Study Report

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	[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	November 2002

2. Study synopsis

Title of the study:
The IONA study. The Impact of Nicorandil in Angina

Investigators:
Principal Investigator: [redacted]

Study Centre(s):
226 Centres in UK 78 Hospital 148 General Practice
The study was co-ordinated by the University of Glasgow (Robertson Centre for Biostatistics and the Clinical Research Centre, Western Infirmary, Glasgow). The protocol stated that monitoring of the study sites would be carried out by the Nottingham Clinical Trial Data Centre (NCTDC), Queen's Medical Centre, University Hospital, Nottingham. Under amendment 2 to the protocol, the monitoring was performed by the CRO, Ingenix International. Subjects were seen in the investigators' clinics in hospitals throughout the UK, and under the terms of protocol amendment 2, in GP practices throughout the UK.

Publication (Reference):
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

Study Period (years): 3.25 (May 1998 to Aug 2001)	**Clinical Phase: 4**

Objectives:
The objective of this trial was to examine the hypothesis that nicorandil, at a target dose of 20mg t wice daily, would reduce the combined endpoints of CHD death, non-fatal myocardial infarction or unplanned cardiac hospitalisation, in subjects with angina of effort.

Methodology:
A multi-centre, randomised, double-blind, placebo-controlled design was used. 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 was expected to take 2 years. The study was planned to continue until a target number of patient-years of follow-up was achieved or until 3 years had passed from the date of the first randomisation, unless early termination was recommended due to overwhelming evidence of benefit or because of evidence of harm.

Number of Subjects:
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 – see table below.

Demographics and CV risk factors		
	Nicorandil	**Placebo**
Male	76%	76%
Mean Age - years	67	67
Mean BMI	28	28
Mean BP mm Hg	138/79	138/79
Smokers (ex-smokers)	16% (61%)	17% (59%)
Diabetic	8%	9%
Hypertensive	47%	46%
Previous MI	66%	66%
Previous CABG	22%	23%
Previous PTCA	14%	15%
Previous Stroke	5%	5%
Previous LVD	9%	8%

Diagnosis and criteria for inclusion:

The planned study population was 5000 patients, men aged >45 years and women aged >55 years, with angina of effort and determined to be at higher than average risk of cardiovascular critical events. Newly diagnosed patients were permitted as long as their angina was stable. Subjects were not allowed to be scheduled for, or require, a coronary artery revascularisation procedure at the time of randomisation.

Inclusion criteria

Patients had to satisfy all 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 at least one of (A), (B) or (C)**

(A) Previous MI

(B) Previous CABG

(C) CHD proven by angiography or a documented positive exercise test ($\geq$ 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 $\leq$45% or EDD >5.5cm)

(C iii) Age$\geq$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)

Test Product, dose, mode of administration:

Nicorandil, orally, 10mg bd., increasing to 20mg bd. after two weeks. Patients intolerant of the 10mg bd. dose had the study medication discontinued.

Duration of treatment:

The target total number of patient years of randomised follow-up was 8750 years (average 21 months per/patient). It was expected that minimum treatment/follow-up for each patient would be 12 months. The maximum follow-up would be 36 months.

The average duration of follow up of the patients was 1.6 years and was similar in both treatment groups. Slightly in excess of 11% of patients withdrew from study medication at or before 2 weeks. By the end of the study nearly 40% of patients in the nicorandil treatment group and over 30% of the patients in the placebo treatment group had withdrawn from study drug. All patients were followed up until the end of the study.

Percentage of Patients Discontinued from study drug		
	Nicorandil	**Placebo**
2 Weeks	16.1	6.4
8 Weeks	22.1	12
6 Months	29.6	19.5
End of Study	39.1	31.6

Reference therapy, dose, mode of administration:

Matching placebo, orally, "10mg" bd., increasing to "20mg" bd. after two weeks. Patients intolerant of the 10mg bd. dose had the study medication discontinued.

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.

The secondary endpoint was CHD death or non-fatal myocardial infarction.

Criteria for evaluation (cont.):

Safety:

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

Other assessments:

Prospective analyses of healthcare resource utilisation were to be performed. This was to be achieved through the assessment of hospitalisation data.

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.
It was estimated that a study of 5000 patients and a primary event rate of 13%, would give 95% power (significance level 5%) to identify a 25% reduction in the primary event rate (80% power to pick up a 20% reduction). Similarly an event rate of 8% was anticipated for the Secondary endpoint which would yield 80% power to pick up a 25% risk reduction.
Clinical outcomes were sought on all patients until death, study closedown, or withdrawal of informed consent for follow-up, whichever came first. For patients lost to follow-up, events were censored at the last visit.
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

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.

	Nicorandil (n=2565)	Placebo (n=2561)	Hazard Ratio (95% CI)	p
Component events				
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				
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

Results

Safety:

This 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.

This 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.

Serious Adverse Events *by body system by event rate in nicorandil group*
Rate = the number of events per thousand person years of follow-up

Body system	**Nicorandil**			**Placebo**		
	Subjects	**events**	**rate***	**subjects**	**events**	**rate***
Myo endo pericardial & valve disorder	435	618	150.04	503	782	191.33
Operations & procedures	292	370	89.83	290	356	87.10
Gastro-intestinal system disorders	163	194	47.10	110	132	32.30
Cardiovascular disorders, general	117	136	33.02	133	153	37.43
Neoplasm	93	135	32.77	88	120	29.36
Respiratory system disorders	86	109	26.46	68	85	20.80
Musculo-skeletal system disorders	76	84	20.39	64	66	16.15
Vascular (extracardiac) disorders	76	83	20.15	75	86	21.04
Heart rate and rhythm disorders	56	67	16.27	50	55	13.46
Urinary system disorders	45	50	12.14	47	59	14.44
Vision disorders	43	46	11.17	26	31	7.58
Metabolic and nutritional disorders	42	45	10.92	24	24	5.87
Central and periph nerv syst disorders	29	36	8.74	29	30	7.34
Body as a whole - general disorders	32	32	7.77	35	37	9.05
Skin and appendages disorders	25	25	6.07	15	15	3.67
Liver and biliary system disorders	14	19	4.61	19	27	6.61
Reproductive disorders male	16	18	4.37	10	10	2.45
Psychiatric disorders	15	16	3.88	12	13	3.18
Resistance mechanism disorders	15	15	3.64	11	11	2.69
Red blood cell disorders	12	14	3.40	11	18	4.40
Neonatal and infancy disorders	13	14	3.40	8	8	1.96
Application site disorders	12	12	2.91	13	13	3.18
Platelet, bleeding & clotting disorder	9	9	2.18	10	10	2.45
Unknown	7	7	1.70	7	7	1.71
Hearing and vestibular disorders	3	4	0.97	5	5	1.22
Reproductive disorders female	2	2	0.49	4	4	0.98
Endocrine disorders	2	2	0.49	0	0	0.00
WBC and reticulo-endo sys disorders	0	0	0.00	1	1	0.24
Total	**1135**	**2162**	**524.88**	**1128**	**2158**	**527.99**

Conclusions:

This large double-blind, randomised, controlled outcome trial has demonstrated that nicorandil reduces cardiovascular events in patients with angina.

- The IONA study showed that 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 reduced (RRR 21% p=0.028)
- There is evidence that the rate of gastrointestinal events may be increased with nicorandil, particularly rectal bleeding and possibly the expression of diverticular disease.

Date: November 2002

TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACE	Angiotensin converting enzyme
ACIP	Asymptomatic Cardiac Ischaemia Pilot study
AE	Adverse event
AII	Angiotensin II
ASIST	Atenolol Silent Ischaemia Study
ATP	Adenosine tri-phosphate
aVL	Augmented limb lead on the ECG relating to the left arm
bd	Twice a day
BMI	Body mass index (weight in kilos x square of height in metres)
BP	Blood pressure
bpm	Beats per minute
CABG	Coronary artery by-pass grafting
CCSF	Canadian Cardiovascular Society Functional classification of angina score
CE	Critical Event (e.g. Critical Event Committee)
CHD	Coronary heart disease
CI	Confidence interval (e.g. 95% CI = 95% confidence interval)
CIOMS	Council for International Organizations of Medical Sciences
CRF	Case report form
CRO	Clinical Research Organisation
CV	Cardiovascular
CV	Curriculum vitae
DBP	Diastolic blood pressure
ECG	Electrocardiogram (usually 12 lead)
EDD	End diastolic ventricular diameter (high values in ventricular dysfunction)
EF	Ejection fraction (usually given as % of predicted value)
GCP	Good clinical practice
GMP	Good manufacturing practice
GP	General practitioner (family doctor)
GP IIb / IIIa	Glycoprotein receptor on surface of platelet important in platelet adhesion
GTN	Glyceryl tri-nitrate
HR	Hazard Ratio (usually calculated by the Cox proportional hazards method)
HR	Heart rate
IEC	Independent Ethics Committee (similar to IRB)

IONA	Impact Of Nicorandil in Angina study
IR	Incidence rate
IRB	Institutional Review Board (similar to IEC)
LREC	Local Research Ethics Committee
LVD	Left ventricular dystrophy
LVH	Left ventricular hypertrophy
MI	Myocardial infarction
MREC	Multicentre Research Ethics Committee
NCTDC	Nottingham Clinical Trials Data Centre
NHS	National health Service (United Kingdom publicly funded health service)
PTCA	Percutaneous transarterial coronary angioplasty
PVC	Polyvinyl chloride
PVD	Peripheral vascular disease
QA	Quality assurance
R	R wave on ECG recording (e.g. tall R wave suggesting LVH)
RRR	Relative risk reduction (difference in risk rates as a % of risk rate on placebo)
Rv6	Measurement made from ECG (e.g. Sv1 + Rv6 > 35mm suggests LVH)
SAE	Serious adverse event
SBP	Systolic blood pressure
SD	Standard deviation
SPC	Summary of product characteristics
ST	Part of ECG wave form (ST depression may suggest cardiac ischaemia)
Sv1	Measurement made from ECG (e.g. Sv1 + Rv6 > 35mm suggests LVH)
T	T wave on ECG recording (e.g. lateral T wave inversions suggests LVH)
TIA	Transient ischaemic attack
TIBET	Total Ischaemic Burden European Trial
UK	United Kingdom of Great Britain and Northern Ireland
WHO	World Health Organisation
WHO-ART	World Health Organisation - Adverse Reaction Terminology
WOSCOPS	West of Scotland Pravastatin Study

5. ETHICS

5.1 INDEPENDENT ETHICS COMMITTEE (INSTITUTIONAL REVIEW BOARD EQUIVALENT)

The study protocol and all major amendments were approved by Independent Ethics Committees (IECs) and by the regulatory authorities, according to English and Scottish law. The study protocol and all amendments were reviewed by the Scottish MREC, Deaconess House, Edinburgh EH8 9RS [redacted] The protocol and amendments were also reviewed by the LRECs responsible for each of the study's centres.

A list of all IECs consulted is given in appendix 16.1.3.

5.2 ETHICAL CONDUCT OF THE STUDY

The study was performed in accordance with the Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996).

5.3 PATIENT INFORMATION AND CONSENT

Prior to inclusion all subjects had to give their informed consent verbally as well as in writing. They were informed about the aims, procedures, potential benefits and hazards when participating in the study. Procedures varied at different centres but consent was generally obtained at a screening visit prior to the randomisation visit at which telephone randomisation to treatment was carried out.

Examples of the written patient information and a sample patient consent form are provided in appendix 16.1.3.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

The administrative structure of the study (principal investigator, coordinating investigator, steering committee, administration, monitoring and evaluation committees, institutions, statistician, contract research organisations (CROs), clinical trial supply management) were as follows :

Scientific steering committee - Voting members

[redacted]

Scientific steering committee - Sponsor representatives (non voting)

[redacted]

Critical events committee

[redacted]

Data and safety monitoring committee

[redacted]

Statistical and data centre - Robertson Centre for Biostatistics, University of Glasgow

[redacted]

Writing Committee

[redacted]

Study monitoring - Ingenix Pharmaceutical Services

[redacted]

See appendix 16.1.4 for a list of the principal investigators with their affiliations.

The signatures of the principal or coordinating investigators, as required by regulatory authorities, are included in appendix 16.1.5.

7. INTRODUCTION

Angina pectoris is important not only as a cause of disability in itself, but also because it is a potential marker for coronary heart disease (CHD). The prevalence of angina is difficult to assess but may vary from 2.3% to 5.1 % in men aged 40 to 59 years[1]. There are about 8 new cases per 10,000 of the population presenting to the NHS every year[2], approximately half of whom attend their General Practitioner first. The average age of presentation is 60 years in men and 67 years in women[3].

Although there has been a decline in CHD in most of the Western countries over the past 15 years, there is still significant morbidity and mortality associated with it. One in eight deaths world-wide and one in four in the UK are attributable to CHD, such that, in 1995 there were 133,000 deaths in England and Wales from this cause[4]. About one quarter of patients presenting with their first myocardial infarct have a preceding history of angina.

The effect of medical treatment on prognosis in angina is uncertain. No large scale clinical trials of specific anti-anginal agents have been carried out, although aspirin has been shown to improve outcome and there is evidence that lipid-lowering agents (statins) are effective.

Nicorandil has been marketed in Japan since 1984 and is currently licenced in the UK, where it is indicated for the prevention and long-term treatment of chronic angina pectoris. Anti-anginal efficacy and safety comparable to conventional oral nitrates, beta-blockers and calcium antagonists has been demonstrated in double blind randomised studies.[5]

Nicorandil is a nicotinamide ester with potassium channel opening properties. The nitrate component of the ester imparts additional properties characteristic of that class of therapeutic agent.

The consequent dual mechanism of action leads to relaxation of both arterial and venous smooth muscle. The potassium channel opening activity is responsible for dilatation of peripheral and coronary resistance arterioles. The nitrate component dilates systemic veins and epicardial coronary arteries. Nicorandil consequently increases coronary blood flow and reduces both cardiac pre- and after-load.[5] The cellular hypoxia that leads to angina and to disturbed myocardial function is thus reduced or abolished.

During ischaemia leading to cellular hypoxia, the decreased cytoplasmic ATP level induces a significantly increased efflux of potassium through the ATP dependent potassium channels. The resulting hyperpolarisation leads to electrical and contractile shut down of cells in the ischaemic area[6]. ATP is conserved, maintaining cellular integrity through the preservation of vital, intracellular metabolic functions. This may represent a natural myocardial protective mechanism[7].

Cardioprotective properties have been demonstrated in animal models of myocardial infarction. The role of potassium channels in this form of protection has been demonstrated during studies utilising the technique of ischaemic preconditioning[8&9]. The mechanisms involved in ischaemic preconditioning may also explain the clinical effects seen following sequential coronary artery occlusions during PTCA procedures and the clinical phenomena of warm-up angina and myocardial stunning[10&11]. A recent pilot study has demonstrated a reduction in the incidence of supraventricular and ventricular tachycardias in patients with unstable angina taking nicorandil, compared to placebo. A reduction in transient myocardial ischaemia was also shown[12].

The aims of this study are to show that cardiovascular events can be reduced in the target population using nicorandil therapy without increasing the rate of other serious adverse events. The study is designed to be able to detect a 25% reduction, with 90% power, in the primary endpoint of CHD death, non-fatal MI or unplanned hospitalisation for chest pain. Such a reduction would clearly represent an important improvement in the prognosis of patients with angina.

Subjects at very high risk are likely to be candidates for revascularisation; those who have been stable but whose angina is worsening would be difficult to randomise to placebo on top of their current medication. This leaves subjects with chronic stable angina and those who have newly been diagnosed with angina but not requiring intervention (a higher risk group) as the candidates for this study.

8. STUDY OBJECTIVES

The objective of this trial is to test the hypothesis that nicorandil, with a target dose of 20mg twice daily, will reduce the combined endpoints of CHD death, non-fatal myocardial infarction or unplanned cardiac hospitalisation, in subjects with angina of effort. The study objectives were therefore:

- To assess the safety and efficacy of oral nicorandil administered at a target dose of 20mg twice daily concomitantly with standard therapy in patients with angina of effort.

The primary hypothesis to be tested was:

- That nicorandil will reduce the incidence of the primary combined endpoint of CHD death, non-fatal myocardial infarction or unplanned hospitalisation for cardiac chest pain, in subjects with angina of effort.

The secondary endpoint to be evaluated was:

- That nicorandil will reduce the incidence of the secondary combined endpoint of CHD death or non-fatal myocardial infarction.

Other endpoints which were to be evaluated were:

- Mortality as a combined outcome and split by mode of death, all cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke, hospitalised TIA, unplanned hospitalisation for chest pain), cardiovascular hospitalisation, cerebrovascular events (fatal and non-fatal stroke or hospitalised TIA), all hospitalisations and worsening of anginal status.

9. INVESTIGATIONAL PLAN

9.1 OVERALL STUDY DESIGN AND PLAN - DESCRIPTION

The study was a randomised double-blind trial of nicorandil versus placebo in addition to standard anti-anginal therapy. At recruitment, subjects were required to have angina of effort which could be recently diagnosed or chronic.

There was a two week titration period - study medication was initiated as nicorandil 10mg bd or matching placebo. Patients clearly intolerant of this dose and showing no evidence of symptom remission were withdrawn from the study. All randomised patients were followed until the end of the study.

After two weeks the dose was increased to nicorandil 20mg bd or matching placebo. Patients persistently intolerant of the higher dose were permitted to have their dose reduced to 10mg bd, and remained on this dose for the duration of their participation in the study. Patients satisfactorily established on the 20 mg bd were not expected to require a subsequent dose reduction unless there was a significant change in their clinical status. Such reductions were permitted, but the investigator had to document clearly the reasons for the action and was

required to consider carefully if the precipitating event could be defined as serious. Patients whose dose was reduced were to be maintained on the lower dose until the end of their participation in the study.

Standard anti-anginal therapy was not specified but was required to be optimal therapy for the individual patient, as judged by the investigator.

It was planned that the study would take three years to complete. It was envisaged that there would be a two year recruitment period and a follow-up period of one year. It was planned that all patients would finish the study at approximately the same time, but after a varying individual study duration. The target total number of patient years of randomised follow-up was 8750 years (average 21 months per/patient). It was expected that minimum follow-up for each patient would be 12 months and that the maximum follow-up would be 36 months. The study was planned to continue until the target number of patient-years of follow-up was achieved or until 3 years had passed from the date of the first randomisation, unless early termination was recommended due to overwhelming evidence of benefit or because of evidence of harm.

The schedule of study procedures is summarised in the following table:

IONA study visits and assessments

Procedure	Screening Phase/ Randomisation	Double-Blind Treatment Visits During Each Year of Study			End of Study
		4 month	8 month	12 month	Final
Record sex and date of birth	X				
Document positive cardiac investigations	X				
Full Informed Consent	X				
Medical History	X				
Angina Classification	X	X	X	X	X
Concomitant Medication	X	X	X	X	X
Height[a], Weight, BP, HR	X				X
Smoking information	X				
12-Lead ECG	X			X	X
Medication Dispensed	X[b]	X	X	X	
Patient Compliance		X	X	X	X
30ml blood sample obtained	X				
Inclusion/Exclusion Checks	X				
Randomisation	X				
Assessment for SAE		X	X	X	X

[a] Height measured during screening assessment only.

[b] 10mg bd nicorandil or matching placebo, increasing to 20mg bd or matching placebo after two weeks.

A copy of the protocol and amendments is included as appendix 16.1.1.

A sample case report form (unique pages only) is included as appendix 16.1.2.

9.2 DISCUSSION OF STUDY DESIGN, INCLUDING THE CHOICE OF CONTROL GROUPS

Clinical trials designed to investigate secondary (and primary) prevention of cardiovascular endpoints all have a number of features in common: double blind, placebo controlled, parallel group design, use of the licensed, marketed dose of the study drug, large sample size, powered to demonstrate a significant difference in abs olute risk for a composite endpoint (cardiovascular death, major cardiovascular event/intervention), long-term follow up (patients recruited early in the study followed up for longer than those recruited late), results analysed by survival analysis (Kaplan Meier method), steering, endpoint and safety monitoring committee structure. The IONA study had all of these features. Indeed it was designed in the light of experience with earlier studies carried out in Scotland (e.g. WOSCOPS). Thus the IONA study applied tried and tested cardiac event prevention methodology, as used previously to demonstrate effects of lipid lowering agents, to the demonstration of similar effects of the novel anti-anginal agent, nicorandil.

9.3 SELECTION OF STUDY POPULATION

It was planned that a total of 5000 subjects would be randomised in equal numbers to nicorandil or placebo, with recruitment from trial centres to be established in major hospitals in the U.K. It was anticipated that up to 100 centres would be required. As the study progressed it became clear that GP centres would also be required if an adequate sample of angina patients was to be recruited in the planned time frame. As a result over 100 GP centres contributed patients to the study.

In addition to the usual opportunistic routes of patient identification, listings of patients who had suffered myocardial infarcts or undergone coronary artery bypass grafting were screened in order to identify suitable subjects.

9.3.1 INCLUSION CRITERIA

To be included in the IONA study patients had to satisfy <u>all</u> of the following criteria:

- Patients had to 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
- Need for regular treatment with one or more oral symptomatic anti- anginal medications (e.g. long acting nitrate formulation, beta blocker, calcium channel bloc ker)
- The patient had to satisfy <u>at least one</u> of **(A)**, **(B)** or **(C)**
- A : Previous MI
- B : Previous CABG
- C : CHD proven by angiography <u>or</u> a documented positive exercise test (≥ 1mm ST depression) in the previous two years, <u>and at least one of the following</u>:
    - (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
    - (C 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 for a TIA, PVD)

9.3.2 EXCLUSION CRITERIA

Patients were excluded if any of the following applied:

- 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. This group of anti-diabetic drugs block potassium channel opening and may antagonise those effects of nicorandil specific to this action.
- 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)

The entry criteria reflected a/ the safety warnings and side effects listed in the SPC for nicorandil, b/ the need to exclude patients whose medical condition was unstable (e.g. recent cardiovascular event) and c/ patients on treatments which might antagonise or confound the proposed therapeutic benefit of nicorandil being studied.

9.3.3 REMOVAL OF PATIENTS FROM THERAPY OR ASSESSMENT

All permanent withdrawals from study medication were documented on a 'Withdrawal from Study Medication' form, whether associated with an adverse event or not. The reason for withdrawal was recorded. Patients withdrawn from study medication were followed-up until study completion to permit recording of SAE data.

Any subject who experienced an adverse event could have been withdrawn at any time from the study at the discretion of the investigator. If a subject was withdrawn wholly or in part because of an adverse event, the appropriate 'Permanent Withdrawal from Study Medication' form had to be completed. SAEs resulting in withdrawal were also to be documented on SAE forms.

Unless there was a medical reason to the contrary, patients experiencing a non-fatal study critical event were continued on randomised therapy.

9.4 TREATMENTS

9.4.1 TREATMENTS ADMINISTERED

Dosage and administration of study medication :
The doses and regimens of nicorandil used for the IONA study were the licensed doses administered according to the SPC.

Patients were informed by the investigator how to take their medication and the investigator ensured that the instructions were understood by the patient.

At each visit, the patients received a pack containing the study medication. They were requested to take one tablet twice a day - morning and evening.

The maximum dose was 40 mg (20mg + 20mg) of nicorandil or matching placebo per day. The highest dose tolerated during the titration period was used for the whole trial period unless subsequent events precluded this.

The investigators increased the dose according to the schedule, unless a justifiable clinical decision was made to not do so.

Investigators were allowed to decrease the dose in case of an adverse event which, in the opinion of the investigator, required a dose reduction. However, an adjustment of the dose of the concomitant anti-anginal treatment (standard) was required to be taken into consideration before changing the dose of the study medication.

If the patient did not tolerate the study medication (10mg bd) during the first two weeks of the administration, they were withdrawn. Patients who were withdrawn for this reason were followed up for the recording of SAEs until the end of the study.

If it was not possible to increase the dosage after the first two weeks, the patient remained on 10 mg twice a day for the rest of the study.

At the end of the trial the study medication was to be discontinued. The option to continue with prescribed medication was at the investigator's discretion.

All unused medication was returned to the study site. An entry was made in the CRF if the Investigator suspected or confirmed a failure in patient compliance. The patient was permitted to continue in the study if the Investigator believed that the patient would subsequently comply, following explanation and advice.

Blinding - Manufacture of the study medication

The study medication was manufactured at the GMP compliant manufacturing facility used to produce the marketed product [redacted] The clinical trial supplies were manufactured in production runs separated in time and routing from the regular commercial production. The formulation of the active product was identical to that of the marketed product. The placebo omitted the nicorandil component but was made to taste bitter because nicorandil is bitter. Primary packaging was carried out by [redacted] using blister packaging material identical to that used for the marketed product except that the foil was not overprinted (necessary to ensure the double blind). The tablets were sealed into desiccant containing, channelled PVC / aluminium blister packs. Each pack contained 10 tablets – corresponding to five day's supply.

Bulk blister packaged product was shipped to [redacted] for secondary packaging in patient treatment packs. The patient treatment pack identification codes were generated by [redacted]

[redacted] the company responsible for the adaptive telephone randomisation procedure. Medication was prepared in instalments as dictated by recruitment rate, production and distribution capacity and materials expiry date constraints.

To minimise storage and shelf life problems with the study medication, drug supplies were delivered to sites on the basis of predicted need (modelled by the [redacted] computer randomisation system). At each site there was an initial supply sufficient for ten patients.

When a patient was enrolled into the study, the investigator telephoned [redacted] with the information about the patient and received a treatment code number according to the packs already supplied to the centre. The relevant pack was then dispensed. This process was repeated each time a medication pack was dispensed. [redacted] logged the supplies that were distributed and dispensed and initiated the re-supply from [redacted] Each active site received a monthly report from [redacted] and the Robertson Centre. Sites were re-supplied unless a veto was received from that site (new stock not needed due to dropouts or withdrawals).

Storage and accountability of study medication
The study medication was to be stored at the study site, safely and separately from other drugs. A warning was issued that it was not to be exposed to direct sunlight or to the warmth given off by heaters.

The investigator (or pharmacist/individual, who was designated by the investigator) maintained records of the delivery of the study medication to the trial site, the inventory at the site, the use by each subject and the return to the sponsor.

Ongoing return of all unused study medication to [redacted] was permitted, but destruction at the study site was preferred.

Patient medication codes were retained at [redacted] and at the [redacted]. Investigators had 24 hour access to [redacted]

9.4.2 IDENTITY OF INVESTIGATIONAL PRODUCT(S)

The study medication was presented as off-white, bevelled edge, circular tablets with scoring on one face. Active and placebo tablets were identical in appearance. Active tablets contained nicorandil and were formulated as for the marketed product. Placebo tablets did not contain nicorandil but were formulated, otherwise as for the marketed product with the addition of bitter flavouring to ensure blinding (nicorandil tastes bitter).

9.4.3 METHOD OF ASSIGNING PATIENTS TO TREATMENT GROUPS

Patients were assigned to treatment with nicorandil or placebo on a 1: 1 basis by a computer driven adaptive randomisation system operated by [redacted]. When a patient was enrolled into the study, the investigator telephoned [redacted] with the information about the patient and received a treatment code number according to the packs already supplied to the centre. The relevant pack was then dispensed.

9.4.4 SELECTION OF DOSES IN THE STUDY

The doses and regimens of nicorandil used for the IONA study were the licensed doses administered according to the SPC.

9.4.5 SELECTION AND TIMING OF DOSE FOR EACH PATIENT

The doses and regimens of nicorandil used for the IONA study were the licensed doses administered according to the SPC.

9.4.6 BLINDING

Active tablets contained nicorandil and were formulated as for the marketed product. Placebo tablets did not contain nicorandil but were formulated, otherwise as for the marketed product with the addition of bitter flavouring to ensure blinding (nicorandil tastes bitter). The primary and secondary packaging carried no distinguishing marks which would have allowed the blind to be broken.

9.4.7 PRIOR AND CONCOMITANT THERAPY

The protocol for the IONA study contains no specific rules about prior and concomitant therapy other than those listed in the entry and exclusion criteria. The exclusion criteria relating to concomitant medication were :

- Treatment with sulphonylureas such as chlorpropamide, glibenclamide, gliclazide or tolbutamide. This group of anti-diabetic drugs block potassium channel opening and may antagonise those effects of nicorandil specific to this action.
- Current treatment with nicorandil.

9.4.8 TREATMENT COMPLIANCE

No specific study related measures were taken to ensure treatment compliance by patients. Treatment compliance was documented by way of drug accountability.

9.5 EFFICACY AND SAFETY VARIABLES

At screening, patients records were reviewed to identify evidence of stable angina of effort (one or more episodes of angina of effort or use of GTN or spray per week for symptomatic relief) and use of oral anti-anginal medications (nitrate, beta-blocker, calcium channel blocker). History of MI, CABG, CHD proven by angiography were also recorded as was evidence of a positive exercise test ($\geq$ 1mm ST depression) in the previous 2 years. In addition evidence of LVH on ECG, left ventricular dysfunction (EF $\leq$45% or EDD$\geq$5.5mm), age, history of diabetes, history of hypertension (treated or SBP>160 or DBP>95) and evidence of other vascular disease were be recorded.

9.5.1 EFFICACY AND SAFETY MEASUREMENTS ASSESSED AND FLOW CHART

The assessments which were performed at the visits are listed below. For any visit a maximum of a 14 day deviation before or after the scheduled date was permitted. In the event of a deviation by more than this, the reason was documented.

Screening Phase/Randomisation Visit

Record sex and date of birth
Record medical history
Obtain Canadian Cardiovascular Society Functional Classification of Angina
Measure height, weight, blood pressure and heart rate
Obtain concomitant medication information
Obtain information on smoking habits
Determine whether patient has had a significant exercise test in previous 12 months
Record 12-Lead ECG
Complete inclusion/exclusion checks
Obtain full informed consent

Eight week visit to ensure tolerability and encourage compliance

Assess study drug compliance
Obtain concomitant medication information
Assess for serious adverse events

Routine 4-month and 8-month Visits

Assess study drug compliance
Obtain concomitant medication information
Obtain Canadian Cardiovascular Society Functional Classification of Angina
Assess for serious adverse events

Routine 12-month Visits

Obtain 12-lead ECG
Assess study drug compliance
Obtain concomitant medication information
Obtain Canadian Cardiovascular Society Functional Classification of Angina
Assess for serious adverse events

Final Visit

Obtain 12-lead ECG
Assess study drug compliance
Obtain concomitant medication information
Obtain Canadian Cardiovascular Society Functional Classification of Angina
Assess for serious adverse events

IONA study summary of efficacy and safety measurements

Procedure	Screening Phase/ Randomisation	Double-Blind Treatment Visits During Each Year of Study			End of Study
		4 month	8 month	12 month	Final
Record sex and date of birth	X				
Document positive cardiac investigations	X				
Full Informed Consent	X				
Medical History	X				
Angina Classification	X	X	X	X	X
Concomitant Medication	X	X	X	X	X
Height[a], Weight, BP, HR	X				X
Smoking information	X				
12-Lead ECG	X			X	X
Medication Dispensed	X[b]	X	X	X	
Patient Compliance		X	X	X	X
30ml blood sample obtained	X				
Inclusion/Exclusion Checks	X				
Randomisation	X				
Assessment for SAE		X	X	X	X

[a] Height measured during screening assessment only.

[b] 10mg bd nicorandil or matching placebo, increasing to 20mg bd or matching placebo after two weeks.

For the purpose of a sub-study, a 30ml blood sample was taken (at study entry only) in a subset of, approximately 2000 patients, to determine any relationship between the presence of coronary heart disease and

(i) total cholesterol and its fractions;
(ii) serum markers for infection, e.g. Helicobacter pylori and Chlamydia pneumoniae;
(iii) genetic polymorphisms, e.g. Angiotensin Converting Enzyme; beta 2 receptor; GP IIb / IIIa platelet receptor.

These samples are to be analysed and reported separately from the main study.

A standard resting 12 lead ECG was recorded at study entry, 12 monthly and at study completion. If an ECG was performed at any other time, at the investigator's discretion, CRF pages were completed to document the information obtained. Any significant abnormalities identified on the ECG were reported on the CRF, particularly any results suggestive of myocardial infarction (previous event at baseline and new events at follow-up).

Study endpoints were evaluated as follows :

The study endpoints were critical medical events: critical events were those prespecified outcomes which were to be used to formulate the scientific interpretation of the trial. In particular, they included the components of the primary and secondary study endpoints.

All critical events were also recorded as SAEs and were documented on the SAE forms. However, to permit the Critical Events Committee to confirm that events satisfied study definitions, additional information was collected on possible critical events and reviewed by the Critical Events Committee.

All critical events as defined in section 10.6 of the protocol and occurring during the study were therefore documented on the appropriate critical event (CE) form. The investigator was prompted to fill in the critical event form by a note on the study SAE form. The critical event forms were not included in the booklet of routine trial visit CRFs, but were provided as separate forms.

As soon as the investigator had documented a critical event, the completed form was forwarded to the Medical Co-ordinator at the Data Centre, who was authorised to contact the investigator for clarification or for supporting documentation as required. A duplicate set of this information was kept in the investigator's files.

Serious adverse event data were collected as follows :

Definition of serious adverse events (SAEs): a serious adverse event was defined as any event that was: fatal, life-threatening, required or prolonged hospitalisation, resulted in persistent or significant disability or incapacity, was a congenital anomaly or birth defect, or considered to be an important medical event.

Important medical events were defined as those which, although not immediately life-threatening, were clearly of major clinical significance (jeopardised the subject or required intervention to prevent one of the other serious outcomes). In particular, these events included all cases of stroke or myocardial infarction whether hospitalised or not.

Hospitalisation was defined to include any event requiring hospital admission whether it involved an overnight stay or not.

The development of cancer, and drug overdosage or abuse were considered to be serious events.

Recording of serious adverse events was carried out as follows: at each contact with the patient, the investigator sought information on serious adverse events by questioning, examining, or investigating the patient as appropriate. Information on all events was required to be recorded promptly in the appropriate section of the CRF. Investigators were asked to group together and record all clearly related signs, symptoms and abnormal diagnostic procedures as a single diagnosis in the CRF. The component parts of the diagnosis could be listed for verification.

All SAEs occurring during the study period (baseline period included) were recorded. The clinical course of each event was followed until resolution, stabilisation or until it had been determined that study treatment or participation in the study was not the cause. SAEs that were still ongoing at the end of the study period were followed up to determine the final outcome.

Any SAE which occurred after the end of the study period and was considered to be possibly related to study treatment or participation in the study was recorded and reported as set out above.

SAE follow up was continued until the end of the study even if the patient was withdrawn from study medication.

Rapid reporting to sponsoring pharmaceutical companies:

In order to allow the pharmaceutical companies which provided financial and or material support for the study to comply with their international drug safety reporting obligations the Data Management Centre had a system for data sharing with Aventis (Aventis carried out the reporting duties for the other interested parties). Thus all serious adverse events occurring during the study period, whether or not considered to be related to study treatment, were reported using the SAE form supplied. The completed form was sent to Aventis within 24 hours or, at the latest, on the following working day. The report was sent by facsimile transmission, to: Pharmacovigilance Department, Aventis, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH Fax 01732 584081

At the time of the initial report, the following information was to be provided as far as possible: study, centre and patient number; the study phase during which the event occurred; a description of the event, date of onset and current status; the start date of treatment, whether treatment had been discontinued and if the study blind had been broken for the patient; the reason why the event was classified as serious; the investigator's current assessment of the association between the event and study treatment.

Within the following 48 hours, the investigator was required to provide written information on each serious adverse event. This included any other diagnostic information which would assist the understanding of the event. Significant new information about on-going serious adverse events was provided promptly to Aventis.

Additional information was requested by the Sponsor, if necessary, within five days of receipt of the SAE report. This was to ensure that the initial reporting of serious adverse reactions was made to regulatory authorities within the required time-frame.

Any SAE that occurred during the course of the study was monitored and followed up until it had resolved, pathological laboratory findings had returned to normal, a steady state had been achieved, or it has been shown to be unrelated to the study medication.

Once the SAE had resolved, the completed information was documented on the study SAE form and forwarded with the rest of the CRF to the Data Centre at the University of Glasgow.

9.5.2 APPROPRIATENESS OF MEASUREMENTS

The efficacy and safety assessments were typical of those used in large phase IV secondary prevention studies. The assessment methods used are widely used in cardiovascular research and are generally recognised as reliable, accurate, and relevant. The use of binary outcomes ensured that the study was able to discriminate between effective and ineffective agents (given the sample size and the predicted event rate). The great virtue of this sort of study design is that it avoids the use of surrogate end points (laboratory measurements or physical measurements or recording of outcomes which are not direct measures of clinical benefit). The methods used in the IONA study have been used in the registration of secondary and primary prevention indications for several lipid lowering agents.

9.5.3 PRIMARY EFFICACY VARIABLES

The primary endpoint of the study was the combined events of CHD death, non-fatal myocardial infarction or unplanned hospitalisation for chest pain. Composite endpoints of this type have been used in a number of large scale clinical trials of treatments for the secondary or primary prevention of major adverse cardiovascular outcomes. The events which occurred were adjudicated by an Endpoints Committee before the blind was broken and in most cases before the end of the follow up phase of the study.

The secondary endpoint was CHD death or non-fatal myocardial infarction.

Other outcomes which were studied included mortality as a combined outcome and split by mode of death, all cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke, hospitalised TIA, unplanned hospitalisation for chest pain), cardiovascular hospitalisation, cerebrovascular events (fatal and non-fatal stroke or hospitalised TIA), all hospitalisations and worsening of anginal status, occurrence of the acute coronary syndrome.

9.5.4 DRUG CONCENTRATION MEASUREMENTS

No drug concentration measurements were made.

9.6 DATA QUALITY ASSURANCE

All study processes were carried out in compliance with GCP, through adherence to internal SOPs. This was assured through independent internal quality assurance (QA) audits carried out periodically during the study. These audits encompassed checks on study documentation, administration, data management, data processing, financial systems, statistics and computing systems.

Data quality assurance and quality control systems were implemented in practice by using a CRO familiar with CGP processes to do the routine monitoring of the study centres. The CRO carried out site initiation and training visits to ensure the use of standard terminology and the collection of accurate, consistent, complete, and reliable data.

Ongoing checks of the data were conducted through internal QC procedures, involving printing out of a predetermined percentage of all the data from all CRFs on the study database, and checking of these against the original CRF information, taking into account all subsequent data amendments.

Critical events which might be study endpoints were reviewed and adjudicated by a centralised independent Critical Events Committee.

All analyses for the study report were checked through independent analysis by a second statistician, and verification that the results obtained were consistent.

9.7 STATISTICAL METHODS PLANNED IN THE PROTOCOL AND DETERMINATION OF SAMPLE SIZE

9.7.1 STATISTICAL AND ANALYTICAL PLANS

The study was analysed according to a predefined analysis plan as set out in the study protocol.

Endpoints analysed: the primary endpoint of the study was the combined events of CHD death, non-fatal myocardial infarction or unplanned hospitalisation for cardiac chest pain. The secondary endpoint was CHD death or non-fatal myocardial infarction. Other outcomes analysed include mortality as a combined outcome and split by mode of death, all cardiovascular events (cardiovascular mortality, non-fatal MI, non-fatal stroke, hospitalised TIA, unplanned hospitalisation for cardiac chest pain), cardiovascular hospitalisation, cerebrovascular events (fatal and non-fatal stroke or hospitalised TIA), all hospitalisations and worsening of anginal status.

Definitions of evaluability: all endpoints were evaluated on an intention to treat basis.

All endpoints, with the exception of worsening of anginal status, were analysed on a time-to-event basis. The outcome was taken to be 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 using the log rank test. Risk reductions were calculated from the Cox proportional hazards model with treatment fitted as the only covariate. These analyses were be 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 (all as evaluated at baseline).

Deterioration in anginal status was defined as an occurrence of hospitalisation for cardiac chest pain or a worsening of CCSF classification of anginal status. Outcomes were compared between treatment groups using a chi-square statistic.

9.7.2 DETERMINATION OF SAMPLE SIZE

The sample size was determined using published data. For example, data from a small community based UK study (Ghandi [13]) suggested that approximately 26% of newly diagnosed subjects with angina would have an event (cardiac death, non-fatal MI or coronary revascularisation) after one year (although many of these subjects may have been candidates for early revascularisation). On the other hand, in a similarly sized group of subjects taking nitrates at baseline in the WOSCOPS [14] trial, approximately 26% died of CHD or had a non-fatal MI after 5 years of follow-up. In the ACIP study [15] of subjects who were positive on exercise test and ambulatory monitoring and who were considered suitable for revascularisation, an estimated 17% had an event within one year in the 'ischaemia-guided medically treated' group. In the TIBET [16], and ASIST [17] studies the event rates were approximately 7% at one year. In TIBET, all subjects had chronic stable angina and a

positive exercise test, while in the ASIST study subjects had either mild or no angina but were positive on exercise test and ambulatory monitoring.

Given the increasing use of statin therapy in this patient group, it was thought necessary to be cautious about assumed event rates in the proposed IONA study population. However, with the inclusion of subjects with newly diagnosed angina of effort and subjects with other risk factors, it was thought reasonable to assume a 13% event rate at 21 months in the combined endpoint of CHD death, non-fatal MI, or unplanned hospitalisation for chest pain.

On this basis, a study of 5000 patients would give 95% power (significance level 5%) to identify a 25% reduction in the event rate (and 80% at the 5% level to detect a 20% reduction). Similarly, an 8% event rate for the combined endpoint of CHD death or non-fatal MI would yield 80% power (5% significance level) to detect a 25% risk reduction.

9.8 CHANGES IN THE CONDUCT OF THE STUDY OR PLANNED ANALYSES

In addition to the planned analyses the data were analysed in two *post hoc* subgroups: patients enrolled at hospital centres and patients enrolled at family doctor (GP) centres. This was done in order to investigate the possibility the patient population recruited in hospital centres was sicker or had a poorer prognosis than those recruited at family doctor (GP) centres. An additional *post hoc* analysis investigated the frequency of unstable ischaemic events in the two treatment groups.

10. STUDY PATIENTS

10.1 DISPOSITION OF PATIENTS

Five thousand one hundred and twenty six (5126) patients were enrolled from 226 centres in the UK between May, 1998, and August, 2000. Two thousand five hundred and sixty five (2565) were randomly assigned nicorandil and 2561 placebo (figure 1). Patients were recruited in about equal numbers from primary care and hospital practices. The mean follow-up was 1·6 years (SD 0.5), with the final study visit in August, 2001. Patients who were withdrawn from treatment for safety reasons were followed for outcomes to the end of the study follow up period.

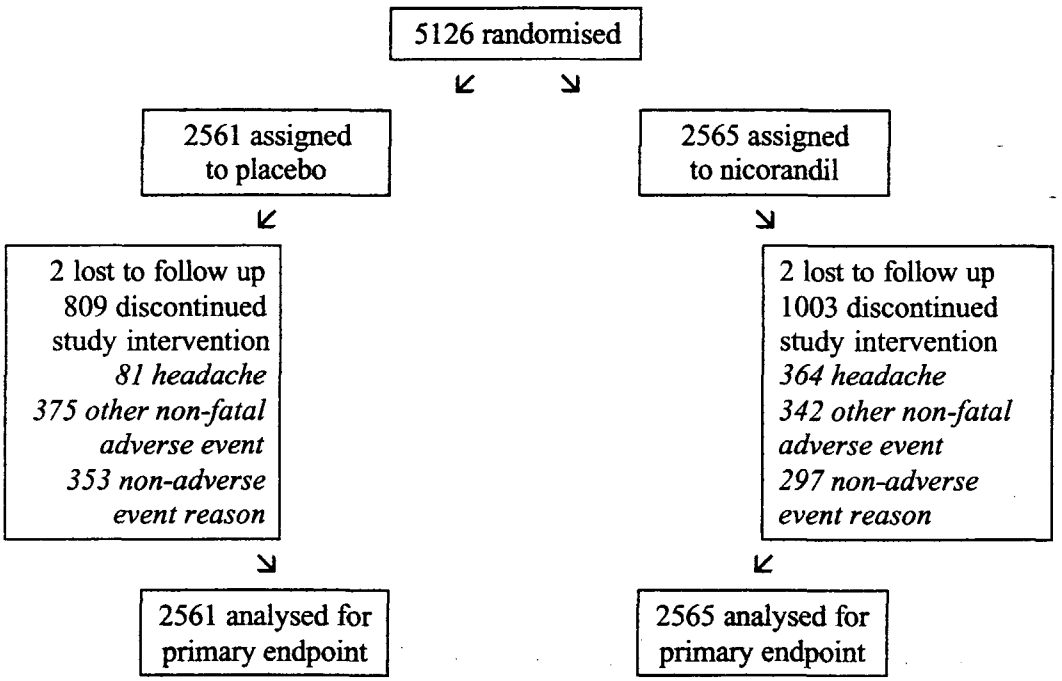
The distribution and other summary statistics of the duration of follow-up of the study subjects are given in Table 1.

In the first two weeks of follow-up there were more withdrawals from study drug in the nicorandil group than the placebo group (16% and 6%, respectively, Table 2). After the first two weeks the numbers of patients who subsequently withdrew from study drug were proportionately similar in the two treatment groups. For example, a further 6% had withdrawn by eight weeks in both groups, and another 8% withdrew in both groups in the next period of the study up to six months follow-up. Overall, 39% of the patients in the nicorandil group withdrew from medication early, and 32% withdrew from the placebo group. Note that a subject was defined to have been withdrawn from medication if the subject had withdrawn for reasons other than death, and also if the patient had not been issued any

medications in the final six months prior to the calculated study-end for that particular patient.

The reasons for withdrawal from medication were also examined (Table 2). Upon examination, it is clear that the excess of withdrawals in the nicorandil group was due to patients suffering headaches (14% for nicorandil, 3% for placebo). The proportions withdrawing for other reasons were similar in the two groups: 13% versus 15% for other adverse events; 1% in both groups for protocol violators; 6% versus 8% for refusal or non-attendance; less than 1% in both groups for not receiving medication in the final six months of follow-up, and; 4% and 5% for other reasons, respectively.

Figure 1 : disposition of patients



10.2 PROTOCOL DEVIATIONS

Individual patients with protocol deviations are listed by centre in appendix 16.2.2,.

11. EFFICACY EVALUATION

11.1 DATA SETS ANALYSED

All available data for all patients receiving nicorandil or placebo were analysed on an intention to treat basis as set out in the study protocol.

11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS

Baseline demographic characteristics and vital signs

	Nicorandil (n=2565)	Placebo (n=2561)
Demographic variables, mean (SD)		
Age (years)	67 (±8)	67 (±9)
Sex male (n, %)	1962 (76%)	1948 (76%)
Height (cm)	169 (±9)	169 (±9)
Weight (kg)	79 (±15)	80 (±15)
BMI (kg/m^2)	28 (±5)	28 (±4)
SBP (mmHg)	138 (±19)	138 (±19)
DBP (mmHg)	79 (±10)	79 (±10)
Heart rate (bpm)	66 (±12)	67 (±12)

The summaries of the demographic characteristics and vital signs of the subjects in the study are presented in Tables 3-23. Each table for the total study group is repeated for those subgroups of patients who were recruited by general practice (GP) centres (2576 subjects) and hospital centres (2550 subjects).

The average age of the subjects in the study was 67 years, and 76% of the subjects were male (Table 3). The average age for males was 66 years, and that for females was 70 years. These summaries were identical in both the nicorandil and placebo treatment groups (2565 and 2561 subjects, respectively). The subjects recruited by general practices (GPs) were similar (75% male, average age 68 years, Table 4) to those recruited by hospital practices (77% male, average age 66 years, Table 5). The average height of the women in the study was 158cm and that for males was 172cm (Table 6). The average female weight was 70kg, and the average weight of the men was 83kg. The average height and weight was similar for the subjects in both the general practices (GPs) (Table 7) and the hospital centres (Table 8). There were no noticeable differences between the two treatment groups with regard to height and weight.

Body mass index was 28 kg /m^2 on average for both males and females (Table 9) and this was also true for subjects in the GP centres and hospital centres (Tables 10 and 11, respectively). The average heart rate was 67bpm overall (Table 9), 68bpm in the GP centres (Table 10), and lower in the hospital centres with an average of 65bpm (Table 11). Systolic blood pressure was 138mmHg on average for all subjects, and the averages for males and females were 137mmHg and 143mmHg, respectively (Table 12). In the GP centres, the average systolic blood pressures were 138mmHg for males and 144mmHg for females (Table 13). However, the equivalent means for hospital centres were slightly lower with 136mmHg for males and 141mmHg for females (Table 14). The average diastolic blood pressure was in the range 78-79mmHg for both sexes, regardless of which type of setting in which the patients had been recruited. The summaries of body mass index, heart rate and blood pressure were similar in both the nicorandil and placebo groups, even when partitioned by the type of centre.

Baseline prognostic factors (risk factors)

	Nicorandil (n=2565)	Placebo (n=2561)
Categorical risk factors, n (%)		
Male	1962 (76%)	1948 (76%)
Diabetic	197 (8%)	232 (9%)
Hypertensive	1197 (47%)	1178 (46%)
Current smoker	417 (16%)	425 (17%)
History of vascular disease, n (%)		
Previous MI	1696 (66%)	1682 (66%)
Previous CABG	572 (22%)	590 (23%)
Previous PTCA	360 (14%)	392 (15%)
Previous angiogram	1508 (59%)	1525 (60%)
Previous stroke	134 (5%)	116 (5%)
Hospitalised for TIA	47 (2%)	55 (2%)
History of PVD	289 (11%)	335 (13%)
History of LVD	230 (9%)	206 (8%)
CCSF classification of angina, n (%)		
I	671 (26%)	692 (27%)
II	1605 (63%)	1583 (62%)
III	272 (11%)	275 (11%)
IV	15 (1%)	9 (<1%)

The summaries of the baseline prognostic factors are shown in Tables 15-20, and these tables are also repeated for the GP and hospital subjects separately. Of the 5126 subjects in the study, 16% were current smokers, 60% were ex-smokers, 8% were diabetic, and 46% had a history of hypertension (Table 15). There was a slightly higher percentage of current smokers in the GP centres (19%, Table 16) than in the hospital centres (14%, Table 17). Otherwise, there were no appreciable differences in smoking, diabetes or hypertension between the types of centre, or indeed between the treatment groups. Clinical history is presented in Table 18; 66% of subjects had a previous myocardial infarction, 23% had experienced a heart bypass, 15% had previously undergone angioplasty and 59% had had an angiogram. Also, 5% of subjects had suffered a stroke, 2% had been hospitalised by a transient ischaemic attack, 12% had a history of peripheral vascular disease and 9% had previous left ventricular dysfunction. A history of myocardial infarction was more common in subjects recruited by GP centres (75%, Table 19) than in the hospital centres (57%, Table 20). On the other hand, there was a lower proportion of subjects with other outcomes before the study in GP patients. For example, 13% had had a PTCA (compared with 17% in the hospital centres), 50% had received an angiogram (versus 68%), 11% and previous peripheral vascular disease (versus 14%), and 7% had a history of left ventricular dysfunction (versus 10%).

The distributions of all of these risk factors were similar in the nicorandil and placebo treatment groups, and this was also true when the subjects were partitioned by the type of recruiting centre.

The anginal status of the patients was assessed by the Canadian Cardiovascular Society Functional classification of angina score (CCSF). Note that the CCSF score has four categories, with level one corresponding to the mildest severity (no pain during normal

activity) and level four corresponding to the most severe (an inability to do any physical activity). At baseline, the proportions of patients in levels I, II, III and IV were 27%, 62%, 11%, and less than 1%, respectively (Table 21). There were proportionately fewer patients in level I, in the GP centres (20%, Table 22) than in the hospital centres (34%, Table 23). However, when split into the two treatment groups, the distributions of CCSF grades were nearly identical for patients randomised to either nicorandil or placebo

Baseline concomitant medications

	Nicorandil (n=2565)	**Placebo (n=2561)**
Cardiac drugs		
Beta-blockers	1469 (57%)	1433 (57%)
ACE inhibitors	739 (29%)	759 (30%)
AII receptor antagonists	69 (3%)	75 (3%)
Diuretics	788 (31%)	760 (30%)
Calcium-channel blockers	1411 (55%)	1397 (55%)
Nitrates (long acting)	1359 (53%)	1358 (53%)
Nitrates (short acting)	1881 (73%)	1875 (73%)
Aspirin/antiplatelets	2283 (89%)	2238 (87%)
Anticoagulants	107 (4%)	120 (5%)
Other antihypertensives	54 (0%)	59 (0%)
Other antiarrhythmic	124 (5%)	105 (5%)
Antidiabetics		
Insulin	77 (3%)	96 (4%)
Oral hypoglycaemics	51 (2%)	58 (2%)
Cholesterol modifiers		
Statins	1449 (56%)	1486 (58%)
Others	65 (3%)	69 (3%)

ACE=angiotensin converting enzyme. AII=angiotensin II.

A breakdown of the proportions of subjects receiving various classes of drugs at baseline is presented by treatment group (Table 24), and as with the other baseline characteristics of the study subjects, this has been partitioned further by whether the subjects were recruited by GPs (Table 25), or hospitals (Table 26).

Fifty-seven percent of subjects were receiving beta blockers at baseline, and 29% had ACE inhibitors, 55% had calcium channel blockers, 53% had received long acting nitrates (nitrates of any sort had been received by 87% of study subjects). Most patients were taking aspirin (or other antiplatelets) (88%), and 57% were receiving statin therapy. Many other types of drugs are also tabulated. The subjects in the GP centres were less likely to receive beta-blockers than the hospital centres (52% and 62%, respectively), more likely to receive short acting nitrates (80% versus 67%), and less likely to receive statins (51% versus 64%). The distribution of types of baseline therapies was similar in the two treatment groups.

The number of types of anti anginal medication the patients were taking was also analysed. Of particular interest are beta-blockers, calcium channel blockers and long acting nitrates. Overall, 14% of subjects had taken all three of these classes of drugs (Table 27). The corresponding figures for the GP centres and the hospital centres were 13% (Table 28) and 15% (Table 29), respectively.

11.3 MEASUREMENTS OF TREATMENT COMPLIANCE

All unused medication was returned to the study site at each follow up visit. An entry was made in the CRF if the Investigator suspected or confirmed a failure in patient compliance.

11.4 EFFICACY RESULTS AND TABULATIONS OF INDIVIDUAL PATIENT DATA

11.4.1 ANALYSIS OF EFFICACY

Adjudicated Endpoint Forms

All of the information on important clinical outcomes was collected together on special summary forms that were adjudicated upon by the critical events committee. The main outcomes of the study were composite outcomes which comprised several different components. The individual components, are summarised separately for the fatal endpoints and the non-fatal endpoints.

There were 111 (4.3%) deaths in the nicorandil group and 129 (5.0%) in the placebo group (Table 30). There were slightly fewer deaths in the nicorandil group due to coronary heart disease (especially sudden death with ten fewer deaths, and myocardial infarction with five fewer deaths). Also, there were five fewer deaths due to 'presumed cardiovascular causes' (five versus ten, respectively).

The other causes of death were roughly equal in the two groups, for example there were exactly 31 deaths (1%) for non-cardiovascular causes in both treatment groups.

In terms of the non fatal endpoints, there were 440 events occurring in 328 subjects in the nicorandil group, and 564 events occurring in 369 subjects in the placebo group (Table 31). This meant that 12.8% of subjects in the nicorandil group and 14.4% of subjects in the placebo group had suffered non-fatal endpoints.

Upon inspection of the different types of nonfatal endpoint the main reductions for nicorandil were for myocardial infarction with 21 fewer subjects, 32 fewer subjects with unplanned hospitalisation for cardiac chest pain, and 15 fewer subjects with other cardiovascular events.

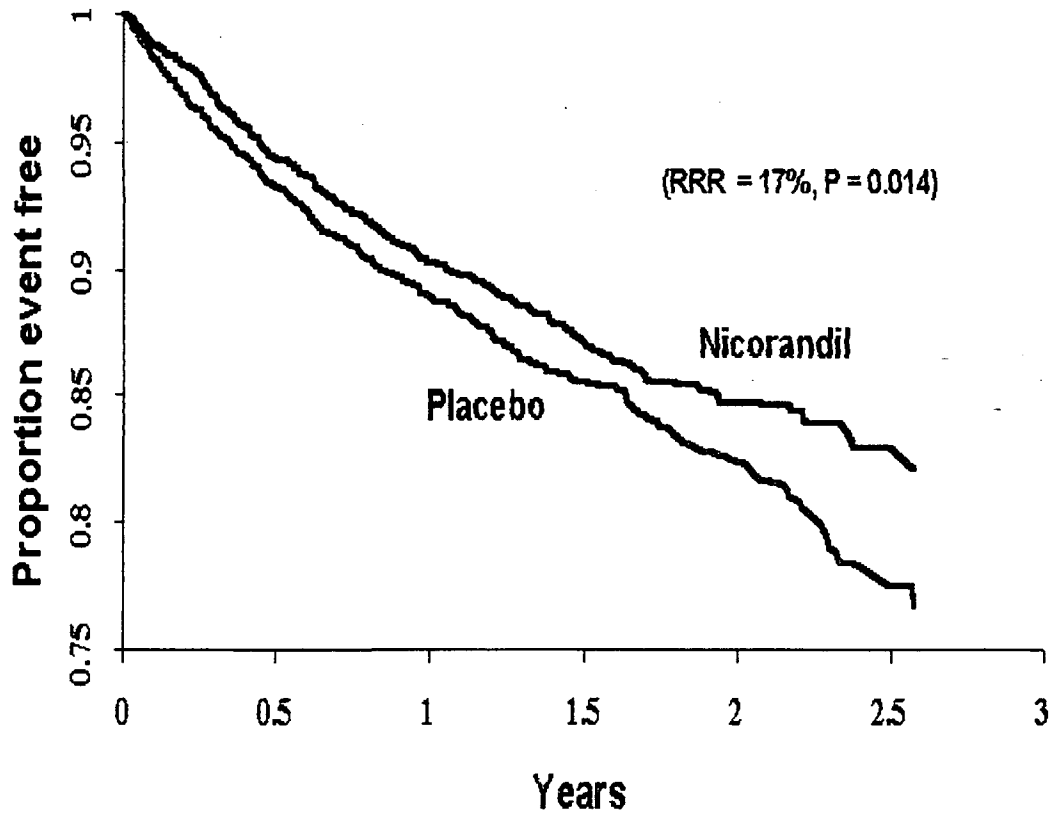
There were similar numbers of patients in the two treatment groups who experienced nonfatal strokes (28 for nicorandil, 29 for placebo), and who were hospitalised with transient ischaemic attacks (five for nicorandil, two for placebo).

Primary Endpoint

The primary outcome was the earliest occurrence of; death due to coronary heart disease, non-fatal myocardial infarction, and unplanned hospitalisation with cardiac chest pain. There were 337 (13.1%) patients with primary endpoints in the nicorandil group, and 398 (15.5%) in the placebo group (Table 32). This reduction in the rate of the primary endpoint was statistically significant with a hazard-ratio (HR) of 0.83 (0.72, 0.97), p=0.014.

The result for the primary endpoint was also analysed by the Kaplan-Meier method. The result of this analysis is given in the following figure (figure 2):

Figure 2: CHD death, non-fatal MI or unplanned hospitalisation for cardiac chest pain



There was slightly larger proportional reduction in the rate of the secondary endpoint, namely the first occurrence of death due to coronary heart disease or a non fatal myocardial infarction, HR=0.79 (0.61, 1.02) (Table 33). However, this difference failed to reach statistical significance (p=0.068) due to the lower number of events for this outcome, i.e. 107 (4.2%) in the nicorandil group and 134 (5.2%) in the placebo group.

There were fewer deaths in the nicorandil group (n=111, 4.3%) than in the placebo group (n=129, 5.0%), although the reduction was not statistically significant, HR=0.85 (0.66, 1.10), p=0.222 (Table 34).

The analysis of the composite endpoint `all cardiovascular events' is given in Table 35. This endpoint consisted of the earliest occurrence of the following components; cardiovascular mortality, non fatal myocardial infarction, nonfatal stroke, hospitalisation for transient ischaemic attack, and unplanned hospitalisation for cardiac chest pain. There were 378 (14.7%) patients with this outcome in the nicorandil group and 436 (17.0%) in the placebo group, and the reduction was statistically significant, HR=0.86 (0.75, 0.98), p=0.027.

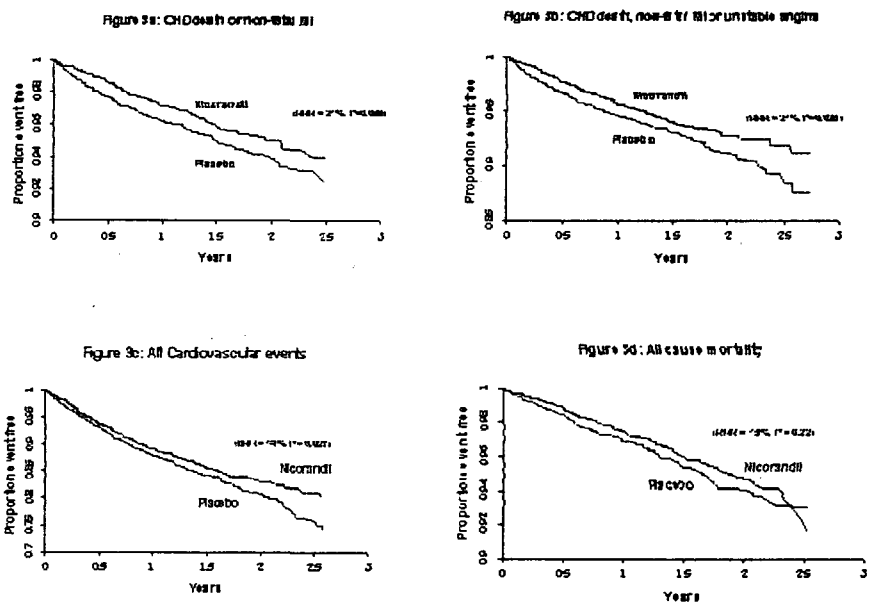
Distribution of major clinical outcomes

	Nicorandil (n=2565)	Placebo (n=2561)	Hazard ratio	(95% CI)	P value
Component events					
CHD death	60 (2.3%)	73 (2.9%)	-	-	-
Non-fatal MI*	56 (2.1%)	72 (2.8%)	-	-	-
Unstable angina*	56 (2.1%)	73 (2.9%)	-	-	-
Definite angina*	115 (4.5%)	127 (5.0%)	-	-	-
Presumed angina*	128 (5.0%)	153 (6.0%)	-	-	-
Stroke or hospital admission for TIA	37 (1.491.)	40 (1.6%)	-	-	-
Composite events					
CHD death, non-fatal MI, or hospital admission for cardiac chest pain	337 (13.1%)	398 (15.5%)	0.83	(0.72-0.97)	0.014
CHD death or non-fatal MI	107 (4.2%)	134 (5.2%)	0.79	(0.61-1.02)	0.068
CHD death, non-fatal MI, or unstable angina	156 (6.1%)	195 (7.6%)	0.79	(0.64-0.98)	0.028
All cardiovascular events	378 (14.7%)	436 (17.0%)	0.86	(0.75-0.98)	0.027
All-cause mortality	111 (4.3%)	129 (5.0%)	0.85	(0.66-1.10)	0.222

156 (6.1%) 195 (7.6%)

CHD=coronary heart disease. MI=myocardial infarction. TIA=transient ischaemic attack.
**Components of hospital admission for cardiac chest pain.*

The following figure summarises the Kaplan-Meier analyses of the secondary endpoint and other composite endpoints (figure 3):



Another of the scheduled types of outcome was `cerebrovascular events', as defined by the earliest occurrence of; fatal stroke, non-fatal stroke, or hospitalisation for transient ischaemic attack (Table 36). The proportions of patients who experience this outcome were roughly equal in the two treatment groups, with 37 events (1.4%) in the nicorandil group and 40 events (1.6%) in the placebo group, HR=0.92 (0.59, 1.44), p=0.715. There were significantly fewer `acute coronary syndromes' in the nicorandil group (Table 37), as defined by the

earliest occurrence of; death due to coronary heart disease, non-fatal myocardial infarction or an unplanned hospitalisation with unstable angina. There were 156 (6.1%) and 195 (7.6%) of patients experiencing these events in the nicorandil and placebo groups, respectively, HR = 0.79 (0.64, 0.98), p = 0.028.

The reduction in events was also statistically significant when unplanned hospitalisation with 'definite angina' (as defined by the endpoint committee) was added as a further component to the 'acute coronary syndromes' composition, HR=0.83 (0.70, 0.98), p=0.025 (Table 38).

Worsening Anginal status and Changes in BP

A full breakdown of the distributions of subjects in each of the four categories of the CCSF angina score for every study visit is shown in Table 39. At the randomisation visit (Visit 1) 26% of the nicorandil subjects and 27% of the placebo patients were in the mildest category of angina severity (grade one). By the final study visit (Visit 12), this had risen to 43% in both treatment groups.

Worsening of the CCSF scores was also examined directly by calculating the changes from baseline in the CCSF score (Table 40). The proportions of patients experiencing a worsening of their angina status were equal in the two treatment groups, for example 8% of patients had worsened by Visit 12 in both treatment groups. Alternatively, 15% of the patients in both treatment groups had suffered a worsening of their anginal status at any of the study visits, odds-ratio=0.97 (0.83, 1.12), p=0.652. Furthermore, when unplanned hospitalisation for cardiac chest pain was added to the definition of worsening of angina the difference was still minimal, with 22% in the nicorandil group and 24% in the placebo group, p=0.259 (Table 41).

There was an average reduction in systolic blood pressure of 4.0mmHg in the nicorandil group, and 3.4mmHg in the placebo group (Table 42). The mean difference between the treatment groups was not significantly different, i.e. 0.5 (-0.6, 1.6), p=0.353. Similarly the average reductions for diastolic blood pressure were similar with 2.4mmHg and 2.1mmHg in the two groups, respectively. The mean difference in reductions of diastolic blood pressure was not significant either, i.e. 0.3 (-0.3, 0.9), p=0.327.

Revascularisation, Heart Failure and Arrhythmias

The number of patients who underwent either percutaneous transluminal coronary angioplasty (PTCA) or coronary artery bypass graft (CABG) is tabulated in Table 45. The table also includes the figures for elective procedures. There were fewer revascularisations in the nicorandil group than in the placebo group with 169 (6.6%) patients receiving these operations versus 204 (8.0%) patients, respectively. The equivalent figures for the elective procedures were 160 (6.2%) patients in the nicorandil group and 192 (7.5%) patients in the placebo group.

There were fewer hospitalisations for heart failure in the nicorandil group with 38 subjects (1.5%), than in the placebo group with 51 subjects (2.0%), and also slightly fewer arrhythmias with 37 subjects versus 42 subjects (Table 46).

11.4.2 STATISTICAL/ANALYTICAL ISSUES

The statistical analysis of the IONA study conformed to the established methods used to analyse large secondary prevention studies. There were no unusual or novel features of the analytical or statistical methods used.

11.4.2.1 Adjustments for Covariates

Multivariate Analysis of the Primary Endpoint

A multivariate version of the analysis of the primary endpoint was carried out (i.e. death due to coronary heart disease, non-fatal myocardial infarction, and unplanned hospitalisation with cardiac chest pain) (Table 47). The following factors were included in the model; treatment (angina vs placebo), age (five year risk), sex (male vs female), anginal score (grades II, III, and IV separately versus I as the referent category), smoking (yes vs no or former smoker), systolic blood pressure (10mmHg risk), heart rate (10bpm risk), body mass index (risk for $2kg/m^2$), myocardial infarction, CABG, hypertension, diabetic, left ventricular hypertrophy (LVH), and left ventricular dystrophy (LVD). The results for each factor were presented in form of hazard ratios and p- values. The univariate (unadjusted) analysis for each factor is presented alongside the multivariate version for ease of comparison.

Treatment with nicorandil was still significantly protective of the primary outcome after adjustment for all of these factors, hazard-ratio =0.82 (0.71, 0.95), p=0.009. Age was narrowly significant, with the hazard ratio for an increase in age of five years being estimated at 1.05 (1.00, 1.11), p=0.035. Smoking was significantly associate with increased risk, hazard- ratio= 1.32 (1.10, 1.60) p=0.004), as was myocardial infarction, hazard- ratio= 1.54 (1.30, 1.83) p<0.001, and LVH, hazard-ratio=1.39 (1.12, 1.73) p=0.003. There was a strong gradient in risk across the CCSF score with a hazard ratio for a CCSF angina score of IV versus I, 5.49 (3.01, 10.00) p<0.001, in the multivariate analysis.

The classes of concomitant medications were summarised in a similar way throughout the study at each of the study visits from Visit 4 until Visit 12. These summaries show that the use of concomitant medications remained roughly stable throughout the study. For example, in the nicorandil group the proportions of subjects who received long acting nitrates at Visits 4-12 were; 53% (n=1324), 52% (n=1274), 55% (n=935), 54% (n=694), 55% (n=453), 54% (n=228), 54% (n=60), 86% (n=6), 50% (n=1219).

11.4.2.2 Handling of Dropouts or Missing Data

All endpoints, with the exception of worsening of anginal status and changes in blood pressure, were analysed by survival analysis. For each clinical event outcome, the variable for analysis was taken to be the time to first occurrence of the event of interest. Event rates in the two treatment groups were compared by the log-rank test, and risk reductions were calculated in the form of hazard ratios and 95% CIs from Cox's proportional hazards models with treatment fitted as the only covariate. These analyses were done on an intention-to-treat basis. Clinical outcomes were sought on all patients until death, study closedown, or withdrawal of informed consent for follow-up, whichever came first. For patients who were lost to follow-up, events were censored at the last visit.

11.4.2.3 Interim Analyses and Data Monitoring

The only interim analyses and data monitoring carried out involved unblinding only of the data and safety monitoring committee. The data and safety monitoring committee used $p<0.001$ for all-cause mortality as a guideline for stopping the trial early because of overwhelming evidence of a difference between treatments. Since the measure used for this purpose was not the study primary endpoint, it was concluded that the activities of this committee were not likely to cause an increase in the risk of a type I error.

11.4.2.4 Multicentre Studies

Analyses of the data sets for individual centres were not performed, however baseline data from GP centres and data from hospital centres were analysed separately. This allowed exploration of the possibility that patients recruited in GP centres differed from those recruited in hospital centres.

11.4.2.5 Multiple Comparison/Multiplicity

The study had only one primary endpoint (outcome variable) which was analysed using the intention to treat population. Statistical adjustment for a type I error was therefore not necessary.

11.4.2.6 Use of an "Efficacy Subset" of Patients

No separate analysis was carried out on an "Efficacy Subset" of patients.

11.4.2.7 Active-Control Studies Intended to Show Equivalence

Not applicable

11.4.2.8 Examination of Subgroups

Subgroup Analyses

The analyses of the primary and secondary outcomes were repeated after partitioning the study subjects into 18 different types of subgroups (Tables 43 and 44). These subgroups were created for factors such as sex, age, pre-existing medical conditions, previous revascularisations, anginal status, final dose of study drug, and classes of drugs that were being taken at baseline. Note that the hazard-ratios for the main analyses were 0.83 ($p=0.014$) for the primary outcome, and 0.79 ($p=0.068$) for the secondary outcome. Only large deviations from these hazard-ratios in subgroups of a reasonable size can be expected to be noteworthy. For this reason, the following trends that have been noted should be interpreted extremely cautiously.

There was a tendency for the treatment effect to be reduced, i.e. for the hazard rate to approach unity, in some of the subgroup analyses of the primary outcome (Table 43). For

example; in female subjects (HR=1.00 (0.74, 1.34), p=0.976), subjects aged 65-70 years (HR=0.94 (0.69, 1.28), p=0.707), subjects with previous hypertension (HR=0.97 (0.79, 1.20), p=0.796), subjects who had undergone CABG before the study (HR=0.98 (0.73, 1.31), p=0.885), subjects with the mildest CCSF angina score (HR=0.91 (0.66, 1.25), p=0.561), and finally subjects who had not received long acting nitrates at baseline (HR=0.92 (0.72, 1.17), p=0.502).

Some of the notable adjustments of hazard ratio for the secondary outcome (Table 44) include the following; in female subjects (HR=0.65 (0.37, 1.14), p=0.130), subjects with previous hypertension (HR=0.92 (0.62, 1.34), p=0.652), subjects with a history of CAGB (HR=1.07 (0.59, 1.95), p=0.824), subjects with the mildest CCSF score (HR=0.56 (0.30, 1.03), p=0.060), subjects who did not receive beta-blockers at baseline (HR=0.92 (0.65, 1.03), p=0.638), and finally subjects who had received ACE-inhibitors at baseline (HR=1.16 (0.77, 1.73), p=0.478). Note that the sub-group variations in the hazard ratios for the secondary outcome in females and the lowest CCSF score are in the opposite direction to the variations that were observed for the primary outcome.

11.4.3 TABULATION OF INDIVIDUAL RESPONSE DATA

Tabulations and listings of individual patient response data (appendix 16.2.6) are available from the Robertson Centre, University of Glasgow, on request.

11.4.4 DRUG DOSE, DRUG CONCENTRATION, AND RELATIONSHIPS TO RESPONSE

No drug concentration information was collected during the IONA study.

11.4.5 DRUG-DRUG AND DRUG-DISEASE INTERACTIONS

No drug disease interactions were noted during the IONA study.

11.4.6 BY-PATIENT DISPLAYS

Not applicable due to the study sample size.

11.4.7 EFFICACY CONCLUSIONS

The efficacy results of the IONA study have demonstrated a significant improvement in outcome from antianginal treatment with nicorandil in patients with stable angina.

Outcome was defined as a combination of morbidity and mortality by a composite primary endpoint of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for chest pain. Event rates in all components of the primary endpoint were lower in patients on nicorandil than on placebo and therefore each contributed to the significance of the primary endpoint.

The elements of the primary endpoint of the IONA study are also the components of the 'acute coronary syndrome', which has become the accepted term encompassing both unstable angina and myocardial infarction (in recognition of their common underlying pathology).

The third component of the composite primary endpoint, unplanned hospital admission for chest pain, was made up of three categories: unstable angina, definite angina, and possible angina. Unstable angina required the patient to have had parenteral therapy including heparin and to have acute electrocardiographic changes indicative of ischaemia. Myocardial infarction was defined according to the standard WHO definition. This definition required the patient to have two of the three criteria of typical clinical presentation (electrocardiographic changes consistent with acute myocardial infarction, or an appropriate increase in the concentration of cardiac enzymes). These endpoints were all adjudicated by the endpoints committee.

Nicorandil therefore significantly reduced, by 21%, the rate of acute coronary syndromes, defined as coronary heart disease deaths, non-fatal myocardial infarction, or unstable angina.

The study was underpowered to show statistical significance with regard to the secondary endpoint coronary heart disease mortality or non-fatal myocardial infarction since the rate of this endpoint in the placebo group (5.2%) was substantially lower than predicted (8%).

Treatment with nicorandil improved outcome in terms of reducing events related to acute coronary disease and the associated requirement for admission to hospital.

In view of these data, and since the rate of all cardiovascular events also fell significantly, it seems likely that the beneficial effect of nicorandil on outcome was mediated through modification of the course of the underlying coronary heart disease.

The IONA study design does not permit any conclusions as to the precise mechanism through which a change in the course of the underlying coronary heart disease might have occurred. The pharmacology of nicorandil is complex and includes nitrate effects and activation not only of sarcolemmal but also of mitochondrial K^+ channels. Never the less it is clear from the efficacy results of the IONA study that treatment with nicorandil delivers meaningful secondary prevention benefits in addition to the symptom relief that has already been demonstrated in previous studies.

12. SAFETY EVALUATION

12.1 EXTENT OF EXPOSURE

The average duration of follow up of the patients was 1.6 years and was similar in both treatment groups. During this time the majority of patients randomised to receive nicorandil received the drug at a dose of 20 mg bd.

12.2 ADVERSE EVENTS (AEs)

12.2.1 BRIEF SUMMARY OF ADVERSE EVENTS

The safety data collected in the IONA study was limited to Serious Adverse Events. The long duration of the study, the long intervals between study visits and the post-marketing status of nicorandil, were thought to be adequate reasons for adopting this policy.

Serious Adverse Events

All of the serious adverse events are summarised with groupings by body system (Table 48), and also by more specific categories (decoded terms) within each of the body systems (Table 49). The coding system used was WHO-ART.

For each treatment group, the serious adverse events are summarised by the number of subjects experiencing an event, the total number of events in a category, and the incidence rate (IR) per thousand person years of follow-up. The following table based on the results given in table 48 shows the percentage of events for each drug attributable to each body system. The ratio of the percentages for each body system for each drug gives an indication of the size of the difference between the rates on nicorandil and those on placebo.

Body system	**Nicorandil**		**Placebo**		**Ratio**
	events	% events	events	% events	N/p
Application site disorders	12	0.56%	13	0.60%	0.92
Body as a whole - general disorders	32	1.48%	37	1.71%	0.86
Cardiovascular disorders, general	136	6.29%	153	7.09%	0.89
Central & periph nerv syst. Disorders	36	1.67%	30	1.39%	1.20
Endocrine disorders	2	0.09%	0	0.00%	n/a
Gastro - intestinal system disorders	194	8.97%	132	6.12%	1.47
Hearing and vestibular disorders	4	0.19%	5	0.23%	0.80
Heart rate and rhythm disorders	67	3.10%	55	2.55%	1.22
Liver and biliary system disorders	19	0.88%	27	1.25%	0.70
Metabolic and nutritional disorders	45	2.08%	24	1.11%	1.87
Musculo -skeletal system disorders	84	3.89%	66	3.06%	1.27
Myo endo pericardial &valve disorder	618	28.58%	782	36.24%	0.79
Neonatal and infancy disorders	14	0.65%	8	0.37%	1.75
Neoplasm	135	6.24%	120	5.56%	1.12
Operations & procedures	370	17.11%	356	16.50%	1.04
Platelet, bleeding & clotting disorder	9	0.42%	10	0.46%	0.90
Psychiatric disorders	16	0.74%	13	0.60%	1.23
Red blood cell disorders	14	0.65%	18	0.83%	0.78
Reproductive disorders, female	2	0.09%	4	0.19%	0.50
Reproductive disorders, male	18	0.83%	10	0.46%	1.80
Resistance mechanism disorders	15	0.69%	11	0.51%	1.36
Respiratory system disorders	109	5.04%	85	3.94%	1.28
Skin and appendages disorders	25	1.16%	15	0.70%	1.66
Unknown	7	0.32%	7	0.32%	1.00
Urinary system disorders	50	2.31%	59	2.73%	0.85
Vascular (extracardiac) disorders	83	3.84%	86	3.99%	0.96
Vision disorders	46	2.13%	31	1.44%	1.48
White blood cell disorders	0	0.00%	1	0.05%	n/a
Total	2162		2158		

In the nicorandil group there was a higher rate of gastrointestinal disorders than in the placebo group (IR=47 versus IR=32), and trends to a higher rate in metabolic and nutritional disorders (IR=11 versus IR=6), respiratory disorders (IR=26 versus IR=21), and vision disorders (IR=11 versus IR=8). There were fewer myocardium and valve disorders in the nicorandil group than in the placebo group (IR=150 versus IR=191), a finding which is consistent with the efficacy result of the IONA study.

Statistical analysis of the difference in frequency of individual adverse events between the groups receiving nicorandil and the group receiving placebo were performed (Table 64). The following events were significantly more common on nicorandil than on placebo: diverticular disease (p=0.039) and rectal bleeding (p=0.013). No other events were significantly more common on nicorandil than on placebo.

When examined in more detail there was no real pattern amongst the types of gastrointestinal disorders, except for a slight excess in the nicorandil group for oesophagitis and rectal bleeding (ten versus five events and thirteen versus two events, respectively, Table 49). 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.

For metabolic and nutritional disorders the small excess of events in the nicorandil group was mostly due to patients being diagnosed with diabetes (33 versus 21 events, respectively). There was also a small excess of patients with chronic obstructive pulmonary disease in the nicorandil group (respiratory disorders; 19 versus 6 events).

Similarly the small excess of vision disorders was due to cataracts (36 versus 25 events). The main types of disorders of the myocardium and valves that appeared to be prevented by nicorandil were angina (114 versus 125 events), unstable angina (114 versus 183 events), and myocardial infarction (72 versus 109 events).

The serious adverse event tables were also repeated for the subgroup of patients who had received long acting nitrates at the baseline visit (Tables 50 and 51), and also for those subjects who had not received long acting nitrates (Tables 52 and 53). There were no obvious differences in the patterns of serious adverse events when the subjects were split into these subgroups.

12.2.2 DISPLAY OF ADVERSE EVENTS

For display of adverse event data please see summary tables 48-53 and 63-64. Changes in vital signs and laboratory variables were not included in the safety analysis (no laboratory measurements made).

12.2.3 ANALYSIS OF ADVERSE EVENTS

See section 12.2.1

12.2.4 LISTING OF ADVERSE EVENTS BY PATIENT

Line listings of all adverse events for each patient (including the same event on several occasions) are listed in appendix 16.2.7 (giving both preferred term and the original term used by the investigator) which is available on request from the Robertson Centre for Biosatistics, University of Glasgow.

12.3 DEATHS, OTHER SERIOUS ADVERSE EVENTS, AND OTHER SIGNIFICANT ADVERSE EVENTS

Deaths formed part of the outcome data collected as the study endpoint. An analysis of all cause mortality is presented in section 11 (efficacy).

12.3.1 LISTING OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

12.3.1.1 Deaths

All deaths during the study, including the post treatment follow-up period, and deaths that resulted from a process that began during the study, are listed by patient in section 14.3.2 of this report which is available on request from the pharmacovigilance department of Aventis (Aventis Pharma Limited. 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH. Tel. 01732 584000 FAX 01732 584080). A simple listing of the fatal adverse events is found in Table 63. It should be noted that Aventis carried out the regulatory reporting of SAEs on behalf of the University of Glasgow to ensure that SAE reporting complied with regulatory guidelines.

All-cause mortality was slightly lower in the nicorandil group (111 deaths, 4.3%) than in the placebo group (129 deaths, 5.0%) but the difference was not statistically significant.

The commonest cause of death on either treatment was cardiac (60 cases on nicorandil compared to 73 on placebo). Sudden death was the leading cause of cardiac death (33 cases on nicorandil vs 43 on placebo). For nicorandil the median time to onset of sudden cardiac death was 226 days vs 132 days on placebo. There were 11 fatal myocardial infarctions in the nicorandil group compared to 16 in the placebo group. Other cardiac causes of death were noted in 16 patients receiving nicorandil compared to 14 on placebo. Deaths presumed to be cardiac were reported in 5 patients receiving nicorandil compared to 10 receiving placebo, but other deaths associated with circulatory disorders and procedures were reported in 10 patients receiving nicorandil vs 5 receiving placebo. Fatal stroke occurred in half as many cases receiving nicorandil (5) compared to placebo (10).

Non-circulatory causes of death were recorded in 31 patients receiving nicorandil and 31 receiving placebo. Of these malignancies accounted for 17 deaths on nicorandil compared to 23 on placebo. Cancers associated with smoking were prominent in both treatment groups. Other causes of death were uncommon: only 14 of the deaths on nicorandil and 8 of the deaths on placebo were due to causes other than cancer and cardiovascular disease.

12.3.1.2 Other Serious Adverse Events

All serious adverse events including death and the serious adverse events temporally associated with or preceding the deaths, are listed in section 14.3.2 of this report which is available on request from the pharmacovigilance department of Aventis (Aventis Pharma Limited. 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH. Tel. 01732 584000 FAX 01732 584080) and are summarised in tables 48-53. The listing does not include laboratory abnormalities, abnormal vital signs and abnormal physical observations.

12.3.1.3 Other Significant Adverse Events

Not applicable.

12.3.2 NARRATIVES OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

Brief narratives describing each death and each serious adverse event (section 14.3.3) are available on request as CIOMS forms from the pharmacovigilance department of Aventis (Aventis Pharma Limited. 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH. Tel. 01732 584000 FAX 01732 584080). It should be noted that Aventis carried out the regulatory reporting of SAEs on behalf of the University of Glasgow to ensure that SAE reporting complied with regulatory guidelines.

12.3.3 ANALYSIS AND DISCUSSION OF DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS

There were fewer deaths in the nicorandil group than in the placebo group but the number of deaths due to non-circulatory causes was the same in the two treatment groups. This observation suggests that treatment with nicorandil is not associated with any excess risk of death from any cause and is protective against cardiovascular death. The non-circulatory causes of death were typical of those expected in a relatively elderly study population. No new major safety issue related to nicorandil was identified in this study.

12.4 CLINICAL LABORATORY EVALUATION

Not applicable.

12.4.1 LISTING OF INDIVIDUAL LABORATORY MEASUREMENTS BY PATIENT (16.2.8) AND EACH ABNORMAL LABORATORY VALUE (14.3.4)

Not applicable.

12.4.2 EVALUATION OF EACH LABORATORY PARAMETER

Not applicable.

12.5 VITAL SIGNS, PHYSICAL FINDINGS AND OTHER OBSERVATIONS RELATED TO SAFETY

Not applicable.

12.6 SAFETY CONCLUSIONS

In general terms the tolerability of nicorandil was acceptable. The drug is known to cause transient headaches in many patients during the first few days of treatment. This fact was confirmed in the IONA study: the higher early drop out rate on nicorandil was due almost entirely to this side effect. No major unfavourable differences in serious adverse event rates were noted for nicorandil by comparison to placebo except for a small excess of cases of rectal bleeding and diverticular disease. It should be noted that no causality assessment has been made in relation to these observations. Interestingly the safety data provide some supporting evidence about the cardioprotective effects of nicorandil.

13. DISCUSSION AND OVERALL CONCLUSIONS

The efficacy results of the IONA study have demonstrated a significant improvement in outcome from antianginal treatment with nicorandil in patients with stable angina. Outcome was defined as a combination of morbidity and mortality by a composite primary endpoint of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for chest pain. Event rates in all components of the primary endpoint were lower in patients on nicorandil than on placebo and therefore each contributed to the significance of the primary endpoint. The elements of the primary endpoint of the IONA study are also the components of the 'acute coronary syndrome', which has become the accepted term encompassing both unstable angina and myocardial infarction (in recognition of their common underlying pathology).

The third component of the composite primary endpoint, unplanned hospital admission for chest pain, was made up of three categories: unstable angina, definite angina, and possible angina. Unstable angina required the patient to have had parenteral therapy including heparin and to have acute electrocardiographic changes indicative of ischaemia. Myocardial infarction was defined according to the standard WHO definition. This definition required the patient to have two of the three criteria of typical clinical presentation (electrocardiographic changes consistent with acute myocardial infarction, or an appropriate increase in the concentration of cardiac enzymes). These endpoints were all adjudicated by the endpoints committee.

Nicorandil therefore significantly reduced, by 21%, the rate of acute coronary syndromes, defined as coronary heart disease deaths, non-fatal myocardial infarction, or unstable angina.

The study was underpowered to show statistical significance with regard to the secondary endpoint coronary heart disease mortality or non-fatal myocardial infarction since the rate of this endpoint in the placebo group (5.2%) was substantially lower than predicted (8%).

Treatment with nicorandil improved outcome in terms of reducing events related to acute coronary disease and the associated requirement for admission to hospital. In view of these data, and since the rate of all cardiovascular events also fell significantly, it seems likely that the beneficial effect of nicorandil on outcome was mediated through modification of the course of the underlying coronary heart disease.

In general terms the tolerability of nicorandil was acceptable. The drug is known to cause transient headaches in many patients during the first few days of treatment. This fact was confirmed in the IONA study: the higher early drop out rate on nicorandil was due almost entirely to this side effect. The following body systems were noted to have a meaningful excess of adverse events in patients receiving nicorandil compared to those receiving placebo: gastrointestinal system disorders (194, 8.97% vs 132, 6.12%). There was a small statistically significant difference in the rate of rectal bleeding and diverticular disease in the nicorandil group by comparison to placebo. It should be noted that no causality assessment has been made in relation to these observations. Interestingly the safety data provide some supporting evidence about the cardioprotective effects of nicorandil.

In conclusion, the IONA study has demonstrated that nicorandil has a significant beneficial effect of preventing the composite endpoint or outcome: coronary heart disease (CHD) related death, non-fatal myocardial infarction or unplanned cardiac hospitalisation, in subjects with angina of effort. This effect is achieved when patients are treated with the current licensed anti-anginal dose of nicorandil.

14. TABLES, FIGURES AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

14.1 DEMOGRAPHIC AND CO-MEDICATION DATA

Summary tables - see tables 1 to 29 and 54 to 62

14.2 EFFICACY DATA

Summary tables – see tables 30 to 47

14.3 SAFETY DATA

Summary tables – see tables 48 to 53 and 63 to 64

14.3.1 DISPLAYS OF ADVERSE EVENTS

See tables 48-53 and 63 to 64

14.3.2 LISTINGS OF DEATHS, OTHER SERIOUS AND SIGNIFICANT ADVERSE EVENTS

See table 63

Line listings are available on request from the Robertson Centre, University of Glasgow.

14.3.3 NARRATIVES OF DEATHS, OTHER SERIOUS AND CERTAIN OTHER SIGNIFICANT ADVERSE EVENTS

Brief narratives describing each death and each serious adverse event (section 14.3.3) are available on request form the pharmacovigilance department of Aventis (Aventis Pharma Limited. 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH. Tel. 01732 584000 FAX 01732 584080). It should be noted that Aventis carried out the regulatory reporting of SAEs on behalf of the University of Glasgow to ensure that SAE reporting complied with regulatory guidelines.

14.3.4 ABNORMAL LABORATORY VALUE LISTING (each patient)

Not applicable

15.1 REFERENCE LIST

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15 Knatterud GL, Bourassa MG, Pepine CJ, et al for the ACIP Investigators.
Effects of treatment strategies to suppress ischemia in patients with coronary artery disease: 12-week results of the Asymptomatic Cardiac Ischemia Pilot (ACIP) study.
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Eur Heart J 1996;17:104-112.

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Effects of treatment on outcome in mildly symptomatic patients with ischaemia during daily life - The Atenolol Silent Ischaemia Study (ASIST).
Circulation 1994;90:762-768

15.2 STUDY TABLES : 1-64

Table 1 Summary of Length of Follow-Up

	Nicorandil (n=2565)	Placebo (n=2561)	Total (n=5126)
Distribution of Follow-Up Times			
Year 1 Months 1 - 3	29 (1%)	36 (1%)	65 (1%)
4 - 6	19 (1%)	22 (1%)	41 (1%)
7 - 9	20 (1%)	29 (1%)	49 (1%)
10 - 12	202 (8%)	211 (8%)	413 (8%)
Year 2 Months 1 - 3	561 (22%)	537 (21%)	1098 (21%)
4 - 6	395 (15%)	405 (16%)	800 (16%)
7 - 9	390 (15%)	371 (14%)	761 (15%)
10 - 12	236 (9%)	246 (10%)	482 (9%)
Year 3 Months 1 - 3	281 (11%)	286 (11%)	567 (11%)
4 - 6	302 (12%)	298 (12%)	600 (12%)
7 - 9	122 (5%)	107 (4%)	229 (4%)
10 - 12	8 (0%)	13 (1%)	21 (0%)
Summary of Follow-Up Times (years)			
Mean	1.61	1.60	1.60
Min & Max	0.00 2.95	0.00 2.97	0.00 2.97
Standard dev	0.54	0.55	0.55

Table 2 Withdrawals from Study Medication

	Nicorandil (n=2565)		Placebo (n=2561)	
	n (%)	n-cumul (%)	n (%)	n-cumul (%)
Withdrawn by 2 Weeks	413 (16.1%)	-	163 (6.4%)	-
Withdrawn by 8 Weeks	153 (6.0%)	566 (22.1%)	145 (5.7%)	308 (12.0%)
Withdrawn by 6 Months	192 (7.5%)	758 (29.6%)	191 (7.5%)	499 (19.5%)
	n (%)		n (%)	
Withdrawn at Any Time	1003 (39.1%)		809 (31.6%)	
Reason for Withdrawal:				
Headache	364 (14.2%)		81 (3.2%)	
Other Adverse Event Protocol Violator	35 (1.4%)		22 (0.9%)	
Refusal/Non-attendance	154 (6.0%)		202 (7.9%)	
Other	100 (3.9%)		114 (4.5%)	
No medication issued *	8 (0.3%)		13 (0.5%)	

* no medication issued in final six months of follow-up (not on withdrawal form)

Table 3 Baseline Demographic Characteristics - Age and Sex

	Nicorandil (n=2565)		Placebo (n=2561)		Total (n=5126)	
Sex						
Male	1962 (76%)		1948 (76%)		3910 (76%)	
Female	603 (24%)		613 (24%)		1216 (24%)	
Age for Males						
Mean	66		66		66	
n	1962		1948		3910	
Min & Max	45	90	44	91	44	91
Standard dev	8		9		9	
Age for Females						
Mean	70		70		70	
n	603		613		1216	
Min & Max	55	90	55	90	55	90
Standard dev	7		7		7	
Age for Males and Females						
Mean	67		67		67	
n	2565		2561		5126	
Min & Max	45	90	44	91	44	91
Standard dev	8		9		8	

Table 4 Baseline Demographic Characteristics - Age and Sex - GP Centres

	Nicorandil (n=1291)		Placebo (n=1285)		Total (n=2576)	
Sex						
Male	970 (75%)		972 (76%)		1942 (75%)	
Female	321 (25%)		313 (24%)		634 (25%)	
Age for Males						
Mean	67		67		67	
n	970		972		1942	
Min & Max	45	90	44	91	44	91
Standard dev	8		9		9	
Age for Females						
Mean	70		70		70	
n	321		313		634	
Min & Max	55	87	55	87	55	87
Standard dev	7		7		7	
Age for Males and Females						
Mean	68		67		68	
n	1291		1285		2576	
Min & Max	45	90	44	91	44	91
Standard dev	8		9		8	

Table 5 Baseline Demographic Characteristics - Age and Sex - Hospital Centres

	Nicorandil (n=1274)		Placebo (n=1276)		Total (n=2550)	
Sex						
Male	992 (78%)		976 (76%)		1968 (77%)	
Female	282 (22%)		300 (24%)		582 (23%)	
Age for Males						
Mean	65		65		65	
n	992		976		1968	
Min & Max	45	86	45	88	45	88
Standard dev	9		9		9	
Age for Females						
Mean	69		69		69	
n	282		300		582	
Min & Max	55	90	55	90	55	90
Standard dev	7		7		7	
Age for Males and Females						
Mean	66		66		66	
n	1274		1276		2550	
Min & Max	45	90	45	90	45	90
Standard dev	8		8		8	

Table 6 Baseline Demographic Characteristics - Height and Weight

	Nicorandil (n=2565)		Placebo (n=2561)		Total (n=5126)	
Height for Males						
Mean	172		172		172	
n	1947		1937		3884	
Min & Max	126	216	136	200	126	216
Standard dev	7		7		7	
Height for Females						
Mean	158		158		158	
n	598		609		1207	
Min & Max	141	190	141	178	141	190
Standard dev	7		6		6	
Height						
Mean	169		169		169	
n	2545		2546		5091	
Min & Max	126	216	136	200	126	216
Standard dev	9		9		9	
Weight for Males						
Mean	82		83		83	
n	1951		1940		3891	
Min & Max	42	187	44	178	42	187
Standard dev	14		14		14	
Weight for Females						
Mean	70		70		70	
n	600		610		1210	
Min & Max	39	133	41	152	39	152
Standard dev	14		13		13	
Weight						
Mean	79		80		80	
n	2551		2550		5101	
Min & Max	39	187	41	178	39	187
Standard dev	15		15		15	

Table 7 Baseline Demographic Characteristics - Height and Weight - GP Centres

	Nicorandil (n=1291)		Placebo (n=1285)		Total (n=2576)	
Height for Males						
Mean	172		172		172	
n	961		968		1929	
Min & Max	149	196	150	192	149	196
Standard dev	7		7		7	
Height for Females						
Mean	157		158		157	
n	320		312		632	
Min & Max	141	174	141	176	141	176
Standard dev	6		6		6	
Height						
Mean	168		169		168	
n	1281		1280		2561	
Min & Max	141	196	141	192	141	196
Standard dev	9		9		9	
Weight for Males						
Mean	81		82		82	
n	967		971		1938	
Min & Max	42	137	44	178	42	178
Standard dev	13		14		14	
Weight for Females						
Mean	69		70		69	
n	320		311		631	
Min & Max	43	113	41	102	41	113
Standard dev	13		12		12	
Weight						
Mean	78		79		79	
n	1287		1282		2569	
Min & Max	42	137	41	178	41	178
Standard dev	14		15		15	

Table 8 Baseline Demographic Characteristics - Height and Weight - Hospital Centres

	Nicorandil (n=1274)		Placebo (n=1276)		Total (n=2550)	
Height for Males						
Mean	172		172		172	
n	986		969		1955	
Min & Max	126	216	136	200	126	216
Standard dev	7		7		7	
Height for Females						
Mean	159		158		159	
n	278		297		575	
Min & Max	142	190	142	178	142	190
Standard dev	7		6		7	
Height						
Mean	169		169		169	
n	1264		1266		2530	
Min & Max	126	216	136	200	126	216
Standard dev	9		9		9	
Weight for Males						
Mean	83		84		84	
n	984		969		1953	
Min & Max	49	187	44	174	44	187
Standard dev	14		14		14	
Weight for Females						
Mean	71		70		71	
n	280		299		579	
Min & Max	39	133	46	152	39	152
Standard dev	15		13		14	
Weight						
Mean	80		81		81	
n	1264		1268		2532	
Min & Max	39	187	44	174	39	187
Standard dev	15		15		15	

Table 9 Baseline Demographic Characteristics - BMI and Heart Rate

	Nicorandil (n=2565)		Placebo (n=2561)		Total (n=5126)	
BMI for Males						
Mean	28		28		28	
n	1938		1933		3871	
Min & Max	17	71	16	54	16	71
Standard dev	4		4		4	
BMI for Females						
Mean	28		28		28	
n	598		608		1206	
Min & Max	16	55	17	63	16	63
Standard dev	5		5		5	
BMI						
Mean	28		28		28	
n	2536		2541		5077	
Min & Max	16	71	16	63	16	71
Standard dev	5		4		5	
Heart Rate for Males						
Mean	66		66		66	
n	1956		1944		3900	
Min & Max	36	120	34	130	34	130
Standard dev	12		12		12	
Heart Rate for Females						
Mean	68		68		68	
n	602		613		1215	
Min & Max	27	118	43	100	27	118
Standard dev	12		11		11	
Heart Rate						
Mean	66		67		67	
n	2558		2557		5115	
Min & Max	27	120	34	130	27	130
Standard dev	12		12		12	

BMI = Body Mass Index

Table 10 Baseline Demographic Characteristics - BMI and Heart Rate - GP Centres

	Nicorandil (n=1291)		Placebo (n=1285)		Total (n=2576)	
BMI for Males						
Mean	28		28		28	
n	960		968		1928	
Min & Max	17	46	17	54	17	54
Standard dev	4		4		4	
BMI for Females						
Mean	28		28		28	
n	320		311		631	
Min & Max	16	50	17	42	16	50
Standard dev	5		5		5	
BMI						
Mean	28		28		28	
n	1280		1279		2559	
Min & Max	16	50	17	54	16	54
Standard dev	4		4		4	
Heart Rate for Males						
Mean	68		68		68	
n	969		971		1940	
Min & Max	39	108	40	130	39	130
Standard dev	11		11		11	
Heart Rate for Females						
Mean	70		69		70	
n	320		313		633	
Min & Max	46	118	45	100	45	118
Standard dev	11		11		11	
Heart Rate						
Mean	68		68		68	
n	1289		1284		2573	
Min & Max	39	118	40	130	39	130
Standard dev	11		11		11	

BMI = Body Mass Index

Table 11 Baseline Demographic Characteristics - BMI and Heart Rate - Hospital Centres

	Nicorandil (n=1274)		Placebo (n=1276)		Total (n=2550)	
BMI for Males						
Mean	28		28		28	
n	978		965		1943	
Min & Max	17	71	16	51	16	71
Standard dev	5		4		4	
BMI for Females						
Mean	28		28		28	
n	278		297		575	
Min & Max	18	55	19	63	18	63
Standard dev	6		5		5	
BMI						
Mean	28		28		28	
n	1256		1262		2518	
Min & Max	17	71	16	63	16	71
Standard dev	5		5		5	
Heart Rate for Males						
Mean	64		65		65	
n	987		973		1960	
Min & Max	36	120	34	108	34	120
Standard dev	12		12		12	
Heart Rate for Females						
Mean	65		68		66	
n	282		300		582	
Min & Max	27	100	43	100	27	100
Standard dev	12		11		12	
Heart Rate						
Mean	65		65		65	
n	1269		1273		2542	
Min & Max	27	120	34	108	27	120
Standard dev	12		12		12	

BMI = Body Mass Index

Table 12 Baseline Demographic Characteristics - Blood Pressure

	Nicorandil (n=2565)		Placebo (n=2561)		Total (n=5126)	
Systolic BP for Males						
Mean	137		137		137	
n	1960		1948		3908	
Min & Max	90	190	85	200	85	200
Standard dev	19		19		19	
Systolic BP for Females						
Mean	143		143		143	
n	603		613		1216	
Min & Max	90	205	91	200	90	205
Standard dev	20		20		20	
Systolic BP						
Mean	138		138		138	
n	2563		2561		5124	
Min & Max	90	205	85	200	85	205
Standard dev	19		19		19	
Diastolic BP for Males						
Mean	78		79		78	
n	1960		1948		3908	
Min & Max	34	114	35	110	34	114
Standard dev	10		10		10	
Diastolic BP for Females						
Mean	79		78		79	
n	603		613		1216	
Min & Max	48	116	46	102	46	116
Standard dev	10		9		10	
Diastolic BP						
Mean	79		79		79	
n	2563		2561		5124	
Min & Max	34	116	35	110	34	116
Standard dev	10		10		10	

Table 13 Baseline Demographic Characteristics - Blood Pressure - GP Centres

	Nicorandil (n=1291)		Placebo (n=1285)		Total (n=2576)	
Systolic BP for Males						
Mean	138		137		138	
n	969		972		1941	
Min & Max	90	190	88	200	88	200
Standard dev	19		19		19	
Systolic BP for Females						
Mean	143		145		144	
n	321		313		634	
Min & Max	90	205	91	200	90	205
Standard dev	19		20		19	
Systolic BP						
Mean	139		139		139	
n	1290		1285		2575	
Min & Max	90	205	88	200	88	205
Standard dev	19		20		19	
Diastolic BP for Males						
Mean	79		78		78	
n	969		972		1941	
Min & Max	52	110	50	110	50	110
Standard dev	10		10		10	
Diastolic BP for Females						
Mean	79		78		79	
n	321		313		634	
Min & Max	55	110	46	102	46	110
Standard dev	10		10		10	
Diastolic BP						
Mean	79		78		79	
n	1290		1285		2575	
Min & Max	52	110	46	110	46	110
Standard dev	10		10		10	

Table 14 Baseline Demographic Characteristics - Blood Pressure - Hospital Centres

	Nicorandil (n=1274)		Placebo (n=1276)		Total (n=2550)	
Systolic BP for Males						
Mean	135		136		136	
n	991		976		1967	
Min & Max	90	190	85	190	85	190
Standard dev	19		19		19	
Systolic BP for Females						
Mean	142		141		141	
n	282		300		582	
Min & Max	90	200	95	199	90	200
Standard dev	20		20		20	
Systolic BP						
Mean	137		137		137	
n	1273		1276		2549	
Min & Max	90	200	85	199	85	200
Standard dev	19		19		19	
Diastolic BP for Males						
Mean	78		79		79	
n	991		976		1967	
Min & Max	34	114	35	110	34	114
Standard dev	10		10		10	
Diastolic BP for Females						
Mean	78		78		78	
n	282		300		582	
Min & Max	48	116	50	102	48	116
Standard dev	10		9		10	
Diastolic BP						
Mean	78		79		78	
n	1273		1276		2549	
Min & Max	34	116	35	110	34	116
Standard dev	10		10		10	

Table 15 Baseline Demographic Characteristics - Risk Factors

	Nicorandil (n=2565)	Placebo (n=2561)	Total (n=5126)
Smoking			
Smoker	417 (16%)	425 (17%)	842 (16%)
Ex-Smoker	1572 (61%)	1519 (59%)	3091 (60%)
Non-Smoker	576 (22%)	616 (24%)	1192 (23%)
Missing		1	1
Diabetic			
Yes	197 (8%)	232 (9%)	429 (8%)
No	2368 (92%)	2329 (91%)	4697 (92%)
Hypertension			
Yes	1197 (47%)	1178 (46%)	2375 (46%)
No	1368 (53%)	1383 (54%)	2751 (54%)

Table 16 Baseline Demographic Characteristics - Risk Factors - GP Centres

	Nicorandil (n=1291)	Placebo (n=1285)	Total (n=2576)
Smoking			
Smoker	255 (20%)	241 (19%)	496 (19%)
Ex-Smoker	788 (61%)	746 (58%)	1534 (60%)
Non-Smoker	248 (19%)	297 (23%)	545 (21%)
Missing		1	1
Diabetic			
Yes	87 (7%)	101 (8%)	188 (7%)
No	1204 (93%)	1184 (92%)	2388 (93%)
Hypertension			
Yes	596 (46%)	562 (44%)	1158 (45%)
No	695 (54%)	723 (56%)	1418 (55%)

Table 17 Baseline Demographic Characteristics - Risk Factors - Hospital Centres

	Nicorandil (n=1274)	Placebo (n=1276)	Total (n=2550)
Smoking			
Smoker	162 (13%)	184 (14%)	346 (14%)
Ex-Smoker	784 (62%)	773 (61%)	1557 (61%)
Non-Smoker	328 (26%)	319 (25%)	647 (25%)
Missing			
Diabetic			
Yes	110 (9%)	131 (10%)	241 (9%)
No	1164 (91%)	1145 (90%)	2309 (91%)
Hypertension			
Yes	601 (47%)	616 (48%)	1217 (48%)
No	673 (53%)	660 (52%)	1333 (52%)

Table 18 Baseline Demographic Characteristics - Vascular Disease

	Nicorandil (n=2565)	Placebo (n=2561)	Total (n=5126)
Previous Myocardial Infarction (MI)			
Yes	1696 (66%)	1682 (66%)	3378 (66%)
No	869 (34%)	879 (34%)	1748 (34%)
Previous Heart Bypass (CABG)			
Yes	572 (22%)	590 (23%)	1162 (23%)
No	1993 (78%)	1971 (77%)	3964 (77%)
Previous Angioplasty (PTCA)			
Yes	360 (14%)	392 (15%)	752 (15%)
No	2205 (86%)	2168 (85%)	4373 (85%)
Missing		1	1
Previous Angiogram			
Yes	1508 (59%)	1525 (60%)	3033 (59%)
No	1057 (41%)	1036 (40%)	2093 (41%)
Previous Stroke			
Yes	134 (5%)	116 (5%)	250 (5%)
No	2431 (95%)	2444 (95%)	4875 (95%)
Missing		1	1
Previous Hospitalisation for Transient Ischaemic Attack (TIA)			
Yes	47 (2%)	55 (2%)	102 (2%)
No	2518 (98%)	2506 (98%)	5024 (98%)
Previous Peripheral Vascular Disease (PVD)			
Yes	289 (11%)	335 (13%)	624 (12%)
No	2276 (89%)	2226 (87%)	4502 (88%)
Previous Left Ventricular Dysfunction (LVD)			
Yes	230 (9%)	206 (8%)	436 (9%)
No	2332 (91%)	2354 (92%)	4686 (91%)
Missing	3	1	4

Table 19 Baseline Demographic Characteristics - Vascular Disease - GP Centres

	Nicorandil (n=1291)	Placebo (n=1285)	Total (n=2576)
Previous Myocardial Infarction (MI)			
Yes	965 (75%)	964 (75%)	1929 (75%)
No	326 (25%)	321 (25%)	647 (25%)
Previous Heart Bypass (CABG)			
Yes	290 (22%)	311 (24%)	601 (23%)
No	1001 (78%)	974 (76%)	1975 (77%)
Previous Angioplasty (PTCA)			
Yes	159 (12%)	167 (13%)	326 (13%)
No	1132 (88%)	1117 (87%)	2249 (87%)
Missing		1	1
Previous Angiogram			
Yes	648 (50%)	647 (50%)	1295 (50%)
No	643 (50%)	638 (50%)	1281 (50%)
Previous Stroke			
Yes	69 (5%)	59 (5%)	128 (5%)
No	1222 (95%)	1225 (95%)	2447 (95%)
Missing		1	1
Previous Hospitalisation for Transient Ischaemic Attack (TIA)			
Yes	31 (2%)	30 (2%)	61 (2%)
No	1260 (98%)	1255 (98%)	2515 (98%)
Previous Peripheral Vascular Disease (PVD)			
Yes	128 (10%)	150 (12%)	278 (11%)
No	1163 (90%)	1135 (88%)	2298 (89%)
Previous Left Ventricular Dysfunction (LVD)			
Yes	103 (8%)	77 (6%)	180 (7%)
No	1185 (92%)	1207 (94%)	2392 (93%)
Missing	3	1	4

Table 20 Baseline Demographic Characteristics - Vascular Disease - Hospital Centres

	Nicorandil (n=1274)	Placebo (n=1276)	Total (n=2550)
Previous Myocardial Infarction (MI)			
Yes	731 (57%)	718 (56%)	1449 (57%)
No	543 (43%)	558 (44%)	1101 (43%)
Previous Heart Bypass (CABG)			
Yes	282 (22%)	279 (22%)	561 (22%)
No	992 (78%)	997 (78%)	1989 (78%)
Previous Angioplasty (PTCA)			
Yes	201 (16%)	225 (18%)	426 (17%)
No	1073 (84%)	1051 (82%)	2124 (83%)
Missing			
Previous Angiogram			
Yes	860 (68%)	878 (69%)	1738 (68%)
No	414 (32%)	398 (31%)	812 (32%)
Previous Stroke			
Yes	65 (5%)	57 (4%)	122 (5%)
No	1209 (95%)	1219 (96%)	2428 (95%)
Missing			
Previous Hospitalisation for Transient Ischaemic Attack (TIA)			
Yes	16 (1%)	25 (2%)	41 (2%)
No	1258 (99%)	1251 (98%)	2509 (98%)
Previous Peripheral Vascular Disease (PVD)			
Yes	161 (13%)	185 (14%)	346 (14%)
No	1113 (87%)	1091 (86%)	2204 (86%)
Previous Left Ventricular Dysfunction (LVD)			
Yes	127 (10%)	129 (10%)	256 (10%)
No	1147 (90%)	1147 (90%)	2294 (90%)
Missing			

Table 21 Baseline Demographic Characteristics - Severity of Angina

	Nicorandil (n=2565)	Placebo (n=2561)	Total (n=5126)
CCSF Classification for Angina			
I	671 (26%)	692 (27%)	1363 (27%)
II	1605 (63%)	1583 (62%)	3188 (62%)
III	272 (11%)	275 (11%)	547 (11%)
IV	15 (1%)	9 (0%)	24 (0%)
Missing	2	2	4

Table 22 Baseline Demographic Characteristics - Severity of Angina - GP Centres

	Nicorandil (n=1291)	Placebo (n=1285)	Total (n=2576)
CCSF Classification for Angina			
I	248 (19%)	255 (20%)	503 (20%)
II	861 (67%)	852 (66%)	1713 (67%)
III	172 (13%)	172 (13%)	344 (13%)
IV	8 (1%)	5 (0%)	13 (1%)
Missing	2	1	3

Table 23 Baseline Demographic Characteristics - Severity of Angina - Hospital Centres

	Nicorandil (n=1274)	Placebo (n=1276)	Total (n=2550)
CCSF Classification for Angina			
I	423 (33%)	437 (34%)	860 (34%)
II	744 (58%)	731 (57%)	1475 (58%)
III	100 (8%)	103 (8%)	203 (8%)
IV	7 (1%)	4 (0%)	11 (0%)
Missing		1	1

Table 24 Selected Baseline Drug Types

	Nicorandil (n=2565)	Placebo (n=2561)	Total (n=5126)
Beta Blockers	1469 (57%)	1433 (56%)	2902 (57%)
ACE-Inhibitors	739 (29%)	759 (30%)	1498 (29%)
AII Receptor Antagonists	69 (3%)	75 (3%)	144 (3%)
Diuretics	788 (31%)	760 (30%)	1548 (30%)
Calcium Channel Blockers	1411 (55%)	1397 (55%)	2808 (55%)
Nitrates: Long Acting	1359 (53%)	1358 (53%)	2717 (53%)
Nitrates: Short Acting	1881 (73%)	1875 (73%)	3756 (73%)
Aspirin / Antiplatelets	2283 (89%)	2238 (87%)	4521 (88%)
Anti-Coagulants	107 (4%)	120 (5%)	227 (4%)
Other Antihypertensives	54 (2%)	59 (2%)	113 (2%)
Other Anti-arrhythmic	124 (5%)	105 (4%)	229 (4%)
Anti-Diabetic: Insulin	77 (3%)	96 (4%)	173 (3%)
Anti-Diabetic: Oral Hypoglycaemics	51 (2%)	58 (2%)	109 (2%)
Cholesterol Modifiers: Statins	1449 (56%)	1486 (58%)	2935 (57%)
Cholesterol Modifiers: Others	65 (3%)	69 (3%)	134 (3%)

Table 25 Selected Baseline Drug Types - GP Centres

	Nicorandil (n=1291)	Placebo (n=1285)	Total (n=2576)
Beta Blockers	660 (51%)	672 (52%)	1332 (52%)
ACE-Inhibitors	359 (28%)	381 (30%)	740 (29%)
AII Receptor Antagonists	23 (2%)	31 (2%)	54 (2%)
Diuretics	424 (33%)	407 (32%)	831 (32%)
Calcium Channel Blockers	716 (55%)	682 (53%)	1398 (54%)
Nitrates: Long Acting	712 (55%)	680 (53%)	1392 (54%)
Nitrates: Short Acting	1031 (80%)	1029 (80%)	2060 (80%)
Aspirin / Antiplatelets	1133 (88%)	1086 (85%)	2219 (86%)
Anti-Coagulants	51 (4%)	66 (5%)	117 (5%)
Other Antihypertensives	31 (2%)	24 (2%)	55 (2%)
Other Anti-arrhythmic	70 (5%)	61 (5%)	131 (5%)
Anti-Diabetic: Insulin	26 (2%)	36 (3%)	62 (2%)
Anti-Diabetic: Oral Hypoglycaemics	20 (2%)	30 (2%)	50 (2%)
Cholesterol Modifiers: Statins	643 (50%)	663 (52%)	1306 (51%)
Cholesterol Modifiers: Others	37 (3%)	41 (3%)	78 (3%)

Table 26 Selected Baseline Drug Types - Hospital Centres

	Nicorandil (n=1274)	Placebo (n=1276)	Total (n=2550)
Beta Blockers	809 (64%)	761 (60%)	1570 (62%)
ACE-Inhibitors	380 (30%)	378 (30%)	758 (30%)
AII Receptor Antagonists	46 (4%)	44 (3%)	90 (4%)
Diuretics	364 (29%)	353 (28%)	717 (28%)
Calcium Channel Blockers	695 (55%)	715 (56%)	1410 (55%)
Nitrates: Long Acting	647 (51%)	678 (53%)	1325 (52%)
Nitrates: Short Acting	850 (67%)	846 (66%)	1696 (67%)
Aspirin / Antiplatelets	1150 (90%)	1152 (90%)	2302 (90%)
Anti-Coagulants	56 (4%)	54 (4%)	110 (4%)
Other Antihypertensives	23 (2%)	35 (3%)	58 (2%)
Other Anti-arrhythmic	54 (4%)	44 (3%)	98 (4%)
Anti-Diabetic: Insulin	51 (4%)	60 (5%)	111 (4%)
Anti-Diabetic: Oral Hypoglycaemics	31 (2%)	28 (2%)	59 (2%)
Cholesterol Modifiers: Statins	806 (63%)	823 (64%)	1629 (64%)
Cholesterol Modifiers: Others	28 (2%)	28 (2%)	56 (2%)

Table 26 Selected Baseline Drug Types - Hospital Centres

	Nicorandil (n=1274)	Placebo (n=1276)	Total (n=2550)
Beta Blockers	809 (64%)	761 (60%)	1570 (62%)
ACE-Inhibitors	380 (30%)	378 (30%)	758 (30%)
AII Receptor Antagonists	46 (4%)	44 (3%)	90 (4%)
Diuretics	364 (29%)	353 (28%)	717 (28%)
Calcium Channel Blockers	695 (55%)	715 (56%)	1410 (55%)
Nitrates: Long Acting	647 (51%)	678 (53%)	1325 (52%)
Nitrates: Short Acting	850 (67%)	846 (66%)	1696 (67%)
Aspirin / Antiplatelets	1150 (90%)	1152 (90%)	2302 (90%)
Anti-Coagulants	56 (4%)	54 (4%)	110 (4%)
Other Antihypertensives	23 (2%)	35 (3%)	58 (2%)
Other Anti-arrhythmic	54 (4%)	44 (3%)	98 (4%)
Anti-Diabetic: Insulin	51 (4%)	60 (5%)	111 (4%)
Anti-Diabetic: Oral Hypoglycaemics	31 (2%)	28 (2%)	59 (2%)
Cholesterol Modifiers: Statins	806 (63%)	823 (64%)	1629 (64%)
Cholesterol Modifiers: Others	28 (2%)	28 (2%)	56 (2%)

Table 27 Selected Combinations of Baseline Drug Types

Key: BB=beta blocker, CCB=calcium channel blocker, Nitrate=long acting nitrate

BB	CCB	Nitrate	Nicorandil (n=2565)	Placebo (n=2561)	Total (n=5126)
No	No	No	97 (4%)	104 (4%)	201 (4%)
No	No	Yes	256 (10%)	270 (11%)	526 (10%)
No	Yes	No	327 (13%)	315 (12%)	642 (13%)
No	Yes	Yes	416 (16%)	439 (17%)	855 (17%)
Yes	No	No	497 (19%)	468 (18%)	965 (19%)
Yes	No	Yes	304 (12%)	322 (13%)	626 (12%)
Yes	Yes	No	285 (11%)	316 (12%)	601 (12%)
Yes	Yes	Yes	383 (15%)	327 (13%)	710 (14%)

Number of drug types taken			
0	97 (4%)	104 (4%)	201 (4%)
1	1080 (42%)	1053 (41%)	2133 (42%)
2	1005 (39%)	1077 (42%)	2082 (41%)
3	383 (15%)	327 (13%)	710 (14%)

Table 28 Selected Combinations of Baseline Drug Types - GP Centres

			Nicorandil (n=1291)	Placebo (n=1285)	Total (n=2576)
Key: BB=beta blocker, CCB=calcium channel blocker, Nitrate=long acting nitrate					
BB	CCB	Nitrate			
No	No	No	52 (4%)	54 (4%)	106 (4%)
No	No	Yes	164 (13%)	174 (14%)	338 (13%)
No	Yes	No	175 (14%)	170 (13%)	345 (13%)
No	Yes	Yes	240 (19%)	215 (17%)	455 (18%)
Yes	No	No	234 (18%)	226 (18%)	460 (18%)
Yes	No	Yes	125 (10%)	149 (12%)	274 (11%)
Yes	Yes	No	118 (9%)	155 (12%)	273 (11%)
Yes	Yes	Yes	183 (14%)	142 (11%)	325 (13%)
Number of drug types taken					
		0	52 (4%)	54 (4%)	106 (4%)
		1	573 (44%)	570 (44%)	1143 (44%)
		2	483 (37%)	519 (40%)	1002 (39%)
		3	183 (14%)	142 (11%)	325 (13%)

Table 29 Selected Combinations of Baseline Drug Types - Hospital Centres

			Nicorandil (n=1274)	Placebo (n=1276)	Total (n=2550)
Key: BB=beta blocker, CCB=calcium channel blocker, Nitrate=long acting nitrate					
BB	CCB	Nitrate			
No	No	No	45 (4%)	50 (4%)	95 (4%)
No	No	Yes	92 (7%)	96 (8%)	188 (7%)
No	Yes	No	152 (12%)	145 (11%)	297 (12%)
No	Yes	Yes	176 (14%)	224 (18%)	400 (16%)
Yes	No	No	263 (21%)	242 (19%)	505 (20%)
Yes	No	Yes	179 (14%)	173 (14%)	352 (14%)
Yes	Yes	No	167 (13%)	161 (13%)	328 (13%)
Yes	Yes	Yes	200 (16%)	185 (14%)	385 (15%)
Number of drug types taken					
		0	45 (4%)	50 (4%)	95 (4%)
		1	507 (40%)	483 (38%)	990 (39%)
		2	522 (41%)	558 (44%)	1080 (42%)
		3	200 (16%)	185 (14%)	385 (15%)

Table 30 Summary of Fatal Endpoint Form

	Nicorandil (n=2565)	Placebo (n=2561)
Coronary Heart Disease	60 (2.34%)	73 (2.85%)
Sudden death	33 (1.29%)	43 (1.68%)
Heart failure	12 (0.47%)	9 (0.35%)
Myocardial Infarction	11 (0.43%)	16 (0.62%)
Cardiac Procedure	4 (0.16%)	5 (0.20%)
Stroke	5 (0.19%)	10 (0.39%)
Cardiovascular Procedure	3 (0.12%)	1 (0.04%)
Other Cardiovascular	7 (0.27%)	4 (0.16%)
Presumed Cardiovascular	5 (0.19%)	10 (0.39%)
Non-Cardiovascular	31 (1.21%)	31 (1.21%)
Total Number of Deaths	111 (4.33%)	129 (5.04%)

Table 31 Summary of Non-Fatal Endpoint Form

	Nicorandil (n=2565)		Placebo (n=2561)	
	Events	Subjects (%)	Events	Subjects (%)
Non-Fatal Myocardial Infarction	59	56 (2.18%)	80	72 (2.81%)
Symptomatic	56	53 (2.07%)	72	65 (2.54%)
Silent	3	3 (0.12%)	8	8 (0.31%)
Unplanned Hospitalisation for Chest Pain	348	260 (10.14%)	452	292 (11.40%)
Unstable Angina	64	56 (2.18%)	86	73 (2.85%)
Definite Angina	132	115 (4.48%)	165	127 (4.96%)
Presumed Angina	152	126 (4.91%)	201	152 (5.94%)
Stroke	28	28 (1.09%)	29	29 (1.13%)
Hospitalised Transient Ischaemic Attack	5	5 (0.19%)	3	2 (0.08%)
Total Number of Non-Fatal Endpoints	440	328 (12.79%)	564	369 (14.41%)
Not a Study Endpoint	190	157 (6.12%)	194	168 (6.56%)
Other Hospitalised Chest Pain	52	51 (1.99%)	46	42 (1.64%)
Other Cardiovascular Event	79	63 (2.46%)	89	78 (3.05%)
Other Event	59	56 (2.18%)	59	57 (2.23%)

Table 32 Analysis of Primary Endpoint (CHD death, MI & hospitalisation for 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	63 2565 (2.46%)	0.02 (0.02, 0.03)	95 2561 (3.71%)	0.04 (0.03, 0.04)
4 - 6	81 2484 (3.26%)	0.06 (0.05, 0.07)	76 2452 (3.10%)	0.07 (0.06, 0.08)
7 - 9	53 2394 (2.21%)	0.08 (0.07, 0.09)	60 2369 (2.53%)	0.09 (0.08, 0.10)
10 - 12	50 2331 (2.15%)	0.10 (0.09, 0.11)	52 2297 (2.26%)	0.11 (0.10, 0.12)
Year 2 Months 1 - 3	29 2094 (1.38%)	0.11 (0.10, 0.12)	36 2051 (1.76%)	0.13 (0.12, 0.14)
4 - 6	27 1563 (1.73%)	0.13 (0.12, 0.14)	24 1545 (1.55%)	0.14 (0.13, 0.16)
7 - 9	19 1193 (1.59%)	0.14 (0.13, 0.16)	22 1163 (1.89%)	0.16 (0.15, 0.18)
10 - 12	7 839 (0.83%)	0.15 (0.14, 0.17)	13 822 (1.58%)	0.18 (0.16, 0.20)
Year 3 Months 1 - 3	5 618 (0.81%)	0.16 (0.14, 0.18)	11 600 (1.83%)	0.20 (0.18, 0.22)
4 - 6	2 362 (0.55%)	0.17 (0.15, 0.19)	8 355 (2.25%)	0.23 (0.20, 0.26)
7 - 9	1 111 (0.90%)	0.18 (0.15, 0.21)	1 96 (1.04%)	0.23 (0.20, 0.27)
10 - 12	0 6 (0.00%)	0.18 (0.15, 0.21)	0 12 (0.00%)	0.23 (0.20, 0.27)
Year 4 Months 1 - 3	0 0 (0.00%)	0.18 (0.15, 0.21)	0 0 (0.00%)	0.23 (0.20, 0.27)
Overall Events (%)	337 2565 (13.1%)		398 2561 (15.5%)	

Log-rank test, p = 0.014

Hazard-ratio (95% CI) = 0.83 (0.72, 0.97)

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

Table 33 Analysis of Secondary Endpoint (CHD death, MI)

	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	17 2565 (0.66%)	0.01 (0.00, 0.01)	33 2561 (1.29%)	0.01 (0.01, 0.02)
4 - 6	20 2530 (0.79%)	0.01 (0.01, 0.02)	24 2512 (0.96%)	0.02 (0.02, 0.03)
7 - 9	18 2501 (0.72%)	0.02 (0.02, 0.03)	21 2479 (0.85%)	0.03 (0.02, 0.04)
10 - 12	15 2473 (0.61%)	0.03 (0.02, 0.03)	18 2444 (0.74%)	0.04 (0.03, 0.05)
Year 2 Months 1 - 3	10 2263 (0.44%)	0.03 (0.03, 0.04)	10 2222 (0.45%)	0.04 (0.04, 0.05)
4 - 6	13 1705 (0.76%)	0.04 (0.03, 0.05)	11 1694 (0.65%)	0.05 (0.04, 0.06)
7 - 9	6 1316 (0.46%)	0.05 (0.04, 0.05)	7 1292 (0.54%)	0.06 (0.05, 0.07)
10 - 12	4 930 (0.43%)	0.05 (0.04, 0.06)	5 928 (0.54%)	0.06 (0.05, 0.07)
Year 3 Months 1 - 3	3 696 (0.43%)	0.06 (0.04, 0.07)	3 685 (0.44%)	0.07 (0.05, 0.08)
4 - 6	1 417 (0.24%)	0.06 (0.05, 0.08)	2 404 (0.50%)	0.08 (0.06, 0.10)
7 - 9	0 128 (0.00%)	0.06 (0.05, 0.08)	0 117 (0.00%)	0.08 (0.06, 0.10)
10 - 12	0 8 (0.00%)	0.06 (0.05, 0.08)	0 13 (0.00%)	0.08 (0.06, 0.10)
Year 4 Months 1 - 3	0 0 (0.00%)	0.06 (0.05, 0.08)	0 0 (0.00%)	0.08 (0.06, 0.10)
Overall Events (%)	107 2565 (4.17%)		134 2561 (5.23%)	

Log-rank test, p = 0.068

Hazard-ratio (95% CI) = 0.79 (0.61, 1.02)

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

Table 34 Analysis of All-Cause Mortality

	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	15 2565 (0.58%)	0.01 (0.00, 0.01)	21 2561 (0.82%)	0.01 (0.00, 0.01)
4 - 6	15 2536 (0.59%)	0.01 (0.01, 0.02)	18 2525 (0.71%)	0.02 (0.01, 0.02)
7 - 9	18 2517 (0.72%)	0.02 (0.01, 0.02)	25 2503 (1.00%)	0.03 (0.02, 0.03)
10 - 12	17 2497 (0.68%)	0.03 (0.02, 0.03)	15 2474 (0.61%)	0.03 (0.02, 0.04)
Year 2 Months 1 - 3	10 2295 (0.44%)	0.03 (0.02, 0.04)	11 2263 (0.49%)	0.04 (0.03, 0.04)
4 - 6	16 1734 (0.92%)	0.04 (0.03, 0.05)	16 1726 (0.93%)	0.05 (0.04, 0.06)
7 - 9	7 1339 (0.52%)	0.05 (0.04, 0.05)	11 1321 (0.83%)	0.06 (0.05, 0.07)
10 - 12	6 949 (0.63%)	0.05 (0.04, 0.06)	4 950 (0.42%)	0.06 (0.05, 0.07)
Year 3 Months 1 - 3	4 713 (0.56%)	0.06 (0.05, 0.07)	5 704 (0.71%)	0.07 (0.06, 0.08)
4 - 6	3 432 (0.69%)	0.07 (0.05, 0.09)	2 418 (0.48%)	0.08 (0.06, 0.10)
7 - 9	0 130 (0.00%)	0.07 (0.05, 0.09)	1 120 (0.83%)	0.09 (0.06, 0.11)
10 - 12	0 8 (0.00%)	0.07 (0.05, 0.09)	0 13 (0.00%)	0.09 (0.06, 0.11)
Year 4 Months 1 - 3	0 0 (0.00%)	0.07 (0.05, 0.09)	0 0 (0.00%)	0.09 (0.06, 0.11)
Overall Events (%)	111 2565 (4.33%)		129 2561 (5.04%)	

Log-rank test, p = 0.222

Hazard-ratio (95% CI) = 0.85 (0.66, 1.10)

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

Table 35 Analysis of All Cardiovascular Events (Cardio deaths, MI, Stroke, TIA, Unplanned Hosp. for 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	74 2565 (2.88%)	0.03 (0.02, 0.04)	95 2561 (3.71%)	0.04 (0.03, 0.04)
4 - 6	87 2476 (3.51%)	0.06 (0.05, 0.07)	83 2452 (3.38%)	0.07 (0.06, 0.08)
7 - 9	62 2382 (2.60%)	0.09 (0.08, 0.10)	68 2364 (2.88%)	0.10 (0.09, 0.11)
10 - 12	54 2314 (2.33%)	0.11 (0.10, 0.12)	62 2287 (2.71%)	0.12 (0.11, 0.13)
Year 2 Months 1 - 3	34 2076 (1.64%)	0.13 (0.11, 0.14)	39 2036 (1.92%)	0.14 (0.13, 0.16)
4 - 6	30 1545 (1.94%)	0.15 (0.13, 0.16)	26 1532 (1.70%)	0.16 (0.14, 0.17)
7 - 9	19 1179 (1.61%)	0.16 (0.14, 0.18)	26 1154 (2.25%)	0.18 (0.16, 0.20)
10 - 12	8 830 (0.96%)	0.17 (0.15, 0.19)	15 817 (1.84%)	0.20 (0.18, 0.21)
Year 3 Months 1 - 3	7 610 (1.15%)	0.18 (0.16, 0.20)	12 594 (2.02%)	0.22 (0.20, 0.24)
4 - 6	2 356 (0.56%)	0.19 (0.17, 0.22)	8 350 (2.29%)	0.25 (0.22, 0.28)
7 - 9	1 107 (0.93%)	0.20 (0.17, 0.23)	2 94 (2.13%)	0.26 (0.22, 0.30)
10 - 12	0 6 (0.00%)	0.20 (0.17, 0.23)	0 11 (0.00%)	0.26 (0.22, 0.30)
Year 4 Months 1 - 3	0 0 (0.00%)	0.20 (0.17, 0.23)	0 0 (0.00%)	0.26 (0.22, 0.30)
Overall Events (%)	378 2565 (14.7%)		436 2561 (17.0%)	

Log-rank test, p = 0.027

Hazard-ratio (95% CI) = 0.86 (0.75, 0.98)

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

Table 36 Analysis of Cerebrovascular Events (Fatal Stroke, Non-Fatal Stroke, TIA)

	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	10 2565 (0.39%)	0.00 (0.00, 0.01)	0 2561 (0.00%)	0.00 (0.00, 0.00)
4 - 6	5 2527 (0.20%)	0.01 (0.00, 0.01)	9 2525 (0.36%)	0.00 (0.00, 0.01)
7 - 9	8 2504 (0.32%)	0.01 (0.01, 0.01)	8 2496 (0.32%)	0.01 (0.00, 0.01)
10 - 12	2 2478 (0.08%)	0.01 (0.01, 0.01)	9 2463 (0.37%)	0.01 (0.01, 0.01)
Year 2 Months 1 - 3	4 2275 (0.18%)	0.01 (0.01, 0.02)	3 2247 (0.13%)	0.01 (0.01, 0.02)
4 - 6	3 1713 (0.18%)	0.01 (0.01, 0.02)	4 1712 (0.23%)	0.01 (0.01, 0.02)
7 - 9	1 1323 (0.08%)	0.01 (0.01, 0.02)	3 1311 (0.23%)	0.02 (0.01, 0.02)
10 - 12	3 939 (0.32%)	0.02 (0.01, 0.02)	2 943 (0.21%)	0.02 (0.01, 0.03)
Year 3 Months 1 - 3	1 702 (0.14%)	0.02 (0.01, 0.03)	1 697 (0.14%)	0.02 (0.01, 0.03)
4 - 6	0 425 (0.00%)	0.02 (0.01, 0.03)	0 412 (0.00%)	0.02 (0.01, 0.03)
7 - 9	0 126 (0.00%)	0.02 (0.01, 0.03)	1 118 (0.85%)	0.03 (0.01, 0.05)
10 - 12	0 8 (0.00%)	0.02 (0.01, 0.03)	0 12 (0.00%)	0.03 (0.01, 0.05)
Year 4 Months 1 - 3	0 0 (0.00%)	0.02 (0.01, 0.03)	0 0 (0.00%)	0.03 (0.01, 0.05)
Overall Events (%)	37 2565 (1.44%)		40 2561 (1.56%)	

Log-rank test, p = 0.715

Hazard-ratio (95% CI) = 0.92 (0.59, 1.44)

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

Table 37 Analysis of CHD death, MI, and unstable Angina

	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	25 2565 (0.97%)	0.01 (0.01, 0.01)	48 2561 (1.87%)	0.02 (0.01, 0.02)
4 - 6	36 2522 (1.43%)	0.02 (0.02, 0.03)	35 2497 (1.40%)	0.03 (0.03, 0.04)
7 - 9	22 2477 (0.89%)	0.03 (0.03, 0.04)	30 2453 (1.22%)	0.04 (0.04, 0.05)
10 - 12	25 2445 (1.02%)	0.04 (0.03, 0.05)	25 2409 (1.04%)	0.05 (0.05, 0.06)
Year 2 Months 1 - 3	16 2228 (0.72%)	0.05 (0.04, 0.06)	14 2182 (0.64%)	0.06 (0.05, 0.07)
4 - 6	16 1673 (0.96%)	0.06 (0.05, 0.07)	12 1666 (0.72%)	0.07 (0.06, 0.08)
7 - 9	7 1288 (0.54%)	0.07 (0.06, 0.08)	11 1270 (0.87%)	0.08 (0.07, 0.09)
10 - 12	5 907 (0.55%)	0.07 (0.06, 0.08)	10 910 (1.10%)	0.09 (0.08, 0.10)
Year 3 Months 1 - 3	2 676 (0.30%)	0.08 (0.06, 0.09)	4 666 (0.60%)	0.10 (0.08, 0.11)
4 - 6	1 401 (0.25%)	0.08 (0.06, 0.10)	5 394 (1.27%)	0.12 (0.09, 0.14)
7 - 9	1 125 (0.80%)	0.09 (0.07, 0.11)	1 110 (0.91%)	0.12 (0.09, 0.15)
10 - 12	0 8 (0.00%)	0.09 (0.07, 0.11)	0 12 (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%)		195 2561 (7.61%)	

Log-rank test, p = 0.028

Hazard-ratio (95% CI) = 0.79 (0.64, 0.98)

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

Table 38 Analysis of CHD death, MI, and unstable or definite Angina

	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	48 2565 (1.87%)	0.02 (0.01, 0.02)	72 2561 (2.81%)	0.03 (0.02, 0.03)
4 - 6	55 2499 (2.20%)	0.04 (0.03, 0.05)	52 2474 (2.10%)	0.05 (0.04, 0.06)
7 - 9	39 2435 (1.60%)	0.06 (0.05, 0.06)	47 2413 (1.95%)	0.07 (0.06, 0.08)
10 - 12	37 2386 (1.55%)	0.07 (0.06, 0.08)	42 2353 (1.78%)	0.08 (0.07, 0.09)
Year 2 Months 1 - 3	26 2160 (1.20%)	0.08 (0.07, 0.09)	25 2115 (1.18%)	0.10 (0.09, 0.11)
4 - 6	20 1615 (1.24%)	0.10 (0.08, 0.11)	18 1606 (1.12%)	0.11 (0.10, 0.12)
7 - 9	13 1240 (1.05%)	0.11 (0.09, 0.12)	12 1218 (0.99%)	0.12 (0.10, 0.13)
10 - 12	6 870 (0.69%)	0.11 (0.10, 0.13)	12 874 (1.37%)	0.13 (0.12, 0.15)
Year 3 Months 1 - 3	2 644 (0.31%)	0.12 (0.10, 0.13)	9 637 (1.41%)	0.15 (0.13, 0.16)
4 - 6	1 380 (0.26%)	0.12 (0.10, 0.14)	7 378 (1.85%)	0.18 (0.15, 0.21)
7 - 9	1 117 (0.85%)	0.13 (0.11, 0.16)	1 103 (0.97%)	0.18 (0.15, 0.22)
10 - 12	0 7 (0.00%)	0.13 (0.11, 0.16)	0 12 (0.00%)	0.18 (0.15, 0.22)
Year 4 Months 1 - 3	0 0 (0.00%)	0.13 (0.11, 0.16)	0 0 (0.00%)	0.18 (0.15, 0.22)
Overall Events (%)	248 2565 (9.67%)		297 2561 (11.6%)	

Log-rank test, p = 0.025

Hazard-ratio (95% CI) = 0.83 (0.70, 0.98)

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

Table 39 Summary of CCSF Severity of Angina Score (I=least severe, IV=most severe)

	Nicorandil					Placebo				
	I	II	III	IV	(Total)	I	II	III	IV	(Total)
Visit										
1	671 (26%)	1605 (63%)	272 (11%)	15 (1%)	2563	692 (27%)	1583 (62%)	275 (11%)	9 (0%)	2559
4	896 (36%)	1357 (55%)	182 (7%)	20 (1%)	2455	895 (37%)	1330 (54%)	213 (9%)	13 (1%)	2451
5	937 (39%)	1259 (53%)	170 (7%)	13 (1%)	2379	916 (39%)	1279 (54%)	172 (7%)	9 (0%)	2376
6	624 (37%)	924 (55%)	110 (7%)	8 (0%)	1666	618 (37%)	907 (55%)	118 (7%)	15 (1%)	1658
7	483 (39%)	675 (54%)	84 (7%)	5 (0%)	1247	446 (36%)	677 (55%)	88 (7%)	11 (1%)	1222
8	314 (39%)	435 (54%)	58 (7%)	6 (1%)	813	283 (36%)	422 (54%)	74 (9%)	8 (1%)	787
9	145 (36%)	224 (55%)	35 (9%)	2 (0%)	406	129 (32%)	232 (57%)	38 (9%)	7 (2%)	406
10	36 (34%)	61 (58%)	7 (7%)	1 (1%)	105	42 (38%)	60 (55%)	7 (6%)	1 (1%)	110
11	0 (0%)	4 (67%)	2 (33%)	0 (0%)	6	1 (14%)	5 (71%)	0 (0%)	1 (14%)	7
12	985 (43%)	1159 (50%)	162 (7%)	9 (0%)	2315	989 (43%)	1124 (49%)	163 (7%)	15 (1%)	2291

Table 40 Worsening CCSF Severity of Angina Score

	Nicorandil number worsened / n (%)	Placebo number worsened / n (%)
Visit		
4	158 / 2454 (6%)	160 / 2451 (7%)
5	174 / 2378 (7%)	160 / 2376 (7%)
6 (annual visit)	140 / 1665 (8%)	129 / 1658 (8%)
7	113 / 1246 (9%)	115 / 1222 (9%)
8	67 / 812 (8%)	78 / 787 (10%)
9 (annual visit)	32 / 406 (8%)	35 / 406 (9%)
10	9 / 105 (9%)	6 / 110 (5%)
11	0 / 6 (0%)	1 / 7 (14%)
12 (final visit)	185 / 2314 (8%)	193 / 2290 (8%)
Worse at Any Visit:	387 / 2565 (15%)	398 / 2561 (16%)

Nicorandil vs Placebo, odds-ratio = 0.97 (0.83, 1.12)

P = 0.652

Table 41 Worsening CCSF and Unplanned Hospitalisation for Cardiac Chest Pain

	Nicorandil number worsened / n (%)	Placebo number worsened / n (%)
Unplanned Hospitalisation for Cardiac Chest Pain	260 / 2565 (10%)	292 / 2561 (11%)
Odds-Ratio = 0.88 (0.73, 1.05)		
P = 0.144		
Worsening CCSF score or Unplanned Hospitalisation for Cardiac Chest Pain	569 / 2565 (22%)	602 / 2561 (24%)
Odds-Ratio = 0.93 (0.81, 1.06)		
P = 0.259		

Table 42 Analysis of Changes in Blood Pressure

	Nicorandil Mean (Std Dev)	Placebo Mean (Std Dev)
Systolic Blood Pressure		
N	2067	2042
Baseline	138.5 (19.2)	138.3 (19.2)
Final Visit	134.5 (20.3)	134.9 (20.1)
Difference	4.0 (20.0)	3.4 (19.8)
Mean difference for Nicorandil vs Placebo = 0.5 (-0.6, 1.6)		
P = 0.353		
Diastolic Blood Pressure		
N	2067	2042
Baseline	78.6 (10.0)	78.6 (9.9)
Final Visit	76.2 (10.2)	76.5 (10.4)
Difference	2.4 (11.7)	2.1 (11.3)
Mean difference for Nicorandil vs Placebo = 0.3 (-0.3, 0.9)		
P = 0.327		

Table 43 Subgroup Analysis - Primary Endpoint

	Nicorandil n-events/total(%)	Placebo n-events/total(%)	Hazard-ratio (95% CI)	P (log-rank test)
Sex: Male	251 / 1962 (12.8%)	311 / 1948 (16.0%)	0.79 (0.67, 0.93)	0.005
Female	86 / 603 (14.3%)	87 / 613 (14.2%)	1.00 (0.74, 1.34)	0.976
Age (years): <65	124 / 1039 (11.9%)	150 / 1046 (14.3%)	0.81 (0.64, 1.03)	0.084
65 - 70	82 / 599 (13.7%)	81 / 567 (14.3%)	0.94 (0.69, 1.28)	0.707
>70	131 / 927 (14.1%)	167 / 948 (17.6%)	0.80 (0.64, 1.01)	0.062
Hypertension: Yes	167 / 1197 (14.0%)	170 / 1178 (14.4%)	0.97 (0.79, 1.20)	0.796
No	170 / 1368 (12.4%)	228 / 1383 (16.5%)	0.73 (0.60, 0.89)	0.002
Myocardial Infarction: Yes	253 / 1696 (14.9%)	300 / 1682 (17.8%)	0.82 (0.70, 0.97)	0.023
No	84 / 869 (9.7%)	98 / 879 (11.2%)	0.86 (0.64, 1.15)	0.299
Diabetic: Yes	27 / 197 (13.7%)	40 / 232 (17.2%)	0.80 (0.49, 1.31)	0.373
No	310 / 2368 (13.1%)	358 / 2329 (15.4%)	0.84 (0.72, 0.98)	0.024
CABG: Yes	88 / 572 (15.4%)	92 / 590 (15.6%)	0.98 (0.73, 1.31)	0.885
No	249 / 1993 (12.5%)	306 / 1971 (15.5%)	0.79 (0.67, 0.94)	0.006
CABG or PTCA: Yes	120 / 842 (14.3%)	136 / 888 (15.3%)	0.91 (0.72, 1.17)	0.473
No	217 / 1723 (12.6%)	262 / 1673 (15.7%)	0.80 (0.66, 0.95)	0.012

continued...Table 43 Subgroup Analysis - Primary Endpoint

	Nicorandil n-events/total(%)	Placebo n-events/total(%)	Hazard-ratio (95% CI)	P (log-rank test)
CCSF score: 1	70 / 671 (10.4%)	79 / 692 (11.4%)	0.91 (0.66, 1.25)	0.561
2	199 / 1605 (12.4%)	241 / 1583 (15.2%)	0.80 (0.66, 0.97)	0.020
3 & 4	68 / 287 (23.7%)	78 / 284 (27.5%)	0.85 (0.61, 1.17)	0.322
Last Dose: 10mg	46 / 280 (16.4%)	20 / 129 (15.5%)	1.03 (0.61, 1.74)	0.909
20mg	291 / 2285 (12.7%)	378 / 2432 (15.5%)	0.81 (0.70, 0.94)	0.007
Classes of drugs*: 0	7 / 97 (7.2%)	10 / 104 (9.6%)	0.75 (0.29, 1.97)	0.556
1	129 / 1080 (11.9%)	141 / 1053 (13.4%)	0.89 (0.70, 1.12)	0.318
2	139 / 1005 (13.8%)	179 / 1077 (16.6%)	0.81 (0.65, 1.01)	0.066
3	62 / 383 (16.2%)	68 / 327 (20.8%)	0.78 (0.55, 1.10)	0.149
Beta Blockers: Yes	185 / 1469 (12.6%)	198 / 1433 (13.8%)	0.90 (0.73, 1.10)	0.291
No	152 / 1096 (13.9%)	200 / 1128 (17.7%)	0.77 (0.63, 0.96)	0.017
Calcium Channel Blockers: Yes	195 / 1411 (13.8%)	241 / 1397 (17.3%)	0.80 (0.66, 0.96)	0.019
No	142 / 1154 (12.3%)	157 / 1164 (13.5%)	0.89 (0.71, 1.12)	0.327
Long Acting Nitrates: Yes	213 / 1359 (15.7%)	264 / 1358 (19.4%)	0.79 (0.66, 0.94)	0.010
No	124 / 1206 (10.3%)	134 / 1203 (11.1%)	0.92 (0.72, 1.17)	0.502

* number of types of drug taken out of; beta-blockers, calcium channel blockers, long acting nitrates

continued...Table 43 Subgroup Analysis - Primary Endpoint

		Nicorandil n-events/total(%)	Placebo n-events/total(%)	Hazard-ratio (95% CI)	P (log-rank test)
ACE-Inhibitors:	Yes	123 / 739 (16.6%)	133 / 759 (17.5%)	0.95 (0.74, 1.22)	0.689
	No	214 / 1826 (11.7%)	265 / 1802 (14.7%)	0.78 (0.65, 0.94)	0.007
Aspirin/Antiplatelets:	Yes	296 / 2283 (13.0%)	345 / 2238 (15.4%)	0.82 (0.71, 0.96)	0.015
	No	41 / 282 (14.5%)	53 / 323 (16.4%)	0.92 (0.61, 1.38)	0.674
Statins:	Yes	171 / 1449 (11.8%)	216 / 1486 (14.5%)	0.79 (0.65, 0.97)	0.021
	No	166 / 1116 (14.9%)	182 / 1075 (16.9%)	0.89 (0.72, 1.09)	0.256
Left Ventricular Dysfunction (LVD):	Yes	43 / 230 (18.7%)	37 / 206 (18.0%)	1.06 (0.68, 1.65)	0.786
	No	293 / 2332 (12.6%)	361 / 2354 (15.3%)	0.80 (0.69, 0.94)	0.006
Left Ventricular Hypertrophy (LVH):	Yes	51 / 259 (19.7%)	51 / 260 (19.6%)	1.04 (0.71, 1.53)	0.840
	No	284 / 2296 (12.4%)	346 / 2299 (15.1%)	0.81 (0.69, 0.94)	0.007

Table 44 Subgroup Analysis - Secondary Endpoint

	Nicorandil n-events/total(%)	Placebo n-events/total(%)	Hazard-ratio (95% CI)	P (log-rank test)
Sex: Male	87 / 1962 (4.43%)	103 / 1948 (5.29%)	0.83 (0.63, 1.11)	0.204
Female	20 / 603 (3.32%)	31 / 613 (5.06%)	0.65 (0.37, 1.14)	0.130
Age (years): <65	29 / 1039 (2.79%)	39 / 1046 (3.73%)	0.74 (0.46, 1.19)	0.212
65 - 70	21 / 599 (3.51%)	24 / 567 (4.23%)	0.80 (0.45, 1.45)	0.467
>70	57 / 927 (6.15%)	71 / 948 (7.49%)	0.83 (0.59, 1.18)	0.295
Hypertension: Yes	50 / 1197 (4.18%)	54 / 1178 (4.58%)	0.92 (0.62, 1.34)	0.652
No	57 / 1368 (4.17%)	80 / 1383 (5.78%)	0.71 (0.50, 0.99)	0.043
Myocardial Infarction: Yes	88 / 1696 (5.19%)	109 / 1682 (6.48%)	0.80 (0.60, 1.05)	0.110
No	19 / 869 (2.19%)	25 / 879 (2.84%)	0.76 (0.42, 1.38)	0.364
Diabetic: Yes	10 / 197 (5.08%)	17 / 232 (7.33%)	0.70 (0.32, 1.53)	0.367
No	97 / 2368 (4.10%)	117 / 2329 (5.02%)	0.81 (0.62, 1.06)	0.120
CABG: Yes	22 / 572 (3.85%)	21 / 590 (3.56%)	1.07 (0.59, 1.95)	0.824
No	85 / 1993 (4.26%)	113 / 1971 (5.73%)	0.74 (0.56, 0.98)	0.033
CABG or PTCA: Yes	28 / 842 (3.33%)	27 / 888 (3.04%)	1.08 (0.64, 1.83)	0.773
No	79 / 1723 (4.59%)	107 / 1673 (6.40%)	0.71 (0.53, 0.95)	0.020

continued...Table 44 Subgroup Analysis - Secondary Endpoint

		Nicorandil n-events/total(%)	Placebo n-events/total(%)	Hazard-ratio (95% CI)	P (log-rank test)
CCSF score:	1	16 / 671 (2.38%)	29 / 692 (4.19%)	0.56 (0.30, 1.03)	0.060
	2	64 / 1605 (3.99%)	81 / 1583 (5.12%)	0.77 (0.56, 1.07)	0.120
	3 & 4	27 / 287 (9.41%)	24 / 284 (8.45%)	1.12 (0.65, 1.94)	0.686
Last Dose:	10mg	14 / 280 (5.00%)	10 / 129 (7.75%)	0.63 (0.28, 1.41)	0.253
	20mg	93 / 2285 (4.07%)	124 / 2432 (5.10%)	0.79 (0.61, 1.04)	0.091
Classes of drugs*:	0	5 / 97 (5.15%)	4 / 104 (3.85%)	1.35 (0.36, 5.01)	0.657
	1	46 / 1080 (4.26%)	56 / 1053 (5.32%)	0.79 (0.53, 1.17)	0.234
	2	43 / 1005 (4.28%)	51 / 1077 (4.74%)	0.90 (0.60, 1.35)	0.599
	3	13 / 383 (3.39%)	23 / 327 (7.03%)	0.48 (0.24, 0.95)	0.031
Beta Blockers:	Yes	50 / 1469 (3.40%)	67 / 1433 (4.68%)	0.71 (0.50, 1.03)	0.070
	No	57 / 1096 (5.20%)	67 / 1128 (5.94%)	0.88 (0.62, 1.25)	0.465
Calcium Channel Blockers:	Yes	55 / 1411 (3.90%)	72 / 1397 (5.15%)	0.76 (0.53, 1.08)	0.124
	No	52 / 1154 (4.51%)	62 / 1164 (5.33%)	0.82 (0.57, 1.19)	0.301
Long Acting Nitrates:	Yes	66 / 1359 (4.86%)	88 / 1358 (6.48%)	0.74 (0.54, 1.02)	0.064
	No	41 / 1206 (3.40%)	46 / 1203 (3.82%)	0.88 (0.58, 1.34)	0.550

* number of types of drug taken out of; beta-blockers, calcium channel blockers, long acting nitrates

continued...Table 44 Subgroup Analysis - Secondary Endpoint

		Nicorandil n-events/total(%)	Placebo n-events/total(%)	Hazard-ratio (95% CI)	P (log-rank test)
ACE-Inhibitors:	Yes	50 / 739 (6.77%)	45 / 759 (5.93%)	1.16 (0.77, 1.73)	0.478
	No	57 / 1826 (3.12%)	89 / 1802 (4.94%)	0.62 (0.44, 0.86)	0.004
Aspirin/Antiplatelets:	Yes	90 / 2283 (3.94%)	110 / 2238 (4.92%)	0.79 (0.60, 1.05)	0.101
	No	17 / 282 (6.03%)	24 / 323 (7.43%)	0.82 (0.44, 1.53)	0.534
Statins:	Yes	41 / 1449 (2.83%)	60 / 1486 (4.04%)	0.69 (0.46, 1.02)	0.061
	No	66 / 1116 (5.91%)	74 / 1075 (6.88%)	0.86 (0.62, 1.20)	0.387
Left Ventricular Dysfunction: (LVD)	Yes	17 / 230 (7.39%)	14 / 206 (6.80%)	1.12 (0.55, 2.27)	0.756
	No	90 / 2332 (3.86%)	120 / 2354 (5.10%)	0.75 (0.57, 0.98)	0.036
Left Ventricular Hypertrophy: (LVH)	Yes	17 / 259 (6.56%)	20 / 260 (7.69%)	0.89 (0.47, 1.70)	0.725
	No	89 / 2296 (3.88%)	114 / 2299 (4.96%)	0.77 (0.58, 1.02)	0.064

Table 45 Summary of Revascularisations

	Nicorandil (n=2565)		Placebo (n=2561)	
	Events	Subjects (%)	Events	Subjects (%)
PTCA	93	83 (3.24%)	111	98 (3.83%)
CABG	88	88 (3.43%)	117	117 (4.57%)
PTCA or CABG	181	169 (6.59%)	228	204 (7.97%)
Elective Procedures Only:				
PTCA	84	76 (2.96%)	101	93 (3.63%)
CABG	86	86 (3.35%)	108	108 (4.22%)
PTCA or CABG	170	160 (6.24%)	209	192 (7.50%)

Table 46 Heart Failure Deaths, Heart Failure Hospitalisations and Arrhythmia

	Nicorandil (n=2565)		Placebo (n=2561)	
	Events	Subjects (%)	Events	Subjects (%)
Heart failure* hospitalisation	51	38 (1.48%)	59	51 (1.99%)
Heart failure death	12	12 (0.47%)	9	9 (0.35%)
Heart failure death or Heart failure hospitalisation	63	49 (1.91%)	68	52 (2.03%)
Arrhythmia†	48	37 (1.44%)	46	42 (1.64%)

* Heart Failure = heart failure, cardiac failure, ventricular failure.

† Arrhythmia = arrhythmia, atrial flutter, atrial tachycardia, atrial fibrillation, ventricular fibrillation, paroxysmal ventricular fibrillation, ventricular tachycardia, ventricular arrhythmia, supraventricular tachycardia

Table 47 Multivariate Model of the Primary Endpoint

All models are based upon n = 5048 subjects with no missing risk factors

		Univariate Models Hazard Rate (95% CI)	p	Multivariate Model Hazard Rate (95% CI)	p
Treatment	(Nicorandil vs Placebo)	0.83 (0.72, 0.96)	0.014	0.82 (0.71, 0.95)	0.009
Age	(5-year risk)	1.06 (1.01, 1.10)	0.014	1.05 (1.00, 1.11)	0.035
Sex	(Male vs Female)	1.00 (0.84, 1.18)	0.966	1.02 (0.86, 1.22)	0.794
CCSF	(Score 2 vs 1)	1.26 (1.05, 1.52)	0.015	1.25 (1.04, 1.51)	0.021
	(Score 3 vs 1)	2.32 (1.83, 2.94)	< 0.001	2.13 (1.67, 2.71)	< 0.001
	(Score 4 vs 1)	6.32 (3.51, 11.38)	< 0.001	5.49 (3.01, 10.00)	< 0.001
Smoking	(Yes vs No/Former)	1.37 (1.14, 1.64)	0.001	1.32 (1.10, 1.60)	0.004
Systolic Blood Pessure	(risk for 10mmHg)	0.99 (0.95, 1.03)	0.602	0.98 (0.94, 1.02)	0.369
Heart Rate	(risk for 10bpm)	1.09 (1.03, 1.16)	0.005	1.05 (0.98, 1.11)	0.171
Body Mass Index	(risk for 2kg/m-squared)	0.96 (0.93, 0.99)	0.018	0.97 (0.93, 1.00)	0.053
Myocardial Infarction	(Yes vs No)	1.62 (1.37, 1.91)	< 0.001	1.54 (1.30, 1.83)	< 0.001
CABG	(Yes vs No)	1.08 (0.91, 1.28)	0.389	1.09 (0.92, 1.30)	0.328
Hypertension	(Yes vs No)	0.99 (0.86, 1.15)	0.931	1.07 (0.91, 1.25)	0.406
Diabetic	(Yes vs No)	1.16 (0.90, 1.49)	0.252	1.11 (0.86, 1.43)	0.437
Left Ventricular Hypertrophy	(Yes vs No)	1.50 (1.21, 1.86)	< 0.001	1.39 (1.12, 1.73)	0.003
Left Ventricular Dysfunction	(Yes vs No)	1.34 (1.06, 1.69)	0.014	1.09 (0.86, 1.39)	0.475

Table 48 Serious Adverse Events by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
APPLICATION SITE DISORDERS	12	12	2.91	13	13	3.18
BODY AS A WHOLE - GENERAL DISORDERS	32	32	7.77	35	37	9.05
CARDIOVASCULAR DISORDERS, GENERAL	117	136	33.02	133	153	37.43
CENTR & PERIPH NERV SYST. DISORDERS	29	36	8.74	29	30	7.34
ENDOCRINE DISORDERS	2	2	0.49	0	0	0.00
GASTRO- INTESTINAL SYSTEM DISORDERS	163	194	47.10	110	132	32.30
HEARING AND VESTIBULAR DISORDERS	3	4	0.97	5	5	1.22
HEART RATE AND RHYTHM DISORDERS	56	67	16.27	50	55	13.46
LIVER AND BILIARY SYSTEM DISORDERS	14	19	4.61	19	27	6.61
METABOLIC AND NUTRITIONAL DISORDERS	42	45	10.92	24	24	5.87
MUSCULO-SKELETAL SYSTEM DISORDERDS	76	84	20.39	64	66	16.15
MYO ENDO PERICARDIAL &VALVE DISORDER	435	618	150.04	503	782	191.33
NEONATAL AND INFANCY DISORDERS	13	14	3.40	8	8	1.96
NEOPLASM	93	135	32.77	88	120	29.36
OPERATIONS & PROCEDURES	292	370	89.83	290	356	87.10
PLATELET, BLEEDING&CLOTTING DISORDER	9	9	2.18	10	10	2.45
PSYCHIATRIC DISORDERS	15	16	3.88	12	13	3.18
RED BLOOD CELL DISORDERS	12	14	3.40	11	18	4.40
REPRODUCTIVE DISORDES,FEMALE	2	2	0.49	4	4	0.98
REPRODUCTIVE DISORDES,MALE	16	18	4.37	10	10	2.45
RESISTANCE MECHANISM DISORDERS	15	15	3.64	11	11	2.69
RESPIRATORY SYSTEM DISORDERS	86	109	26.46	68	85	20.80
SKIN AND APPENDAGES DISORDERS	25	25	6.07	15	15	3.67
UNKNOWN	7	7	1.70	7	7	1.71
URINARY SYSTEM DISORDERS	45	50	12.14	47	59	14.44
VASCULAR (EXTRACARDIAC) DISORDERS	76	83	20.15	75	86	21.04
VISION DISORDERS	43	46	11.17	26	31	7.58
WHITE BLOOD CELL AND RES DISORDERS	0	0	0.00	1	1	0.24
TOTAL	1135	2162	524.88	1128	2158	527.99

* rate = number of events per thousand person-years of follow-up

Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
APPLICATION SITE DISORDERS						
ALLERGY CONTACT	1	1	0.24	0	0	0.00
APPLICATION SITE DAMAGE	0	0	0.00	1	1	0.24
CELLULITIS	10	10	2.43	9	9	2.20
FASCIITIS NECROTIZING	0	0	0.00	1	1	0.24
FISTULA WITH INFECTION	1	1	0.24	0	0	0.00
IMPLANTATION COMPLICATION	0	0	0.00	1	1	0.24
INFLAMMATION LOCALIZED	0	0	0.00	1	1	0.24
BODY AS A WHOLE - GENERAL DISORDERS						
ALLERGIC REACTION	3	3	0.73	1	1	0.24
ANAPHYLACTIC SHOCK	1	1	0.24	0	0	0.00
BURNS	1	1	0.24	0	0	0.00
CHEST DISCOMFORT	1	1	0.24	0	0	0.00
CHEST TIGHTNESS OF	1	1	0.24	0	0	0.00
CRYOGLOBULINEMIA	0	0	0.00	1	1	0.24
DEATH	6	6	1.46	8	8	1.96
DEATH FROM PROGRESSIVE DISEASE	1	1	0.24	0	0	0.00
DRUG INTERACTION	1	1	0.24	0	0	0.00
EDEMA	0	0	0.00	1	1	0.24
FOOD POISONING	1	1	0.24	0	0	0.00
GRANULOMA SALIVARYGLAND	1	1	0.24	0	0	0.00
GRANULOMATOUS LESION	1	1	0.24	1	1	0.24
HYPERTROPHY	0	0	0.00	1	1	0.24
INFARCT	2	2	0.49	0	0	0.00
OCCLUSION	0	0	0.00	6	6	1.47
OTHER GENERAL SYMPTOMS	2	2	0.49	2	2	0.49
OVERDOSE EFFECT	0	0	0.00	1	1	0.24
PAIN	5	5	1.21	5	5	1.22
SIDE EFFECTS NOS	3	3	0.73	1	1	0.24
SUDDEN DEATH	0	0	0.00	1	1	0.24
SWELLING ARMS	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
SWELLING LEG	1	1	0.24	2	2	0.49
SWELLING TISSUE	0	0	0.00	1	1	0.24
WEAKNESS POSTURAL	0	0	0.00	1	2	0.49
WEIGHT DECREASE	0	0	0.00	3	3	0.73
CARDIOVASCULAR DISORDERS, GENERAL						
ANEURYSM	7	7	1.70	2	2	0.49
ANGINA EXERCISE INDUCED	1	1	0.24	2	2	0.49
BLACK-OUT (NOT AMNESIA)	1	1	0.24	2	2	0.49
CARDIAC DYSFUNCTION	1	1	0.24	3	3	0.73
CARDIAC FAILURE	5	6	1.46	16	18	4.40
CARDIAC FAILURE LEFT	2	2	0.49	1	1	0.24
CARDIOVASCULAR COLLAPSE	1	1	0.24	2	2	0.49
CIRCULATORY DISORDERS	1	1	0.24	0	0	0.00
COLLAPSE CIRCULATORY	1	1	0.24	1	1	0.24
COLLAPSE TRANSIENT	10	11	2.67	5	7	1.71
CONGESTIVE HEART FAILURE	17	19	4.61	14	15	3.67
COR PULMONALE	0	0	0.00	1	1	0.24
CORONARY ATHEROSCLEROSIS	1	1	0.24	7	7	1.71
ECG ABNORMAL	1	1	0.24	2	2	0.49
ELECTROCARDIOGRAM ABNORMAL NON-SP	0	0	0.00	1	1	0.24
FAINTNESS	1	1	0.24	0	0	0.00
HEART DAMAGE	0	0	0.00	1	1	0.24
HEART DISEASE	26	29	7.04	40	42	10.28
HEART DISORDER	2	2	0.49	0	0	0.00
HEART FAILURE ANEMIC	0	0	0.00	1	1	0.24
HYPERTENSION	2	2	0.49	0	0	0.00
HYPERTENSION ESSENTIAL	0	0	0.00	1	1	0.24
HYPOTENSION	3	3	0.73	2	2	0.49
HYPOTENSION ORTHOSTATIC	1	1	0.24	0	0	0.00
HYPOTENSION POSTURAL	2	2	0.49	0	0	0.00
LEFT VENTRICULAR FAILURE	25	28	6.80	20	24	5.87
PRE-SYNCOPE	0	0	0.00	2	2	0.49

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
SHOCK CARDIOGENIC	0	0	0.00	2	2	0.49
SHOCK SEPTICEMIC	1	1	0.24	0	0	0.00
SYNCOPE	9	9	2.18	7	7	1.71
SYNCOPE VAGOVAGAL	1	1	0.24	0	0	0.00
SYNCOPE VASOVAGAL	0	0	0.00	1	1	0.24
VASOVAGAL ATTACK	4	4	0.97	4	4	0.98
VENTRICULAR INSUFFICIENCY LEFT	0	0	0.00	1	2	0.49
CENTR & PERIPH NERV SYST. DISORDERS						
BELL'S PALSY	0	0	0.00	1	1	0.24
CEREBRAL ATROPHY	1	1	0.24	0	0	0.00
CEREBRAL DISTURBANCES	2	2	0.49	0	0	0.00
CEREBRAL HEMORRHAGE	1	1	0.24	1	1	0.24
CEREBRAL PALSY	1	1	0.24	0	0	0.00
CEREBRAL SYMPTOMS	0	0	0.00	1	1	0.24
COMA	0	0	0.00	1	1	0.24
DIZZINESS	4	4	0.97	3	3	0.73
DIZZY ON STANDING	1	1	0.24	0	0	0.00
EPILEPSY GRAND MAL	0	0	0.00	1	1	0.24
EPILEPTIFORM FITS NOS	1	1	0.24	0	0	0.00
EYELID PTOSIS	1	1	0.24	0	0	0.00
FALLING	2	2	0.49	1	1	0.24
GAIT UNSTEADY	1	1	0.24	0	0	0.00
HEADACHE	8	9	2.18	5	5	1.22
HEMORRHAGE INTRACRANIAL	0	0	0.00	1	1	0.24
LETHARGY	1	1	0.24	0	0	0.00
LIMB WEAKNESS	0	0	0.00	1	1	0.24
MIGRAINE	0	0	0.00	1	1	0.24
MUSCLE STIFFNESS	0	0	0.00	1	1	0.24
MYASTHENIA GRAVIS	1	3	0.73	0	0	0.00
MYELOPATHY	0	0	0.00	1	1	0.24
NERVE DAMAGE	1	1	0.24	1	1	0.24
NEURITIS	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
NEUROLOGIC SYMPTOMS	0	0	0.00	2	2	0.49
PARKINSON'S DISEASE	0	0	0.00	1	1	0.24
POLYNEUROPATHY	1	1	0.24	0	0	0.00
POLYNEUROPATHY DIABETIC	0	0	0.00	1	1	0.24
POLYNEUROPATHY SENSORY	0	0	0.00	1	1	0.24
PTOSIS	1	1	0.24	1	1	0.24
SCIATIC COMPLAINTS	1	1	0.24	0	0	0.00
SEIZURES CEREBRAL	1	1	0.24	0	0	0.00
SUBARACHNOID HEMORRHAGE	0	0	0.00	1	1	0.24
SUBDURAL HEMATOMA	0	0	0.00	1	1	0.24
UNCONSCIOUSNESS	0	0	0.00	1	1	0.24
VOCAL CORD DAMAGE	1	3	0.73	0	0	0.00
ENDOCRINE DISORDERS						
THYROID DISORDER	1	1	0.24	0	0	0.00
THYROTOXICOSIS	1	1	0.24	0	0	0.00
GASTRO- INTESTINAL SYSTEM DISORDERS						
ABDOMINAL DISCOMFORT	3	3	0.73	0	0	0.00
ABDOMINAL PAIN	9	14	3.40	13	14	3.43
ABDOMINAL PAIN LOWER	0	0	0.00	1	1	0.24
ABDOMINAL PAIN UPPER	2	2	0.49	1	1	0.24
ANAL SPHINCTER DISORDER	1	1	0.24	1	1	0.24
APPENDICITIS	1	1	0.24	0	0	0.00
BLEEDING ABDOMINAL	0	0	0.00	1	1	0.24
BLEEDING ULCER	0	0	0.00	1	1	0.24
BOWEL OBSTRUCTION	2	2	0.49	3	3	0.73
BOWEL PERFORATION	0	0	0.00	1	1	0.24
COFFEE GROUND VOMITING	1	2	0.49	0	0	0.00
COLITIS	3	3	0.73	0	0	0.00
COLITIS ISCHEMIC	0	0	0.00	1	1	0.24
COLITIS PSEUDOMEMBRANOUS	1	1	0.24	0	0	0.00
COLITIS ULCERATIVE	3	3	0.73	2	2	0.49

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
COLITIS ULCERATIVE AGGRAVATED	1	1	0.24	1	1	0.24
CONSTIPATION	6	6	1.46	5	7	1.71
CROHN'S DISEASE	1	1	0.24	2	2	0.49
DIARRHEA	7	7	1.70	4	4	0.98
DISEASES OF ESOPHAGUS	1	1	0.24	0	0	0.00
DIVERTICULAR DISEASE	8	8	1.94	1	1	0.24
DIVERTICULITIS	6	6	1.46	2	2	0.49
DIVERTICULOSIS	6	6	1.46	2	2	0.49
DUODENAL ULCER	3	3	0.73	2	4	0.98
DUODENITIS	2	2	0.49	0	0	0.00
DYSPEPSIA	4	5	1.21	6	6	1.47
DYSPHAGIA	1	1	0.24	2	2	0.49
EPIGASTRIC PAIN NOT FOOD-RELATED	4	4	0.97	1	1	0.24
ESOPHAGEAL PERFORATION	1	1	0.24	0	0	0.00
ESOPHAGITIS	10	10	2.43	4	5	1.22
ESOPHAGUS COMPLAINTS	0	0	0.00	2	3	0.73
ESOPHAGUS MUCOSA DISTURBANCE	0	0	0.00	1	1	0.24
FECAL FISTULA	2	2	0.49	0	0	0.00
FECAL INCONTINENCE	1	1	0.24	1	1	0.24
GASTRESOPHAGEAL REFLUX	1	1	0.24	0	0	0.00
GASTRIC BLEEDING	1	1	0.24	1	1	0.24
GASTRIC EROSION	0	0	0.00	1	1	0.24
GASTRIC HEMORRHAGE	1	1	0.24	0	0	0.00
GASTRIC INFLAMMATION	0	0	0.00	1	1	0.24
GASTRIC OBSTRUCTION	1	1	0.24	0	0	0.00
GASTRIC ULCER	6	9	2.18	3	3	0.73
GASTRITIS	7	7	1.70	4	4	0.98
GASTRITIS ANTRUM	5	5	1.21	0	0	0.00
GASTRITIS EROSIVE	1	1	0.24	1	1	0.24
GASTRITIS HEMORRHAGIC	0	0	0.00	1	1	0.24
GASTRO-INTESTINAL DISORDER NOS	3	3	0.73	1	1	0.24
GASTRODUODENITIS	2	2	0.49	0	0	0.00
GASTROENTERITIS	5	5	1.21	4	4	0.98

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
GASTROINTESTINAL DAMAGE	0	0	0.00	1	1	0.24
GASTROINTESTINAL TRACT BLEED NOS	0	0	0.00	4	4	0.98
GI HEMORRHAGE	1	1	0.24	4	4	0.98
HEARTBURN	1	1	0.24	1	1	0.24
HEMATEMESIS	4	4	0.97	1	1	0.24
HEMATEMESIS GASTRIC ULCER	1	1	0.24	0	0	0.00
HEMORRHOIDS	3	3	0.73	1	1	0.24
HERNIA HIATUS	12	12	2.91	9	9	2.20
INDIGESTION	0	0	0.00	1	1	0.24
INFLAMMATION PYLORUS	1	1	0.24	0	0	0.00
INTESTINAL OBSTRUCTION	3	3	0.73	1	1	0.24
IRRITABLE BOWEL SYNDROME	1	1	0.24	2	2	0.49
MALABSORPTION	0	0	0.00	1	1	0.24
MELENA	4	4	0.97	3	3	0.73
MOUTH ULCERATION	2	2	0.49	0	0	0.00
ORAL ULCERATION	1	1	0.24	0	0	0.00
PAIN STOMACH	0	0	0.00	1	1	0.24
PANCREATITIS	2	3	0.73	2	2	0.49
PANCREATITIS ACUTE	0	0	0.00	2	2	0.49
PERITONITIS	1	1	0.24	0	0	0.00
PROCTITIS	2	2	0.49	1	1	0.24
PYLORIC STENOSIS	0	0	0.00	1	1	0.24
RECTAL BLEEDING	12	13	3.16	2	2	0.49
RECTAL DISORDER	1	1	0.24	0	0	0.00
RECTAL PAIN	0	0	0.00	1	1	0.24
REFLUX DUODENO-GASTRIC	0	0	0.00	1	1	0.24
REFLUX ESOPHAGITIS	1	1	0.24	4	4	0.98
SMALL INTESTINE OBSTRUCTION	2	2	0.49	0	0	0.00
STOMACH ULCER	0	0	0.00	1	1	0.24
TOOTH CARIES	0	0	0.00	1	1	0.24
ULCER	1	1	0.24	0	0	0.00
ULCER GINGIVA	1	1	0.24	0	0	0.00
ULCER PALATE	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
ULCER PYLORIC	1	1	0.24	1	1	0.24
HEARING AND VESTIBULAR DISORDERS						
EAR BLOCKAGE	1	1	0.24	0	0	0.00
EAR DRUM PERFORATION	1	1	0.24	0	0	0.00
EAR INFECTION	1	1	0.24	1	1	0.24
EAR PAIN	0	0	0.00	1	1	0.24
LABYRINTHINE DISORDER	1	1	0.24	1	1	0.24
TINNITUS	0	0	0.00	1	1	0.24
VERTIGO	0	0	0.00	1	1	0.24
HEART RATE AND RHYTHM DISORDERS						
ARRHYTHMIA	0	0	0.00	1	1	0.24
ARRHYTHMIA VENTRICULAR	1	1	0.24	1	1	0.24
ATRIAL FIBRILLATION PAROXYSMAL	6	7	1.70	3	3	0.73
ATRIAL FLUTTER	3	5	1.21	3	3	0.73
AV BLOCK SECOND DEGREE	1	1	0.24	0	0	0.00
AV DISSOCIATION	0	0	0.00	1	1	0.24
BRADYARRHYTHMIA	0	0	0.00	1	1	0.24
BRADYCARDIA	5	5	1.21	2	2	0.49
CARDIAC ARREST	9	9	2.18	4	4	0.98
CARDIAC ARRHYTHMIA NOS	0	0	0.00	3	3	0.73
CARDIAC DEATH	4	4	0.97	2	2	0.49
CARDIOPULMONARY ARREST	1	1	0.24	1	1	0.24
FIBRILLATION ATRIAL	20	24	5.83	19	22	5.38
FIBRILLATION VENTRICULAR	0	0	0.00	1	1	0.24
HEART BLOCK	1	1	0.24	1	1	0.24
LEFT BUNDLE BRANCH BLOCK	0	0	0.00	1	1	0.24
PALPITATION	3	3	0.73	2	2	0.49
SINUS BRADYCARDIA	1	1	0.24	1	1	0.24
SUDDEN CARDIAC DEATH	2	2	0.49	0	0	0.00
SYNDROME SICK SINUS	0	0	0.00	1	1	0.24
TACHYCARDIA	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
TACHYCARDIA SUPRAVENTRICULAR PAROXYSMAL	0	0	0.00	1	1	0.24
TACHYCARDIA VENTRICULAR	3	3	0.73	2	2	0.49
LIVER AND BILIARY SYSTEM DISORDERS						
BILIARY COLIC	1	1	0.24	4	4	0.98
BILIARY STONES	1	1	0.24	0	0	0.00
BILIARY TRACT DISORDER UNSPECIFIED	1	1	0.24	0	0	0.00
CHOLANGITIS	1	1	0.24	0	0	0.00
CHOLECYSTITIS	6	6	1.46	8	10	2.45
CHOLELITHIASIS	7	7	1.70	3	3	0.73
GALL BLADDER DISORDER	0	0	0.00	1	1	0.24
GALL BLADDER STONES	1	1	0.24	2	2	0.49
HEPATITIS CHRONIC	1	1	0.24	0	0	0.00
JAUNDICE	0	0	0.00	4	4	0.98
LIVER ENZYME DISORDER	0	0	0.00	1	1	0.24
LIVER FUNCTION TESTS ABNORMAL NOS	0	0	0.00	2	2	0.49
METABOLIC AND NUTRITIONAL DISORDERS						
DIABETES MELLITUS	33	33	8.01	21	21	5.14
DIABETES MELLITUS AGGRAVATED	1	1	0.24	0	0	0.00
GOUT	3	4	0.97	1	1	0.24
HYPERCHOLESTEROLEMIA	1	2	0.49	0	0	0.00
HYPERGLYCEMIA	2	2	0.49	1	1	0.24
HYPOGLYCEMIA	0	0	0.00	1	1	0.24
KETOACIDOSIS	1	1	0.24	0	0	0.00
KETOSIS	1	1	0.24	0	0	0.00
RETINOPATHY DIABETIC	1	1	0.24	0	0	0.00
MUSCULO-SKELETAL SYSTEM DISORDERDS						
ARTHRITIC-LIKE PAIN	1	1	0.24	0	0	0.00
ARTHRITIS	2	2	0.49	1	1	0.24
ARTHRITIS RHEUMATOID	1	1	0.24	1	1	0.24
ARTHRITIS RHEUMATOID AGGRAVATED	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
ARTHRITIS SEPTIC	0	0	0.00	1	1	0.24
BACK PAIN	3	3	0.73	6	6	1.47
BONE REFRACTURED	1	1	0.24	0	0	0.00
CARPAL TUNNEL SYNDROME	5	6	1.46	4	4	0.98
COMPRESSION FRACTURES	0	0	0.00	1	1	0.24
COSTOCHONDRITIS	1	1	0.24	0	0	0.00
DISLOCATION OF HIP	2	3	0.73	1	1	0.24
DISPLACEMENT OF INTERVERTEBRAL DISC	0	0	0.00	1	1	0.24
DUPUYTREN'S CONTRACTURE	1	1	0.24	3	3	0.73
FRACTURE RIB	4	4	0.97	1	1	0.24
FRACTURES	22	24	5.83	15	15	3.67
HERNIA	5	5	1.21	2	2	0.49
INTERVERTEBRAL DISC DISORDER	0	0	0.00	1	1	0.24
JOINT COMPLAINTS	1	1	0.24	2	2	0.49
LEG DISCOMFORT	1	1	0.24	0	0	0.00
LIGAMENT DISORDER	0	0	0.00	1	1	0.24
LOIN PAIN	2	2	0.49	0	0	0.00
MUSCLE ATROPHY NEUROLOGICAL	1	1	0.24	0	0	0.00
MUSCLE PAIN	4	4	0.97	1	1	0.24
MUSCULOSKELETAL DISORDERS	2	2	0.49	1	1	0.24
NECROSIS HIP	1	2	0.49	0	0	0.00
OSTEOARTHRITIS	10	10	2.43	10	10	2.45
PAIN HIP	2	2	0.49	0	0	0.00
PAIN KNEE	2	2	0.49	1	1	0.24
PAIN LEG	2	2	0.49	0	0	0.00
PAIN LOWER EXTREMITY	1	1	0.24	1	1	0.24
PAIN NECK	1	1	0.24	2	2	0.49
PAIN SHOULDER	0	0	0.00	1	1	0.24
PAIN WRIST	0	0	0.00	1	1	0.24
POLYARTHRITIS	0	0	0.00	1	1	0.24
ROTATOR CUFF SYNDROME OF SHOULDER	0	0	0.00	1	1	0.24
SPONDYLITIS	0	0	0.00	1	1	0.24
TEAR OF MENISCUS	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
TENDON RUPTURE	0	0	0.00	2	2	0.49
WEAKNESS KNEE	0	0	0.00	1	1	0.24
MYO ENDO PERICARDIAL &VALVE DISORDER						
ANGINA	93	114	27.68	104	125	30.58
ANGINA CRESCENDO	1	1	0.24	1	1	0.24
ANGINA PECTORIS	13	15	3.64	13	15	3.67
ANGINA PECTORIS AGGRAVATED	8	9	2.18	7	7	1.71
ANGINA UNSTABLE	99	114	27.68	128	183	44.77
ANGINA VARIANT	1	1	0.24	0	0	0.00
ANGINAL ATTACK	0	0	0.00	4	4	0.98
ANGINAL PAIN	1	1	0.24	3	3	0.73
ANGINAL SYNDROME	0	0	0.00	1	1	0.24
AORTIC STENOSIS	0	0	0.00	2	2	0.49
AORTIC VALVE ABNORMALITY	0	0	0.00	1	1	0.24
ARTERIOSCLEROTIC HEART DISEASE	3	4	0.97	5	5	1.22
CARDIAC ISCHEMIA	42	45	10.92	47	53	12.97
CARDIOMYOPATHY	0	0	0.00	2	3	0.73
CHEST PAIN	82	96	23.31	94	108	26.42
CORONARY ARTERY DISORDER	15	16	3.88	11	12	2.94
CORONARY ARTERY OCCLUSION	9	9	2.18	14	14	3.43
CORONARY ATHEROMA	0	0	0.00	2	2	0.49
CORONARY DISEASE	89	100	24.28	94	106	25.93
CORONARY INSUFFICIENCY	2	2	0.49	4	5	1.22
CORONARY SPASM	0	0	0.00	1	1	0.24
CORONARY STENOSIS	5	5	1.21	5	6	1.47
CORONARY THROMBOEMBOLISM	0	0	0.00	1	1	0.24
MYOCARDIAL INFARCTION	65	72	17.48	102	109	26.67
MYOCARDIAL ISCHEMIA	10	11	2.67	9	11	2.69
PAIN HEART ISCHEMIC	0	0	0.00	1	1	0.24
PERICARDIAL EFFUSION	0	0	0.00	1	1	0.24
PERICARDITIS	2	2	0.49	0	0	0.00
POST MI	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
THROMBOSIS CORONARY	0	0	0.00	2	2	0.49
NEONATAL AND INFANCY DISORDERS						
HERNIA INGUINAL	10	11	2.67	8	8	1.96
HERNIA UMBILICAL	2	2	0.49	0	0	0.00
HYDROCEPHALUS	1	1	0.24	0	0	0.00
NEOPLASM						
ADENOCARCINOMA BLADDER	0	0	0.00	1	1	0.24
ADENOCARCINOMA COLON	1	2	0.49	1	1	0.24
ADENOCARCINOMA LUNG	1	2	0.49	1	2	0.49
ADENOCARCINOMA NOS	0	0	0.00	1	1	0.24
ADENOCARCINOMA PROSTATA	2	2	0.49	4	4	0.98
ADENOCARCINOMA RECTAL MUCINOUS	1	1	0.24	0	0	0.00
ADENOMA	2	3	0.73	2	5	1.22
BASAL CELL CARCINOMA	6	7	1.70	7	8	1.96
BLADDER CARCINOMA	5	6	1.46	7	7	1.71
BLADDER PAPILLOMA	1	1	0.24	0	0	0.00
BREAST NEOPLASM BENIGN FEMALE	0	0	0.00	1	1	0.24
BREAST NEOPLASM MALIGNANT FEMALE	2	2	0.49	0	0	0.00
CANCER BLADDER	1	1	0.24	2	2	0.49
CANCER COLON	4	5	1.21	1	1	0.24
CANCER ESOPHAGUS	0	0	0.00	2	2	0.49
CANCER KIDNEY	1	1	0.24	1	2	0.49
CANCER LUNG NON-SMALL CELL	1	5	1.21	0	0	0.00
CANCER LUNG SQUAMOUS CELL	5	6	1.46	4	4	0.98
CANCER PROSTATE	2	2	0.49	2	4	0.98
CARCINOMA	4	4	0.97	2	3	0.73
CARCINOMA BASAL CELL	1	1	0.24	1	1	0.24
CARCINOMA BLADDER TRANSITIONAL CELL	5	12	2.91	1	1	0.24
CARCINOMA BREAST	1	1	0.24	0	0	0.00
CARCINOMA BRONCHUS	2	4	0.97	0	0	0.00
CARCINOMA COLON	4	6	1.46	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
CARCINOMA EPIGLOTTIS	1	1	0.24	0	0	0.00
CARCINOMA GASTROINTESTINAL	0	0	0.00	1	1	0.24
CARCINOMA LARYNX	1	2	0.49	0	0	0.00
CARCINOMA MOUTH	1	1	0.24	0	0	0.00
CARCINOMA OF ESOPHAGUS	0	0	0.00	4	5	1.22
CARCINOMA OF RECTUM	0	0	0.00	2	2	0.49
CARCINOMA PROSTATE	5	5	1.21	5	6	1.47
CARCINOMA RENAL CELL	0	0	0.00	1	1	0.24
CARCINOMA THYROID	1	2	0.49	0	0	0.00
CARCINOMA TONGUE	1	3	0.73	0	0	0.00
CARCINOMA VOCAL TRUE CORD	0	0	0.00	1	1	0.24
CARCINOMATOSIS	1	1	0.24	2	2	0.49
COLON CARCINOMA	1	1	0.24	0	0	0.00
CYST	7	7	1.70	3	3	0.73
CYST PANCREATIC	1	1	0.24	0	0	0.00
EPIDIDYMAL CYST	2	2	0.49	0	0	0.00
ESOPHAGEAL CARCINOMA	0	0	0.00	2	2	0.49
GALL BLADDER CARCINOMA	0	0	0.00	1	1	0.24
GASTRIC CARCINOMA	2	2	0.49	2	3	0.73
GOITRE NODULAR	1	1	0.24	0	0	0.00
HEPATIC NEOPLASM MALIGNANT	0	0	0.00	1	1	0.24
LEUKEMIA B CELL CHRONIC LYMPH.	1	1	0.24	0	0	0.00
LEUKEMIA LYMPHOBLASTIC	1	2	0.49	0	0	0.00
LIPOMA	1	1	0.24	1	1	0.24
LYMPHOMA NON-HODGKIN'S	1	1	0.24	0	0	0.00
MELANOMA	1	1	0.24	1	1	0.24
MELANOMA MALIGNANT	2	3	0.73	1	1	0.24
MESOTHELIOMA	0	0	0.00	2	2	0.49
METASTASES GROWTH	2	2	0.49	2	3	0.73
MULTIPLE MYELOMA	1	1	0.24	1	1	0.24
MYELOMA	0	0	0.00	1	2	0.49
MYELOPROLIFERATIVE DISORDER	0	0	0.00	1	1	0.24
NEOPLASM MALIGNANT	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	Nicorandil events	Nicorandil rate*	Placebo subjects	Placebo events	Placebo rate*
NEOPLASM NOS	3	3	0.73	1	1	0.24
NEOPLASM PULMONARY MALIGNANT	1	1	0.24	5	5	1.22
PANCREAS CARCINOMA	0	0	0.00	2	3	0.73
PAPILLOMA	1	1	0.24	1	1	0.24
POLYP COLON	5	5	1.21	6	7	1.71
POLYP ENDOMETRIUM	0	0	0.00	1	1	0.24
PULMONARY CARCINOMA	1	1	0.24	0	0	0.00
RECTAL CARCINOMA	1	1	0.24	1	1	0.24
RENAL CARCINOMA	0	0	0.00	1	1	0.24
SARCOMA	1	1	0.24	1	1	0.24
SKIN CARCINOMA	0	0	0.00	1	1	0.24
SKIN NEOPLASM MALIGNANT	0	0	0.00	1	1	0.24
SKIN TUMOR-LIKE CONDITION NOS	1	1	0.24	0	0	0.00
STOMACH CARCINOMA	2	3	0.73	0	0	0.00
TESTIS NEOPLASM MALIGNANT	1	1	0.24	0	0	0.00
TUMOR BENIGN NOS	0	0	0.00	1	2	0.49
TUMOR GASTROINTESTINAL	1	1	0.24	0	0	0.00
TUMOR URINARY BLADDER	1	1	0.24	2	3	0.73
OPERATIONS & PROCEDURES						
AMPUTATION LOWER LEG	0	0	0.00	1	1	0.24
AMPUTATION TOE PHALANX	0	0	0.00	1	1	0.24
ANALGESIC TREATMENT OF NERVE	0	0	0.00	1	1	0.24
ANEURYSMECTOMY	1	1	0.24	1	1	0.24
ANGIOCARDIOGRAPHY	57	58	14.08	67	68	16.64
ANGIOGRAPHY CAROTIS	7	7	1.70	5	5	1.22
APPARATUS TECHNIQUE /SPEC.PROCEDURES	13	13	3.16	9	10	2.45
APPENDECTOMY	1	1	0.24	0	0	0.00
ARTERIOGRAPHY	4	4	0.97	2	2	0.49
ARTERY LIGATION	0	0	0.00	1	1	0.24
ARTHRODESIS OF FOOT	1	1	0.24	0	0	0.00
ARTHROPLASTY (HIP)	3	3	0.73	2	2	0.49
ARTHROPLASTY (KNEE)	3	3	0.73	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
ARTHROSCOPY KNEE	2	2	0.49	3	3	0.73
BIOPSY (HEAD, SOFT TISSUE)	2	2	0.49	0	0	0.00
BLADDER CATHETERIZATION	1	1	0.24	1	2	0.49
BONE TRANSPLANTATION OF HAND	1	1	0.24	0	0	0.00
BRONCHOSCOPY	6	6	1.46	2	3	0.73
CARDIOVASCULAR DRUG THERAPY	0	0	0.00	2	2	0.49
CARDIOVERSION, DEFIBRILATION	4	7	1.70	3	3	0.73
CATHETERIZATION OF HEART	6	6	1.46	5	5	1.22
CHOLECYSTECTOMY	2	2	0.49	4	4	0.98
CIRCUMCISION	1	1	0.24	1	1	0.24
CLOSURE OF COLOSTOMY	0	0	0.00	2	2	0.49
COLONOSCOPY	13	14	3.40	9	9	2.20
CORR. SURGERY STOMA/ANUS PRAETER	0	0	0.00	1	1	0.24
COSMETIC SURGERY	0	0	0.00	1	1	0.24
CYSTOSTOMY	0	0	0.00	1	1	0.24
DIAGNOSTIC PREPARATION OF ANESTHESIA	0	0	0.00	2	2	0.49
DISCISSION, EXTRACTION OF LENSE	3	3	0.73	1	1	0.24
EPIDIDYMECTOMY	1	1	0.24	0	0	0.00
EXCISION OF COLONIC POLYP	3	3	0.73	0	0	0.00
EXCISION SKIN, SUBCUTIS	3	3	0.73	3	3	0.73
EXPLORATORY THORACOTOMY	2	2	0.49	0	0	0.00
FASCIECTOMY	2	2	0.49	1	1	0.24
GASTROSCOPY	21	21	5.10	22	24	5.87
HEMICOLECTOMY	1	1	0.24	2	2	0.49
HEMICOLECTOMY LEFT SIDE	1	1	0.24	0	0	0.00
HEMORRHOIDECTOMY	1	1	0.24	1	1	0.24
HERNIA INGUINALIS REPAIR	2	2	0.49	2	2	0.49
HERNIA REPAIR	8	8	1.94	7	8	1.96
INCISION OF SKIN, SUBCUTIS	1	1	0.24	0	0	0.00
LAMINECTOMY	0	0	0.00	1	1	0.24
LARYNGOSCOPY	0	0	0.00	1	1	0.24
LOBECTOMY	0	0	0.00	1	1	0.24
MITRAL VALVE REPLACEMENT	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 4) Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
MULTIPLE AC BYPASS	1	1	0.24	2	2	0.49
MUSCLE BIOPSY	2	2	0.49	0	0	0.00
NASAL POLYPECTOMY	2	2	0.49	1	1	0.24
NEPHRECTOMY	1	1	0.24	1	1	0.24
O.SURGERY (MEDIASTINUM,THORACIC WALL)	0	0	0.00	1	1	0.24
O.SURGERY LOWER LEG SKIN, SUBCUTAN TISSUE	0	0	0.00	1	1	0.24
OP AORTA ANEURYSM	1	1	0.24	1	1	0.24
OPERATION GLAUCOMA	1	1	0.24	0	0	0.00
OTHER BONE SURGERY (FEMUR)	0	0	0.00	1	1	0.24
OTHER BONE SURGERY OF FOOT	1	1	0.24	0	0	0.00
OTHER OP HAND, SOFT TISSUE	1	1	0.24	1	1	0.24
OTHER OP SPINE	0	0	0.00	1	1	0.24
OTHER SURGERIES (HIP,SOFT TISSUE)	1	1	0.24	0	0	0.00
OTHER SURGERY (ARTICULAR ANKLE)	0	0	0.00	1	1	0.24
OTHER SURGERY (BRONCHI,LUNG,PLEURA)	1	1	0.24	0	0	0.00
OTHER SURGERY (EXTERNAL EAR)	2	2	0.49	1	2	0.49
OTHER SURGERY (EYEBALL)	7	8	1.94	9	10	2.45
OTHER SURGERY (HAND BONES)	1	1	0.24	0	0	0.00
OTHER SURGERY (HEART)	3	3	0.73	7	8	1.96
OTHER SURGERY (HUMERUS)	0	0	0.00	1	1	0.24
OTHER SURGERY (LACR.SAC,LACRIMAL DUCT)	2	2	0.49	0	0	0.00
OTHER SURGERY (MIDDLE EAR)	1	1	0.24	1	1	0.24
OTHER SURGERY (MUSCLES,FASCIAE)	2	2	0.49	0	0	0.00
OTHER SURGERY (NOSE, PARANASAL SINUSES)	1	1	0.24	0	0	0.00
OTHER SURGERY (PORTIO VAGINALIS UTERI)	1	1	0.24	0	0	0.00
OTHER SURGERY (SKIN, SUBCUTIS)	3	3	0.73	1	1	0.24
OTHER SURGERY (SKULL)	0	0	0.00	1	1	0.24
OTHER SURGERY (SMALL INTESTINE)	1	1	0.24	0	0	0.00
OTHER SURGERY (TOES,SOFT TISSUE)	0	0	0.00	1	1	0.24
OTHER SURGERY (URETER)	0	0	0.00	1	2	0.49
OTHER SURGERY (UTERUS,ABDOMEN)	0	0	0.00	1	1	0.24
OTHER SURGERY (VAGINA,VULVA,PERINEUM)	0	0	0.00	2	2	0.49
OTHER SURGERY (VEINS)	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
OTHER SURGERY ARTERY	8	8	1.94	5	5	1.22
OTHER SURGERY ARTERY, PLASTY	28	30	7.28	28	29	7.10
OTHER SURGERY BLADDER	1	1	0.24	0	0	0.00
OTHER SURGERY LENS	6	7	1.70	5	7	1.71
OTHER SURGERY LIVER,GALLBLADDER	1	1	0.24	1	1	0.24
OTHER SURGERY LOWER LEG VEINS	1	1	0.24	1	1	0.24
OTHER SURGERY MAMMA	0	0	0.00	1	1	0.24
OTHER SURGERY ON EYELID	0	0	0.00	2	2	0.49
OTHER SURGERY ON RETINA	1	1	0.24	0	0	0.00
OTHER SURGERY PROSTATE	2	2	0.49	0	0	0.00
OTHER SURGERY UTERUS VAGINA	1	1	0.24	0	0	0.00
PART.ARTHROPLASTY WITH IMPLANT (KNEE)	0	0	0.00	1	1	0.24
PARTIAL GASTRIC RESECTION	0	0	0.00	1	1	0.24
PROSTATAECTOMY	0	0	0.00	1	1	0.24
PUNCTION AND/OR DRAINAGE	1	1	0.24	0	0	0.00
RECTOSIGMOIDOSCOPY	6	7	1.70	3	3	0.73
REVASCULARISATION MYOCARD O. SURGERY	0	0	0.00	2	2	0.49
REVASCULARISATION OF MYOCARD	22	22	5.34	28	28	6.85
REVISION OF MIDDLE EAR AND MASTOID	0	0	0.00	1	1	0.24
RHINOPLASTY	1	1	0.24	0	0	0.00
S.A. ARTHROPLASTY (KNEE)	1	1	0.24	0	0	0.00
S.A. OTHER SURGERY LENS	2	2	0.49	0	0	0.00
S.A.OTHER SURGERY (EYEBALL)	1	1	0.24	1	1	0.24
S.A.OTHER SURGERY (HEART)	1	1	0.24	0	0	0.00
SEGM. RESECTION OF COLON	2	2	0.49	1	1	0.24
SINGLE AC-BYPASS	0	0	0.00	2	2	0.49
SUBCUTANEOUS MASTECTOMY	0	0	0.00	1	1	0.24
SURGERIES OF INTERVERTEBRAL APERTURE	0	0	0.00	1	1	0.24
SURGERY FOR HEMO-/PERITON.DIALYSIS	0	0	0.00	1	1	0.24
SURGERY OF ANAL FISTULA	1	1	0.24	1	1	0.24
SURGERY ON SOFT PALATE	1	1	0.24	0	0	0.00
SURGERY VOCAL LIGAMENTS	1	1	0.24	0	0	0.00
TECHNICAL MEASURES	1	1	0.24	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	Nicorandil events	Nicorandil rate*	Placebo subjects	Placebo events	Placebo rate*
TEETH EXTRACTION	1	1	0.24	1	1	0.24
THROMBENDARTERECTOMY	1	1	0.24	1	1	0.24
TOTAL ARTHROPLASTY WITH IMPLANT (KNEE)	4	4	0.97	4	4	0.98
TOTAL ARTHROPLASTY WITH IMPLANTAT (HIP)	4	4	0.97	4	4	0.98
TOTAL HYSTERECTOMY	0	0	0.00	1	1	0.24
TRANSURETHR. RESECT. OF PROSTATE	4	4	0.97	3	3	0.73
TRANSURETHRAL CYSTOSCOPY	23	34	8.25	16	20	4.89
TRANSURETHRAL SURGERY URINARY BLADDER	3	3	0.73	1	1	0.24
TRIPLE AC BYPASS	0	0	0.00	2	2	0.49
VAGINAL HYSTERECTOMY	0	0	0.00	2	2	0.49
VENOUS LIGATIONS	0	0	0.00	1	1	0.24
VESSEL REPLACEMENT OR BYPASS	5	5	1.21	5	5	1.22
PLATELET, BLEEDING&CLOTTING DISORDER						
CAROTID OCCLUSION	1	1	0.24	1	1	0.24
COAGULATION DISORDER	1	1	0.24	0	0	0.00
EMBOLISM PULMONARY	7	7	1.70	6	6	1.47
HEMORRHAGE NOS	0	0	0.00	1	1	0.24
THROMBOCYTOPENIA	0	0	0.00	2	2	0.49
PSYCHIATRIC DISORDERS						
ABSTAINING SYMPTOMS	1	1	0.24	0	0	0.00
ALCOHOLISM	1	1	0.24	1	1	0.24
AMNESIA	1	1	0.24	0	0	0.00
ANXIETY	0	0	0.00	1	1	0.24
ANXIETY ATTACK	1	1	0.24	0	0	0.00
BIPOLAR DISORDER	2	2	0.49	0	0	0.00
CONFUSION	0	0	0.00	1	1	0.24
CONSCIOUSNESS CLOUDED	1	1	0.24	0	0	0.00
DEMENTIA	2	2	0.49	0	0	0.00
DEPRESSION	1	1	0.24	3	3	0.73
DEPRESSION PSYCHOTIC	1	1	0.24	0	0	0.00
EFFORT SYNDROME	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
INTENTIONAL OVERDOSE	2	2	0.49	2	3	0.73
MANIC PSYCHOSIS	1	1	0.24	0	0	0.00
PACING	1	1	0.24	3	3	0.73
PANIC ATTACK	0	0	0.00	1	1	0.24
RED BLOOD CELL DISORDERS						
ANEMIA	8	9	2.18	4	8	1.96
ANEMIA GI BLEEDING	0	0	0.00	1	1	0.24
ANEMIA HEMOLYTIC	1	2	0.49	1	1	0.24
ANEMIA IRON DEFICIENCY	2	2	0.49	5	7	1.71
HEMOGLOBIN DECREASED	1	1	0.24	1	1	0.24
REPRODUCTIVE DISORDES,FEMALE						
BLEEDING POSTMENOPAUSAL	2	2	0.49	3	3	0.73
UTERINE HEMORRHAGE	0	0	0.00	1	1	0.24
REPRODUCTIVE DISORDES,MALE						
ERECTILE IMPOTENCE	0	0	0.00	1	1	0.24
GENITALIA EXTERNAL PAINFUL	0	0	0.00	1	1	0.24
GYNECOMASTIA	0	0	0.00	1	1	0.24
ORCHITIS	0	0	0.00	1	1	0.24
PAIN TESTICULAR	1	1	0.24	0	0	0.00
PENIS DISORDER	1	1	0.24	0	0	0.00
PROSTATE ENLARGED	10	11	2.67	2	2	0.49
PROSTATIC DISORDER	3	4	0.97	4	4	0.98
PROSTATISM AGGRAVATED	1	1	0.24	0	0	0.00
RESISTANCE MECHANISM DISORDERS						
ABSCESS	1	1	0.24	1	1	0.24
ABSCESS ANAL	2	2	0.49	1	1	0.24
ABSCESS LEG	1	1	0.24	1	1	0.24
HERPES	1	1	0.24	0	0	0.00
HERPES ZOSTER	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	Nicorandil events	Nicorandil rate*	Placebo subjects	Placebo events	Placebo rate*
INFECTION	3	3	0.73	0	0	0.00
INFECTION BACTERIAL	1	1	0.24	1	1	0.24
INFECTION VIRAL	1	1	0.24	1	1	0.24
SEPSIS	2	2	0.49	0	0	0.00
SEPTICEMIA	1	1	0.24	3	3	0.73
WOUND INFECTION	2	2	0.49	2	2	0.49
RESPIRATORY SYSTEM DISORDERS						
APNEA	1	1	0.24	0	0	0.00
ASPIRATION	1	1	0.24	0	0	0.00
ASTHMA	1	1	0.24	3	3	0.73
ASTHMA AGGRAVATED	1	1	0.24	0	0	0.00
BREATHING DIFFICULT	0	0	0.00	1	1	0.24
BREATHLESSNESS	2	2	0.49	0	0	0.00
BRONCHIAL DAMAGE	0	0	0.00	1	1	0.24
BRONCHIEKTASIS	0	0	0.00	1	1	0.24
BRONCHITIS	0	0	0.00	3	3	0.73
BRONCHOPNEUMONIA	4	4	0.97	1	1	0.24
CHRONIC OBSTR. PULM. DISEASE	13	19	4.61	6	6	1.47
COPD	2	2	0.49	1	1	0.24
DYSPNEA	1	1	0.24	4	4	0.98
DYSPNEA EXERTIONAL	1	1	0.24	1	1	0.24
EDEMA PULMONARY	2	2	0.49	3	3	0.73
EMPHYSEMA	0	0	0.00	1	2	0.49
EPISTAXIS	4	4	0.97	0	0	0.00
HEMOPTYSIS	3	3	0.73	2	3	0.73
INFECTION BRONCHOPULMONARY	0	0	0.00	1	1	0.24
INFECTION CHEST	17	19	4.61	18	21	5.14
INFECTION LUNG	1	1	0.24	1	1	0.24
LARYNX EDEMA	1	1	0.24	0	0	0.00
NASAL POLYP	4	4	0.97	1	1	0.24
NASAL SEPTUM DEVIATION	1	1	0.24	0	0	0.00
NOSEBLEED	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
OBSTRUCTION PULMONARY	0	0	0.00	1	1	0.24
PHARYNGITIS	1	1	0.24	0	0	0.00
PLEURAL CHANGES	1	2	0.49	0	0	0.00
PLEURAL EFFUSION	4	7	1.70	3	3	0.73
PLEURAL PAIN	3	3	0.73	2	2	0.49
PLEURISY	2	2	0.49	0	0	0.00
PNEUMONIA	15	16	3.88	12	12	2.94
PNEUMONIA LOBAR	0	0	0.00	1	1	0.24
PNEUMOTHORAX	0	0	0.00	1	1	0.24
PULMONARY COLLAPSE	0	0	0.00	1	1	0.24
PULMONARY COMPLICATIONS	0	0	0.00	1	1	0.24
PULMONARY DAMAGE	0	0	0.00	1	1	0.24
PULMONARY DISEASE	1	1	0.24	1	1	0.24
RESPIRATORY DISORDER	0	0	0.00	2	2	0.49
RESPIRATORY FAILURE	1	1	0.24	0	0	0.00
SHORTNESS OF BREATH	5	5	1.21	3	3	0.73
SINUSITIS MAXILLARY	1	1	0.24	0	0	0.00
UPPER RESP TRACT INFECTION	0	0	0.00	2	2	0.49
VOCAL CORD EDEMA	1	1	0.24	0	0	0.00
SKIN AND APPENDAGES DISORDERS						
ALOPECIA	1	1	0.24	0	0	0.00
BRUISE	0	0	0.00	1	1	0.24
ECZEMA	1	1	0.24	1	1	0.24
ERYSIPELAS	1	1	0.24	0	0	0.00
FISSURES	1	1	0.24	0	0	0.00
HEMATOMA	2	2	0.49	0	0	0.00
HYPERKERATOTIC LESION	0	0	0.00	1	1	0.24
INFLAMMATION SKIN	1	1	0.24	1	1	0.24
INGROWN TOENAIL	0	0	0.00	1	1	0.24
KERATOLYSIS	0	0	0.00	1	1	0.24
KERATOSIS	2	2	0.49	0	0	0.00
MUCOCUTANEOUS LESION	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System		Nicorandil			Placebo		
		subjects	events	rate*	subjects	events	rate*
	NAIL DISORDER	0	0	0.00	1	1	0.24
	NECROSIS TOE	1	1	0.24	0	0	0.00
	PILONIDAL CYST	1	1	0.24	0	0	0.00
	PSORIASIS	1	1	0.24	0	0	0.00
	RASH	0	0	0.00	2	2	0.49
	SKIN DEFECTS SUPERFICIAL	4	4	0.97	1	1	0.24
	SKIN DISEASE	1	1	0.24	0	0	0.00
	SKIN DISORDER	1	1	0.24	2	2	0.49
	SKIN LESION PAPULAR	1	1	0.24	0	0	0.00
	SKIN NODULE	1	1	0.24	0	0	0.00
	SKIN ULCERATION	1	1	0.24	0	0	0.00
	ULCER FOOT	1	1	0.24	1	1	0.24
	ULCER LEG	1	1	0.24	2	2	0.49
	URTICARIA	1	1	0.24	0	0	0.00
UNKNOWN							
	UNKNOWN	7	7	1.70	7	7	1.71
URINARY SYSTEM DISORDERS							
	BLADDER CALCULUS	1	1	0.24	1	1	0.24
	BLADDER DISORDER	2	2	0.49	0	0	0.00
	BLADDER DYSFUNCTION	1	1	0.24	1	1	0.24
	BLADDER INABILITY TO EMPTY	0	0	0.00	1	1	0.24
	BLADDER IRRITATION	1	1	0.24	0	0	0.00
	CYSTITIS	2	2	0.49	0	0	0.00
	CYSTOCELE	1	1	0.24	0	0	0.00
	DYSURIA	0	0	0.00	1	1	0.24
	FLANK PAIN	1	1	0.24	0	0	0.00
	GLOMERULONEPHRITIS	1	1	0.24	0	0	0.00
	HEMATURIA	8	8	1.94	6	6	1.47
	HEMATURIA MICROSCOPIC	1	1	0.24	1	1	0.24
	HYDRONEPHROSIS	1	2	0.49	0	0	0.00
	INFECTION URINARY BLADDER	2	2	0.49	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
INFECTION UROGENITAL TRACT	0	0	0.00	1	1	0.24
KIDNEY DYSFUNCTION	1	1	0.24	0	0	0.00
KIDNEY FAILURE	1	1	0.24	0	0	0.00
KIDNEY STONE	0	0	0.00	2	2	0.49
MICTURITION FREQUENCY	0	0	0.00	5	5	1.22
NOCTURIA	1	1	0.24	0	0	0.00
OBSTRUCTIVE UROPATHY	0	0	0.00	1	1	0.24
PAIN ILIACFOSSA	0	0	0.00	1	1	0.24
POLYURIA	0	0	0.00	1	1	0.24
PYELONEPHRITIS	1	1	0.24	0	0	0.00
RENAL CALCULUS	1	1	0.24	2	7	1.71
RENAL COLIC	2	2	0.49	2	2	0.49
RENAL FAILURE ACUTE	1	1	0.24	2	2	0.49
RENAL FAILURE ACUTE ISCHEMIC	0	0	0.00	1	1	0.24
RENAL FAILURE CHRONIC	1	1	0.24	1	1	0.24
RENAL FUNCTION ABNORMAL	0	0	0.00	1	1	0.24
URETERAL DISORDER	1	1	0.24	0	0	0.00
URETHRAL DISORDER	3	3	0.73	2	2	0.49
URETHRAL OBSTRUCTION	2	2	0.49	5	5	1.22
URINARY RETENTION	6	6	1.46	9	11	2.69
URINARY SYMPTOMS GENERAL	0	0	0.00	1	1	0.24
URINARY TRACT INFECTION	4	4	0.97	3	3	0.73
URINARY URGENCY	1	1	0.24	0	0	0.00
URINATION FREQUENT	0	0	0.00	1	1	0.24
URINE VOLUME DEFICIENT	1	1	0.24	0	0	0.00
VASCULAR (EXTRACARDIAC) DISORDERS						
ANEURYSM RUPTURE	4	4	0.97	1	1	0.24
ARTERIOSCLEROSIS	1	1	0.24	0	0	0.00
ARTERIOVENOUS FISTULA	0	0	0.00	1	1	0.24
ARTERITIS	1	1	0.24	2	2	0.49
ARTERY DISEASE PERIPHERAL	2	2	0.49	0	0	0.00
CARDIOVASCULAR ACCIDENT	2	2	0.49	3	3	0.73

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	Nicorandil events	Nicorandil rate*	Placebo subjects	Placebo events	Placebo rate*
CEREBRAL INFARCTION	4	4	0.97	2	2	0.49
CEREBRAL VASCULAR DISTURBANCE	1	1	0.24	1	1	0.24
CEREBROVASCULAR ATTACK	8	8	1.94	3	3	0.73
CLAUDICATIO	0	0	0.00	1	2	0.49
CLAUDICATION INTERMITTENT	3	3	0.73	3	3	0.73
CVA	13	13	3.16	11	11	2.69
INTESTINAL INFARCTION	1	1	0.24	0	0	0.00
INTESTINAL ISCHEMIA	1	1	0.24	1	1	0.24
ISCHEMIA PERIPHERAL	0	0	0.00	1	1	0.24
ISCHEMIC ATTACKS TRANSIENT	11	11	2.67	17	17	4.16
MESENTERIC ARTERIAL OCCLUSION	1	1	0.24	0	0	0.00
PERIPHERAL ISCHEMIA	1	1	0.24	0	0	0.00
PERIPHERAL VASCULAR DISEASE	4	4	0.97	8	9	2.20
PERIPHERAL VASCULAR DISEASE.	0	0	0.00	1	1	0.24
RENAL ARTERY STENOSIS	0	0	0.00	1	1	0.24
STENOSIS ARTERIAL	4	4	0.97	4	4	0.98
STROKE	6	6	1.46	9	9	2.20
THROMBOPHLEBITIS	2	2	0.49	0	0	0.00
THROMBOPHLEBITIS DEEP	1	1	0.24	0	0	0.00
THROMBOPHLEBITIS LEG DEEP	1	1	0.24	1	1	0.24
THROMBOPHLEBITIS SUPERFICIAL	1	1	0.24	0	0	0.00
THROMBOSIS ARTERIAL	0	0	0.00	1	1	0.24
THROMBOSIS PELVIC VEINS	0	0	0.00	1	1	0.24
THROMBOSIS VENOUS DEEP	6	6	1.46	7	9	2.20
VARICOSE VEINS	1	1	0.24	0	0	0.00
VASCULAR DISORDER	0	0	0.00	1	1	0.24
VASCULITIS	1	1	0.24	0	0	0.00
VASOSPASM	0	0	0.00	1	1	0.24
VEIN DISORDER	1	1	0.24	0	0	0.00
VENOUS STENOSIS	1	1	0.24	0	0	0.00
VISION DISORDERS						
BLEPHAROPHIMOSIS	1	1	0.24	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 49 Serious Adverse Events by Decoded Terms, Grouped by Body System

Body System	Nicorandil subjects	Nicorandil events	Nicorandil rate*	Placebo subjects	Placebo events	Placebo rate*
CATARACT	34	36	8.74	21	25	6.12
CENTRAL RETINAL VEIN OCCLUSION	1	1	0.24	0	0	0.00
EDEMA MACULAR	1	1	0.24	0	0	0.00
EPIPHORA	1	1	0.24	0	0	0.00
EYE ABNORMALITY	1	1	0.24	0	0	0.00
EYE IRRITATION	1	1	0.24	1	1	0.24
GLAUCOMA	2	2	0.49	1	1	0.24
HYPHEMA	0	0	0.00	2	2	0.49
PTERYGIUM	1	1	0.24	0	0	0.00
RETINAL ARTERY OCCLUSION	1	1	0.24	0	0	0.00
RETINAL VEIN THROMBOSIS	0	0	0.00	1	1	0.24
VITREOUS DETACHMENT	0	0	0.00	1	1	0.24
WHITE BLOOD CELL AND RES DISORDERS						
EOSINOPHILIA	0	0	0.00	1	1	0.24

* rate = number of events per thousand person-years of follow-up

Table 50 Serious Adverse Events by Body System for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
APPLICATION SITE DISORDERS	7	7	3.17	10	10	4.56
BODY AS A WHOLE - GENERAL DISORDERS	23	23	10.42	24	25	11.41
CARDIOVASCULAR DISORDERS, GENERAL	80	96	43.49	82	99	45.17
CENTR & PERIPH NERV SYST. DISORDERS	19	25	11.33	18	18	8.21
ENDOCRINE DISORDERS	1	1	0.45	0	0	0.00
GASTRO- INTESTINAL SYSTEM DISORDERS	105	130	58.90	74	88	40.15
HEARING AND VESTIBULAR DISORDERS	3	4	1.81	5	5	2.28
HEART RATE AND RHYTHM DISORDERS	37	46	20.84	30	33	15.06
LIVER AND BILIARY SYSTEM DISORDERS	9	11	4.98	11	14	6.39
METABOLIC AND NUTRITIONAL DISORDERS	27	30	13.59	15	15	6.84
MUSCULO-SKELETAL SYSTEM DISORDERDS	48	54	24.46	40	40	18.25
MYO ENDO PERICARDIAL &VALVE DISORDER	252	361	163.55	310	494	225.40
NEONATAL AND INFANCY DISORDERS	10	11	4.98	2	2	0.91
NEOPLASM	55	81	36.70	59	81	36.96
OPERATIONS & PROCEDURES	181	231	104.65	167	208	94.91
PLATELET, BLEEDING&CLOTTING DISORDER	6	6	2.72	7	7	3.19
PSYCHIATRIC DISORDERS	10	11	4.98	7	8	3.65
RED BLOOD CELL DISORDERS	8	10	4.53	8	8	3.65
REPRODUCTIVE DISORDES,FEMALE	1	1	0.45	0	0	0.00
REPRODUCTIVE DISORDES,MALE	6	7	3.17	6	6	2.74
RESISTANCE MECHANISM DISORDERS	9	9	4.08	8	8	3.65
RESPIRATORY SYSTEM DISORDERS	62	82	37.15	45	58	26.46
SKIN AND APPENDAGES DISORDERS	19	19	8.61	6	6	2.74
UNKNOWN	5	5	2.27	5	5	2.28
URINARY SYSTEM DISORDERS	24	25	11.33	32	43	19.62
VASCULAR (EXTRACARDIAC) DISORDERS	45	49	22.20	44	51	23.27
VISION DISORDERS	29	31	14.04	20	25	11.41
TOTAL	672	1366	618.87	676	1357	619.18

* rate = number of events per thousand person-years of follow-up

Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	Nicorandil events	Nicorandil rate*	Placebo subjects	Placebo events	Placebo rate*
APPLICATION SITE DISORDERS						
APPLICATION SITE DAMAGE	0	0	0.00	1	1	0.46
CELLULITIS	6	6	2.72	7	7	3.19
FASCIITIS NECROTIZING	0	0	0.00	1	1	0.46
FISTULA WITH INFECTION	1	1	0.45	0	0	0.00
INFLAMMATION LOCALIZED	0	0	0.00	1	1	0.46
BODY AS A WHOLE - GENERAL DISORDERS						
ALLERGIC REACTION	2	2	0.91	0	0	0.00
BURNS	1	1	0.45	0	0	0.00
CHEST DISCOMFORT	1	1	0.45	0	0	0.00
CHEST TIGHTNESS OF	1	1	0.45	0	0	0.00
CRYOGLOBULINEMIA	0	0	0.00	1	1	0.46
DEATH	6	6	2.72	6	6	2.74
DEATH FROM PROGRESSIVE DISEASE	1	1	0.45	0	0	0.00
FOOD POISONING	1	1	0.45	0	0	0.00
GRANULOMATOUS LESION	1	1	0.45	1	1	0.46
HYPERTROPHY	0	0	0.00	1	1	0.46
INFARCT	1	1	0.45	0	0	0.00
OCCLUSION	0	0	0.00	2	2	0.91
OTHER GENERAL SYMPTOMS	2	2	0.91	1	1	0.46
OVERDOSE EFFECT	0	0	0.00	1	1	0.46
PAIN	4	4	1.81	4	4	1.83
SIDE EFFECTS NOS	1	1	0.45	1	1	0.46
SUDDEN DEATH	0	0	0.00	1	1	0.46
SWELLING LEG	1	1	0.45	2	2	0.91
SWELLING TISSUE	0	0	0.00	1	1	0.46
WEAKNESS POSTURAL	0	0	0.00	1	2	0.91
WEIGHT DECREASE	0	0	0.00	1	1	0.46
CARDIOVASCULAR DISORDERS, GENERAL						
ANEURYSM	5	5	2.27	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
BLACK-OUT (NOT AMNESIA)	1	1	0.45	0	0	0.00
CARDIAC DYSFUNCTION	0	0	0.00	2	2	0.91
CARDIAC FAILURE	4	5	2.27	11	13	5.93
CARDIAC FAILURE LEFT	2	2	0.91	1	1	0.46
CARDIOVASCULAR COLLAPSE	1	1	0.45	1	1	0.46
CIRCULATORY DISORDERS	1	1	0.45	0	0	0.00
COLLAPSE TRANSIENT	7	7	3.17	4	6	2.74
CONGESTIVE HEART FAILURE	16	18	8.15	12	13	5.93
COR PULMONALE	0	0	0.00	1	1	0.46
CORONARY ATHEROSCLEROSIS	1	1	0.45	4	4	1.83
ECG ABNORMAL	1	1	0.45	1	1	0.46
ELECTROCARDIOGRAM ABNORMAL NON-SP	0	0	0.00	1	1	0.46
FAINTNESS	1	1	0.45	0	0	0.00
HEART DISEASE	17	20	9.06	24	26	11.86
HEART DISORDER	2	2	0.91	0	0	0.00
HEART FAILURE ANEMIC	0	0	0.00	1	1	0.46
HYPERTENSION	1	1	0.45	0	0	0.00
HYPOTENSION	2	2	0.91	1	1	0.46
HYPOTENSION POSTURAL	1	1	0.45	0	0	0.00
LEFT VENTRICULAR FAILURE	14	16	7.25	14	18	8.21
PRE-SYNCOPE	0	0	0.00	2	2	0.91
SHOCK SEPTICEMIC	1	1	0.45	0	0	0.00
SYNCOPE	6	6	2.72	3	3	1.37
SYNCOPE VAGOVAGAL	1	1	0.45	0	0	0.00
SYNCOPE VASOVAGAL	0	0	0.00	1	1	0.46
VASOVAGAL ATTACK	3	3	1.36	3	3	1.37
CENTR & PERIPH NERV SYST. DISORDERS						
BELL'S PALSY	0	0	0.00	1	1	0.46
CEREBRAL ATROPHY	1	1	0.45	0	0	0.00
CEREBRAL DISTURBANCES	1	1	0.45	0	0	0.00
CEREBRAL HEMORRHAGE	1	1	0.45	1	1	0.46
CEREBRAL PALSY	1	1	0.45	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
COMA	0	0	0.00	1	1	0.46
DIZZINESS	1	1	0.45	3	3	1.37
EPILEPSY GRAND MAL	0	0	0.00	1	1	0.46
EPILEPTIFORM FITS NOS	1	1	0.45	0	0	0.00
EYELID PTOSIS	1	1	0.45	0	0	0.00
FALLING	2	2	0.91	1	1	0.46
GAIT UNSTEADY	1	1	0.45	0	0	0.00
HEADACHE	3	4	1.81	1	1	0.46
HEMORRHAGE INTRACRANIAL	0	0	0.00	1	1	0.46
LIMB WEAKNESS	0	0	0.00	1	1	0.46
MIGRAINE	0	0	0.00	1	1	0.46
MUSCLE STIFFNESS	0	0	0.00	1	1	0.46
MYASTHENIA GRAVIS	1	3	1.36	0	0	0.00
MYELOPATHY	0	0	0.00	1	1	0.46
NERVE DAMAGE	1	1	0.45	1	1	0.46
NEUROLOGIC SYMPTOMS	0	0	0.00	2	2	0.91
POLYNEUROPATHY	1	1	0.45	0	0	0.00
PTOSIS	1	1	0.45	0	0	0.00
SCIATIC COMPLAINTS	1	1	0.45	0	0	0.00
SEIZURES CEREBRAL	1	1	0.45	0	0	0.00
SUBARACHNOID HEMORRHAGE	0	0	0.00	1	1	0.46
VOCAL CORD DAMAGE	1	3	1.36	0	0	0.00
ENDOCRINE DISORDERS						
THYROTOXICOSIS	1	1	0.45	0	0	0.00
GASTRO- INTESTINAL SYSTEM DISORDERS						
ABDOMINAL DISCOMFORT	2	2	0.91	0	0	0.00
ABDOMINAL PAIN	9	14	6.34	8	8	3.65
ABDOMINAL PAIN LOWER	0	0	0.00	1	1	0.46
ABDOMINAL PAIN UPPER	1	1	0.45	1	1	0.46
ANAL SPHINCTER DISORDER	1	1	0.45	1	1	0.46
APPENDICITIS	1	1	0.45	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
BLEEDING ABDOMINAL	0	0	0.00	1	1	0.46
BOWEL OBSTRUCTION	1	1	0.45	3	3	1.37
COFFEE GROUND VOMITING	1	2	0.91	0	0	0.00
COLITIS	2	2	0.91	0	0	0.00
COLITIS ISCHEMIC	0	0	0.00	1	1	0.46
COLITIS PSEUDOMEMBRANOUS	1	1	0.45	0	0	0.00
COLITIS ULCERATIVE	3	3	1.36	0	0	0.00
CONSTIPATION	3	3	1.36	3	4	1.83
CROHN'S DISEASE	1	1	0.45	1	1	0.46
DIARRHEA	5	5	2.27	3	3	1.37
DISEASES OF ESOPHAGUS	1	1	0.45	0	0	0.00
DIVERTICULAR DISEASE	4	4	1.81	0	0	0.00
DIVERTICULITIS	5	5	2.27	1	1	0.46
DIVERTICULOSIS	4	4	1.81	1	1	0.46
DUODENAL ULCER	1	1	0.45	1	1	0.46
DUODENITIS	1	1	0.45	0	0	0.00
DYSPEPSIA	2	2	0.91	6	6	2.74
DYSPHAGIA	0	0	0.00	2	2	0.91
EPIGASTRIC PAIN NOT FOOD-RELATED	4	4	1.81	0	0	0.00
ESOPHAGEAL PERFORATION	1	1	0.45	0	0	0.00
ESOPHAGITIS	6	6	2.72	4	5	2.28
ESOPHAGUS COMPLAINTS	0	0	0.00	2	3	1.37
ESOPHAGUS MUCOSA DISTURBANCE	0	0	0.00	1	1	0.46
FECAL INCONTINENCE	1	1	0.45	1	1	0.46
GASTRIC EROSION	0	0	0.00	1	1	0.46
GASTRIC HEMORRHAGE	1	1	0.45	0	0	0.00
GASTRIC INFLAMMATION	0	0	0.00	1	1	0.46
GASTRIC OBSTRUCTION	1	1	0.45	0	0	0.00
GASTRIC ULCER	4	7	3.17	1	1	0.46
GASTRITIS	4	4	1.81	3	3	1.37
GASTRITIS ANTRUM	1	1	0.45	0	0	0.00
GASTRITIS HEMORRHAGIC	0	0	0.00	1	1	0.46
GASTRO-INTESTINAL DISORDER NOS	3	3	1.36	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
GASTRODUODENITIS	1	1	0.45	0	0	0.00
GASTROENTERITIS	5	5	2.27	3	3	1.37
GASTROINTESTINAL DAMAGE	0	0	0.00	1	1	0.46
GASTROINTESTINAL TRACT BLEED NOS	0	0	0.00	3	3	1.37
GI HEMORRHAGE	0	0	0.00	1	1	0.46
HEARTBURN	0	0	0.00	1	1	0.46
HEMATEMESIS	2	2	0.91	1	1	0.46
HEMATEMESIS GASTRIC ULCER	1	1	0.45	0	0	0.00
HEMORRHOIDS	2	2	0.91	1	1	0.46
HERNIA HIATUS	7	7	3.17	6	6	2.74
INFLAMMATION PYLORUS	1	1	0.45	0	0	0.00
INTESTINAL OBSTRUCTION	3	3	1.36	0	0	0.00
IRRITABLE BOWEL SYNDROME	0	0	0.00	2	2	0.91
MALABSORPTION	0	0	0.00	1	1	0.46
MELENA	3	3	1.36	3	3	1.37
MOUTH ULCERATION	2	2	0.91	0	0	0.00
PAIN STOMACH	0	0	0.00	1	1	0.46
PANCREATITIS	2	3	1.36	1	1	0.46
PANCREATITIS ACUTE	0	0	0.00	2	2	0.91
PROCTITIS	2	2	0.91	0	0	0.00
PYLORIC STENOSIS	0	0	0.00	1	1	0.46
RECTAL BLEEDING	9	10	4.53	1	1	0.46
RECTAL PAIN	0	0	0.00	1	1	0.46
REFLUX ESOPHAGITIS	0	0	0.00	3	3	1.37
SMALL INTESTINE OBSTRUCTION	2	2	0.91	0	0	0.00
TOOTH CARIES	0	0	0.00	1	1	0.46
ULCER	1	1	0.45	0	0	0.00
ULCER PALATE	1	1	0.45	0	0	0.00
ULCER PYLORIC	0	0	0.00	1	1	0.46
HEARING AND VESTIBULAR DISORDERS						
EAR BLOCKAGE	1	1	0.45	0	0	0.00
EAR DRUM PERFORATION	1	1	0.45	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
EAR INFECTION	1	1	0.45	1	1	0.46
EAR PAIN	0	0	0.00	1	1	0.46
LABYRINTHINE DISORDER	1	1	0.45	1	1	0.46
TINNITUS	0	0	0.00	1	1	0.46
VERTIGO	0	0	0.00	1	1	0.46
HEART RATE AND RHYTHM DISORDERS						
ARRHYTHMIA	0	0	0.00	1	1	0.46
ARRHYTHMIA VENTRICULAR	0	0	0.00	1	1	0.46
ATRIAL FIBRILLATION PAROXYSMAL	5	6	2.72	2	2	0.91
ATRIAL FLUTTER	1	2	0.91	1	1	0.46
BRADYARRHYTHMIA	0	0	0.00	1	1	0.46
BRADYCARDIA	4	4	1.81	2	2	0.91
CARDIAC ARREST	5	5	2.27	2	2	0.91
CARDIAC ARRHYTHMIA NOS	0	0	0.00	3	3	1.37
CARDIAC DEATH	3	3	1.36	1	1	0.46
CARDIOPULMONARY ARREST	0	0	0.00	1	1	0.46
FIBRILLATION ATRIAL	14	18	8.15	11	13	5.93
FIBRILLATION VENTRICULAR	0	0	0.00	1	1	0.46
HEART BLOCK	1	1	0.45	0	0	0.00
PALPITATION	3	3	1.36	0	0	0.00
SINUS BRADYCARDIA	0	0	0.00	1	1	0.46
SUDDEN CARDIAC DEATH	2	2	0.91	0	0	0.00
TACHYCARDIA	0	0	0.00	1	1	0.46
TACHYCARDIA SUPRAVENTRICULAR PAROXYSMAL	0	0	0.00	1	1	0.46
TACHYCARDIA VENTRICULAR	2	2	0.91	1	1	0.46
LIVER AND BILIARY SYSTEM DISORDERS						
BILIARY COLIC	1	1	0.45	3	3	1.37
BILIARY STONES	1	1	0.45	0	0	0.00
CHOLECYSTITIS	4	4	1.81	3	3	1.37
CHOLELITHIASIS	3	3	1.36	1	1	0.46
GALL BLADDER STONES	1	1	0.45	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
HEPATITIS CHRONIC	1	1	0.45	0	0	0.00
JAUNDICE	0	0	0.00	4	4	1.83
LIVER ENZYME DISORDER	0	0	0.00	1	1	0.46
LIVER FUNCTION TESTS ABNORMAL NOS	0	0	0.00	1	1	0.46
METABOLIC AND NUTRITIONAL DISORDERS						
DIABETES MELLITUS	20	20	9.06	12	12	5.48
DIABETES MELLITUS AGGRAVATED	1	1	0.45	0	0	0.00
GOUT	2	3	1.36	1	1	0.46
HYPERCHOLESTEROLEMIA	1	2	0.91	0	0	0.00
HYPERGLYCEMIA	2	2	0.91	1	1	0.46
HYPOGLYCEMIA	0	0	0.00	1	1	0.46
KETOACIDOSIS	1	1	0.45	0	0	0.00
RETINOPATHY DIABETIC	1	1	0.45	0	0	0.00
MUSCULO-SKELETAL SYSTEM DISORDERDS						
ARTHRITIS	1	1	0.45	1	1	0.46
ARTHRITIS RHEUMATOID	1	1	0.45	1	1	0.46
BACK PAIN	2	2	0.91	3	3	1.37
BONE REFRACTURED	1	1	0.45	0	0	0.00
CARPAL TUNNEL SYNDROME	3	4	1.81	1	1	0.46
COMPRESSION FRACTURES	0	0	0.00	1	1	0.46
COSTOCHONDRITIS	1	1	0.45	0	0	0.00
DISLOCATION OF HIP	1	2	0.91	1	1	0.46
DISPLACEMENT OF INTERVERTEBRAL DISC	0	0	0.00	1	1	0.46
DUPUYTREN'S CONTRACTURE	1	1	0.45	2	2	0.91
FRACTURE RIB	3	3	1.36	1	1	0.46
FRACTURES	14	16	7.25	9	9	4.11
HERNIA	3	3	1.36	1	1	0.46
INTERVERTEBRAL DISC DISORDER	0	0	0.00	1	1	0.46
JOINT COMPLAINTS	1	1	0.45	1	1	0.46
LOIN PAIN	2	2	0.91	0	0	0.00
MUSCLE PAIN	1	1	0.45	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued..Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
MUSCULOSKELETAL DISORDERS	2	2	0.91	1	1	0.46
OSTEOARTHRITIS	8	8	3.62	4	4	1.83
PAIN HIP	2	2	0.91	0	0	0.00
PAIN KNEE	1	1	0.45	0	0	0.00
PAIN LEG	1	1	0.45	0	0	0.00
PAIN LOWER EXTREMITY	0	0	0.00	1	1	0.46
PAIN NECK	1	1	0.45	2	2	0.91
PAIN SHOULDER	0	0	0.00	1	1	0.46
PAIN WRIST	0	0	0.00	1	1	0.46
POLYARTHRITIS	0	0	0.00	1	1	0.46
ROTATOR CUFF SYNDROME OF SHOULDER	0	0	0.00	1	1	0.46
TEAR OF MENISCUS	0	0	0.00	1	1	0.46
TENDON RUPTURE	0	0	0.00	2	2	0.91
MYO ENDO PERICARDIAL &VALVE DISORDER						
ANGINA	55	63	28.54	66	82	37.42
ANGINA CRESCENDO	0	0	0.00	1	1	0.46
ANGINA PECTORIS	6	7	3.17	9	10	4.56
ANGINA PECTORIS AGGRAVATED	5	5	2.27	4	4	1.83
ANGINA UNSTABLE	65	78	35.34	88	131	59.77
ANGINAL PAIN	0	0	0.00	3	3	1.37
AORTIC STENOSIS	0	0	0.00	2	2	0.91
ARTERIOSCLEROTIC HEART DISEASE	2	3	1.36	4	4	1.83
CARDIAC ISCHEMIA	26	28	12.69	31	34	15.51
CHEST PAIN	51	60	27.18	54	59	26.92
CORONARY ARTERY DISORDER	8	8	3.62	8	9	4.11
CORONARY ARTERY OCCLUSION	5	5	2.27	9	9	4.11
CORONARY ATHEROMA	0	0	0.00	1	1	0.46
CORONARY DISEASE	51	57	25.82	48	54	24.64
CORONARY INSUFFICIENCY	1	1	0.45	4	5	2.28
CORONARY SPASM	0	0	0.00	1	1	0.46
CORONARY STENOSIS	2	2	0.91	2	3	1.37
MYOCARDIAL INFARCTION	33	36	16.31	65	72	32.85

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
MYOCARDIAL ISCHEMIA	6	7	3.17	6	7	3.19
PAIN HEART ISCHEMIC	0	0	0.00	1	1	0.46
POST MI	1	1	0.45	0	0	0.00
THROMBOSIS CORONARY	0	0	0.00	2	2	0.91
NEONATAL AND INFANCY DISORDERS						
HERNIA INGUINAL	7	8	3.62	2	2	0.91
HERNIA UMBILICAL	2	2	0.91	0	0	0.00
HYDROCEPHALUS	1	1	0.45	0	0	0.00
NEOPLASM						
ADENOCARCINOMA BLADDER	0	0	0.00	1	1	0.46
ADENOCARCINOMA COLON	1	2	0.91	0	0	0.00
ADENOCARCINOMA LUNG	0	0	0.00	1	2	0.91
ADENOCARCINOMA NOS	0	0	0.00	1	1	0.46
ADENOCARCINOMA PROSTATA	2	2	0.91	2	2	0.91
ADENOCARCINOMA RECTAL MUCINOUS	1	1	0.45	0	0	0.00
ADENOMA	1	1	0.45	2	5	2.28
BASAL CELL CARCINOMA	5	6	2.72	4	4	1.83
BLADDER CARCINOMA	5	6	2.72	6	6	2.74
BLADDER PAPILLOMA	1	1	0.45	0	0	0.00
BREAST NEOPLASM BENIGN FEMALE	0	0	0.00	1	1	0.46
BREAST NEOPLASM MALIGNANT FEMALE	1	1	0.45	0	0	0.00
CANCER BLADDER	1	1	0.45	1	1	0.46
CANCER COLON	3	4	1.81	0	0	0.00
CANCER ESOPHAGUS	0	0	0.00	2	2	0.91
CANCER KIDNEY	1	1	0.45	1	2	0.91
CANCER LUNG NON-SMALL CELL	1	5	2.27	0	0	0.00
CANCER LUNG SQUAMOUS CELL	4	5	2.27	0	0	0.00
CANCER PROSTATE	1	1	0.45	2	4	1.83
CARCINOMA	3	3	1.36	1	1	0.46
CARCINOMA BASAL CELL	0	0	0.00	1	1	0.46
CARCINOMA BLADDER TRANSITIONAL CELL	3	8	3.62	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
CARCINOMA BRONCHUS	1	2	0.91	0	0	0.00
CARCINOMA COLON	3	3	1.36	0	0	0.00
CARCINOMA GASTROINTESTINAL	0	0	0.00	1	1	0.46
CARCINOMA LARYNX	1	2	0.91	0	0	0.00
CARCINOMA OF ESOPHAGUS	0	0	0.00	4	5	2.28
CARCINOMA OF RECTUM	0	0	0.00	1	1	0.46
CARCINOMA PROSTATE	3	3	1.36	2	2	0.91
CARCINOMA RENAL CELL	0	0	0.00	1	1	0.46
CARCINOMA VOCAL TRUE CORD	0	0	0.00	1	1	0.46
CARCINOMATOSIS	0	0	0.00	1	1	0.46
CYST	2	2	0.91	2	2	0.91
CYST PANCREATIC	1	1	0.45	0	0	0.00
EPIDIDYMAL CYST	2	2	0.91	0	0	0.00
ESOPHAGEAL CARCINOMA	0	0	0.00	1	1	0.46
GALL BLADDER CARCINOMA	0	0	0.00	1	1	0.46
GASTRIC CARCINOMA	2	2	0.91	1	1	0.46
HEPATIC NEOPLASM MALIGNANT	0	0	0.00	1	1	0.46
LEUKEMIA B CELL CHRONIC LYMPH.	1	1	0.45	0	0	0.00
LIPOMA	1	1	0.45	0	0	0.00
MELANOMA	1	1	0.45	0	0	0.00
MELANOMA MALIGNANT	1	1	0.45	1	1	0.46
MESOTHELIOMA	0	0	0.00	1	1	0.46
METASTASES GROWTH	0	0	0.00	2	3	1.37
MULTIPLE MYELOMA	1	1	0.45	1	1	0.46
MYELOMA	0	0	0.00	1	2	0.91
MYELOPROLIFERATIVE DISORDER	0	0	0.00	1	1	0.46
NEOPLASM MALIGNANT	0	0	0.00	1	1	0.46
NEOPLASM NOS	1	1	0.45	0	0	0.00
NEOPLASM PULMONARY MALIGNANT	1	1	0.45	4	4	1.83
PANCREAS CARCINOMA	0	0	0.00	2	3	1.37
PAPILLOMA	0	0	0.00	1	1	0.46
POLYP COLON	1	1	0.45	4	4	1.83
POLYP ENDOMETRIUM	0	0	0.00	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
PULMONARY CARCINOMA	1	1	0.45	0	0	0.00
RECTAL CARCINOMA	0	0	0.00	1	1	0.46
RENAL CARCINOMA	0	0	0.00	1	1	0.46
SARCOMA	0	0	0.00	1	1	0.46
SKIN TUMOR-LIKE CONDITION NOS	1	1	0.45	0	0	0.00
STOMACH CARCINOMA	2	3	1.36	0	0	0.00
TESTIS NEOPLASM MALIGNANT	1	1	0.45	0	0	0.00
TUMOR GASTROINTESTINAL	1	1	0.45	0	0	0.00
TUMOR URINARY BLADDER	1	1	0.45	2	3	1.37
OPERATIONS & PROCEDURES						
AMPUTATION TOE PHALANX	0	0	0.00	1	1	0.46
ANALGESIC TREATMENT OF NERVE	0	0	0.00	1	1	0.46
ANEURYSMECTOMY	1	1	0.45	1	1	0.46
ANGIOCARDIOGRAPHY	38	39	17.67	40	40	18.25
ANGIOGRAPHY CAROTIS	5	5	2.27	2	2	0.91
APPARATUS TECHNIQUE /SPEC.PROCEDURES	11	11	4.98	6	7	3.19
APPENDECTOMY	1	1	0.45	0	0	0.00
ARTERIOGRAPHY	3	3	1.36	2	2	0.91
ARTHRODESIS OF FOOT	1	1	0.45	0	0	0.00
ARTHROPLASTY (HIP)	2	2	0.91	2	2	0.91
ARTHROPLASTY (KNEE)	3	3	1.36	0	0	0.00
ARTHROSCOPY KNEE	1	1	0.45	2	2	0.91
BIOPSY (HEAD, SOFT TISSUE)	2	2	0.91	0	0	0.00
BLADDER CATHETERIZATION	1	1	0.45	1	2	0.91
BONE TRANSPLANTATION OF HAND	1	1	0.45	0	0	0.00
BRONCHOSCOPY	5	5	2.27	1	1	0.46
CARDIOVASCULAR DRUG THERAPY	0	0	0.00	2	2	0.91
CARDIOVERSION, DEFIBRILATION	0	0	0.00	1	1	0.46
CATHETERIZATION OF HEART	3	3	1.36	4	4	1.83
CHOLECYSTECTOMY	2	2	0.91	2	2	0.91
CIRCUMCISION	0	0	0.00	1	1	0.46
CLOSURE OF COLOSTOMY	0	0	0.00	2	2	0.91

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
COLONOSCOPY	6	6	2.72	9	9	4.11
DISCISSION, EXTRACTION OF LENSE	3	3	1.36	1	1	0.46
EPIDIDYMECTOMY	1	1	0.45	0	0	0.00
EXCISION OF COLONIC POLYP	2	2	0.91	0	0	0.00
EXCISION SKIN, SUBCUTIS	1	1	0.45	2	2	0.91
EXPLORATORY THORACOTOMY	1	1	0.45	0	0	0.00
FASCIECTOMY	1	1	0.45	1	1	0.46
GASTROSCOPY	12	12	5.44	12	12	5.48
HEMICOLECTOMY	1	1	0.45	1	1	0.46
HERNIA INGUINALIS REPAIR	1	1	0.45	1	1	0.46
HERNIA REPAIR	5	5	2.27	3	3	1.37
INCISION OF SKIN, SUBCUTIS	1	1	0.45	0	0	0.00
LAMINECTOMY	0	0	0.00	1	1	0.46
MITRAL VALVE REPLACEMENT	0	0	0.00	1	1	0.46
MULTIPLE AC BYPASS	1	1	0.45	1	1	0.46
MUSCLE BIOPSY	2	2	0.91	0	0	0.00
NASAL POLYPECTOMY	1	1	0.45	0	0	0.00
NEPHRECTOMY	0	0	0.00	1	1	0.46
O.SURGERY (MEDIASTINUM,THORACIC WALL)	0	0	0.00	1	1	0.46
OPERATION GLAUCOMA	1	1	0.45	0	0	0.00
OTHER BONE SURGERY (FEMUR)	0	0	0.00	1	1	0.46
OTHER OP HAND, SOFT TISSUE	1	1	0.45	0	0	0.00
OTHER OP SPINE	0	0	0.00	1	1	0.46
OTHER SURGERIES (HIP,SOFT TISSUE)	1	1	0.45	0	0	0.00
OTHER SURGERY (ARTICULAR ANKLE)	0	0	0.00	1	1	0.46
OTHER SURGERY (BRONCHI,LUNG,PLEURA)	1	1	0.45	0	0	0.00
OTHER SURGERY (EXTERNAL EAR)	1	1	0.45	0	0	0.00
OTHER SURGERY (EYEBALL)	5	6	2.72	5	6	2.74
OTHER SURGERY (HAND BONES)	1	1	0.45	0	0	0.00
OTHER SURGERY (HEART)	3	3	1.36	2	3	1.37
OTHER SURGERY (LACR.SAC,LACRIMAL DUCT)	1	1	0.45	0	0	0.00
OTHER SURGERY (MIDDLE EAR)	0	0	0.00	1	1	0.46
OTHER SURGERY (MUSCLES,FASCIAE)	2	2	0.91	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
OTHER SURGERY (NOSE, PARANASAL SINUSES)	1	1	0.45	0	0	0.00
OTHER SURGERY (PORTIO VAGINALIS UTERI)	1	1	0.45	0	0	0.00
OTHER SURGERY (SKIN, SUBCUTIS)	1	1	0.45	1	1	0.46
OTHER SURGERY (SKULL)	0	0	0.00	1	1	0.46
OTHER SURGERY (SMALL INTESTINE)	1	1	0.45	0	0	0.00
OTHER SURGERY (TOES,SOFT TISSUE)	0	0	0.00	1	1	0.46
OTHER SURGERY (URETER)	0	0	0.00	1	2	0.91
OTHER SURGERY (UTERUS,ABDOMEN)	0	0	0.00	1	1	0.46
OTHER SURGERY (VAGINA,VULVA,PERINEUM)	0	0	0.00	2	2	0.91
OTHER SURGERY ARTERY	6	6	2.72	5	5	2.28
OTHER SURGERY ARTERY, PLASTY	14	15	6.80	14	14	6.39
OTHER SURGERY BLADDER	1	1	0.45	0	0	0.00
OTHER SURGERY LENS	3	4	1.81	4	6	2.74
OTHER SURGERY LIVER,GALLBLADDER	1	1	0.45	1	1	0.46
OTHER SURGERY ON EYELID	0	0	0.00	1	1	0.46
OTHER SURGERY PROSTATE	1	1	0.45	0	0	0.00
OTHER SURGERY UTERUS VAGINA	1	1	0.45	0	0	0.00
PART.ARTHROPLASTY WITH IMPLANT (KNEE)	0	0	0.00	1	1	0.46
PUNCTION AND/OR DRAINAGE	1	1	0.45	0	0	0.00
RECTOSIGMOIDOSCOPY	3	3	1.36	3	3	1.37
REVASCULARISATION MYOCARD O. SURGERY	0	0	0.00	2	2	0.91
REVASCULARISATION OF MYOCARD	12	12	5.44	17	17	7.76
REVISION OF MIDDLE EAR AND MASTOID	0	0	0.00	1	1	0.46
S.A. ARTHROPLASTY (KNEE)	1	1	0.45	0	0	0.00
S.A. OTHER SURGERY LENS	1	1	0.45	0	0	0.00
S.A.OTHER SURGERY (EYEBALL)	0	0	0.00	1	1	0.46
S.A.OTHER SURGERY (HEART)	1	1	0.45	0	0	0.00
SEGM. RESECTION OF COLON	2	2	0.91	1	1	0.46
SURGERIES OF INTERVERTEBRAL APERTURE	0	0	0.00	1	1	0.46
SURGERY FOR HEMO-/PERITON.DIALYSIS	0	0	0.00	1	1	0.46
SURGERY OF ANAL FISTULA	1	1	0.45	0	0	0.00
SURGERY VOCAL LIGAMENTS	1	1	0.45	0	0	0.00
TEETH EXTRACTION	1	1	0.45	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
TOTAL ARTHROPLASTY WITH IMPLANT (KNEE)	1	1	0.45	3	3	1.37
TOTAL ARTHROPLASTY WITH IMPLANTAT (HIP)	2	2	0.91	2	2	0.91
TRANSURETHR. RESECT. OF PROSTATE	1	1	0.45	2	2	0.91
TRANSURETHRAL CYSTOSCOPY	17	27	12.23	11	13	5.93
TRANSURETHRAL SURGERY URINARY BLADDER	3	3	1.36	0	0	0.00
TRIPLE AC BYPASS	0	0	0.00	1	1	0.46
VAGINAL HYSTERECTOMY	0	0	0.00	1	1	0.46
VESSEL REPLACEMENT OR BYPASS	2	2	0.91	1	1	0.46
PLATELET, BLEEDING&CLOTTING DISORDER						
CAROTID OCCLUSION	0	0	0.00	1	1	0.46
COAGULATION DISORDER	1	1	0.45	0	0	0.00
EMBOLISM PULMONARY	5	5	2.27	3	3	1.37
HEMORRHAGE NOS	0	0	0.00	1	1	0.46
THROMBOCYTOPENIA	0	0	0.00	2	2	0.91
PSYCHIATRIC DISORDERS						
ABSTAINING SYMPTOMS	1	1	0.45	0	0	0.00
ALCOHOLISM	0	0	0.00	1	1	0.46
ANXIETY ATTACK	1	1	0.45	0	0	0.00
BIPOLAR DISORDER	2	2	0.91	0	0	0.00
CONFUSION	0	0	0.00	1	1	0.46
CONSCIOUSNESS CLOUDED	1	1	0.45	0	0	0.00
DEMENTIA	1	1	0.45	0	0	0.00
DEPRESSION	1	1	0.45	1	1	0.46
DEPRESSION PSYCHOTIC	1	1	0.45	0	0	0.00
EFFORT SYNDROME	1	1	0.45	0	0	0.00
INTENTIONAL OVERDOSE	1	1	0.45	1	2	0.91
MANIC PSYCHOSIS	1	1	0.45	0	0	0.00
PACING	0	0	0.00	2	2	0.91
PANIC ATTACK	0	0	0.00	1	1	0.46
RED BLOOD CELL DISORDERS						
ANEMIA	5	6	2.72	3	3	1.37

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
* rate = number of events per thousand person-years of follow-up						
ANEMIA HEMOLYTIC	1	2	0.91	1	1	0.46
ANEMIA IRON DEFICIENCY	1	1	0.45	3	3	1.37
HEMOGLOBIN DECREASED	1	1	0.45	1	1	0.46
REPRODUCTIVE DISORDES,FEMALE						
BLEEDING POSTMENOPAUSAL	1	1	0.45	0	0	0.00
REPRODUCTIVE DISORDES,MALE						
GENITALIA EXTERNAL PAINFUL	0	0	0.00	1	1	0.46
GYNECOMASTIA	0	0	0.00	1	1	0.46
PENIS DISORDER	1	1	0.45	0	0	0.00
PROSTATE ENLARGED	2	2	0.91	2	2	0.91
PROSTATIC DISORDER	3	4	1.81	2	2	0.91
RESISTANCE MECHANISM DISORDERS						
ABSCESS	1	1	0.45	1	1	0.46
ABSCESS ANAL	2	2	0.91	0	0	0.00
ABSCESS LEG	1	1	0.45	1	1	0.46
HERPES ZOSTER	0	0	0.00	1	1	0.46
INFECTION	2	2	0.91	0	0	0.00
INFECTION BACTERIAL	0	0	0.00	1	1	0.46
INFECTION VIRAL	0	0	0.00	1	1	0.46
SEPSIS	1	1	0.45	0	0	0.00
SEPTICEMIA	1	1	0.45	2	2	0.91
WOUND INFECTION	1	1	0.45	1	1	0.46
RESPIRATORY SYSTEM DISORDERS						
ASPIRATION	1	1	0.45	0	0	0.00
ASTHMA	1	1	0.45	1	1	0.46
BREATHING DIFFICULT	0	0	0.00	1	1	0.46
BRONCHIAL DAMAGE	0	0	0.00	1	1	0.46
BRONCHIEKTASIS	0	0	0.00	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
BRONCHITIS	0	0	0.00	2	2	0.91
BRONCHOPNEUMONIA	3	3	1.36	1	1	0.46
CHRONIC OBSTR. PULM. DISEASE	10	16	7.25	4	4	1.83
COPD	1	1	0.45	1	1	0.46
DYSPNEA	1	1	0.45	2	2	0.91
DYSPNEA EXERTIONAL	0	0	0.00	1	1	0.46
EDEMA PULMONARY	1	1	0.45	2	2	0.91
EMPHYSEMA	0	0	0.00	1	2	0.91
EPISTAXIS	4	4	1.81	0	0	0.00
HEMOPTYSIS	2	2	0.91	1	1	0.46
INFECTION BRONCHOPULMONARY	0	0	0.00	1	1	0.46
INFECTION CHEST	11	13	5.89	12	13	5.93
INFECTION LUNG	1	1	0.45	1	1	0.46
LARYNX EDEMA	1	1	0.45	0	0	0.00
NASAL POLYP	3	3	1.36	1	1	0.46
NASAL SEPTUM DEVIATION	1	1	0.45	0	0	0.00
OBSTRUCTION PULMONARY	0	0	0.00	1	1	0.46
PHARYNGITIS	1	1	0.45	0	0	0.00
PLEURAL CHANGES	1	2	0.91	0	0	0.00
PLEURAL EFFUSION	4	7	3.17	2	2	0.91
PLEURAL PAIN	3	3	1.36	2	2	0.91
PLEURISY	1	1	0.45	0	0	0.00
PNEUMONIA	12	13	5.89	8	8	3.65
PNEUMOTHORAX	0	0	0.00	1	1	0.46
PULMONARY COLLAPSE	0	0	0.00	1	1	0.46
PULMONARY DAMAGE	0	0	0.00	1	1	0.46
PULMONARY DISEASE	1	1	0.45	1	1	0.46
RESPIRATORY DISORDER	0	0	0.00	1	1	0.46
RESPIRATORY FAILURE	1	1	0.45	0	0	0.00
SHORTNESS OF BREATH	3	3	1.36	2	2	0.91
UPPER RESP TRACT INFECTION	0	0	0.00	2	2	0.91
VOCAL CORD EDEMA	1	1	0.45	0	0	0.00
SKIN AND APPENDAGES DISORDERS						
ALOPECIA	1	1	0.45	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System		Nicorandil			Placebo		
		subjects	events	rate*	subjects	events	rate*
	BRUISE	0	0	0.00	1	1	0.46
	FISSURES	1	1	0.45	0	0	0.00
	HEMATOMA	2	2	0.91	0	0	0.00
	INFLAMMATION SKIN	1	1	0.45	1	1	0.46
	KERATOSIS	1	1	0.45	0	0	0.00
	MUCOCUTANEOUS LESION	1	1	0.45	0	0	0.00
	NECROSIS TOE	1	1	0.45	0	0	0.00
	PILONIDAL CYST	1	1	0.45	0	0	0.00
	PSORIASIS	1	1	0.45	0	0	0.00
	RASH	0	0	0.00	2	2	0.91
	SKIN DEFECTS SUPERFICIAL	4	4	1.81	0	0	0.00
	SKIN DISEASE	1	1	0.45	0	0	0.00
	SKIN DISORDER	1	1	0.45	0	0	0.00
	SKIN NODULE	1	1	0.45	0	0	0.00
	SKIN ULCERATION	1	1	0.45	0	0	0.00
	ULCER FOOT	0	0	0.00	1	1	0.46
	ULCER LEG	0	0	0.00	1	1	0.46
	URTICARIA	1	1	0.45	0	0	0.00
UNKNOWN							
	UNKNOWN	5	5	2.27	5	5	2.28
URINARY	SYSTEM DISORDERS						
	BLADDER CALCULUS	1	1	0.45	0	0	0.00
	BLADDER DYSFUNCTION	0	0	0.00	1	1	0.46
	CYSTITIS	2	2	0.91	0	0	0.00
	CYSTOCELE	1	1	0.45	0	0	0.00
	HEMATURIA	7	7	3.17	3	3	1.37
	HEMATURIA MICROSCOPIC	1	1	0.45	0	0	0.00
	INFECTION URINARY BLADDER	1	1	0.45	0	0	0.00
	INFECTION UROGENITAL TRACT	0	0	0.00	1	1	0.46

* rate = number of events per thousand person-years of follow-up

continued...Table 51 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
ISCHEMIA PERIPHERAL	0	0	0.00	1	1	0.46
ISCHEMIC ATTACKS TRANSIENT	10	10	4.53	10	10	4.56
MESENTERIC ARTERIAL OCCLUSION	1	1	0.45	0	0	0.00
PERIPHERAL ISCHEMIA	1	1	0.45	0	0	0.00
PERIPHERAL VASCULAR DISEASE	2	2	0.91	6	7	3.19
PERIPHERAL VASCULAR DISEASE.	0	0	0.00	1	1	0.46
RENAL ARTERY STENOSIS	0	0	0.00	1	1	0.46
STENOSIS ARTERIAL	1	1	0.45	3	3	1.37
STROKE	2	2	0.91	6	6	2.74
THROMBOPHLEBITIS	2	2	0.91	0	0	0.00
THROMBOPHLEBITIS DEEP	1	1	0.45	0	0	0.00
THROMBOPHLEBITIS LEG DEEP	1	1	0.45	1	1	0.46
THROMBOPHLEBITIS SUPERFICIAL	1	1	0.45	0	0	0.00
THROMBOSIS PELVIC VEINS	0	0	0.00	1	1	0.46
THROMBOSIS VENOUS DEEP	3	3	1.36	1	1	0.46
VARICOSE VEINS	1	1	0.45	0	0	0.00
VASCULAR DISORDER	0	0	0.00	1	1	0.46
VASCULITIS	1	1	0.45	0	0	0.00
VASOSPASM	0	0	0.00	1	1	0.46
VEIN DISORDER	1	1	0.45	0	0	0.00
VISION DISORDERS						
CATARACT	26	28	12.69	15	19	8.67
EYE ABNORMALITY	1	1	0.45	0	0	0.00
EYE IRRITATION	1	1	0.45	1	1	0.46
GLAUCOMA	1	1	0.45	1	1	0.46
HYPHEMA	0	0	0.00	2	2	0.91
RETINAL VEIN THROMBOSIS	0	0	0.00	1	1	0.46
VITREOUS DETACHMENT	0	0	0.00	1	1	0.46

* rate = number of events per thousand person-years of follow-up

Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
APPLICATION SITE DISORDERS						
ALLERGY CONTACT	1	1	0.52	0	0	0.00
CELLULITIS	4	4	2.09	2	2	1.06
IMPLANTATION COMPLICATION	0	0	0.00	1	1	0.53
BODY AS A WHOLE - GENERAL DISORDERS						
ALLERGIC REACTION	1	1	0.52	1	1	0.53
ANAPHYLACTIC SHOCK	1	1	0.52	0	0	0.00
DEATH	0	0	0.00	2	2	1.06
DRUG INTERACTION	1	1	0.52	0	0	0.00
EDEMA	0	0	0.00	1	1	0.53
GRANULOMA SALIVARYGLAND	1	1	0.52	0	0	0.00
INFARCT	1	1	0.52	0	0	0.00
OCCLUSION	0	0	0.00	4	4	2.11
OTHER GENERAL SYMPTOMS	0	0	0.00	1	1	0.53
PAIN	1	1	0.52	1	1	0.53
SIDE EFFECTS NOS	2	2	1.05	0	0	0.00
SWELLING ARMS	1	1	0.52	0	0	0.00
WEIGHT DECREASE	0	0	0.00	2	2	1.06
CARDIOVASCULAR DISORDERS, GENERAL						
ANEURYSM	2	2	1.05	1	1	0.53
ANGINA EXERCISE INDUCED	1	1	0.52	2	2	1.06
BLACK-OUT (NOT AMNESIA)	0	0	0.00	2	2	1.06
CARDIAC DYSFUNCTION	1	1	0.52	1	1	0.53
CARDIAC FAILURE	1	1	0.52	5	5	2.64
CARDIOVASCULAR COLLAPSE	0	0	0.00	1	1	0.53
COLLAPSE CIRCULATORY	1	1	0.52	1	1	0.53
COLLAPSE TRANSIENT	3	4	2.09	1	1	0.53
CONGESTIVE HEART FAILURE	1	1	0.52	2	2	1.06
CORONARY ATHEROSCLEROSIS	0	0	0.00	3	3	1.58
ECG ABNORMAL	0	0	0.00	1	1	0.53

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
HEART DAMAGE	0	0	0.00	1	1	0.53
HEART DISEASE	9	9	4.71	16	16	8.44
HYPERTENSION	1	1	0.52	0	0	0.00
HYPERTENSION ESSENTIAL	0	0	0.00	1	1	0.53
HYPOTENSION	1	1	0.52	1	1	0.53
HYPOTENSION ORTHOSTATIC	1	1	0.52	0	0	0.00
HYPOTENSION POSTURAL	1	1	0.52	0	0	0.00
LEFT VENTRICULAR FAILURE	11	12	6.28	6	6	3.17
SHOCK CARDIOGENIC	0	0	0.00	2	2	1.06
SYNCOPE	3	3	1.57	4	4	2.11
VASOVAGAL ATTACK	1	1	0.52	1	1	0.53
VENTRICULAR INSUFFICIENCY LEFT	0	0	0.00	1	2	1.06
CENTR & PERIPH NERV SYST. DISORDERS						
CEREBRAL DISTURBANCES	1	1	0.52	0	0	0.00
CEREBRAL SYMPTOMS	0	0	0.00	1	1	0.53
DIZZINESS	3	3	1.57	0	0	0.00
DIZZY ON STANDING	1	1	0.52	0	0	0.00
HEADACHE	5	5	2.62	4	4	2.11
LETHARGY	1	1	0.52	0	0	0.00
NEURITIS	0	0	0.00	1	1	0.53
PARKINSON'S DISEASE	0	0	0.00	1	1	0.53
POLYNEUROPATHY DIABETIC	0	0	0.00	1	1	0.53
POLYNEUROPATHY SENSORY	0	0	0.00	1	1	0.53
PTOSIS	0	0	0.00	1	1	0.53
SUBDURAL HEMATOMA	0	0	0.00	1	1	0.53
UNCONSCIOUSNESS	0	0	0.00	1	1	0.53
ENDOCRINE DISORDERS						
THYROID DISORDER	1	1	0.52	0	0	0.00
GASTRO- INTESTINAL SYSTEM DISORDERS						
ABDOMINAL DISCOMFORT	1	1	0.52	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
ABDOMINAL PAIN	0	0	0.00	5	6	3.17
ABDOMINAL PAIN UPPER	1	1	0.52	0	0	0.00
BLEEDING ULCER	0	0	0.00	1	1	0.53
BOWEL OBSTRUCTION	1	1	0.52	0	0	0.00
BOWEL PERFORATION	0	0	0.00	1	1	0.53
COLITIS	1	1	0.52	0	0	0.00
COLITIS ULCERATIVE	0	0	0.00	2	2	1.06
COLITIS ULCERATIVE AGGRAVATED	1	1	0.52	1	1	0.53
CONSTIPATION	3	3	1.57	2	3	1.58
CROHN'S DISEASE	0	0	0.00	1	1	0.53
DIARRHEA	2	2	1.05	1	1	0.53
DIVERTICULAR DISEASE	4	4	2.09	1	1	0.53
DIVERTICULITIS	1	1	0.52	1	1	0.53
DIVERTICULOSIS	2	2	1.05	1	1	0.53
DUODENAL ULCER	2	2	1.05	1	3	1.58
DUODENITIS	1	1	0.52	0	0	0.00
DYSPEPSIA	2	3	1.57	0	0	0.00
DYSPHAGIA	1	1	0.52	0	0	0.00
EPIGASTRIC PAIN NOT FOOD-RELATED	0	0	0.00	1	1	0.53
ESOPHAGITIS	4	4	2.09	0	0	0.00
FECAL FISTULA	2	2	1.05	0	0	0.00
GASTRESOPHAGEAL REFLUX	1	1	0.52	0	0	0.00
GASTRIC BLEEDING	1	1	0.52	1	1	0.53
GASTRIC ULCER	2	2	1.05	2	2	1.06
GASTRITIS	3	3	1.57	1	1	0.53
GASTRITIS ANTRUM	4	4	2.09	0	0	0.00
GASTRITIS EROSIVE	1	1	0.52	1	1	0.53
GASTRODUODENITIS	1	1	0.52	0	0	0.00
GASTROENTERITIS	0	0	0.00	1	1	0.53
GASTROINTESTINAL TRACT BLEED NOS	0	0	0.00	1	1	0.53
GI HEMORRHAGE	1	1	0.52	3	3	1.58
HEARTBURN	1	1	0.52	0	0	0.00
HEMATEMESIS	2	2	1.05	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
HEMORRHOIDS	1	1	0.52	0	0	0.00
HERNIA HIATUS	5	5	2.62	3	3	1.58
INDIGESTION	0	0	0.00	1	1	0.53
INTESTINAL OBSTRUCTION	0	0	0.00	1	1	0.53
IRRITABLE BOWEL SYNDROME	1	1	0.52	0	0	0.00
MELENA	1	1	0.52	0	0	0.00
ORAL ULCERATION	1	1	0.52	0	0	0.00
PANCREATITIS	0	0	0.00	1	1	0.53
PERITONITIS	1	1	0.52	0	0	0.00
PROCTITIS	0	0	0.00	1	1	0.53
RECTAL BLEEDING	3	3	1.57	1	1	0.53
RECTAL DISORDER	1	1	0.52	0	0	0.00
REFLUX DUODENO-GASTRIC	0	0	0.00	1	1	0.53
REFLUX ESOPHAGITIS	1	1	0.52	1	1	0.53
STOMACH ULCER	0	0	0.00	1	1	0.53
ULCER GINGIVA	1	1	0.52	0	0	0.00
ULCER PYLORIC	1	1	0.52	0	0	0.00
HEART RATE AND RHYTHM DISORDERS						
ARRHYTHMIA VENTRICULAR	1	1	0.52	0	0	0.00
ATRIAL FIBRILLATION PAROXYSMAL	1	1	0.52	1	1	0.53
ATRIAL FLUTTER	2	3	1.57	2	2	1.06
AV BLOCK SECOND DEGREE	1	1	0.52	0	0	0.00
AV DISSOCIATION	0	0	0.00	1	1	0.53
BRADYCARDIA	1	1	0.52	0	0	0.00
CARDIAC ARREST	4	4	2.09	2	2	1.06
CARDIAC DEATH	1	1	0.52	1	1	0.53
CARDIOPULMONARY ARREST	1	1	0.52	0	0	0.00
FIBRILLATION ATRIAL	6	6	3.14	8	9	4.75
HEART BLOCK	0	0	0.00	1	1	0.53
LEFT BUNDLE BRANCH BLOCK	0	0	0.00	1	1	0.53
PALPITATION	0	0	0.00	2	2	1.06
SINUS BRADYCARDIA	1	1	0.52	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
SYNDROME SICK SINUS	0	0	0.00	1	1	0.53
TACHYCARDIA VENTRICULAR	1	1	0.52	1	1	0.53
LIVER AND BILIARY SYSTEM DISORDERS						
BILIARY COLIC	0	0	0.00	1	1	0.53
BILIARY TRACT DISORDER UNSPECIFIED	1	1	0.52	0	0	0.00
CHOLANGITIS	1	1	0.52	0	0	0.00
CHOLECYSTITIS	2	2	1.05	5	7	3.69
CHOLELITHIASIS	4	4	2.09	2	2	1.06
GALL BLADDER DISORDER	0	0	0.00	1	1	0.53
GALL BLADDER STONES	0	0	0.00	1	1	0.53
LIVER FUNCTION TESTS ABNORMAL NOS	0	0	0.00	1	1	0.53
METABOLIC AND NUTRITIONAL DISORDERS						
DIABETES MELLITUS	13	13	6.80	9	9	4.75
GOUT	1	1	0.52	0	0	0.00
KETOSIS	1	1	0.52	0	0	0.00
MUSCULO-SKELETAL SYSTEM DISORDERDS						
ARTHRITIC-LIKE PAIN	1	1	0.52	0	0	0.00
ARTHRITIS	1	1	0.52	0	0	0.00
ARTHRITIS RHEUMATOID AGGRAVATED	1	1	0.52	0	0	0.00
ARTHRITIS SEPTIC	0	0	0.00	1	1	0.53
BACK PAIN	1	1	0.52	3	3	1.58
CARPAL TUNNEL SYNDROME	2	2	1.05	3	3	1.58
DISLOCATION OF HIP	1	1	0.52	0	0	0.00
DUPUYTREN'S CONTRACTURE	0	0	0.00	1	1	0.53
FRACTURE RIB	1	1	0.52	0	0	0.00
FRACTURES	8	8	4.18	6	6	3.17
HERNIA	2	2	1.05	1	1	0.53
JOINT COMPLAINTS	0	0	0.00	1	1	0.53
LEG DISCOMFORT	1	1	0.52	0	0	0.00
LIGAMENT DISORDER	0	0	0.00	1	1	0.53

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
MUSCLE ATROPHY NEUROLOGICAL	1	1	0.52	0	0	0.00
MUSCLE PAIN	3	3	1.57	0	0	0.00
NECROSIS HIP	1	2	1.05	0	0	0.00
OSTEOARTHRITIS	2	2	1.05	6	6	3.17
PAIN KNEE	1	1	0.52	1	1	0.53
PAIN LEG	1	1	0.52	0	0	0.00
PAIN LOWER EXTREMITY	1	1	0.52	0	0	0.00
SPONDYLITIS	0	0	0.00	1	1	0.53
WEAKNESS KNEE	0	0	0.00	1	1	0.53
MYO ENDO PERICARDIAL &VALVE DISORDER						
ANGINA	38	51	26.68	38	43	22.68
ANGINA CRESCENDO	1	1	0.52	0	0	0.00
ANGINA PECTORIS	7	8	4.18	4	5	2.64
ANGINA PECTORIS AGGRAVATED	3	4	2.09	3	3	1.58
ANGINA UNSTABLE	34	36	18.83	40	52	27.43
ANGINA VARIANT	1	1	0.52	0	0	0.00
ANGINAL ATTACK	0	0	0.00	4	4	2.11
ANGINAL PAIN	1	1	0.52	0	0	0.00
ANGINAL SYNDROME	0	0	0.00	1	1	0.53
AORTIC VALVE ABNORMALITY	0	0	0.00	1	1	0.53
ARTERIOSCLEROTIC HEART DISEASE	1	1	0.52	1	1	0.53
CARDIAC ISCHEMIA	16	17	8.89	16	19	10.02
CARDIOMYOPATHY	0	0	0.00	2	3	1.58
CHEST PAIN	31	36	18.83	40	49	25.85
CORONARY ARTERY DISORDER	7	8	4.18	3	3	1.58
CORONARY ARTERY OCCLUSION	4	4	2.09	5	5	2.64
CORONARY ATHEROMA	0	0	0.00	1	1	0.53
CORONARY DISEASE	38	43	22.49	46	52	27.43
CORONARY INSUFFICIENCY	1	1	0.52	0	0	0.00
CORONARY STENOSIS	3	3	1.57	3	3	1.58
CORONARY THROMBOEMBOLISM	0	0	0.00	1	1	0.53
MYOCARDIAL INFARCTION	32	36	18.83	37	37	19.52

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
MYOCARDIAL ISCHEMIA	4	4	2.09	3	4	2.11
PERICARDIAL EFFUSION	0	0	0.00	1	1	0.53
PERICARDITIS	2	2	1.05	0	0	0.00
NEONATAL AND INFANCY DISORDERS						
HERNIA INGUINAL	3	3	1.57	6	6	3.17
NEOPLASM						
ADENOCARCINOMA COLON	0	0	0.00	1	1	0.53
ADENOCARCINOMA LUNG	1	2	1.05	0	0	0.00
ADENOCARCINOMA PROSTATA	0	0	0.00	2	2	1.06
ADENOMA	1	2	1.05	0	0	0.00
BASAL CELL CARCINOMA	1	1	0.52	3	4	2.11
BLADDER CARCINOMA	0	0	0.00	1	1	0.53
BREAST NEOPLASM MALIGNANT FEMALE	1	1	0.52	0	0	0.00
CANCER BLADDER	0	0	0.00	1	1	0.53
CANCER COLON	1	1	0.52	1	1	0.53
CANCER LUNG SQUAMOUS CELL	1	1	0.52	4	4	2.11
CANCER PROSTATE	1	1	0.52	0	0	0.00
CARCINOMA	1	1	0.52	1	2	1.06
CARCINOMA BASAL CELL	1	1	0.52	0	0	0.00
CARCINOMA BLADDER TRANSITIONAL CELL	2	4	2.09	0	0	0.00
CARCINOMA BREAST	1	1	0.52	0	0	0.00
CARCINOMA BRONCHUS	1	2	1.05	0	0	0.00
CARCINOMA COLON	1	3	1.57	1	1	0.53
CARCINOMA EPIGLOTTIS	1	1	0.52	0	0	0.00
CARCINOMA MOUTH	1	1	0.52	0	0	0.00
CARCINOMA OF RECTUM	0	0	0.00	1	1	0.53
CARCINOMA PROSTATE	2	2	1.05	3	4	2.11
CARCINOMA THYROID	1	2	1.05	0	0	0.00
CARCINOMA TONGUE	1	3	1.57	0	0	0.00
CARCINOMATOSIS	1	1	0.52	1	1	0.53
COLON CARCINOMA	1	1	0.52	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
CYST	5	5	2.62	1	1	0.53
ESOPHAGEAL CARCINOMA	0	0	0.00	1	1	0.53
GASTRIC CARCINOMA	0	0	0.00	1	2	1.06
GOITRE NODULAR	1	1	0.52	0	0	0.00
LEUKEMIA LYMPHOBLASTIC	1	2	1.05	0	0	0.00
LIPOMA	0	0	0.00	1	1	0.53
LYMPHOMA NON-HODGKIN'S	1	1	0.52	0	0	0.00
MELANOMA	0	0	0.00	1	1	0.53
MELANOMA MALIGNANT	1	2	1.05	0	0	0.00
MESOTHELIOMA	0	0	0.00	1	1	0.53
METASTASES GROWTH	2	2	1.05	0	0	0.00
NEOPLASM NOS	2	2	1.05	1	1	0.53
NEOPLASM PULMONARY MALIGNANT	0	0	0.00	1	1	0.53
PAPILLOMA	1	1	0.52	0	0	0.00
POLYP COLON	4	4	2.09	2	3	1.58
RECTAL CARCINOMA	1	1	0.52	0	0	0.00
SARCOMA	1	1	0.52	0	0	0.00
SKIN CARCINOMA	0	0	0.00	1	1	0.53
SKIN NEOPLASM MALIGNANT	0	0	0.00	1	1	0.53
TUMOR BENIGN NOS	0	0	0.00	1	2	1.06
OPERATIONS & PROCEDURES						
AMPUTATION LOWER LEG	0	0	0.00	1	1	0.53
ANGIOCARDIOGRAPHY	19	19	9.94	27	28	14.77
ANGIOGRAPHY CAROTIS	2	2	1.05	3	3	1.58
APPARATUS TECHNIQUE /SPEC.PROCEDURES	2	2	1.05	3	3	1.58
ARTERIOGRAPHY	1	1	0.52	0	0	0.00
ARTERY LIGATION	0	0	0.00	1	1	0.53
ARTHROPLASTY (HIP)	1	1	0.52	0	0	0.00
ARTHROPLASTY (KNEE)	0	0	0.00	1	1	0.53
ARTHROSCOPY KNEE	1	1	0.52	1	1	0.53
BRONCHOSCOPY	1	1	0.52	1	2	1.06
CARDIOVERSION, DEFIBRILATION	4	7	3.66	2	2	1.06

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
CATHETERIZATION OF HEART	3	3	1.57	1	1	0.53
CHOLECYSTECTOMY	0	0	0.00	2	2	1.06
CIRCUMCISION	1	1	0.52	0	0	0.00
COLONOSCOPY	7	8	4.18	0	0	0.00
CORR. SURGERY STOMA/ANUS PRAETER	0	0	0.00	1	1	0.53
COSMETIC SURGERY	0	0	0.00	1	1	0.53
CYSTOSTOMY	0	0	0.00	1	1	0.53
DIAGNOSTIC PREPARATION OF ANESTHESIA	0	0	0.00	2	2	1.06
EXCISION OF COLONIC POLYP	1	1	0.52	0	0	0.00
EXCISION SKIN, SUBCUTIS	2	2	1.05	1	1	0.53
EXPLORATORY THORACOTOMY	1	1	0.52	0	0	0.00
FASCIECTOMY	1	1	0.52	0	0	0.00
GASTROSCOPY	9	9	4.71	10	12	6.33
HEMICOLECTOMY	0	0	0.00	1	1	0.53
HEMICOLECTOMY LEFT SIDE	1	1	0.52	0	0	0.00
HEMORRHOIDECTOMY	1	1	0.52	1	1	0.53
HERNIA INGUINALIS REPAIR	1	1	0.52	1	1	0.53
HERNIA REPAIR	3	3	1.57	4	5	2.64
LARYNGOSCOPY	0	0	0.00	1	1	0.53
LOBECTOMY	0	0	0.00	1	1	0.53
MULTIPLE AC BYPASS	0	0	0.00	1	1	0.53
NASAL POLYPECTOMY	1	1	0.52	1	1	0.53
NEPHRECTOMY	1	1	0.52	0	0	0.00
O.SURGERY LOWER LEG SKIN, SUBCUTAN TISSUE	0	0	0.00	1	1	0.53
OP AORTA ANEURYSM	1	1	0.52	1	1	0.53
OTHER BONE SURGERY OF FOOT	1	1	0.52	0	0	0.00
OTHER OP HAND, SOFT TISSUE	0	0	0.00	1	1	0.53
OTHER SURGERY (EXTERNAL EAR)	1	1	0.52	1	2	1.06
OTHER SURGERY (EYEBALL)	2	2	1.05	4	4	2.11
OTHER SURGERY (HEART)	0	0	0.00	5	5	2.64
OTHER SURGERY (HUMERUS)	0	0	0.00	1	1	0.53
OTHER SURGERY (LACR.SAC,LACRIMAL DUCT)	1	1	0.52	0	0	0.00
OTHER SURGERY (MIDDLE EAR)	1	1	0.52	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
OTHER SURGERY (SKIN, SUBCUTIS)	2	2	1.05	0	0	0.00
OTHER SURGERY (VEINS)	1	1	0.52	0	0	0.00
OTHER SURGERY ARTERY	2	2	1.05	0	0	0.00
OTHER SURGERY ARTERY, PLASTY	14	15	7.85	14	15	7.91
OTHER SURGERY LENS	3	3	1.57	1	1	0.53
OTHER SURGERY LOWER LEG VEINS	1	1	0.52	1	1	0.53
OTHER SURGERY MAMMA	0	0	0.00	1	1	0.53
OTHER SURGERY ON EYELID	0	0	0.00	1	1	0.53
OTHER SURGERY ON RETINA	1	1	0.52	0	0	0.00
OTHER SURGERY PROSTATE	1	1	0.52	0	0	0.00
PARTIAL GASTRIC RESECTION	0	0	0.00	1	1	0.53
PROSTATAECTOMY	0	0	0.00	1	1	0.53
RECTOSIGMOIDOSCOPY	3	4	2.09	0	0	0.00
REVASCULARISATION OF MYOCARD	10	10	5.23	11	11	5.80
RHINOPLASTY	1	1	0.52	0	0	0.00
S.A. OTHER SURGERY LENS	1	1	0.52	0	0	0.00
S.A.OTHER SURGERY (EYEBALL)	1	1	0.52	0	0	0.00
SINGLE AC-BYPASS	0	0	0.00	2	2	1.06
SUBCUTANEOUS MASTECTOMY	0	0	0.00	1	1	0.53
SURGERY OF ANAL FISTULA	0	0	0.00	1	1	0.53
SURGERY ON SOFT PALATE	1	1	0.52	0	0	0.00
TECHNICAL MEASURES	1	1	0.52	1	1	0.53
THROMBENDARTERECTOMY	1	1	0.52	1	1	0.53
TOTAL ARTHROPLASTY WITH IMPLANT (KNEE)	3	3	1.57	1	1	0.53
TOTAL ARTHROPLASTY WITH IMPLANTAT (HIP)	2	2	1.05	2	2	1.06
TOTAL HYSTERECTOMY	0	0	0.00	1	1	0.53
TRANSURETHR. RESECT. OF PROSTATE	3	3	1.57	1	1	0.53
TRANSURETHRAL CYSTOSCOPY	6	7	3.66	5	7	3.69
TRANSURETHRAL SURGERY URINARY BLADDER	0	0	0.00	1	1	0.53
TRIPLE AC BYPASS	0	0	0.00	1	1	0.53
VAGINAL HYSTERECTOMY	0	0	0.00	1	1	0.53
VENOUS LIGATIONS	0	0	0.00	1	1	0.53
VESSEL REPLACEMENT OR BYPASS	3	3	1.57	4	4	2.11

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
PLATELET, BLEEDING&CLOTTING DISORDER						
CAROTID OCCLUSION	1	1	0.52	0	0	0.00
EMBOLISM PULMONARY	2	2	1.05	3	3	1.58
PSYCHIATRIC DISORDERS						
ALCOHOLISM	1	1	0.52	0	0	0.00
AMNESIA	1	1	0.52	0	0	0.00
ANXIETY	0	0	0.00	1	1	0.53
DEMENTIA	1	1	0.52	0	0	0.00
DEPRESSION	0	0	0.00	2	2	1.06
INTENTIONAL OVERDOSE	1	1	0.52	1	1	0.53
PACING	1	1	0.52	1	1	0.53
RED BLOOD CELL DISORDERS						
ANEMIA	3	3	1.57	1	5	2.64
ANEMIA GI BLEEDING	0	0	0.00	1	1	0.53
ANEMIA IRON DEFICIENCY	1	1	0.52	2	4	2.11
REPRODUCTIVE DISORDES,FEMALE						
BLEEDING POSTMENOPAUSAL	1	1	0.52	3	3	1.58
UTERINE HEMORRHAGE	0	0	0.00	1	1	0.53
REPRODUCTIVE DISORDES,MALE						
ERECTILE IMPOTENCE	0	0	0.00	1	1	0.53
ORCHITIS	0	0	0.00	1	1	0.53
PAIN TESTICULAR	1	1	0.52	0	0	0.00
PROSTATE ENLARGED	8	9	4.71	0	0	0.00
PROSTATIC DISORDER	0	0	0.00	2	2	1.06
PROSTATISM AGGRAVATED	1	1	0.52	0	0	0.00
RESISTANCE MECHANISM DISORDERS						
ABSCESS ANAL	0	0	0.00	1	1	0.53

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
HERPES	1	1	0.52	0	0	0.00
INFECTION	1	1	0.52	0	0	0.00
INFECTION BACTERIAL	1	1	0.52	0	0	0.00
INFECTION VIRAL	1	1	0.52	0	0	0.00
SEPSIS	1	1	0.52	0	0	0.00
SEPTICEMIA	0	0	0.00	1	1	0.53
WOUND INFECTION	1	1	0.52	1	1	0.53
RESPIRATORY SYSTEM DISORDERS						
APNEA	1	1	0.52	0	0	0.00
ASTHMA	0	0	0.00	2	2	1.06
ASTHMA AGGRAVATED	1	1	0.52	0	0	0.00
BREATHLESSNESS	2	2	1.05	0	0	0.00
BRONCHITIS	0	0	0.00	1	1	0.53
BRONCHOPNEUMONIA	1	1	0.52	0	0	0.00
CHRONIC OBSTR. PULM. DISEASE	3	3	1.57	2	2	1.06
COPD	1	1	0.52	0	0	0.00
DYSPNEA	0	0	0.00	2	2	1.06
DYSPNEA EXERTIONAL	1	1	0.52	0	0	0.00
EDEMA PULMONARY	1	1	0.52	1	1	0.53
HEMOPTYSIS	1	1	0.52	1	2	1.06
INFECTION CHEST	6	6	3.14	6	8	4.22
NASAL POLYP	1	1	0.52	0	0	0.00
NOSEBLEED	1	1	0.52	0	0	0.00
PLEURAL EFFUSION	0	0	0.00	1	1	0.53
PLEURISY	1	1	0.52	0	0	0.00
PNEUMONIA	3	3	1.57	4	4	2.11
PNEUMONIA LOBAR	0	0	0.00	1	1	0.53
PULMONARY COMPLICATIONS	0	0	0.00	1	1	0.53
RESPIRATORY DISORDER	0	0	0.00	1	1	0.53
SHORTNESS OF BREATH	2	2	1.05	1	1	0.53
SINUSITIS MAXILLARY	1	1	0.52	0	0	0.00
SKIN AND APPENDAGES DISORDERS						
ECZEMA	1	1	0.52	1	1	0.53

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System		Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
	ERYSIPELAS	1	1	0.52	0	0	0.00
	HYPERKERATOTIC LESION	0	0	0.00	1	1	0.53
	INGROWN TOENAIL	0	0	0.00	1	1	0.53
	KERATOLYSIS	0	0	0.00	1	1	0.53
	KERATOSIS	1	1	0.52	0	0	0.00
	NAIL DISORDER	0	0	0.00	1	1	0.53
	SKIN DEFECTS SUPERFICIAL	0	0	0.00	1	1	0.53
	SKIN DISORDER	0	0	0.00	2	2	1.06
	SKIN LESION PAPULAR	1	1	0.52	0	0	0.00
	ULCER FOOT	1	1	0.52	0	0	0.00
	ULCER LEG	1	1	0.52	1	1	0.53
UNKNOWN							
	UNKNOWN	2	2	1.05	2	2	1.06
URINARY SYSTEM DISORDERS							
	BLADDER CALCULUS	0	0	0.00	1	1	0.53
	BLADDER DISORDER	2	2	1.05	0	0	0.00
	BLADDER DYSFUNCTION	1	1	0.52	0	0	0.00
	BLADDER INABILITY TO EMPTY	0	0	0.00	1	1	0.53
	BLADDER IRRITATION	1	1	0.52	0	0	0.00
	DYSURIA	0	0	0.00	1	1	0.53
	FLANK PAIN	1	1	0.52	0	0	0.00
	GLOMERULONEPHRITIS	1	1	0.52	0	0	0.00
	HEMATURIA	1	1	0.52	3	3	1.58
	HEMATURIA MICROSCOPIC	0	0	0.00	1	1	0.53
	HYDRONEPHROSIS	1	2	1.05	0	0	0.00
	INFECTION URINARY BLADDER	1	1	0.52	0	0	0.00
	KIDNEY DYSFUNCTION	1	1	0.52	0	0	0.00
	MICTURITION FREQUENCY	0	0	0.00	2	2	1.06
	NOCTURIA	1	1	0.52	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil subjects	events	rate*	Placebo subjects	events	rate*
PYELONEPHRITIS	1	1	0.52	0	0	0.00
RENAL CALCULUS	1	1	0.52	0	0	0.00
RENAL COLIC	1	1	0.52	1	1	0.53
RENAL FAILURE CHRONIC	1	1	0.52	0	0	0.00
URETERAL DISORDER	1	1	0.52	0	0	0.00
URETHRAL DISORDER	1	1	0.52	1	1	0.53
URETHRAL OBSTRUCTION	1	1	0.52	1	1	0.53
URINARY RETENTION	4	4	2.09	3	4	2.11
URINARY TRACT INFECTION	2	2	1.05	0	0	0.00
VASCULAR (EXTRACARDIAC) DISORDERS						
ANEURYSM RUPTURE	2	2	1.05	0	0	0.00
ARTERIOSCLEROSIS	1	1	0.52	0	0	0.00
ARTERY DISEASE PERIPHERAL	1	1	0.52	0	0	0.00
CARDIOVASCULAR ACCIDENT	1	1	0.52	2	2	1.06
CEREBRAL INFARCTION	2	2	1.05	2	2	1.06
CEREBRAL VASCULAR DISTURBANCE	1	1	0.52	1	1	0.53
CEREBROVASCULAR ATTACK	5	5	2.62	2	2	1.06
CLAUDICATION INTERMITTENT	1	1	0.52	0	0	0.00
CVA	5	5	2.62	6	6	3.17
INTESTINAL INFARCTION	1	1	0.52	0	0	0.00
ISCHEMIC ATTACKS TRANSIENT	1	1	0.52	7	7	3.69
PERIPHERAL VASCULAR DISEASE	2	2	1.05	2	2	1.06
STENOSIS ARTERIAL	3	3	1.57	1	1	0.53
STROKE	4	4	2.09	3	3	1.58
THROMBOSIS ARTERIAL	0	0	0.00	1	1	0.53
THROMBOSIS VENOUS DEEP	3	3	1.57	6	8	4.22
VENOUS STENOSIS	1	1	0.52	0	0	0.00
VISION DISORDERS						
BLEPHAROPHIMOSIS	1	1	0.52	0	0	0.00
CATARACT	8	8	4.18	6	6	3.17
CENTRAL RETINAL VEIN OCCLUSION	1	1	0.52	0	0	0.00

* rate = number of events per thousand person-years of follow-up

continued...Table 53 Serious Adverse Events by Decoded Terms, Grouped by Body System: for Subjects Not Taking Long Acting Nitrates at Baseline

Body System	Nicorandil			Placebo		
	subjects	events	rate*	subjects	events	rate*
EDEMA MACULAR	1	1	0.52	0	0	0.00
EPIPHORA	1	1	0.52	0	0	0.00
GLAUCOMA	1	1	0.52	0	0	0.00
PTERYGIUM	1	1	0.52	0	0	0.00
RETINAL ARTERY OCCLUSION	1	1	0.52	0	0	0.00
WHITE BLOOD CELL AND RES DISORDERS						
EOSINOPHILIA	0	0	0.00	1	1	0.53

* rate = number of events per thousand person-years of follow-up

Table 54 Selected Drug Types - Visit 4

	Nicorandil (n=2498)	Placebo (n=2498)
Beta Blockers	1406 (56%)	1369 (55%)
ACE-Inhibitors	731 (29%)	770 (31%)
AII Receptor Antagonists	73 (3%)	82 (3%)
Diuretics	787 (32%)	766 (31%)
Calcium Channel Blockers	1357 (54%)	1357 (54%)
Nitrates: Long Acting	1324 (53%)	1311 (52%)
Nitrates: Short Acting	1781 (71%)	1795 (72%)
Aspirin / Antiplatelets	2196 (88%)	2159 (86%)
Anti-Coagulants	114 (5%)	126 (5%)
Other Antihypertensives	8 (0%)	6 (0%)
Other Anti-arrhythmic	131 (5%)	111 (4%)
Anti-Diabetic: Insulin	72 (3%)	90 (4%)
Anti-Diabetic: Oral Hypoglycaemics	64 (3%)	68 (3%)
Cholesterol Modifiers: Statins	1475 (59%)	1513 (61%)
Cholesterol Modifiers: Others	59 (2%)	61 (2%)

Table 55 Selected Drug Types - Visit 5

	Nicorandil (n=2431)	Placebo (n=2435)
Beta Blockers	1357 (56%)	1326 (54%)
ACE-Inhibitors	726 (30%)	759 (31%)
AII Receptor Antagonists	71 (3%)	83 (3%)
Diuretics	790 (32%)	765 (31%)
Calcium Channel Blockers	1292 (53%)	1322 (54%)
Nitrates: Long Acting	1274 (52%)	1270 (52%)
Nitrates: Short Acting	1705 (70%)	1712 (70%)
Aspirin / Antiplatelets	2140 (88%)	2095 (86%)
Anti-Coagulants	108 (4%)	126 (5%)
Other Antihypertensives	8 (0%)	7 (0%)
Other Anti-arrhythmic	130 (5%)	113 (5%)
Anti-Diabetic: Insulin	63 (3%)	88 (4%)
Anti-Diabetic: Oral Hypoglycaemics	73 (3%)	74 (3%)
Cholesterol Modifiers: Statins	1482 (61%)	1507 (62%)
Cholesterol Modifiers: Others	56 (2%)	62 (3%)

Table 56 Selected Drug Types - Visit 6

	Nicorandil (n=1700)	Placebo (n=1703)
Beta Blockers	933 (55%)	914 (54%)
ACE-Inhibitors	517 (30%)	541 (32%)
AII Receptor Antagonists	52 (3%)	57 (3%)
Diuretics	561 (33%)	557 (33%)
Calcium Channel Blockers	931 (55%)	941 (55%)
Nitrates: Long Acting	935 (55%)	932 (55%)
Nitrates: Short Acting	1234 (73%)	1240 (73%)
Aspirin / Antiplatelets	1499 (88%)	1456 (85%)
Anti-Coagulants	77 (5%)	95 (6%)
Other Antihypertensives	8 (0%)	6 (0%)
Other Anti-arrhythmic	93 (5%)	85 (5%)
Anti-Diabetic: Insulin	40 (2%)	63 (4%)
Anti-Diabetic: Oral Hypoglycaemics	67 (4%)	57 (3%)
Cholesterol Modifiers: Statins	1050 (62%)	1029 (60%)
Cholesterol Modifiers: Others	36 (2%)	38 (2%)

Table 57 Selected Drug Types - Visit 7

	Nicorandil (n=1275)	Placebo (n=1255)
Beta Blockers	710 (56%)	680 (54%)
ACE-Inhibitors	380 (30%)	399 (32%)
AII Receptor Antagonists	39 (3%)	42 (3%)
Diuretics	415 (33%)	399 (32%)
Calcium Channel Blockers	705 (55%)	721 (57%)
Nitrates: Long Acting	694 (54%)	691 (55%)
Nitrates: Short Acting	933 (73%)	910 (73%)
Aspirin / Antiplatelets	1139 (89%)	1084 (86%)
Anti-Coagulants	54 (4%)	75 (6%)
Other Antihypertensives	6 (0%)	4 (0%)
Other Anti-arrhythmic	59 (5%)	58 (5%)
Anti-Diabetic: Insulin	27 (2%)	44 (4%)
Anti-Diabetic: Oral Hypoglycaemics	55 (4%)	46 (4%)
Cholesterol Modifiers: Statins	796 (62%)	763 (61%)
Cholesterol Modifiers: Others	25 (2%)	32 (3%)

Table 58 Selected Drug Types - Visit 8

	Nicorandil (n= 829)	Placebo (n= 815)
Beta Blockers	455 (55%)	439 (54%)
ACE-Inhibitors	224 (27%)	260 (32%)
AII Receptor Antagonists	28 (3%)	29 (4%)
Diuretics	274 (33%)	269 (33%)
Calcium Channel Blockers	464 (56%)	494 (61%)
Nitrates: Long Acting	453 (55%)	450 (55%)
Nitrates: Short Acting	614 (74%)	613 (75%)
Aspirin / Antiplatelets	753 (91%)	707 (87%)
Anti-Coagulants	34 (4%)	61 (7%)
Other Antihypertensives	5 (1%)	3 (0%)
Other Anti-arrhythmic	37 (4%)	42 (5%)
Anti-Diabetic: Insulin	16 (2%)	26 (3%)
Anti-Diabetic: Oral Hypoglycaemics	36 (4%)	40 (5%)
Cholesterol Modifiers: Statins	514 (62%)	506 (62%)
Cholesterol Modifiers: Others	20 (2%)	14 (2%)

Table 59 Selected Drug Types - Visit 9

	Nicorandil (n= 421)	Placebo (n= 414)
Beta Blockers	236 (56%)	218 (53%)
ACE-Inhibitors	123 (29%)	138 (33%)
AII Receptor Antagonists	14 (3%)	16 (4%)
Diuretics	149 (35%)	152 (37%)
Calcium Channel Blockers	246 (58%)	251 (61%)
Nitrates: Long Acting	228 (54%)	248 (60%)
Nitrates: Short Acting	305 (72%)	343 (83%)
Aspirin / Antiplatelets	372 (88%)	361 (87%)
Anti-Coagulants	21 (5%)	26 (6%)
Other Antihypertensives	3 (1%)	3 (1%)
Other Anti-arrhythmic	25 (6%)	21 (5%)
Anti-Diabetic: Insulin	7 (2%)	9 (2%)
Anti-Diabetic: Oral Hypoglycaemics	20 (5%)	19 (5%)
Cholesterol Modifiers: Statins	270 (64%)	269 (65%)
Cholesterol Modifiers: Others	7 (2%)	7 (2%)

Table 60 Selected Drug Types - Visit 10

	Nicorandil (n= 111)	Placebo (n= 112)
Beta Blockers	56 (50%)	54 (48%)
ACE-Inhibitors	35 (32%)	35 (31%)
AII Receptor Antagonists	5 (5%)	6 (5%)
Diuretics	40 (36%)	44 (39%)
Calcium Channel Blockers	65 (59%)	72 (64%)
Nitrates: Long Acting	60 (54%)	70 (63%)
Nitrates: Short Acting	84 (76%)	88 (79%)
Aspirin / Antiplatelets	92 (83%)	100 (89%)
Anti-Coagulants	6 (5%)	7 (6%)
Other Antihypertensives	0 (0%)	0 (0%)
Other Anti-arrhythmic	7 (6%)	6 (5%)
Anti-Diabetic: Insulin	3 (3%)	2 (2%)
Anti-Diabetic: Oral Hypoglycaemics	8 (7%)	5 (4%)
Cholesterol Modifiers: Statins	73 (66%)	70 (63%)
Cholesterol Modifiers: Others	2 (2%)	1 (1%)

Table 61 Selected Drug Types - Visit 11

	Nicorandil (n= 7)	Placebo (n= 7)
Beta Blockers	3 (43%)	3 (43%)
ACE-Inhibitors	2 (29%)	5 (71%)
AII Receptor Antagonists	0 (0%)	1 (14%)
Diuretics	2 (29%)	4 (57%)
Calcium Channel Blockers	5 (71%)	3 (43%)
Nitrates: Long Acting	6 (86%)	2 (29%)
Nitrates: Short Acting	4 (57%)	6 (86%)
Aspirin / Antiplatelets	6 (86%)	5 (71%)
Anti-Coagulants	0 (0%)	2 (29%)
Other Antihypertensives	0 (0%)	0 (0%)
Other Anti-arrhythmic	0 (0%)	0 (0%)
Anti-Diabetic: Insulin	1 (14%)	0 (0%)
Anti-Diabetic: Oral Hypoglycaemics	1 (14%)	0 (0%)
Cholesterol Modifiers: Statins	6 (86%)	6 (86%)
Cholesterol Modifiers: Others	0 (0%)	0 (0%)

Table 62 Selected Drug Types - Visit 12

	Nicorandil (n=2461)	Placebo (n=2447)
Beta Blockers	1326 (54%)	1292 (53%)
ACE-Inhibitors	782 (32%)	793 (32%)
AII Receptor Antagonists	89 (4%)	97 (4%)
Diuretics	810 (33%)	777 (32%)
Calcium Channel Blockers	1246 (51%)	1283 (52%)
Nitrates: Long Acting	1219 (50%)	1212 (50%)
Nitrates: Short Acting	1633 (66%)	1640 (67%)
Aspirin / Antiplatelets	2104 (85%)	2064 (84%)
Anti-Coagulants	124 (5%)	150 (6%)
Other Antihypertensives	8 (0%)	8 (0%)
Other Anti-arrhythmic	134 (5%)	110 (4%)
Anti-Diabetic: Insulin	66 (3%)	85 (3%)
Anti-Diabetic: Oral Hypoglycaemics	112 (5%)	102 (4%)
Cholesterol Modifiers: Statins	1557 (63%)	1570 (64%)
Cholesterol Modifiers: Others	45 (2%)	53 (2%)

Table 63 Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	127	1: CHD - sudden	
	Placebo	315	2: Stroke	
	Nicorandil	754	6: Non-cardiovascular	SEPTICEMIA (RESISTANCE MECHANISM DISORDERS)
	Placebo	50	1: CHD - sudden	
	Placebo	26	1: CHD - sudden	
	Nicorandil	353	1: CHD - sudden	
	Placebo	806	2: Stroke	
	Nicorandil	512	1: CHD - sudden	
	Placebo	196	6: Non-cardiovascular	KIDNEY FAILURE (URINARY SYSTEM DISORDERS)
	Placebo	721	1: CHD - sudden	
	Placebo	901	6: Non-cardiovascular	PANCREAS CARCINOMA (NEOPLASM)
	Placebo	58	1: CHD - MI	
	Nicorandil	5	1: CHD - sudden	
	Placebo	785	6: Non-cardiovascular	CARCINOMA BRONCHUS (NEOPLASM)
	Placebo	461	6: Non-cardiovascular	ESOPHAGEAL CARCINOMA (NEOPLASM)
	Placebo	130	1: CHD - sudden	
	Placebo	61	1: CHD - sudden	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	490	1: CHD - heart failure	
	Placebo	438	1: CHD - sudden	
	Placebo	596	6: Non-cardiovascular	INTESTINAL PERFORATION (GASTRO- INTESTINAL SYSTEM DISORDERS)
	Nicorandil	375	6: Non-cardiovascular	PULMONARY CARCINOMA (NEOPLASM)
	Nicorandil	484	6: Non-cardiovascular	CANCER LUNG SQUAMOUS CELL (NEOPLASM)
	Placebo	240	6: Non-cardiovascular	NEOPLASM PULMONARY MALIGNANT (NEOPLASM)
	Nicorandil	80	6: Non-cardiovascular	NEOPLASM PULMONARY MALIGNANT (NEOPLASM)
	Placebo	264	6: Non-cardiovascular	PANCREAS CARCINOMA (NEOPLASM)
	Placebo	213	1: CHD - sudden	
	Nicorandil	377	1: CHD - heart failure	
	Nicorandil	48	5: Presumed cardiovascular	
	Placebo	635	3: Cardiovascular procedure	
	Nicorandil	17	1: CHD - sudden	
	Nicorandil	28	1: CHD - sudden	
	Placebo	32	1: CHD - sudden	
	Placebo	440	1: CHD - MI	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	706	1: CHD - sudden	
	Nicorandil	545	6: Non-cardiovascular	SPINAL CHORD DISORDER (CENTR & PERIPH NERV SYST. DISORDERS)
	Placebo	33	1: CHD - sudden	
	Placebo	925	2: Stroke	
	Nicorandil	386	1: CHD - sudden	
	Nicorandil	265	5: Presumed cardiovascular	
	Placebo	116	1: CHD - sudden	
	Nicorandil	329	6: Non-cardiovascular	CARCINOMA BRONCHUS (NEOPLASM)
	Nicorandil	457	2: Stroke	
	Placebo	650	1: CHD - sudden	
	Nicorandil	60	1: CHD - MI	
	Placebo	219	1: CHD - heart failure	
	Nicorandil	616	1: CHD - cardiac procedure	
	Nicorandil	458	1: CHD - cardiac procedure	
	Nicorandil	869	1: CHD - sudden	
	Placebo	157	6: Non-cardiovascular	ESOPHAGEAL CARCINOMA (NEOPLASM)
	Nicorandil	373	4: Other cardiovascular	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	212	1: CHD - MI	
	Nicorandil	221	1: CHD - sudden	
	Nicorandil	533	1: CHD - sudden	
	Placebo	829	1: CHD - MI	
	Placebo	194	1: CHD - heart failure	
	Nicorandil	418	1: CHD - sudden	
	Placebo	588	1: CHD - heart failure	
	Placebo	754	6: Non-cardiovascular	CARCINOMA OF ESOPHAGUS (NEOPLASM)
	Placebo	756	1: CHD - sudden	
	Nicorandil	61	1: CHD - MI	
	Placebo	345	2: Stroke	
	Nicorandil	7	1: CHD - heart failure	
	Nicorandil	762	2: Stroke	
	Placebo	22	6: Non-cardiovascular	PNEUMONIA (RESPIRATORY SYSTEM DISORDERS)
	Nicorandil	733	2: Stroke	
	Nicorandil	272	1: CHD - sudden	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	501	1: CHD - MI	
	Placebo	521	4: Other cardiovascular	
	Placebo	395	1: CHD - cardiac procedure	
	Placebo	217	1: CHD - sudden	
	Placebo	282	1: CHD - sudden	
	Placebo	168	1: CHD - heart failure	
	Placebo	469	1: CHD - sudden	
	Placebo	545	1: CHD - MI	
	Placebo	624	6: Non-cardiovascular	SEPTICEMIA (RESISTANCE MECHANISM DISORDERS)
	Nicorandil	601	5: Presumed cardiovascular	
	Nicorandil	701	1: CHD - heart failure	
	Placebo	243	6: Non-cardiovascular	RENAL CARCINOMA (NEOPLASM)
	Placebo	509	1: CHD - heart failure	
	Nicorandil	842	6: Non-cardiovascular	STOMACH CARCINOMA (NEOPLASM)
	Placebo	535	1: CHD - cardiac procedure	
	Nicorandil	336	1: CHD - heart failure	
	Placebo	628	6: Non-cardiovascular	RENAL CARCINOMA (NEOPLASM)

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	658	1: CHD - sudden	
	Nicorandil	132	1: CHD - sudden	
	Nicorandil	440	6: Non-cardiovascular	CIRRHOSIS (LIVER AND BILIARY SYSTEM DISORDERS)
	Placebo	432	1: CHD - MI	
	Placebo	618	5: Presumed cardiovascular	
	Placebo	532	1: CHD - sudden	
	Nicorandil	528	1: CHD - sudden	
	Placebo	75	1: CHD - sudden	
	Placebo	196	2: Stroke	
	Placebo	368	1: CHD - MI	
	Nicorandil	509	1: CHD - sudden	
	Placebo	602	6: Non-cardiovascular	GLIOBLASTOMA MULTIFORME (NEOPLASM)
	Placebo	611	1: CHD - MI	
	Placebo	649	6: Non-cardiovascular	MESOTHELIOMA (NEOPLASM)
	Placebo	74	1: CHD - sudden	
	Placebo	353	6: Non-cardiovascular	BRONCHOPNEUMONIA (RESPIRATORY SYSTEM DISORDERS)

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Placebo	270	1: CHD - cardiac procedure	
	Placebo	54	1: CHD - sudden	
	Placebo	536	6: Non-cardiovascular	CARCINOMA BILE DUCT (NEOPLASM)
	Nicorandil	282	6: Non-cardiovascular	SEPTICEMIA (RESISTANCE MECHANISM DISORDERS)
	Placebo	643	6: Non-cardiovascular	CARCINOMA OF ESOPHAGUS (NEOPLASM)
	Nicorandil	687	6: Non-cardiovascular	COLON CARCINOMA (NEOPLASM)
	Nicorandil	513	6: Non-cardiovascular	CARCINOMA PROSTATE (NEOPLASM)
	Nicorandil	83	2: Stroke	
	Placebo	8	1: CHD - sudden	
	Placebo	210	1: CHD - sudden	
	Nicorandil	185	3: Cardiovascular procedure	
	Nicorandil	289	1: CHD - cardiac procedure	
	Placebo	582	5: Presumed cardiovascular	
	Nicorandil	279	1: CHD - sudden	
	Placebo	748	6: Non-cardiovascular	INTESTINAL ISCHEMIA (VASCULAR (EXTRACARDIAC) DISORDERS)
	Nicorandil	198	1: CHD - sudden	
	Nicorandil	210	1: CHD - sudden	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	848	6: Non-cardiovascular	ISCHEMIA (VASCULAR (EXTRACARDIAC) DISORDERS)
	Placebo	215	1: CHD - sudden	
	Placebo	58	1: CHD - sudden	
	Placebo	191	6: Non-cardiovascular	RESPIRATORY FAILURE (RESPIRATORY SYSTEM DISORDERS)
	Placebo	170	5: Presumed cardiovascular	
	Placebo	164	4: Other cardiovascular	
	Placebo	402	4: Other cardiovascular	
	Nicorandil	621	6: Non-cardiovascular	CHRONIC OBSTR. PULM. DISEASE (RESPIRATORY SYSTEM DISORDERS)
	Nicorandil	517	4: Other cardiovascular	
	Placebo	242	6: Non-cardiovascular	NEOPLASM PULMONARY MALIGNANT (NEOPLASM)
	Nicorandil	65	1: CHD - sudden	
	Nicorandil	11	1: CHD - sudden	
	Nicorandil	189	2: Stroke	
	Placebo	112	2: Stroke	
	Nicorandil	217	6: Non-cardiovascular	INTESTINAL OBSTRUCTION (GASTRO- INTESTINAL SYSTEM DISORDERS)
	Nicorandil	230	4: Other cardiovascular	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	239	1: CHD - MI	
	Placebo	461	1: CHD - MI	
	Placebo	6	1: CHD - sudden	
	Nicorandil	82	1: CHD - sudden	
	Nicorandil	288	6: Non-cardiovascular	PULMONARY CARCINOMA (NEOPLASM)
	Placebo	458	6: Non-cardiovascular	STOMACH CARCINOMA (NEOPLASM)
	Nicorandil	164	6: Non-cardiovascular	BLEEDING ULCER (GASTRO- INTESTINAL SYSTEM DISORDERS)
	Placebo	356	6: Non-cardiovascular	NEOPLASM PULMONARY MALIGNANT (NEOPLASM)
	Nicorandil	227	1: CHD - heart failure	
	Placebo	217	2: Stroke	
	Nicorandil	326	1: CHD - sudden	
	Nicorandil	465	3: Cardiovascular procedure	
	Nicorandil	426	4: Other cardiovascular	
	Nicorandil	309	6: Non-cardiovascular	SEPTICEMIA (RESISTANCE MECHANISM DISORDERS)
	Nicorandil	784	5: Presumed cardiovascular	
	Nicorandil	554	1: CHD - MI	
	Nicorandil	94	1: CHD - sudden	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Placebo	205	5: Presumed cardiovascular	
	Nicorandil	466	1: CHD - heart failure	
	Nicorandil	155	6: Non-cardiovascular	PNEUMONIA (RESPIRATORY SYSTEM DISORDERS)
	Nicorandil	601	1: CHD - cardiac procedure	
	Nicorandil	173	1: CHD - sudden	
	Nicorandil	524	1: CHD - heart failure	
	Placebo	570	1: CHD - MI	
	Placebo	609	1: CHD - sudden	
	Nicorandil	652	6: Non-cardiovascular	NEOPLASM PULMONARY MALIGNANT (NEOPLASM)
	Placebo	259	1: CHD - cardiac procedure	
	Placebo	204	5: Presumed cardiovascular	
	Nicorandil	119	5: Presumed cardiovascular	
	Placebo	400	1: CHD - sudden	
	Nicorandil	560	6: Non-cardiovascular	CARCINOMA PROSTATE (NEOPLASM)
	Nicorandil	29	1: CHD - MI	
	Placebo	478	5: Presumed cardiovascular	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Placebo	9	1: CHD - sudden	
	Placebo	198	1: CHD - sudden	
	Placebo	103	1: CHD - sudden	
	Placebo	432	2: Stroke	
	Placebo	72	1: CHD - sudden	
	Placebo	92	1: CHD - sudden	
	Placebo	471	6: Non-cardiovascular	CARCINOMA COLON (NEOPLASM)
	Placebo	437	1: CHD - sudden	
	Nicorandil	352	6: Non-cardiovascular	CARCINOMA PROSTATE (NEOPLASM)
	Placebo	484	1: CHD - heart failure	
	Placebo	215	1: CHD - sudden	
	Placebo	119	1: CHD - MI	
	Nicorandil	561	1: CHD - heart failure	
	Nicorandil	642	6: Non-cardiovascular	PERITONITIS (GASTRO- INTESTINAL SYSTEM DISORDERS)
	Nicorandil	508	1: CHD - sudden	
	Placebo	355	6: Non-cardiovascular	CARCINOMA RECTAL SQUAMOUS CELL (NEOPLASM)
	Nicorandil	143	4: Other cardiovascular	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Placebo	479	6: Non-cardiovascular	CARCINOMA BRONCHUS (NEOPLASM)
	Placebo	441	1: CHD - heart failure	
	Placebo	107	5: Presumed cardiovascular	
	Placebo	339	1: CHD - sudden	
	Placebo	149	1: CHD - MI	
	Nicorandil	372	1: CHD - sudden	
	Placebo	229	1: CHD - cardiac procedure	
	Placebo	474	6: Non-cardiovascular	RENAL CARCINOMA (NEOPLASM)
	Placebo	126	1: CHD - MI	
	Placebo	269	5: Presumed cardiovascular	
	Nicorandil	330	6: Non-cardiovascular	CARCINOMA COLON (NEOPLASM)
	Nicorandil	157	1: CHD - sudden	
	Placebo	530	1: CHD - sudden	
	Placebo	70	1: CHD - sudden	
	Nicorandil	106	6: Non-cardiovascular	RENAL FAILURE ACUTE (URINARY SYSTEM DISORDERS)
	Placebo	93	1: CHD - sudden	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Nicorandil	67	3: Cardiovascular procedure	
	Nicorandil	181	1: CHD - MI	
	Nicorandil	346	6: Non-cardiovascular	CARCINOMA HEPATOCELLULAR (NEOPLASM)
	Placebo	282	1: CHD - sudden	
	Placebo	293	2: Stroke	
	Nicorandil	320	4: Other cardiovascular	
	Nicorandil	130	1: CHD - MI	
	Nicorandil	226	1: CHD - sudden	
	Placebo	36	1: CHD - sudden	
	Nicorandil	383	6: Non-cardiovascular	SEPTICEMIA (RESISTANCE MECHANISM DISORDERS)
	Placebo	10	1: CHD - sudden	
	Nicorandil	451	1: CHD - heart failure	
	Placebo	352	6: Non-cardiovascular	PULMONARY CARCINOMA (NEOPLASM)
	Placebo	361	6: Non-cardiovascular	PULMONARY CARCINOMA (NEOPLASM)
	Placebo	187	5: Presumed cardiovascular	
	Nicorandil	118	1: CHD - MI	
	Placebo	329	2: Stroke	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Placebo	150	6: Non-cardiovascular	DEATH (BODY AS A WHOLE - GENERAL DISORDERS)
	Placebo	48	1: CHD - heart failure	
	Nicorandil	181	1: CHD - heart failure	
	Nicorandil	283	1: CHD - sudden	
	Placebo	188	1: CHD - MI	
	Nicorandil	293	1: CHD - heart failure	
	Placebo	280	5: Presumed cardiovascular	
	Nicorandil	20	1: CHD - MI	
	Placebo	164	1: CHD - MI	
	Placebo	104	1: CHD - MI	
	Nicorandil	198	6: Non-cardiovascular	AMYLOIDOSIS (METABOLIC AND NUTRITIONAL DISORDERS)
	Nicorandil	269	6: Non-cardiovascular	METASTASES GROWTH (NEOPLASM)
	Placebo	349	6: Non-cardiovascular	RECTAL CARCINOMA (NEOPLASM)
	Placebo	30	1: CHD - heart failure	
	Nicorandil	184	1: CHD - sudden	
	Placebo	19	1: CHD - MI	

IONA - 19NOV02

Listing of Deaths (Non-Cardiovascular Deaths have Decodes)

Patient	Treatment	Days of Follow-up	Category	Details for Non-Cardiovascular Deaths
[redacted]	Placebo	432	4: Other cardiovascular	
	Placebo	222	1: CHD - sudden	
	Nicorandil	330	6: Non-cardiovascular	DUODENAL ULCER PERFORATED (GASTRO- INTESTINAL SYSTEM DISORDERS)
	Nicorandil	175	1: CHD - sudden	
	Nicorandil	258	6: Non-cardiovascular	CARCINOMA OVARY (NEOPLASM)
	Nicorandil	188	6: Non-cardiovascular	CARCINOMA TONGUE (NEOPLASM)
	Placebo	363	1: CHD - sudden	
	Nicorandil	351	4: Other cardiovascular	
	Placebo	134	1: CHD - sudden	

Table 64 – SAE - statistical significance testing

DECBODY=APPLICATION SITE DISORDERS

DECODE	PVALUE	FLAG
ALLERGY CONTACT	1.000	
APPLICATION SITE DAMAGE	0.500	
CELLULITIS	1.000	
FASCIITIS NECROTIZING	0.500	
FISTULA WITH INFECTION	1.000	
IMPLANTATION COMPLICATION	0.500	
INFLAMMATION LOCALIZED	0.500	

DECBODY=BODY AS A WHOLE - GENERAL DISORDERS

DECODE	PVALUE	FLAG
ALLERGIC REACTION	0.625	
ANAPHYLACTIC SHOCK	1.000	
BURNS	1.000	
CHEST DISCOMFORT	1.000	
CHEST TIGHTNESS OF	1.000	
CRYOGLOBULINEMIA	0.500	
DEATH	0.606	
DEATH FROM PROGRESSIVE DISEASE	1.000	
DRUG INTERACTION	1.000	
EDEMA	0.500	
FOOD POISONING	1.000	
GRANULOMA SALIVARYGLAND	1.000	
GRANULOMATOUS LESION	1.000	
HYPERTROPHY	0.500	
INFARCT	0.500	
OCCLUSION	0.016	* placebo > nicorandil
OTHER GENERAL SYMPTOMS	1.000	
OVERDOSE EFFECT	0.500	
PAIN	1.000	
SIDE EFFECTS NOS	0.625	
SUDDEN DEATH	0.500	

SWELLING ARMS	1.000	
SWELLING LEG	0.625	
SWELLING TISSUE	0.500	
WEAKNESS POSTURAL	0.500	
WEIGHT DECREASE	0.125	

---------- DECBODY=CARDIOVASCULAR DISORDERS, GENERAL ----------

DECODE	PVALUE	FLAG
ANEURYSM	0.179	
ANGINA EXERCISE INDUCED	0.625	
BLACK-OUT (NOT AMNESIA)	0.625	
CARDIAC DYSFUNCTION	0.374	
CARDIAC FAILURE	0.017	* placebo > nicorandil
CARDIAC FAILURE LEFT	1.000	
CARDIOVASCULAR COLLAPSE	0.625	
CIRCULATORY DISORDERS	1.000	
COLLAPSE CIRCULATORY	1.000	
COLLAPSE TRANSIENT	0.301	
CONGESTIVE HEART FAILURE	0.719	
COR PULMONALE	0.500	
CORONARY ATHEROSCLEROSIS	0.039	* placebo > nicorandil
ECG ABNORMAL	0.625	
ELECTROCARDIOGRAM ABNORMAL NON-SP	0.500	
FAINTNESS	1.000	
HEART DAMAGE	0.500	
HEART DISEASE	0.084	
HEART DISORDER	0.500	
HEART FAILURE ANEMIC	0.500	
HYPERTENSION	0.500	
HYPERTENSION ESSENTIAL	0.500	
HYPOTENSION	1.000	
HYPOTENSION ORTHOSTATIC	1.000	
HYPOTENSION POSTURAL	0.500	
LEFT VENTRICULAR FAILURE	0.550	
PRE-SYNCOPE	0.250	
SHOCK CARDIOGENIC	0.250	
SHOCK SEPTICEMIC	1.000	

SYNCOPE	0.803
SYNCOPE VAGOVAGAL	1.000
SYNCOPE VASOVAGAL	0.500
VASOVAGAL ATTACK	1.000
VENTRICULAR INSUFFICIENCY LEFT	0.500

---------- DECBODY=CENTR & PERIPH NERV SYST. DISORDERS ----------

DECODE	PVALUE	FLAG
BELL'S PALSY	0.500	
CEREBRAL ATROPHY	1.000	
CEREBRAL DISTURBANCES	0.500	
CEREBRAL HEMORRHAGE	1.000	
CEREBRAL PALSY	1.000	
CEREBRAL SYMPTOMS	0.500	
COMA	0.500	
DIZZINESS	1.000	
DIZZY ON STANDING	1.000	
EPILEPSY GRAND MAL	0.500	
EPILEPTIFORM FITS NOS	1.000	
EYELID PTOSIS	1.000	
FALLING	1.000	
GAIT UNSTEADY	1.000	
HEADACHE	0.581	
HEMORRHAGE INTRACRANIAL	0.500	
LETHARGY	1.000	
LIMB WEAKNESS	0.500	
MIGRAINE	0.500	
MUSCLE STIFFNESS	0.500	
MYASTHENIA GRAVIS	1.000	
MYELOPATHY	0.500	
NERVE DAMAGE	1.000	
NEURITIS	0.500	
NEUROLOGIC SYMPTOMS	0.250	
PARKINSON'S DISEASE	0.500	
POLYNEUROPATHY	1.000	
POLYNEUROPATHY DIABETIC	0.500	
POLYNEUROPATHY SENSORY	0.500	

PTOSIS	1.000
SCIATIC COMPLAINTS	1.000
SEIZURES CEREBRAL	1.000
SUBARACHNOID HEMORRHAGE	0.500
SUBDURAL HEMATOMA	0.500
UNCONSCIOUSNESS	0.500
VOCAL CORD DAMAGE	1.000

---------- DECBODY=ENDOCRINE DISORDERS ----------

DECODE	PVALUE	FLAG
THYROID DISORDER	1.000	
THYROTOXICOSIS	1.000	

---------- DECBODY=GASTRO- INTESTINAL SYSTEM DISORDERS ----------

DECODE	PVALUE	FLAG
ABDOMINAL DISCOMFORT	0.250	
ABDOMINAL PAIN	0.404	
ABDOMINAL PAIN LOWER	0.500	
ABDOMINAL PAIN UPPER	1.000	
ANAL SPHINCTER DISORDER	1.000	
APPENDICITIS	1.000	
BLEEDING ABDOMINAL	0.500	
BLEEDING ULCER	0.500	
BOWEL OBSTRUCTION	0.687	
BOWEL PERFORATION	0.500	
COFFEE GROUND VOMITING	1.000	
COLITIS	0.250	
COLITIS ISCHEMIC	0.500	
COLITIS PSEUDOMEMBRANOUS	1.000	
COLITIS ULCERATIVE	1.000	
COLITIS ULCERATIVE AGGRAVATED	1.000	
CONSTIPATION	1.000	
CROHN'S DISEASE	0.625	
DIARRHEA	0.548	
DISEASES OF ESOPHAGUS	1.000	

DIVERTICULAR DISEASE	0.039	* nicorandil > placebo
DIVERTICULITIS	0.289	
DIVERTICULOSIS	0.289	
DUODENAL ULCER	1.000	
DUODENITIS	0.500	
DYSPEPSIA	0.548	
DYSPHAGIA	0.625	
EPIGASTRIC PAIN NOT FOOD-RELATED	0.375	
ESOPHAGEAL PERFORATION	1.000	
ESOPHAGITIS	0.179	
ESOPHAGUS COMPLAINTS	0.250	
ESOPHAGUS MUCOSA DISTURBANCE	0.500	
FECAL FISTULA	0.500	
FECAL INCONTINENCE	1.000	
GASTRESOPHAGEAL REFLUX	1.000	
GASTRIC BLEEDING	1.000	
GASTRIC EROSION	0.500	
GASTRIC HEMORRHAGE	1.000	
GASTRIC INFLAMMATION	0.500	
GASTRIC OBSTRUCTION	1.000	
GASTRIC ULCER	0.507	
GASTRITIS	0.548	
GASTRITIS ANTRUM	0.062	
GASTRITIS EROSIVE	1.000	
GASTRITIS HEMORRHAGIC	0.500	
GASTRO-INTESTINAL DISORDER NOS	0.625	
GASTRODUODENITIS	0.500	
GASTROENTERITIS	1.000	
GASTROINTESTINAL DAMAGE	0.500	
GASTROINTESTINAL TRACT BLEED NOS	0.062	
GI HEMORRHAGE	0.218	
HEARTBURN	1.000	
HEMATEMESIS	0.375	
HEMATEMESIS GASTRIC ULCER	1.000	
HEMORRHOIDS	0.625	
HERNIA HIATUS	0.663	
INDIGESTION	0.500	
INFLAMMATION PYLORUS	1.000	
INTESTINAL OBSTRUCTION	0.625	
IRRITABLE BOWEL SYNDROME	0.625	

MALABSORPTION	0.500	
MELENA	1.000	
MOUTH ULCERATION	0.500	
ORAL ULCERATION	1.000	
PAIN STOMACH	0.500	
PANCREATITIS	1.000	
PANCREATITIS ACUTE	0.250	
PERITONITIS	1.000	
PROCTITIS	1.000	
PYLORIC STENOSIS	0.500	
RECTAL BLEEDING	0.013	* nicorandil > placebo
RECTAL DISORDER	1.000	
RECTAL PAIN	0.500	
REFLUX DUODENO-GASTRIC	0.500	
REFLUX ESOPHAGITIS	0.218	
SMALL INTESTINE OBSTRUCTION	0.500	
STOMACH ULCER	0.500	
TOOTH CARIES	0.500	
ULCER	1.000	
ULCER GINGIVA	1.000	
ULCER PALATE	1.000	
ULCER PYLORIC	1.000	

---------- DECBODY=HEARING AND VESTIBULAR DISORDERS ----------

DECODE	PVALUE	FLAG
EAR BLOCKAGE	1.000	
EAR DRUM PERFORATION	1.000	
EAR INFECTION	1.000	
EAR PAIN	0.500	
LABYRINTHINE DISORDER	1.000	
TINNITUS	0.500	
VERTIGO	0.500	

---------- DECBODY=HEART RATE AND RHYTHM DISORDERS ----------

DECODE	PVALUE	FLAG
ARRHYTHMIA	0.500	
ARRHYTHMIA VENTRICULAR	1.000	
ATRIAL FIBRILLATION PAROXYSMAL	0.507	
ATRIAL FLUTTER	1.000	
AV BLOCK SECOND DEGREE	1.000	
AV DISSOCIATION	0.500	
BRADYARRHYTHMIA	0.500	
BRADYCARDIA	0.453	
CARDIAC ARREST	0.266	
CARDIAC ARRHYTHMIA NOS	0.125	
CARDIAC DEATH	0.687	
CARDIOPULMONARY ARREST	1.000	
FIBRILLATION ATRIAL	1.000	
FIBRILLATION VENTRICULAR	0.500	
HEART BLOCK	1.000	
LEFT BUNDLE BRANCH BLOCK	0.500	
PALPITATION	1.000	
SINUS BRADYCARDIA	1.000	
SUDDEN CARDIAC DEATH	0.500	
SYNDROME SICK SINUS	0.500	
TACHYCARDIA	0.500	
TACHYCARDIA SUPRAVENTRICULAR PAROXYSMAL	0.500	
TACHYCARDIA VENTRICULAR	1.000	

---------- DECBODY=LIVER AND BILIARY SYSTEM DISORDERS ----------

DECODE	PVALUE	FLAG
BILIARY COLIC	0.218	
BILIARY STONES	1.000	
BILIARY TRACT DISORDER UNSPECIFIED	1.000	
CHOLANGITIS	1.000	
CHOLECYSTITIS	0.606	
CHOLELITHIASIS	0.343	
GALL BLADDER DISORDER	0.500	
GALL BLADDER STONES	0.625	
HEPATITIS CHRONIC	1.000	
JAUNDICE	0.062	

LIVER ENZYME DISORDER	0.500
LIVER FUNCTION TESTS ABNORMAL NOS	0.250

---------- DECBODY=METABOLIC AND NUTRITIONAL DISORDERS ----------

DECODE	PVALUE	FLAG
DIABETES MELLITUS	0.132	
DIABETES MELLITUS AGGRAVATED	1.000	
GOUT	0.625	
HYPERCHOLESTEROLEMIA	1.000	
HYPERGLYCEMIA	1.000	
HYPOGLYCEMIA	0.500	
KETOACIDOSIS	1.000	
KETOSIS	1.000	
RETINOPATHY DIABETIC	1.000	

---------- DECBODY=MUSCULO-SKELETAL SYSTEM DISORDERDS ----------

DECODE	PVALUE	FLAG
ARTHRITIC-LIKE PAIN	1.000	
ARTHRITIS	1.000	
ARTHRITIS RHEUMATOID	1.000	
ARTHRITIS RHEUMATOID AGGRAVATED	1.000	
ARTHRITIS SEPTIC	0.500	
BACK PAIN	0.343	
BONE REFRACTURED	1.000	
CARPAL TUNNEL SYNDROME	1.000	
COMPRESSION FRACTURES	0.500	
COSTOCHONDRITIS	1.000	
DISLOCATION OF HIP	1.000	
DISPLACEMENT OF INTERVERTEBRAL DISC	0.500	
DUPUYTREN'S CONTRACTURE	0.374	
FRACTURE RIB	0.375	
FRACTURES	0.322	

HERNIA	0.453
INTERVERTEBRAL DISC DISORDER	0.500
JOINT COMPLAINTS	0.625
LEG DISCOMFORT	1.000
LIGAMENT DISORDER	0.500
LOIN PAIN	0.500
MUSCLE ATROPHY NEUROLOGICAL	1.000
MUSCLE PAIN	0.375
MUSCULOSKELETAL DISORDERS	1.000
NECROSIS HIP	1.000
OSTEOARTHRITIS	1.000
PAIN HIP	0.500
PAIN KNEE	1.000
PAIN LEG	0.500
PAIN LOWER EXTREMITY	1.000
PAIN NECK	0.625
PAIN SHOULDER	0.500
PAIN WRIST	0.500
POLYARTHRITIS	0.500
ROTATOR CUFF SYNDROME OF SHOULDER	0.500
SPONDYLITIS	0.500
TEAR OF MENISCUS	0.500
TENDON RUPTURE	0.250
WEAKNESS KNEE	0.500

---------- DECBODY=MYO ENDO PERICARDIAL &VALVE DISORDER ----------

DECODE	PVALUE	FLAG
ANGINA	0.425	
ANGINA CRESCENDO	1.000	
ANGINA PECTORIS	1.000	
ANGINA PECTORIS AGGRAVATED	1.000	
ANGINA UNSTABLE	0.049	*placebo > nicorandil
ANGINA VARIANT	1.000	
ANGINAL ATTACK	0.062	
ANGINAL PAIN	0.374	
ANGINAL SYNDROME	0.500	
AORTIC STENOSIS	0.250	

AORTIC VALVE ABNORMALITY	0.500	
ARTERIOSCLEROTIC HEART DISEASE	0.507	
CARDIAC ISCHEMIA	0.595	
CARDIOMYOPATHY	0.250	
CHEST PAIN	0.358	
CORONARY ARTERY DISORDER	0.556	
CORONARY ARTERY OCCLUSION	0.306	
CORONARY ATHEROMA	0.250	
CORONARY DISEASE	0.707	
CORONARY INSUFFICIENCY	0.453	
CORONARY SPASM	0.500	
CORONARY STENOSIS	1.000	
CORONARY THROMBOEMBOLISM	0.500	
MYOCARDIAL INFARCTION	0.004	**placebo > nicorandil
MYOCARDIAL ISCHEMIA	1.000	
PAIN HEART ISCHEMIC	0.500	
PERICARDIAL EFFUSION	0.500	
PERICARDITIS	0.500	
POST MI	1.000	
THROMBOSIS CORONARY	0.250	

---------- DECBODY=NEONATAL AND INFANCY DISORDERS ----------

DECODE	PVALUE	FLAG
HERNIA INGUINAL	0.814	
HERNIA UMBILICAL	0.500	
HYDROCEPHALUS	1.000	

---------- DECBODY=NEOPLASM ----------

DECODE	PVALUE	FLAG
ADENOCARCINOMA BLADDER	0.500	
ADENOCARCINOMA COLON	1.000	
ADENOCARCINOMA LUNG	1.000	
ADENOCARCINOMA NOS	0.500	
ADENOCARCINOMA PROSTATA	0.453	
ADENOCARCINOMA RECTAL MUCINOUS	1.000	

ADENOMA	1.000
BASAL CELL CARCINOMA	0.790
BLADDER CARCINOMA	0.580
BLADDER PAPILLOMA	1.000
BREAST NEOPLASM BENIGN FEMALE	0.500
BREAST NEOPLASM MALIGNANT FEMALE	0.500
CANCER BLADDER	0.625
CANCER COLON	0.375
CANCER ESOPHAGUS	0.250
CANCER KIDNEY	1.000
CANCER LUNG NON-SMALL CELL	1.000
CANCER LUNG SQUAMOUS CELL	1.000
CANCER PROSTATE	1.000
CARCINOMA	0.687
CARCINOMA BASAL CELL	1.000
CARCINOMA BLADDER TRANSITIONAL CELL	0.218
CARCINOMA BREAST	1.000
CARCINOMA BRONCHUS	0.500
CARCINOMA COLON	0.375
CARCINOMA EPIGLOTTIS	1.000
CARCINOMA GASTROINTESTINAL	0.500
CARCINOMA LARYNX	1.000
CARCINOMA MOUTH	1.000
CARCINOMA OF ESOPHAGUS	0.062
CARCINOMA OF RECTUM	0.250
CARCINOMA PROSTATE	1.000
CARCINOMA RENAL CELL	0.500
CARCINOMA THYROID	1.000
CARCINOMA TONGUE	1.000
CARCINOMA VOCAL TRUE CORD	0.500
CARCINOMATOSIS	0.625
COLON CARCINOMA	1.000
CYST	0.343
CYST PANCREATIC	1.000
EPIDIDYMAL CYST	0.500
ESOPHAGEAL CARCINOMA	0.250
GALL BLADDER CARCINOMA	0.500
GASTRIC CARCINOMA	1.000
GOITRE NODULAR	1.000
HEPATIC NEOPLASM MALIGNANT	0.500

LEUKEMIA B CELL CHRONIC LYMPH.	1.000
LEUKEMIA LYMPHOBLASTIC	1.000
LIPOMA	1.000
LYMPHOMA NON-HODGKIN'S	1.000
MELANOMA	1.000
MELANOMA MALIGNANT	1.000
MESOTHELIOMA	0.250
METASTASES GROWTH	1.000
MULTIPLE MYELOMA	1.000
MYELOMA	0.500
MYELOPROLIFERATIVE DISORDER	0.500
NEOPLASM MALIGNANT	0.500
NEOPLASM NOS	0.625
NEOPLASM PULMONARY MALIGNANT	0.125
PANCREAS CARCINOMA	0.250
PAPILLOMA	1.000
POLYP COLON	0.774
POLYP ENDOMETRIUM	0.500
PULMONARY CARCINOMA	1.000
RECTAL CARCINOMA	1.000
RENAL CARCINOMA	0.500
SARCOMA	1.000
SKIN CARCINOMA	0.500
SKIN NEOPLASM MALIGNANT	0.500
SKIN TUMOR-LIKE CONDITION NOS	1.000
STOMACH CARCINOMA	0.500
TESTIS NEOPLASM MALIGNANT	1.000
TUMOR BENIGN NOS	0.500
TUMOR GASTROINTESTINAL	1.000
TUMOR URINARY BLADDER	0.625

---------- DECBODY=OPERATIONS & PROCEDURES ----------

DECODE	PVALUE	FLAG
AMPUTATION LOWER LEG	0.500	
AMPUTATION TOE PHALANX	0.500	
ANALGESIC TREATMENT OF NERVE	0.500	
ANEURYSMECTOMY	1.000	

ANGIOCARDIOGRAPHY	0.365
ANGIOGRAPHY CAROTIS	0.774
APPARATUS TECHNIQUE /SPEC.PROCEDURES	0.523
APPENDECTOMY	1.000
ARTERIOGRAPHY	0.687
ARTERY LIGATION	0.500
ARTHRODESIS OF FOOT	1.000
ARTHROPLASTY (HIP)	1.000
ARTHROPLASTY (KNEE)	0.625
ARTHROSCOPY KNEE	0.687
BIOPSY (HEAD, SOFT TISSUE)	0.500
BLADDER CATHETERIZATION	1.000
BONE TRANSPLANTATION OF HAND	1.000
BRONCHOSCOPY	0.289
CARDIOVASCULAR DRUG THERAPY	0.250
CARDIOVERSION, DEFIBRILATION	1.000
CATHETERIZATION OF HEART	1.000
CHOLECYSTECTOMY	0.453
CIRCUMCISION	1.000
CLOSURE OF COLOSTOMY	0.250
COLONOSCOPY	0.523
CORR. SURGERY STOMA/ANUS PRAETER	0.500
COSMETIC SURGERY	0.500
CYSTOSTOMY	0.500
DIAGNOSTIC PREPARATION OF ANESTHESIA	0.250
DISCISSION, EXTRACTION OF LENSE	0.625
EPIDIDYMECTOMY	1.000
EXCISION OF COLONIC POLYP	0.250
EXCISION SKIN, SUBCUTIS	1.000
EXPLORATORY THORACOTOMY	0.500
FASCIECTOMY	1.000
GASTROSCOPY	0.880
HEMICOLECTOMY	0.625
HEMICOLECTOMY LEFT SIDE	1.000
HEMORRHOIDECTOMY	1.000
HERNIA INGUINALIS REPAIR	1.000
HERNIA REPAIR	1.000
INCISION OF SKIN, SUBCUTIS	1.000
LAMINECTOMY	0.500
LARYNGOSCOPY	0.500

LOBECTOMY	0.500
MITRAL VALVE REPLACEMENT	0.500
MULTIPLE AC BYPASS	0.625
MUSCLE BIOPSY	0.500
NASAL POLYPECTOMY	1.000
NEPHRECTOMY	1.000
O.SURGERY (MEDIASTINUM,THORACIC WALL)	0.500
O.SURGERY LOWER LEG SKIN, SUBCUTAN TISSUE	0.500
OP AORTA ANEURYSM	1.000
OPERATION GLAUCOMA	1.000
OTHER BONE SURGERY (FEMUR)	0.500
OTHER BONE SURGERY OF FOOT	1.000
OTHER OP HAND, SOFT TISSUE	1.000
OTHER OP SPINE	0.500
OTHER SURGERIES (HIP,SOFT TISSUE)	1.000
OTHER SURGERY (ARTICULAR ANKLE)	0.500
OTHER SURGERY (BRONCHI,LUNG,PLEURA)	1.000
OTHER SURGERY (EXTERNAL EAR)	1.000
OTHER SURGERY (EYEBALL)	0.628
OTHER SURGERY (HAND BONES)	1.000
OTHER SURGERY (HEART)	0.226
OTHER SURGERY (HUMERUS)	0.500
OTHER SURGERY (LACR.SAC,LACRIMAL DUCT)	0.500
OTHER SURGERY (MIDDLE EAR)	1.000
OTHER SURGERY (MUSCLES,FASCIAE)	0.500
OTHER SURGERY (NOSE, PARANASAL SINUSES)	1.000
OTHER SURGERY (PORTIO VAGINALIS UTERI)	1.000
OTHER SURGERY (SKIN, SUBCUTIS)	0.625
OTHER SURGERY (SKULL)	0.500
OTHER SURGERY (SMALL INTESTINE)	1.000
OTHER SURGERY (TOES,SOFT TISSUE)	0.500
OTHER SURGERY (URETER)	0.500
OTHER SURGERY (UTERUS,ABDOMEN)	0.500
OTHER SURGERY (VAGINA,VULVA,PERINEUM)	0.250
OTHER SURGERY (VEINS)	1.000
OTHER SURGERY ARTERY	0.581
OTHER SURGERY ARTERY, PLASTY	1.000
OTHER SURGERY BLADDER	1.000
OTHER SURGERY LENS	1.000
OTHER SURGERY LIVER,GALLBLADDER	1.000

OTHER SURGERY LOWER LEG VEINS	1.000
OTHER SURGERY MAMMA	0.500
OTHER SURGERY ON EYELID	0.250
OTHER SURGERY ON RETINA	1.000
OTHER SURGERY PROSTATE	0.500
OTHER SURGERY UTERUS VAGINA	1.000
PART.ARTHROPLASTY WITH IMPLANT (KNEE)	0.500
PARTIAL GASTRIC RESECTION	0.500
PROSTATAECTOMY	0.500
PUNCTION AND/OR DRAINAGE	1.000
RECTOSIGMOIDOSCOPY	0.507
REVASCULARISATION MYOCARD O. SURGERY	0.250
REVASCULARISATION OF MYOCARD	0.398
REVISION OF MIDDLE EAR AND MASTOID	0.500
RHINOPLASTY	1.000
S.A. ARTHROPLASTY (KNEE)	1.000
S.A. OTHER SURGERY LENS	0.500
S.A.OTHER SURGERY (EYEBALL)	1.000
S.A.OTHER SURGERY (HEART)	1.000
SEGM. RESECTION OF COLON	1.000
SINGLE AC-BYPASS	0.250
SUBCUTANEOUS MASTECTOMY	0.500
SURGERIES OF INTERVERTEBRAL APERTURE	0.500
SURGERY FOR HEMO-/PERITON.DIALYSIS	0.500
SURGERY OF ANAL FISTULA	1.000
SURGERY ON SOFT PALATE	1.000
SURGERY VOCAL LIGAMENTS	1.000
TECHNICAL MEASURES	1.000
TEETH EXTRACTION	1.000
THROMBENDARTERECTOMY	1.000
TOTAL ARTHROPLASTY WITH IMPLANT (KNEE)	1.000
TOTAL ARTHROPLASTY WITH IMPLANTAT (HIP)	1.000
TOTAL HYSTERECTOMY	0.500
TRANSURETHR. RESECT. OF PROSTATE	1.000
TRANSURETHRAL CYSTOSCOPY	0.335
TRANSURETHRAL SURGERY URINARY BLADDER	0.625
TRIPLE AC BYPASS	0.250
VAGINAL HYSTERECTOMY	0.250
VENOUS LIGATIONS	0.500
VESSEL REPLACEMENT OR BYPASS	1.000

---------- DECBODY=PLATELET, BLEEDING&CLOTTING DISORDER ----------

DECODE	PVALUE	FLAG
CAROTID OCCLUSION	1.000	
COAGULATION DISORDER	1.000	
EMBOLISM PULMONARY	1.000	
HEMORRHAGE NOS	0.500	
THROMBOCYTOPENIA	0.250	

---------- DECBODY=PSYCHIATRIC DISORDERS ----------

DECODE	PVALUE	FLAG
ABSTAINING SYMPTOMS	1.000	
ALCOHOLISM	1.000	
AMNESIA	1.000	
ANXIETY	0.500	
ANXIETY ATTACK	1.000	
BIPOLAR DISORDER	0.500	
CONFUSION	0.500	
CONSCIOUSNESS CLOUDED	1.000	
DEMENTIA	0.500	
DEPRESSION	0.374	
DEPRESSION PSYCHOTIC	1.000	
EFFORT SYNDROME	1.000	
INTENTIONAL OVERDOSE	1.000	
MANIC PSYCHOSIS	1.000	
PACING	0.374	
PANIC ATTACK	0.500	

---------- DECBODY=RED BLOOD CELL DISORDERS ----------

DECODE	PVALUE	FLAG
ANEMIA	0.387	
ANEMIA GI BLEEDING	0.500	
ANEMIA HEMOLYTIC	1.000	
ANEMIA IRON DEFICIENCY	0.288	
HEMOGLOBIN DECREASED	1.000	

---------- DECBODY=REPRODUCTIVE DISORDES,FEMALE ----------

DECODE	PVALUE	FLAG
BLEEDING POSTMENOPAUSAL	0.687	
UTERINE HEMORRHAGE	0.500	

---------- DECBODY=REPRODUCTIVE DISORDES,MALE ----------

DECODE	PVALUE	FLAG
ERECTILE IMPOTENCE	0.500	
GENITALIA EXTERNAL PAINFUL	0.500	
GYNECOMASTIA	0.500	
ORCHITIS	0.500	
PAIN TESTICULAR	1.000	
PENIS DISORDER	1.000	
PROSTATE ENLARGED	0.038	* act>pl
PROSTATIC DISORDER	0.726	
PROSTATISM AGGRAVATED	1.000	

---------- DECBODY=RESISTANCE MECHANISM DISORDERS ----------

DECODE	PVALUE	FLAG
ABSCESS	1.000	
ABSCESS ANAL	1.000	
ABSCESS LEG	1.000	
HERPES	1.000	
HERPES ZOSTER	0.500	
INFECTION	0.250	
INFECTION BACTERIAL	1.000	
INFECTION VIRAL	1.000	
SEPSIS	0.500	
SEPTICEMIA	0.374	
WOUND INFECTION	1.000	

---------- DECBODY=RESPIRATORY SYSTEM DISORDERS ----------

DECODE	PVALUE	FLAG
APNEA	1.000	
ASPIRATION	1.000	
ASTHMA	0.374	
ASTHMA AGGRAVATED	1.000	
BREATHING DIFFICULT	0.500	
BREATHLESSNESS	0.500	
BRONCHIAL DAMAGE	0.500	
BRONCHIEKTASIS	0.500	
BRONCHITIS	0.125	
BRONCHOPNEUMONIA	0.375	
CHRONIC OBSTR. PULM. DISEASE	0.166	
COPD	1.000	
DYSPNEA	0.218	
DYSPNEA EXERTIONAL	1.000	
EDEMA PULMONARY	0.687	
EMPHYSEMA	0.500	
EPISTAXIS	0.125	
HEMOPTYSIS	1.000	
INFECTION BRONCHOPULMONARY	0.500	
INFECTION CHEST	0.867	
INFECTION LUNG	1.000	
LARYNX EDEMA	1.000	
NASAL POLYP	0.375	
NASAL SEPTUM DEVIATION	1.000	
NOSEBLEED	1.000	
OBSTRUCTION PULMONARY	0.500	
PHARYNGITIS	1.000	
PLEURAL CHANGES	1.000	
PLEURAL EFFUSION	1.000	
PLEURAL PAIN	1.000	
PLEURISY	0.500	
PNEUMONIA	0.700	
PNEUMONIA LOBAR	0.500	
PNEUMOTHORAX	0.500	
PULMONARY COLLAPSE	0.500	
PULMONARY COMPLICATIONS	0.500	

PULMONARY DAMAGE	0.500
PULMONARY DISEASE	1.000
RESPIRATORY DISORDER	0.250
RESPIRATORY FAILURE	1.000
SHORTNESS OF BREATH	0.726
SINUSITIS MAXILLARY	1.000
UPPER RESP TRACT INFECTION	0.250
VOCAL CORD EDEMA	1.000

---------- DECBODY=SKIN AND APPENDAGES DISORDERS ----------

DECODE	PVALUE	FLAG
ALOPECIA	1.000	
BRUISE	0.500	
ECZEMA	1.000	
ERYSIPELAS	1.000	
FISSURES	1.000	
HEMATOMA	0.500	
HYPERKERATOTIC LESION	0.500	
INFLAMMATION SKIN	1.000	
INGROWN TOENAIL	0.500	
KERATOLYSIS	0.500	
KERATOSIS	0.500	
MUCOCUTANEOUS LESION	1.000	
NAIL DISORDER	0.500	
NECROSIS TOE	1.000	
PILONIDAL CYST	1.000	
PSORIASIS	1.000	
RASH	0.250	
SKIN DEFECTS SUPERFICIAL	0.375	
SKIN DISEASE	1.000	
SKIN DISORDER	0.625	
SKIN LESION PAPULAR	1.000	
SKIN NODULE	1.000	
SKIN ULCERATION	1.000	
ULCER FOOT	1.000	
ULCER LEG	0.625	
URTICARIA	1.000	

DECBODY=UNKNOWN

DECODE	PVALUE	FLAG
UNKNOWN	1.000	

DECBODY=URINARY SYSTEM DISORDERS

DECODE	PVALUE	FLAG
BLADDER CALCULUS	1.000	
BLADDER DISORDER	0.500	
BLADDER DYSFUNCTION	1.000	
BLADDER INABILITY TO EMPTY	0.500	
BLADDER IRRITATION	1.000	
CYSTITIS	0.500	
CYSTOCELE	1.000	
DYSURIA	0.500	
FLANK PAIN	1.000	
GLOMERULONEPHRITIS	1.000	
HEMATURIA	0.790	
HEMATURIA MICROSCOPIC	1.000	
HYDRONEPHROSIS	1.000	
INFECTION URINARY BLADDER	0.500	
INFECTION UROGENITAL TRACT	0.500	
KIDNEY DYSFUNCTION	1.000	
KIDNEY FAILURE	1.000	
KIDNEY STONE	0.250	
MICTURITION FREQUENCY	0.031	*placebo > nicorandil
NOCTURIA	1.000	
OBSTRUCTIVE UROPATHY	0.500	
PAIN ILIACFOSSA	0.500	
POLYURIA	0.500	
PYELONEPHRITIS	1.000	
RENAL CALCULUS	0.625	
RENAL COLIC	1.000	
RENAL FAILURE ACUTE	0.625	
RENAL FAILURE ACUTE ISCHEMIC	0.500	
RENAL FAILURE CHRONIC	1.000	

RENAL FUNCTION ABNORMAL	0.500
URETERAL DISORDER	1.000
URETHRAL DISORDER	1.000
URETHRAL OBSTRUCTION	0.288
URINARY RETENTION	0.454
URINARY SYMPTOMS GENERAL	0.500
URINARY TRACT INFECTION	1.000
URINARY URGENCY	1.000
URINATION FREQUENT	0.500
URINE VOLUME DEFICIENT	1.000

---------- DECBODY=VASCULAR (EXTRACARDIAC) DISORDERS ----------

DECODE	PVALUE	FLAG
ANEURYSM RUPTURE	0.375	
ARTERIOSCLEROSIS	1.000	
ARTERIOVENOUS FISTULA	0.500	
ARTERITIS	0.625	
ARTERY DISEASE PERIPHERAL	0.500	
CARDIOVASCULAR ACCIDENT	0.687	
CEREBRAL INFARCTION	0.687	
CEREBRAL VASCULAR DISTURBANCE	1.000	
CEREBROVASCULAR ATTACK	0.226	
CLAUDICATIO	0.500	
CLAUDICATION INTERMITTENT	1.000	
CVA	0.838	
INTESTINAL INFARCTION	1.000	
INTESTINAL ISCHEMIA	1.000	
ISCHEMIA PERIPHERAL	0.500	
ISCHEMIC ATTACKS TRANSIENT	0.263	
MESENTERIC ARTERIAL OCCLUSION	1.000	
PERIPHERAL ISCHEMIA	1.000	
PERIPHERAL VASCULAR DISEASE	0.266	
PERIPHERAL VASCULAR DISEASE.	0.500	
RENAL ARTERY STENOSIS	0.500	
STENOSIS ARTERIAL	1.000	
STROKE	0.454	
THROMBOPHLEBITIS	0.500	

THROMBOPHLEBITIS DEEP	1.000
THROMBOPHLEBITIS LEG DEEP	1.000
THROMBOPHLEBITIS SUPERFICIAL	1.000
THROMBOSIS ARTERIAL	0.500
THROMBOSIS PELVIC VEINS	0.500
THROMBOSIS VENOUS DEEP	0.790
VARICOSE VEINS	1.000
VASCULAR DISORDER	0.500
VASCULITIS	1.000
VASOSPASM	0.500
VEIN DISORDER	1.000
VENOUS STENOSIS	1.000

---------- DECBODY=VISION DISORDERS ----------

DECODE	PVALUE	FLAG
BLEPHAROPHIMOSIS	1.000	
CATARACT	0.103	
CENTRAL RETINAL VEIN OCCLUSION	1.000	
EDEMA MACULAR	1.000	
EPIPHORA	1.000	
EYE ABNORMALITY	1.000	
EYE IRRITATION	1.000	
GLAUCOMA	1.000	
HYPHEMA	0.250	
PTERYGIUM	1.000	
RETINAL ARTERY OCCLUSION	1.000	
RETINAL VEIN THROMBOSIS	0.500	
VITREOUS DETACHMENT	0.500	

---------- DECBODY=WHITE BLOOD CELL AND RES DISORDERS ----------

DECODE	PVALUE	FLAG
EOSINOPHILIA	0.500	