16. APPENDICES

16.1 STUDY INFORMATION

16.1.1 Protocol and protocol amendments

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.

The **IONA** Study (**I**mpact **O**f **N**icorandil in **A**ngina)

Sponsors:

MERCK PHARMACEUTICALS LIMITED
Harrier House, High Street
West Drayton, Middlesex UB7 7QG
01895 452200 Fax 01895 420605

RHÔNE-POULENC RORER LIMITED
50 Kings Hill Avenue, Kings Hill
West Malling, Kent ME19 4AH
01732 584000 Fax 01732 584080

Compound name: Nicorandil {N-(2hydroxyethyl) nicotinamide nitrate ester}

Protocol identification: IONA

Date: 08/12/1997

Total pages:

Personnel

Principal Investigator [redacted]	[redacted]
Statistics and Data Management [redacted]	[redacted]
Safety Committee Chairman [redacted]	[redacted]
Endpoints Committee Chairman [redacted]	[redacted]
Merck Pharmaceuticals Limited [redacted]	[redacted]
Rhône-Poulenc Rorer Limited [redacted]	[redacted]

Protocol Acceptance

	Signature and date
[redacted] University of Glasgow	[redacted]
[redacted] University of Glasgow	
[redacted] University of Nottingham	
[redacted] Nottingham Clinical Trials Data Centre	
[redacted]	
[redacted] Rhône-Poulenc Rorer Limited	
[redacted] Rhône-Poulenc Rorer Limited	
[redacted] Merck Pharmaceuticals Limited	

Protocol Acceptance

	Signature and date
[redacted] University of Glasgow	
[redacted] University of Glasgow	
[redacted] University of Nottingham	
[redacted] Nottingham Clinical Trials Data Centre	
[redacted] Royal Brompton Hospital	
[redacted] Rhône-Poulenc Rorer Limited	[redacted]
[redacted] Rhône-Poulenc Rorer Limited	
[redacted] Merck Pharmaceuticals Limited	

Abbreviations

ABPI	Association of the British Pharmaceutical Industry
ATP	Adenosine Triphosphate
BP	Blood Pressure
CABG	Coronary Artery Bypass Graft surgery
CE	Critical Event
CEC	Critical Events Committee
CHD	Coronary Heart Disease
CRF	Case Report Form
DBP	Diastolic Blood Pressure
EC	European Community
ECG	Electrocardiograph
EDD	End Diastolic Diameter
EF	Ejection Fraction
GCP	Good Clinical research Practice
HR	Heart Rate
ISC	Independent Statistical Centre
LREC	Local Research Ethics Committee
LVH	Left Ventricular Hypertrophy
MI	Myocardial Infarction
MREC	Multi-Centre Research Ethics Committee
NHS	National Health Service
PTCA	Percutaneous Transluminal Coronary Angioplasty
PVD	Peripheral Vascular Disease
SAE	Serious Adverse Event
SBP	Systolic Blood Pressure
SmPC	Summary of Product Characteristics
TIA	Transient Ischaemic Attack

Table of contents

1 Summary

Objective

The objective of this trial is to examine 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 trial is conducted within the licenced indication.

Study Sites

The study will be co-ordinated by the University of Glasgow (Robertson Centre for Biostatistics and the Clinical Research Centre, Western Infirmary, Glasgow) with monitoring of the study sites carried out by the Nottingham Clinical Trial Data Centre (NCTDC), Queen's Medical Centre, University Hospital, Nottingham NG7 2UH. Tel 0115 956 771 Subjects will be seen in the investigators clinics in hospitals throughout the U.K.

Subject Population

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 are permitted. Subjects must not be scheduled for, or considered to require, a coronary artery revascularisation procedure at the time of randomisation.

Study Design and Duration

A multi-centre, randomised, double blind, placebo controlled design will be used. Subjects satisfying the inclusion and exclusion criteria will be 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) will have the study medication discontinued. During the follow-up period subjects will be seen 4 monthly for clinic visits. It is expected that recruitment will take 2 years. The target total number of patient years of randomised follow-up is 8750 years (average 21 months per/patient). It is expected that minimum follow-up for each patient will be 12 months. The maximum follow-up will be 36 months. The study will continue until the target number of patient-years of follow-up is achieved or until 3 years have passed from the date of the first randomisation, unless early termination is recommended due to overwhelming evidence of benefit or because of evidence of harm.

Efficacy measure

The primary endpoint of the study will be the combined events of CHD death, non-fatal myocardial infarction or unplanned hospitalisation for chest pain.

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

Safety

Safety will 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 will be performed. This will be achieved through the assessment of hospitalisation.

2 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.

3 Objectives

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 is 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 will be CHD death or non-fatal myocardial infarction.

Other outcomes to be studied will 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 chest pain), cardiovascular hospitalisation, cerebrovascular events (fatal and non-fatal stroke or hospitalised TIA), all hospitalisations and worsening of anginal status.

4 Design

The study will be a randomised double-blind trial of nicorandil versus placebo on top of standard anti-anginal therapy. At recruitment, subjects will have angina of effort which could be recently diagnosed or chronic.

There will be a two week titration period - study medication will be initiated at 10mg bd or matching placebo. Patients clearly intolerant of this dose and showing no evidence of symptom

6.2 Inclusion criteria

Patients must satisfy all of the following criteria: 6.2.1 - 6.2.5.

6.2.1 Patients must provide written informed consent prior to their inclusion in the study.

6.2.2 Men (aged > 45 years) or women (aged > 55 years)

6.2.3 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

6.2.4 Need for regular treatment with one or more oral symptomatic anti- anginal medications (e.g. long acting nitrate formulation, beta blocker, calcium channel blocker)

6.2.5 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 (≥ 1mm ST depression) in the previous two years, and at least one of the following:

- (C i) LVH on ECG (tall R in aVL, Sv1 + Rv6 > 35mm, lateral T inversion)
- (C ii) Evidence of left ventricular dysfunction (EF ≤ 45% or EDD > 5.5cm)
- (C iii) Age ≥ 65 years
- (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 TIA, PVD)

6.3 Exclusion Criteria

Patients will be excluded for any of the reasons 6.3.1 - 6.3.11.

6.3.1 Pregnancy or lactation

6.3.2 Legal incapacity or limited legal capacity

6.3.3 Participation in another clinical study within the past 30 days

6.3.4 Presence of contra-indications to the study medication(s)

6.3.5 Known drug or alcohol abuse

6.3.6 Uncontrolled cardiac failure or arrhythmias

6.3.7 Unstable angina, CABG or MI in the previous three months

6.3.8 PTCA in the previous six months

6.3.9 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.

6.3.10 The presence of other disease that in the investigator's opinion would reduce the patient's life expectancy or influence significantly their cardiovascular condition.

6.3.11 Current treatment with nicorandil.

6.2.12 Uncontrolled hypertension (SBP >180 or DBP >110mmHg)

7 Clinical Assessments

7.1 Medical history and investigative findings

At screening, patients records will be 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 will also be recorded as will 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 will be recorded.

7.2 Laboratory

A 30ml blood sample will be taken (at study entry only) 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.

7.3 ECG

A standard 12 lead ECG at rest must be recorded at study entry, 12 monthly and at study completion. If an ECG is performed at any other time, at the investigator's discretion, pages will be provided in the CRF to document the information obtained. There will be an ECG page for each visit. Any significant abnormalities identified on the ECG must be reported on the CRF, particularly any results suggestive of myocardial infarction (previous event at baseline and new events at follow-up).

7.4 Adverse events and serious adverse events

Adverse events will not be recorded unless they are defined as serious Serious adverse events will be documented as detailed in sections 10.1 to 10.5.

7.5 Permanent withdrawal from study medication

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

7.6 Study critical events

Study critical events are a subset of serious adverse events and are described and defined in the Critical Events Section of the Trial Centre Manual, supplied separately.

8 Patient Visit Schedule

The assessments to be performed at the visits are listed below. Is important that the scheduled visit intervals are respected. For any visit a maximum of a 14 day deviation before or after the scheduled date is permitted. In the event of a deviation more than this, the reason must be documented and justified.

Screening Phase/Randomisation

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

Call [redacted] to obtain randomisation number, and then dispense placebo bd or nicorandil 10mg bd. [redacted] will supply each site with the appropriate contact numbers and site identification codes. Training in the use of the remote interactive randomisation system will be provided to the appropriate site staff by [redacted]

The dose will be increased to 20mg bd at a visit two weeks following study medication initiation.

At eight weeks following study medication initiation there will be a visit to ensure tolerability and encourage compliance. A further supply of medication will be given at this visit - allocation of supply being directed by ClinPhone, . A reduction in dose back to 10mg bd, or matching placebo, is permitted if intolerance of the 20mg bd dose is considered evident by the investigator. A justifiable reason for any reduction must be documented in the CRF. Patients given 10mg bd, or placebo, will continue on this dose until the end of the study.

Double-Blind Study Medication Administration

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
Dispense study medication

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
Dispense study medication

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
Complete study withdrawal form

9 Ethics

9.1 Responsibilities of the investigator

The investigator shall be responsible for ensuring that the clinical study is performed in accordance with the protocol, Declaration of Helsinki (revised version of Somerset West, Republic of South Africa, 1996; see Appendix VI) as well as with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) dated July 17, 1996 (see Appendix VII). These documents set forth among other conditions that the informed consent of the patients is an essential precondition for participation in the clinical study.

9.2 Patient information

Before participation in the clinical study a patient **must** give his/her fully informed consent. having been informed about the following points:

a) objectives of the study
b) therapeutic effects of and potential adverse reactions to the study medication
c) potential benefit of participation in the study and therapeutic alternatives
d) risks and additional examinations that the study may entail
e) for women, the warning that clinical studies may not be carried out in pregnant women and that pregnancy should therefore be avoided - and that if pregnancy occurs, the investigator must be notified immediately
f) possible risks upon discontinuation of the study
g) procedure of the study, allocation to the individual study medication groups
h) non-permitted concomitant medication
i) the expected duration of the patient's participation in the study
j) the approximate number of patients expected to take part in the study
k) insurance coverage and the requirements of the policy - that he/she may undertake additional medical treatment during the clinical study only with the express permission of the investigator, unless indicated in an emergency.
l) the voluntary nature of participation in the study and the possibility to withdraw from the study at any time without stating reasons and without any disadvantages
m) opportunity for obtaining further information and sufficient time to consider participation
n) warning that the patient may not have taken part in any other clinical study or used any other unlicensed medication during the past 30 days
o) that all present concomitant medication must be reported to the investigator at each visit.
p) that study-relevant data will be collected in anonymous case report forms
q) consent for the forwarding of medical data on anonymous case report forms to the University of Glasgow
r) permission for access to their medical records, some of which may be held on computer, for study staff from the University of Glasgow and the Nottingham Clinical Trials Data Centre, on the condition that all data will be treated in the strictest confidence in agreement with data-protection regulations
s) permission from the patient for inspection of medical records in the strictest confidence by personnel from RPR Ltd and Merck Pharmaceuticals Ltd, Regulatory Bodies and Quality Assurance personnel appointed by RPR Ltd and Merck Pharmaceuticals Ltd
t) that the patient's family doctor will be notified of his/her participation in the study
u) that any significant new findings concerning the study drug which may affect a patient's wish to participate (including changes to examinations/procedures of the protocol) will be provided, with the option to re-consent.
v) The investigator must inform the patient verbally. The information must be given both verbally as well as in writing. The wording must be chosen in such a way as for the content to be fully and readily understandable by laypersons.

9.3 Patient consent

The consent of the patient to participate in the clinical study must be given in writing prior to participation in the study.

The consent shall be confirmed in the CRF by the investigator. The signed and dated declaration of informed consent shall remain at the investigator's site and must be stored in the patient file. A copy will be supplied to the Data Centre in the University of Glasgow. These copies will be stored separately from other study records in the locked cabinets and will not be accessible to study personnel or to the sponsor.

Prior to participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated written informed consent form and any other written information provided to the subjects.

During a subject's participation in the trial, the subject or the subject's legally acceptable representative should receive a copy of the signed and dated consent form updates and a copy of any amendments to the written information provided to subjects.

9.4 Patient insurance coverage

From the time of entry to the study (i.e. date of given consent or visit 1), compulsory insurance coverage (so-called patient's insurance) shall be provided for all patients involved in the study (for insurance confirmation and insurance regulations see Appendix V). This insurance is in accordance with the UK ABPI Guidelines.

The investigator and relevant Health Authority (if requested) are given indemnity. A specimen Letter of Indemnity is given in Appendix V. It is required that these are completed and signed prior to commencement of the study.

9.5 Ethics Committee

Prior to commencement of the start of the study, the study protocol will be submitted together with its associated documents to the appropriate Multi-Centre Research Ethics Committee (MREC), established through the Health Service Guidelines HSG(97)23, 14 April 1997. The MREC will appraise and give approval if deemed fit and in consideration of the relevant Department of Health Standards, Research Ethics Committees, documents (1995) and guidance published by the Royal Colleges of Physicians and other professional bodies. It will subsequently be reviewed by the Local Research Ethics Committees (LRECs). The steps in the process are summarised:

- Principal researcher submits proposal to designated multi-centre research ethics committee
- Designated MREC considers proposal
- Designated MREC issues decision to principal researcher
- Principal researcher sends approval letter and endorsed protocols to local researchers
- Local researchers send approval letter and endorsed protocols to LRECs
- LRECs consider issues affecting local acceptability
- LRECs issue local decisions
- Local researchers and NHS bodies and the designated MREC note LREC decisions

The Ethics Committee's written approval/appraisal of the study shall be appended to the standard study documents at the University of Glasgow Co-ordination Centre, at the Sponsors' Clinical Research Departments and at the location of the investigators.

The study will only commence following provision of written approval. Documentation of the date of the meeting, constitution of the committee and voting members present at the meeting will be requested. Copies of the minutes in respect of the submitted protocol will be obtained.

Any amendments to the protocol will be submitted to the Multi-centre Research Ethics Committee and the Multi-centre Research Ethics Committee will be informed of serious adverse events which are likely to affect the safety of the subjects or the conduct of the trial.

9.6 Notification of regulatory authority

The study is performed within the licenced application. The Medicines Control Agency will be informed about the intent to undertake it.

10 Safety

10.1 Definition of serious adverse events (SAEs)

A serious adverse event is any event that is:

- fatal
- life-threatening
- requires or prolongs hospitalisation
- results in persistent or significant disability or incapacity
- a congenital anomaly or birth defect
- an important medical event.

Important medical events are those which may not be immediately life-threatening, but are clearly of major clinical significance. They may jeopardise the subject, and may require intervention to prevent one of the other serious outcomes. In particular, these events will be taken to include all cases of stroke or myocardial infarction whether hospitalised or not. A hospitalisation will be taken to be any event requiring hospital admission whether it involves an overnight stay or not. The development of cancer, and drug overdosage or abuse will be considered as serious.

10.2 Recording of Serious Adverse Events

At each contact with the patient, the investigator must seek information on serious adverse events by questioning, examination, or investigation as appropriate. Information on all events should be recorded immediately in the appropriate section of the CRF. All clearly related signs, symptoms and abnormal diagnostic procedures should be grouped together and recorded as a single diagnosis in the CRF. The component parts of the diagnosis may be listed for verification.

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

Any SAE which occurs after the study period and is considered to be possibly related to study treatment or study participation must be recorded and reported immediately.

SAEs must continue to be recorded until the end of the study even if the patient is withdrawn from study medication.

10.3 Reporting of Serious Adverse Events

Rapid Reporting to Sponsor

All serious adverse events occurring during the study period, whether or not considered to be related to study treatment, must be reported using the SAE form supplied. The completed form must be sent to the Sponsor within 24 hours or, at the latest, on the following working day. The report should be made, preferably by facsimile transmission, to the following:

Pharmacovigilance Department, Rhône-Poulenc Rorer Limited , RPR House, 50 Kings Hill Avenue, Kings Hill, West Malling, Kent ME19 4AH

[redacted]

At the time of the initial report, the following information should be provided if 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 has been discontinued and if the study blind has been broken for the patient; the reason why the event is classified as serious; the investigator's current assessment of the association between the event and study treatment.

Within the following 48 hours, the investigator must provide written information on each serious adverse event. This should include any other diagnostic information which will assist the understanding of the event. Significant new information about on-going serious adverse events should be provided promptly to the Sponsor or authorised representative.

Additional information will be requested by the Sponsor, if necessary, within 5 days of receipt of the SAE report. This is to ensure that the initial reporting of serious adverse reactions is made to regulatory authorities within the required time-frame.

Study SAE Reporting

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

10.4 Subject Withdrawal from Study Therapy due to Adverse Events

Any subject who experiences an adverse event may be withdrawn at any time from the study at the discretion of the investigator.

If a subject is withdrawn wholly or in part because of an adverse event, the appropriate 'Permanent Withdrawal from Study Medication' form should be completed. SAEs resulting in withdrawal should also be documented on SAE forms as described above. Unless there is a medical reason to the contrary, patients experiencing a non-fatal study critical event should be continued on randomised therapy.

10.5 Monitoring of patients with SAEs

Any SAE that occurs in the course of a clinical study must be monitored and followed up until

- it has resolved;
- pathological laboratory findings have returned to normal;
- steady state has been achieved; or
- it has been shown to be unrelated to the study medication.

10.6 Definition of Critical Events

Critical events are outcomes which will be used to formulate the scientific interpretation of the trial. In particular, they will include the components of the primary and secondary study endpoints.

All critical events are SAEs and will be documented on the SAE forms. However, to permit the Critical Events Committee to confirm that events satisfy study definitions, additional information will be required on possible critical events.

10.7 Methods of Reporting and Recording Critical Events

All critical events as defined in section 10.6 and occurring during the study must be documented on the appropriate critical event (CE) form.

The investigator will be prompted to fill in the critical event form by a note on the the study SAE form.

The critical event forms are not included in the booklet of routine trial visit CRFs, but will be provided as separate forms.

As soon as the investigator has documented a critical event, the completed form must be forwarded to the Medical Co-ordinator at the Data Centre, who may have to contact the investigator for clarification or for support documentation for some of these events. One duplicate must be kept in the investigator's files.

10.8 Overdoseage and Intoxication with the Study Medication

In the event of overdose, the therapy with the study medication must be discontinued.

Acute overdosage is likely be associated with peripheral vasodilatation, decreased blood pressure and reflex tachycardia. Cardiac function should be monitored and general supportive measures employed. If necessary, circulating plasma volume should be increased by infusion of suitable fluid. In life threatening situations administration of vasopressors should be considered.

11 Concomitant Therapy

In the event that additional, or a reduction of, anti-anginal therapy becomes necessary during the study, this must be documented.

Current anti-anginal medication will be recorded at each visit.

12 Statistical methodology

12.1 Primary and secondary endpoint variables

The primary endpoint of the study will be the combined events of CHD death, non-fatal myocardial infarction or unplanned hospitalisation for cardiac chest pain.

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

Other outcomes to be studied will 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.

12.2 Definitions of evaluability

All endpoints will be evaluated, in the first instance, on an intention to treat basis. The results for the primary and secondary endpoint will also be reported on the basis of an on-treatment analysis.

12.3 Definitions of statistical analysis

All endpoints, with the exception of worsening of anginal status, will be analysed on a time-to-event basis. The outcome will be taken to be the time to first occurrence of the event of interest or the end of study follow-up, whichever comes first. The date of occurrence of silent myocardial infarction will be taken to be the midpoint between the dates of the diagnostic ECG and the previous ECG Treatment groups will be compared on the basis of the log rank test. Risk reductions will be calculated from the Cox proportional hazards model with treatment fitted as the only covariate. These analyses will 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 will be defined as an occurrence of hospitalisation for cardiac chest pain or a worsening of CCSF classification of anginal status. Outcomes will be compared between treatment groups using a chi-square statistic.

12.4 Sample size

In a small recent community based UK study, Ghandi [13] estimated 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. At the other end of the spectrum, 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 would make sense to be cautious about assumed event rates in the proposed study population. However, with the inclusion of subjects with newly diagnosed angina of effort and subjects with other risk factors, it might be 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. 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 pick up 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 pick up a 25% risk reduction.

12.5 Data and Safety Monitoring Committee (DSMC)

Data collected during the trial will be reviewed and monitored by an independent Data and Safety Monitoring Committee. This committee will be an advisory committee to the study Steering Committee. The Study Steering Committee will retain the responsibility to take decisions in relation to study continuation. The DSMC will receive, approximately 6 monthly, blinded data files from the Study Data Centre from which it will be able to construct unblinded reports. The DSMC will carry out three interim analyses for evidence of efficacy after approximately 25%, 50% and 75% of the target patient years of follow-up have accrued. Overwhelming evidence of benefit in the primary endpoint ($p < 0.001$) will be required for the DSMC to consider a recommendation of early stopping of the trial to the Steering Committee. In addition, the DSMC will be responsible for reviewing SAE data and withdrawals from study medication for evidence of harm. The DSMC will take as a guideline for early discontinuation a result at one of the formal analyses where there is significant evidence that the event rate of the primary endpoint cluster is high in the nicorandil group ($p < 0.005$, one sided). The DSMC may also recommend discontinuing the study if there is clear evidence of harm from nicorandil treatment which becomes clear in other ways. The DSMC will take into account any information about nicorandil which may become available outside the context of this clinical trial.

The Committee will record and retain a formal record of all of its meetings with a copy of the reports reviewed. These will form part of the overall study documentation and will be made available to the Study Data Centre and to the Sponsor at the end of the trial.

13 Study medication

13.1 Description of study medication

From the study documentation, it must be possible to retrace the composition and pharmaceutical quality of the study medication, according to the current GMP guidelines.

The study medication is presented as off-white, bevelled edge, circular tablets with scoring on one face. Active and placebo tablets will be identical in appearance

13.2 Allocation of the study medication

There will be an initial supply for each site sufficient for ten patients.

The investigator will telephone [redacted](details -Section 8) with the information about the patient and receive a treatment code number according to the packs already supplied to the centre. The relevant pack will be dispensed. [redacted] will log the supplies that are distributed and dispensed and will initiate the re-supply from [redacted]. The site will receive a monthly report from [redacted] and the Robertson centre regarding active centres. The site will be re-supplied unless a veto is received from that site.

13.3 Production, packaging, labelling and distribution of study medication

Medication will be prepared in instalments as dictated by recruitment rate, production and distribution capacity and materials expiry date constraints.

Ten mg and 20mg tablets of nicorandil will be prepared together with matching placebo tablets by RPR's production plant in [redacted]. The clinical trial supplies will be manufactured in production runs separated in time and routing from the regular commercial production.

The active and placebo tablets will be identical in size, shape, colour and taste (nicorandil is bitter).

The tablets will be sealed into desiccant containing, channelled PVC / aluminium blister packs. Each pack will contain 10 tablets - five day's supply.

The blister packs will be transferred to an independent clinical trials packaging and labelling centre:

[redacted]

The blister packs will be labelled and compiled into boxes for distribution and patient use

Labelling will comply with the latest guidelines on GCP as a minimum, and will include randomisation coding.

13.4 Dosage and administration of study medication

Patients will be informed by the investigator how to take their medication and the investigator must ensure that the instructions are understood by the patient.

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

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

The investigators should increase the dose according to the schedule, unless a justifiable clinical decision is made to not do so.

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

14 Practical Considerations

14.1 Case report form handling

The investigator has to keep a written or electronic patient file for every patient participating in the clinical study. In this patient file it must be possible to identify each patient by using this patient file. The period during which the patient is participating in the clinical study must be clearly stated.

Additionally, any other documents with source data, especially original print-outs of data that were generated by technical equipment have to be filed. This includes for example laboratory value listings, ECG recordings, etc. All these documents have to bear at least patient initials, patient number and the printing date to indicate to which patient and to which study procedure the document belongs and to enable the identification of study patients.

Data to be recorded directly on the CRFs (i.e. no prior written or electronic record of data) and to be considered as source data will be identified as such.

The main objective is to obtain a complete documentation from each patient.

The data recorded in the course of this study shall be documented in the case report forms that have been specially compiled for this clinical study, and must be forwarded to the University of Glasgow. They shall then be recorded, evaluated, and stored in anonymous form in accordance with the data-protection regulations.

At randomisation, the investigator will be required to provide the University of Glasgow with the patient's name, address, date of birth and NHS number (where available). This information will be used solely for flagging subjects with national databases for death, cancer etc. All such flagging will be co-ordinated through the office of the Registrar General for Scotland and will be subject to approval by the relevant privacy committees and conducted according to Data Protection Laws. In particular, details of patient names and addresses will be stored separately from other CRFs in locked cabinets and will not in any circumstances be made available to the trial Sponsors or any other organisation.

The investigator shall ensure that the case report forms and any other documents contain no mention of patient names or other identifying data.

It shall be the duty of the investigator to ensure that confidential patient documentation is stored for at least 15 years beyond the completion or discontinuation of the clinical study. In the event that the investigator leaves his/her present place of employment (e.g. retirement, relocation), a colleague must be nominated to uphold the responsibility for storage. The Sponsors will make arrangements for the storage of non-confidential, study related documentation.

The case report forms must be filled in completely and legibly (with either black or blue ball-point pen, acceptable for use on official documents). Any amendments and corrections necessary shall be undertaken and countersigned by the investigator, stating the date of the

amendment/correction. Errors must remain legible and may not be deleted with correction aids (e.g. Tipp-Ex®). The investigator must state his/her reasons for the correction of important data.

In the case of missing data/remarks, the entry spaces provided for in the case report form should be cancelled out so as to avoid unnecessary follow-up inquiries.

The case report forms are formal study documents and must be suitable for submission to authorities.

14.2 Monitoring, supervision by authorities and quality assurance

This study is to be conducted in accordance with the Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95) dated July 17, 1996. The appointed Clinical Monitors will contact the trial centres on a regular basis, the frequency dependent on recruiting rates, and must arrange to visit every six months in order to check progress with the study. The monitors will require access to the patient records to confirm that the patient satisfies the study entry criteria and that all SAEs have been reported and documented accurately. A minimum of 25% source document verification will be carried out at all study sites. Patient records to be reviewed at each site will be selected at random by the University of Glasgow. In the case of significant discrepancies being identified, more complete review will be necessary. All CRFs submitted to the Study Data Centre will be reviewed carefully. Centres will be queried concerning important problems with the CRFs directly by Data Centre Staff.

The study protocol, each step of the data-recording procedure, and the handling of the data as well as the study report shall be subject to the independent Clinical Quality Assurance at Merck Pharmaceuticals Limited or Rhône-Poulenc Rorer Limited. Audits can be conducted to assure the validity of the study data.

14.3 Amendments to the study protocol

Changes in the study protocol must take the form of written study-protocol amendments. These shall require the approval of all persons responsible for the study.

In the case of multi-centre studies, signature of the study-protocol amendment by the principal investigator shall be considered sufficient. The other investigators involved in the study receive the amendment for acknowledgement and shall be requested to confirm by their signature that they will adhere to the amended study protocol.

Any amendments to the protocol which affect the patient, e.g. changes in procedures/assessments or matters relating to patient safety, require the approval of the Multi-centre research Ethics Committee. Changes of a purely administrative nature must be notified to the Multi-centre Research Ethics Committee, but do not require formal approval. Any amendment affecting the patient requires further informed consent from each patient prior to implementation.

14.4 Deviations from the protocol - study medication

Deviations from the protocol with regard to the administration of the study medication are not to be permitted under any circumstances. Any such deviations will not be covered by the statutory patient insurance.

14.5 Patient discontinuation

Patients are free to withdraw from the study at any time without stating their reason(s).

Patients must be withdrawn from study medication in the case of any of the following:

- withdrawal of consent
- occurrence of an exclusion criterion which is clinically relevant and affects patient safety, if discontinuation is considered necessary by the investigator and/or Safety Committee
- therapeutic failure requiring urgent additional medication
- occurrence of adverse events, if discontinuation is desired or considered necessary by the investigator and/or patient
- lack of patient compliance

If a patient has not continued to present him-/herself in the course of a clinical study, the investigator must determine the reasons and the circumstances as completely and accurately as possible.

In case of premature discontinuation of trial medication, the patient should be followed up until the end of the study for SAEs and where possible the end of study assessment should be completed. Even if withdrawn from study medication the patient should be encouraged to attend visits.

The case report form section entitled "End of study" must be completed.

14.6 Study discontinuation

The clinical study can be discontinued at the discretion of the principal investigator, of the executive committee, of the sponsors, and in the case of any of the following:

- occurrence of SAEs unknown to date in respect of their nature, severity, and duration or the unexpected incidence of known SAEs
- insufficient recruitment of patients
- cancellation of drug development

14.7 Confidentiality statement

The investigator must agree to maintain the confidentiality of the study at all times and must not reveal information relating to the Investigator's Brochure, protocol, case report forms or

associated documents without express permission of Merck Pharmaceuticals Limited and Rhône-Poulenc Rorer Limited.

14.8 Study report and publication policy

Copyright and any other intellectual property rights in the protocol or any other documentation provided by, or on behalf of the Sponsors shall remain the exclusive property of the Sponsors.

The Steering Committee have sole responsibility to analyse, report and publish the data in a manner that is best fitting to the nature of the data and the benefits that publishing the data will bring to patients who have participated in the trial, and to patients who may reasonably be expected to benefit, or otherwise, from treatment with nicorandil if the results of the study were publicly known. At the discretion of the Principal Investigator, participating investigators shall be given two weeks to review documentation and make comment.

The Sponsors will be permitted eight weeks to make reasonable comment on any manuscript to be submitted for publication or slides or other visual aids for presentation by the Steering Committee. The comments of the Sponsors will be reasonably incorporated into the manuscript and/or presentations by the Steering Committee.

In all cases the parties will abide by the directions of the contractual agreements.

14.9 Proposed study management

The study will be managed by an independent study data and co-ordination centre linked to Glasgow University and will be directed and overseen by committees made up of independent experts. These Committee's will consist of a scientific committee headed by the study chairman, a safety committee and a critical events committee.

The scientific committee will be responsible for the study design including the protocol and will approve all study documentation and procedures. The committee will consist of clinical experts, company medical representatives and statisticians.

The safety committee will be responsible for ongoing review of the safety and end-point data of the study. The safety committee will report to the steering committee who will have ultimate authority and responsibility to stop the study. Such a stop decision will be made according to a predetermined set of rules. The committee will consist of clinical experts and a statistician.

The critical events committee will be responsible for reviewing and validating all critical events data and will consist of clinical experts.

The sponsors will be represented on the scientific Committee, providing input into the study design but acting as non- voting members of this committee.

14.10 Clinical centres

In each participating hospital a main investigator will be responsible for the co-ordination of all the operations at that clinical centre, in particular:

Maintenance of study procedures
Permanent training and information of the various participants
Recruitment of patients
Follow-up of patients
Collection of study data

The principal investigator will check that all patients corresponding to the target population are considered for entry. She/he will verify the completeness and accuracy of study documents before their transmission to the Data Centre.

15 References

1 Tunstall-Pedoe H
Angina pectoris: epidemiolody and risk factors
Eur Heart J 1985; 6 (supp F): 1-5

2 Cleland J
Angina: are drugs a cut above surgery
Economics, Medicines and Health 1995; Autumn: 22-24

3 Greener M
What does angina really cost?
Costs and Options in Angina 1997; Issue II: 6-7

4 Gandhi M M
Clinical epidemiology of Coronary heart disease in the UK
British Journal Hospital Medicine 1997; 58-1 : 23-27

5 Frampton J, Buckley MM, Fitton A
Nicorandil: a review of its pharmacology and therapeutic efficacy in angina pectoris
Drugs 1992;44 (4): 625-655

6 Gross JG, Auchampach JA
Role of ATP dependent potassium channels in myocardial ischaemia
Cardiovasc Res 1992; 26: 1011-1016

7 Auchampach JA, Cavero I, Gross GJ
Nicorandil attenuates myocardial dysfunction associated with transient ischaemia by opening ATP dependent potassium channels
Cardiovasc Pharmacol 1992; 20: 765-771

8 Yellon DM
Preconditioning the myocardium: experimental and clinical perspectives
Br J Cardiol 1995; 2 (2): 39-42

9 Gross JG, Auchampach JA, Maruyama M et al
Cardioprotective effects of nicorandil
J Cardiovasc Pharmacol 1992; 20: 522-528

10 Waltier DC, Gross JG, Auchampach JA
Relationship of severity of myocardial stunning to ATP dependent potassium channel modulation
J Cardiovasc Surgery 1993; 8: S279-S283

11 Saito S, Tamura Y, Moriuchi M et al
Comparative efficacy and safety of nitroglycerine, verapamil and nicorandil during coronary angioplasty
J Am Coll Cardiol 1991; 17: 337 (abstract)

12 Patel D J, Purcell H, Wright C, Clarke D, Fox K, on behalf of Nicorandil Unstable Angina Study Investigators
Nicorandil reduces myocardial ischaemia and tachycarrhythmias in unstable angina: results of a randomised placebo-controlled multicentre study.
Abstract, XIXth Congress of the European Society of Cardiology, Stockholm, August 24-28, 1997

13 Gandhi MM, Lampe FC, Wood DA
Incidence, clinical characteristics, and short-term prognosis of angina pectoris
Br Heart J 1995;73:193-198

14 Shepherd J, Cobbe SM, Ford I, et al for the West of Scotland Coronary Prevention Study Group.
Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia.
New Engl J Med 1995:333:1301-1307

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.
J Am Coll Cardiol 1994;24:11-20.

16 Dargie HJ, Ford I, Fox KM, on behalf of the TIBET Study Group.
Total Ischaemic Burden European Trial (TIBET) : effects of ischaemia and treatment with atenolol, nifedipine SR and their combination on outcome.
Eur Heart J 1996;17:104-112.

17 Pepine CJ, Cohn PF, Deedwania PC, et al for the ASIST Group.
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

Amendment No: 1

Protocol No: EMD 36385-147

Title: IONA Study
(Impact Of Nicorandil in Angina)

A double-blind, parallel group, placebo controlled, multi-centre study to examine the hypothesis that nicorandil, with a target dose of 20 mg 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.

Date of final Protocol: 08.12.97

Date of amendment: 26.04.99

Investigator Name: .....

Investigator Signature: .....

Date: .....

Change to Protocol

The protocol is being amended to make the definition of angina clearer.

6.2 Inclusion Criteria

Page 11 Subsection 6.2.3

Old text

Evidence of stable angina of effort (one or more episodes of angina or use of GTN tablet or spray) for the symptomatic relief at least once per week.

New text

Patients with evidence of angina of effort for whom further medical treatment may be appropriate.

The rationale behind this amendment is to help improve recruitment and to provide a clearer definition of the patients to be included. It will not have an effect on the study outcome as the frequency of angina attacks is not related and it will exclude those patients who are currently controlled on their current anti anginal medication.

List of Signatories

	Signature and date
[redacted] University of Glasgow	
[redacted] University of Glasgow	
[redacted] University of Nottingham	
[redacted] Nottingham Clinical Trials Data Centre	
[redacted]	
[redacted] Rhône-Poulenc Rorer Limited	
[redacted] Merck Pharmaceuticals Limited	

Amendment No: 2

Protocol No: EMD 36385-147

Title: IONA Study
(Impact Of Nicorandil in Angina)

A double-blind, parallel group, placebo controlled, multi-centre study to examine the hypothesis that nicorandil, with a target dose of 20 mg 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.

Date of final Protocol: 08.12.97

Date of amendment 1: 26.04.99

Date of amendment 2: 31.03.00

Investigator Name: .....

Investigator Signature: .....

Date: .....

Amendment I

Change to Protocol
The study period is to be extended by four months.

1 Study summary – Study Design and Duration

Page 6

Old text

"The maximum follow-up will be 36 months."

New text
"The maximum follow-up will be 40 months."

5 Study Schedule

Page 10

Old text

"The total study will complete in three years, comprising an expected two year recruitment period and a follow-up period of one year.....The maximum follow-up will be 36 months."

New text
"The total study will complete in three years, four months, comprising an expected two years and four months recruitment period and a follow-up period of one year.....The maximum follow-up will be 40 months."

Rational
This amendment is necessary to accrue sufficient patient years of data. A slower than expected recruitment in the first six months of the study means that the 8,750 patient years of data required by the protocol will not be achieved until September 2001, four months later than originally anticipated.

Amendment II

Change to Protocol
The monitoring of the study is being carried out by Ingenix International rather than Nottingham Clinical Trial Data Centre.

1 Summary – Study Sites

Page 6

Old text

"..with monitoring of the study sites carried out by the Nottingham Clinical Trial data Centre (NCTDC), Queen's Medical Centre, University Hospital, Nottingham NG7 2UH. [redacted]

New text
"...with monitoring of the study sites carried out by Ingenix International Ltd, Number 7, Castle Gate, Castle Street, Hertford, Hertfordshire, SG14 1HD. [redacted]

Amendment III

Change to Protocol
The number of centres has been expanded from 100 to 219 sites and from hospital centres to hospital and primary care centres.

1 Summary – Study Sites

Page 6

Old text
" Subjects will be seen in the investigators clinics in hospitals throughout the UK."

New Text

" Subjects will be seen in the investigators' clinics in hospitals and primary care centres throughout the UK."

6 Patient Selection

6.1 Number of Patients and Study Sites

Page 10

Old Text
"It is anticipated that up to 100 study centres will be required."

New Text

"It is anticipated that up to 220 study centres will be required."

14 Practical Considerations

14.10 Clinical Centres

Page 29

Old Text
"In each participating hospital centre a main investigator will be responsible for the co-ordination of all the operations at that clinical centre....."

New Text
"In each participating hospital or primary care centre a main investigator will be responsible for the co-ordination of all the operations at that clinical centre....."

Amendment IV

7 Clinical Assessments

7.2 Laboratory

Page 12

Old Text
A 30ml blood sample will be taken (at study entry only) to determine any relationship between the presence of coronary heart disease and

(i) total cholesterol and its fractions;
(ii) (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.

New Text
A 30ml blood sample will be taken (at study entry only) in the first 2,500 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.

Patient information Sheet.

Appendix III

Second page

Old Text
One blood sample will be taken at the start of the study

New Text
This sentence will be deleted.

Rational
It was agreed by the study steering committee that 2,500 samples would be sufficient for the 'sub studies' to be conducted on these blood samples, the calculation of 5,000 patients being based upon the primary end point of the study.

Amendment V

8 Patient visit Schedule
Page 14

Final Visit

Old Text
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
Complete study withdrawal form

New Text
Obtain 12-lead ECG
Measure blood pressure
Assess study drug compliance
Obtain concomitant medication information
Obtain Canadian Cardiovascular society functional Classification of angina
Assess for serious adverse events
Complete study withdrawal form

Rational
It was agreed by the study steering committee that it may prove of value to analyse final blood pressure, comparing the two treatment groups and comparing final blood pressure with baseline blood pressure.

List of Signatories

	Signature and date
[redacted] University of Glasgow	
[redacted] University of Glasgow	
[redacted] University of Nottingham	
[redacted] Nottingham Clinical Trials Data Centre	
[redacted]	
[redacted] Rhône-Poulenc Rorer Limited	
[redacted] Merck Pharmaceuticals Limited	