Combined Medical & Statistical Review
Heart Outcomes Prevention Evaluation (HOPE) Study

NDA #19-901, S-028

Division of Cardio-Renal Drugs, HFD-110

April 3, 2000

Overview

The sponsor has submitted a supplement for NDA 19-901, seeking approval for Altace® (ramipril) tablets as a treatment to reduce the risk of myocardial infarction, stroke, and cardiovascular mortality in "high risk" patients, defined as those with vascular or coronary disease, or diabetes with at least one other cardiovascular risk factor. This is a joint medical-statistical review of the submission.

Ramipril is currently approved for hypertension and post-myocardial infarction (MI) congestive heart failure (CHF); the latter approval was based on results from the Acute Infarction Ramipril Efficacy (AIRE) trial, a 2006 patient randomized, double-blind, placebo-controlled, parallel-group study in patients with CHF immediately post MI, which showed a reduction in the risk of death, progression of CHF, and CHF-related hospitalization[1]

The sponsor now has presented the results (databases with an annotated case report form) of the HOPE (Heart Outcomes Prevention Evaluation) study, as well as manuscripts from The New England Journal of Medicine 342:145-153, 2000 (ramipril)[2], The New England Journal of Medicine 342: 154-160, 2000 (Vitamin E)[3] and The Lancet 355: 253-259, 2000 (diabetes substudy)[4] to support the new indication and usage. Efficacy data from substudies evaluating low-dose ramipril (2.5 mg per day), effects on echocardiograms in HOPE subjects (3 centers), and effects on carotid ultrasounds (SECURE study) were not provided in this submission and therefore are not included in this review. While Vitamin E was a randomized treatment in the factorial design of HOPE, its efficacy will not be discussed in great detail; the Vitamin E portion of this study is ongoing, and no related indications are being sought at this time.

Draft labeling was received by the reviewers on February 22, 2000. Event forms for 50 patients were received on March 1, 2000. Ethnic/racial data were received on March 2, 20[illegible] Also provided in the submission were protocols, protocol amendments, and minutes of the [illegible] and Safety Monitoring Board. No Study Report was included in this submission.

The clinical data were reviewed jointly by Dr. Shari Targum (HOPE trial) and Dr. Jame[illegible] Hung of Biometrics (statistical analysis). The secondary reviewer was Dr. Shaw Chen.

The Table of Contents can be found on the next page.

Table of Contents:

Background and History of Protocol Development:

Vascular disease resulting from atherosclerosis continues to be the number one cause of death in Western countries. Experimental evidence suggests that the development of atherosclerotic lesions is a complex chain of events involving oxidized low density liproproteins (LDL), endothelium, macrophages, vascular smooth muscle, platelets and circulating coagulation factors.

There has been experimental (in vitro and animal studies) and epidemiological evidence implicating the renin-angiotensin-aldosterone system in development of atherosclerosis. The hypothesis that angiotensin converting enzyme (ACE) inhibitors may be protective is supported by the several large trials of ACE inhibitors where there was a reduction in myocardial infarction (MI) compared to placebo. In the SOLVD trials, there were reductions in MI and unstable angina with enalapril use compared to placebo.[5] In the SAVE trial, there was a reduction in recurrent MI with captopril use compared to placebo.[6]

Since oxidized LDL is believed to be causally related to atherosclerosis, the question arose as to cardioprotective benefit with anti-oxidants. The question arose whether Vitamin E, as an anti-oxidant, could play a cardioprotective role.

A protocol (December 22, 1993), blank Case Report Form (CRF), and Ramipril Investigator's Brochure (revised October 1, 1990), were submitted to the Agency on Decem 30, 1993 as an Investigator IND. In a January 31, 1994 letter to the sponsor (who, at that ti was the Principal Investigator), the Agency communicated the following concerns about th protocol:

1) Failure to exclude patients with prior congestive heart failure (CHF) or asymptomatic le ventricular dysfunction. The Agency recommended prospectively measuring ejection fraction in all patients, or measuring ejection fraction in a prospectively defined subgro see if there were differences in effect;
2) Definition of the primary endpoint to include "cause-specific mortality." The Agency strongly recommended that the primary combined endpoint be modified to "all cause mortality" instead;
3) Involvement of study physicians in the event report reviews and event adjudication. It was recommended that a panel of physicians blinded to therapy, and not involved in the conduct of the trial, review the events. It was also recommended that the Events Adjudication Committee review all cardiovascular deaths, rather than just those in which there is a discrepancy;
4) The Agency recommended that the decision to extend the follow-up period, if the total event rate is low, should be made by those independent of all aspects of the trial and blinded to the results. Those making this decision should only be informed of the total event rate, or the event rate in the placebo group only. Furthermore, this decision should be made at the time of the first or second interim analysis.
5) Inadequate definition of MI and inadequate MI documentation in the CRF;

6) The Agency recommended that the sponsor consider changing nephropathy/dialysis to a primary endpoint. The portion of the trial evaluating the progression of diabetic nephropathy was felt inadequate with regard to the determination of baseline measurements and documentation of events (i.e., proteinuria and dialysis). "Overt nephropathy" was inadequately defined. Also, baseline urine collection was inadequate for defining those with microalbuminuria. The Division recommended 24 hour urine collection either on all diabetics prior to the run-in, or at least in those with a positive morning urine.
7) Type of diabetes was not recorded on the CRF;
8) With the approval of captopril for diabetic nephropathy, it was recommended that this information be incorporated into the protocol and informed consent.
9) The protocol and consent form did not discuss precautions for patients on ramipril with hepatic insufficiency, elderly, requiring a diuretic, hypotension, history of angioedema, and on lithium;
10) The Agency recommended that concomitant medication, at least aspirin and beta blocker use, be recorded at all follow-up visits.
11) The design strategy could overestimate the effect of ramipril or vitamin E alone when synergism occurs;
12) If statistical analysis was not unequivocally reached on the primary endpoint, then analysis of the secondary endpoints will not be reliable enough to lead to definitive conclusions on the secondary endpoints;
13) The Agency requested the plan for interim analysis.

In a February 1, 1994 response, the sponsor agreed to prospectively study a 700 patient subgroup with 2D echocardiography, to determine the sample proportion with low ejection fraction. Patients with diabetic nephropathy would be excluded from randomization. Diabetics would be screened yearly for development of nephropathy. Those who developed diabetic nephropathy may be withdrawn from the study and offered open-label captopril or another ACE inhibitor, depending on their type of diabetes. Overt nephropathy remained a secondary endpoint and was defined, in that February 1, 1994 letter, as a 24 hour urine protein excretion of $\geq$ 500 mg, a 24 hour urine albumin excretion of $\geq$ 300 mg or a urinary albumin excretion rate of $\geq$ 200 micrograms per minute (in the protocol, the urinary albumin excretion rate is listed as > 200 micrograms per minute); this definition was not in the protocol amendments. In adjudicating events, the sponsor planned to have a random proportion of events independently checked by the Event Adjudication Committee (this was not in the protocol amendments). It was proposed that the Data and Safety Monitoring Board make the decision early in the process (e.g. before one-third of the events are in) whether to extend the study. Inclusion criteria for coronary artery bypass (CABG) and myocardial infarction (MI) were clarified and amended.

A summary of protocol amendments, dated March 21, 1994, was included in this submission. Many of the protocol amendments, such as additional eligibility definitions (for example, adding stress test results to define eligible patients), secondary endpoints, and safety monitoring, were added to a subsequent second version of the protocol, dated December 22, 1993 (while labeled "final version," this protocol is actually different from the other December 22, 1993 "final version" that the Agency received in December, 1993). The only change in definition of primary or secondary endpoints is the addition of Q wave/R wave criteria to the definition of a Q-wave MI . Changes to the older version of the protocol received in 1993 are—where applicable-- italicized below and include: changes in participant eligibility, data collection (in unusual circumstances medications could be mailed to patients), and safety monitoring. A "suggestion" for early termination of the trial was proposed in the protocol amendments but "formal stopping rules of a statistical sort" were subsequently rejected by the Data Safety and Monitoring Board.

The Claims:

In FDA form 356h, ,the sponsor proposed the following new indication for ramipril: "significant reduction of mortality, myocardial infarction, stroke, revascularization procedures, and heart failure in high risk patients."

In the submitted draft labeling, the sponsor has proposed the following new claim: "In patients 55 years or older with a history of coronary artery disease, stroke, peripheral vascular disease, or diabetes plus one other cardiovascular risk factor (hypertension, elevated total cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria), ALTACE ® is indicated as adjunctive therapy to reduce the risk of MI, stoke, or death from cardiovascular causes. In addition, ALTACE ® is indicated to reduce the incidence of these preselected clinically relevant secondary endpoints: coronary revascularization procedures, complications related to diabetes, and hospitalizations for heart failure."

Financial Disclosure:

Financial disclosure statements were received on March 10, 2000. A completed FDA Form 3454 was received with box 2 checked, certifying that no investigators had a proprietary interest in the product, no compensation affected by study outcome, and no significant equity interest in the sponsor. The HOPE International Steering Committee, chaired by Dr. Salim Yusuf, administered and disbursed all funding for the HOPE trial. Funding sources for the study as well as the names and addresses of 905 investigators were provided. There appear to be no financial conflicts of interest.

The HOPE Protocol

Four different versions of the HOPE protocol, dated September 27, 1993, two versions dated December 22, 1993, and another version dated March 21, 1994, respectively, were submitted to the Agency. In addition, a summary of protocol amendments, dated 3/21/94, was submitted; these changes were then incorporated into the final version of the protocol. Since the study began in December, 1993, changes subsequent to the earlier second version of the HOPE protocol are underlined and italicized below.

Title of Study: Heart Outcomes Prevention Evaluation

Objectives:
There were two primary objectives:
1. To evaluate if ramipril use reduces the composite endpoint of myocardial infarction, stroke and cardiovascular death in patients at risk for cardiovascular events.
2. To evaluate if Vitamin E use reduces the composite endpoint of myocardial infarction, stroke and cardiovascular death in patients at risk for cardiovascular events.

The primary endpoint was, therefore, the occurrence of myocardial infarction, stroke, or cardiovascular death.

Secondary endpoints:
Secondary endpoints were: hospitalization for congestive heart failure, acute ischemic cardiac syndromes (MI, unstable angina or severe angina requiring emergency coronary artery bypass surgery or angioplasty), all cardiovascular revascularization procedures, cardiovascular mortality, total mortality, overt nephropathy or dialysis among diabetics, cancer by site and morphology.

Study Design:
This was a randomized, placebo-controlled, double-blind trial, utilizing a 2 x 2 factorial design (see below), with a 3 week run-in period followed by 48 months of treatment.

Number of Patients to be Recruited:
8,000 total (see Sample Size calculation), to be recruited over a one year period, including about 4,000-5,000 cardiac, 1,000 peripheral vascular, and 3,000-4,000 high risk diabetics (including 1,000-2,000 with cardiac disease).

Investigators and Sites of Investigation:
The Principal Investigator was Dr. Salim Yusuf, McMaster University, Toronto, Canada.
The protocol specified 200 sites, distributed as 100-120 sites in Canada, 20-30 in the United States, 50 in Europe, and 30 in South America. The NEJM manuscript[2] noted 129 centers in Canada, 27 centers in the United States, 76 centers in 14 western European countries, 30 centers in Argentina and Brazil, and 5 centers in Mexico.

Patient Population:
Males and females aged 55 and over at high risk of developing a major cardiovascular event.

Inclusion Criteria:
1. Coronary disease:
- Previous MI
- *Stable or* unstable angina with documented multivessel coronary disease, *defined as >50% stenosis in at least two major coronary arteries or positive stress (ST depression > 2 mm) or positive thallium*
- Multivessel PTCA

(patients can be entered into run-in phase one week after these events but should only be randomized one month after these events).

- Multivessel CABG (more than 4 years ago *or with angina*)
- Multivessel coronary disease (*defined as above*) on angiography.

2. Peripheral vascular disease:
- Previous limb bypass surgery or percutaneous transluminal angioplasty
- Previous limb *or foot* amputation
- History of intermittent claudication with ankle/arm blood pressure ratio of 0.80 or lower *in at least one side*
- *Significant stenosis (>50%) documented by angiography*

3. Previous nondebilitating stroke: (more than one month ago)

4. Diabetes (insulin-dependent or noninsulin-dependent) with one of the following cardiac risk factors:
- Hypertension (BP > 160 mmHg systolic or > 90 mmHg diastolic or on treatment)
- Total cholesterol > 5.2 mmol/L (>200 mg/dl)
- HDL cholesterol < 0.9 mmol/l (35 mg/dl)
- Current cigarette smoking
- Known microalbuminuria *or any evidence of previous vascular disease*

Exclusion Criteria:
- Use of ACE inhibitors or Vitamin E with an inability to discontinue these medications;
- Known hypersensitivity to ACE inhibitors or Vitamin E.
- Ejection fraction < 40% (only if known).
- Hemodynamically significant primary valvular or outflow tract obstruction.
- Constrictive Pericarditis.
- Complex congenital heart disease.
- Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias.
- Planned cardiac surgery or angioplasty within 3 months (patients may be reconsidered after the procedure).
- Uncontrolled hypertension.
- Cor pulmonale.
- Heart transplant recipient.
- Significant renal disease, defined as
  1. Renal artery stenosis
  2. Creatinine clearance < 0.6 ml/second or serum creatinine ≥ 200 Meq/L (> 2.26 mg/dl)
  3. Overt nephropathy: ≥ 1 plus proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hours)
  4. Hyperkalemia; K > 5.5 mEq/L.
- Any other major noncardiac illness expected to reduce life expectancy or interfere with study participation.
- Simultaneously taking another experimental drug.
- Previously randomized to HOPE.

Withdrawal Criteria:

- Congestive heart failure: Patients who developed congestive heart failure were to be discontinued from ramipril and given open-label ACE inhibitors.
- Cardiac Transplantation.
- Severe adverse experiences: Withdrawal was at the discretion of the treating physician.
- Overt nephropathy: Development of overt nephropathy during the trial was not strictly a criteria for withdrawal, but was left up to the "judgement of the investigator." All patients withdrawn from study medication would remain in the study and were to be analyzed in their originally allocated group.

In the management of MI, unstable angina, hospitalization for other medical illnesses or for surgery, CABG, percutaneous transluminal coronary angioplasty (PTCA), hyperkalemia, or uncontrolled hypertension, patients were encouraged to either continue medication or temporarily hold and restart medication as soon as feasible. In the case of azotemia, it was recommended to continue ramipril at a lower dose. None of these conditions were considered to be criteria for withdrawal from study medication.

Randomization:

Randomization was provided by the Canadian Cardiovascular Collaboration Program Office (C3PO).

Dosage/Administration:

Patients were randomized to ramipril (2.5 mg once daily (QD) for one week, then 5 mg QD for 3 weeks, then 10 mg QD) or placebo AND Vitamin E 400 IU QD or placebo. The time of administration (i.e., day or evening) was not specified in the protocol or case report form.

Duration of Study:

The protocol specified a follow-up schedule out to 48 months. Patients were to be followed for an average of 3.5 years. The study was to end after the last patient was followed for at least 3 years. According to the C3PO the study was to have ended in November 1998. The study was extended to November, 1999 to allow for late-appearing Vitamin E effects. In March, 1999, the Data and Safety Monitoring Board, which had access to the unblinded data, recommended stopping the ramipril portion of the study for efficacy reasons.

Study Plan:

Eligible patients entered a 3 week run-in period where they received 2.5 mg ramipril for 7-10 days followed by placebo ramipril for 10-14 days. Urine dipstick for proteinuria was to be done on the first visit, and serum creatinine and potassium were to be performed between days 7 and 10 of the run-in period (on active ramipril). In diabetics, a glycosylated hemoglobin (Hb A1c) would be done. Patients were eligible to enter the double-blind phase if they were compliant (>80 %), had no contraindications to therapy, met eligibility requirements, did not have gross elevations in potassium or creatinine, $\geq$ 1+ proteinuria or severe adverse effects. Patients were then randomized to the following groups:

Ramipril + Vitamin E (2,000)	Placebo Ramipril + Vitamin E (2,000)
Rampril + Placebo Vitamin E (2,000)	Placebo Ramipril + Placebo Vitamin E (2,000)

During the double-blind phase, follow-up visits occurred at 1 and 6 months, then every 6 months up to 48 months post-randomization. Patients without diabetes would have a serum creatinine and potassium at the 1 month visit only. Diabetics would have yearly serum creatinine and glycosylated hemoglobin.

Schedule and Methods of Assessment:

Run-In Visit (visit 1) (-3 weeks)	Demographics, Eligibility Determination If diabetic, urine dipstick for proteinuria
Prior to randomization (visit 2) (week 0)	Mortality, hospitalization, serious, related adverse event Medical History, including risk factors, medication use Physical Exam, including heart rate, blood pressure, ankle blood pressure, height, weight Waist and Hip Circumference 12-lead ECG (within last 12 months if no new CV event) Compliance to run-in medication Blood samples for creatinine, potassium and (if diabetic) glycosylated Hb Urine sample for microalbuminuria (central lab) Blood sample, 8 hour fasting, selected sites (central lab)
Follow-Up (visit 3) (1 month)	Mortality Compliance ....h study medication Clinical events recorded Heart rate, arm blood pressure, ankle blood pressure Creatinine and potassium (local lab)
At 6 months (visit 4)	Mortality, Clinical events and serious adverse events, compliance
At 1 year (visit 5)	Mortality, Clinical events and serious adverse events Compliance with study medication If diabetic, record serum creatinine, glycosylated Hb(local lab) If diabetic, urine dipstick for proteinuria (urine sample to be sent to HOPE central lab)

Schedule and Methods of Assessment (continued):

At 1.5 years (visit 6)	Mortality, Clinical events and serious adverse events Compliance with study medication
At 2 years (visit 7)	Mortality, Clinical events and serious adverse events Compliance with study medication Medication history If diabetic, record serum creatinine, glycosylated Hb (local lab) and urine dipstick (urine sample to be sent to HOPE central lab) Heart rate, arm blood pressure, ankle blood pressure 12-lead ECG
At 2.5 years (visit 8)	Mortality, Clinical events and serious adverse events Compliance with study medication
At 3 years (visit 9), 4 years (visit 11), 5 years (visit 13)	Mortality, Clinical events and serious adverse events Compliance with study medication If diabetic, record serum creatinine and glycosylated Hb from local lab If diabetic, urine dipstick for proteinuria (need not be centrally)
At 3.5 years (visit 10), 4.5 years (visit 12), and 5.5 years (visit 14)	Mortality, Clinical events and serious adverse events Compliance with study medication
At penultimate visit	Medication history, ECG, urine sample (central lab), creatinine and glycosylated Hb from local lab
Final visit	Heart rate, arm and ankle blood pressures, height/wei

Definitions of Efficacy Endpoints

Primary Endpoints:

Measures of efficacy were described as "primary endpoints." The primary endpoint was defined in the protocol as the first occurrence of either nonfatal MI, nonfatal stroke, or death from a cardiovascular cause.*

1. Nonfatal MI:

(a) Q wave MI: New significant Q waves (*≥ 0.04 seconds duration or 3-4 mm depth and loss in height of ensuing R wave)* in at least two leads on the standard 12 lead ECG and at least one of :

* see Event Adjudication Committee, next page, for which events were adjudicated.

- typical associated symptoms (e.g. chest pain) and/or
- significant enzyme elevation—any one of the following:
  --CPK-MB above the upper limit of normal within 36 hours of onset of symptoms plus total CPK at least twice the upper limit of normal
  --SGOT, LDH, or other cardiac enzymes at least twice the upper limit of normal for the laboratory that performed the test with a characteristic pattern.

(b) MI without ECG changes or minimal ECG changes: patients with characteristic symptoms plus characteristic elevation of cardiac enzymes. In such cases ECG changes may be minimal, transient or non-diagnostic.
(c) Non Q wave MI: New, persistent ST or T wave changes on the ECG with significant enzyme elevation and/or symptoms of chest pain.
(d) Silent Q wave MI: New Q waves in at least 2 adjacent leads (without symptoms or enzyme elevation).

The diagnosis of MI was made at the site.

2. Stroke: Neurologic deficits persisting for more than 24 hours. Strokes were further classified, based on clinical symptoms, autopsy and/or CT/MRI as:
a) Definite or probable ischemic stroke
b) Definite or probable hemorrhagic stroke
c) Definite stroke, type uncertain.

3. Cardiovascular death: Any deaths due to MI, stroke, pulmonary emboli, arrhythmia or other cardiovascular events (i.e. ruptured aorta). This includes sudden death without any other documented cause.

Secondary Endpoints:

1) Acute ischemic cardiac syndromes: MI, plus unstable angina or severe angina requiring emergency CABG or PTCA (i.e., within 7 days of symptom onset).
2) All cardiovascular revascularization procedures to include CABG surgery, coronary PTCA, carotid endarterectomy (for stenosis of carotid luminal wall, transient ischemic attacks or stroke), peripheral cardiovascular surgery or angioplasty (for limb ischemia), or limb amputation.
3) Cardiovascular mortality.(Although listed this way, this endpoint is the same as "cardiovascular death", counted as an individual component (per C3PO) rather than a composite.)
4) Total mortality.
5) Development of overt nephropathy or dialysis among diabetics.
6) Hospitalization for congestive heart failure.
7) Cancer by site and morphology.

Event Adjudication:

According to the protocol, the Event Adjudication Committee were to review only those major events (MI, stroke, CV death) where there was a discrepancy between the hospital record or death certificate and the case report form/event form. A C3PO physician was to review all discharge summaries and event forms for consistency.

According to additional information supplied by the C3PO (not in the protocol or amendments), all primary and secondary endpoints (event reports and supporting documentation) were reviewed by a member of the Event Adjudication Committee. If there was disagreement between the committee member and investigator, the event was sent to the committee chair (Dr. Dagenais) for final decision. Only certain committee members were allowed to adjudicate deaths. In addition, a blinded committee member reviewed 10% of those events confirmed by an adjudicator.

According to the C3PO, the primary endpoint was the composite of the "first event." A hypothetical patient who sequentially developed an MI, then a stroke, and then died of a pulmonary embolus would have reached the primary endpoint with the MI (the first event).

Case Report Forms

The blank Case Report Forms, as provided in the submission are, in general, adequately designed for collection of pertinent data. For diabetics, age of diabetes onset and medications (but not dosages) were elicited. Specific concurrent medications were elicited at the randomization visit, at the 2 year visit, and at the penultimate visit. There were specific Event Forms for: hospitalization, MI, stroke, death, unstable angina and serious adverse experiences.

Organization and Monitoring of the HOPE Study:

Sites/Investigators: Sites to consist of universities, community hospitals, and private clinics. Investigators to recruit and follow patients, and meet annually to discuss overall trial conduct and hold educational forum.

Regional Coordinators: Regional follow-up, organize screening and recruitment

Canadian Cardiovascular Collaboration Project Office (C3PO)—day to day conduct of the trial

International Steering Committee: Includes chairs and regional coordinators. Disbursed funding (see Financial Disclosure). Chaired by Principal Investigator, Dr. Yusuf

Events Adjudication Committee: Review and classify components of the primary composite endpoint where questions or discrepancies occurred.

Data Safety & Monitoring Board: Independent scientific review of protocol, recommend changes, early termination of study, ensure event rates are reasonable.

The C3PO was the most important group in organizing and managing the trial, and, together with the International Steering Committee and the Events Adjudication Committee, had overall responsibility for the trial. As mentioned above, the International Steering Committee disbursed funding.

Several members of the International Steering Committee were also members of the Events Adjudication Committee (G. Dagenais, E. Lonn, M. Arnold, H. Gerstein, and A. Avezum); E. Lonn was also a Coordinator of the study.

The Data Safety and Monitoring Board (DSMB), the only group that had access to unblinded data, did not include investigators or coordinators as members. According to DSMB minutes, the Principal Investigator (Dr. Yusuf) was not in attendance when unblinded data were shown; it was agreed –per DSMB minutes—that the Principal Investigator would remain blinded to efficacy data until about six months prior to the expected end of the study.

The manufacturer of Ramipril, Hoechst and its related companies were to arrange for data verification by auditing case records on a random basis. A random 25% of those case records with a primary endpoint were to have chart audits, and a random 5% of those not suffering a primary endpoint were to have chart audits. In addition, all centers were to be audited at least twice during the study to ensure adherence to study protocol; these visits were to be coordinated by the C3PO and Regional Coordinator.

Sample Size Calculation:

The study proposed a sample size of 8,000-9,000 subjects recruited in one year and followed for 3 more years. Based on a review of the literature of over 93,000 patients, there was an expected overall 5% per year event rate for the primary combined endpoint of MI, stroke, and cardiovascular death. The study of 6,000-8,000 patients will be able to detect, with an 80-90% power, risk reductions with active treatment in the 15-20% range. Also, increasing the study size by another 1,000-1,500 would protect the study power in the event of a lower than expected event rate.

Plan of Data Analysis:

The primary endpoint and secondary endpoints are to be analyzed using time-to-event approach. Data will be summarized for each treatment group in the form of a survival curve which is estimated using Kaplan-Meier procedure. The survival curves will be compared between treatments using the log-rank test, based on an intent-to-treat approach.

The factorial design will require that the comparison of ramipril will be stratified by Vitamin E (and vice versa), and clinical center. The possibility of synergism will be investigated by formally testing the interaction term in a Cox model allowing for potential non-multiplicative effects.. Subgroup analyses will be done by retrospective, stratified analysis, including tests of interaction in the Cox model. The Cox model will also be used for treatment effect estimates which are adjusted for baseline-prognostic imbalances. Data derived findings will not have a p value assigned.

An analysis plan was not provided for the secondary questions listed in the diabetes substudy.

Interim Analysis:

The independent DSMB will monitor the progress of all aspects of the study. In particular, data on key study endpoints will be monitored at regular intervals to ensure that the event rates meet protocol projections. If the event rates are lower than expected, the DSMB can recommend an extension in the duration of follow-up to maintain study power. The criterion based on which an extension will be recommended was not provided in the protocol. Four formal interim analyses are planned, equally spaced, with respect to accumulating years at risk. In a protocol amendment, it was stated that one suggestion for early stopping is that a reduction in events by four standard deviations or a three standard deviation excess in the first half of the trial, or a reduction in events by three standard deviation or a two standard deviation excess in the second half of the trial. The decision to continue or stop the trial would be based on a number of factors in addition to the main results.

Safety:

Amended to the protocol was safety data collection: Those adverse events *that resulted in temporary or permanent withdrawal of study medication or a change in dosage* were to be collected and periodically reported to the DSMB. Management of adverse events was at the discretion of the patient's physician.

HOPE Diabetes substudy:

This was a substudy of the HOPE trial looking at the cardioprotective effects of rampril and/or Vitamin E in the diabetic population in the study.

Objectives:

The primary objective, as stated in the protocol, was to determine if an ACE inhibitor and/or Vitamin E protects patients with diabetes (with at least one other risk factor) from cardiovascular disease.

Rather than endpoints, there was a listing of "specific primary research questions." These were the following:

1) In patients with IDDM or NIDDM, 55 years of age and older, with at least one other cardiac risk factor, does ramipril reduce the occurrence of MI, stroke, or cardiovascular death?
2) In patients with IDDM or NIDDM, 55 years of age and older, with at least one other cardiac risk factor, does Vitamin E reduce the occurrence of MI, stroke, or cardiovascular death?

Secondary objectives were not listed as "objectives" but as "secondary questions."
These were:

1. In the study population noted above, does an ACE inhibitor/Vitamin E decrease the occurrence of :
   a) other significant cardiovascular events;**
   b) total cardiovascular mortality;
   c) total mortality;
2. In this same study population, does an ACE inhibitor/Vitamin E prevent:
   a) incipient diabetic nephropathy; **
   b) progression of incipient nephropathy to overt nephropathy needing hospitalization or dialysis;
   c) deterioration in renal function;**
3. Does an ACE inhibitor/Vitamin E:
   a) improve glucose control (Hgb A1c);
   b decrease the occurrence of diabetic retinopathy requiring laser therapy;
   c) decrease the rate of limb amputations and foot infections requiring antibiotics?
4. Analysis of effects among all diabetics in the presence or absence of established cardiac disease.

**These questions were not further defined in the protocol.

Study design:
As in the HOPE trial, diabetic patients will take ramipril or matching placebo AND Vitamin E or matching placebo in a 2 x 2 factorial design (see HOPE Study design). They will be followed every 6 months up to 48 months.

Patient population:
This patient population represents the same diabetic population that was recruited as part of the HOPE trial, namely diabetics with at least one other of four cardiac risk factors (See above: hypertension, hyperlipidemia, active smoking, or known microalbuminuria. Other risk factors such as family history, obesity, etc. were not part of the eligibility criteria). This population included those with non-insulin-dependent diabetes mellitus (NIDDM) and insulin-dependent diabetes mellitus (IDDM), and those with and without coronary disease.

Exclusion criteria:
These would be the same exclusion criteria as in the main HOPE trial, and include absolute indications or contraindications for the use of ACE inhibitor or Vitamin E, or medical problems that would either interfere with participation in the trial or lead to the inability to complete the trial.

Study plan:
This would entail the same dosage/administration and schedule of events as in the main trial. Additional information collected during the run-in phase and at each year visit would include serum creatinine and glycosylated Hgb (Hgb A1c), as well as a urine sample for microalbuminuria. Also collected was reporting of laser surgery for retinopathy.

Summary of Reviewer Comments on Protocol:

- The eligibility criteria broadly defined those "at risk" for vascular events; these criteria included post MI or post PTCA patients regardless of stress test results. In this regard, a hypothetical post MI patient (without stress test or coronary angiogram results) would have been included whereas a patient with angina and single vessel disease would have been excluded.
- The primary endpoint in the main study was a composite, including "cause-specific" (i.e., cardiovascular causes) mortality. All-cause mortality was defined as a secondary endpoint.
- According to the protocol, major events (the components of the primary composite endpoint) were adjudicated centrally only in the case of questionable events or discrepancies.

- The diagnosis and type of diabetes was not predefined. Age of onset of diabetes, but not type (Insulin-dependent/Noninsulin-dependent diabetes) was specified on the Case Report Form. According to the February 1, 1994 letter from the sponsor to the Agency, the two groups were distinguished by age of onset of diabetes. However, this distinction was not prospectively defined, nor can any definition be found in the protocol or protocol amendments. C peptide levels, reflecting endogenous insulin production, were not drawn. According to the Lancet manuscript[4], the two groups were distinguished by age of diabetes onset (age 30 was used as a cutoff) or medication use (i.e., not on insulin). The age definition might misclassify some patients.
- Deaths from pulmonary emboli were included in cardiovascular mortality. Pulmonary emboli can occur in the absence of atherosclerotic disease.
- In the protocol, overt nephropathy was prespecified as a "secondary research question." In the manuscript, overt nephropathy was a "main outcome in a substudy."
- Differing definitions of overt nephropathy:
  - According to the protocol, overt nephropathy (see Exclusion) was defined as $\geq$ 1+ proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hours).
  - According to the Principal Investigator (letter to the Agency, February 1, 1994), "Patients with an albumin creatinine ratio of 30 at the one year follow-up and at the end of the study will be considered to have possible overt diabetic nephropathy. This information will be communicated to the investigators who will be asked to confirm the presence of overt diabetic nephropathy."
  - According to the published diabetes substudy design,[7] the albumin-to-creatinine ratio and urine protein dipstick were to be used as screening tests for overt nephropathy and the diagnosis was to be confirmed with 24 hour or timed urine albumin or protein.
  - According to the Lancet manuscript,[4] patients with a first morning urinary albumin/creatinine ratio of 36 mg/mmol or higher were asked to give a 24 hour urine sample which was assayed in a local laboratory. Overt nephropathy was defined as 24-hour urine albumin of 300 mg or more per day, 24-hour urine total protein excretion of 500 mg or more per day, or if the albumin/creatinine ratio was higher than 36 mg/mmol and no 24-hour urine result was available (central assessment was done for 24 hour urines in cases of overt nephropathy). This definition was not in the protocol or amendments.
- Microalbuminuria was not predefined in the protocol or protocol amendments. In the Lancet manuscript[4] microalbuminuria was defined as an albumin/creatinine ratio of $\geq$2 mg/mmol and the reader is referred to another journal article describing the HOPE trial methods.[7] In this reference, microalbuminuria is defined as a urine albumin excretion rate of 20-200 µg/min.
- In diabetics, glucose control was a "secondary question" but analysis of this parameter was not further predefined in the protocol or amendments.
- In the protocol, the only prespecified "composite endpoint" was that of the primary endpoint. A "combined microvascular outcome" of overt nephropathy, dialysis, or laser therapy, as published in the manuscript,[4] was not prespecified.
- In the protocol, deterioration in renal function was mentioned as a "secondary question" but was not further defined.

- Congestive heart failure was not a predefined outcome and was not further defined in the protocol or amendments. There was a Congestive Heart Failure form (plate 052), with information on diagnosis and treatment, which was not included in this submission and not previously submitted to the Agency. Hospitalization for congestive heart failure, but not congestive heart failure itself, was a prespecified secondary endpoint.
- Information regarding laser therapy in diabetics was collected by patient history and checking a box on the CRF next to the question, "has the patient required laser therapy for diabetic retinopathy since the last study visit." No retinal photos or angiograms were specifically elicited either at baseline or during the study. A baseline imbalance in retinopathy between ramipril and placebo cannot be excluded in this study. Changes from baseline in retinopathy, or recommendations for laser therapy, were not assessed. Since this is a self-reported measure, there is the error introduced by patient interpretation and understanding of the question and laser procedure.
- Management of adverse events were at the discretion of the patient's physician. "When in doubt," the treating physician was encouraged to discuss an individual patient's management with the C3PO. A potential bias resulting from advice provided by the C3PO cannot be excluded.

Termination of HOPE study

As mentioned previously, the statistical monitoring boundary indicating that ramipril had a beneficial effect was a difference in the primary endpoint of 4 standard deviations between groups during the first half of the study and of 3 standard deviations during the second half. According to the New England Journal of Medicine article, on March 22, 1999, the Data Safety Monitoring Board (DSMB) recommended termination of the HOPE study because of the clear evidence of a beneficial effect of ramipril (consistent crossing of the monitoring boundaries in two consecutive reviews). At that time, the data showed a 20 percent reduction in the relative risk of the primary endpoint (95% CI of 12% to 28 % reduction; z statistic = -4.5, $p < 0.001$). The results of the study were disclosed to the investigators at two meetings on April 17 and April 24, 1999. The cutoff date for all events included in the main analysis was set for April 15, 1999, and the final visits were scheduled to be completed by June 30, 1999.

Comments: The DSMB meeting minutes of March 22, 1999 reported that they concluded that the data were extremely convincing for the efficacy of ramipril for both primary and secondary outcomes. There was no meeting minutes reporting that the data had crossed the monitoring boundaries in two consecutive reviews.

Results:

Patient Description:

Patient Disposition:
In the database provided, 10, 585 patients entered the run-in phase; 1044 patients were excluded from randomization.* Reasons for rejection were:

1044 patients rejected from randomization: †
Refused/withdrew consent/administrative: 338
Did not meet eligibility criteria**: 345

Patients who did not meet eligibility criteria:

Age < 55	83
CHF/EF < 40%	16
>1+ proteinuria	11
Insufficient coronary artery disease	18
CABG < 4 years without symptoms	17
Increased potassium/creatinine during run-in	58
On Vitamin E/ACE inhibitor	23
noncompliant during run-in	108
other/unspecified**	11

** One patient (ID #550052) was not randomized due to "revised entry criteria."

Adverse events during run-in:	259
Died during run-in period:	10
Other medical illness/clinically unstable:	74
No show/lost to followup:	18

Of the adverse events leading to withdrawal during run-in, the most commonly reported were

Unspecified	52
Cough	39
Dizziness	34
Nausea	27
Headache	21

Facial swelling/angioedema was reported in 3 patients.

---

* According to the NEJM manuscript,[2] 10, 576 eligible patients entered into the run-in phase. Of these, 1035 patients were excluded from randomization because of noncompliance, side effects, abnormal serum creatinine or potassium levels, or withdrawal of consent.

† These data were generated by the reviewer from the visit 2 (randomization visit) database (spreadsheet) supplied by the sponsor. Eligibility was determined from a checkbox, labeled yes/no. Under the reasons patients were excluded from randomization, several entries were in languages other than English or not specified. "Didn't feel well" without clarification was classified as adverse event, unspecified.

Of the remaining 9541 patients, 4645 were randomly assigned to ramipril 10 mg per day, and 4652 were randomly assigned to matching placebo; 244 patients were randomly assigned to receive ramipril 2.5 mg per day—these low-dose patients were not included in the efficacy analysis in this submission.
In the database provided there were 8514 patients who underwent a final visit; 8 patients were unaccounted for/lost to follow-up: 5 in the placebo group, and 3 patients in the ramipril group.*

Demographics and Baseline Characteristics:

The ramipril group and the placebo group appeared to be well balanced at baseline (Table 1).

Table 1. Demographics and baseline characteristics

	Ramipril (N=4645)	Placebo (N=4652)
Gender		
Male	72.5%	74.2%
Female	27.5%	25.8%
Ethnic group		
Caucasian	89.7%	89.7%
Hispanics	5.7%	5.8%
Asian	1.7%	1.6%
Blacks	1.6%	1.4%
Native	0.3%	0.3%
Others	0.9%	0.9%
Age (in yr)	66±7	66±7
SBP/DBP (in mm Hg)	139±20/79±11	139±20/79±11
Heart rate (in bpm)	69±11	69±11
Body mass index	28±4	28±4
History of cardiovascular disease	86.8%	88.8%
History of coronary artery disease	79.5%	81.4%
Myocardial infarction	51.9%	53.4%
Within ≤ 1 year	9.7%	9.6%
Within > 1 year	42.2%	43.8%
Stable angina	54.8%	56.3%
Unstable angina	25.4%	25.5%
CABG	25.7%	25.9%
PTCA	18.4%	17.3%
Stroke or transient ischemic attacks	10.8%	11.0%
Peripheral vascular disease	40.0%	42.3%
Hypertension	47.6%	46.1%

* According to the C3PO there were 6 patients lost to follow-up after randomization: 4 in the placebo group and 2 in the ramipril group.

Table 1. Demographics and baseline characteristics (continued)

	Ramipril (N=4645)	Placebo (N=4652)
Documented elevated total cholesterol level	65.4%	66.4%
Documented low HDL cholesterol level	18.1%	18.9%
Current cigarette smoking	13.9%	14.5%
Medications		
Beta blockers	39.2%	39.8%
Aspirin or antiplatelet agents	75.3%	76.9%
Lipid-lowering agents	28.4%	28.8%
Diuretics	15.3%	15.2%
Calcium-channel blockers	46.3%	47.9%
Left ventricular hypertrophy on electrocardiography	8.2%	8.7%
Diabetes	38.9%	38.0%
Microalbuminuria	20.5%	21.6%

Protocol Violations/Deviations:
Protocol violations/deviations were not mentioned in the protocol or any of the manuscripts.

According to the DSMB minutes, "procedural deficiencies" were noted in 2 centers, and "protocol violations" were noted in center 6. However, according to the C3PO, no centers were excluded because of protocol violations. Also, excluding center 6 did not affect the analysis and results, according to the reviewers' analysis.

Six randomized patients, 4 to placebo ramipril and 2 to ramipril, were noncompliant during the run-in period and therefore did not meet that eligibility criterion. *
One patient (ID #823124), randomized to the ramipril treatment group, had a rise in potassium during the run-in period and was therefore ineligible on that basis.

Concomitant Therapies:
Information concerning selected concomitant therapies was collected at randomization, at the 2 year visit, and at the penultimate visit. As noted above, the two groups were evenly distributed regarding the use of beta blockers, aspirin/antiplatelet agents, lipid-lowering agents, diuretics, and calcium channel blockers.

Eight patients (3 in the placebo ramipril and 5 in the active ramipril group) had no history of diabetes but were on oral hypoglycemic agents.

* Data regarding patient eligibility were generated from analysis of the visit 2 database provided by the sponsor.

One patient (ID #162141) on placebo ramipril had no history of diabetes but was on insulin.
Two patients (ID #3018062, 903204) on active ramipril had no history of diabetes but were on insulin.*
The above table lists concomitant medications at randomization. Other concomitant medications for ramipril and placebo at randomization included:

Table 2. Other concomitant medications—baseline

Medication	Ramipril (N=4645) n	Placebo (N=4652) n
Estrogen	115	151
Vitamin C	280	257
Beta carotene	61	62
Multivitamins	331	323
Alcohol	1842	1870

This table was generated by the reviewer from the visit 2 and treatment group databases.

At the two year visit, concomitant medications were as follows:
Table 2.1. concomitant medications—2 year visit

Medication	Ramipril (N=4645) n	Placebo (N=4652) n
Beta blockers	1733	1731
Aspirin	3151	3171
Oral anticoagulants	252	222
Diuretics	833	757
Nitrates	1299	1362
Cholesterol-lowering drugs	1704	1716
Diltiazem/verapamil	1033	1075
Other calcium channel blockers	988	895
Estrogen	144	144
Folate		25
Vitamin C	267	228
Multivitamins	304	289
Nonsteroidal anti-inflammatory drugs	278	302
Alcohol	1644	1560
Beta carotene	40	38
If diabetic:* Insulin	584	556
Oral hypoglycemic agents	979	959

*For baseline diabetic treatment please see table 18.
This table was generated by the reviewer from the visit 5 and treatment group databases.

* These data were generated from analysis of the visit 2 database provided by the sponsor.

At the penultimate visit, concomitant medications were as follows:

Table 2.2. Concomitant medications—penultimate visit

Medication	Ramipril (N=4099) n	Placebo (N=4047) n
Beta blockers	1565	1764
Aspirin	2807	2863
Antiplatelet agents	256	277
Oral anticoagulants	294	286
Diuretics	816	942
Nitrates	1100	1184
Cholesterol lowering drugs	2048	2022
Diltiazem/verapamil	806	808
Other calcium channel blockers	894	928
Estrogen replacement	100	132
Folate	90	102
Vitamin C	257	242
Beta Carotene	52	32
Insulin	614	591
Oral hypoglycemic agents	916	950
Nonsteroidal anti-inflammatory agents	253	237
Alcohol	1416	1401

This table was generated by the reviewer from the penultimate visit and treatment group databases.

Compliance:

Compliance was defined on the CRF as the patient taking at least 75% of study drug. The following table was generated from the visit and treatment group databases.

Table 3. Compliance

	1 year (visit 5)	2 year (visit 7)	3 year (visit 9)	4 year (visit 11)	Final visit
Ramipril group					
N	4580	4645	4364	3957	4188
Compliance > 75%	3788 (82.7%)	3580 (77.1%)	3270 (74.9%)	2848 (72.0%)	2870 (68.5%)
On 10 mg ramipril	3766 (82.2%)*	3488 (75.1%)	3103 (71.1%)	2705 (68.4%)	2705 (65.0%)
Ramipril stopped	665 (14.5%)	756 (16.3%)	996 (22.8%)	1040 (26.3%)	1235 (29.5%)
Ramipril dose changed**	149	N/A	N/A	N/A	N/A
Using nonstudy ACE inhibitor	101 (2.2%)	241 (5.2%)	259 (5.9%)	307 (7.8%)	401 (9.6%)
Using A2 antagonist	N/A	28 (0.6%)	36 (0.8%)	59 (1.5%)	68 (1.6%)
Placebo group					
N	4578	4652	4331	3897	4104
Using nonstudy ACE inhibitor	153 (33.4%)	217 (4.7%)	348 (8.0%)	418 (10.7%)	504 (12.3%)
Using A2 antagonist	N/A	22 (0.5%)	48 (1.1%)	58 (1.5%)	79 (1.9%)

* no separate entry. Number derived from: [total N- (n with dose change + n where ramipril stopped)] divided by total N. That result was multiplied by 100 to arrive at a percentage.
**This check box was only present at the 1 year visit.

For drug discontinuation and reasons for stopping please see Safety Data.

Efficacy:

Primary clinical outcomes

The primary efficacy endpoint is the composite endpoint of cardiovascular death, myocardial infarction and stroke. Table 4 summarizes the comparisons of the two treatment groups on the primary clinical outcomes. Ramipril gave a statistically significant reduction in the incidence of cardiovascular death, MI and stroke and the incidence of all-cause death, MI and stroke. The effect of ramipril on each component event is consistent with that on the composite endpoint.

In 106 deaths, there were differences between the database report and the Events Adjudication Committee (e. g. the database reported a death as "MI" where the Event Adjudication Committee reported the same death as "non-cardiovascular" or the event was classified as "non-cardiovascular" but the Event Adjudication Committee reported the death as "cardiovascular"). The reviewer's analysis of the composite endpoint using the primary cause of death as classification criterion give the results almost identical to that of the composite endpoint using the adjudicated events.

Table 4. Incidence of primary and related component outcomes

	Ramipril (N=4645)	Placebo (N=4652)	Hazard ratio (95% CI)	p-value
Cardiovascular death, MI, Stroke	651 (14.0%)	826 (17.8%)	0.78 (0.70, 0.86)	0.0001
Cardiovascular death	282 (6.1%)	377 (8.1%)	0.74 (0.70, 0.90)	0.0002
Myocardial Infarction	459 (9.9%)	570 (12.3%)	0.80 (0.70, 0.90)	0.0003
Stroke	156 (3.4%)	226 (4.9%)	0.68 (0.56, 0.84)	0.0002
Noncardiovascular death	200 (4.3%)	192 (4.1%)	1.03 (0.85, 1.26)	0.74
All-cause death	482 (10.4%)	569 (12.2%)	0.84 (0.75, 0.95)	0.005
All-cause death, MI, Stroke	822 (17.7%)	992 (21.3%)	0.81 (0.74, 0.89)	0.0001

Mortality data:

The next table provides a breakdown of the primary cause of death, as classified in the database.

Table 5. All cause deaths: Primary cause of death

Event	Ramipril n	Placebo n
MI	84	111
Stroke	33	49
Ventricular tachyarrhythmia	17	24
Other sudden cardiac death	68	88
Worsening CHF	26	34
Pulmonary embolus	6	6
Other embolism	--	1

Table 5. Primary cause of death (continued)

	Ramipril n	Placebo n
Other cardiovascular	52	59 (+2)*
Amputation-related	2	1
Ketoacidosis	--	2
Nephropathy/Renal failure	1	2
Cancer	112	108
Other non-CV	81	82
Totals	482	569

This table was generated from the death and treatment databases.
*Two patients in the placebo group (ID # 6583237, 3199109) did not have listed more specific primary causes of death. These patients were coded as "cardiovascular deaths" and are, therefore, entered into the "other cardiovascular" category.

Myocardial Infarction:

The following table lists data obtained from the MI database, obtained from the MI event sheets (unadjudicated). Note that these numbers represent numbers of events, not numbers of patients.

Table 6. Myocardial Infarction by treatment

	Ramipril	Placebo
Symptoms (present)	383	472
Thrombolytic therapy	112	143
If unknown	14	24
ECG done	453	540
Anterior Q waves*	83	114
Anterolateral Q waves*	12	14
Lateral Q waves*	10	14
Inferior Q waves*	11	12
New Bundle Branch Block	21	37

This table was generated from the Myocardial Infarction Event database provided by the sponsor.
*These categories are not mutually exclusive (e.g., patient ID #557063 had both anterolateral and lateral Q waves on ECG).

Secondary and other clinical outcomes

Table 7. Incidence of secondary outcomes and other outcomes

	Ramipril (N=4645)	Placebo (N=4652)	Hazard ratio* (95% CI)	p-value*
Secondary outcomes				
Revascularization	743 (16.0%)	854 (18.4%)	0.86 (0.78, 0.95)	0.002
Hospitalization for unstable angina	554 (11.9%)	567 (12.2%)	0.98 (0.87, 1.10)	0.67
Hospitalization for heart failure	141 (3.0%)	161 (3.5%)	0.86 (0.69, 1.08)	0.20
Other outcomes (not prespecified)				
Cardiac arrest	37 (0.8%)	59 (1.3%)	0.62 (0.41, 0.94)	0.024
Heart failure**	417 (9.0%)	534 (11.5%)	0.77 (0.68, 0.87)	0.0001
Worsening angina$	1010 (21.7%)	1117 (24.0%)	0.88 (0.81, 0.96)	0.005
Hospitalization for unstable angina with ECG changes	175 (3.8%)	180 (3.9%)	0.97 (0.79, 1.19)	0.76

*All deaths are censored at the time of death

** This was a checkbox at every visit on the CRF

$ Worsening angina was defined a check box on the Unstable Angina Event Form next to the question "Was it increasing in severity or frequency?"

New Diagnosis of Diabetes
(not a prespecified endpoint)

There is a box in the randomization, 1 year follow-up, 2 year follow-up, 3 year follow-up, 4 year follow-up, 5 year follow-up, and penultimate forms for checking to indicate whether a patient is diabetic. Based on these data, the following table is constructed to summarize the new diabetes in the patients who did not have diabetes at baseline. There were a total of 257 new diabetic cases. Ramipril appeared to yield a greater reduction in the incidence of new diabetes. Of the 257 new diabetic cases, only 35 had primary clinical outcomes (cardiovascular death, MI, stroke). The correlation between development of new diabetes and primary clinical outcomes is almost zero. The correlation between time to new diabetes and time to primary clinical outcomes is < 0.15. Both treatment groups show the same correlation pattern. Therefore, new diagnosis of diabetes is an endpoint independent of the primary clinical outcome in the patients who did not have diabetes at baseline. This makes interpretation of the nominal p-value of new diabetes difficult.

Table 8. Incidence of new diagnosis of diabetes in patients who did not have diabetes at baseline

	Ramipril (N=2837) n (%)	Placebo (N=2883) n (%)	Hazard ratio* (95% CI)	p-value*
New diagnosis of diabetes	102 (3.6%)	155 (5.4%)	0.66 (0.51, 0.85)	0.001

*All deaths are censored at the time of death

By vitamin E results

The beneficial effects of ramipril in reducing the incidence of the composite events appear to be similar between vitamin E and no vitamin E strata (Table 9).

Table 9. Incidence of primary outcome by vitamin E stratification

	Ramipril n (%)	Placebo n (%)	Hazard ratio (95% CI)	p-value
Vitamin E group				
Cardiovascular death, MI, Stroke	338 (14.5%)	421 (18.2%)	0.76 (0.66, 0.89)	0.0003
All-cause death, MI, Stroke	424 (18.2%)	497 (21.5%)	0.83 (0.73, 0.95)	0.006
No Vitamin E group				
Cardiovascular death, MI, Stroke	313 (13.5%)	405 (17.3%)	0.79 (0.68, 0.91)	0.0009
All-cause death, MI, Stroke	398 (17.2%)	495 (21.1%)	0.79 (0.70, 0.91)	0.0006

Subgroup results

Listed below is a subgroup analysis of the primary endpoint. At first glance, ramipril does not appear to be effective in the Black or Asian subgroup. However, the numbers (both N and incidence of the primary endpoint) are small relative to the study population. Given the hazard ratio and the wide confidence interval, the reviewers cannot make conclusive statements regarding these two subgroups.
Otherwise, there was no evidence that the effect of ramipril is inconsistent across the subgroups.

Table 10. Incidence of primary endpoint by baseline subgroups

	Ramipril		Placebo		Hazard ratio
	N	%	N	%	(95% CI)
Gender					
Male	3366	15.0%	3451	18.8%	0.78 (0.70, 0.88)
Female	1279	11.3%	1201	14.9%	0.76 (0.61, 0.94)
Ethnic group					
Caucasians	4168	14.1%	4175	18.1%	0.77 (0.69, 0.85)
Hispanics	264	11.0%	269	14.9%	0.71 (0.44, 1.15)
Asians	81	14.8%	74	12.2%	1.14 (0.48, 2.71)
Blacks	75	18.7%	66	12.2%	1.59 (0.66, 3.79)
Natives	16	20.8%	24	20.8%	0.60 (0.12, 3.10)
Others	41	14.6%	44	22.7%	0.64 (0.23, 1.77)
Age					
< 65 yrs	2055	11.9%	2114	14.2%	0.83 (0.70, 0.98)
≥ 65 yrs	2590	15.7%	2538	20.7%	0.74 (0.65, 0.84)
BMI					
< median (27.2)	2350	13.7%	2308	17.6%	0.76 (0.66, 0.88)
≥ median (27.2)	2295	14.4%	2344	17.9%	0.79 (0.69, 0.91)
Cardiovascular disease	4032	14.9%	4130	18.7%	0.78 (0.70, 0.87)
Yes	613	8.2%	522	10.2%	0.81 (0.55, 1.19)
No					
Coronary artery disease	3691	15.0%	3786	18.6%	0.79 (0.71, 0.88)
Yes	954	10.3%	866	14.2%	0.72 (0.55, 0.93)
No					

Table 10. Incidence of primary endpoint by baseline subgroups (continued)

	Ramipril		Placebo		Hazard ratio
	N	%	N	%	(95% CI)
Prior myocardial infarction					
Yes	2410	16.8%	2482	20.9%	0.78 (0.69, 0.89)
No	2235	11.1%	2170	14.2%	0.77 (0.65, 0.91)
Angina					
Yes	2921	14.7%	2990	18.1%	0.80 (0.70, 0.91)
No	1724	12.8%	1662	17.2%	0.74 (0.62, 0.88)
Cerebrovascular disease					
Yes	500	19.6%	513	25.9%	0.75 (0.57, 0.97)
No	4145	13.3%	4139	16.7%	0.78 (0.70, 0.88)
Peripheral vascular disease					
Yes	1859	17.1%	1969	22.4%	0.74 (0.64, 0.85)
No	2786	12.0%	2683	14.4%	0.83 (0.72, 0.96)
Hypertension					
Yes	2212	14.7%	2143	19.5%	0.75 (0.65, 0.86)
No	2433	13.4%	2509	16.3%	0.80 (0.70, 0.93)
Diabetes					
Yes	1808	15.3%	1769	19.8%	0.75 (0.64, 0.88)
No	2837	13.2%	2883	16.5%	0.79 (0.69, 0.90)
Microalbuminuria					
Yes	952	19.5%	1004	26.4%	0.71 (0.59, 0.86)
No	3693	12.6%	3648	15.4%	0.81 (0.72, 0.92)

Results by baseline concomitant medication

The effect of ramipril in reduction of incidence of the primary events seemed to be smaller in patients who took aspirin (p=0.002) and patients who took aspirin or other antiplatelet agents (p = 0.016) , compared to patients who did not.

Table 11. Incidence of primary endpoint by baseline medication

	Ramipril		Placebo		Hazard ratio
	N	%	N	%	(95% CI)
Beta blockers					
Yes	1820	14.2%	1853	18.2%	0.77 (0.65, 0.90)
No	2825	13.9%	2799	17.4%	0.78 (0.68, 0.89)

Table 11. Incidence of primary endpoint by baseline medication (continued)

	Ramipril		Placebo		Hazard ratio
	N	%	N	%	(95% CI)
Aspirin or other antiplatelet agents	3497	14.9%	3577	17.7%	0.83 (0.74, 0.93)
Yes	1148	11.3%	1075	18.1%	0.61 (0.49, 0.76)
No					
Aspirin					
Yes	3368	14.9%	3445	17.3%	0.85 (0.76, 0.96)
No	1277	11.6%	1207	19.1%	0.59 (0.48, 0.72)
Diuretics					
Yes	713	17.7%	706	23.2%	0.75 (0.59, 0.94)
No	3932	13.4%	3946	16.8%	0.78 (0.70, 0.88)
Channel calcium blockers	2152	16.3%	2228	19.0%	0.85 (0.73, 0.97)
Yes	2493	12.1%	2424	16.6%	0.71 (0.61, 0.83)
No					

The aspirin results are consistent with literature reports of decreased ACE inhibitor efficacy with concomitant aspirin therapy.[8] It should however, be noted that there was a risk reduction in the ramipril group even with aspirin. Also, this study was not designed to specifically assess effects with and without aspirin.
Otherwise, there is no evidence that the effect of ramipril is inconsistent with and without the above medications.

Geographic Differences

In most countries, the N is too small to make meaningful conclusions.

Table 12. Incidence of primary endpoint by country

	Ramipril		Placebo		Rampril minus
	N	%	N	%	placebo (%)
Canada	2727	13.8	2737	18.9	-5.1
United-States	399	13.8	399	15.3	-1.5
Austria	14	35.7	13	7.7	28.0
Belgium	76	6.6	79	11.4	-4.8
Denmark	39	12.8	38	26.3	-13.5
Finland	31	19.4	30	26.7	-7.3
France	8	0	7	0	0

Table 12. Incidence of primary endpoint by country (cont'd.)

	Ramipril		Placebo		Rampril minus placebo (%)
	N	%	N	%	
Germany	81	13.6	76	5.3	8.3
Netherlands	63	6.3	64	18.8	-12.4
Italy	202	12.4	196	10.2	2.2
Norway	28	32.1	28	14.3	17.9
Spain	40	15.0	37	13.5	1.5
Sweden	280	16.8	282	21.3	-4.5
Switzerland	33	9.1	33	9.1	0
UK/Ireland	104	19.2	104	26.0	-6.7
Argentina	130	13.1	133	12.8	0.3
Brazil	230	16.5	236	19.9	-3.4
Mexico	160	11.9	160	12.5	-0.6

Table 13. Incidence of primary endpoint by region

	Ramipril		Placebo		Rampril minus placebo (%)
	N	%	N	%	
Canada	2727	13.8	2737	18.9	-5.1
United-States	399	13.8	399	15.3	-1.5
Europe	999	14.6	987	16.5	-1.9
South America	360	15.3	369	17.3	-2.1
Mexico	160	11.9	160	12.5	-0.6

Primary clinical outcomes in Canada and US

Table 14. Incidence of primary endpoint in Canada versus US

	Ramipril		Placebo		Rampril minus placebo (%)	Hazard ratio (95% CI)
	N	%	N	%		
Canada	2727	13.8	2737	18.9	-5.1	0.71 (0.62, 0.81)
United-States	399	13.8	399	15.3	-1.5	0.91 (0.63, 1.31)

Canada numerically appears to show a greater ramipril effect.

Since the United States population was 83.0 % White, 12.6% Black, and 3.6% Asian/Pacific Islander (in July, 1995),[9] could the differences between Canada and the United States be explained by differences in demographic composition?

The following table was done to address this question:

Table 15. Incidence of primary endpoint in whites

	Ramipril		Placebo		Rampril minus placebo (%)	Hazard ratio (95% CI)
	N	%	N	%		
Canada	2609	13.7	2626	18.9	-5.2	0.71 (0.62, 0.81)
United-States	329	12.8	334	15.6	-2.8	0.83 (0.55, 1.24)

One cannot explain the apparent difference between Canada and the United States on the basis of demographic differences.

Baseline characteristics of canadian region and noncanadian region

Table 16. Incidence of primary events in canada versus in other regions

	Ramipril		Placebo		Hazard ratio (95% CI)
	N	%	N	%	
Canada	2727	13.8%	2737	18.9%	0.71 (0.62, 0.81)
Other regions	1918	14.3%	1915	16.1%	0.89 (0.75, 1.04)

Other regions are defined as: US, Europe, South America and Mexico.

The effect of ramipril in reduction of the primary endpoint appears to be greater in canada than in other regions. From the following table, there appears to be a small difference in the baseline characteristics of the patient populations in canada and other regions.

Table 17. Baseline characteristics

	U.S., Europe, South America, Mexico		Canada	
	Ramipril (N=1918)	Placebo (N=1915)	Ramipril (N=2727)	Placebo (N=2737)
Gender				
Male	69.3%	71.1%	74.7%	76.4%
Female	30.7%	28.9%	25.3%	23.6%
Age (in yr)	66±7	66±7	66±7	66±7
SBP/DBP (in mm Hg)	142±20/82±11	143±20/82±11	136±19/77±10	136±19/77±10
Heart rate (in bpm)	70±12	71±11	67±11	67±11
Body mass index	28±4	28±4	28±4	28±4
History of cardiovascular disease	82.3%	85.5%	90.0%	91.1%
History of coronary artery disease	70.9%	75.0%	85.5%	85.8%
Myocardial infarction	45.2%	48.6%	56.6%	56.7%
Within ≤ 1 year	9.5%	9.7%	9.9%	9.5%
Within > 1 year	35.7%	39.0%	46.7%	47.1%
Stable angina	43.9%	45.1%	62.4%	64.1%
Unstable angina	17.6%	17.4%	30.9%	31.2%
CABG	23.9%	24.0%	26.9%	27.3%
PTCA	17.5%	16.8%	19.0%	17.7%
Stroke or transient ischemic attacks	11.9%	11.6%	10.0%	10.6%
Peripheral vascular disease	38.7%	40.4%	41.0%	43.7%
Hypertension	53.6%	52.1%	43.5%	41.8%
Documented elevated total cholesterol level	69.5%	70.2%	62.5%	63.8%
Documented low HDL cholesterol level	18.4%	19.1%	17.9%	18.9%

Table 17. Baseline characteristics (continued)

	U.S., Europe, South America, Mexico		Canada	
	Ramipril (N=1918)	Placebo (N=1915)	Ramipril (N=2727)	Placebo (N=2737)
Current cigarette smoking	13.6%	14.3%	14.1%	14.7%
Medications				
Beta blockers	35.0%	34.9%	42.1%	43.3%
Aspirin or antiplatelet agents	69.7%	72.4%	79.2%	80.0%
Lipid-lowering agents	26.5%	26.8%	29.7%	30.2%
Diuretics	20.2%	17.4%	12.0%	13.6%
Calcium-channel blockers	42.2%	43.7%	49.2%	50.9%
Left ventricular hypertrophy on electrocardiography	10.5%	10.9%	6.5%	7.2%
Diabetes	45.1%	44.7%	34.6%	33.4%
Microalbuminuria	26.3%	28.9%	16.4%	16.4%

Efficacy: Vitamin E vs. placebo:

There were no statistically significant benefits in the primary composite endpoint or its components in the Vitamin E group compared to placebo (mean follow-up period of 4.5 years). In fact, there appeared to be slight, nonsignificant but consistent increases in events (composite outcome, MI, stroke, CV death) in the Vitamin E group compared to placebo. The all-cause mortality was approximately equal between the two groups. The occurrence of heart failure appeared to be significantly higher (p=.02) in the Vitamin E group compared to placebo. The reviewers are unable to fully interpret these findings.

Diabetes Substudy:

Baseline characteristics of diabetic subgroup

The two treatment groups appeared to be well balanced at baseline (Table 18).

Table 18. Baseline characteristics of diabetes patients

	Ramipril (N=1808)	Placebo (N=1789)
Gender		
Male	62%	65%
Female	38%	35%
Age (in yr)	66±6	66±7
SBP/DBP (in mm Hg)	142±20/80±11	142±20/79±11
Heart rate (in bpm)	72±11	73±11
Body mass index	29±5	29±5
Waist circumferences	100±13	100±12
Waist/hip ratio	0.93±0.09	0.93±0.08
HbA1c (%)*	123 ±30	125 ± 32
Serum creatinine (μmol/l)	93.8 ± 22.3	94.0 ± 27.6
Duration of diabetes	11.1±10.2	11.8±10.7
Microalbuminuria	30.6%	32.8%
Type II diabetes**	98.1%	97.3%
History of cardiovascular disease	33.4%	28.8%
History of coronary artery disease	57.9%	61.1%
Stroke	8.5%	11.0%
Peripheral vascular disease	41.7%	46.3%
Hypertension	57.8%	53.8%
Documented elevated total cholesterol level	64.9%	65.6%
Current cigarette smoking	15.2%	15.3%
Medications		
Beta blockers	28.2%	28.6%
Aspirin	54.3%	55.8%
Lipid-lowering agents	22.6%	22.1%
Diuretics	19.4%	19.8%
Calcium-channel blockers	42.9%	45.3%
Insulin therapy alone	23.9%	26.9%
Oral hyperglycemic control agents alone	52.9%	50.0%
Insulin plus oral hyperglycemic agents	4.9%	5.1%
Dietary therapy alone	18.3%	16.8%

*presented as percentage over the upper limit of normal for the local laboratory.
**defined according to the manuscript: age of onset ≥ 30 years or not on insulin.

Based on the above data, it can be said with confidence that 71.2% of the ramipril group, and 66.8 % of the placebo group had non-insulin dependent diabetes (type II). An imbalance between the two groups cannot be excluded regarding type I and type II diabetes.

Compliance:

The following table for the diabetic subgroup was generated from the visits and treatment databases (those with diabetes at baseline).

Table 19. Compliance in the diabetic group

	1 year (visit 5)	2 years (visit 7)	3 years (visit 9)	Final visit
Ramipril				
N	1782	1736	1694	1623
>75% compliance	1435 (80.5%)	1314 (75.7%)	1200 (70.8%)	1038 (64.0%)
Ramipril 10 mg QD	1438 (80.7%)*	1265 (72.9%)	1161 (68.5%)	991 (61.1%)
Ramipril stopped	290	379	460	558
Ramipril dose changed	54	N/A	N/A	N/A
Using nonstudy ACE inhibitors	55 (3.1%)	113 (6.5%)	152 (9.0%)	228 (14.0%)
Using A2 antagonists	N/A	14 (0.8%)	18 (1.1%)	43 (2.6%)
Placebo				
N	1735	1687	1618	1528
Using nonstudy ACE inhibitors	68 (3.9%)	141 (8.3%)	185 (11.4%)	268 (17.5%)
Using A2 antagonists	N/A	15 (0.9%)	24 (1.5%)	43 (2.6%)

*This value was calculated from { [N-(ramipril stopped + ramipril dose changed)] /N} x 100

Primary and Secondary Outcomes:

The following tables and data were generated in order to address "primary and secondary research questions" listed in the protocol under Specific Objectives related to Diabetes.

Primary outcome

(predefined composite endpoint)-- as shown below and in Table 10.

Incidence of primary endpoint (from Table 10)

	Ramipril		Placebo		Hazard ratio
	N	%	N	%	(95% CI)
Cardiovascular death, MI, stroke	277	(15.3%)	351	(19.8%)	0.75 (0.64, 0.88)

Because female diabetics were defined in the protocol as being at increased risk, the following subgroup analysis was done:

Table 20. Incidence of primary outcomes in female diabetics

	Ramipril		Placebo		Hazard ratio
	N	%	N	%	(95% CI)
Female diabetics patients	696	12.5%	626	16.1%	0.77 (0.58, 1.02)
Others	3949	14.3%	4026	18.0%	0.78 (0.70, 0.87)

Secondary and other clinical outcomes:

According to the protocol, a "secondary question" related to the study objectives was whether an ACE inhibitor decreases the occurrence of other significant cardiovascular events, total cardiovascular mortality or total mortality. "Other significant cardiovascular events" was not further defined; the reviewers addressed this question with the table below.

Cardiovascular outcomes

Table 21. Incidence of cardiovascular outcomes

	Ramipril (N=1808)	Placebo (N=1769)	Hazard ratio* (95% CI)	nominal p-value*
Cardiovascular death, MI, Stroke	277 (15.3%)	351 (19.8%)	0.75 (0.64, 0.88)	0.0004
Cardiovascular death	112 (6.2%)	172 (9.7%)	0.63 (0.49, 0.79)	0.0001
Myocardial Infarction	185 (10.2%)	229 (12.9%)	0.78 (0.64, 0.94)	0.01
Stroke	76 (4.2%)	108 (6.1%)	0.67 (0.50, 0.90)	0.0074
All-cause death	196 (10.8%)	248 (14.0%)	0.76 (0.63, 0.92)	0.004
Revascularization	255 (14.1%)	292 (16.5%)	0.84 (0.71, 0.99)	0.037
Hospitalizations for unstable angina	213 (11.8%)	208 (11.8%)	0.99 (0.82, 1.20)	0.92
Hospitalizations for heart failure	81 (4.5%)	79 (4.5%)	0.97 (0.71, 1.33)	0.87

*All deaths are censored at the time of death

Glycated Hb response profile

According to the Lancet article, HbA_{1C} was reported as percentage above upper limit of normal for local laboratory. To explore whether ramipril improves glucose control, the percentages of HbA_{1C} above upper limit of normal were computed at baseline and at post-randomization all visits when the measurements are available. Mean change from baseline in this percentage was then computed for the two treatment groups. The Lancet article reports adjusted mean changes which were obtained using ANCOVA with HbA_{1C} as the covariate. These results are confirmed by the reviewer as given in the followint table. Numerically, ramipril appeared to have a better glucose control in the first two years and seemingly become worse than placebo after that. The p-values in the table are nominal p-value which are difficult to interpret because of testing for multiple visits. In our view, no statistical conclusion can be drawn for potential beneficial effect of ramipril on glucose control.

Table 22. Adjusted[$] mean changes from baseline in HbA_{1C} over the visits

	Ramipril		Placebo		p-value
	N	change	N	change	
1 year	1592	1.5%	1557	3.4%	0.04
2 year	1524	-0.1%	1489	2.2%	0.02
3 year	1444	2.4%	1385	0.8%	0.26
4 year	1252	2.1%	1207	1.2%	0.34
5 year	84	0.2%	73	4.1%	0.27
penultimate	1006	3.2%	967	2.5%	0.54

$ adjusted mean changes were generated using ANCOVA with baseline HbA_{1C} as the covariate

Renal outcomes

According to the protocol, overt nephropathy was defined as patient with ≥ 1+ proteinuria on dipstick or urine albumin excretion > 200 microgram/min (or 300 mg/24 hours). In the reviewers' analysis, patients who had ≥ 1+ proteinuria reported at at least one of the yearly visits or urine albumin excretion > 200 microgram/min (or 300 mg/24 hours) reported in urine 24 hours database were identified as those having overt nephropathy. The results are presented in the following table. The Lancet article presents three definitions of overt nephropathy, all of which are quite different from the protocol definition. The best p-value (p = 0.083) from the Lancet definitions for overt nephropathy was based on the definition of "develop an albumin/creatinine ratio of more than 36 mg/mmol if no 24 hour urine result available or have 24 hour protein excretion ≥ 500 mg or 24 hour urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours)". The result using this definition is also included in the table. There is no evidence that ramipril reduces the incidence of overt nephropathy, renal dialysis, need for laser therapy, microalbuminuria, or doubling creatinine at any post-randomization visit.

Table 23. Incidence of renal outcome/laser therapy endpoints

	Ramipril (N=1808)	Placebo (N=1769)	Hazard ratio* (95% CI)	nominal p-value*
Overt nephropathy[$]	122 (6.8%)	110 (6.2%)	1.07 (0.83, 1.39)	0.60
Overt nephropathy[@]	122 (6.8%)	151 (8.5%)	0.81 (0.63, 1.03)	0.083
Renal dialysis[#]	10 (0.6%)	8 (0.5%)	1.20 (0.47, 3.05)	0.70
Laser therapy[#]	170 (9.4%)	186 (10.5%)	0.88 (0.72, 1.09)	0.24
Microalbuminuria[&]	431 (23.8%)	451 (25.5%)	0.92 (0.80, 1.05)	0.22
Doubling creatinine from baseline at any visit after randomization[!]	40 (2.2%)	28 (1.6%)	1.35 (0.83, 2.19)	0.23

[$] according to protocol definition: ≥ 1+ proteinuria reported in at least one of the yearly visits or urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) reported in urine 24 hours database

[@] develop an albumin/creatinine ratio of more than 36 mg/mmol if no 24 hour urine result available or have 24 hour protein excretion ≥ 500 mg or 24 hour urine albumin excretion ≥ 200 micrograms/min (or ≥ 300 mg / 24 hours) [used in the Lancet article]

[#] from check box on case report form [also used in the Lancet article]

[&] definition provided by the HOPE group

[!] derived from the boxes on case report form

*All deaths are censored at the time of death

Composite endpoints:

The Lancet article presents the results on incidence of composite endpoint of overt nephropathy, renal dialysis, or need for laser therapy. In the reviewers' analyses, several composite renal and microvascular endpoints are examined as shown in the following table. Overt nephropathy was again analyzed using protocol definition and the Lancet definition that gives the best p-value. The results are quite different based on the definitions of overt nephropathy in term of nominal p-value and hazard ratio. In our view, there is no sufficient evidence to conclude that ramipril reduces the incidence of renal endpoints.

Table 24. Incidence of composite endpoints

	Ramipril (N=1808)	Placebo (N=1769)	Hazard ratio* (95% CI)	nominal p-value*
Overt nephropathy[$], laser therapy, renal dialysis	282 (15.6%)	281 (15.9%)	0.97 (0.82, 1.14)	0.70
Overt nephropathy[@], laser therapy, renal dialysis	278 (15.4%)	314 (17.8%)	0.86 (0.73, 1.01)	0.07
Overt nephropathy[$], laser therapy, renal dialysis, microalbuminuria	652 (36.1%)	672 (38.0%)	0.92 (0.83, 1.03)	0.16
Overt nephropathy[@], laser therapy, renal dialysis, microalbuminuria	657 (36.3%)	717 (40.5%)	0.87 (0.78, 0.98)	0.016
Overt nephropathy[$], laser therapy, renal dialysis, microalbuminuria, revascularization	814 (45.0%)	846 (47.8%)	0.91 (0.82, 1.00)	0.054
Overt nephropathy[@], laser therapy, renal dialysis, microalbuminuria, revascularization	814 (45.0%)	880 (49.8%)	0.87 (0.79, 0.96)	0.005

[$] according to protocol definition: ≥ 1+ proteinuria reported at at least one of the yearly visits or urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) reported in urine 24 hours database
[@] develop an albumin/creatinine ratio of more than 36 mg/mmol if no 24 hour urine result available or have 24 hour protein excretion ≥ 500 mg or 24 hour urine albumin excretion > 200 micrograms/min (or 300 mg / 24 hours) [used in the Lancet article]
[#] from check box on case report form [also used in the Lancet article]
[&] definition provided by the HOPE group
[!] derived from the boxes on case report form
*All deaths are censored at the time of death

Other prespecified secondary questions:
Information regarding limb amputation/foot infections is presented under Safety, Hospitalizations.

Outstanding issues regarding the design and/or analysis of this study are:

- Whether albumin excretion rate and/or albumin/creatinine ratio are valid surrogates for diabetic nephropathy.
- Also see Comments on Protocol.

SAFETY:

Safety data were collected as reasons for discontinuation of treatment/temporary interruption or treatment. In addition, there were event sheets for serious adverse events and hospitalizations.

Discontinuation from treatment

The following table summarizes the reasons for discontinuation of treatment in HOPE study patients.

Table 25. Discontinuation of treatment

	Ramipril (N=4645)	Placebo (N=4652)
Discontinuation at any time	1575 (33.9%)	1493 (32.1%)
Permanent discontinuation	1357 (29.2%)	1284 (27.6%)
Reasons for stopping		
Cough	339 (7.3%)	84 (1.8%)
Hypotension	87 (1.9%)	70 (1.5%)
Angioedema	15 (0.3%)	6 (0.1%)
Hypertension	109 (2.4%)	182 (3.9%)
Clinical events	306 (6.6%)	415 (8.9%)
Cancer	32 (0.7%)	32 (0.7%)
Fatigue	34 (0.7%)	27 (0.6%)
GI disorder	62 (1.3%)	50 (1.1%)
Headache	19 (0.4%)	23 (0.5%)
Nausea	19 (0.4%)	17 (0.4%)
Hospitalization	107 (2.3%)	118 (2.5%)
Physician advice	161 (3.5%)	156 (3.4%)
Non-study ACE-I use	42 (0.9%)	62 (1.3%)
Patient refusal	698 (15.0%)	645 (13.9%)
Other	139 (3.0%)	138 (3.0%)

The numbers in this table are constructed based on the SAS database provided by the sponsor.

The following table summarizes the reasons for discontinuation of treatment in diabetic patients.

Table 26. Discontinuation of treatment—diabetic subgroup

	Ramipril (N=1808)	Placebo (N=1769)
Discontinuation at any time	694 (38.4%)	676 (38.2%)
Permanent discontinuation	605 (33.5%)	597 (33.7%)
Reasons for stopping		
Cough	132 (7.3%)	36 (2.0%)
Hypotension	30 (1.7%)	24 (1.4%)
Angioedema	3 (0.2%)	1 (0.1%)
Hypertension	60 (3.3%)	100 (5.7%)
Clinical events	138 (7.6%)	170 (9.6%)
Cancer	12 (0.7%)	14 (0.8%)
Fatigue	7 (0.4%)	7 (0.4%)
GI disorder	24 (1.3%)	14 (0.8%)
Headache	10 (0.6%)	7 (0.4%)
Nausea	9 (0.5%)	6 (0.3%)
Hospitalization	56 (3.1%)	53 (3.0%)
Physician advice	72 (4.0%)	69 (3.9%)
Non-study ACE-I use	20 (1.1%)	32 (1.8%)
Patient refusal	314 (17.4%)	290 (16.4%)
Other	81 (4.5%)	84 (4.70%)

The numbers in this table are constructed based on the SAS database provided by the sponsor.

Serious adverse events:

According to the C3PO, the sites were to complete the serious adverse event form if a patient developed a serious, unexpected, drug-related adverse event. A serious adverse event database was included in this submission; these events were not adjudicated. Furthermore, the C3PO has informed the Agency that sites were not required to fill out serious adverse event forms in the case of cancer. Consequently, cancers may be under-represented in this table.

The following data were collected from the serious adverse event forms:

Table 27. Serious Adverse Events (AE)

Serious AE	Ramipril n	Placebo n
Required hospitalization	169	178
Prolonged hospitalization	11	17
Lifethreatening	41	24
Fatal	27	25
Cancer	54	35*

*Includes patient ID #9039505, on placebo, who had lung cancer but who was not coded under "cancer."

The following table lists selected serious adverse events (from the serious adverse events database).

Table 28. Selected/most common serious adverse events

Serious adverse event **	Ramipril n	Placebo n
Cough	16	9
Rash	--	4
Angioedema	5	1
Vertigo	5	2
Dizziness	9	4
Diarrhea	4	--
Headache	5	6
Nausea	5	2
Vertigo	5	2
Rash	--	4
Chest pain	28	32
Angina (including unstable angina)	34	37
MI	25	28
Congestive heart failure	11	7
Pulmonary edema	2	6
Pneumonia	3	4
Syncope/loss of consciousness	3	1
Atrial fibrillation	8	5
Cardiac arrest/sudden death	12	10
TIA	3	1
Stroke/CVA	10	15
Hypertension	2	5
Hypotension	2	3
Hyperkalemia	2	--
Renal failure	3	1
Hyperglycemia	1	--
Hypoglycemia	1	2
Neutropenia/leukopenia	1	1
Jaundice	2	2
Abnormal liver function	1	--
Pancreatitis	4	2
GI Bleeding	5	3

**These are not mutually exclusive.

Of the reported cancers, the following were the most common:

Table 29. Cancer occurrence by site

Cancer Site	Ramipril n	Placebo n
Prostate	10	8
Colorectal	9	1
Lung	5	7
Pancreas	4	1
Breast	3	1

This was generated from the serious adverse event database.

In the low dose Ramipril group, five serious adverse experiences were reported. These were: seizure, renal cancer, pulmonary edema/MI, unstable angina, and abdominal/chest pain.

Other Clinical Events:

Hospitalization:

The next table represents hospitalizations as events (i.e., one patient hospitalized twice would be counted as two events).

Table 30. Hospitalizations

Event	Ramipril	Placebo
All causes	5797	6195
Cardiovascular:		
Unstable angina	1067	1138
MI	510	626
Cardiac arrest	37	60
CHF	429	482
Cerebrovascular:		
Stroke	175	252
TIA	59	85
Revascularization:		
Peripheral angioplasty	152	175
CABG	339	423
PTCA	338	380
Carotid endarterectomy	66	74
Diabetes-related:		
Ketoacidosis	9	5
Hyperglycemia	89	106
Hypoglycemia	33	38
Nephropathy/Renal Failure	32	38
Limb/Foot infections	95	89

Table 30. Hospitalizations (continued)

Event	Ramipril	Placebo
Amputations	40	44
Other		
Pulmonary embolus	26	22
Cancer	408	398
Psychiatric	57	41
Genito-Urinary	265	274
Gastrointestinal	422	431
Hematologic	71	44

This table was generated from the hospitalization and treatment databases.

Summary of the findings of HOPE study

Main study

Ramipril significantly reduced the incidence of cardiovascular death, MI, and stroke and the incidence of all-cause mortality, MI, and stroke in "high risk" patients with vascular or coronary disease, or diabetes with at least one other cardiovascular risk factor (22% reduction, 95% CI: 14% to 30% reduction, p = 0.0001). The effect of ramipril on each component event of these composite endpoints appeared to be consistent with that on the composite endpoint.

The effect of ramipril on the primary outcome (cardiovascular death, MI and stroke) appeared to be similar between vitamin E and no vitamin E strata, across the baseline subgroups, or between with and without the baseline concomitant medications. The data suggest that the ramipril treatment gave a smaller effect in patients who took aspirin or other antiplatelet agents.

Ramipril appeared to significantly reduce revascularization, a prespecified secondary endpoint. Ramipril did not significantly reduce hospitalization for heart failure, a prespecified secondary endpoint, though it appeared to reduce incidence of heart failure, (not a prespecified endpoint). Similar observation was made for unstable angina.

Diabetes Substudy

As previously, ramipril also significantly reduced the incidence of cardiovascular death, MI, and stroke in diabetics (25%, 95% CI: 12% to 36% reduction, p = 0.0004). The effect of ramipril on each component event of this composite endpoint and total mortality appeared to be similar to that on the composite endpoint.

For renal and microvascular outcomes, most of the endpoints were not defined in the protocol, see Summary of Reviewer Comments on Protocol. We find that the results are highly dependent on how overt nephropathy is defined (see Tables 23 and 24). In our view, there is not sufficient evidence to conclude that ramipril reduces the incidences of overt nephropathy, renal dialysis, need for laser therapy, microalbuminuria, or their composite endpoints in this patient population. Nor can we conclude that ramipril improves glucose control (see Table 22).

References:

1. The Acute Infarction Ramipril Efficacy (AIRE) Study Investigators. Effects of ramipril on mortality and morbidity of survivors of acute myocardial infarction with clinical evidence of heart failure. Lancet 1993; 342: 821-828.
2. The Heart Outcomes Prevention Evaluation Study Investigators. Effects of an Angiotensin-Converting Enzymes Inhibitor, Ramipril, on Death from Cardiovascular Causes, Myocardial Infarction and Stroke in High-risk Patients. N Engl J Med 2000; 342:145-153.
3. The Heart Outcomes Prevention Evaluation Study Investigators. Vitamin E Supplementation and Cardiovascular Events in High Risk Patients. N Engl. J. Med 2000; 342: 154-160.
4. Heart Outcomes Prevention Evaulation Study Investigators. Effects of ramipril on cardiovascular and microvascular outcomes in people with diabetes mellitus: results of the HOPE study and MICRO-HOPE substudy. Lancet 2000; 355: 253-259.
5. Yusuf, S et al. Effect of enalapril on myocardial infarction and unstable angina in patients with low ejection fractions. Lancet 1992; 340: 1173-1178.
6. Pfeffer MA, Braunwald E, Moye LA et al. Effect of Captopril on Mortality and Morbidity in patients with Left Ventricular dysfunction After Myocardial Infarction. N Engl J Med 1992; 327: 669-677.
7. Gerstein HC et. al. Rationale and Design of a Large Study to Evaluate the Renal and Cardiovascular Effects of an ACE Inhibitor and Vitamin E in High-Risk Patients with Diabetes. Diabetes Care 1996; 19: 1225-1228.
8. Spaulding C, Charbonnier B, Cohen-Solal A, et. al. Acute Hemodynamic Interaction of Aspirin and Ticlopidine with Enalapril. Circulation 1998; 98:757-765.
9. Census data. http://www.census.gov/population/estimates/nation/intfile3-1.txt

Appendix A:

The primary endpoint was analyzed by censoring the noncardiovascular death at the time of death. The survived patients who did not have myocardial infarction or stroke were censored at the time of the last available visit. Because noncardiovascular death might be a potential competing risk for this composite endpoint, the reviewers also analyzed the composite endpoint of all-cause mortality, myocardial infarction and stroke. Table A-1 shows that the two treatment groups are well balanced with respect to the censoring distributions for both endpoints. Thus, the statistical comparison of ramipril with placebo with respect to the time to the first occurrence of the primary endpoint is valid.

Table A-1. Censoring distribution

	Cardiovascular death, MI, stroke		All-cause death, MI, stroke	
	Ramipril (N=4625)	Placebo (N=4652)	Ramipril (N=4625)	Placebo (N=4652)
# of censored cases	3994	3826	3823	3660
Mean	1573	1573	1603	1601
Standard deviation	208	204	126	126
Maximum	1919	1919	1919	1919
99th percentile	1887	1880	1887	1884
95th percentile	1822	1814	1827	1816
75th percentile	1675	1675	1680	1680
Median	1593	1596	1598	1599
25th percentile	1479	1477	1487	1487
5th percentile	1411	1411	1423	1423
1st percentile	523	589	1405	1409
Minimum	12	32	1292	1352

Shari L. Targum, M.D.

H. M. James Hung, Ph.D.

Concur: George Chi, Ph.D.

CC:
ORIG: NDA 19-901/S-028
HFD-110
HFD-110/CSO
HFD-110/Targum
HFD-110/Chen
HFD-710/Majoub
HFD-710/Hung
HFD-710/Chi