Study Report Addendum

Study title	The **IONA** Study (**I**mpact **O**f **N**icorandil in **A**ngina)
Name of test drug	Ikorel (nicorandil / N-(2hydroxyethyl) nicotinamide nitrate ester)
Indication studied	Secondary prevention of : the combined endpoints of coronary heart disease (CHD) related death, non-fatal myocardial infarction or unplanned cardiac hospitalisation, in subjects with angina of effort.
Brief description of study	A double-blind, parallel group, placebo controlled, multi-centre study to examine the hypothesis that nicorandil, with a target dose of 20mg twice daily, reduces the combined endpoints of coronary heart disease (CHD) related death, non-fatal myocardial infarction or unplanned cardiac hospitalisation, in subjects with angina of effort.
Name of the sponsors	University of Glasgow West Medical Building University of Glasgow Glasgow G12 8QQ Tel 0141 3304761 Fax 0141 3371651 Merck Pharmaceuticals Limited Harrier House, High Street West Drayton, Middlesex UB7 7QG 01895 452200 Fax 01895 420605 Aventis Pharma Limited 50 Kings Hill Avenue, Kings Hill West Malling, Kent ME19 4AH 01732 584000 Fax 01732 584080
Protocol identification	EMD 26385-147
Development phase of study	IV
Study initiation date	May 1998 (first patient enrolled)
Study completion date	August 2001 (last patient completed)
Name and affiliation of principal or coordinating investigator	[redacted]
Name of sponsor signatories of original report	[redacted]
Telephone number and fax number of the sponsor contact persons	[redacted]
Compliance with Good Clinical Practices (GCP)	The study was performed in compliance with Good Clinical Practices (GCP)
Date of the report	June 2003

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1/ Introduction

Aventis has submitted a type 2 variation to add a secondary prevention indication to the SPC for nicorandil based on the positive results of the IONA (Impact of Nicorandil in Angina) Study. The MHRA has considered the application and has asked for additional statistical analyses to be carried out in which cardiac mortality is replaced by total mortality in three composite endpoints reported in the original study report and publication [1]. The purpose of this addendum to the study report is to present the results of these analyses.

2/ Summary of IONA study

The IONA study was a major cardiovascular endpoint study sponsored and co-ordinated by the University of Glasgow (Robertson Centre for Biostatistics and the Clinical Research Centre, Western Infirmary, Glasgow), monitored by the CRO, Ingenix International and funded by grants from 3 pharmaceutical companies: Aventis (the UK license holders), Chugai and Merck.

Aim

The objective of the IONA study was to examine the hypothesis that nicorandil, at a target dose of 20mg twice daily, would reduce the combined primary endpoints of CHD death, non-fatal myocardial infarction or unplanned cardiac hospitalisation, in subjects with angina of effort. A secondary endpoint of interest was the impact of treatment on the number of cases of acute coronary syndrome reported during the study.

Design

The study was a multi-centre, randomised, double-blind, parallel group, placebo-controlled trial. Subjects satisfying the inclusion and exclusion criteria were randomised in a 1:1 ratio to receive placebo or nicorandil 10mg bd., increasing to 20mg bd. after two weeks. Patients intolerant of the 10mg bd. dose (or matching placebo) had the study medication discontinued. During the follow-up period subjects were seen 4 monthly for clinic visits. Recruitment took place over about 2 years and the study continued until the target number of patient-years of follow-up was achieved (8750 patient years).

Inclusion criteria

Patients had to satisfy <u>all</u> of the following criteria:

- Patients must provide written informed consent prior to their inclusion in the study.
- Men (aged >45 years) or women (aged >55 years)
- Evidence of stable angina of effort (one or more episodes of angina or use of GTN tablet or spray) for symptomatic relief at least once per week. This inclusion criteria was changed under amendment 1 of the protocol to read "Patients with evidence of angina of effort for whom further medical treatment may be appropriate".
- Need for regular treatment with one or more oral symptomatic anti-anginal medications (e.g. long acting nitrate formulation, beta blocker, calcium channel blocker)
- The patient must satisfy <u>at least one</u> of (A), (B) or (C)

(A) Previous MI
(B) Previous CABG

(C) CHD proven by angiography or a documented positive exercise test (≥1mm ST depression) in the previous two years, and at least one of the following:
(C i) LVH on ECG (tall R in aVL, Sv1 + Rv6 > 35mm, lateral T inversion)
(C ii) Evidence of left ventricular dysfunction (EF ≤45% or EDD >5.5cm)
(C iii) Age ≥65 years
iv) Diabetes (Types I or II)
(C v) Hypertension (treated and/or SBP >160 or DBP >95)
(C vi) Documented evidence of other vascular disease (stroke, hospitalised TIA, PVD)

Exclusion Criteria

Patients were excluded for any of the following reasons

- Pregnancy or lactation
- Legal incapacity or limited legal capacity
- Participation in another clinical study within the past 30 days
- Presence of contra-indications to the study medication(s)
- Known drug or alcohol abuse
- Uncontrolled cardiac failure or arrhythmias
- Unstable angina, CABG or MI in the previous three months
- PTCA in the previous six months
- Treatment with sulphonylureas such as chlorpropamide, glibenclamide, gliclazide or tolbutamide.
- The presence of other disease that in the investigator's opinion would reduce the patient's life expectancy or influence significantly their cardiovascular condition.
- Current treatment with nicorandil.
- Uncontrolled hypertension (SBP >180 or DBP >110mmHg)

Criteria for evaluation

Efficacy: The primary endpoint of the study was the combined events of CHD death, non-fatal myocardial infarction or unplanned hospitalisation for chest pain. Secondary endpoints included a/ CHD death or non-fatal myocardial infarction and b/ acute coronary syndrome.

Safety: Safety was evaluated throughout the study by assessment of serious adverse events and reasons for cessation of randomised therapy.

Statistical Methods

Outcomes studied included the Primary and Secondary endpoint as well as mortality as a combined outcome and split by mode of death, all cardiovascular events, cardiovascular hospitalisation, cerebro-vascular events and all hospitalisations.

All endpoints were evaluated on an intention to treat basis. All clinical outcomes were analysed on a survival basis. The outcome was taken as the time to first occurrence of the event of interest or the end of study follow-up, whichever came first. The date of occurrence of silent myocardial infarction was taken to be the midpoint between the dates of the diagnostic ECG and the previous ECG. Treatment groups were compared on the basis of the log-rank test. Risk reductions and 95% CI's were calculated from the Cox proportional hazards model with treatment fitted as the only co-variate. These analyses were repeated,

adjusting for the following covariates: age; sex; history of MI; history of CABG; history of hypertension; history of diabetes; LVH on ECG; evidence of LVD and smoking status (as evaluated at baseline). Changes in blood pressure were compared by Student's two-sample *t* test with associated 95% CI.

The data and Safety monitoring committee used a value of $p<0{\cdot}001$ for all-cause mortality as a guideline for stopping the trial early if there was overwhelming evidence of benefit.

Results

Demographic and baseline data: 5126 patients were randomised into the study, 2550 from hospital centres and 2576 from general practice. 2565 patients were randomised to receive nicorandil and 2561 were randomised to receive placebo. Patients had an average age of 67 years and 76% of the patients were male. 96% of the patients included had evidence of coronary heart disease on a previous angiogram. 60% of the patients were former smokers and 16% were current smokers. Only 8% of patients were diabetic, which is low for a population with angina but explained by the exclusion of any patient taking a sulphonylurea. Patients in the two treatment groups were comparable in terms of demographics and cardiovascular risk factors

Efficacy: The combined endpoints of CHD death, non-fatal MI or hospital admission for cardiac chest pain showed a 17% reduction in the nicorandil group which was statistically significant (HR: 0·83, (0·72–0·97), p=0.014). Such a marked reduction in these events is of clear clinical significance. The benefit shown appeared to start early with a divergence between the two treatment groups appearing almost immediately and increasing over time. There was no statistically significant difference in the rate of the secondary endpoint—coronary heart disease death or non-fatal myocardial infarction, between the nicorandil group and the placebo group (HR: 0·79 (0·61–1·02), p=0·068). The distributions of patients with non-fatal coronary events are given in the table below. There were fewer events in the nicorandil group in all sub-categories. Exploratory analyses on additional composite endpoints were carried out. Acute coronary syndromes and all cardiovascular events were significantly less common on nicorandil than placebo. All-cause mortality was not significantly different between the groups. There was a similar number of cerebrovascular events and non-cardiovascular deaths on nicorandil as on placebo.

Component events	Nicorandil (n=2565)	Placebo (n=2561)	Hazard Ratio (95% CI)	p
CHD death	60	73	-	-
Non-fatal MI	56	72	-	-
Unstable angina	56	73	-	-
Definite angina	115	127	-	-
Presumed angina	126	152	-	-
Stroke or Hospital admission for TIA	37	40	-	-

Composite Events	Nicorandil (n=2565)	Placebo (n=2561)	Hazard Ratio (95% CI)	p
CHD death, non-fatal MI or hospital admission for chest pain	337	398	0.83	0.014
CHD death or non-fatal MI	107	134	0.79	0.068
CHD death, non-fatal MI or unstable angina	156	195	0.79	0.028
All cardiovascular events	378	436	0.86	0.027
All cause Mortality	111	129	0.85	0.222

Safety: The study was conducted with the minimum of interventions and deviations from normal clinical care. No routine laboratory tests were requested as part of the main study. The study confirmed the significant incidence of headache that occurs at the start of treatment with nicorandil. 81 patients withdrew from treatment in the placebo group compared with 364 in the nicorandil group for headache alone.

All serious adverse events were collected and analysed. In total there were 4320 SAEs, 2162 in the nicorandil group and 2158 in the placebo group. Overall, the incidence of serious adverse events is similar in the two groups. In the placebo-treated group, 375 patients withdrew because of adverse events other than headache compared with 342 in the nicorandil treated group.

The notable differences between the two groups are a reduction in cardiovascular events and an increase in gastrointestinal events in the patients treated with nicorandil compared to placebo. In particular, there were 13 cases of rectal bleeding in the nicorandil treated group compared with only 2 cases in the placebo treated group. An increase in diverticular disease in the nicorandil treated group also contributed to the overall increase in gastrointestinal SAEs in the nicorandil treated group with 20 cases compared with 5 in the placebo treated group.

Original conclusions

IONA Study was a large double-blind, randomised, controlled outcome trial whch demonstrated that nicorandil reduced cardiovascular events in patients with angina. Nicorandil reduced the combined event rates of cardiovascular death, MI and hospitalisation for chest pain (RRR=17%) compared with placebo (p=0.014). The rate of acute coronary syndromes was also reduced (RRR 21% p=0.028).

3/ Results of new analyses

Extended Primary endpoint

As requested by the MHRA an analysis has now been carried out for the primary endpoint, using all-cause mortality instead of CHD death. The summary results show that the proportion of patients with the extended primary endpoint are: 14.9% for nicorandil compared to 17.3% for placebo ($p<0.05$). The results of the log-rank test, and hazard ratios are given in the following table and a Kaplan-Meier plot is given in figure 1.

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All Deaths / Non-Fatal MI / Unplanned Hospitalisation with Cardiac Chest Pain

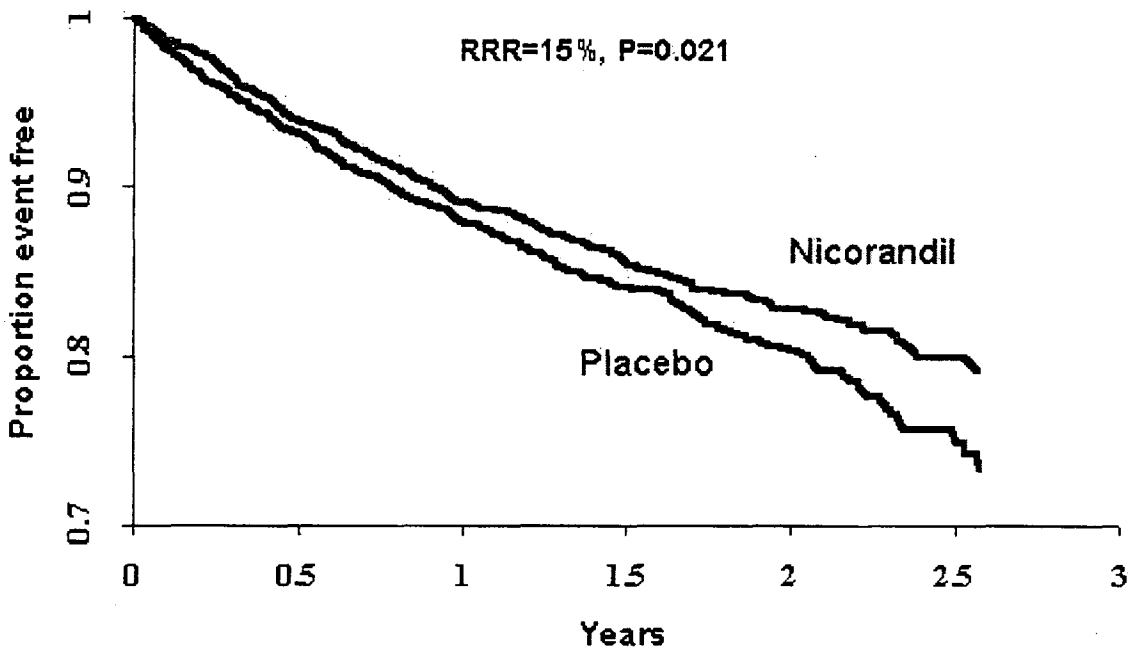
	Nicorandil n-events/at risk(%)	Nicorandil event-proportion* (95% CI)	Placebo n-events/at risk(%)	Placebo event-proportion* (95% CI)
Year 1 Months 1 - 3	67 2565 (2.61%)	0.03 (0.02, 0.03)	96 2561 (3.75%)	0.04 (0.03, 0.04)
4 - 6	86 2484 (3.46%)	0.06 (0.05, 0.07)	79 2452 (3.22%)	0.07 (0.06, 0.08)
7 - 9	61 2394 (2.55%)	0.08 (0.07, 0.09)	69 2369 (2.91%)	0.10 (0.08, 0.11)
10 - 12	60 2331 (2.57%)	0.11 (0.10, 0.12)	63 2297 (2.74%)	0.12 (0.11, 0.13)
Year 2 Months 1 - 3	33 2094 (1.58%)	0.12 (0.11, 0.14)	39 2051 (1.90%)	0.14 (0.13, 0.15)
4 - 6	32 1563 (2.05%)	0.14 (0.13, 0.16)	30 1545 (1.94%)	0.16 (0.14, 0.17)
7 - 9	21 1193 (1.76%)	0.16 (0.14, 0.18)	27 1163 (2.32%)	0.18 (0.16, 0.20)
10 - 12	10 839 (1.19%)	0.17 (0.15, 0.19)	14 822 (1.70%)	0.20 (0.18, 0.21)
Year 3 Months 1 - 3	7 618 (1.13%)	0.19 (0.17, 0.20)	15 600 (2.50%)	0.22 (0.20, 0.25)
4 - 6	4 362 (1.10%)	0.20 (0.18, 0.23)	8 355 (2.25%)	0.25 (0.22, 0.28)
7 - 9	1 111 (0.90%)	0.21 (0.18, 0.24)	2 96 (2.08%)	0.27 (0.23, 0.30)
10 - 12	0 6 (0.00%)	0.21 (0.18, 0.24)	0 12 (0.00%)	0.27 (0.23, 0.30)
Year 4 Months 1 - 3	0 0 (0.00%)	0.21 (0.18, 0.24)	0 0 (0.00%)	0.27 (0.23, 0.30)
Overall Events (%)	382 2565 (14.9%)		442 2561 (17.3%)	

Log-rank test, p = 0.021

Hazard-ratio (95% CI) = 0.85 (0.74, 0.98)

* event-proportion = 1 - Kaplan-Meier estimate of survival

Figure 1 - Extended Primary endpoint



Extended acute coronary syndrome endpoint

As requested by the MHRA an analysis has now been carried out for the composite endpoint acute coronary syndrome, using all-cause mortality instead of CHD death. The summary results show that the proportion of patients with the extended primary endpoint are: 7.9% for

nicorandil compared to 9.6% for placebo ($p<0.05$). The results of the log-rank test, and hazard ratios are given in the following table and a Kaplan-Meier plot is given in figure 2.

IONA - 20MAY03

All Deaths / Non-Fatal MI / Unstable Angina

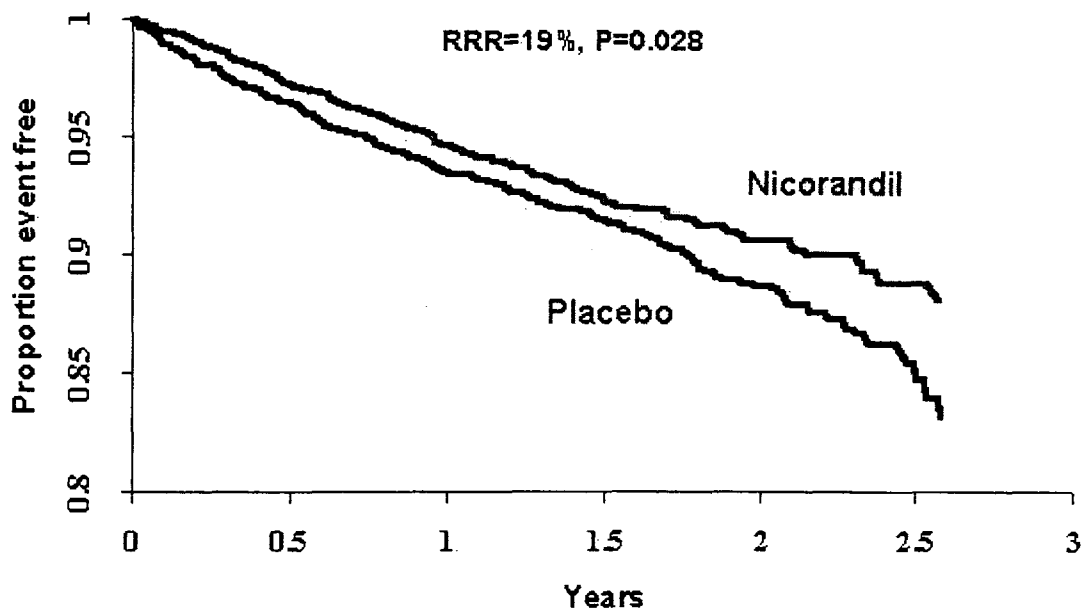
	Nicorandil			Placebo		
	n-events/at risk(%)	event-proportion* (95% CI)		n-events/at risk(%)	event-proportion* (95% CI)	
Year 1 Months 1 - 3	29 2565 (1.13%)	0.01	(0.01, 0.02)	49 2561 (1.91%)	0.02	(0.01, 0.02)
4 - 6	41 2522 (1.63%)	0.03	(0.02, 0.03)	40 2497 (1.60%)	0.03	(0.03, 0.04)
7 - 9	30 2477 (1.21%)	0.04	(0.03, 0.05)	40 2453 (1.63%)	0.05	(0.04, 0.06)
10 - 12	35 2445 (1.43%)	0.05	(0.04, 0.06)	36 2409 (1.49%)	0.07	(0.06, 0.07)
Year 2 Months 1 - 3	21 2228 (0.94%)	0.06	(0.05, 0.07)	17 2182 (0.78%)	0.07	(0.06, 0.08)
4 - 6	21 1673 (1.26%)	0.08	(0.07, 0.09)	19 1666 (1.14%)	0.09	(0.07, 0.10)
7 - 9	10 1288 (0.78%)	0.08	(0.07, 0.10)	18 1270 (1.42%)	0.10	(0.09, 0.11)
10 - 12	8 907 (0.88%)	0.09	(0.08, 0.11)	12 910 (1.32%)	0.11	(0.10, 0.13)
Year 3 Months 1 - 3	4 676 (0.59%)	0.10	(0.09, 0.12)	8 666 (1.20%)	0.13	(0.11, 0.14)
4 - 6	3 401 (0.75%)	0.11	(0.09, 0.13)	6 394 (1.52%)	0.15	(0.12, 0.18)
7 - 9	1 125 (0.80%)	0.12	(0.09, 0.14)	2 110 (1.82%)	0.17	(0.13, 0.20)
10 - 12	0 8 (0.00%)	0.12	(0.09, 0.14)	0 12 (0.00%)	0.17	(0.13, 0.20)
Year 4 Months 1 - 3	0 0 (0.00%)	0.12	(0.09, 0.14)	0 0 (0.00%)	0.17	(0.13, 0.20)
Overall Events (%)	203 2565 (7.91%)			247 2561 (9.64%)		

Log-rank test, p = 0.028

Hazard-ratio (95% CI) = 0.81 (0.67, 0.98)

* event-proportion = 1 - Kaplan-Meier estimate of survival

Figure 2 - Extended acute coronary syndrome endpoint



Extended all-cause mortality or MI endpoint

As requested by the MHRA an analysis has now been carried out for the composite endpoint all-cause mortality or MI. The summary results show that the proportion of patients with the

extended primary endpoint are: 6.1% for nicorandil compared to 7.3% for placebo (trend). The results of the log-rank test, and hazard ratios are given in the following table and a Kaplan-Meier plot is given in figure 3.

IONA - 20MAY03

All Deaths / Non-Fatal MI

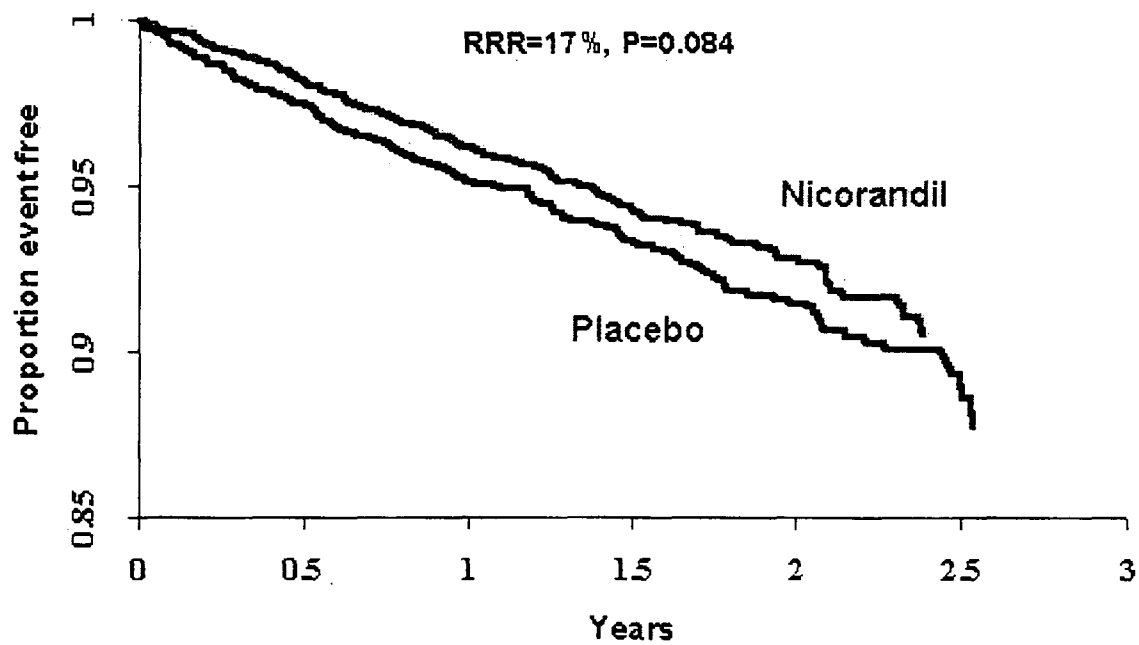
	Nicorandil			Placebo		
	n-events/at risk(%)	event-proportion*	(95% CI)	n-events/at risk(%)	event-proportion*	(95% CI)
Year 1 Months 1 - 3	21 2565 (0.82%)	0.01	(0.00, 0.01)	34 2561 (1.33%)	0.01	(0.01, 0.02)
4 - 6	25 2530 (0.99%)	0.02	(0.01, 0.02)	29 2512 (1.15%)	0.02	(0.02, 0.03)
7 - 9	26 2501 (1.04%)	0.03	(0.02, 0.03)	31 2479 (1.25%)	0.04	(0.03, 0.04)
10 - 12	25 2473 (1.01%)	0.04	(0.03, 0.05)	29 2444 (1.19%)	0.05	(0.04, 0.06)
Year 2 Months 1 - 3	15 2263 (0.66%)	0.05	(0.04, 0.05)	13 2222 (0.59%)	0.06	(0.05, 0.06)
4 - 6	18 1705 (1.06%)	0.06	(0.05, 0.07)	18 1694 (1.06%)	0.07	(0.06, 0.08)
7 - 9	9 1316 (0.68%)	0.06	(0.05, 0.07)	14 1292 (1.08%)	0.08	(0.07, 0.09)
10 - 12	7 930 (0.75%)	0.07	(0.06, 0.08)	7 928 (0.75%)	0.08	(0.07, 0.10)
Year 3 Months 1 - 3	7 696 (1.01%)	0.08	(0.07, 0.10)	7 685 (1.02%)	0.10	(0.08, 0.11)
4 - 6	3 417 (0.72%)	0.09	(0.07, 0.11)	3 404 (0.74%)	0.11	(0.09, 0.14)
7 - 9	0 128 (0.00%)	0.09	(0.07, 0.11)	1 117 (0.85%)	0.12	(0.09, 0.15)
10 - 12	0 8 (0.00%)	0.09	(0.07, 0.11)	0 13 (0.00%)	0.12	(0.09, 0.15)
Year 4 Months 1 - 3	0 0 (0.00%)	0.09	(0.07, 0.11)	0 0 (0.00%)	0.12	(0.09, 0.15)
Overall Events (%)	156 2565 (6.08%)			186 2561 (7.26%)		

Log-rank test, p = 0.084

Hazard-ratio (95% CI) = 0.83 (0.67, 1.03)

* event-proportion = 1 - Kaplan-Meier estimate of survival

Figure 3 - Extended all-cause mortality or MI endpoint



4/ Conclusions

The additional analyses carried out at the request of the MHRA confirm the findings of the original statistical analyses and provide reassurance that the original results were due in part to a beneficial effect of nicorandil on cardiovascular mortality rather than an effect of shifting the cause of death from cardiovascular to non-cardiovascular.

The finding for the primary endpoint reworked using all cause mortality shows a relative risk reduction of 15% (absolute risk reduction of 2.4%, p=0.021). This results supports the validity of the original results.

Perhaps more interesting in angina patients is the potential impact of nicorandil in preventing acute coronary syndrome. The acute coronary syndrome composite reworked using all cause mortality shows a relative risk reduction 19% (absolute risk reduction 1.73%, p=0.028). Given that acute coronary syndrome is a common end-stage event in angina patients any reduction in this condition is of considerable benefit both to patients and to health care providers.

The finding of a trend in favour of nicorandil for the composite endpoint of MI and all cause mortality is also reassuring since it confirms that intervention with nicorandil is not harmful.

In summary, the results of the additional analyses requested by the MHRA are supportive of the original findings of the IONA study and confirm that secondary prevention of cardiovascular events in angina patients treated with nicorandil does not occur at the cost of significant alternative morbidity and mortality.

5/ Reference

1 The IONA Study Group.
Effect of nicorandil on coronary events in patients with stable angina: The Impact of Nicorandil in Angina (IONA) randomised trial.
Lancet 2002; 359: 1269-75

6/ Signature

I the undersigned, fully endorse the contents of this addendum to the clinical trial report on the IONA study (clinical documentation of nicorandil tablets).

[redacted]

Aventis Pharma, West Malling, Kent.

June 2003