascular
CVA	cerebral vascular accident
DB	double-blind
D/C	discontinuation
Diff	difference
DM	Diabetes Mellitus
EAC	Event Adjudication Committee
ECG	electrocardiogram
Ena	enalapril
EOT	end of titration
ER	emergency room
FDA	Food and Drug Administration
fmol	fantomol
g/dL	grams/deciliter
GCP	Good Clinical Practice
GI	gastrointestinal

<b>Term</b>	<b>Definition</b>
g/m <sup>2</sup>	grams per milliliter squared
HCTZ	hydrochlorothiazide
HDFP	Hypertension Detection and follow up Program
HDL	high density lipoprotein
HF	heart failure
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
HOT	hypertension optimal treatment
HR	heart rate
hr	hour
i.e.	Latin id est, that is
ICD	International Classification of Diseases
IDNT	Irbesartan Diabetic Nephropathy Trial
IDH	isolated diastolic hypertension
IRB	Institutional Review Board
ISE	Integrated Summary of Efficacy
ISH	isolated systolic hypertension
ISS	Integrated Summary of Safety
JNC	Joint National Commission
kg	kilogram(s)
Ki	inhibitory constant
L	liter
LCL	lower confidence limit
LD, LDH	lactate dehydrogenase
LDL	low density lipoprotein
LFT	liver function test
LIFE	Losartan Intervention for Endpoints Trial
Lis	lisinopril

<b>Term</b>	<b>Definition</b>
LOCF	last observation carried forward
Los	losartan
LT	long term
LVH	left ventricular hypertrophy
LVMI	left ventricular mass index
mEq/L	milliequivalents/liter
mg	milligram(s)
mg/dL	milligram/deciliter
MI	myocardial infarction
min	minute
μ/L	microliter(s)
mmHg	millimeters of mercury
mmol/dL	millimole(s)/deciliter
mmol/L	millimole(s)/liter
MRFIT	Multiple Risk Factor Intervention Trial
mV	millivolts
N, n	number
NDA	new drug application
NEP	neutral endopeptidase
NHANES	National Health and Nutrition Examination Survey
nM	nanomol
NSAID	nonsteroidal anti-inflammatory drug
NYHA	New York Heart Association
OCTAVE	Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril
Oma	omapatrilat
OVERTURE	<u>O</u> mapatrilat <u>V</u> ersus <u>E</u> nalapril <u>R</u> andomized <u>T</u> rial of <u>U</u> tility in <u>R</u> educing <u>E</u> vents
Patient 0000/000	e.g., Patient 0034/003: Investigator site #0034 / Patient #003

<b>Term</b>	<b>Definition</b>
Pbo	placebo
PCI	percutaneous coronary interventions
PLA	placebo
pm	latin: post meridian, after noon
PP	pulse pressure
PRA	plasma renin activity
Pre Rx	pretreatment
PRN	Latin pro re nata, as circumstances may require
PROGRESS	Perindopril Protection Against Recurrent Stroke Study
PST	post
RAS	renin angiotensin system
RMP	risk management program
RR	relative risk
RRR	relative risk ratio
SAE	serious adverse event
SC	systemic hypertensive care
sd	standard deviation
se	standard error of the mean
SE	special event
SeBP	seated blood pressure
SeHR	seated heart rate
SHEP	Systolic Hypertension in the Elderly Study
RAAS	renin-angiotensin-aldosterone system
SOLVD	Studies of Left Ventricular Dysfunction
TIA	transient ischemic attack
TOD	target organ damage
UCL	upper confidence level

<b>Term</b>	<b>Definition</b>
UKPDS	United Kingdom Prospective Diabetes Study
URI	upper respiratory infection
U.S.	United States of America
VPI	vasopeptidase inhibitor
WBC	white blood cells
Wks	weeks
WHO	World Health Organization

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**Table S.4.2: Overall and Long-term Exposure to Omapatrilat in Reported Hypertension Studies by Age**

	<b>OCTAVE N = 12,609</b>	<b>All Hypertension Studies Including OCTAVE N = 18,723</b>
All Ages	12609	18723
for > 90 days	10755	12995
for > 180 days	290	2186
for > 365 days	0	1478
< 65 years	9040	13670
for > 90 days	7709	9236
for > 180 days	234	1540
for > 365 days	0	990
≥ 65 years	3569	5053
for > 90 days	3046	3759
for > 180 days	56	646
for > 365 days	0	488
≥ 75 years	1058	1350
for > 90 days	881	1026
for > 180 days	14	129
for > 365 days	0	96

FDA Advisory Briefing Book  
 Integrated Summary of Safety, 2001, Table 2.0B

**Table S.6.4.10: Combined Incidence of Treatment-Emergent Events of Angioedema or Head/Neck Edema by Time in Long-Term Study**

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Table S.17.2.5 :  
 Combined Incidence of Treatment-Emergent Events of Angioedema or Head/Neck Edema by Time in Long-Term Study

STUDY PERIOD (DAYS)	FIRST OF EITHER EVENT n/N (%)
1-180	15/1763 (0.9%)
181-365	10/1547 (0.6%)
366-730	12/1323 (0.9%)
731-1095	3/759 (0.4%)
1096-1460	2/307 (0.7%)
>1460	0/49 (0.0%)

n = number of subjects with events in interval  
 N = number exposed at beginning of interval  
 The earlier treatment-emergent counted event of either angioedema or head/neck edema is used.

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**Table S.6.5A: Summary of Adverse Events During and up to 14 days Post Double-Blind Therapy, by Gender and Age**

Demographic Characteristic	Number (%) of Patients				
	AE, Total	ADE <sup>a</sup>	Death <sup>a</sup>	SAE <sup>a</sup>	D/C due to AE <sup>a</sup>
Gender					
Males					
Oma (n = 6570)	3219 (49.0%)	1468 (22.3%)	14 (0.2%)	243 (3.7%)	451 (6.9%)
Ena (n = 6510)	3108 (47.7%)	1338 (20.6%)	15 (0.2%)	258 (4.0%)	409 (6.3%)
Females					
Oma (n = 6039)	3207 (53.1%)	1550 (25.7%)	5 (0.1%)	198 (3.3%)	556 (9.2%)
Ena (n = 6047)	3219 (53.2%)	1462 (24.2%)	7 (0.1%)	212 (3.5%)	549 (9.1%)
Age Category					
< 65 years					
Oma (n = 9040)	4589 (50.8%)	2153 (23.8%)	12 (0.1%)	262 (2.9%)	641 (7.1%)
Ena (n = 9045)	4561 (50.4%)	1989 (22.0%)	13 (0.1%)	268 (3.0%)	604 (6.7%)
≥ 65 years					
Oma (n = 3569)	1837 (51.5%)	865 (24.2%)	7 (0.2%)	179 (5.0%)	366 (10.3%)
Ena (n = 3512)	1766 (50.3%)	811 (23.1%)	9 (0.3%)	202 (5.8%)	354 (10.1%)
≥ 75 years					
Oma (n = 1058)	530 (50.1%)	250 (23.6%)	3 (0.3%)	60 (5.7%)	115 (10.9%)
Ena (n = 1044)	539 (51.6%)	235 (22.5%)	4 (0.4%)	86 (8.2%)	105 (10.1%)

CV137-120, Table 12.1.4.1A

Note: N = Number of patients included in the analysis of safety.

Special Events are not included in this summary.

<sup>a</sup> Subsets of total AEs: patients may be represented in more than one AE category.

**Table S.6.5B: Summary of Adverse Events During and up to 14 Days Post Double-Blind Therapy, by Race**

Race Category	Number (%) of Patients				
	AE, Total	ADE <sup>a</sup>	Death <sup>a</sup>	SAE <sup>a</sup>	D/C due to AE <sup>a</sup>
White					
Oma (n = 11101)	5665 (51.0%)	2702 (24.3%)	15 (0.1%)	398 (3.6%)	881 (7.9%)
Ena (n = 11126)	5572 (50.1%)	2496 (22.4%)	18 (0.2%)	410 (3.7%)	831 (7.5%)
Black					
Oma (n = 1300)	650 (50.0%)	263 (20.2%)	4 (0.3%)	40 (3.1%)	100 (7.7%)
Ena (n = 1237)	653 (52.8%)	256 (20.7%)	2 (0.2%)	55 (4.4%)	109 (8.8%)
Asian/Pacific Islander					
Oma (n = 184)	92 (50.0%)	45 (24.5%)	0	3 (1.6%)	24 (13.0%)
Ena (n = 165)	82 (49.7%)	40 (24.2%)	2 (1.2%)	4 (2.4%)	16 (9.7%)
Other					
Oma (n = 24)	19 (79.2%)	8 (33.3%)	0	0	2 (8.3%)
Ena (n = 29)	20 (69.0%)	8 (27.6%)	0	1 (3.4%)	2 (6.9%)

CV137-120, Table 12.1.4.1B

Note: N = Number of patients included in the analysis of safety.

Special Events are not included in this summary.

<sup>a</sup> Subsets of total AEs: patients may be represented in more than one AE category.

**Table S.6.5C: Summary of Adverse Events During and up to 14 Days Post Double-Blind Therapy, by Type/Severity of Hypertension and Comorbidity**

Comorbidity	Number (%) of Patients				
	AE, Total	ADE <sup>a</sup>	Death <sup>a</sup>	SAE <sup>a</sup>	D/C due to AE <sup>a</sup>
<b>Severe Hypertension</b>					
Oma (n = 3774)	2006 (53.2%)	968 (25.6%)	11 (0.3%)	176 (4.7%)	358 (9.5%)
Ena (n = 3680)	1971 (53.6%)	910 (24.7%)	15 (0.4%)	193 (5.2%)	346 (9.4%)
<b>Diabetes Mellitus</b>					
Oma (n = 1712)	848 (49.5%)	340 (19.9%)	10 (0.6%)	93 (5.4%)	147 (8.6%)
Ena (n = 1646)	816 (49.6%)	325 (19.7%)	4 (0.2%)	106 (6.4%)	126 (7.7%)
<b>Isolated Systolic HTN</b>					
Oma (n = 682)	364 (53.4%)	152 (22.3%)	0 (0%)	20 (2.9%)	49 (7.2%)
Ena (n = 677)	365 (53.9%)	173 (25.6%)	3 (0.4%)	22 (3.2%)	49 (7.2%)
<b>Atherosclerotic Disease</b>					
Oma (n = 1184)	591 (49.9%)	273 (23.1%)	6 (0.5%)	78 (6.6%)	96 (8.1%)
Ena (n = 1169)	558 (47.7%)	252 (21.6%)	6 (0.5%)	86 (7.4%)	96 (8.2%)
<b>Renal Disease<sup>b</sup></b>					
Oma (n = 302)	147 (48.7%)	72 (23.8%)	0 (0%)	20 (6.6%)	25 (8.3%)
Ena (n = 307)	152 (49.5%)	72 (23.5%)	1 (0.3%)	23 (7.5%)	30 (9.8%)
<b>Heart Failure</b>					
Oma (n = 116)	70 (60.3%)	30 (25.9%)	2 (1.7%)	16 (13.8%)	10 (8.6%)
Ena (n = 122)	73 (59.8%)	30 (24.6%)	3 (2.5%)	15 (12.3%)	15 (12.3%)

CV137-120, Table 12.1.4.2A

Note: N = Number of patients included in the analysis of safety.

Special Events are not included in this summary.

<sup>a</sup> Subsets of total AEs: patients may be represented in more than one AE category.

<sup>b</sup> Defined as renal disease by medical history, or baseline serum creatinine > 1.5 mg/dL.

**Table S.6.5D: Summary of Adverse Events During and up to 14 Days Post Double-Blind Therapy, by Smoking History**

Smoking History	Number (%) of Patients				
	AE, Total	ADE <sup>a</sup>	Death <sup>a</sup>	SAE <sup>a</sup>	D/C due to AE <sup>a</sup>
Never					
Oma (n = 6576)	3275 (49.8%)	1556 (23.7%)	6 (0.1%)	201 (3.1%)	524 (8.0%)
Ena (n = 6594)	3219 (48.8%)	1461 (22.2%)	9 (0.1%)	238 (3.6%)	496 (7.5%)
Former					
Oma (n = 3732)	2013 (53.9%)	976 (26.2%)	11 (0.3%)	155 (4.2%)	315 (8.4%)
Ena (n = 3683)	1952 (53.0%)	891 (24.2%)	8 (0.2%)	161 (4.4%)	318 (8.6%)
Current					
Oma (n = 2264)	1123 (49.6%)	479 (21.2%)	2 (0.1%)	83 (3.7%)	163 (7.2%)
Ena (n = 2233)	1134 (50.8%)	438 (19.6%)	5 (0.2%)	70 (3.1%)	142 (6.4%)
Unknown					
Oma (n = 37)	15 (40.5%)	7 (18.9%)	0 (0%)	2 (5.4%)	5 (13.5%)
Ena (n = 47)	22 (46.8%)	10 (21.3%)	0 (0%)	1 (2.1%)	2 (4.3%)

CV137-120, Table 12.1.4.2B

Note: N = Number of patients included in the analysis of safety.

Special Events are not included in this summary.

<sup>a</sup> Subsets of total AEs: patients may be represented in more than one AE category.

## **APPENDIX 1 DETAILED SUMMARY OF PHARMACOLOGY AND TOXICOLOGY**

### **1 NON-CLINICAL PHARMACOLOGY AND TOXICOLOGY**

#### **1.1 Pharmacology of Omapatrilat**

Omapatrilat, an orally active vasopeptidase inhibitor, is a single molecule with potent, long acting and selective inhibitory activities against neutral endopeptidase (enkephalinase, neprilysin, EC 3.4.24.11) and angiotensin converting enzyme (EC 3.4.15.1). Studies in animals have shown simultaneous inhibition of tissue NEP and ACE by omapatrilat. The  $K_i$  values for NEP and ACE are 8.9 nM and 6.0 nM, respectively, demonstrating balanced inhibition of the two enzymes. As a result, omapatrilat increases multiple endogenous vasodilatory peptides including atrial natriuretic peptide (ANP), bradykinin and adrenomedullin, while simultaneously inhibiting the generation of the vasoconstrictive peptide, angiotensin II.

##### **1.1.1 Importance of NEP and its Substrates**

Mice lacking NEP due to targeted gene disruption have a relatively normal overall phenotype but lower blood pressure and reduced cardiac mass. Transgenic and gene transfer studies resulting in over-expression of the vasodilators ANP or ADM indicated that, relative to normal animals, the transgenics also had a normal phenotype along with lower blood pressures and reduced cardiac mass. Conversely, mice lacking the receptor for ANP and brain natriuretic peptide (BNP) (as a result of targeted gene disruption) suffer from hypertension, left ventricular hypertrophy, and a reduced life span. Recent clinical observations indicate that polymorphisms of the ANP gene leading to less active forms of the peptide appear to increase the risk of stroke in humans.<sup>1</sup> In an experimental model of asymptomatic left ventricular dysfunction, antagonism of the receptor for ANP and BNP resulted in coronary vasoconstriction, increased plasma renin activity, sodium retention, and an impairment of left ventricular relaxation.<sup>2</sup> These data suggest that ANP and BNP help to maintain normal cardiovascular function, including in early heart failure.

### **1.1.2 Omapatrilat in Animal Models**

Beneficial effects of combined NEP and ACE inhibition have been demonstrated in pre-clinical models of hypertension, heart failure and myocardial ischemia.

Omapatrilat significantly lowers blood pressure in a variety of animal models of hypertension, regardless of renin status. In Dahl salt-sensitive hypertensive rats, omapatrilat corrected endothelial dysfunction as measured by acetylcholine-induced vascular relaxation.

In cardiomyopathic hamsters with heart failure, when compared to the ACE inhibitor captopril, treatment with omapatrilat resulted in a greater increase in survival time. In this model, omapatrilat also produced beneficial hemodynamic effects not observed with either the NEP inhibitor, SQ 28603, or the ACE inhibitor, enalaprilat, alone, suggesting a synergistic effect of these two activities with omapatrilat. In a canine model of cardiac dysfunction secondary to rapid ventricular pacing, omapatrilat decreased pulmonary capillary wedge pressure and increased glomerular filtration rate; these effects were partially blocked by co-administration of a natriuretic peptide receptor antagonist, demonstrating the contribution of these vasodilator peptides to the mechanism of action.

In a Langendorff rat heart model of global ischemia, cardioprotective effects of omapatrilat were attenuated by a bradykinin B2 receptor antagonist or the nitric oxide synthase inhibitor L-NAME, demonstrating the contribution of nitric oxide in mediating the cardioprotective effects of omapatrilat. In a canine model of exercise-induced ischemic myocardial dysfunction, omapatrilat improved exercise capacity and preserved cardiac wall function in the ischemic region during exercise. These effects were not observed with the ACE inhibitor, fosinoprilat.

## **1.2 Toxicology**

Omapatrilat is generally well tolerated in animals at doses yielding drug exposures several-fold greater compared to humans administered omapatrilat at 80 mg/day.

Omapatrilat was not carcinogenic when administered at maximally tolerated doses to mice and rats for 21 and 24 months, respectively. The maximally tolerated doses (2000 mg/kg/day for mice and 1000 mg/kg/day for rats) provided systemic exposures to

omapatrilat that were approximately 32 to 58 times (mice) and 57 to 180 times (rats) the anticipated exposure to humans given omapatrilat at 80 mg/day.

Omapatrilat was not mutagenic in the Ames microbial mutagenesis test or in the CHO-cell forward-mutation assay. Omapatrilat did not produce increases in chromosomal aberrations in cultured human peripheral lymphocytes and was found to be non-genotoxic in the rat bone-marrow micronucleus test.

There were no adverse effects on the reproductive organs/tissues, sperm motility, or sperm counts in male rats given omapatrilat at doses up to 400 mg/kg (up to 42 times the anticipated exposure to humans given omapatrilat at 80 mg/day) daily for 1 month. In addition, there were no adverse effects on reproductive performance or early embryonic development in rats treated with omapatrilat up to 500 mg/kg/day, a dose that results in at least 13 to 19 times the anticipated systemic exposures to humans given omapatrilat at 80 mg/day. No teratogenic effects attributable to omapatrilat were seen in pregnant rats and rabbits. At 25 mg/kg in rabbits, a fetal malformation (exencephaly) was noted in the litters of two does, one that died and one that was sacrificed following abortion. Thus, effects in rabbit fetuses occurred only at a dose that also caused severe maternal toxicity and death, which indicates that omapatrilat does not cause selective developmental toxicity (i.e., an effect on the fetus with no evidence of maternal toxicity). The administration of high doses (1000 mg/kg/day for rats and 25 mg/kg/day for rabbits) resulted in maternal toxicity and systemic exposures to omapatrilat that were approximately 129 times (rats) and 0.06 times (rabbits) the anticipated exposure to humans given omapatrilat at 80 mg/day. While the exposure in rabbits was low compared to other species, the reason for this difference is not clear. However, rabbits are known to be very sensitive to the hypotensive effects of reductions in angiotensin II. The use of drugs that inhibit the renin-angiotensin system can cause fetal and neonatal morbidity and death when administered to pregnant women during the second and third trimesters of pregnancy. Intrauterine drug exposure limited to the first trimester does not appear to result in adverse effects. Because omapatrilat acts partially through this system, similar findings would be expected.

## **2 CLINICAL PHARMACOLOGY**

### **2.1 Mechanism of Action**

Inhibition of neutral endopeptidase results in increases of endogenous vasodilator peptides. Inhibition of angiotensin converting enzyme results in a decrease in the vasoconstrictor peptide, angiotensin II, which leads to decreased vasopressor activity and to decreased aldosterone secretion. Inhibition of neutral endopeptidase as well as inhibition of angiotensin converting enzyme reduces the degradation of the vasodilator peptide, bradykinin. Omapatrilat has been shown to increase atrial natriuretic peptide (ANP), brain natriuretic peptide (BNP) of myocardial cell origin, bradykinin, cyclic GMP (a second messenger for ANP and bradykinin) and adrenomedullin, and to reduce angiotensin II.

#### **2.1.1 Effects of NEP Inhibition Alone**

In subjects with heart failure or renal failure, NEP inhibitors produce a mild natriuresis. However, NEP inhibition alone is not effective in essential hypertension. The lack of antihypertensive efficacy of pure NEP inhibitors may have several explanations. First, angiotensin II is degraded by NEP, and clinical studies have shown increases in circulating angiotensin II following the administration of a NEP inhibitor. Second, angiotensin II has been shown to down-regulate natriuretic peptide receptors, decrease the formation of cyclic guanine monophosphate (cGMP) upon natriuretic peptide receptor activation, and up-regulate the phosphodiesterase that hydrolyzes cGMP, all of which could diminish the vasodilator effects of the natriuretic peptides. Thirdly, decreases in blood pressure after NEP inhibition could be blunted by reflex sympathetic activation, renin release and a further rise in angiotensin II levels. Thus, concomitant antagonism of the renin-angiotensin system may be critical in hypertension to fully realize the potential the benefits of NEP inhibition.

#### **2.1.2 Effects of ACE inhibition Alone**

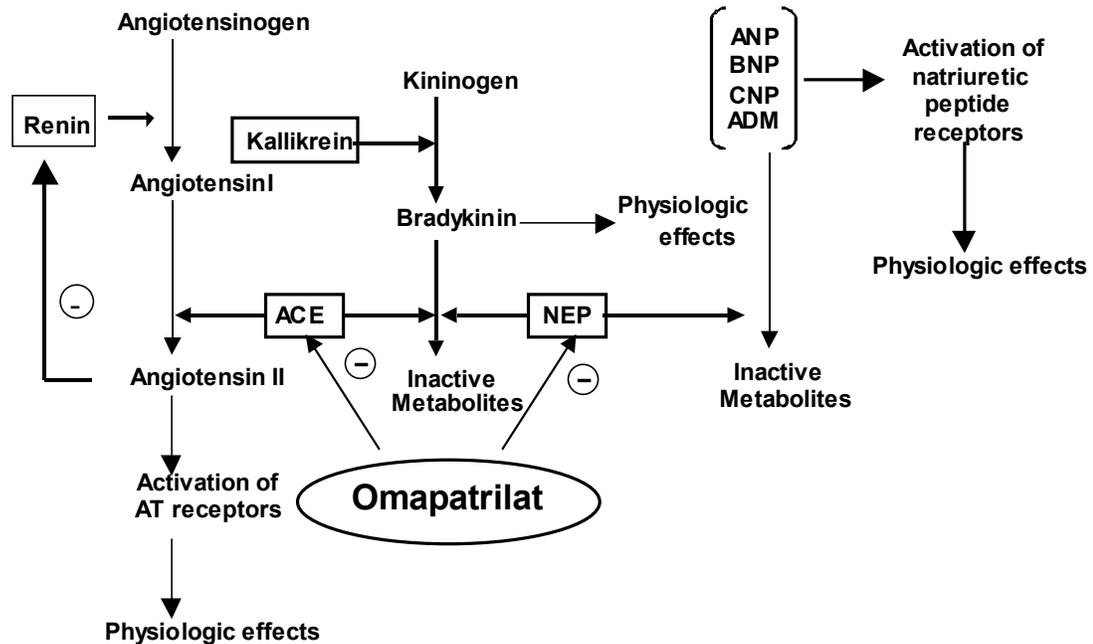
The renin-angiotensin-aldosterone system (RAAS) plays a key role in fluid and electrolyte balance, and in the control of blood-pressure.<sup>3</sup> Renin and ACE are two key enzymes involved in the formation of angiotensin II, a potent vasoconstrictor with

anti-natriuretic and proliferative actions. Inhibition of ACE blocks the generation of angiotensin II. In addition, ACE inactivates bradykinin, a potent vasodilator. In addition, ACE inhibition decreases aldosterone, a hormone which increases sodium re-absorption in exchange for potassium.

### 2.1.3 Mechanism of Action

Omapatrilat is a potent, orally active, long-acting, selective competitive inhibitor of both NEP and ACE. As a result, omapatrilat potentiates multiple endogenous vasodilatory peptides including ANP and adrenomedullin, while simultaneously inhibiting the generation of the vasoconstrictive peptide, angiotensin II (Figure 2.1.3).

**Figure 2.1.3 Proposed Mechanism of Action of Omapatrilat**



Omapatrilat, through vasopeptidase inhibition has been shown to reduce both systolic and diastolic BP effectively in a broad range of subjects, regardless of renin status.

## **2.2 Clinical Pharmacology**

An extensive clinical pharmacology program was undertaken consisting of ~800 healthy volunteers and subjects in single and multiple ascending-dose tolerance studies, radio-labeled drug disposition studies, food effect, formulation and pharmacokinetic studies including 4 special-population studies and 8 drug-drug interaction studies.

## **2.3 Pharmacokinetics**

Omapatrilat is an orally active agent that does not require biotransformation for activity. Following oral administration, omapatrilat is rapidly absorbed. Peak plasma concentrations of omapatrilat generally occur within 2 hours of dosing. The C<sub>max</sub> and AUC values of omapatrilat increase with dose. The increment in the AUC of omapatrilat, upon doubling the dose, is about 20% more than that predicted by the increase in dosage. The absolute bioavailability ranges between 22-31%. In healthy volunteers, co-administration of omapatrilat with food results in a reduction in C<sub>max</sub> and AUC (approximately 57% and 30%, respectively); however, there is no apparent effect of food on the extent of inhibition of neutral endopeptidase or angiotensin converting enzyme by omapatrilat.

Based on plasma drug levels obtained during multiple dosing, the effective half-life of omapatrilat is 14-19 hours, with steady-state concentrations reached within 3-4 days. Plasma concentrations of omapatrilat exhibit a prolonged terminal elimination phase, which does not contribute to drug accumulation. The steady-state volume of distribution of omapatrilat after intravenous administration is approximately 23 L/kg, indicative of the extensive tissue distribution of omapatrilat. Studies in rats indicate that omapatrilat and/or its metabolites cross the blood-brain barrier poorly.

Approximately 80% of intravenous and 64% of oral radiolabeled doses of omapatrilat were recovered in urine, with less than 1% of the urinary excretion of radioactivity representing unchanged drug. Omapatrilat readily forms disulfide bonds with endogenous thiols and is extensively metabolized via S-methylation, amide hydrolysis, S-oxidation, and glucuronidation. The circulating metabolites do not add to the pharmacological activity of omapatrilat. Based on biotransformation data in vivo, cytochrome P450 enzymes do not appear to be involved in the metabolism of omapatrilat.

S-methylation of omapatrilat was shown to be mediated by microsomal thiol methyl transferase and not by cytosolic thiopurine methyl transferase enzymes. Subsequent S-oxidation of S-methylated omapatrilat is mediated by microsomal flavin monooxygenase. In vitro studies show omapatrilat and its metabolites do not inhibit cytochrome P450 isozymes CYP1A2, CYP2A6, CYP3A4, CYP2C9, CYP2C19, and CYP2D6, suggesting that omapatrilat is unlikely to alter the metabolism of co-administered drugs that are metabolized by these enzymes.

Although the propensity of the sulfhydryl group to form reversible disulfide bonds in biological media prevents the exact measurement of protein binding, the estimated binding of omapatrilat in plasma, inclusive of binding to sulfhydryl-containing proteins, is moderate (approximately 77%). No clinically significant interaction was observed with omapatrilat and the highly protein-bound drug, warfarin.

## **2.4 Special Populations**

### **Pediatric**

Omapatrilat pharmacokinetics have not been investigated in subjects or healthy volunteers less than 18 years of age.

### **Gender**

No gender-related differences in plasma AUC or C<sub>max</sub> of omapatrilat were observed in a study conducted with male and female volunteers.

### **Nursing Mothers**

It is not known whether omapatrilat or its metabolites are excreted in human milk. Omapatrilat and/or its metabolites are excreted in the milk of lactating female rats.

### **Geriatric**

No clinically significant age-related differences were seen in the plasma C<sub>max</sub> or AUC in a study conducted in healthy young (18-40 years) and elderly (65-80 years) volunteers. Although the C<sub>max</sub> and AUC of omapatrilat were about 40% higher in elderly volunteers

compared to the young subjects, there was no apparent difference in the pharmacodynamic response of omapatrilat in the two groups.

### **Race**

In healthy black volunteers, omapatrilat AUC and C<sub>max</sub> values were similar to those in non-blacks in a pooled analysis.

### **Renal Insufficiency**

In a study in subjects with impaired versus normal renal function, the pharmacokinetics of omapatrilat were not dependent on creatinine clearance. Omapatrilat is not removed from the circulation by hemodialysis.

### **Heart Failure**

In a single-dose study, the absolute oral bioavailability and pharmacokinetics of omapatrilat given as a 25 mg oral dose or 10 mg IV were determined in New York Heart Association (NYHA) Class II or III heart failure (HF) subjects or controls. The oral bioavailability and disposition of omapatrilat in subjects with HF is similar to that in normal volunteers. After multiple-dose administration, the pharmacokinetic data for HF subjects were similar to the data obtained for healthy volunteers in previous studies.

### **Hepatic Insufficiency**

The effective half-life of omapatrilat in subjects with mild-to-moderate liver cirrhosis is similar to that of healthy volunteers with normal liver function. In these subjects with liver cirrhosis, the mean C<sub>max</sub> and AUC of orally administered omapatrilat were approximately 68-92% and 12-21% higher, respectively. The pharmacokinetics of omapatrilat in subjects with severe hepatic insufficiency have not been studied.

## **2.5 Drug Interactions**

### **Concomitant Diuretic and Other Antihypertensive Therapy**

Omapatrilat has been safely co-administered with other classes of antihypertensive agents: thiazides, beta-blockers, angiotensin receptor blockers and long-acting calcium channel blockers. No significant drug interactions have been found in specific studies

with furosemide, hydrochlorothiazide and atenolol. In healthy volunteers receiving maintenance doses of furosemide, omapatrilat had no effect on the steady-state natriuretic or diuretic profile of furosemide. No clinically significant pharmacokinetic interactions were observed for either drug when atenolol was co-administered with omapatrilat. The pharmacological inhibitory effect of atenolol on heart rate is not affected by co-administration of omapatrilat.

### **Agents Increasing Serum Potassium**

Omapatrilat can attenuate potassium loss caused by thiazide diuretics and increase serum potassium when used alone.

### **Antacids**

Administration of aluminum/magnesium hydroxide containing antacids within a few hours of omapatrilat may result in a modest reduction (approximately 25-35%) in the systemic bioavailability of omapatrilat, which is not considered to be of clinical significance when used occasionally.

### **VIAGRA<sup>®</sup> (sildenafil)**

Sildenafil has additive blood pressure lowering effects when co-administered to volunteers receiving omapatrilat. As with other antihypertensive agents, care is advised when co-administering sildenafil with omapatrilat due to the potential for additional lowering of blood pressure.

### **Other Drugs**

No significant drug interactions have been found with digoxin and warfarin. In separate studies of healthy volunteers receiving maintenance doses of digoxin or warfarin, omapatrilat had no effect on the steady-state pharmacodynamics of warfarin (prothrombin time), or the steady-state pharmacokinetics of digoxin. The pharmacokinetics and pharmacodynamics of omapatrilat were not affected by co-administration of digoxin.

Omapatrilat has also been safely administered with aspirin, HMG-CoA reductase inhibitors, nitrates, and estrogen replacement agents.

## **P450 Isozymes**

Based on *in vitro* data, no interactions would be expected to occur with drugs metabolized via cytochrome P450 isozymes CYP1A2, CYP2A6, CYP3A4, CYP2C9, CYP2C19, and CYP2D6.

## **2.6 Pharmacodynamics**

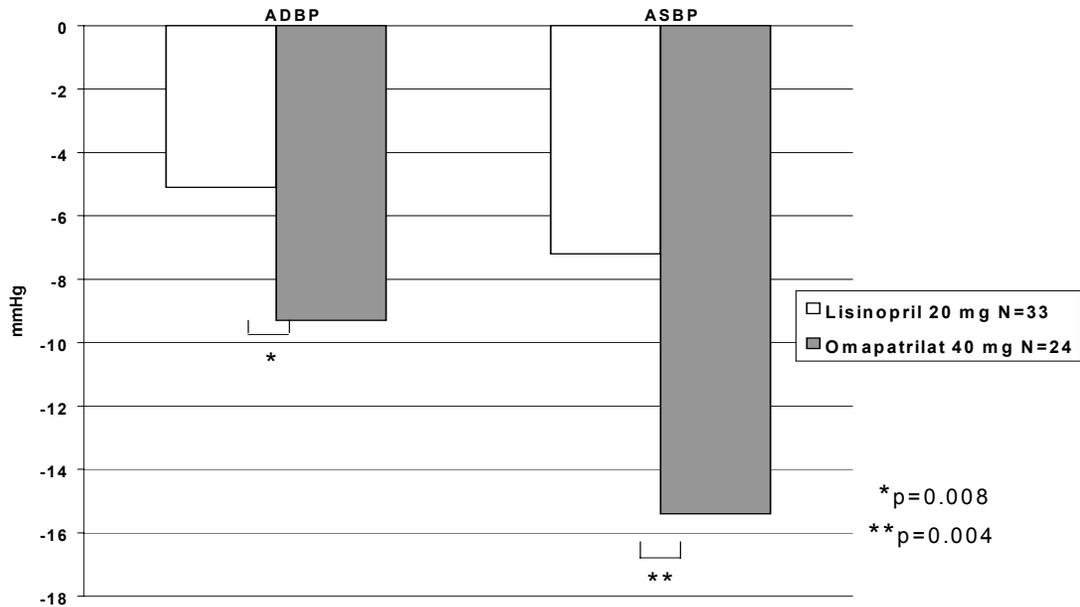
Inhibition of NEP was demonstrated in multiple studies by dose-related increases in urinary ANP. The extent of NEP inhibition appears to be modest with the 10-mg dose, and is significantly higher at doses of 25-125 mg, whereas doses of 10-125 once daily significantly inhibit plasma ACE activity to a similar extent. Omapatrilat does not demonstrate diuretic, natriuretic or kaliuretic effects in healthy volunteers, hypertensive subjects with preserved renal function, or subjects with renal impairment.

### **2.6.1 Effects on Blood Pressure**

Omapatrilat reduces BP dose-dependently in a normotensive man, and in low and high-renin states of hypertension, without affecting heart rate. Omapatrilat's initial antihypertensive effect is apparent within 4 hours after the first dose, and approximately 80-90% of the effect is attained within 2 weeks. At steady-state, the peak antihypertensive effect occurs approximately 7 hours after administration. After withdrawal of omapatrilat, blood pressure gradually returns toward baseline within approximately 2 weeks.

The effect of combined inhibition of ACE and NEP by omapatrilat vs. ACE inhibition alone was studied in salt-sensitive hypertensive subjects (CV137-017). Omapatrilat 40 mg once daily produced a significantly greater reduction in 24-hour ambulatory systolic and diastolic blood pressure (ASBP, ADBP) compared to lisinopril 20 mg (Figure 2.6.1A).

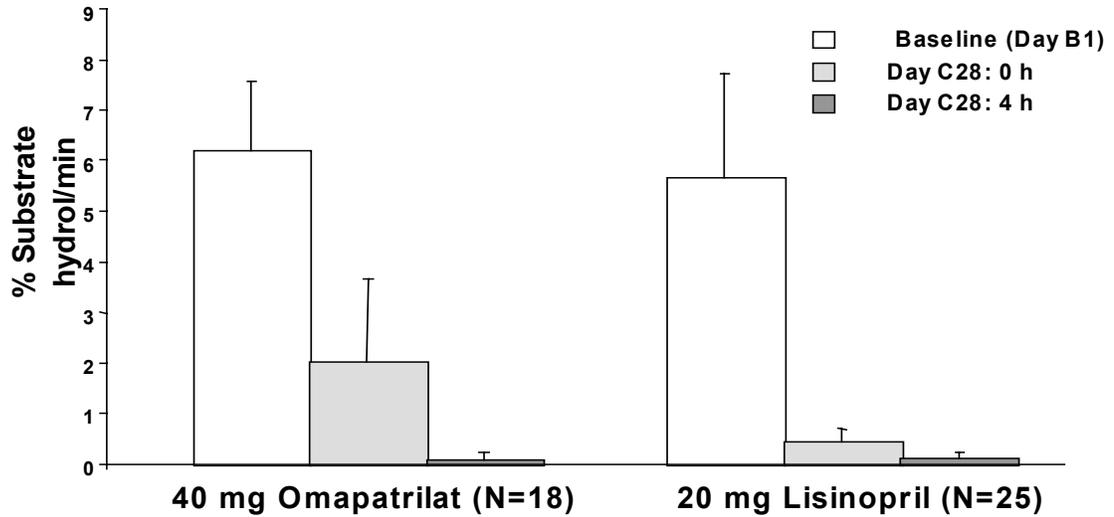
**Figure 2.6.1A: Adjusted Mean Changes from Baseline in ADBP and ASBP in Salt-sensitive Hypertensive Subjects**



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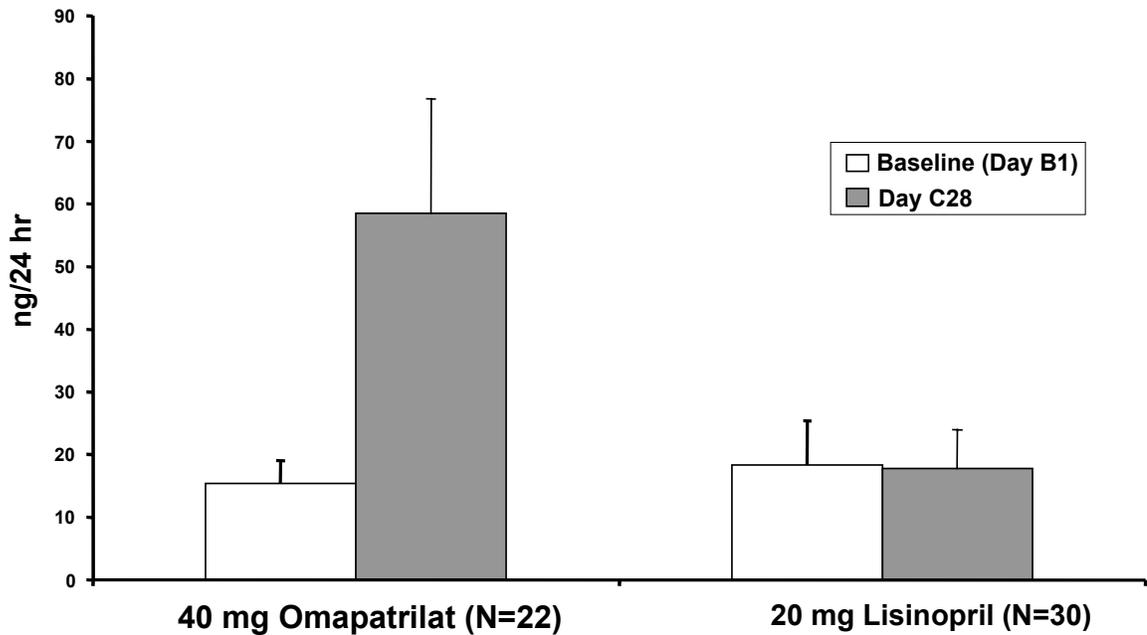
The superior effect of omapatrilat on both ASBP and ADBP could not be explained by differences in plasma ACE inhibition (Figure 2.6.1B). In contrast, substrates for NEP (plasma adrenomedullin and plasma and urinary ANP) were increased in omapatrilat-treated subjects and were unchanged in lisinopril-treated subjects, suggesting the contribution of NEP inhibition to the greater therapeutic effects of omapatrilat (Figure 2.6.1C).

**Figure 2.6.1B: Reductions in Plasma ACE Activity in Salt-Sensitive Hypertensive Subjects**



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**Figure 2.6.1C: 24-Hour Urinary ANP Excretion in Salt-Sensitive Hypertensive Subjects**



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## **2.6.2 Effects of Dose Interruption**

Dose interruption with omapatrilat was studied prospectively in CV137-122. In this study, healthy volunteers received randomized doses of omapatrilat (5, 10 or 40 mg), placebo or lisinopril 20 mg once daily for 14 days and then another single dose following a 3- or 7-day dose interruption. Baseline values of plasma bradykinin were found to be unacceptably high and variable (~18 fmol/mL) so that no definitive conclusions could be made for this parameter. However, urinary bradykinin (BK) excretion was increased transiently in a dose-related manner after omapatrilat administration. Black volunteers had similar baseline urinary BK levels, but had a higher peak response compared to non-black volunteers following omapatrilat 40 mg. With repeated dosing, neither accumulation nor attenuation of the urinary bradykinin response was seen. Following dose interruption and then resumption of omapatrilat, no overshoot of urine bradykinin occurred. There were only small and inconsistent changes in urinary des-Arg9-bradykinin excretion rates.

After the first dose of omapatrilat 40 mg, urinary excretion of prostacyclin metabolite 2,3-dinor-6-keto-PGF $1\alpha$  increased 2-fold over baseline at the 3-6 hour interval. On Day 14, there was nearly complete disappearance of this effect consistent with development of pharmacological tolerance. Placebo and lisinopril had no effects on the prostacyclin metabolite. Forehead skin temperatures significantly increased with all omapatrilat treatments on Day 1 while lisinopril showed increases that did not reach statistical significance; on Day 14, no difference was observed among treatment groups.

Body weight was used as a surrogate for cumulative diuresis and showed no statistically significant changes from pre-dose values for any treatment group.

## **2.6.3 Ancillary Effects**

Omapatrilat has no significant effects on fasting plasma triglycerides, total cholesterol, low density lipoprotein (LDL)-cholesterol, high density lipoprotein (HDL)-cholesterol or fasting plasma glucose concentrations.

## **2.7 Conclusions from the Clinical Pharmacology Program**

The pharmacokinetics and pharmacodynamics of omapatrilat, following doses of omapatrilat given alone or along with other drugs or food to a diverse population of healthy volunteers and subjects, support a once daily regimen, without adjustments in dose.

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- 2 Yamamoto K, Burnett JC, Jr, Redfield MM, Effect of endogenous natriuretic peptide system on ventricular and coronary function in failing heart. *Am J Physiol* 1997;273(5 Pt 2):H2406-14.
- 3 Sealey JE and Laragh JH. The renin-angiotensin-aldosterone system for normal regulation of blood pressure and sodium and potassium homeostasis. In: Laragh JH, Brenner BM, eds. Hypertension: pathophysiology, diagnosis and management, New York: Raven Press, 1990:1287-317.

## **APPENDIX 2      CLINICAL EVALUATIONS OF OTHER CARDIOVASCULAR EFFECTS**

### **1            Angina**

Study CV137-071 was a randomized, double-blind, placebo-controlled, parallel group, Phase II study designed to assess the anti-anginal and anti-ischemic efficacy of omapatrilat administered orally for 4 weeks in patients with documented coronary artery disease and chronic stable angina pectoris. Following a single-blind placebo lead-in period of up to three weeks, patients were randomized to received either omapatrilat (10 mg for 7 days, followed by titration to 40 mg and then 80 mg) or placebo once-daily for four weeks. Concomitant beta-blocker therapy was allowed. As this was a Phase II, proof of principle study, exercise time at 2 hours post dose (estimated time of peak plasma concentration) was selected to be the primary outcome measure. A total of 348 patients were randomized, and 331 patients completed double-blind therapy. The maximum tolerated dose of omapatrilat was 80 mg in 85% of patients.

At 2 hours post dose at Week 4, the omapatrilat group had a larger mean increase from baseline in maximal treadmill exercise time than did the placebo group (76.6 seconds vs. 28.7 seconds,  $p < 0.001$ ). Patients receiving omapatrilat also had longer mean exercise time to Level 3 angina pectoris ( $p < 0.001$ ) and longer mean time to onset of 0.1 mV ST segment depression ( $p < 0.001$ ). Omapatrilat reduced the heart rate-pressure product at peak exercise more than placebo, but this difference was not statistically significant. The reduction was accounted for by a blunting of peak exercise systolic blood pressure.

At trough ( $24 \pm 3$  hours after the previous dose) at Week 4, the mean increase from baseline in maximal treadmill exercise time was 39.9 seconds in the omapatrilat group and 28.5 seconds in the placebo group ( $p = 0.215$ ). Patients receiving omapatrilat had slightly longer mean time to Level 3 angina pectoris and mean time to onset of 0.1 mV ST segment depression than patients receiving placebo, but these differences were not statistically significant.

There was no statistically significant difference between treatment groups in either the change from baseline in angina frequency or the change from baseline in nitroglycerin consumption.

The change from baseline in standing systolic blood pressure at trough at Week 4 was -7.7 mmHg for omapatrilat and -2.3 mmHg for placebo. The change from baseline in standing diastolic blood pressure was -4.1 mmHg for omapatrilat and -0.6 mmHg for placebo.

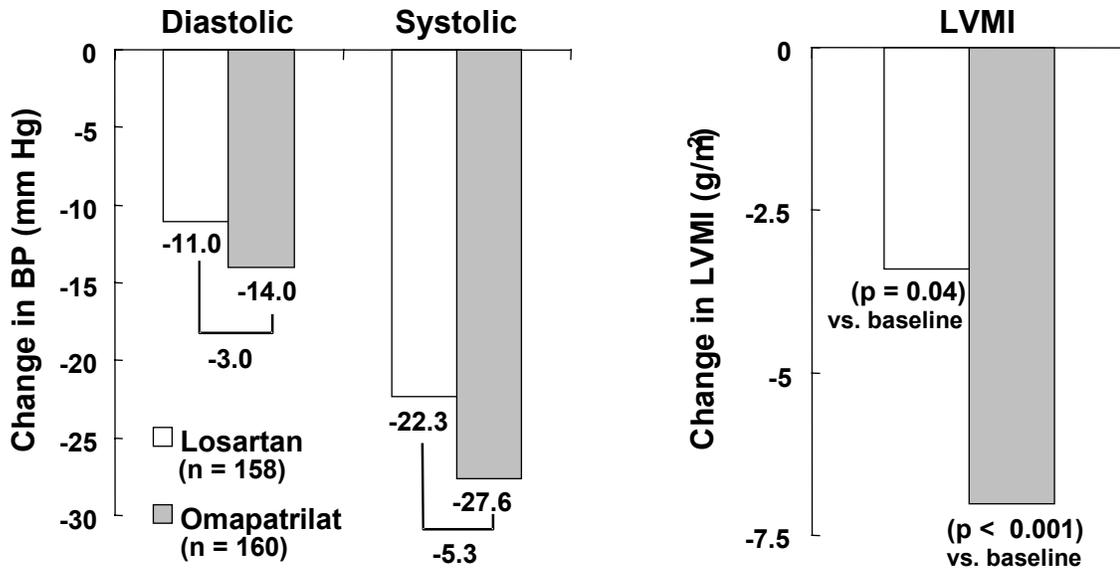
## **2 Left Ventricular Hypertrophy**

Study CV137-038 was a 52 week double-blind study comparing the effects of omapatrilat and losartan on left ventricular mass index in patients with LVH and mild-to-moderate hypertension (trough diastolic blood pressure 95-115 mmHg and/or systolic blood pressure 160-200 mmHg). The first 24 weeks compared the effects of omapatrilat (20 mg starting dose, force-titrated to 40 mg at Week 8 and 80 mg at Week 16) and losartan (50 mg starting dose, force-titrated to 100 mg at Week 8 and mock-titrated to 100 mg at Week 16) as monotherapy, with adjunctive antihypertensive medication permitted only if clinically indicated.

At Week 24, LVMI was significantly reduced in omapatrilat-treated patients (-7.2 g/m<sup>2</sup>, p < 0.001) and losartan-treated patients (-3.4 g/m<sup>2</sup>, P = 0.04) compared with baseline, with a trend favoring omapatrilat-treated patients (P = 0.11). Greater reductions in trough systolic blood pressure and diastolic blood pressure were observed in the omapatrilat group compared to the losartan group.

At Week 52, omapatrilat and losartan both produced significant (p < 0.001) reductions from baseline in mean left ventricular wall mass index (-13.6 g/m<sup>2</sup> and -13.2 g/m<sup>2</sup>, respectively). The difference between groups was not statistically significant. Reductions in left ventricular mass were associated with reductions in end-diastolic posterior wall thickness and interventricular septal thickness in both groups. Use of adjunctive antihypertensive therapy during double-blind treatment was lower in the omapatrilat group than in the losartan group (34.9% of patients vs. 58.7%). Mean changes in seated BP were -32.8/-16.3 mmHg in the omapatrilat group and -29.0/-15.9 mmHg in the losartan group.

**Figure 2: Mean Change in BP and Left Ventricular Mass Index at Week 24 (CV137-038)**



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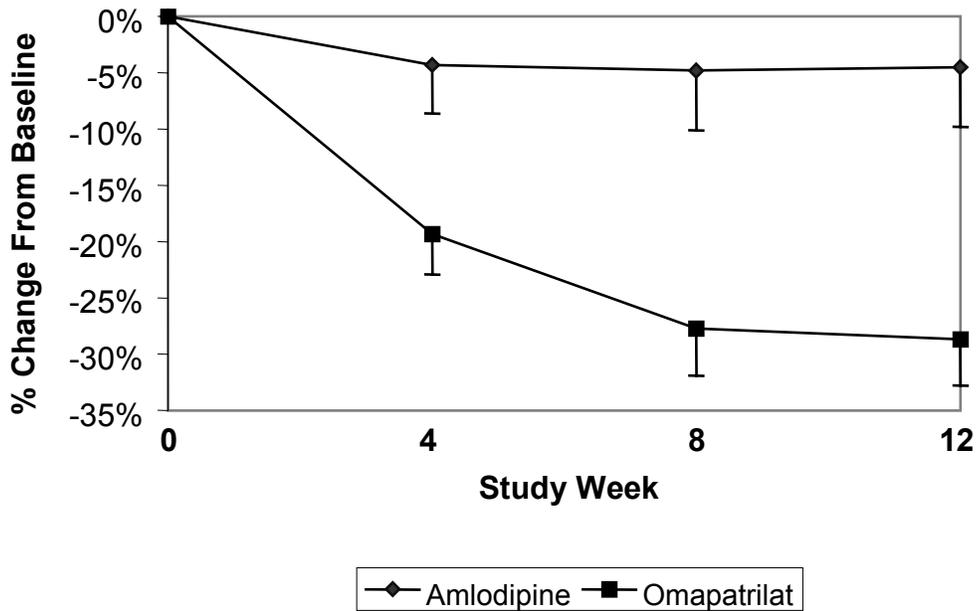
### 3 Renal Disease

Study CV137-046 was designed to evaluate the antiproteinuric effects of omapatrilat and amlodipine in type 2 diabetics with hypertension, preserved renal function, and microalbuminuria or overt nephropathy. Three hundred nineteen (319) subjects were randomized in a 1:1 ratio to treatment with omapatrilat or amlodipine for 12 weeks. Subjects randomized to omapatrilat received 20 mg for 4 weeks, with elective titration to 40 mg at Week 4 and 80 mg at Week 8. Subjects randomized to amlodipine received 2.5 mg for 4 weeks, with elective titration to 5 mg at Week 4 and 10 mg at Week 8. Elective titration was performed to achieve seated diastolic blood pressure < 80 mmHg and seated systolic blood pressure < 125 mmHg. Open-label adjunctive antihypertensive therapy with alpha blockers, beta blockers, or diuretics was permitted for subjects receiving the maximum tolerated dose of double-blind study medication. The primary outcome measure was the percent change from baseline to Week 12 in 24 hour urine albumin excretion rate.

At Week 12, omapatrilat-treated subjects had a greater reduction in 24 hour urine albumin excretion rate compared to amlodipine-treated subjects (Figure 3). The reduction

was 28.7% for omapatrilat versus 4.5% for amlodipine ( $p < 0.001$ ). Titration to the highest level of study drug occurred in 64% of subjects in the amlodipine group and 55% in the omapatrilat group. Despite this difference, the reduction in seated diastolic blood pressure at Week 12 was similar with the omapatrilat and amlodipine regimens (9.6 mmHg and 9.0 mmHg, respectively), and the reduction in seated systolic blood pressure was slightly greater with omapatrilat compared to amlodipine (17.1 mmHg and 15.5 mmHg, respectively). No statistical comparisons were carried out on the differences in BP reduction between the two groups.

**Figure 3: Adjusted Geometric Mean Percent Change (SE of Mean) from Baseline for Albumin Excretion Rate**



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The results for omapatrilat are comparable to those obtained with the ACE inhibitor captopril in previous studies. Two captopril studies in subjects with microalbuminuria<sup>1,2</sup> when combined yielded reductions in albumin excretion rate from baseline to 3 months of 27.3%, compared with 29.4% for omapatrilat-treated subjects with microalbuminuria in Study CV137-046. The captopril diabetic nephropathy trial,<sup>3</sup> which was conducted in subjects with overt nephropathy, showed a reduction from baseline at 3 months in protein

excretion rate of 25.0%, as compared to 22.2% for omapatrilat-treated subjects with overt nephropathy in Study CV137-046. The effects of amlodipine treatment on proteinuria have not been definitively investigated in adequately powered and well controlled studies although several small, uncontrolled studies have suggested that urine albumin excretion may fall with short term treatment.<sup>4,5,6</sup>

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3. Lewis EJ, Hunsicker LG, Bain RP, Rhode RD. The effect of angiotensin-converting-enzyme inhibition on diabetic nephropathy. *N Engl J Med* 1993; 329:1456-62.
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6. Letizia C, DeCiocchis A, Cerci S, Coassin S, Fisher H, Tarsitani P, Scavo D. Amlodipine in ambulatory hypertensive patients: humoral and haemodynamic effects. *Int J Clin Pharm Res*. 1993; 13:151-9.

### **APPENDIX 3 RISK MANAGEMENT PROGRAM**

The risk of angioedema would be managed through implementation of a proactive, ongoing and comprehensive Risk Management Plan for Omapatrilat (RMPO). BMS is in active discussion with the FDA, leading risk management and communication consultants, representatives of professional organizations and members of academia to develop this plan.

#### **Rationale**

BMS believes that the RMPO will be effective in minimizing the rate and severity of angioedema associated with omapatrilat in actual use for the following reasons:

- Based upon our extensive experience with the OCTAVE trial, angioedema is a highly symptomatic condition with a largely characteristic presentation that can be effectively described through educational methods. Therefore, angioedema lends itself to management through education of the prescriber, patient, and pharmacist;
- The risk factors for angioedema have been identified, and the time course, symptomatology and treatment have been characterized through the omapatrilat clinical development program. There are two clearly identifiable patient groups, African-American and smokers, who appear to be at higher risk for angioedema than the general population; careful consideration should be given to patient selection to help reduce the overall angioedema risk;
- BMS is committed to establishing awareness of angioedema and to implementation of the RMPO as an integral part of the initial marketing and launch of omapatrilat. Thus, the risks associated with and appropriate use of omapatrilat would be established as part of the product profile from launch forward, and not as a reaction to a risk that emerges post-marketing. With other products, proactive risk management has been successful (e.g., metformin and lactic acidosis);
- BMS has undertaken research plans to assure that the key messages concerning the risk of angioedema would be understood by the important stakeholders in the treatment continuum (prescribers, patients, and pharmacists) and would effect

appropriate actions by them in response to the signs and symptoms of angioedema. As a result of this research, BMS plans to implement the most effective means of communicating the important messages.

- To assure that the RMPO works in the “real world”, we propose surveillance programs and post-marketing surveys to measure program effectiveness.
- System approaches are widely considered required elements of risk management. Specifically, the FDA has encouraged stakeholders to devise and participate in programs that incorporate checks and balances, redundancies, and other systems approaches to assure the products are used appropriately. This principle has been incorporated into the RMPO through creation of a web of communication and education programs.

### **Objectives**

The Program focuses on the three primary objectives:

- Physicians who prescribe omapatrilat have adequate knowledge of hypertension and omapatrilat including its benefits and risks, and are capable of recognizing and treating angioedema;
- Patients who are prescribed omapatrilat are knowledgeable of the signs and symptoms of angioedema and will react appropriately if they encounter signs and symptoms;
- The effectiveness of the RMPO is monitored, specifically in regard to program components implemented to minimize the risk and severity of angioedema.

Components of the RMPO are based upon currently accepted principles of risk management. The RMPO would employ communication and educational programs, designed to reach the key stakeholders (patient, physician, and pharmacist), at each relevant stage in the treatment process (pre-therapy, at therapy initiation, and during ongoing therapy). Multiple and redundant delivery of the key benefit and risk messages is critical to ensure achievement of the risk management goals.

To assure patient awareness of and appropriate reaction to the risk of angioedema associated with omapatrilat, the RMPO would require patients to enroll in a pharmacist-to-patient counseling program. This program would complement the role of the prescriber and retail pharmacist in educating patients on the benefits and risks of omapatrilat therapy.

### **Pre- and Post-Marketing Comprehension Testing**

The RMPO relies to a great extent on education. The comprehension of each key message of the RMPO will be critical to its success. BMS plans to conduct qualitative and quantitative cognition testing of the proposed messages.

### **Post-Marketing Surveillance**

To assess the rate of angioedema in real world use and to monitor the effectiveness of the RMPO, BMS would employ both active and passive surveillance methodology. Angioedema cases that are fatal or require intubation would be evaluated through the use of a large hospital-based claims database that will allow estimation of a proportional rate in the covered population. In addition, a cohort study of ~10,000 patients would be established to evaluate the rate of angioedema requiring epinephrine use and the rate of angioedema requiring hospitalization.

Serious spontaneously reported cases of angioedema would be reported on an expedited basis to FDA. The evaluation of spontaneously reported adverse events will be enhanced using specific data collection forms for angioedema. These forms will be actively utilized by staff at the BMS AE Call Center and by BMS Product Safety Physicians upon notification of possible cases of angioedema. Information will be collected regarding the frequency of intubation/tracheostomy, hospitalization, and epinephrine or corticosteroid treatment.

Opportunities to evaluate compliance with the RMPO elements will be sought within the above surveillance activities and can be developed once the details of the RMPO and the post-marketing programs are finalized. BMS intends to provide FDA frequent updates on all reported cases of angioedema, estimated market exposure, status and results of post-marketing surveillance studies, and results of evaluations of compliance.