REPORT

Trial to show the impact of nicorandil in angina (IONA): design, methodology, and management

The IONA Study Group

Abstract

Objective—IONA (impact of nicorandil in angina) is a randomised, double blind, placebo controlled trial that will test the hypothesis that nicorandil (target dose of 20 mg twice daily) will reduce the incidence of cardiovascular events in a cohort of men and women with effort angina and additional risk factors.

Methods—The primary composite end point of the study is coronary heart disease death, non-fatal myocardial infarction or unplanned hospital admission for cardiac chest pain, and the secondary end point is the combined outcome of coronary heart disease death or non-fatal myocardial infarction. Other cardiovascular outcomes and all cause mortality will also be reported.

Results—More than 5000 subjects have been randomised to receive nicorandil or placebo in addition to normal antianginal treatment. The target population, the assessments made, and the management of the trial are described in detail.

Conclusions—The IONA study has achieved its first aim of randomising more than 5000 high risk subjects with effort angina. Subject follow up will be complete in the third quarter of 2001. (*Heart* 2001;85:e9)

Keywords: stable angina of effort; cardiovascular events; nicorandil

Angina pectoris is important both as a cause of disability and as a marker for underlying coronary heart disease. The prevalence of angina is difficult to assess, but may vary from 2.3% to 5.1% in men aged 40–59 years.¹ Approximately eight new cases per 10 000 of the population present to the National Health Service (NHS) every year,² approximately half of whom visit 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 age specific coronary heart disease deaths in most western countries over the past 15 years, there is significant morbidity and mortality associated with this condition. One in eight deaths worldwide and one in four in the UK are attributable to coronary heart disease, 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 history of angina.

The effect of medical treatment on outcome in angina is uncertain. With the exception of β blockers in survivors of myocardial infarction,^{5–8} no other specific antianginal treatment has been shown to improve outcome, although other treatments—including aspirin,⁹ angiotensin converting enzyme inhibitors,¹⁰ and lipid modifying agents^{11–14}—have been shown to reduce the risk of cardiovascular events in particular subgroups of subjects with coronary heart disease.

Nicorandil has been marketed in Japan since 1984 and is currently licensed in the UK for the prevention and long term treatment of chronic angina pectoris. Antianginal efficacy and safety comparable to that achieved with conventional oral nitrates,^{15–16} β blockers,^{17–20} and calcium antagonists^{21–24} have been demonstrated in double blind randomised studies.

Nicorandil is a nicotinamide ester with potassium channel opening properties. The nitrate component dilates systemic veins and epicardial coronary arteries. 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. Nicorandil consequently increases coronary blood flow and reduces both cardiac preload and afterload.^{25–28}

During ischaemia leading to cellular hypoxia, the decreased cytoplasmic adenosine triphosphate (ATP) concentration 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.²⁹ ATP is conserved, maintaining cellular integrity through the preservation of vital intracellular metabolic functions. This may represent a natural myocardial protective mechanism.³⁰

Cardioprotective properties have been demonstrated in animal models of myocardial infarction. The role of potassium channels in

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Accepted 28 February 2001

Figure 1 Visit schedule.

this form of protection has been proven during studies that use the technique of ischaemic preconditioning.^{31 32} The mechanisms involved in ischaemic preconditioning may also explain the clinical effects seen following sequential coronary artery occlusions during percutaneous transluminal coronary angioplasty (PTCA) procedures, and the clinical phenomena of warm up angina and myocardial stunning.^{33 34} A recent pilot study showed a reduction in the incidence of supraventricular and ventricular tachycardias in patients with unstable angina who were taking nicorandil when compared with placebo. A reduction in transient myocardial ischaemia was also shown.³⁵

The impact on life events of these putative mechanisms of benefit will be assessed for the first time in the IONA (impact of nicorandil in angina) study.

Study design

STUDY SUBJECTS AND RECRUITMENT

More than 5000 subjects who had angina of effort and for whom further treatment was appropriate have been randomised into a double blind trial to receive nicorandil or placebo on top of standard antianginal treatment. The angina of effort could be recently diagnosed or chronic. Standard background antianginal treatment was not specified but was to be optimal treatment as judged by the investigator for the individual patient. Subjects were recruited in more than 200 trial centres in hospitals and general practices throughout the UK.

The study recruited men (aged ≥ 45 years) and women (aged ≥ 55 years), with evidence of stable angina of effort, who also required regular treatment with one or more symptom relieving oral antianginal drugs (long acting nitrate formulation, β blocker, or calcium channel blocker) and had experienced *at least one* of the following:

- previous myocardial infarction;
- previous coronary artery bypass graft;
- coronary heart disease proven by angiography or a documented positive exercise test (≥ 1 mm ST depression) in the previous two years.

The last of the three inclusion criteria was required to be accompanied by at least one of the following: left ventricular hypertrophy on ECG (tall R in aVL, SV1 + RV6 > 35 mm, lateral T inversion); evidence of left ventricular dysfunction (ejection fraction $\leq 45\%$ or end diastolic dimension > 5.5 cm); age ≥ 65 years; diabetes (types I or II); hypertension (treated, and/or systolic blood pressure > 160 mm Hg or diastolic blood pressure > 95 mm Hg); documented evidence of other vascular disease

(stroke, transient ischaemic attack requiring hospital admission, peripheral arterial disease).

The strategy of recruiting subjects with clearly established coronary heart disease or a positive exercise test with additional risk factors was adopted to ensure that the study would recruit a group of subjects who were at high risk of suffering a primary end point during the period of randomised follow up.

Patients with any of the following were excluded:

- uncontrolled cardiac failure or arrhythmias;
- unstable angina;
- coronary artery bypass graft or myocardial infarction in the previous three months;
- percutaneous transluminal coronary angioplasty (PTCA) in the previous six months;
- uncontrolled hypertension (systolic blood pressure > 180 mm Hg or diastolic blood pressure > 110 mm Hg);
- the presence of other diseases that in the investigator's opinion would reduce life expectancy or influence significantly the patient's cardiovascular condition;
- current treatment with nicorandil;
- current treatment with sulfonylureas (this group of antidiabetic drugs blocks potassium channel opening);
- pregnancy or lactation;
- legal incapacity or limited legal capacity;
- participation in another clinical study within the previous 30 days;
- presence of contraindications to the study medication;
- known drug or alcohol abuse.

All subjects provided written informed consent before inclusion in the study.

STUDY VISITS AND FOLLOW UP

Subjects were randomised to nicorandil 10 mg twice daily or matching placebo; after two weeks, in subjects tolerating the initial treatment the dose was increased to 20 mg twice daily or matching placebo. At eight weeks after randomisation, there was a visit to ensure tolerability and encourage compliance. At this visit there was an opportunity to down titrate if appropriate. Thereafter, study visits will be scheduled at 16 week intervals to a maximum of three years and a minimum of one year. A study closedown visit will be conducted for each subject at the end of the study. The visit schedule is depicted in fig 1. All subjects will be followed until study closedown, independently of their compliance with the study drug administration schedule.

METHODS OF ASSESSMENT

Prerandomisation

Written informed consent was obtained. Before randomisation, data were recorded on age, sex, height, weight, blood pressure, heart rate, smoking status, medical history (vascular disease, diabetes, hypertension, cancer, chronic and ongoing illnesses), and concomitant drug treatment. Anginal status was assessed using the Canadian Cardiovascular Society functional classification of angina (CCSF). At baseline a 12 lead ECG was recorded. In a

substudy involving approximately half the subjects, a blood sample was taken for subsequent assessment of cholesterol and serum markers of infection and genetic polymorphisms. Inclusion and exclusion criteria were checked. Randomisation was completed by a call to a central interactive voice response system and the study preparation was issued.

Two week assessment

Compliance will be assessed and serious adverse events documented.

Eight week assessment

Compliance will be assessed and serious adverse events documented.

Sixteen weekly assessments

At all visits, compliance will be assessed and serious adverse events documented, anginal status will be assessed using the CCSF classification of angina, and concomitant drug treatment documented. At the third, sixth, and ninth 16 week assessment a 12 lead ECG will be recorded.

Closedown assessment

In addition to data collected at the third, sixth, and ninth 16 week assessment visits, blood pressure will also be recorded.

Occasional data collection

In addition to the data collected routinely at study visits, case report forms will be completed to document permanent discontinuation of the study preparation, serious adverse events, and study end points.

A *serious adverse event* is any event that is fatal, life threatening, requires or prolongs hospital admission, or results in persistent or significant disability or incapacity; a congenital anomaly or birth defect; a development of cancer; a drug overdose or drug abuse; or an important medical event.

Important medical events are those that 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 they involve hospital admission or not. *Study critical events* will be a subset of the serious adverse events, will be documented in greater detail, and will provide the study end point data.

Subject flagging with national registries

All subjects will be flagged with the national registries for death in Scotland, England and Wales, and Northern Ireland and, in Scotland, with the Scottish record linkage project for mortality, hospital admissions, and incident cancers.

STUDY END POINTS

The primary end point of the study is the combined outcome of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for cardiac chest

pain. The secondary end point is coronary heart disease death or non-fatal myocardial infarction. Other outcomes to be reported will include all cause mortality and death from specific causes, all cardiovascular events (cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, transient ischaemic attacks requiring hospital admission, and unplanned hospital admission for cardiac chest pain), cardiovascular hospital admission, cerebrovascular events (fatal and non-fatal stroke or transient ischaemic attacks requiring hospital admission), all cause hospital admission, and worsening of anginal status as assessed from the CCSF classification of angina or unplanned hospital admission for cardiac chest pain. Formal definitions of the study end points are given in appendix 1.

STATISTICAL METHODS

Sample size

In a small community based study, Ghandi and colleagues estimated that approximately 26% of newly diagnosed subjects with angina would have a coronary event (cardiac death, non-fatal myocardial infarction, or coronary revascularisation) after one year.³⁶ However, many of these subjects may have been candidates for early revascularisation. At the other end of the spectrum, in a similarly sized group of hypercholesterolaemic subjects being treated for angina at baseline in the WOSCOPS (west of Scotland coronary prevention study) trial,³⁷ approximately 26% died of coronary heart disease or had a non-fatal myocardial infarct after five years of follow up. In the ACIP (asymptomatic cardiac ischaemia pilot) study 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.³⁸ In the TIBET (total ischaemic burden European trial)³⁹ and ASIST (atenolol silent ischaemia)⁴⁰ studies, the event rates were approximately 7% at one year. In TIBET, all the subjects had chronic stable angina and a positive exercise test, while in ASIST the subjects had either mild or no angina but were positive on exercise test and ambulatory monitoring. Given the increasing use of HMG CoA reductase inhibitors in this patient group, event rates may be lower than has previously been seen in this type of study population. However, with the inclusion of subjects with newly diagnosed angina of effort and those with other risk factors, it might be reasonable to assume a 13% event rate after an average of 21 months of follow up in the combined end point of coronary heart disease death, non-fatal myocardial infarction, or unplanned hospital admission for chest pain. On the basis of these assumptions, a study of 5000 patients with 8750 subject years of follow up will give 95% power (5% significance level) to detect a 25% reduction in the primary end point event rate (and 80% at the 5% level to detect a 20% reduction). Similarly, an 8% event rate for the combined end point of coronary heart disease death or non-fatal myocardial infarction would yield 80% power (5%

significance level) to detect a 25% risk reduction.

Statistical analysis

All end points will be evaluated on an intention to treat basis as the primary analysis. The results for the primary and secondary end point will also be reported on the basis of an on-treatment analysis. All end points with the exception of worsening of angina will be analysed using survival analysis methodology. For each end point, the outcome for analysis 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. Event rates in the two treatment groups will be compared using the log rank test. Risk reductions will be calculated in the form of hazard ratios from the Cox proportional hazards model, with treatment fitted as the only covariate. Additional analyses will be conducted to investigate the predictive value of, and possible interaction with, treatment of the following risk factors recorded at baseline: age, sex, history of myocardial infarction, history of coronary artery bypass graft, history of hypertension, history of diabetes, left ventricular hypertrophy on ECG, evidence of left ventricular dysfunction, and smoking status. Deterioration in angina will be defined as an occurrence of hospital admission for cardiac chest pain or a worsening of the CCSF classification of anginal status. Outcomes will be compared between treatment groups using a χ^2 statistic.

STUDY COORDINATION AND MANAGEMENT

The study is coordinated by an independent statistical and data centre, and is directed and overseen by committees made up of independent experts. These committees consist of a scientific steering committee headed by the study chairman, a data and safety monitoring committee, and a critical events committee. The responsibilities and activities of these committees and coordinating groups are described below. Committee memberships and other key members of the IONA study group are listed in appendix 2.

Coordination and data centre

This centre is in the Robertson Centre for Biostatistics, University of Glasgow. The centre contracts with study trial centres, receives all study data, is responsible for all aspects of data management, investigator reimbursement, and generation of reports for key committees, provides clinical and other advice to trial centres, and will conduct all statistical analyses for study publications.

Trial centre monitoring

The activities of the trial centres and adherence to the principles of good clinical practice are monitored by staff from Ingenix Pharmaceutical Services.

Scientific steering committee

This committee is responsible for the protocol and other aspects of the study design, and approves all study documentation and procedures.

Data and safety monitoring committee

This committee is responsible for the ongoing review of the safety and end point data of the study. The data and safety monitoring committee reports to the scientific committee which has the ultimate authority and responsibility for stopping the study prematurely. The data and safety monitoring committee will be responsible for reviewing, for evidence of harm, serious adverse event data and withdrawals from treatment with study preparations. The data will be considered from both clinical and statistical viewpoints. Three interim analyses will be carried out to test for evidence of efficacy, after approximately 25%, 50% and 75% of the target patient years of follow up have accrued. Overwhelming evidence of benefit for the primary end point or all cause mortality ($p < 0.001$) will be required for the data and safety monitoring committee to consider a recommendation of early stopping of the trial to the scientific steering committee.

Critical events committee

This committee is responsible for reviewing and validating all critical event data according to the formal definitions given in appendix 1.

Discussion

In the third quarter of 2000, the IONA study achieved its first target of randomising more than 5000 subjects. The number of subjects recruited was approximately equal in general practice and in hospital centres. The strategy of recruiting both in general practice and in hospitals is important as it will ensure that the results of the study will have the widest applicability. Nitrates, β blockers, calcium channel blockers, and nicorandil all provide important symptomatic relief for angina of effort. With its large population of high risk subjects with angina of effort, IONA will provide important information on whether or not nicorandil, on top of standard treatment, provides additional benefit in terms of the prevention of major cardiovascular outcomes. In addition to the important information to be obtained from the comparison of the randomised treatment groups, the long term follow up of the IONA recruits will provide important information on prognosis for patients who are medically managed in the UK. The final study visits will be completed in the third quarter of 2001 and the results of the study will be made available as soon as possible thereafter.

The IONA study is sponsored by Merck Pharmaceuticals Ltd, Aventis Pharma Ltd, and Chugai Pharmaceutical Co Ltd.

Appendix 1

End point definitions to be used by the critical events committee (unless otherwise indicated)

1. Miscellaneous definitions

1.1. Hospital admission

An admission to hospital is defined as any attendance at hospital requiring completion of the hospital admission procedures and usually at least an overnight stay.

1.2. Unplanned admission

Unplanned admission is defined as an emergency or other urgent, non-elective admission precipitated by general practitioner (GP) referral or self referral to an accident and emergency department, urgent GP referral to hospital in some other way, emergency call to the ambulance service, or urgent admission from a hospital outpatient clinic. The admission must be precipitated by a need for urgent investigation or treatment which cannot be provided on an outpatient basis and which cannot be deferred on an inpatient basis.

2. Non-fatal events

2.1. Events not leading to hospital admission

2.1.1. Silent myocardial infarction

An ECG, at an annual or at an unscheduled visit, that is diagnostic of myocardial infarction (new Q waves ≥ 0.04 ms in duration in at least two consecutive leads) and which was not evident on the previous ECG.

2.1.2. Stroke

All strokes will be counted as events whether occurring spontaneously or directly as a consequence of an investigation/procedure/operation. A stroke will be diagnosed if both of the following criteria are fulfilled:

(a) New localising neurological deficit and/or change in level of consciousness, lasting > 24 hours, or leading to death.

(b) No other cerebral process (for example, a brain tumour) or other disorder (for example, a metabolic disturbance such as hypoglycaemia) or peripheral lesion that could cause a localising neurological deficit or coma.

2.2. Events leading to hospital admission

2.2.1. Cardiovascular, involving chest pain

2.2.1.1 *Acute myocardial infarction*—All definite myocardial infarcts will be counted as events whether they occurred spontaneously or as the direct consequence of an investigational procedure or operation. A diagnosis of myocardial infarction will be made if two of the following three criteria are met:

(a) At least one of the following:

(i) cardiac ischaemic type pain lasting at least 30 minutes;

(ii) pulmonary oedema;

(iii) cardiogenic shock not otherwise explained.

(b) Development of new abnormal Q waves (≥ 0.04 ms in duration) in at least two consecutive ECG leads not present on an ECG recorded before the current event, or transient elevation of ST segment followed by T wave inversion in at least two consecutive leads, or new left bundle branch block, or transient elevation of ST segment, new bundle branch block, or other typical ECG changes leading to emergency angiography during which a complete acute occlusion of at least one coronary artery is demonstrated and following which successful emergency percutaneous revascularisation (recannulation) is performed.

(c) An elevation of cardiac enzymes defined as a transient increase in at least one set of enzymes. (Elevation to at least twice the upper limit of the local normal reference range, or creatine kinase (CK) MB fraction $\geq 10\%$ of total CK)

2.2.1.2. Chest pain which is not associated with a myocardial infarct but requires unplanned admission to hospital:

Unstable angina—Typical cardiac ischaemic type chest pain requiring hospital admission for treatment but not meeting the definition of myocardial infarction. The patient must also:

(a) develop new or evolving ST segment/T wave changes on the ECG and

(b) have treatment with parenteral (buccal—other than with short acting preparations, intravenous, transcutaneous or subcutaneous) heparin and/or glyceryl trinitrate, isosorbide dinitrate, or other nitrate.

Definite angina—Typical cardiac ischaemic type chest pain requiring hospital admission for treatment but not meeting the definition of myocardial infarction or definite unstable angina and requiring additional antianginal treatment (new antianginal drugs and/or increased dose of current treatment and/or referral for “revascularisation”).

Presumed angina—Admission with chest pain not fulfilling any of the above criteria and where there is no other recorded cause for the pain. That is, any admission with chest pain that is not caused by myocardial infarction, unstable angina, or definite angina is “presumed angina” unless a firm diagnosis to the contrary is recorded by the treating physician.

2.2.2. Cardiovascular: stroke, transient ischaemic attacks

2.2.2.1. *Stroke*—All strokes will be counted as events whether occurring spontaneously or directly as a consequence of an investigation/procedure/operation. A stroke will be diagnosed if both of the following criteria are fulfilled:

(a) New localising neurological deficit and/or change in level of consciousness lasting > 24 hours or leading to death.

(b) No other cerebral process (for example, a brain tumour) or other disorder (for example, a metabolic disturbance such as hypoglycaemia) or peripheral lesion that could cause a localising neurological deficit or coma.

2.2.2.2. *Transient ischaemic attack*—A transient ischaemic attack will be diagnosed when neurological signs and symptoms develop rapidly, last at least one minute, and disappear completely within 24 hours. The following neurological symptoms/signs may occur: hemiplegia, hemianaesthesia, hemianopia, hemiparesis, aphasia, amaurosis fugax (complete loss of vision of one eye or of the upper or lower half of the visual field, excluding blurred, distorted or grey vision).

3. Fatal events

3.1. All cause mortality

This will consist of all deaths.

3.2. Cardiovascular deaths

A cardiovascular death will be defined as either a coronary heart disease death meeting the definition below, or other cardiovascular death—for example, a stroke, ruptured aortic aneurysm, or pulmonary embolism.

3.2.1 *Coronary heart disease deaths* All deaths shall be considered coronary heart disease unless an unequivocal non-coronary heart disease cause can be established. Coronary heart disease deaths will include sudden deaths, death due to myocardial infarction, death due to heart failure, death due to a cardiac investigation/procedure/operation (procedure related death).

3.2.1.1. *Sudden death*—Deaths fulfilling any one of the following criteria:

(a) witnessed and instantaneous, without new or worsening symptoms;

(b) witnessed and preceded or accompanied by symptoms attributable to myocardial ischaemia but without other new or worsening symptoms;

(c) witnessed and preceded by symptoms attributable to a cardiac arrhythmia—for example, syncope or near syncope;

(d) patients resuscitated from cardiac arrest in the absence of worsening heart failure or other causes of death, including acute myocardial infarction, and who die within 24 hours or without regaining consciousness; similar patients who die despite attempted resuscitation;

(e) unwitnessed death in the absence of worsening heart failure or other causes of death.

3.2.1.2. *Death from heart failure*—Death occurring when at least one of the following is present in the 48 hours before death:

(a) new or increasing symptoms and/or signs (including worsening renal function) of heart failure requiring the initiation of, or an increase in, treatment directed at

heart failure or occurring in a patient already receiving maximum treatment for heart failure;
 (b) heart failure symptoms or signs requiring continuous intravenous treatment or oxygen administration;
 (c) confinement to bed but only if confinement is for heart failure symptoms;
 (d) pulmonary oedema sufficient to cause tachypnoea and distress not occurring in the context of an acute myocardial infarct or as the consequence of an arrhythmia.

3.2.1.3. *Death from myocardial infarction*—Death occurring up to 28 days after a documented myocardial infarct. Deaths from a myocardial infarct occurring as a direct result of an investigation, procedure, or operation will be classified as a death caused by myocardial infarction and a procedure related death.

3.2.1.4. *Coronary heart disease procedure related*—Deaths deemed to be directly related to that investigation/procedure/operation.

3.2.1.5 *Presumed coronary heart disease death*—Death not fulfilling any of the above coronary heart disease categories and any definite cardiovascular or non-cardiovascular definition below.

3.2.2. *Death from stroke*

Death occurring up to 28 days after a documented stroke. Deaths from stroke occurring as a direct consequence of an investigation/procedure/operation will be classified as a death caused by a stroke and a procedure related death.

3.2.3. *Cardiovascular procedure related deaths*

Death occurring within seven days of a cardiovascular investigation, procedure or operation and deemed to be directly related to that investigation/procedure/operation.

3.2.4. *Death from other cardiovascular causes*

Death must be caused by a fully documented cardiovascular cause not included above—for example, pulmonary embolism, ruptured aortic aneurysm, and so on.

3.3. Non-cardiovascular deaths

Deaths will be considered non-cardiovascular only if an unequivocal and documented non-cardiovascular cause can be established.

4. Study end points

Study end points will be defined as follows:

4.1. Coronary heart disease death

This will consist of all events satisfying definition 3.2.1 above.

4.2. Non-fatal myocardial infarction

This will consist of all events satisfying definitions 2.1.1 and 2.2.1.1 above.

4.3. Unplanned hospital admission for cardiac chest pain

This will consist of all events satisfying definition 2.2.1 above.

4.4. Worsening angina

This will be determined from the CCSF classification recorded at the routine follow up visits, and will not be validated by the critical events committee.

4.5. Cardiovascular death

This will consist of all events satisfying definition 3.2 above.

4.6. Cardiovascular hospital admission

This outcome will be derived from an explicit investigator completed field on the case report form.

4.7. Fatal and non-fatal stroke and transient ischaemic attacks requiring hospital admission

These end points will consist of all events satisfying, respectively, definitions 3.2.2, 2.1.2 and 2.2.2.1, and 2.2.2.2.

Appendix 2

IONA study group

SCIENTIFIC STEERING COMMITTEE

Voting members

Professor H J Dargie (Chairman, Glasgow Western Infirmary, Glasgow), Professor I Ford (Glasgow University, Glasgow), Dr K M Fox (Royal Brompton Hospital, London), Professor W S Hillis (Glasgow University, Glasgow).

Sponsor Representatives (non-voting)

Dr M Morris (Merck Pharmaceuticals Ltd), Dr M Ford (Aventis Pharma Ltd).

CRITICAL EVENTS COMMITTEE

Professor W S Hillis (Glasgow University, Glasgow), Professor J J V McMurray (Glasgow University, Glasgow), Dr A L Clark (University of Hull, Kingston upon Hull).

DATA AND SAFETY MONITORING COMMITTEE

Professor J Hampton (chairman, University Hospital, Nottingham), Dr A Skene (Nottingham Clinical Research Ltd), Dr J Birkhead (Northampton General Hospital, Northampton).

STATISTICAL AND DATA CENTRE

Robertson Centre for Biostatistics, University of Glasgow, Glasgow: Professor I Ford (director), Dr A D McMahon (study statistician), Ms A Trainer (database manager), Ms C Ferrell (study administrator), Dr B Shaw (clinical coordinator).

STUDY MONITORING

Ingenix Pharmaceutical Services: Ms V Diment (project manager)

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