



DIVISION OF CARDIO-RENAL DRUG PRODUCTS
Joint Statistical-Clinical Review

NDA: 21-188 (omapatrilat for hypertension)
Sponsor: Bristol-Myers Squibb
Submission: NDA resubmission dated 14 December 2001, including the results of the OCTAVE study.

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Summary: Omapatrilat has been shown to be an effective antihypertensive, probably superior to recommended once-daily dosing regimens of enalapril and perhaps other approved treatments. Effectiveness in reducing blood pressure comes at the expense of a markedly higher rate of angioedema and a disproportionately higher incidence of more severe angioedema, including airway compromise. A substantial fraction of this risk cannot be avoided by any established means. If omapatrilat lowered blood pressure when addition of safer agents could not, then perhaps this risk would be worth undertaking in this population, but omapatrilat is not known to work under these conditions.

Distribution: NDA 21-188
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1 Introduction

The submission includes final study reports or interim reports for 26 studies in progress or completed since the NDA was withdrawn in 1999. These studies are listed in Table 1.

Table 1. List of studies.

Study	Design¹	N	Duration
CV137-120	Rand, DB, el, AC	25166	24 weeks
CV137-009	OL	1098	24 weeks
CV137-028	Rand, DB, el, AC	367	1 year
CV137-029LT	OL	203	18 months
CV137-037LT	Rand, DB, el, AC	504	4 months
CV137-038LT	Rand, DB, el, AC	341	1 year
CV137-042LT	OL	429	>1 year
CV137-046	Rand, DB, el, AC	319	12 weeks
CV137-049LT	OL	167	2 years
CV137-050	Rand, DB, el, PC	747	6 months
CV137-059	Rand, DB, XO, PC, AC	25	1 day
CV137-066	Rand, DB, el, AC	812	6 weeks
CV137-071	Rand, DB, el, PC	348	4 weeks
CV137-072	Rand, DB, el, AC	488	4 weeks
CV137-073	Rand, DB, el, AC	275	4 weeks
CV137-077	Rand, DB, el, AC		10 weeks
CV137-087	Rand, DB, el, PC, AC	32	7 days
CV137-091	Rand, DB, el, AC	404	9 weeks
CV137-098	OL	115	12 weeks
CV137-099	OL	63	12 weeks
CV137-102	OL	15	4 weeks
CV137-123	Rand, DB, el, PC	88	2 weeks
CV137-141	OL	6	1 day
CV137-142	OL	7	1 week
CV137-144	OL, PC	35	1 day

Over 90% of the exposure to study drug is in study CV137-120 (OCTAVE). This review considers OCTAVE in detail and describes the other 25 studies only with respect to their characterization of angioedema.

¹ Rand = randomized, DB = double-blind, OL = open-label, AC = active control, PC = placebo control, ||el = parallel design, XO = crossover design.

2 CV137-1 20: Omapatrilat cardiovascular treatment assessment versus enalapril (OCTAVE)

2.1 Basis of review

This review of the protocol is based upon the original protocol dated 21 July 2000 and dated amendments and administrative letters.

The review of the study results is based upon the final study report dated 11 December 2001 and electronic datasets.

2.2 Protocol

2.2.1 Population

The plan was to enroll 25,000 subjects with previously treated or previously untreated mild-to-moderate essential hypertension. Subjects with mild hypertension (140/90 to 160/100 mmHg) on original therapy would be switched to randomized therapy; up to 5000 of these subjects could have been receiving ACE inhibitors. Subjects with moderate to severe hypertension (up to 180/110 mmHg) on prior treatment (not including ACE inhibitor) would have randomized treatment added to background therapy. Up to 10% of subjects could be Black. Other exclusion criteria included prior hypersensitivity to or intolerance of ACE inhibitors, any angioedema or drug-related rash, major cardiovascular event within 3 months, respiratory hospitalization within 6 months, autoimmune renal disease, end-stage renal disease, treated malignancy within 6 months, or prior exposure to omapatrilat. Baseline laboratory assessments had to show hemoglobin >10 g/dL, platelets >100 /nL, WBC >2000 / μ L, potassium \leq 5.7 mM, creatinine \leq 3 mg/dL, SGOT and SGPT \leq 150 u/L, and total bilirubin \leq 2.0 mg/dL.

2.2.2 Procedures

This was a randomized, double-blind, parallel, enalapril-controlled study. Subjects were evenly randomized to treatment with once-daily enalapril (starting at 5 mg) or omapatrilat (starting at 10 mg). Subjects were followed for safety for two hours after the first dose. At 2, 4, and 6 weeks, subjects were eligible to have the dose of study drug up-titrated to (enalapril) 10, 20 and 40 mg or (omapatrilat) 20, 40 or 80 mg, for blood pressures greater than goal (140/90 mmHg). Amendment 2 (31 August 2000) called for a two-hour observation period after increments in study drug dose. At subsequent visits (weeks 8 and 16), subjects were eligible to have additional antihypertensive therapy added to randomized treatment (and background therapy). The final visit was at 24 weeks.

Only ACE inhibitors were prohibited concomitant antihypertensive treatments. It was recommended to use thiazides first, but no other direction was given.

2.2.3 End points

The sponsor defined 6 primary end points, between-group comparisons for trough systolic pressure at 8 weeks (before add-on therapy) and proportion of subjects requiring add-on therapy at 24 weeks, evaluated in 3 cohorts—subjects with untreated hypertension at baseline, subjects with mild hypertension despite treatment at baseline, and subjects with moderate to severe hypertension despite treatment at baseline. The analysis plan called for a Bonferroni correction for these 6 end points.

Although no further allocation of alpha was suggested, the analysis plan called for a comparison in the rates of adjudicated angioedema cases with one-sided testing at $p=0.05$ to test the hypothesis that the rate of angioedema on omapatrilat was not more than twice as high as for enalapril.

2.2.4 Monitoring

There was a Steering Committee charged with oversight of the overall study. There was a Data Safety Monitoring Committee viewing unblinded safety data. There was a blinded Endpoint Adjudication Committee reviewing cases of angioedema.

2.3 Results

2.3.1 Conduct

Enrollment and study participation ran from 29 August 2000 to 27 July 2001.

A total of 3298 centers in the US (2175), Germany (643), Russia (114), UK (85), Canada (66), Netherlands (56), Spain (45), Austria (41), Belgium (25), Poland (20), Italy (16), and Israel (12) screened 33745 and randomized a total of 25302 subjects. Of these, 25166 received at least one dose of study drug and 20652 (82%) completed 24 weeks of double-blind treatment.

Status in study is shown as a function of time in Figure 1.

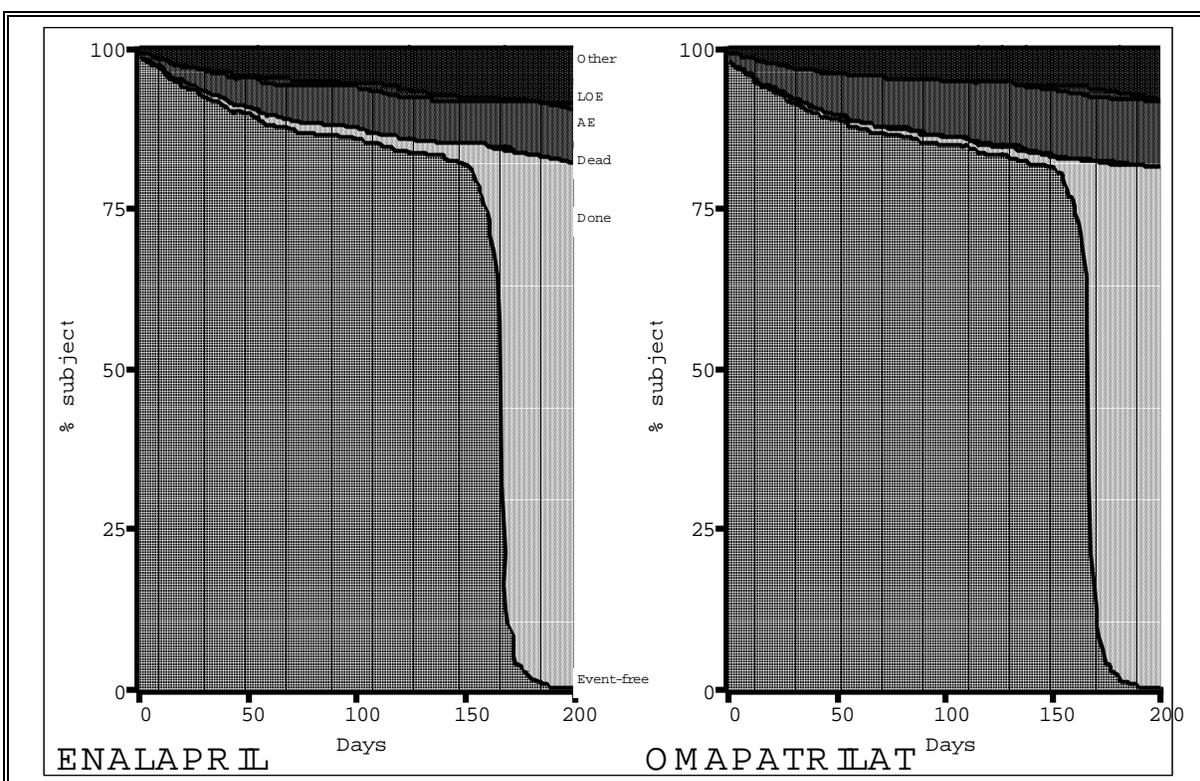


Figure 1. Disposition of subjects²

The panes show the disposition of all subjects at all points in time. It is a stacked bar chart for each day of study. The "Other" category includes "withdrew consent", "subject discontinue", "lost to follow-up", "sponsor request", "physician discretion", "pregnancy", and "other".

From early in the study and progressively through the study, a greater proportion of subjects on omapatrilat withdrew for adverse events. Forty-three subjects are described as "completers", although they completed with less than 20 weeks of treatment (as early as 15 weeks).

² Reviewer's analysis.

Three interim safety analyses were conducted by the Data Safety Monitoring Committee, with about 25% and 75% recruitment and after all subjects had completed 8 weeks of treatment. No actions were recommended at these meetings.

2.3.2 Population

Of 25302 randomized subjects, 9292 were previously untreated, 11224 had prior treatment replaced by randomized treatment, and 4751 had randomized treatment added to prior treatment. Subjects with at least one post-baseline assessment in the first 8 weeks contributed to the analysis of SBP; 97% of subjects in each cohort did so. Subjects with at least one visit after 8 weeks contributed to the analysis of need for adjunctive treatment; 87 to 90% of subjects in each cohort did so.

Baseline and demographic characteristics of the 3 cohorts are shown in Table 2. Not surprisingly, there were no significant differences between the treatment groups for any of these factors (not shown).

Table 2. Demographic and baseline characteristics³

	Naïve N=9292	Replacement N=11224	Add-on N=4751
Age mean	53	58	60
>75 (%)	6%	9%	12%
Male	56%	51%	49%
Black	9%	12%	9%
US	58%	65%	48%
SBP±SD	156±14	150±9	166±11
DBP±SD	96±9	91±7	97±9
History of			
hypercholesterolemia	25	36%	36%
Diabetes	9%	17%	17%
Angina	2%	5%	10%
Myocardial infarction	1%	3%	5%
Treatment at screening	—		
One drug		64%	50%
>2 drugs		9%	15%
ACE inhibitor		39%	3%
Diuretic		31%	42%
Beta-blocker		25%	46%
Calcium channel blocker		30%	43%
Angiotensin receptor		15%	20%
Any prior ACEI usage	13%	53%	64%

2.3.3 Dosing

The distribution of doses of study drug is shown in Table 3.

³ Based on sponsor's analyses.

Table 3. Distribution⁴ of study drug doses.

Week	Enalapril				Omapatrilat			
	5	10	20	40	10	20	40	80
2	99	0	0	0	99	0	0	0
4	0	99	0	0	0	99	0	0
6	0	35	64	0	0	43	57	0
8	0	28	31	41	0	35	32	33
16	0	28	31	40	0	36	32	32
24	0	28	31	40	0	36	32	31

Few subjects remained on the starting dose of either drug. There were no significant changes in dosing of the study drug after week 8.

Compliance (>70% utilization) was >98% in both treatment groups at the 24-week visit.

2.3.4 Effectiveness

2.3.4.1 Blood pressure in the first 8 weeks

The last-observation-carried-forward analysis of effects on blood pressure (change from baseline and enalapril) are shown in Table 4.

Table 4. Blood pressure effects (omapatrilat minus enalapril) at week 8 (LOCF)⁵.

	Naïve		Replacement		Add-on	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
SBP	-3.2	-3.9, -2.6	-3.9	-4.5, -3.3	-3.6	-4.6, -2.6
DBP	-1.9	-2.3, -1.5	-2.3	-2.6, -1.9	-1.7	-2.3, -1.1

Between-group differences in systolic and diastolic pressure were all highly statistically significant in all three cohorts. By the sponsor's analyses, these differences were consistent across subgroups based upon the baseline treatment being replaced or supplemented.

Subjects randomized to omapatrilat were more likely to meet blood pressure control criteria (<140/90 mmHg), but the proportions are difficult to interpret without a placebo group and because the proportions depend upon the distribution of blood pressures at baseline.

Effects were generally consistent in subgroups above and below age 65 or 75, in Caucasians and Asians, and in males and females. Blacks tended to have a larger between group difference in blood pressure than did Caucasians (-5.2/-2.5 vs. -3.5/-2.0), tribute more to the power of the study than to the magnitude of the effect of race.

2.3.4.2 Need for adjunctive treatment after 8 weeks

Subjects on enalapril were more likely to need adjunctive treatment during weeks 9 to 24, as shown in Table 5.

⁴ Percentage of subjects continuing in study at given visits. Based on sponsor's analysis.

⁵ Sponsor's analysis.

Table 5. Need for adjunctive treatment during weeks 9-24⁶.

	Naïve		Replacement		Add-on	
	Enal	Omap	Enal	Omap	Enal	Omap
Any	19%	13%	35%	25%	22%	17%
Added 1	16%	11%	27%	21%	19%	14%
Added 2	3%	1%	7%	4%	3%	2%
Added 3	0%	0%	1%	1%	0%	1%

All of the between-group differences were highly statistically significant.

Between group differences in the need for adjunctive treatment were consistent in subgroups based on age, race, and gender.

2.3.4.3 Other end points

Adjunctive treatment during weeks 8 to 24 might have been expected to reduce the differences in blood pressure between groups, but it did not have much effect, as shown in Table 6.

Table 6. Blood pressure effects (omapatrilat minus enalapril) at week 24 (LOCF)⁷.

	Naïve		Replacement		Add-on	
	Mean	95% CI	Mean	95% CI	Mean	95% CI
SBP	-3.1	-3.8, -2.4	-3.1	-3.7, -2.5	-2.8	-3.8, -1.8
DBP	-1.6	-2.0, -1.2	-1.9	-2.2, -1.5	-1.2	-1.8, -0.5

Of course, this difference led to some differences in the rate of blood pressure control at 24 weeks, but once again the differences are difficult to interpret without a placebo group and because of the dependence on the distribution of blood pressures at baseline.

2.3.5 Safety

2.3.5.1 Deaths

Deaths on omapatrilat are described below.

Subject 173-35 was a 78 year old Black male with history of hypertension. He was randomized to omapatrilat in cohort 2 and was on 20 mg. He discontinued on day 36 with prostatic adenocarcinoma and he died about 1 month later.

Subject 173-198 was a 54 year old Black male with a history of stroke and diabetes. He was randomized to omapatrilat in cohort 2 and was on 40 mg. Death on study day 89 was attributed to cardiopulmonary arrest not otherwise characterized.

Subject 273-005 was a 52 year old White male with a history of myocardial infarction. He was randomized to omapatrilat in cohort 2 and was titrated to 80 mg. He completed study with no notable events. He had a sudden cardiac death 19 days later.

Subject 342-6 was a 51 year old White male with a history of hypertension, diabetes, and chest pain. He was randomized to omapatrilat in cohort 3 and was titrated to 80 mg. Death on study day 158 was attributed to myocardial infarction.

Subject 507-008 was a 70 year old White female with a history of hypertension and atrial fibrillation. She was randomized to omapatrilat in cohort 3 and was titrated to 80 mg. On day 48 she experienced a subdural hematoma and she died on day 54.

⁶ Sponsor's analyses.

⁷ Sponsor's analysis.

Subject 559-5 was a 72 year old White female with a history of hypercholesterolemia and diabetes. She was randomized to omapatrilat in cohort 2 and was titrated to 80 mg. Death on study day 130 was attributed to subarachnoid hemorrhage, experienced 7 days earlier.

Subject 1152-4 was a 45 year old White male with a history of hypertension, heart failure, diabetes, and CHF. He was randomized to omapatrilat in cohort 2 and was on 80 mg. Death on study day 96 was attributed to pneumonia.

Subject 1182-2 was a 57 year old White male with a history of hypertension and obesity. He was randomized to omapatrilat in cohort 1 and was on 20 mg. Death on study day 19 was attributed to myocardial infarction.

Subject 1245-10 was a 57 year old Black female with a history of diabetes. She was randomized to omapatrilat in cohort 2 and was titrated to 40 mg. She was hospitalized for sepsis and diabetes management on about week 23. Death about 1 week later was attributed to sepsis.

Subject 1447-1 was a 66 year old White male with a history of hypertension and hypercholesterolemia. He was randomized to omapatrilat in cohort 2 and was on 20 mg. Death on study day 24 was attributed to myocardial infarction.

Subject 1487-8 was a 63 year old White male with a history of hypertension and diabetes. He was randomized to omapatrilat in cohort 1 and was on 80 mg. Death on study day 171 was attributed to pulmonary embolus subsequent to lower limb cellulitis.

Subject 1501-6 was a 52 year old White female with a history of hypertension and hypercholesterolemia. She was randomized to omapatrilat in cohort 1 and was titrated to 20 mg. She had a mild stroke on day 16 and discontinued. Sudden cardiac death followed about 3 weeks later.

Subject 1556-4 was a 75 year old White male with a history of diabetes, myocardial infarction, and heart failure. He was randomized to omapatrilat in cohort 2 (3?) and was on 20 mg. There was one intercurrent episode of atrial fibrillation. Death on study day 121 was unobserved but was attributed to arrhythmia.

Subject 1629-26 was a 71 year old White male with a history of diabetes, hypercholesterolemia, hypertension, and angina. He was randomized to omapatrilat in cohort 2 and was on 10 mg. Death on study day 8 was attributed to myocardial infarction.

Subject 2010-16 was a 54 year old White male with a history of hypertension. He was randomized to omapatrilat in cohort 1 and was on 20 mg. Death on study day 19 was attributed to suicide.

Subject 2260-10 was a 59 year old White female with a history of hypertension and hypercholesterolemia. She was randomized to omapatrilat in cohort 2 and was titrated to 80 mg. She completed study and died 7 days later from myocardial infarction.

Subject 3557-28 was a 43 year old Black male with a history of hypertension and pancreatitis. He was randomized to omapatrilat in cohort 2 (3?) and was on 20 mg. Death on study day 18 was attributed to a motor vehicle accident in which he appeared to be the driver at fault.

Subject 3574-122 was a 72 year old White male with a history of diabetes and hypertension. He was randomized to omapatrilat in cohort 2 and was on 20 mg. Death unobserved on study day 61 was attributed to diabetes.

Subject 3574-141 was a 51 year old White female with a history of hypercholesterolemia and diabetes. She was randomized to omapatrilat in cohort 2 and

was on 20 mg. Death unobserved at home on study day 98 was attributed to atherosclerotic disease.

Subject 6852-005 was a 47 year old White male with a history of hypertension and hypercholesterolemia. He was randomized to omapatrilat in cohort 3 and was titrated to 20 mg. He had a myocardial infarction on day 20 and a severe stroke on day 21. He died 14 days later.

Subject 8500-23 was a 44 year old White male with a history of diabetes. He was randomized to omapatrilat in cohort 1 and was on 20 mg. Death on study day 136 was attributed to kidnapping and murder.

Subject 8521-51 was a 76 year old White male with a history of hypercholesterolemia and angina. He was randomized to omapatrilat in cohort 2 and was titrated to 40 mg. He was hospitalized for pneumonia on day 132 and was diagnosed with metastatic lymphoma. He died about a month later.

Subject 8962-2 was a 54 year old White male with a history of diabetes, hypercholesterolemia, myocardial infarction, heart failure, and angina. He was randomized to omapatrilat in cohort 2 and was titrated to 40 mg. Death unobserved at home on study day 111 was attributed to progressive heart failure.

On treatment or within 14 days of treatment, there were 23 deaths in the enalapril group and 19 deaths in the omapatrilat group. Of these, there were 11 deaths in each group attributed to cardiovascular causes, including myocardial infarction (n=8). These events do not appear to represent a safety concern.

2.3.5.2 Angioedema

There were no deaths attributed to angioedema. The special interest in angioedema makes it less likely than usual that such a mortal event would be misinterpreted. On the other hand, there were 4 unobserved deaths after 9 to 99 days of treatment with omapatrilat for which there was no autopsy⁸. It is not clear how to exclude angioedema as a cause of death in these cases.

The closest such history in a subject randomized to enalapril is subject 3856-2, an 81 year old White female, found dead at home on day 123, and believed, without autopsy, to have had a myocardial infarction.

The sponsor's null hypothesis with respect to angioedema was that the hazard ratio for omapatrilat versus enalapril would be ≥ 2 . There were 360 adjudicated angioedema events, 274 on omapatrilat and 86 on enalapril. Crude event rates were 2.2% on omapatrilat and 0.7% on enalapril. The one-sided p-value was greater than 0.9999 and therefore, the trial failed to show that the relative risk is less than 2. The sponsor's analysis of the risk ratio is actually about 3.2 with 95% confidence limits of 2.5 to 4.1.

A life table analysis for angioedema-free survival is shown in Figure 2.

⁸ See subjects 1629-26, 1447-1, 3574-122, and 3574-141, among whom are 3 White males and one White female.

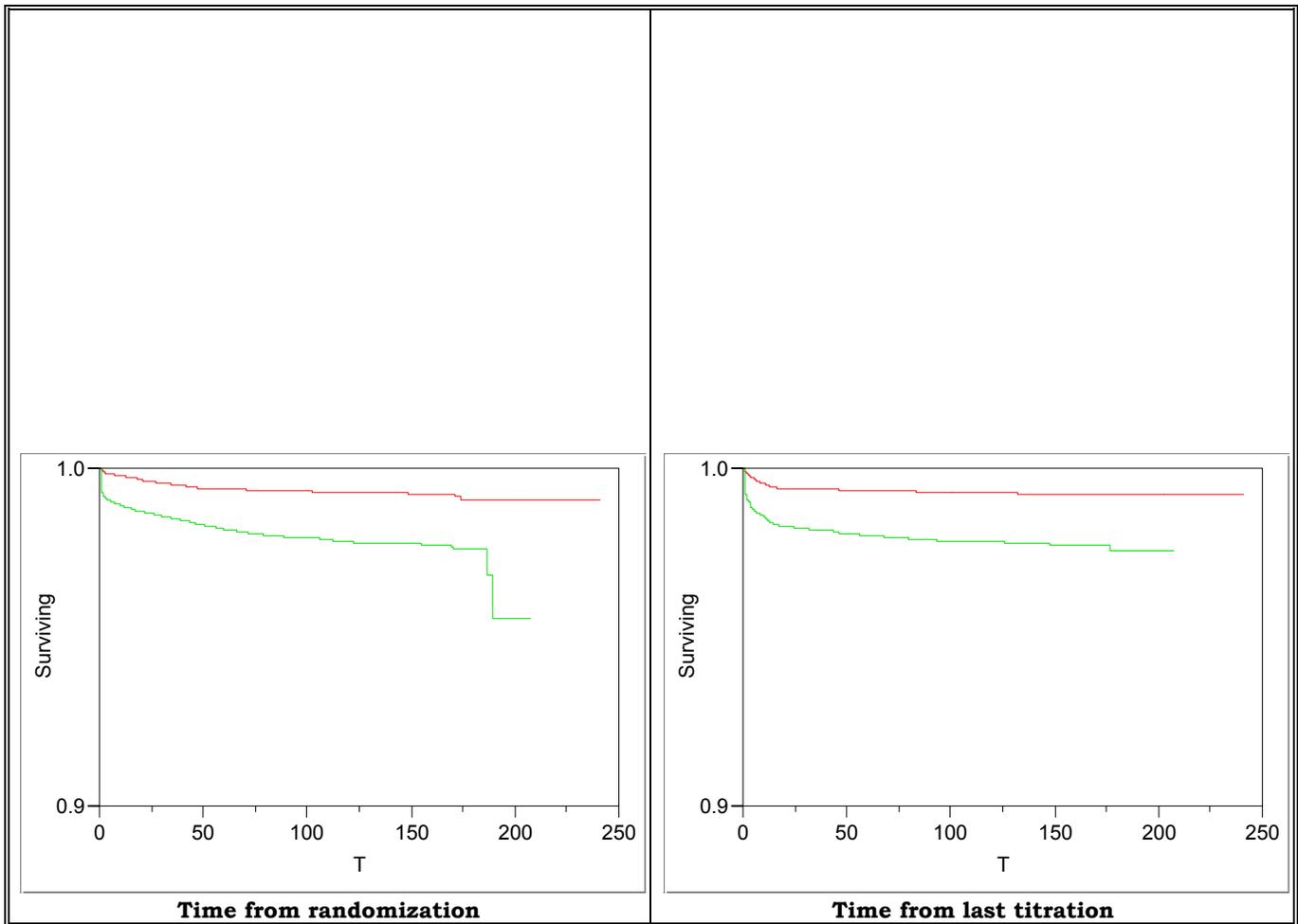


Figure 2. Angioedema-free survival

Curves for enalapril are red. Curves for omapatrilat are green. The analysis censored subjects at the time of death.

The difference between the treatment groups develops early, within the first day, and widens throughout the period of exposure. The relationship is similar whether one measures from the first exposure or from the time of dose titration.

There were 91 cases of angioedema on the first day of exposure to study drug. Of these, 88 were in the omapatrilat group and 3 were in the enalapril group⁹. Two-thirds of these first-day cases were manifest in the first 2 hours.

By the sponsor's analyses, the relative risk of angioedema on omapatrilat versus enalapril was little affected by age, gender, race, baseline hypertension, cardiovascular comorbidities, or prior experience with ACE inhibitors. Risk factors associated with angioedema on omapatrilat were Black race (2.97-fold increase), current or prior smoker (2.49-, 1.47-fold increases), female gender (1.49-fold increase), history of seasonal allergies (1.52-fold increase), and history of diabetes (0.58-fold decrease).

Two severe cases of angioedema are described, both from the group receiving omapatrilat. Subject 81-2, a 62 year old Black female, experienced oropharyngeal edema and laryngeal edema requiring airway protection after 10 weeks on omapatrilat.

⁹ Reviewer's analysis. One subject counted with the omapatrilat group was randomized to enalapril but received omapatrilat.

Subject 8215-16, a 56 year old White female, experienced anaphylaxis after the first dose of omapatrilat. Although she was said to have airway compromise, she did not require airway protection.

Based on two cases, the sponsor estimated that the upper 95% confidence limit on the risk of airway compromise with omapatrilat is 5.7 cases per 10000 patients treated and that the upper limit to the mortal risk is 2.9 cases per 10000 patients treated. This is a worst-case analysis for risk.

Most cases (63%) of angioedema required no treatment or only antihistamines. The relative risk on omapatrilat versus enalapril was about 2.5. One hundred thirteen cases of angioedema were treated with catecholamines or steroids. The relative risk for omapatrilat versus enalapril was 4.9. Nineteen cases of angioedema resulted in hospitalization. The relative risk for omapatrilat versus enalapril was 8.5. These data suggest that not only is the risk of angioedema higher with omapatrilat, but that the disparate relative risk grows with the severity of angioedema.

In 3 cases of angioedema on omapatrilat, the events took place on the first dose following a lapse in treatment of 5 days to 3 months¹⁰.

Further analyses of angioedema are described in Section 4, page 2.

2.3.5.3 Other cardiovascular events

The sponsor analyzed the crude incidence of cardiovascular events—death from any cause, or hospitalizations for myocardial infarction, heart failure, stroke, renal failure, or cardiopulmonary arrest—in the first 6 months following randomization. Their analysis found an incidence of 0.83% on omapatrilat and 0.96% on enalapril, with no statistical comparison given.

As part of this review, the first such event up to withdrawal¹¹ from study was determined, and the resulting survival analysis is shown in Figure 3, again without a statistical comparison.

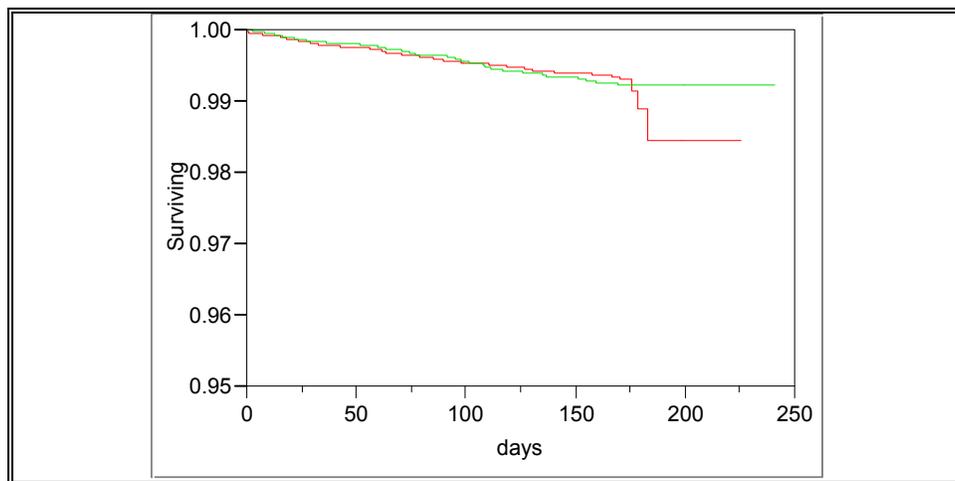


Figure 3. Event-free survival for cardiovascular events

This is the reviewer's time to first event analysis of death, heart failure, myocardial infarction, renal failure, stroke, or unstable angina, based on the sponsor's CVHOSP dataset. Omapatrilat is shown in green.

¹⁰ These were subjects 796-20, 823-1, and 2114-1. No subject, including these 3, has a record in the DOSING or EXP (exposure) datasets showing a treatment-free period.

¹¹ This results in about 50 fewer events than in the sponsor's analysis.

On omapatrilat, there were 82 subjects with cardiovascular mortality, myocardial infarction, heart failure, or stroke, compared with 89 on enalapril.

2.4 Summary and recommendations

2.4.1 Findings of OCTAVE

2.4.1.1 Safety

OCTAVE's primary safety hypothesis was that by reducing the starting dose of omapatrilat to 10 mg, the incidence of angioedema would be no worse than twice that observed with enalapril, putting it in the ballpark of other ACE inhibitors. The results of OCTAVE convincingly denied this hypothesis; it is estimated that the risk of developing angioedema on omapatrilat is 3.2 times as great as it is on enalapril.

If the risk of higher grades of angioedema were proportional to the overall risk, then the higher grades should also be about 3 times more common on omapatrilat. There were 113 cases of angioedema requiring more than antihistamines; in this class of events, the relative risk was 5-fold higher on omapatrilat. Of 19 observed cases of angioedema requiring hospitalization, 17 of these cases were on omapatrilat. The two most serious cases, one of which required airway support, were both on omapatrilat.

There were no deaths attributed to angioedema, but there are 4 unobserved deaths, all on omapatrilat, for which angioedema cannot be excluded, compared with, perhaps, one less suspicious case on enalapril.

Based on the observed cases of life-threatening angioedema over the entire development program, the sponsor puts the estimated rate of life-threatening angioedema at about 3 per 10000 patients in the first year of exposure and then somewhat less. The upper 95% confidence limit on this rate is about 9 events per 10000 patient-years¹².

The risk of developing angioedema appeared to be greater on omapatrilat at all times during the study, but the difference is most marked with the first dose. Of 91 first-dose cases, 88 were on omapatrilat. There are no data from which to evaluate the effect of a dosing-free period on the risk of angioedema.

2.4.1.2 Effectiveness

Unequivocally, omapatrilat was associated with a reduction in blood pressure in OCTAVE, compared with once-daily enalapril¹³. There were reductions in systolic and diastolic pressure in all three study cohorts—newly diagnosed hypertensives, previously adequately treated hypertensives switched to study drug, and persistently uncontrolled hypertensives in whom study drug was added. Such differences were seen despite use of the highest approved dose of enalapril once a day and the differences persisted into weeks 9 to 24 during which other antihypertensive treatments were allowed in all groups.

Although this was a large study, it had limited power to detect effects on cardiovascular outcomes. There was a trend toward a reduction in the incidence of cardiovascular outcomes on omapatrilat, but the difference developed very late in the study and is not a plausible treatment effect.

2.4.2 Risk-benefit

The new safety data related to angioedema are derived mostly from the experience in the OCTAVE study. The results did not support the sponsor's hypothesis, generated by

¹² Sponsor's analysis; personal communication.

¹³ Although enalapril is indicated for use once or twice daily, neither the primary medical review nor the Summary Basis of Approval document for the original hypertension indication describes data supporting the superiority of twice-daily dosing.

a retrospective analysis of the original NDA database, that the risk of angioedema was avoidable by uptitration from the 10-mg dose. Instead, the data from OCTAVE suggest that compared with a regimen of once-daily dose escalation with enalapril, the risk of angioedema is about 3-fold higher with omapatrilat.

2.4.2.1 Risk management

The data also suggest that the risk of more severe angioedema is disproportionately higher on omapatrilat.

Should omapatrilat be approved, OCTAVE findings point to some ways to reduce the risk of a fatal outcome with omapatrilat, by identifying patients at high risk and by specific interventions.

As with other ACE inhibitors, the risk of angioedema is 3-fold higher in Blacks than in Caucasians and perhaps other ethnic groups. There is a risk of a similar magnitude in patients who smoke.

A greater proportion of the angioedema events on omapatrilat occurs on the first dose and is manifest in the first 8 hours of this dose. Careful monitoring, perhaps having the drug started and keeping patients in the clinic for the first 8 hours, would reduce the risk of a fatal outcome¹⁴. However, the OCTAVE data do suggest that, throughout the time of exposure, the risk of developing angioedema is higher on omapatrilat than on enalapril, and, of the two severe cases in OCTAVE, only one occurred with the first dose.

2.4.2.2 Potential benefits

The sponsor acknowledges there is some unavoidable increased risk of serious, life-threatening angioedema with omapatrilat, but argues that the risk is more than offset by the benefits of better blood pressure control, as evidenced in the OCTAVE study, and the predictable reduction in cardiovascular events—death, myocardial infarction, and stroke.

2.4.2.2.1 Diastolic blood pressure

This small reduction in diastolic blood pressure might have a substantial public health benefit, as shown in Figure 4.

¹⁴ There are no data to address the question of how the risk of angioedema relates to the length of an interruption in dosing.

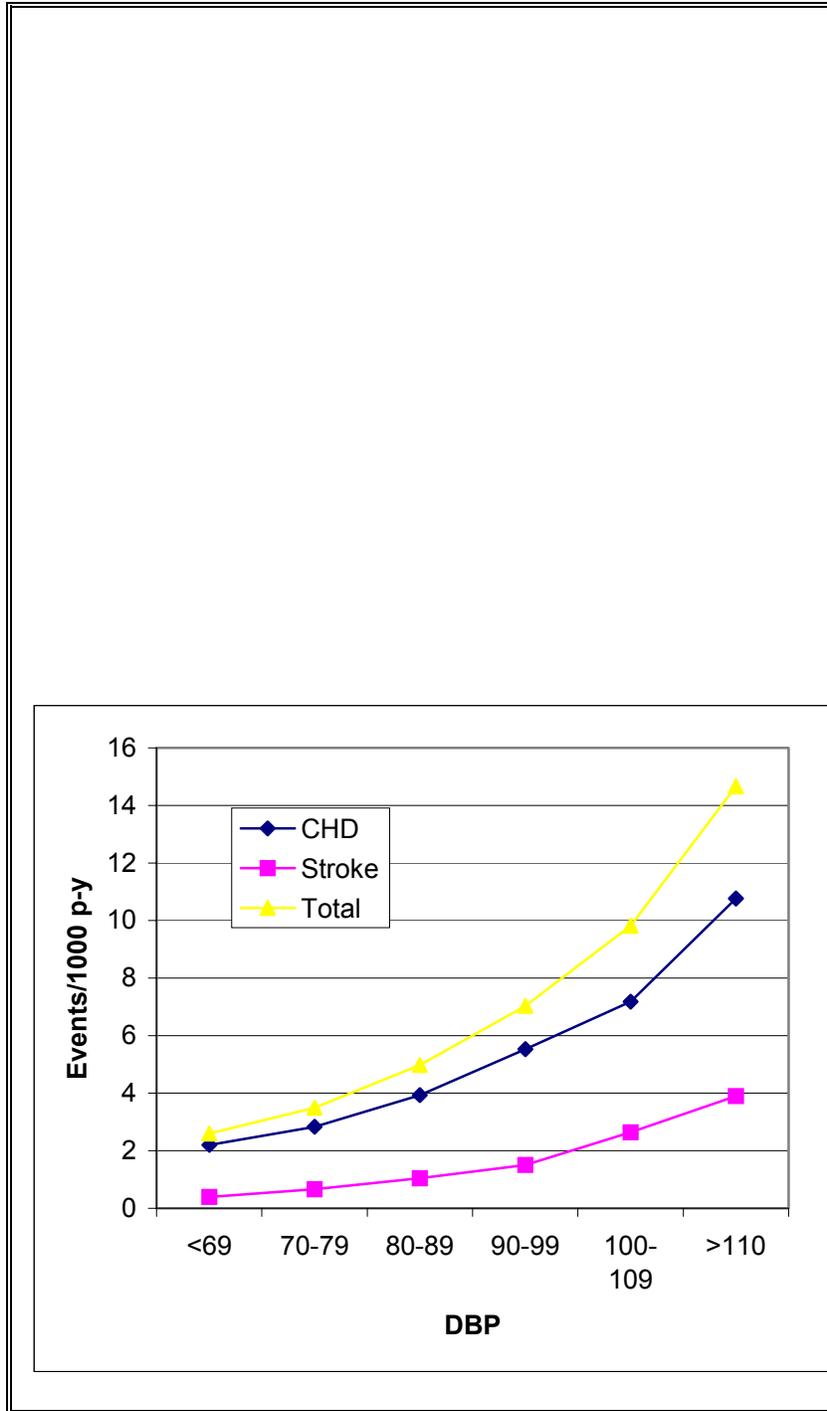


Figure 4. Cardiovascular risk (historical).

Absolute event rates were obtained from a meta-analysis of 9 prospective observational studies, as reviewed by MacMahon et al¹⁵.

Antihypertensive treatment appears to result in the reduction¹⁶ in cardiovascular risk to a level commensurate with the achieved level of blood pressure. For a baseline risk of

¹⁵ MacMahon S, Peto R, Cutler J, et al. 1990. Blood pressure, stroke, and coronary heart disease. *Lancet* 335:765-774.

15 events per 1000 patient-years, the high end of the curves, the reduction in risk is about 0.5 events per 1000 patient-years per mmHg reduction in diastolic pressure. With a 2-mmHg mean reduction in diastolic pressure, omapatrilat might then be expected to reduce cardiovascular events by about 1 event per 1000 patient-years.

There were a total of 171 subjects in OCTAVE with at least one cardiovascular death, myocardial infarction, heart failure, and stroke. This corresponds to about 15 events per 1000 patient-years of exposure, in the ballpark of the high-risk end of Figure 4.

With about 12000 subjects per group, omapatrilat might have been expected to reduce cardiovascular morbidity and mortality by about 6 events over a 6-month study.

The sponsor suggests that OCTAVE demonstrated a reduction in cardiovascular events on omapatrilat. While a numeric difference in incidence exists, and it is about 6 events, the reviewers' analysis of time to event clearly shows this difference arises very late, and it is not plausibly a real treatment effect. Neither the sponsor nor the reviewers computed a p-value for these analyses.

2.4.2.2.2 Systolic blood pressure

There are also expected benefits for reductions in systolic blood pressure. Since OCTAVE, like other studies, evidences effects on both systolic and diastolic pressure, one should consider the benefit attributable to systolic pressure as an alternative to the benefit attributable to diastolic pressure, rather than as an independent benefit.

On the basis of a meta-analysis reported with the HOPE results, shown in Figure 5, the sponsor estimates a 15 to 20% reduction in event rates resulting from a 3 mmHg mean reduction in systolic pressure. The sponsor then applies that event rate reduction to a baseline estimated event rate of 20 to 40 cardiovascular events per 1000 patient-years to arrive at a predicted absolute event rate reduction of 4 to 8 events per 1000 patient-years.

¹⁶ How rapidly is not clear. The studies upon which Figure 4 is based were years long.

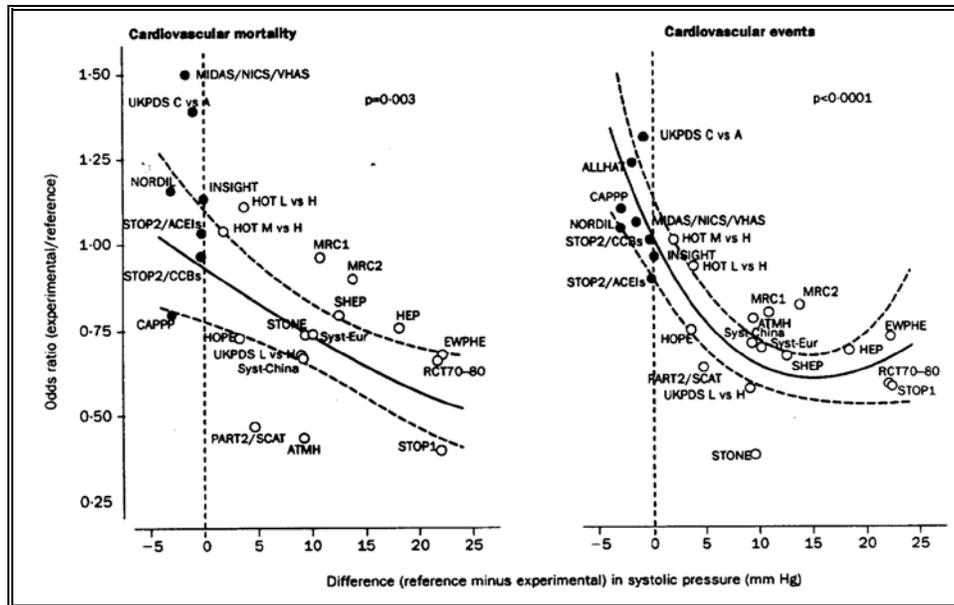


Figure 5. Risk reduction by effect on systolic pressure¹⁷.

The enalapril event rate was about 1% over 6 months, which is in line with the lower end of the sponsor's estimates of expected event rates. Thus, the OCTAVE study had about 75% power to detect a 30% change in event rate¹⁸ and less power to detect the difference predicted by the sponsor (15-20%). The observed change was much smaller. The nominal difference between treatment groups was about 1 event per 1000 patient-years, about 1/4 of what the sponsor would have predicted. Consequently, although there were many cardiovascular events, OCTAVE was not powered to detect the expected difference between treatment groups.

A recent reanalysis¹⁹ of the Framingham data suggests that cardiovascular risk is an increasing function of systolic pressure and age only above about 150 mmHg. For a patient about 60 years old, the risk increases by about 0.7 events per 1000 patient-years per mmHg²⁰.

SHEP²¹ randomized 4736 subjects with blood pressure >160/<90 to placebo or chlorthalidone and followed them for an average of 4.5 years. On treatment blood pressures averaged 155/72 on placebo and 143/68 mmHg on active treatment. Active treatment was associated with a reduction of 30 strokes per 1000 subjects and 55 cardiovascular deaths or nonfatal myocardial infarctions per 1000 subjects (6.7 strokes or 12 cardiovascular events per 1000 patient-years). The reduction in diastolic pressure by 4 mmHg probably accounts for less than 1 stroke or cardiovascular event prevented per 1000 patient-years (see Figure 4 above). Thus reduction in systolic pressure can be credited with prevention of about 1.5 events (strokes or other cardiovascular events) per 1000 patient-years per mmHg.

¹⁷ The HOPE Study Investigators. 2000. Effects of angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *New Eng J Med* 342(3):145-153.

¹⁸ Reviewers' estimate.

¹⁹ Port S, Demer L, Jennrich R, et al. 2000. Systolic blood pressure and mortality. *Lancet* 355:175-180.

²⁰ The older analyses of Framingham data overestimate risk at lower systolic pressures and underestimate the risk of higher systolic pressures.

²¹ SHEP Cooperative Research Group. 1991. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). *JAMA* 265(24):3255-3264.

Across cohorts of naïve hypertensives to persistent hypertensives, and despite 16 weeks of optional adjunctive treatment, subjects randomized to omapatrilat had lower blood pressure than subjects randomized to enalapril, by about 3/1-2 mmHg. In a subject for whom the SHEP results pertain (possibly only those with systolic pressure > 160 mmHg), the effect of a 3/2 mmHg blood pressure reduction would be expected to be about 2-3 cardiovascular events prevented per 1000 patient-years or 12-24 events difference between groups over the course of the OCTAVE study. The actual difference is about half that large, probably not significantly different, and perhaps explained by the relative scarcity of OCTAVE subjects with systolic pressure >160 mmHg (26%)²².

If OCTAVE meant that one can obtain an additional 3/2 mmHg blood pressure reduction in a regimen including omapatrilat that cannot be obtained through the addition of other antihypertensive agents, then the expected prevention of even 3 cardiovascular events per 1000 patient-years is about 30-fold larger than the nominal risk of life-threatening angioedema in the first year of exposure and maybe 10-fold larger than the upper estimate of the apparent risk of life-threatening angioedema. After the first year, the net clinical benefit would be expected to be even larger.

However, this is an argument dependent on the belief that omapatrilat achieved blood pressure reductions that could not have been achieved with more aggressive use of concomitant medications.

2.4.2.2.3 Concomitant medications

Certainly, the gap in blood pressure between the two groups was not much different at the end of the first 8 weeks, when other drugs were prohibited, and after 24 weeks, when other drugs were permitted²³. Does this mean that a treatment regimen including omapatrilat will generally be superior to one including enalapril?

Only about 23% of subjects received adjunctive treatment for hypertension during the last 16 weeks, so only they could have contributed to narrowing the between-group blood pressure difference at week 24. However, if adjunctive therapy has the same effect when added to enalapril and omapatrilat, then it is only the between-group difference in the proportion of subjects receiving 1, 2, or 3 adjunctive medications who could have contributed to narrowing the blood pressure gap. Table 5 (page 2) shows that overall this amounts to only about 8% of the entire population.

If one assumes that the first, second, and third adjunctive drugs contribute the same effect on blood pressure, one can solve for that effect, given the overall mean blood pressure differences at weeks 8 and 24 and the observed proportions of subjects receiving adjunctive therapy. The result is that each adjunctive drug contributes about 6/3 mmHg.

Thus relatively small differences in the proportions of subjects on enalapril and omapatrilat receiving adjunctive therapy account for observed small differences in blood pressure at 8 and 24 weeks. This was not evidence that a regimen including omapatrilat was intrinsically superior to one including enalapril.

2.4.3 Summary

There are potential benefits of achieving lower blood pressure, in the reduction of cardiovascular events. Depending on the model one has for the relationship between blood pressure and cardiovascular risk reduction, OCTAVE either was or was not

²² Subjects on omapatrilat also received fewer concomitant antihypertensive medications during weeks 9-24, so they should have fewer dose-independent adverse events, but given the relatively benign nature of such events generally, this seems like a small benefit.

²³ This difference is about 0.6/0.3 mmHg.

powered to have seen such an effect, but, regardless, no such difference was demonstrated.

One cannot rely on the observed average difference in blood pressure at the end of the addition of other treatments to inform about what can be accomplished with them. OCTAVE's results do not imply that omapatrilat produces a blood pressure lower than can be achieved with enalapril and additional agents.

On average, then, if the patient population resembles the subjects enrolled in OCTAVE, one could achieve equivalent reductions in blood pressure using regimens of enalapril or omapatrilat if the rate of use of adjunctive therapy were about 50% higher on enalapril than on omapatrilat (or, probably, if enalapril were given twice daily in a somewhat larger proportion of subjects). It is against this risk—an average of about 1 additional antihypertensive drug per 2 patients—that the risk of life-threatening angioedema should be compared.

Omapatrilat should not be approved for the treatment of essential hypertension.

3 Other studies reported with resubmission

3.1 Study 137-009: Long-term open-label study of the antihypertensive activity and safety of omapatrilat (BMS-186716) in the treatment of hypertension.

This study is ongoing as of the interim report date of 15 October 200; electronic data are not available. This is a long-term, open-label, uncontrolled study of subjects previously completing studies 137-006, 137-022, and 137-024. Enrollment is 1098 subjects, of whom about 10% are Black. To date, the mean exposure is greater than 2 years and about half of the subjects are receiving omapatrilat without other antihypertensive treatments. The median dose is 20 mg; the distribution of doses does not appear to shift much over time.

The crude incidence of angioedema is 0.9%; another 2.1% have reported head/neck edema. Cases were reported after more than 4 years of treatment and they appear to be distributed across all doses of omapatrilat. Several subjects reported multiple incidents of head or neck edema preceding angioedema.

There have been 4 deaths. Two of these were sudden deaths attributed to myocardial infarction, but there is no compelling documentation.

Subject 7-18 was a 61 year old male who was receiving omapatrilat 10 mg when he died in his sleep on day 381.

Subject 81-2 was a 60 year old male receiving omapatrilat 20 mg when he died following snow shoveling on day 141.

3.2 Study CV1 37-028: Inhibition of metalloprotease by BMS-186716 in a randomized exercise and symptoms study in subjects with heart failure - the IMPRESS trial.

This description is based on the final study report dated 16 January 2001, pertaining only to a long-term, but blinded follow-on study. Enrollment was from April 1998 to February 2000 at 55 centers in the US and 32 in Canada. Subjects (n=367) who completed a 24-week double-blind study continued on randomized treatment—lisinopril 5 to 20 mg (n=180) or omapatrilat 10 to 40 mg (n=187)—for up to 12 months.

On omapatrilat, there were 11 deaths on drug or within 14 days of the last dose (5.8%) versus 8 (4.4%) on lisinopril. None of these events is believed to relate to treatment.

There were no cases reported for angioedema, but there was one case of lip swelling on omapatrilat 40 mg.

3.3 Study CV1 37-029LT: Placebo-controlled study of omapatrilat in elderly subjects with mild-to-moderate hypertension: long-term open-label extension.

This description is based on the interim report for this ongoing study, dated 25 September 2001. Ninety centers in the US have enrolled 203 subjects for a mean of about 18 months. Eighty percent of subjects are receiving no other treatment for hypertension.

There was one unwitnessed death.

Subject 27-6 was a 71 year old male with a history of CABG and MI. He died at home after about 25 months of treatment with omapatrilat.

There were two cases of angioedema, one of which was described as severe.

Subject 41-14 was a 65 year old White female who had a history of angioedema to enalapril. She had severe angioedema, and was hospitalized, apparently with respiratory symptoms, although laryngoscopy determined there was no airway compromise.

3.4 Study CV1 37-037LT: A multicenter, randomized, double-blind, lisinopril and placebo controlled trial of the antihypertensive efficacy and safety of omapatrilat in black subjects with mild to moderate hypertension: 4-month double-blind extension.

This description is based on the final study report dated 20 August 2001. The study was conducted between May 1998 and August 2001 by 102 centers in the US. Five hundred and four Black subjects completing study CV137-037 (10 weeks) were randomized to lisinopril 10 to 40 mg (n=248) or omapatrilat 20 to 80 mg (n=256) and followed for up to 4 months (mean of 3 months).

There were no deaths.

One subject, a 71 year old female, experienced an event reported as angioedema (lip swelling) after 182 days on omapatrilat. Another subject, a 69 year old female had severe angioedema on omapatrilat but attributed to a newly introduced drug. There were 7 cases reported as head/neck edema, 5 on omapatrilat and 2 on lisinopril.

3.5 Study CV1 37-038LT: A multicenter, randomized, double-blind study of the effect of omapatrilat and losartan on left ventricular hypertrophy associated with mild to moderate hypertension: Period C—52-week double-blind phase.

This description is based on the addendum to the final study report dated 27 July 2000. The study was conducted between June 1998 and March 2000 at 76 centers in Eastern and Northern Europe, Russia, Israel, South Africa, UK, and Spain. The original study compared LVMI in groups receiving losartan (force-titrated 50 to 100 mg) or omapatrilat (force-titrated 20 to 80 mg) for 24 weeks. Three-hundred forty-one subjects were randomized, of whom 318 completed 24 weeks and 312 completed 52 weeks. Five percent of randomized subjects were Black. Mean exposure was about 11 months.

There was one unwitnessed death on omapatrilat 80 mg after 199 days. This subject had developed angina pectoris during the study.

No cases of angioedema or head/neck edema are described²⁴.

3.6 Study CV1 37-042LT: Placebo-controlled study of omapatrilat in subjects with isolated systolic hypertension including the long-term open-label extension.

This description is based on the interim report dated 28 September 2001. The study is ongoing. Enrollment in the long-term extension came from 97 centers in the US, France, Spain, UK, Canada, and Austria. Four hundred twenty-nine subjects were randomized, 371 completed a 13-week double-blind period, and 295 entered the long-term, open-label phase (not all centers).

There were no deaths.

During double-blind treatment, there were 5 cases described as angioedema (including the one database case requiring airway support), and 6 cases described as head/neck

²⁴ There were 170 pages of imaged line listings of adverse events that were not searched manually for these events. Serious adverse events were separately listed and do not include angioedema or like events.

edema. All cases were on omapatrilat. During open-label treatment, there were 7 cases reported as angioedema and 9 cases reported as head/neck edema, none reported as serious.

3.7 Study CV1 37-046: A study of the antiproteinuric effects of omapatrilat and amlodipine in type II diabetics with hypertension and microalbuminuria or overt nephropathy.

This description is based on the final study report dated 13 March 2001. The study was conducted between July 1998 and April 2000 at 68 centers in the US, 5 in Brazil, and 3 in Russia. Subjects were randomized to amlodipine 2.5 to 10 mg or omapatrilat 20 to 80 mg titrated to achieve blood pressure control. Three hundred nineteen subjects were randomized and 281 completed 12 weeks of follow-up.

There was one sudden death on amlodipine.

There was one case reported as angioedema on omapatrilat. There were 4 cases of head/neck edema, 2 of which were on omapatrilat, and none of which resulted in discontinuation.

3.8 Study CV1 37-049LT: A multicenter, randomized, double-blind study of the efficacy and safety of omapatrilat (BMS-186716) and enalapril in the treatment of subjects with severe hypertension (long-term open-label extension).

This description is based on the addendum to the final study report dated 25 September 2001. The study was conducted between August 1998 and June 2001 at 39 centers in the US (23 sites), South Africa, Canada, Brazil, and Mexico. The double-blind study randomized 189 subjects to enalapril or omapatrilat 20 to 80 mg (titrated to blood pressure goal) for 10 weeks. One hundred sixty-seven subjects entered the open-label extension for up to 2 years, all receiving omapatrilat. Mean follow-up was 21 months.

There were no deaths.

Two subjects experienced angioedema during open-label exposure, both after receiving enalapril during the double-blind period. There were 5 cases reported as head/neck edema. Five of the 7 cases here were in Blacks, 11% of Blacks entered the open-label study (several of whom had been on enalapril during the double-blind phase).

3.9 Study CV1 37-050: PACIFIC pilot study (prevention with a combined inhibitor and folate in coronary heart disease): A factorial, randomized, placebo-controlled trial of the combined ACE/NEP inhibitor, omapatrilat, and the B-group vitamin, folic acid, in subjects with coronary heart disease.

This description is based on the final report dated 20 September 2001. The study was conducted between September 1998 and March 2000 at 16 sites in Australia and 12 sites in New Zealand. This was a 3x3 factorial trial with placebo and omapatrilat 20 and 40 mg. Seven hundred forty-seven subjects received a test dose of omapatrilat 20 mg, 721 were randomized, and 605 completed 6 months of follow-up. There were no Black subjects on active treatment.

There was one death (myocardial infarction) on omapatrilat 40 mg and 2 on placebo.

One subject administered the test dose discontinued because of angioedema; this subject complained of difficulty breathing. During double-blind treatment, 4 subjects on omapatrilat and no subjects on placebo were reported to have angioedema, none of the cases apparently serious. There was one case of head/neck edema on placebo and 2 on omapatrilat.

3.10 Study CV1 37-059: Pharmacodynamic effects of single-dose omapatrilat (40 and 80 mg p.o.) and fosinopril (20 mg p.o.) in high and low sodium status in normal healthy male volunteers: a placebo-controlled, double-blind, randomised, parallel-group, 4-way crossover study.

This description is based on the final study report dated 7 September 2001. The study was conducted between February and May 2000 at 1 center in France. Twenty-five subjects received single doses of omapatrilat 40 and 80 mg.

There were no deaths and no reported events of angioedema or head/neck edema.

3.11 Study CV1 37-066: A randomized, double-blind, amlodipine- and losartan-controlled study of omapatrilat in subjects with mild-to-moderate hypertension

This description is based on the final study report dated 1 February 2001; electronic data are available. Enrollment was from April to December 1999. The study was conducted at 153 centers in the US (119), Canada (24), and Australia (10). The primary end point was 24-hour mean ambulatory diastolic pressure (which has not been a basis for making regulatory decisions). Subjects with mild-to-moderate essential hypertension were randomized to amlodipine (n=357; force-titrated from 2.5 to 10 mg), losartan (n=105; force-titrated from 50 to 100 mg), or omapatrilat (n=350; force titrated from 20 to 80 mg) and maintained for 6 weeks.

Angioedema was reported for 3 subjects on omapatrilat (0.9%) and head/neck edema by 2 subjects (0.6%) on the first day of exposure versus none in the other two arms. For the entire study plus 14-day post-study follow-up, there were 6 cases of angioedema, all on omapatrilat (1.7%), and 15 cases of head/neck edema, 10 on omapatrilat (2.9% vs. 1% on amlodipine and losartan). The most severe cases are described below:

Subject 51-2 was a 43 year old White female who developed severe angioedema (throat, face, and tongue swelling; nausea; vomiting; tachycardia) after the first dose of omapatrilat 20 mg. She was treated with methylprednisolone and loratidine.

Subject 56-7 was a 71 year old Hispanic male who developed angioedema (swollen tongue, lips, and throat; loss of voice) after the first dose of omapatrilat 20 mg.

Subject 73-2 was a 59 year old Black male who developed angioedema (swollen tongue and face) on day 49 (80 mg).

3.12 Study CV1 37-071: Double-blind, randomized, multicenter phase II trial of omapatrilat compared with placebo for the symptomatic treatment of subjects with chronic stable angina pectoris.

This description is based on the final study report dated 16 March 2001. The study was conducted between September 1999 and June 2000 at 109 sites in the US (49 sites), Canada, Israel, Poland, Russia, Hungary, and UK. Three hundred forty-eight subjects were randomized to placebo or omapatrilat (titrated from 10 to 80 mg or highest tolerated dose) and followed for 4 weeks. Fewer than 2% of subjects were Black.

There were no deaths on treatment or within 14 days.

There was one case of angioedema (first dose of omapatrilat). There was one case of head/neck edema reported on omapatrilat 80 mg.

3.13 Study CV1 37-072: A randomized, double-blind, active-controlled evaluation of the antihypertensive response to omapatrilat in subjects uncontrolled on calcium channel blocker therapy.

This description is based on the final study report dated 30 August 2001. The study was conducted between August 1999 and October 2000 at 182 centers in the US. The primary end point was 24-hour mean ambulatory blood pressure (not usually a basis for making regulatory decisions). Subjects who remained hypertensive on maximum recommended doses of a calcium channel blocker (possibly including amlodipine) and perhaps other drugs were randomized to amlodipine (n=239) or omapatrilat (n=247) with the dose force titrated to 10 mg (amlodipine) or 80 mg (omapatrilat). The starting doses were halved from 5 mg (amlodipine) or 20 mg (omapatrilat) about midway through recruiting. About 20% of subjects were Black.

There were no deaths. There was one case described as serious angioedema:

Subject 24-6 was a 75 year old Black male receiving omapatrilat 40 mg on day 13 when he developed swelling of the face and lips considered moderately severe. There was no treatment beyond discontinuation.

Overall, there were 8 subjects reported with angioedema or head/neck edema, all on omapatrilat. Of these 6 cases were among subjects begun at 10 mg (5.6%) and 2 cases were among subjects begun on 20 mg (1.4%).

3.14 Study CV1 37-073: A randomized, double-blind, active-controlled evaluation of the antihypertensive response to omapatrilat in subjects uncontrolled on ACE inhibitor therapy.

This description is based on the final study report dated 28 March 2001. The study was conducted between August 1999 and June 2000 at 182 centers in the US. Subjects had to be hypertensive on highest allowed doses of ACE inhibitors (alone or with other antihypertensive agents). Two hundred seventy-five subjects discontinued their ACE inhibitor and were randomized to lisinopril (force-titrated from 20 to 40 mg) or omapatrilat 20 to 80 mg on top of other background treatments. The titrated dose was maintained for 4 weeks. Eleven percent of subjects were Black.

There were no deaths.

There was one case of angioedema on omapatrilat 80 mg, one case of head/neck edema on omapatrilat 80 mg, and 3 allergic reactions, 2 on omapatrilat 80 mg and one on lisinopril 40 mg. None of these cases were considered serious.

3.15 Study CV1 37-077: A randomized, double-blind study of the antihypertensive efficacy and safety of omapatrilat compared to losartan.

This description is based on the final study report dated 28 February 2001. The study was conducted between December 1999 and June 2000 at 58 centers in the US. Subjects were randomized to placebo, losartan (force-titrated from 50 to 100 mg), or omapatrilat 20 to 80 mg, and followed for a total of 10 weeks. Fourteen percent of subjects were Black.

There were no deaths.

There were 3 cases of angioedema or head/neck edema, all on omapatrilat. All were considered nonserious.

3.16 Study CV1 37-087: Exploratory placebo-controlled, double-blind, parallel-group study to determine the renal hemodynamics and tubular effects of omapatrilat in normal healthy subjects.

This description is based on the final study report dated 30 August 2001. The study was conducted between March and July 2000 at one site in Switzerland. Thirty-two subjects were randomized to placebo, fosinopril 20 mg plus HCTZ 12.5 mg, or omapatrilat 40 or 80 mg and followed for 7 days, during which they ate a high-sodium diet.

There were no deaths, serious adverse events, angioedema, or head/neck edema.

3.17 Study CV1 37-091: A randomized, double-blind study of omapatrilat versus losartan as assessed by 24-hour ambulatory blood pressure monitoring (ABPM) technique.

This description is based on the final study report dated 25 July 2001. The study was conducted between April 2000 and January 2001 at 49 sites in Western Europe and Israel. Four hundred and four subjects were randomized to losartan (force-titrated from 50 to 100 mg) or omapatrilat 10 to 40 mg and followed for a total of 9 weeks. Only one subject was Black.

There were no deaths.

One subject developed bilateral parotid swelling after the first dose of omapatrilat, but he received no treatment and completed the study.

3.18 Study CV1 37-098: Late clinical phase II trial of BMS-186716 for hypertension [Single treatment].

This description is based on an interim report dated 27 December 2000. The study was conducted between December 1998 and January 2000 at 63 sites in Japan. This was an uncontrolled study in which 115 subjects received increasing doses of omapatrilat 5 to 20 mg over 8 to 12 weeks.

There were no deaths or serious adverse events. There is no mention of angioedema or head/neck edema.

3.19 Study CV1 37-099: Late clinical phase II trial of BMS-186716 for hypertension [Concomitant treatment].

This description is based on an interim report dated 27 December 2000. The study was conducted between December 1998 and January 2000 at 56 sites in Japan. This was an uncontrolled study in which 63 subjects received increasing doses of omapatrilat 5 to 20 mg over 8 to 12 weeks.

There were no deaths. There were 2 serious cardiac events. There is no mention of angioedema or head/neck edema.

3.20 Study CV1 37-102: Study of the hypotensive effects of administering 10 mg to 40 mg BMS-186716.

This description is based on an interim report dated 2 February 2001. The study was conducted between November 1999 and May 2000 at one center in Japan. There were 2 groups. Both received omapatrilat 10 mg during the first 2 weeks; for a second 2 weeks, one group (n=9) received 20 mg and the other (n=6) received 40 mg. There is no mention of randomization or blinding.

There were no deaths. There is mention of angioedema or head/neck edema.

3.21 Study CV1 37-123: The effect of low dose omapatrilat pretreatment (versus placebo) on the pharmacodynamic responses that occur with dose escalation in hypertensive patients.

This description is based on an interim report dated 10 October 2001. The study was conducted between October 2000 and March 2001 at 5 sites in the US. Subjects were randomized to placebo or omapatrilat 10 mg for 2 weeks and then all received a single placebo, omapatrilat 10 mg, or omapatrilat 20 mg (total of 88 subjects in 6 arms, of whom 48% were Black).

There were no deaths. There were no events reported as angioedema or head/neck edema.

3.22 Study CV1 37-141: Follow-up clinical phase I trial of BMS-186716 . Single administration.

This description is based on a study report summary dated 9 August 1999. The study was conducted between May and July 1998 among normal adults recruited at one center in Japan. Six subjects received single doses of omapatrilat 20 and 40 mg.

There were no deaths or serious adverse events. Among adverse events reported were submandibular swelling, enlargement of the tonsils, and numbness of the lips.

3.23 Study CV1 37-122: the effect of omapatrilat and lisinopril on pharmacodynamic parameters and evaluation of PK/PD correlation following 2 weeks of dosing and after interruption in healthy subjects.

This description is based on the final study report dated 24 October 2001. The study was conducted between September to December 2000. There was one study center. Sixty normal volunteers were randomized to placebo, lisinopril 20 mg, or omapatrilat 5, 10, or 40 mg once daily for 14 days. Subjects were then randomized to a 3 or 7 day treatment-free period before returning for a single dose of originally randomized treatment. About half of the subjects were Black.

There were no deaths or serious adverse events. Three subjects, one each on omapatrilat 10 mg, omapatrilat 40 mg, and lisinopril developed mild angioedema and were withdrawn.

3.24 Study CV1 37-142: Follow-up clinical phase I trial of BMS-186716—Repeated administration.

This description is based on the "overall trial report" dated 10 August 1999. The study was conducted between June and August 1998 at one site in Japan. Seven normal volunteers received placebo (n=2) or omapatrilat 20 mg daily for 7 days.

The safety summary reads in part:

"Adverse events that could not be disproven to have a causal relationship with the drug were seen in all five subjects administered the real drug and consisted of orthostatic syncope in four cases, facial flushing in three, discomfort in the neck in two, and bulbar conjunctival hyperemia, reddening of the pharynx, and discomfort in the tongue in one each. Nonetheless, all symptoms were mild and improved without requiring treatment."

3.25 Study CV1 37-144: Phase I clinical study—Single dose.

This description is based on the final study report dated 2 July 1999. The study was conducted between January and March 1996 at one site in Japan. Subjects received single oral doses of placebo (n=12) or omapatrilat (n=23) 2.5, 5, 12.5, 25, or 50 mg.

No angioedema-like events were reported.

4 Further analyses of angioedema

In OCTAVE, there were 360 cases of angioedema, about twice as many cases as had been reported in controlled studies for all 9 ACE inhibitors approved up to 1994 (when the race signal was studied). OCTAVE, then, represents an unparalleled opportunity to investigate the risk factors for angioedema, and the sponsor did a commendable job of that in their study report. As part of this review, investigations were undertaken to examine the time course of angioedema events.

Angioedema-free survival curves for enalapril and omapatrilat are shown in Figure 6.

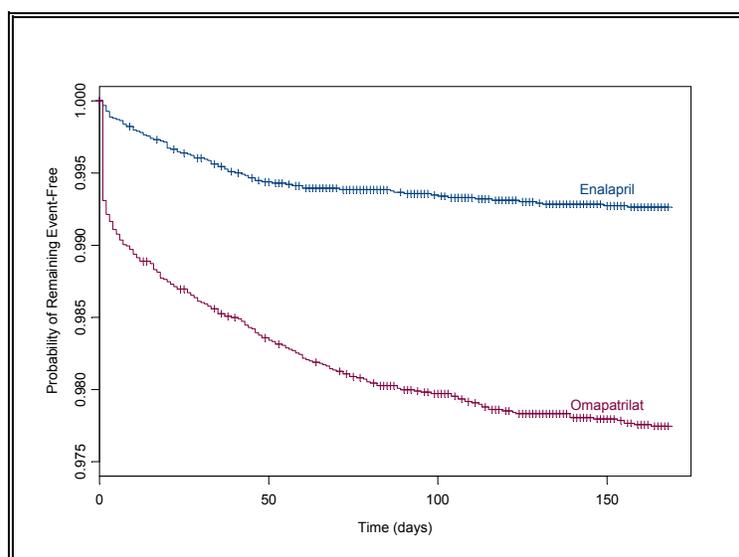


Figure 6. Angioedema-free survival for enalapril and omapatrilat
Figure shows time to first event for adjudicated angioedema on enalapril and omapatrilat.

The simplest model would be that the risk of angioedema is constant and the same for the entire population exposed to drug. Assuming a constant hazard ratio in the Omapatrilat arm, the estimated daily event rate is about 0.000147.

Using the binomial or Poisson tail probabilities with this estimated rate, the probability of observing 12 or more cases on day 2 out of 12394 patients at risk is found to be less than 10^{-6} . Under the same assumptions, the probability of observing 87 or more cases out of 12601 at risk on Day 1 is very nearly zero. Note that we would only expect about

$$\theta = 12601 \times 1.47 \times 10^{-4} \approx 1.85$$

events. Out of academic interest, an approximation for the nominal p-value can be obtained using first the Wilson-Hilferty approximation²⁵ and then Norton's approximation for the tail probabilities of the standard normal distribution²⁶.

Letting X denote a Poisson random variable with mean θ , these approximations give us

²⁵ *Proceedings of the National Academy of Sciences*, 1931. **17**:684-688.

²⁶ *The American Statistician*, 1989. **43**:24-26.

$$P[X \geq 87] = 1 - P[X \leq 86] \approx \Phi\left(3\left[\sqrt[3]{\frac{\theta}{87}} - 1 + \frac{1}{9 \times 87}\right]\sqrt{87}\right) \approx \Phi(-20.19) \approx \frac{e^{-\frac{20.19^2}{2}}}{20.19\sqrt{2\pi}} \approx 6 \times 10^{-91}$$

The two nominal p-values above indicate how unusual is the observed number of cases on the first two days, under the assumption of a constant hazard function. A global test of the constant hazard function can be obtained using the standard Chi-square goodness of fit test. Here, it is customary to group data together so that the expected number of events per cell is larger. Hence, we will count the number of events each week and compare the observed number to the expected number under the constant hazard assumption. The observed chi-square statistic is approximately 1087. A p-value is found by finding the probability that a chi-square random variable with 23 degrees of freedom exceeds this observed value. The adequacy of the chi-square approximation was validated using resampling. Appealing to the same two approximations used before, the p-value is approximately

$$\Phi\left(3\left[\sqrt[3]{\frac{23}{1087}} - 1 + \frac{1}{9 \times 1087}\right]\sqrt{1087}\right) \approx \Phi(-71.54) \approx \frac{e^{-\frac{71.54^2}{2}}}{71.54\sqrt{2\pi}} \approx 2 \times 10^{-1114}$$

The main contribution to the chi-square statistic comes from the first week. There were 125 events observed during the first week, nearly ten times the 12.7 that would be predicted under the constant hazard assumption.

A similar chi-square goodness of fit test can be done with the data from the patients in the enalapril arm. There, the constant hazard hypothesis is also rejected ($p = 10^{-16}$).

The next simplest model is that subjects are classifiable as low- or high-risk with respect to angioedema. Best fits for this model are shown in Figure 7.

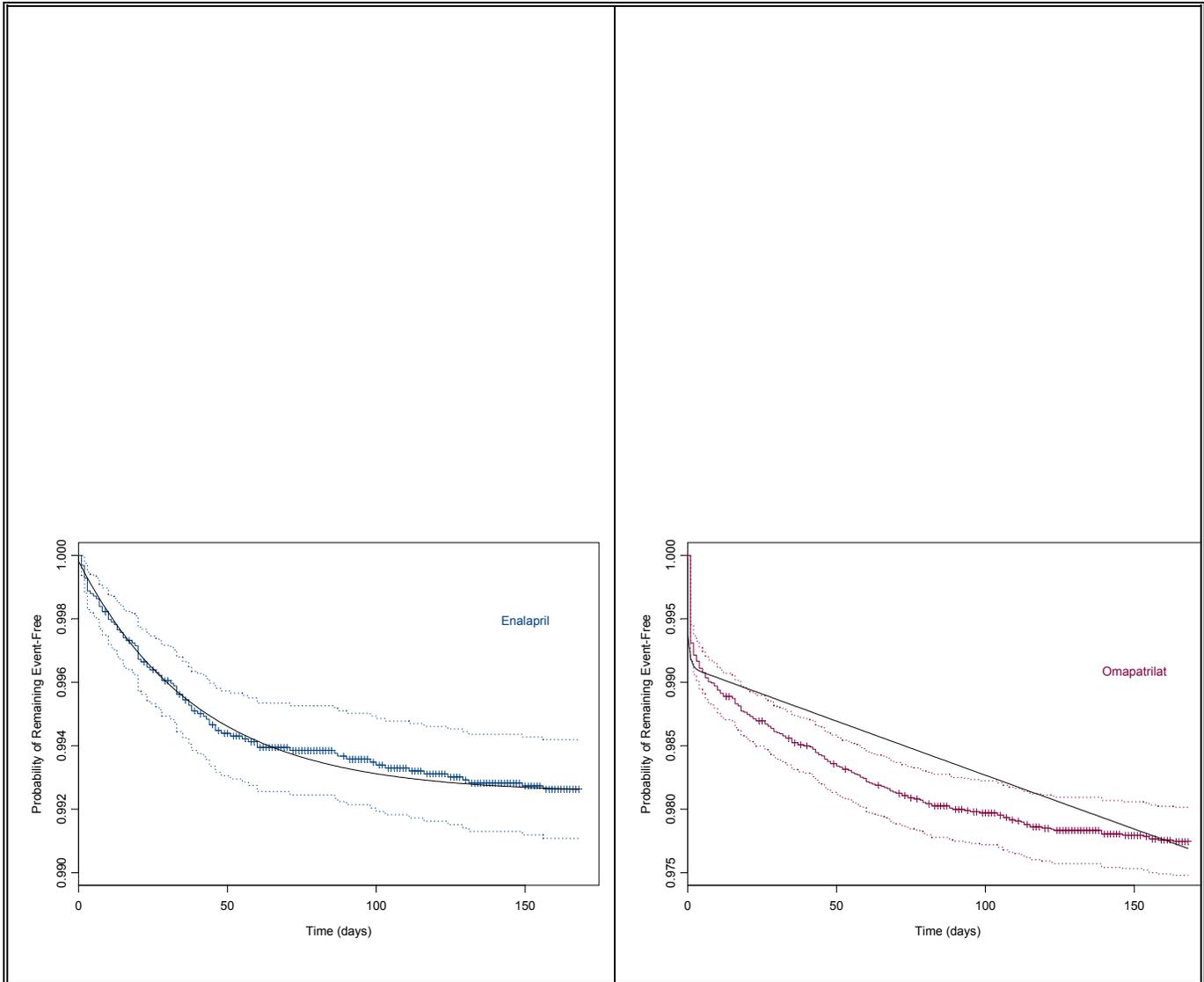


Figure 7. Two-exponential model fits for enalapril and omapatrilat.

Data on time to first angioedema event for enalapril or omapatrilat were fit to the model: $L \xrightarrow{k_L} A \xleftarrow{k_H} H$ where L and H represent low- and high-risk states and A is the state of manifesting angioedema.

The model fit for enalapril is quite good. It suggests that about 0.6% of subjects are at high risk (about 0.04 per day) and that the risk in the rest of the population is about 10^{-5} per day. The fit in the omapatrilat group is much less good.

Adding rate constants to allow for movement between the low- and high-risk states did not improve the fit for omapatrilat. As shown in Figure 8, a model in which subjects are initially in one of 3 at-risk states fit the data for omapatrilat well.

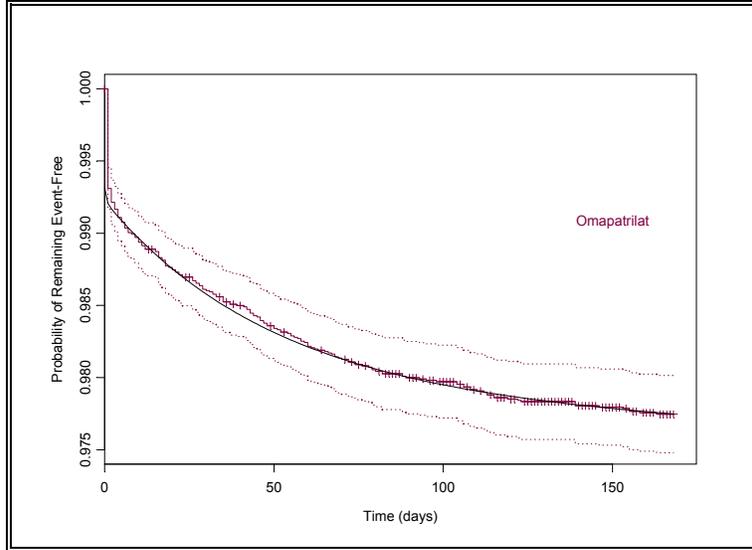
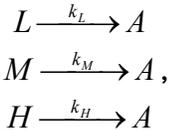


Figure 8. Three-exponential fit to angioedema on omapatrilat.

Time to first angioedema data were fit to a 4-compartment model:



L, M, and H are the proportion of subjects at low, medium, and high risk.

The data are fit with 0.7% of subjects at highest risk (about 0.89 per day), 1.4% at intermediate risk (about 0.02 per day), and the remainder at about 10^{-5} per day (same as the low risk group on enalapril).

In summary, on either enalapril or omapatrilat, most subjects are at low risk (about 10^{-5} per day); this may represent the background rate in the population, but there is no placebo group here to confirm that. At all times, the risk of angioedema is higher on omapatrilat than on enalapril, but the difference is greatest initially and settles to about 3-fold greater after the first 6 weeks. The data for enalapril can be well fit by a model in which the population is fixed in low- or high-risk states at the time of exposure (2 exponentials), but the data for omapatrilat require 3 such states (3 exponentials) for a good fit. Attempts to further simplify the results and relate the differences between omapatrilat and enalapril to one or two parameters were not successful.