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					
Yes	3497	14.9%	3577	17.7%	0.83 (0.74, 0.93)
No	1148	11.3%	1075	18.1%	0.61 (0.49, 0.76)
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					
Yes	2152	16.3%	2228	19.0%	0.85 (0.73, 0.97)
No	2493	12.1%	2424	16.6%	0.71 (0.61, 0.83)

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.

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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

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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 [redacted], 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	Placebo
	n	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

/S/

Shari L. Targum, M.D.

/S/

H. M. James Hung, Ph.D.

/S/

Concar George Chi, Ph.D.

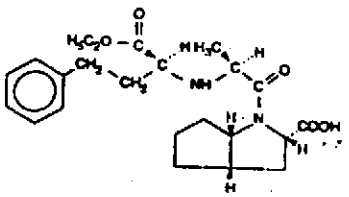
cc:
ORIG: NDA 19-901/S-028
HFD-110
HFD-110/CSO
HFD-110/Targum
HFD-110/Chen
HFD-710/Majoub
HFD-710/Hung
HFD-710/Chi

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-901/S-028

CHEMISTRY REVIEW

APR 2 0 2000

CHEMIST'S REVIEW	1. ORGANIZATION HFD-110	2. NDA Number 19-901
3. Name and Address of Applicant (City & State) King Pharmaceuticals, Bristol, TN 37620		4. Supplement(s) Number(s) Date(s) SE-028 1/14/00
5. Drug Name Altace Capsules	6. Nonproprietary Name ramipril	8. Amendments & Other (reports, etc.) - Dates S/A 2/17/00 S/A 3/9/00 S/A 3/27/00 For complete list (Non-CMC submissions) –check Doc/Rec.Card
7. Supplement Provides for: new indications for the use of Altace.		
9. Pharmacological Category An angiotensin-converting enzyme (ACE) for the treatment of Hypertension.	10. How Dispensed (√) Rx ( ) OTC	11. Related IND(s)/ NDA(s)/DMF(s):
12. Dosage Form: : Hard gelatin capsules	Potency(ies) 1.25, 2.50, 5.0 and 10.0mg/Capsules	
14. Chemical Name The CAS Registry Number is 87333-19-5. Ramipril's chemical name is (2*S*,3a*S*,6a*S*)-1[(*S*)-*N*-[(*S*)-1-Carboxy-3-phenylpropyl]alanyl]octahydrocyclopenta [*b*]pyrrole-2-carboxylic acid, 1-ethyl ester; its structural formula is: 		15. Records/Reports Current

Comments: This is a prior approval supplement. This is most importantly an efficacy supplement.

GENERAL CMC ASSESSMENT PERSPECTIVES: The applicant is not changing the manufacturing controls for this NDA 19-901/S-028 since there is no change in the use of the currently available strengths of the dosage formulation and there are no other formulation changes or related manufacturing changes. Hence, it is only necessary to evaluate certain of the review categories that are relevant. Only two critical review categories are relevant for CMC evaluation. one deals with the labeling (e.g., evaluation of the *How Supplied* section of the package insert and any other related labeling involved) and other is concerned with the potential need to include an environmental status update since there is the perceived question concerning whether or not there may be an increased production capacity involved. These two review aspects have been evaluated and found to be acceptable as noted under "Review Notes"..

)S-028(1-14-00)N19901

17. Conclusions and Recommendations: Consider that this supplement be approved from the standpoint of this discipline and recommend that the related labeling issue be resolved as given in the "Draft Letter" section of this review.

18. REVIEWER

Name	Signature	Date Completed
Stuart Zimmerman	/S/	4/12/00

Distribution: Original Jacket ( ) Reviewer ( ) Division File ( ) CSO ( )

/S/

4-20-00

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:
19-901/S-028

ADMINISTRATIVE DOCUMENTS

Patent and Exclusivity Information

Patent Information:

This Supplement (S-028) seeks approval of new indications as defined in 21CFR§314.53(d)(2)(B) for the product Altace (ramipril) Capsules. Pursuant to the requirements of 21CFR§314.53(a), please be advised that there are no new patents to declare that are relevant to the new indications listed within this supplement at this time. As previously declared to FDA, the patents listed below cover the composition and method of use of Altace, a product currently approved under section 505 of the Federal Food, Drug, and Cosmetic Act. These patents and their original declarations remain relevant to the product.

Patent Number	Assignee	Issue Date	Type	Expiry
US 5,061,722	Hoechst AG	10/29/91	Compound, use, composition	10/19/08
US 4,587,258	Schering Corporation	5/06/86	Compound, use, composition	1/27/05*

* This patent term has been extended for 632 days from the original expiration date of 5/06/03.

Exclusivity Information:

In accordance with the provisions of 21CFR§314.50(j), we request three (3) years of marketing exclusivity for the newly proposed indications. This Supplemental Application is supported by new clinical investigations that are essential to approval of the application. The results of the study are published in the *New England Journal of Medicine* (Volume 342, No. 3) in an article by the HOPE Study Investigators titled "Effects of an Angiotensin-Converting-Enzyme Inhibitor, Ramipril, on Cardiovascular Events in High-Risk Patients"; however, the study is based upon data to which King Pharmaceuticals, Inc. has acquired exclusive rights in the United States. We believe that the literature citations in this article, as well as other articles provided in this submission, adequately demonstrate that with the exception of the subject article, there is not sufficient basis for approval of the new indications for which we are seeking approval.

Further, and as required by 21CFR§314.50(j)(4)(iii), please be advised that King Pharmaceuticals, Inc., and our predecessor of interest, Hoechst-Marion Roussel, provided significant collective funding in support of this study as evidenced by the letter from Dr. Salim Yusuf included on the following page. The Canadian government also supported the study, but no public funding was obtained from the United States government. Additionally, ramipril was the single Angiotensin-Converting-Enzyme Inhibitor used in the entire study. King Pharmaceuticals, Inc. has acquired exclusive rights to the study data within the United States territory.

3/9/00
Date

Thomas K. Rogers, III
Vice President Regulatory Affairs
King Pharmaceuticals, Inc.

d) Did the applicant request exclusivity?

YES /___/ NO /✓/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

e) Has pediatric exclusivity been granted for this Active Moiety?

NO

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. Has a product with the same active ingredient(s), dosage form, strength, route of administration, and dosing schedule, previously been approved by FDA for the same use? (Rx to OTC switches should be answered NO-please indicate as such)

YES /___/ NO /✓/

If yes, NDA #_____. Drug Name _____.

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

3. Is this drug product or indication a DESI upgrade?

YES /___/ NO /✓/

IF THE ANSWER TO QUESTION 3 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /___/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /✓/ NO /___/

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /✓/ NO /___/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

_____

_____

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /✓/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /✓/

If yes, explain: _____

_____

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /✓/

If yes, explain: _____

_____

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

_____

_____

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES /__ / NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /___/ NO /✓/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

HOPE Study _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /✓/

If yes, explain: _____

_____

/S/

Signature
Title: Consumer Safety Officer Date 5/25/00

/S/

Signature of Office
Division Director Date 5/24/00

cc: Original NDA Division File HFD-93 Mary Ann Holovac

PEDIATRIC PAGE

(Complete for all original applications and all efficacy supplements)

: A new Pediatric Page must be completed at the time of each action even though one was prepared at ... time of the last action.

(NDA)/BLA # 19-901 Supplement # 028 Circle one: (SE1) SE2 SE3 SE4 SE5 SE6

HFD-110 Trade and generic names/dosage form: ALTACE (ramipril) Capsules Action: AP (AE) NA

Applicant King Pharmaceuticals, Inc. Therapeutic Class 10.2.2.101 ACE Inhibitors

Indication(s) previously approved Treatment for hypertension and heart failure post-myocardial infarct.

Pediatric information in labeling of approved indication(s) is adequate ___ inadequate ✓

Indication proposed in this application Prevention of myocardial infarction, stroke and death from cardiovascular causes.

FOR SUPPLEMENTS, ANSWER THE FOLLOWING QUESTIONS IN RELATION TO THE PROPOSED INDICATION.

IS THE DRUG NEEDED IN ANY PEDIATRIC AGE GROUPS? ___Yes (Continue with questions) ✓No (Sign and return the form)

IN WHAT PEDIATRIC AGE GROUPS IS THE DRUG NEEDED? (Check all that apply)

___Neonates (Birth-1month) ___Infants (1month-2yrs) ___Children (2-12yrs) ___Adolecents(12-16yrs)

___1. **PEDIATRIC LABELING IS ADEQUATE FOR ALL PEDIATRIC AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for all pediatric age groups. Further information is not required.

___2. **PEDIATRIC LABELING IS ADEQUATE FOR CERTAIN AGE GROUPS.** Appropriate information has been submitted in this or previous applications and has been adequately summarized in the labeling to permit satisfactory labeling for certain pediatric age groups (e.g., infants, children, and adolescents but not neonates). Further information is not required.

___3. **PEDIATRIC STUDIES ARE NEEDED.** There is potential for use in children, and further information is required to permit adequate labeling for this use.

___a. A new dosing formulation is needed, and applicant has agreed to provide the appropriate formulation.

___b. A new dosing formulation is needed, however the sponsor is either not willing to provide it or is in negotiations with FDA.

___c. The applicant has committed to doing such studies as will be required.

- ___ (1) Studies are ongoing,
- ___ (2) Protocols were submitted and approved.
- ___ (3) Protocols were submitted and are under review.
- ___ (4) If no protocol has been submitted, attach memo describing status of discussions.

___d. If the sponsor is not willing to do pediatric studies, attach copies of FDA's written request that such studies be done and of the sponsor's written response to that request.

✓4. **PEDIATRIC STUDIES ARE NOT NEEDED.** The drug/biologic product has little potential for use in pediatric patients. Attach memo explaining why pediatric studies are not needed.

See next page.

___5. **If none of the above apply,** attach an explanation, as necessary.

ARE THERE ANY PEDIATRIC PHASE 4 COMMITMENTS IN THE ACTION LETTER? ___ Yes ✓No

ATTACH AN EXPLANATION FOR ANY OF THE FOREGOING ITEMS, AS NECESSARY.

This page was completed based on information from _____ (e.g., medical review, medical officer, team leader)

/S/

Signature of Preparer and Title

5/26/00

Date

Orig NDA/BLA # 19-901/S-028

HFD-110/Div File

NDA/BLA Action Package

~~HFD-006/ KRoberts~~ HFD-104/T. Crescenzi

FOR QUESTIONS ON COMPLETING THIS FORM, CONTACT KHYATI ROBERTS, HFD-6 (ROBERTSK)

(revised 10/20/97)

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax: 1-423-989-6113

Thomas K. Rogers, III, M.S.
Vice President, Regulatory Affairs

February 4, 2000

Raymond J. Lipicky, M.D., Director
Food and Drug Administration
Center for Drug Evaluation and Research
Division of Cardio-Renal Drug Products (HFD-110)
1451 Rockville Pike
Rockville, Maryland 20852-1420

NDA SUPPL AMEND
(BM)
SE1-028

Re: NDA 19-901/S028
Altace® (ramipril) Capsules
User Fee ID #: 3892
Amendment to Supplement

Dear Dr. Lipicky:

Certain additional documents relative to the Supplemental Application referenced above were requested in a telephone conversation of January 24, 2000. The requested information on study protocols and amendments, as well as minutes of the Data and Safety Monitoring Board, are being provided under separate cover directly from Dr. Yusuf's group at the Canadian Cardiovascular Collaboration (CCC).

Contained within this amendment are the following documents:

1. *Signed debarment certification*: An original debarment certification from King Pharmaceuticals, Inc., is provided and is further supported by a secondary certification from the CCC, the organization responsible for conducting the study under the direction of Dr. Salim Yusuf, Principal Investigator.

2. *Amended User Fee Cover Sheet*: A new User Fee Cover Sheet is provided. This form is amended from the original submission to correct an erroneous date of submission.

We further acknowledge a subsequent request for draft labeling to include the newly proposed indications for Altace. This information will be supplied as an amendment to the NDA under separate cover. Please advise if the information being supplied from CCC is not received or if additional information is required.

CENTER FOR DRUG EVALUATION AND RESEARCH
RECD
FEB – 7 2000
HFD-110

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice President Regulatory Affairs

King Pharmaceuticals, Inc.
501 Fifth Street
Bristol, Tennessee 37620

1-800-336-7783
1-423-989-8001
Fax 1-423-989-6113

February 4, 2000

DEBARMENT CERTIFICATION

King Pharmaceuticals, Inc. hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Thomas K. Rogers, III
Vice President Regulatory Affairs

2/4/2000
Date

...comes
...evention
...luation

Canadian Cardiovascular Collaboration

Collaboration Canadienne Cardiovasculaire

Canadian Regional Coordinators

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Fax: 403-670-1592

Manitoba
A. Morris
Tel: 204-237-2023
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Western Ontario
M. Arnold
...l: 519-667-6650
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...entral Ontario
...Baigrie
...l: 416-480-4522
...ax: 416-480-4072

Eastern Ontario
R. Davies
Tel: 613-761-4729
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G. Dagenais
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Fax: 514-343-7089

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D. Johnstone
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Fax: 902-428-2271

B. Sussex
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U.S. Coordinators
J. Probstfield
Tel: 206-667-2836
Fax: 206-667-4142

J. Young
Tel: 713-790-2781
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CCC Project Office (C3PO)
S. Yusuf, H.Gerstein, W.Taylor, E.Lonn, J.Pogue, J.Bosch
237 Barton Street East
Hamilton, Ontario,
L8L 2X2
Tel: 800-263-9428(WHAT)
...ax: 905-521-1166

...ty Chairs:
...Yusuf, T. Montague
...vice Chair:
G. Dagenais
UROHOPE Chair:
P. Sleight
Data Safety & Monitoring Board
D. Sackett (Chair)
R. Collins, C. Furberg, C. Hennekens, B. Pitt, E. Davis

HOPE

The Canadian Cardiovascular Collaboration, hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application.

Jackie Bosch

Jackie Bosch
HOPE Study Co-ordinator

Financial Disclosure by Clinical Investigators

In compliance with the requirements of 21CFR§54.4, information is provided herewith relative to the financial disclosure by clinical investigators who participated in clinical studies submitted as Supplemental Application S-028 to NDA 19-901, Altace (ramipril) Capsules. Financial Disclosure requirements for this supplement were discussed with Ms. Linda Carter of the Office of Drug Evaluation I. A completed FDA Form 3454 is provided and is supported by additional information described as follows:

The Heart Outcome Prevention Evaluation (HOPE) study was administered by the HOPE International Steering Committee chaired by Dr. Salim Yusuf. Funding for the study was provided from The Medical Research Council of Canada, Hoechst-Marion Roussel, Astra Zenecca, King Pharmaceuticals, Natural Source Vitamin E Association and Negma, and the Heart Stroke Foundation of Ontario. Dr. Yusuf was supported by a Senior Scientist Award of the Medical Research Council of Canada and a Heart and Stroke Foundation of Ontario Research Chair.

All funding for the study was administered and disbursed by the International Steering Committee. As indicated on the Form 3454, no investigators involved in the study have proprietary interest in the product. None of the investigators own patent rights or trademarks associated with Altace.

A letter from Dr. Yusuf is provided as certification that no compensation affected by the outcome of clinical studies, as defined in 21CFR§54.2(a), was provided to any of the study investigators. A list of all clinical investigators is also provided with this certification.

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☐ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		

☒ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Thomas K. Rogers, III	Vice President, Regulatory Affairs
FIRM/ORGANIZATION	
King Pharmaceuticals, Inc.	
SIGNATURE	**DATE**
[signature]	3 3 2000

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

FORM FDA 3454 (3/99)

Created by Electronic Document Services/USDHHS: (301) 443-2454 EF

Printed by Sandra Birdsong

Electronic Mail Message

Date: 24-Feb-2000 12:47pm
From: Linda Carter
CARTERL
Dept: HFD-101 WOC2 6015
Tel No: 301-594-6758 FAX 301-594-5298

Subject: NDA 19-901 HOPE Study

Diana and Sandy, I have had a number of discussions with Tom Rogers of King Pharmaceuticals, Inc. concerning the reporting of financial information on the HOPE study. I also discussed the issue with Dr. Temple. In a telecon with Mr. Rogers today (February 24, 2000), based on discussions with Dr. Temple, I requested that he provide information on proprietary information of investigators and outcome payments. Since the study was completed before February 2, 1999, reporting of equity interest and significant payments of other sorts is not required. Since Dr. Usef (spelling) ran the study, and received the funding for the study, I suggested that Mr. Rogers ask Dr. Usef about the outcome payments. However, it is up to Mr. Rogers to decide how best to obtain the information. Since Hoechst originally held the rights to Ramipril, and King Pharmaceuticals, Inc. purchased the U.S. rights to Ramipril from Hoechst, it seems that none of the investigators would have any proprietary interest in the product. Mr. Rogers will address this in a submission to the NDA on financial information. I suggested that he use the Form 3454, and to contact me if he needs help in completing the form.

MAR 21 2000

Minutes of a Teleconference

Date:	March 8, 2000
Product:	NDA 19-901/S-028 Altace (ramipril HCl)
Sponsor:	King Pharmaceuticals, Inc.
Purpose:	To discuss May 1, 2000 Advisory Committee Meeting
Teleconference Chair:	Raymond Lipicky, M.D.
Teleconference Recorder:	Sandy Birdsong

Participants:

FDA

Raymond Lipicky, M.D.	Director, Division of Cardio-Renal Drug Products (HFD-110)
Robert Fenichel, Ph.D., M.D.	Deputy Director (HFD-110)
Shaw Chen, M.D., Ph.D.	Medical Team Leader (HFD-110)
Norman Stockbridge, M.D.	Medical Team Leader (HFD-110)
Shari Targum, M.D.	Medical Officer (HFD-110)
James Hung, Ph.D.	Statistician, Division of Biometrics I (HFD-110)
Sandra Birdsong	Regulatory Health Project Manager

HOPE Study

Salim Yusuf, D.Phil., FRCPC	HOPE Study Principal Investigator
Jackie Bosch, MSc.	HOPE Study Coordinator
Janice Pogue, MSc.	HOPE Study Statistician

King Pharmaceuticals, Inc.

Jefferson Gregory	President
Henry Richards, M.D.	Executive Vice President Medical Affairs
Nuoyu Huang, M.D., Ph.D.	Senior Director Medical Affairs
Ed Reilly	Vice President Marketing
Thomas Rogers	Vice President Regulatory Affairs
Dean Cirotta	Senior Director Regulatory Affairs
Greg Carrier	Director Regulatory Affairs

Background

Dr. Lipicky requested this meeting to prepare for the May 2000 Advisory Committee Meeting.

The Teleconference

Specifics of the Advisory Committee meeting were given to the sponsor by Dr. Lipicky. The meeting will take place in the afternoon of May 1, 2000 in the Mazur Auditorium at the National Institutes of Health. Dr. Lipicky indicated that no further meetings will be needed prior to the Advisory Committee. It was agreed, however, that two-way communication will continue should issues arise.

Two articles regarding the HOPE Study have been published in The New England Journal of Medicine, January 20, 2000, and one article in The Lancet, January 22, 2000. Dr. Lipicky said these articles are all the sponsor needs to submit to the Advisory Committee. He emphasized that the Advisory Committee must have pertinent materials no later than April 1, 2000 and no trade secrets should be in the manuscripts. If trade secrets appear, the material must be redacted by mid-March. The sponsor stated that there are no trade secrets revealed and Dr. Lipicky indicated that a letter should be addressed to the Division to this effect.

The Division will have a draft of questions to be submitted to the Committee three to four weeks prior to the meeting. The final questions for the Advisory Committee will be completed one day prior to the meeting. Division reviews will be sent to the sponsor, but perhaps not until some time in April due to more stringent rules. Dr. Lipicky indicated that there appear to be no major problems and the major findings will stay.

Dr. Lipicky said that the thrust of the meeting is uncertain, but he does not think the major question will be whether the primary endpoint was met. One question might be whether two separate components (i.e., ramipril and vitamin E) should be studied at the same time. An interesting topic concerns the increase in cost in doing two studies and Dr. Yusuf indicated that a discussion of factorial designs might be helpful.

The data on congestive heart failure was discussed, with the Division of the opinion that this will not produce a new indication, but be seen as part of the overall result. The Division's thinking is that heart failure was not well defined. Dr. Lipicky stated that the results indicate that the heart failure developed gradually and did not necessitate hospitalization. Dr. Yusuf responded that there was a box on the case report form for heart failure, and that the difference in heart failure, while not a predefined endpoint, was statistically significant and related to the mortality difference. A definition of heart failure by the frequency of hospitalization is statistically significant. Dr. Lipicky said this might be worthy of discussion at the Advisory Committee.

Regarding the Clinical Pharmacology section, Dr. Lipicky said it is not clear how far the reviewers will be able to proceed with the diabetes material. The Division's bias is that diabetes is not prevented and that an endpoint of proteinuria is not valid as an

index of nephropathy. Dr. Yusuf stated that microalbuminuria is a marker of vascular damage and diabetics are important in this study because of the high vascular events in this population. He suggested that a discussion that helps to distinguish between microalbuminuria and gross proteinuria would be useful.

The sponsor suggested having a nephrologist and diabetologist present at the Advisory Committee, and some names were suggested.

Dr. Lipicky indicated that the above discussion will serve as the frame of reference for the Advisory Committee. Comparing the data from Canada and the remaining study subjects may not be discussed. Dr. Lipicky will write the draft of questions and will share them as soon as possible. He stated that the sponsor is free to ask questions or challenge what the Division writes.

Minutes Preparation:

/S/

Sandra Birdsong

Concurrence, Meeting Chair:

/S/

Raymond Lipicky, M.D.

cc:
NDA 19-901/S-028
HFD-110
HFD-110/SMatthews
HFD-110/ABlount
HFD-110/SBirdsong

Drafted: slb/3/15/00; Final: 3/21/00

RD:		
	RFenichel	3/15/00
	SChen	3/15/00
	NStockbridge	3/15/00
	STargum	3/15/00
	JHung	3/15/00
	NMorgenstern	3/17/00

B.ND 19-901

JAN 13 2000

Minutes of a Teleconference
January 13, 2000

Application: NDA 19-901
Altace (ramipril) Tablets

Sponsor: King Pharmaceuticals, Inc.

Attending:

King Pharmaceuticals:

Thomas K. Rogers III	Vice President, Regulatory Affairs
Norman Huang, M.D.	Director, Medical Affairs
Greg Carrier	Director, Regulatory Affairs

King Pharmaceuticals Consultants:

Salim Yusuf, FRCPC, FACC	Professor of Medicine, Division of Cardiology, McMaster University, Hamilton, Ontario, Canada
Jackie Bosch	HOPE Study Coordinator, McMaster University, Hamilton, Ontario, Canada

FDA:

Raymond Lipicky, M.D.	Division Director, HFD-110
Diana Willard	Regulatory Health Project Manager, HFD-110

Background: This teleconference was requested by Dr. Lipicky to discuss the submission status of the ramipril efficacy supplement containing data from the HOPE trial.

Teleconference: Dr. Lipicky began by stating his understanding that there has been a delay from the original estimated timeframe for submission of the ramipril efficacy supplement containing data from the HOPE trial. He asked if there was anything the Division had done to cause the delay and also if there was anything the Division could do to help expedite the submission.

Mr. Rogers stated that at the November 19, 1999 meeting, King Pharmaceuticals had indicated that the efficacy supplement would be submitted by mid-January 2000. The current estimate for submission is late January/early February 2000.

Mr. Rogers stated that a disc containing part of the SAS data set and an annotated CRF had been sent to Dr. Hung for review. Dr. Hung found both the formatting of the SAS data set and the annotated CRF acceptable. King Pharmaceuticals plans to obtain the

information needed for the submission from Dr. Yusuf's office this week. Ms. Bosch stated that the CDROMs would be "burned" tomorrow.

Dr. Yusuf stated that if the data are first provided to King Pharmaceuticals and then forwarded by King Pharmaceuticals to the Division, the submission would probably be submitted in about two weeks. If the data are sent directly to the Division, however, the submission could arrive by Monday, January 17, 2000. Dr. Lipicky stated that it is acceptable for a cover letter detailing the submission, FDA Form 356h, and the User Fee to be submitted by King Pharmaceuticals and the data to be submitted by Dr. Yusuf. Mr. Rogers indicated that this would be acceptable to King Pharmaceuticals.

Dr. Yusuf stated that reprints of the articles published on the HOPE trial in the *New England Journal of Medicine* would also be submitted with the data. A paper to be published in *Lancet* on the diabetes arm of the trial will be submitted at a later date.

[redacted] requested that any data submitted from [redacted] remain confidential. Dr. Lipicky stated that a description of the [redacted] arm of the trial would appear in the review but assured Dr. Yusuf that the data would remain confidential.

Dr. Lipicky stated that if the data are submitted next week, the HOPE trial would most probably be presented to the Cardio-renal Advisory Committee at the May 1-2, 2000 meeting.

Signature, Minutes Preparer /S/ Diana Willard

Concurrence, Meeting Chair /S/ Raymond Lipicky, M.D.

cc: original
HFD-110
HFD-110/DWillard
HFD-110/SMatthews
HFD-110/ABlount
HFD-110/SBirdsong

Drafted: 1/14/00; Final: 1/14/00

Minutes of a Meeting
November 19, 1999

Applications:	NDA 19-901/Altace (Ramipril) Capsules [redacted]/Ramipril Capsules
Sponsors:	King Pharmaceuticals, Inc. (NDA 19-901) Salim Yusuf[redacted]
Purpose:	Discuss HOPE Study/NDA content
Meeting Chair:	Robert Fenichel, Ph.D., M.D.
Meeting Recorder:	Sandy Birdsong

Participants:

FDA

Robert Fenichel, Ph.D.,M.D.	Deputy Director, HFD-110
Juan Carlos Pelayo, M.D.	Medical Officer, HFD-110
Shari Targum, M.D.	Medical Officer, HFD-110
James Hung, Ph.D.	Statistician, HFD-110
Diana Willard	Regulatory Health Project Manager, HFD-110
Sandy Birdsong	Consumer Safety Officer, HFD-110

King Pharmaceuticals, Inc.

Jefferson J. Gregory	President and Chief Operations Officer
R. Henry Richards M.D.	Executive Vice President, Medical Affairs
Thomas K. Rogers	Vice President, Regulatory Affairs
Tom Der, R.Ph.	Manager, Regulatory Affairs

Monarch Division of King Pharmaceuticals, Inc.

Edward Reilly	Vice President, Brand Management,
Angi Osborne	Administrative Assistant, Brand Management

King Pharmaceuticals, Inc. Consultants

Salim Yusuf, DPHIL, FRCPC	Professor of Medicine, Division of Cardiology, McMaster University, Hamilton, Ontario, Canada
Wolfgang Scnulz. M.D.	European Regulatory Affairs, Hoescht Marion Russell
Robert W. Pollock	Vice President, Lachman Consultant Services, Inc.
Jackie Bosch	HOPE Study Coordinator, McMaster University, Hamilton, Ontario, Canada

Background

[redacted] was submitted by Dr. Yusuf on January 3, 1994 to evaluate the effects of Ramipril, an ACE-Inhibitor, and Vitamin E, in the prevention of myocardial infarctions, stroke, and cardiovascular mortality. The expectation was that Vitamin E and ACE-Inhibitors would have a main effect on cardiovascular-related endpoints during this trial.

On March 22, 1999, the Data Safety Monitoring Board recommended stopping the Ramipril/placebo arm of the study due to the favorable results of Ramipril. In a letter dated June 9, 1999 to [redacted] Dr. Yusuf summarized the data from both arms of the study.

This meeting was arranged by Dr. Fenichel to discuss what will be submitted in the efficacy supplement.

Meeting

It was clarified that King Pharmaceuticals is the parent company and Monarch is a wholly-owned subsidiary responsible for sales and marketing

King Pharmaceuticals reviewed their acquisition of Ramipril from Hoechst, Marion and Roussel (HMR) in December of 1998. King Pharmaceuticals owns all of the rights to the product, with rights to all applications and sale of the product in the U.S.

HOPE Study

The HOPE Study, began in 1994 and enrolled over 9,000 patients. Those included in the study were patients in treatment with cardiovascular indications and high risk patients over 55 years old. There were 250 patients in the SECURE portion of the study, that measured changes in the thickness of the carotid artery. The HOPE Study concluded in May due to favorable results.

Results indicate that Ramipril significantly decreases mortality, myocardial infarction, stroke, and prevents diabetic complications in high risk patients.

The protocol included a large number of women, about 25%. The sponsor believes that the HOPE Study enrolled the largest single group of diabetics ever studied in a clinical trial. The indications for prevention of diabetes mellitus showed a more than 30% decrease in new diagnoses. The sponsor would like to eventually pursue a new indication for reduction in diabetes. Other findings from the trial included a decrease in vascular effects and, more significantly, a decrease in stroke.

King Pharmaceuticals plans to submit this supplement in the first quarter of 2000.

NDA Efficacy Supplement

The Division outlined what is needed for the submission of the efficacy supplement:

- Original protocol and all amendments.
- The manuscript containing the results of the Hope Study, as will be published in the New England Journal of Medicine should be submitted. This manuscript is available electronically from the Internet.
- Data in computer-readable format. The Division most frequently uses SAS. An annotated Case Report Form, with the SAS data names identified, should be provided. The SAS program used by the sponsor to analyze the data should also be submitted.

In addition, it would be useful to provide in the supplement a thorough description of the population studied. The Division stated that specific case report forms may be requested as the review progresses.

Blinding

King Pharmaceuticals stated that a complete adjudication data base will be submitted.

Other Issues

Within the next two weeks, the database for the HOPE Study will be locked. The Division stated that this submission would probably receive a priority review. There is also a high probability that the application would be presented to the Advisory Committee in May or June of 2000. As the review progresses, the Division will consult with Dr. Temple be necessary.

The current Agency guideline is that the agenda of the Advisory Committee is locked at the end of the month prior to the scheduled meeting. Those deadlines may become even more stringent; there is a proposal to change the deadline. Dr. Yusef proposed that the Agency could act on the new indications and labeling changes for Ramipril that are clearly supported by the HOPE Study. Action on secondary, not as clearly defined

claims, such as the prevention of diabetes could be deferred until presented to the Advisory Committee.

Due to the current status of lawsuits pending against the Agency, the Division stated that it is not possible to send reviews to the sponsor at this time. After approval, information contained in the NDA may be requested under the Freedom of Information Act.

If the supplement is approved, the labeling will be changed to contain a description as well as outcomes of the Hope Study as demonstrated by the data.

Summary

The sponsor summarized the results of the Ramipril HOPE Study. The Division outlined data and formatting that would be useful in the NDA efficacy supplement for Ramipril. The sponsor plans to submit the supplement in mid-January 2000.

Signature, Minutes Prepar /S/ Sandy Birdsong

Concurrence, Meeting Chair /S/ Robert Fenichel, M.D.

cc: original
HFD-110
HFD-110/SBirdsong
HFD-110/SMatthews
HFD-110/ABlount

Drafted: 12/6/99; Final 12/15/99

RD:		
	Fenichel	12/6/99
	Hung	12/15/88
	Targum	12/6/99
	Pelayo	12/6/99
	Morgenstern	12/14/99
	Willard	12/7/99

MESSAGE CONFIRMATION

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DIVISION OF CARDIO-RENAL DRUG PRODUCTS
FOOD AND DRUG ADMINISTRATION

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5600 Fishers Lane
Rockville, MD 20857

Woodmont II
1451 Rockville Pike
Rockville, MD 20852

Transmitted to FAX Number: 9-1-419-389-9960

Attention: **Joan Standerdt**

Company Name: CDER

Phone: 419-389-6952

Subject: **Competing Products**

Date: 2/9/00

Pages including this sheet: 2

From: **Sandy Birdsong**
Phone: **301-594-5312**
Fax: **301-594-5494**

2/9/00

Dear Joan,

The following is a list of closely competing products for NDA 19-901/S-028 (ramipril):

NDA 18-343, Capoten (captopril) Tablets
Sponsor: Bristol-Myers Squibb
Indications: hypertension and congestive heart failure

NDA 18-998, Vasotec (enalapril) Tablets
Sponsor: Merck
Indications: hypertension and congestive heart failure

NDA 19-558, Prinivil (lisinopril) Tablets
Sponsor: Merck
Indication: hypertension

NDA 19-851, Lotensin (benazepril) Tablets
Sponsor: Novartis
Indication: hypertension

NDA 19-885, Accupril (quinapril) Tablets
Sponsor: Parke-Davis
Indication: hypertension

NDA 19-915, Monopril (fosinopril) Tablets
Sponsor: Bristol-Myers Squibb
Indications: hypertension

NDA 20-184, Aceon (perinodopril) Tablets
Sponsor: Solvay
Indication: hypertension

NDA 20-240, Renormax (spirapril) Tablets
Sponsor: Schering Corporation
Indication: hypertension

NDA 20-312, Univasc (moexipril) Tablets
Sponsor: Schwarz Pharma, Inc.
Indication: hypertension

NDA 20-528, Mavik (trandolapril) Tablets
Sponsor: Knoll
Indication: hypertension

NDA 21-188 (omapatrilat)
Sponsor: Bristol Myers Squibb
Indication: hypertension

Hope-Too

FAX

HOPE-TOO Study
2nd Floor McMaster Clinic
Hamilton General Hospital
237 Barton Street E.
Hamilton, Ontario
L8L 2X2

Christine Nurnberg
Hope-Too Administrative Assistant
Phone: 1-800-263-9428 or
(905) 577-1454 x 44512
FAX: (905) 527-5380
Email: nurnberg@ccc.mcmaster.ca

To: Ms. Sandra Birdsong — Centre for Drug Evaluation & Research FDA

Fax: 1-301-594-5495

Phone: 1-301-594-5312

Pages: 2 **Date:** February 28, 2000

☐ **Urgent** ☐ **For Review** ☐ **Please Comment** ☐ **Please Reply** ☐ **Please Recycle**

RE: NDA Altace 19-901 S-028

Dear Ms. Birdsong,

Thank you for your call and please find enclosed the addresses, Principal investigators' names telephone numbers and fax numbers for centre 006, 026, 303, and 307.

Please do not hesitate to contact me if you have any further questions.

Yours Truly,

Jackie Bosch

J. Bosch

HOPE Study Co-ordinator

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Hamilton Health Sciences Corporation
237 Barton Street East
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PI: Dr. William Wickemeyer Tel: 1-515-235-5000

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Cleveland Clinic foundation
9500 euclid Avenue
PVCD Research
Desk C-51
Cleveland, Ohio
44195
USA
Tel: 1-216-445-1124
Fax: 1-216-445-6885
PI: Dr. Byron Hoogwerf Tel:1-416-444-8347

Date: May 3, 2000
From: Joan C. Standaert, Executive Secretary

Subject: 90th Meeting of the Cardiovascular and Renal Drugs Advisory Committee, May 1-2, 2000: INFORMATION ALERT MEMORANDUM

The committee convened in open session on May 1, 2000, to review an application for Altace (ramapril), King Pharmaceuticals, to be indicated for prevention of cardiovascular death, myocardial infarction, stroke and the incidence of all cause mortality. Altace would also be indicated for patients 55 years or older, with a history of coronary artery disease, stroke, peripheral vascular disease or diabetes plus at least one other cardiovascular risk factor (hypertension, elevated cholesterol levels, low HDL levels, cigarette smoking, or documented microalbuminuria).

The evidence presented by the sponsor was from the HOPE (Heart Outcomes Prevention Evaluation Study). A large (9541 patients) simple, randomized trial of ramapril and vitamin E in patients at high risk for cardiovascular events. This trial was conducted in 267 hospitals from 19 countries in North and South America and Europe.

In response to FDA questions the committee unanimously recommended that the study established a beneficial effect of ranüpril on the combined endpoint of myocardial infarction, stroke and death from cardiovascular causes. With the exception of diabetes + one risk factor, the proposed labeling adequately described the cardiovascular risk factors of the HOPE study population (8-yes-2-no) and did recommend (6-yes-4-no) that "allcause mortality" be included in the indications portion of the labeling.

They unanimously recommended that there were no differences in the primary endpoint with respect to gender, age and race. Geographic difference were too small to ev4uate. They also unanimously recommended that the effects of ramapril on the diabetic subpopulation were a new finding that should be mentioned in the clinical trials and indications sections of the labeling.

Unanimously, they did not recommend that effects on the incidence of new diabetes or glycemic control be mentioned in labeling. They defeaed comment on diabetic nephropathy and microvascular complications of diabetes. They voted no (5-4) that the effects of ramipril on the need for coronary revascularization should be mentioned in the indications section of labeling and no (7-2) that these effects be mentioned in the clinical trials section. They also voted 8-no-l-yes, that findings on congestive heart failure be mentioned in labeling.

On May 2, the committee reviewed NDA 20-807/ S-004, Refludan (lepirudin), Aventis Pharmaceuticals, to be indicated as an anticoagulant in adult patients with acute coronary syndromes (unstable angina and acute MI without ST segment elevation on ECO). In this setting, Refluden® has been shown to decrease the rate of CV death or new MI (combined double endpoint) as well as the rate of CV death, new MI or refractory angina (combined triple endpoint). Refludan® is currently approved for heparin-induced thrombocytopenia. The sponsor submitted two studies to support the new claim, OASISI and OASIS-2 conducted by the Organization to Assess Strategies for Ischemic Syndromes based in Hamilton Canada.

OASIS-1 was a Canadian, multicenter, randomized, partially-blinded pilot study of a parallel design that compared treatment with lepirudin low dose, lepirudin medium dose or heparin given for three days in 909 patients with unstable angina or non-Q-wave MI. Primary assessment was at 7 days. OASIS-2 was a multinational, randomized, double-blind study of parallel design that compared treatment with lepirudin medium dose or heparin given for 72 hours in 10,141 patients wit unstable angina or non-Q-wave MI. The primary assessment was at 7 days.

In response to questions from the FDA the committee voted 9-yes-2-no, that the composite endpoint of cardiovascular death, new myocardia] infarction or refractory angina, as defined and assessed in the OASIS-2 trial was acceptable. They voted 7-yes, 4-no, that the heparin regimens used in the OASIS trials, were effective in the study population (patients with unstable *angina or* acute MI without ST segment elevation).

They voted 7 no, 4 yes that the data provide adequate evidence of the effectiveness of Refludan® for its proposed indication.

They voted 10 yes, 1 no that there were any safety concerns regarding Refludan® for this indication.

Safety concerns included bleeding, bleeding with interventions and strokes.

They voted 7 no, 4 yes that given the data from the OASIS trials, the benefits of Refludan® exceed its risks for the sponsor's proposed indication.

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March 31, 2000

Thomas K. R
Vice President,

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AVAILABLE FOR PUBLIC DISCLOSURE WITHOUT REDACT

Mr. John Treacy
Advisors and Consultants Staff (HFD-21)
Food and Drug Administration
Center for Drug Evaluation and Research
5630 Fishers Lane
Rockville, MD 20857

Re: NDA 19-901/S028
Altace® (ramipril) Capsules
User Fee ID #: 3892
Cardio-Renal Advisory Committee – Briefing Package

Dear Mr. Treacy:

A Supplemental Application seeking approval of additional indications for Altace (ramipril) Capsules was submitted to FDA's Division of Cardio-Renal Drug Products on January 18, 2000. The Division Director, Dr. Raymond Lipicky, advised the firm that this submission will be considered by the Cardio-Renal Advisory Committee on May 1, 2000.

We are providing the enclosed Briefing Packages for distribution to members of the Committee and to FDA's reviewing Division. Under separate cover, we are also providing a copy of the package to Ms. Joan Standaert, Executive Secretary to the Committee. As indicated above, we believe that all of the materials provided herein are fully disclosable under the Freedom of Information Act.

The application is founded upon the results of the Heart Outcomes Prevention Evaluation (HOPE) Study conducted by the HOPE Study Investigators and reported in *The New England Journal of Medicine* and *The Lancet*. Briefing materials provided include a submission backgrounder, copies of the related published journal articles, study protocols, definitions for terms of adjudication, and proposed labeling as submitted to FDA.

Most of the documents included within the Briefing Package are also provided electronically on the accompanying disc. Please advise if you have questions or if we can be of further assistance in this matter.

Sincerely,
KING PHARMACEUTICALS, INC.

Thomas K. Rogers, III
Vice President Regulatory Affairs

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Section

THE HOPE (HEART OUTCOMES PREVENTION EVALUATION) STUDY

A large, randomized trial of the ACE inhibitor, ramipril, and Vitamin E in patients at high risk of cardiovascular events

Investigators:	Multinational study
	Principal Investigator: Prof S Yusuf, McMaster University, Hamilton, CA
	Co-Principal Investigators:
	Prof P Sleight, Oxford University, Oxford, UK Dr. G. Dagenais, University of Laval, Quebec City, CA
Date first subject was enrolled:	23rd December 1993
Date last subject completed the study:	July 1999
Study manager:	J Bosch Canadian Project Office, Hamilton General Hospital, Ontario, Canada
	L Richardson European Project Office Bucks, England
Biostatistician:	J Pogue Canadian Project Office, Hamilton General Hospital, Ontario, Canada
Report type:	Briefing Document
Date of issue:	March 27, 2000

STUDY SYNOPSIS

Title

THE HOPE (HEART OUTCOMES PREVENTION EVALUATION) STUDY: A large, randomized trial of the ACE inhibitor, ramipril, and Vitamin E in patients at high risk of cardiovascular events

Investigator(s), study site(s)

This was a multicentre study conducted in 267 centres in 19 countries as follows: 129 in Canada, 76 in Europe, 27 in the USA, 30 in South America and 5 in Mexico.

Objectives

- to compare the effects of treatment with ramipril or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high risk patients

- to compare the effects of treatment with Vitamin E or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high risk patients

Secondary objectives included the investigation of treatment differences incidence of hospitalizations for unstable angina or revascularization procedures (CABG or PTCA), carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation, development of congestive heart failure (for ramipril), cardiovascular mortality and total mortality.

A prospective secondary analysis of incidence of nephropathy was included for diabetic patients. Consistency of results were investigated by examining the effects of treatment across various sub-groups i.e. patients with coronary disease, with cerebrovascular or peripheral cardiovascular diseases, with diabetes, male and female and by age.

Design

The study was a randomized placebo-controlled, double blind clinical trial designed to recruit at least 9000 patients who were at significant risk of CVD events (including patients with previous MI, previous angina, previous multivessel CABG or multivessel PTCA, multivessel coronary disease seen on angiography, previous stroke, peripheral arterial disease, diabetics with at least one other risk factor) using a 2 x 2 factorial design and a simple and focused protocol.

Methods

9541 patients were entered into the programme. 244 of these patients were entered into the low dows (2.5 mg per day) arm of the SECURE substudy. 9297 patients were included in the main study. These were high-risk patients (55 years of age or older) who had evidence of vascular disease or diabetes plus one other cardiovascular risk factor and who were not known to have a low ejection fraction or heart failure. They were randomly assigned to receive ramipril (10 mg per day orally) or matching placebo or vitamin E (400 IU per day orally) or matching placebo for a mean of five years. The primary outcome was a composite of myocardial infarction, stroke, or death from cardiovascular causes.

Following a screening and run-in phase eligible patients were randomized. Follow-up visits occurred at one month, six months and then every six months thereafter. At each visit a routine clinical examination was carried out, the results of which were recorded on the relevant page of the case report forms. Relevant history and event details were also recorded. In addition, at baseline, 2 years and end of study, centres were asked to collect an electrocardiogram (ECG) on each patient.

For each primary outcome, centres were asked to complete a seperate event form (i.e. MI, stroke or death). In addition secondary outcome data were collected on hospitalization forms. Specific forms recorded hospitalizations as a result of unstable angina or congestive heart failure. Assessments of local serum creatinine, local serum potassium, local glycated Hb, local urine dipstick, local 24-hour urine collections and central assay or urinary albumin and creatinine were carried out at various intervals during the study.

Study duration and dates

Patients were recruited from December 1993 to August 1995 and were all followed until the study was terminated in April 1999 because of clear benefit from ramipril. Final Visits took place between May and August 1999. The majority of patients are currently continuing in the vitamin E extension of the study.

Statistical Procedures

The study was originally designed to follow participants for a mean of 3.5 years. However, before the end of this period, the steering committee (whose members were unaware of any of the unblinded results) recommended increasing the duration of follow-up to five years to account for the impact of a possible time lag before treatment had its full effect. Assuming an event rate of 4 percent per year for five years, 9000 patients would be required for the study to have 90 percent power to detect a 13.5 percent reduction in the relative risk with a two-sided alpha level of 0.05 and with data analyzed on an intention-to-treat basis. Survival curves were estimated according to the Kaplan-Meier procedure, and treatments were compared with use of the log-rank test. This model was used to estimate the effects of treatment after stratification for randomization to vitamin E or its placebo. Subgroup analyses were conducted with the use of tests for interactions in the Cox regression model.

Interim Analyses

An Independent Data and Safety Monitoring Board (DSMB) monitored the progress of all aspects of the study. Four formal interim analyses were planned originally. Because of the study extension the DSMB met 4 times during the study (plus one additional confirmation meeting). On March 22, 1999, the monitoring board recommended termination of the ramipril arm of the study because of the clear evidence of a beneficial effect of ramipril .

Results

Note that since the vitamin E arm of the study is continuing only limited data on the vitamin E arm of the study are presented in this report.

Results – Study Subjects and Conduct

Patients were recruited from December 1993 to August 1995 at 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.

Of the 9541 randomized patients, 4645 were assigned to receive 10 mg of ramipril per day, 4652 were randomly assigned to receive matching placebo, and 244 were assigned to receive a low dose (2.5 mg per day) of ramipril. Only the primary he results from the 244 patients who received a 2.5mg dose are included in this report.

As intended a high risk population was recruited to this study. The number of patients in each of the important subgroups was as follows: 2480 women, 5128 patients who were at least 65 years old,

8162 who had cardiovascular disease, 4355 who had hypertension, and 3577 who had diabetes. There were no significant differences in baseline characteristics between the treatment groups.

The number of patients for whom information on status was obtained remained high throughout the study with information on 99.9% (9,537 of 9,541) of eligible patients being collected at the final visit. Since visit compliance was balanced and comprehensive for both groups there are no visit compliance issues for this study.

Results - Efficacy

There was significant benefit in the ramipril group when the composite primary outcome of myocardial infarction, stroke or cardiovascular death was examined: a total of 651 patients in the ramipril group (14.0 percent) died of cardiovascular causes or had a myocardial infarction or stroke, as compared with 826 patients in the placebo group (17.8 percent; relative risk, 0.78; 95 percent confidence interval, 0.70 to 0.86; P<0.001).

In addition there were significant benefits in the ramipril group across most of the secondary outcomes. Significantly fewer patients in the ramipril group than in the placebo group underwent revascularization (743 (16.0 percent) vs. 854 (18.4 percent); relative risk, 0.85; P=0.0014), and there was a trend towards fewer hospitalizations for heart failure in the ramipril group (141 (3.2 percent) vs. 161 (3.5 percent); relative risk, 0.87; P=0.22). In addition, significantly fewer patients in the ramipril group than in the placebo group had a cardiac arrest (37 (0.8 percent) vs. 59 (1.3 percent); relative risk, 0.62; P=0.02), worsening angina (1107 (23.8 percent) vs. 1222 (26.3 percent); relative risk, 0.88; P=0.003), heart failure (417 (9.0 percent) vs. 534 (11.5 percent); relative risk, 0.77; P<0.001), a new diagnosis of diabetes (102 (3.6 percent) vs. 155 (5.4 percent) ; relative risk, 0.66; P<0.001), or complications related to diabetes (303 (6.5 percent) vs. 356 (7.7 percent); relative risk, 0.85; P=0.038). However, treatment with ramipril had no effect on the likelihood of hospitalization for unstable angina.

The beneficial effect of treatment with ramipril on the composite outcome was consistently observed among the following predefined subgroups: patients with diabetes and those without diabetes, women and men, those with evidence of cardiovascular disease and those without such evidence, those younger than 65 years of age and those 65 years of age or older, those with hypertension at base line and those without it, and those with microalbuminuria and those without it.

Results - Safety

Ramipril was well tolerated and the only adverse event worthy of note is an increase in the number of patients experiencing cough in the ramipril group. More patients in the ramipril group than in the placebo group stopped treatment because of cough (7.3 percent vs. 1.8 percent). There was only one serious adverse event that met the criteria for expedited reporting to regulatory authorities. This event was a ruptured esophagus (secondary to excessive coughing) and was in the ramipril group. The patient was hospitalized and underwent surgery. Symptoms abated and the patient was subsequently discharged without sequelae.

Conclusions

Ramipril significantly reduces the rates of death, myocardial infarction, and stroke in a broad range of high-risk patients who are not known to have a low ejection fraction or heart failure. This effect is consistent across many important subgroups including those with and without cardiovascular disease, those with and without hypertension, those with and without diabetes and in both older and younger patients.

The magnitude of the benefit of treatment with ramipril with respect to the primary outcome is at least as large as that observed with other proven secondary prevention measures, such as treatment with beta-blockers, aspirin, and lipid-lowering agents, over four years. In addition, there were reductions in the rates of revascularization, heart failure, complications related to diabetes, and new diagnoses of diabetes. The rapid and sustained response to ramipril and the continuing divergence in results between the ramipril group and the placebo group indicate that longer-term treatment may yield even better results.

It should be noted that HOPE study medication (ramipril/placebo) was in addition to standard therapy. The benefits of ramipril were observed among patients who were already taking a number of effective treatments such as aspirin, beta-blockers, and lipid-lowering agents, indicating that the inhibition of angiotensin-converting enzyme offers an additional approach to the prevention of atherothrombotic complications.

Ramipril was well tolerated and the only adverse event worthy of note is an increase in the number of patients experiencing cough in the ramipril group.

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Please note: Ramipril Active/Placebo in Table Headings always refers to the 10 mg group unless otherwise specified

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ABBREVIATIONS AND DEFINITIONS

Abbreviation	Definition
AABP	Ankle Arm Blood Pressure Ratio
ACE	Angiotensin converting enzyme
AE	Adverse event
BP	Blood pressure
CABG	Coronary artery bypass graft
CAD	Coronary artery disease
CCC	Canadian Cardiovascular Collaboration
CCU	Coronary care unit
CHF	Congestive heart failure
CI	Confidence interval
CRF	Case report form
CV	Cardiovascular
CVD	Cardiovascular disease
DM	Diabetes Mellitus
DSMB	Data and Safety Monitoring Board
EC	Ethics committee
ECG	Electrocardiogram
GCP	Good clinical practice
Hb	Hemoglobin
HMR	Hoechst Marion Roussel
HOPE	Heart Outcomes Prevention Evaluation
IRB	Institutional review board
MI	Myocardial infarction
PAD	Peripheral arterial disease
PTCA	Percutaneous transluminal angioplasty
QC	Quality Control
SD	Standard deviation
UA	Unstable angina
UK	United Kingdom
ULN	Upper Limit of Normal

1.0 INTRODUCTION AND STUDY RATIONALE

Cardiovascular disease remains the primary cause of death in the western world despite advances in medical care. Although it is well established that elevated cholesterol, smoking and hypertension are major risk factors for cardiovascular disease[1] (CVD), these factors do not fully account for the risks of developing CVD in a population[2]. Therefore, identification and modification of other risk factors is needed to further reduce death and disability from CVD.

Epidemiological and molecular data suggest that activation of the renin-angiotensin system has a strong role in increasing the risk of CVD events, such as myocardial infarction (MI). Additionally, studies in animals suggest that angiotensin converting enzyme (ACE)-inhibitors which block the activation of the renin-angiotensin system may retard atherosclerosis. Three large clinical trials of ACE inhibitors (SOLVD trials and the SAVE trial) which randomized more than 9000 patients with low ejection fractions found a significant 23% reduction in risk of MI ($2p<0.0002$)[3,4,5,6]. This benefit was seen in a wide range of patients in these trials and raises the possibility that reductions in ischemic heart events may be applicable to a wider range of patients, including those with preserved ejection fractions. Parallel lines of evidence from observational animal and human studies suggest that ACE

inhibitors may provide benefit through several mechanisms, including blood pressure reduction, antiproliferative effects, hormonal/vascular effects and anti-atherogenic effects[7,8,9,10]. However, widespread acceptance of ACE-Inhibitors as preventive therapy must be preceded by direct proof of benefit from randomized trials in patients with preserved ejection fractions. The Heart Outcomes Prevention Evaluation (HOPE) study is a large randomized controlled trial designed to evaluate whether ACE inhibition reduces ischemic cardiovascular events in this group.

Evidence from experimental studies suggests that oxidation of lipids may be important in the formation and progression of atherosclerosis and that vitamin E is an effective anti-oxidant[11,12]. Several large observational studies of vitamin E have shown that users of vitamin E have a substantially reduced risk of events such as MI and stroke in comparison with non-users[13,14,15]. However these observational studies may be subject to considerable bias, such as vitamin E consumers more often adopting other healthy lifestyle changes e.g. exercise, less smoking etc. It is therefore possible that the degree of benefit apparent from antioxidant use may be overestimated by the non randomized studies. The efficacy of vitamin E should be established by large randomized clinical trials before its use becomes widespread.

The study was organized and coordinated by the Canadian Cardiovascular Collaboration Project Office at McMaster University in Hamilton, Ontario. Adjunct offices were located in London, United Kingdom; Sao Paulo, Brazil; and Rosario, Argentina. The overall responsibility for HOPE rested with the independent steering committee. Two important sub-committees of the steering committee were the Events Adjudication committee and the sub-study/publication policy committee. An independent Data and Safety Monitoring Board monitored the progress of all aspects of the study and carried out the appropriate unblinded interim analyses.

On March 22, 1999 the independent Data and Safety Monitoring board recommended early termination of the ramipril arm of the study due to clear benefit. Subsequently on April 17th the Steering Committee accepted this recommendation and the relevant study close-out procedures were implemented. The vitamin E arm of the study is continuing and therefore only minimal data regarding that arm of the study is included in this report.

2.0 STUDY OBJECTIVES

2.1 Primary objective

The objective of the study was to compare the effects of treatment with ramipril (10mg/day) or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high-risk patients, and/or to compare the effects of treatment with Vitamin E (400IU/day) or placebo on the incidence of myocardial infarction, stroke or cardiovascular death in high risk-patients.

2.2 Secondary objectives

Secondary objectives were to investigate treatment effects on the incidence of hospitalizations for unstable angina, the need for revascularization procedures (including coronary artery bypass graft (CABG), percutaneous transluminal angioplasty (PTCA), carotid endarterectomy, peripheral vascular angioplasty/surgery and limb amputation), hospitalization for congestive heart failure, overt nephropathy and total mortality.

Additionally the effect of treatment on important subgroups (women, older patients (>65 years), patients with hypertension, patients with coronary disease, patients with cerebrovascular disease, patients with peripheral arterial disease and patients with diabetes) were to be examined. Diabetic patients were seen to be a particularly important group because of their known high risk of cardiovascular disease.

3.0 INVESTIGATIONAL PLAN

3.1 Study design

The HOPE study was a randomized placebo-controlled, double blind clinical trial, the design of which has been previously published[16]. The original design included 9000 high-risk patients, however to ensure high statistical power in all important subgroups the sample size was increased to 9,500 prior to the start of the study. The study used a 2 x 2 factorial design to examine the effects of ramipril (10mg/day) versus placebo and/or vitamin E versus placebo on cardiovascular outcomes. The study starting recruiting patients in December 1993 and randomizing patients in January 1994. Randomization was complete in August 1995. Initially follow up was scheduled for an average of 3.5 years however as a result of emerging information indicating a possible time-lag in full treatment effect, while still blinded, the steering committee agreed to extend the study to an average of 4.5 years of follow-up. One of the main strengths of the study was its simple and focused protocol.

3.1.1 Logistics

The study was carried out in the following regions; Canada, Europe (Austria, Belgium, Denmark, Finland, France, Germany, Holland, Italy, Ireland, Norway, Spain, Sweden, Switzerland and the United Kingdom), Latin America (Argentina, Brazil and Mexico) and the United States of America.

Protocol: The development and design of the HOPE study took place over many months between early 1992 and late 1993 and various draft versions of the protocol were developed. Patient enrollment was completed on version 13 of the protocol. There was one protocol amendment that allowed for an extension of the follow up period. A summary of the protocol versions is shown below.

	Version	Dates
North American Protocol (English) * Also used in Argentina and Mexico	V11	August 1993 (used in early IRB submissions in North America)
	V12	December 1993 (incorporated corrections to version 11)
	V13	March 1994 * Differences between V13 and previous versions are noted in italics in protocol
European Protocol (English) * European Investigators also used North American protocol		February 1994 (based on V12)
Brazilian Protocol (Portuguese)		March 1994 (based on V13)

Minor variations in the content of each protocol have arisen due to errors in transcription etc. but since all centres also received the North American protocol and other instructions on study conduct, these differences are not considered significant and are not discussed in detail. Essentially all centres met the standards of version 13 of the protocol and the same data were collected in all areas.

Regulatory and Ethics Submissions: Regional/national submissions were made to regulatory authorities as/if required. In addition, each centre submitted the protocol to appropriate local ethics committees. The approvals for each centre are available at the Canadian Project Office. Ethics approval (both original and extension if required) is available for all 267 centres.

Informed Consent: Written informed consent was obtained prior to the conduct of any study-related procedures. Site-specific versions are archived at the Canadian Project Office. Note that in some countries/centres a new consent form for the extension study was not required.

Investigators: Since the patient population recruited spanned a wide area of medical care, participating investigators could be from a variety disciplines (i.e. cardiology, neurology, surgeons, diabetologists, primary care). One physician at each centre took overall responsibility for the study.

Signed agreement letters, curricula vitae and regulatory forms (where applicable) are available at the Project Office for these individuals. In some countries investigators were asked to sign a contractual agreement while in others, agreement to participate in the study was confirmed by signature on a protocol signature page. The principle investigator at each site was responsible for signing these agreements. Centres 120 and 123 amalgamated during the study as did centres 11 and 146 as a result of physician re-location. Two new sites were established in the UK during the study to follow two patients that moved from Canada to the UK.

3.2 Selection of Subjects

The wide inclusion criteria allowed us to capture a truly high-risk population. There were several groups within this population that were of particular interest and recruitment efforts were targeted at these groups. They included:

- Women: Every effort was made to recruit as many female patients as possible (as historically this is an underrepresented group in cardiovascular clinical trials).
- Patients with diabetes and high risk of cardiovascular disease: This group was of specific interest because of the known high rate of cardiovascular morbidity and mortality. In addition, MICROHOPE [17] study examined the progression of microalbuminuria in-patients with diabetes.

3.2.1 Inclusion Criteria

Patients were included in the study if they were 55 years of age or older and at high risk of developing cardiovascular disease. This included patients with:

- coronary disease (previous myocardial infarction, stable or unstable angina with documented multivessel coronary disease (>50% stenosis in at least two major coronary arteries) or positive stress testing (ST depression ≥ 2mm or a positive thallium), or multivessel PTCA (patients could be entered into Run-in Phase one week after these events but could only be randomized one month after these events), multivessel CABG (more than 4 years prior to randomization or with angina) or multivessel coronary disease seen on angiography)

- cerebrovascular disease (previous stroke more than one month ago)

- peripheral arterial 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),

- Diabetes (insulin-dependent or non-insulin dependent) with one of the following cardiovascular risk factors: hypertension, (B.P. >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(3.5 mg/dl); current cigarette smoking; known microalbuminuria or any evidence of previous vascular disease.

3.2.2 Exclusion Criteria

Exclusion criteria relate primarily to absolute indications or contra-indications for the use of ACE-I or Vitamin E, and to the presence of other medical problems that would either interfere with participation in the trial or lead to the inability to complete the trial. These include:

- Drug use: Current use of ACE-I (eg, for congestive heart failure, EF<40% or severe hypertension) or current use of Vitamin E and inability to discontinue these medications; or known hypersensitivity to ACE-I or Vitamin E.

- Cardiovascular diseases:

- Ejection fraction <40% (only if known).
- Hemodynamically significant primary valvular or outflow tract obstruction (eg. mitral valve stenosis, asymmetric septal hypertrophy, malfunctioning prosthetic valve).
- Constrictive pericarditis.
- Complex congenital heart disease.
- Syncopal episodes presumed to be due to uncontrolled life-threatening arrhythmias (asymptomatic cardiac arrhythmias including ventricular tachycardia were not an exclusion criterion).
- Planned cardiac surgery or angioplasty within 3 months (patient could be reconsidered for the trial after the procedure).
- Uncontrolled hypertension.
- Cor pulmonale.
- Heart transplant recipient.

• Other conditions:

- Significant renal disease defined as: a) renal artery stenosis; b) creatinine clearance <0.6 ml/second or serum creatinine ≥ 200 mEq/L (≥2.26 mg/dl); c) overt nephropathy: ≥1 plus proteinuria on dipstick or urinary albumin excretion > 200 micrograms/minute (300 mg/24 hrs); d) hyperkalemia; K>5.5 mEq/L.
- Any other major non-cardiac illness expected to reduce life expectancy or interfere with study participation.
- Patient is simultaneously taking another experimental drug.
- Previously randomized to HOPE.

3.3 Study treatments

After an initial single blind run-in period, during which patients received 2.5mg once daily of active ramipril for 7-10 days followed by placebo ramipril for 10-14 days, patients were randomized (in a double blind fashion) to ramipril (2.5mg once daily for 7 days followed by 5.0mg once daily for 21-31 days, then 10mg once daily for the remainder of the study) or placebo and Vitamin E (400 IU once daily) or placebo, using a factorial 2 x 2 design. Patients were followed on a regular basis at six month intervals during which all cardiovascular events and hospitalizations were monitored.

3.3.1 Details of study treatments

Patients were to be randomized to ramipril (10mg/day) or placebo and/or Vitamin E (400 IU/day) or placebo using a 2x2 factorial design as shown below:

	Ramipril Active	Ramipril Placebo
Vitamin E Active	Vitamin E Active + Ramipril Active	Vitamin E Active + Ramipril Placebo
Vitamin E Placebo	Vitamin E Placebo + Ramipril Active	Vitamin E Placebo + Ramipril Placebo

The dose of ramipril was 2.5mg once daily for 7 days followed by 5.0mg once daily for 21-31 days, then 10mg once daily for the remainder of the study. The dose of Vitamin E was 400 IU once daily throughout. Details of dose adjustments are shown below (see 3.3.5).