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**CLINICAL TRIAL PROTOCOL
Incorporating Amendments 1, 2 and 3**

Version 1.2 / 2 May 2003

AD-4833 / Pioglitazone

PROactive*

***PROspective PioglitAzone Clinical Trial In MacroVascular Events**

A Macrovascular Outcome Study in Type 2 Diabetic Patients
Comparing Pioglitazone with Placebo in Addition to Existing Therapy

A Randomised, Double-Blind, Parallel-Group, Multi-Centre Study

Protocol/Trial Identification: AD-4833/EC444

Confidentiality Statement

The information provided in this document is strictly confidential and is available for review to investigators, potential investigators and appropriate Ethics Committees or Investigational Review Boards. No disclosure should take place without written authorisation from Takeda Europe R&D Centre Limited, except to the extent necessary to obtain informed consent from potential patients.

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APPENDICES

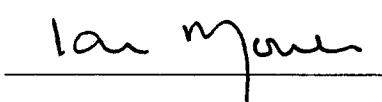
Appendix 1	Example Investigator Statement
Appendix 2	Patient Information Sheet and Consent Form (Master Template)
Appendix 3	Declaration of Helsinki (Edinburgh, Scotland, October 2000)
Appendix 4	NYHA Classification

1 PRELIMINARY

1.1 Signatures

The undersigned agree to conduct the PROactive clinical trial (Takeda study code: AD-4833/EC444) in accordance with the requirements of this Protocol and the following:

- Declaration of Helsinki (Edinburgh, Scotland, October 2000)
- Good Clinical Practice of the European Community, CPMP/ICH/135/95
- Applicable laws and regulations
- Regulatory requirements for the reporting of serious adverse events, as indicated in section 8.2

Name	Signature	Date
Prof J A Dormandy Study Chairman		<u>8/5/2003</u>
Mr I Moules European Development Director (Takeda Europe R&D Centre Limited)		<u>9.5.03</u>
Dr B Voet Director of IT, Biometrics and Data Management (Takeda Europe R&D Centre Limited)		<u>12/05/2003</u>

Note

Each investigator will sign a copy of the Investigator Statement, a copy of which is given in Appendix 1.

1.2 Contacts

Emergency Unblinding:

Nottingham Clinical Research Limited

Helpline: (24-hour service) via the central telephone randomisation service (IVRS) available by calling the free phone number indicated in the study materials and selecting option 6 (special assistance) or by direct call to +44 (0) 7968 989 063.

Medical Assistance (Safety):

Dr G Belcher, Director of Drug Safety
Takeda Europe R&D Centre Limited

Tel.: +44 (0)20 7484 9026

Fax: +44 (0)20 7484 9065

Mobile: +44 (0)78 0389 6005

Notification of Serious Adverse Events:

Complete an Alert Report Booklet and fax immediately to:

Nottingham Clinical Research Limited (NCRL)

Isaac Newton Centre

Nottingham Science and Technology Park

Nottingham NG7 2RH

United Kingdom

Fax: +44 (0)115 956 7722

Tel: +44 (0)115 956 7711

Your study monitor or NCRL should also be contacted by telephone if any help is required with the reporting of a Serious Adverse Event.

Administrative Assistance:

Contact your study monitor: Contact details are provided in the Investigator Site File.

Additional Assistance:

Additional help with operational matters may be obtained by contacting:

Lucy Bennett

Senior Project Manager

Nottingham Clinical Research Limited

Tel: +44 (0)115 956 7711 / +44 (0)115 956 7719

Fax: +44 (0)115 922 0960

Or

Hilary Thomas
Clinical Project Manager
ICON Clinical Research
Tel: +44 2380 688 500
Fax: +44 2380 688 501

1.3 Organisation

The parties to this clinical trial, together with their roles and responsibilities, are as follows:

1.3.1 Sponsor

Takeda Europe R&D Centre Limited (Takeda)
Savannah House
11-12 Charles II Street
London SW1Y 4QU
United Kingdom

Representative:

Mr Ian Moules
European Development Director
Tel: +44 (0)207 484 9006
Fax: +44 (0)207 484 9060

1.3.2 Study Partner

Eli Lilly and Company (Lilly) is a partner in this study.

1.3.3 Contract Research Organisations

Nottingham Clinical Research Limited (NCRL)

Isaac Newton Centre
Nottingham Science and Technology Park
Nottingham NG7 2RH
United Kingdom

NCRL will act as the Primary Study Coordinating Centre, responsible for project and data management, statistics, central randomisation and materials distribution.

ICON Clinical Research (ICON)

Heinrich-Hertz-Straße 26
D-63225 Langen
Germany

ICON will provide regulatory affairs, site management and site monitoring services.

ICON Laboratories

South County Business Park
Leopardstown
Dublin 18
Ireland

ICON laboratories will be responsible for the central measurement of laboratory parameters.

Brecon Pharmaceuticals Limited (Brecon)

Pharos House
Wye Valley Business Park
Hay-on-Wye
Hereford HR3 5PG
United Kingdom

Brecon will package, label and release the study medication.

1.3.4 International Steering Committee

The International Steering Committee (ISC) will be responsible for the overall design and conduct of the trial. The ISC will be chaired by Professor J Dormandy (the Study Chairman) and will comprise the Executive Committee (see below) together with a panel of investigators (the National Coordinators), each representing a country or region participating in the study. Additional persons may be co-opted as required. Members of the Steering Committee will also assist with site recruitment and promotion of the study at a regional level.

1.3.5 Executive Committee

The Executive Committee (EC) will have the following membership:

Professor J Dormandy (Study Chairman)
Professor B Charbonnel
Professor E Erdmann
Professor M Massi-Benedetti
Mr Ian Moules (Takeda)
Dr M Tan (Lilly)
Dr A Skene (NCRL)

The EC will be responsible for overall management of the study on behalf of the ISC. Decision making within this Committee will be by consensus. The EC, on behalf of the ISC, will be the point of contact for the Data and Safety Monitoring Committee and will be involved in any decision to terminate or otherwise change the conduct of the study.

1.3.6 Operations Committee

The Operations Committee will comprise:

The Study Chairman
Dr I Moules (Takeda)
Dr G Belcher (Takeda)
Dr R Urquhart (Takeda)
Dr S Lenton (Takeda)
Dr J Kinley (Takeda)
Mrs L Bennett (NCRL)
Mr A Kempton (NCRL)
Ms H Thomas (ICON)

together with representatives of the EC and additional personnel from the Sponsor and the CROs, as required. This Committee, which will report to the EC, will have responsibility for defining the Manuals of Operation for the study and ensuring the smooth day-to-day progress of the study.

1.3.7 Data and Safety Monitoring Committee

The Data and Safety Monitoring Committee (DSMC) will have the following membership:

Professor P Lefèbvre (Chairman)
Professor R Wilcox (Vice-Chairman)
Professor G Murray (Director of the Independent Statistical Centre)
Professor L Wilhelmsen
Professor E Standl

The DSMC will be responsible for the interests of patients and, to this end, will undertake regular reviews of the safety data. In addition, the DSMC will be required to undertake additional duties with respect to the interpretation of two planned interim analyses. The specific responsibilities and duties will be described in a DSMC Charter which will be ratified by the ISC and DSMC prior to the commencement of recruitment. The preparation of reports for consideration by the DSMC will be assigned to an Independent Statistical Centre at the University of Edinburgh directed by Professor G Murray.

1.3.8 Endpoint Adjudication Committee and Panel

Primary and secondary endpoints of the study will be subject to central review and classification. This process will be overseen by an Endpoint Adjudication Committee (EAC) chaired by Professor P Brunetti. In addition to the Chairman, the EAC shall consist of at least one cardiologist, one vascular surgeon and one neurologist. The Endpoint Adjudication Committee will have the following membership:

Professor P Brunetti (Chairman)
Professor M-G Bousser (Neurologist)
Professor L Norgren (Vascular Surgeon)
Professor D Thomas (Cardiologist)

Membership of the EAC, its responsibilities together with a detailed description of the review process will be given in an Endpoint Adjudication Charter which will be ratified by the ISC and EAC prior to the commencement of recruitment.

1.3.9 Manuals of Operation

PROactive is a large multinational study requiring significant logistical and administrative structures and procedures for its efficient execution. Details of these will be defined in a set of study-specific Manuals of Operations (MOPs). The MOPs will govern the following areas of operation:

- Project management
- Data management
- Serious adverse event processing
- Site management and monitoring (including source data verification)
- Study treatment and materials distribution
- Central telephone randomisation service (IVRS)
- Statistical analysis plan

This protocol addresses all ethical, scientific, clinical and safety issues pertaining to the study. Reference should be made to the relevant MOP(s) for additional administrative details.

1.4 Abbreviations

°C	Degree Celsius
ABPI	Ankle Brachial Pressure Index
ACE	Angiotensin-Converting-Enzyme
AD-4833	Code Name of Pioglitazone
AE	Adverse Event
ALT	Alanine Aminotransferase
ALP	Alkaline Phosphatase
AST	Aspartate Aminotransferase
BMI	Body Mass Index
CABG	Coronary Artery Bypass Graft
CK	Creatine Kinase
CK-MB	Creatine Kinase MB isoenzyme
CPK	Creatine Phosphokinase
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
CRO	Contract Research Organisation
CV	Curriculum Vitae
dl	Decilitre
DCCT	Diabetes Control and Complications Trial
DSMC	Data and Safety Monitoring Committee
EAC	Endpoint Adjudication Committee
EC	Executive Committee
ECG	Electrocardiogram
FBG	Fasting Blood Glucose
FPG	Fasting Plasma Glucose
GCP	Good Clinical Practice
HbA _{1c}	Glycosylated Haemoglobin A _{1c}
HDL	High Density Lipoprotein
HIV	Human Immunodeficiency Virus
HMGCoA	β -hydroxy- β -methylglutaryl coenzyme A
ICH	International Conference for Harmonisation
IDF	International Diabetes Federation
INN	International Non-proprietary Name
ISC	International Steering Committee
IUD	Intra-uterine Device
IVRS	Interactive Voice Response System (Telephone Randomisation)
LBBB	Left Bundle Branch Block
LDH	Lactate Dehydrogenase
LDL	Low Density Lipoprotein
mg	Milligram
ml	Millilitre
mmol	Millimole
ms	Millisecond
MOP	Manual of Operations
No.	Number
NCR	No Carbon Required
NYHA	New York Heart Association

PCI	Percutaneous Coronary Intervention
PPAR γ	Peroxisome Proliferator-Activated Receptor Gamma
PTCA	Percutaneous Transluminal Coronary Angioplasty
SAE	Serious Adverse Event
SDV	Source Data Verification
SOP	Standard Operating Procedure
TIA	Transient Ischaemic Attack
ULN	Upper Limit of Normal

2 TRIAL SUMMARY

2.1 Title

PROspective PioglitAzone Clinical Trial In MacroVascular Events (PROactive)

A macrovascular outcome study in type 2 diabetic patients comparing pioglitazone with placebo in addition to existing therapy.

2.2 Objectives

- To demonstrate that pioglitazone reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes mellitus
- To further characterise the safety of pioglitazone in this group of type 2 diabetes patients

2.3 Rationale

Diabetes mellitus is one of the most common non-communicable diseases globally. In the European region of the International Diabetes Federation there are over 22 million persons with diabetes. Complications of diabetes, both microvascular and macrovascular, are resulting in increased disability and reduced life expectancy¹.

Conventional agents used to treat diabetes have not shown an improvement in macrovascular outcomes in the way that they have for microvascular complications. Nevertheless, there is now much indirect evidence that peroxisome proliferator-activated receptor (PPAR) agonists may favourably influence macrovascular outcomes, either through modification of risk factors (such as lipids) or through direct effects on the vessel wall².

Pioglitazone is a newly developed PPAR- γ agonist for the treatment of type 2 diabetes mellitus. The overall pattern of changes induced by pioglitazone suggests a general amelioration of the metabolic syndrome which should result in reduced macrovascular morbidity.

The present study will examine whether the incidence of macrovascular events is reduced in patients receiving pioglitazone in combination with their usual medication for glycaemic management compared with a control group of patients who will receive placebo in combination with their usual treatment.

2.4 Patient Population

Inclusion criteria

Patients with type 2 diabetes mellitus are potentially eligible for entry into the study if each of the following is met:

- Male or female patients, aged 35-75 years inclusive
- HbA_{1C} above the upper limit of normal (i.e. the local equivalent of 6.5% for a DCCT traceable assay) as determined by the local laboratory at screening or at any time in the previous two months
- Established history of macrovascular disease, defined as one or more of:
 - myocardial infarction at least 6 months before entry into the study (as documented in the patient's medical record or a discharge summary)
 - stroke at least 6 months before entry into the study
 - (acute focal neurological deficit lasting more than 24 hours which was diagnosed as being due to a cerebral lesion of vascular origin but excluding known subarachnoid haemorrhage. Wherever possible, diagnosis should have been made on the basis of diagnostic neuro-imaging but in instances where this was not performed, a clinical diagnosis may be accepted)
 - PCI or CABG at least 6 months before entry into the study
 - acute coronary syndrome at least 3 months before entry into the study
 - (treatment in a hospital setting as a consequence of one or more episodes of ischaemic discomfort at rest and characterised by ECG changes and/or an elevation of a cardiac serum marker to an extent *not* indicative of myocardial infarction)
 - objective evidence of coronary artery disease including any one of the following: a positive exercise test, angiography showing at least one lesion of $\geq 50\%$ stenosis or positive scintigraphy at any time prior to entry into the study
 - peripheral arterial obstructive disease
 - (current symptoms of intermittent claudication confirmed by an ankle brachial pressure index (ABPI) or toe brachial pressure index (TBPI) of < 0.90 obtained at any time in the previous 12 months); or
 - (a healed amputation of the leg(s) at any level above the ankle which was performed for documented peripheral arterial obstructive disease as defined above)
- Patient is willing and able to give written informed consent

Exclusion criteria

Patients should be excluded from the study if any of the following criteria apply:

- Signs of type 1 diabetes (including any history of ketoacidosis or requirement for insulin within 1 year of first diagnosis)
- Patients prescribed insulin as sole therapy for glycaemic control of diabetes for two weeks or more at any time in the previous three months
- Myocardial infarction, stroke, CABG or PCI in the six months prior to enrolment
- Acute coronary syndrome (see definition above) in the three months prior to enrolment
- Heart failure at entry defined as patient having an NYHA functional score of II or above
- Patient has an appointment for a coronary angiogram or endovascular or surgical intervention
- Leg ulcers, gangrene or ischaemic rest pain [Note: previous ulceration which has healed or rest pain which has resolved are not considered to be grounds for exclusion of the patient]
- Patient has an appointment for an angiogram or endovascular or surgical intervention for leg ischaemia
- Patient has undergone a major operation (defined as a surgical procedure lasting for more than 30 minutes) at any time in the previous four weeks
- Significantly impaired hepatic function, defined as ALT > 2.5 x ULN [Note: Local measurement of ALT is required at the time of screening to confirm eligibility for entry into the study]
- Familial polyposis coli
- Patient requires dialysis

Additional general exclusion criteria will also apply. A full list of the exclusion criteria is given in section 5.3.

2.5 Design

The overall design of this study is defined as follows:

- Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study
- Phase IIIb, intention-to-treat analysis
- Treatments:

- Pioglitazone (15 mg, 30 mg or 45 mg; titrated)
- Matching placebo

A total of 5,000 patients will be randomised to treatment with equal allocation to the two treatment groups. The study will be conducted in 300-500 centres in Europe.

Recruitment is anticipated to be completed within 18 months. All patients will continue in the study until the final patient recruited has been followed for a minimum of 2.5 years (30 months). However, in order to maintain 90% power to detect a 20% reduction in the primary event rate, endpoint events must be observed for at least 760 patients. Blinded follow-up of all patients will continue, therefore, until both of the following targets are achieved:

- Last patient recruited is followed for at least 30 months
- The number of patients with one or more endpoint events is at least 760

2.6 Endpoints

Primary endpoint

The primary endpoint variable will be the time from randomisation to the first occurrence of any of the events in the following composite:

- all-cause mortality
- non-fatal myocardial infarction (including silent myocardial infarction)
- acute coronary syndrome
- cardiac intervention including coronary artery bypass graft or percutaneous coronary intervention
- stroke
- major leg amputation (above the ankle)
- bypass surgery or revascularisation in the leg

Secondary endpoints

- Individual components of the primary endpoint
- Cardiovascular mortality

2.7 Study Plan

Visit	1a [†]	1b [‡]	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Final	
Type of follow-up visit	-	-	A	A	A	B	A	A	C	D	E	D	C	D	E	D	C	D	E	D	F	
Month	0	0	1	2	4	6	8	10	12	15	18	21	24	27	30	33	36	39	42	45	§	
Informed consent	X																					
Entry criteria	X	X ⁽¹⁾																				
Demography	X																					
Medical history	X																					
Physical examination	X																				X	
Serious adverse events		◆																				▶
Study endpoints		◆																				▶
Non-serious AEs		◆																				▶
Concomitant medication		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
ALT (local lab) ⁽²⁾	X																					
HbA _{1c} (local lab) ⁽³⁾	X																					
Urine pregnancy test ⁽⁵⁾		X																				
HbA _{1c} ⁽⁴⁾		X				X			X				X				X				X	
Triglycerides, HDL, LDL ⁽⁴⁾		X				X			X		X		X		X		X		X		X	
ALT, AST, ALP, total bilirubin ⁽⁴⁾		X	X	X	X	X	X	X	X		X		X		X		X		X		X	
Creatinine ⁽⁴⁾		X				X			X		X		X		X		X		X		X	
Body weight		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Waist measurement		X				X			X		X		X		X		X		X		X	
Blood pressure		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
12-lead ECG		X							X				X				X				X	
Drug dispensing (via IVRS)		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Drug retrieval			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X

† Screening procedures

‡ Randomisation procedures

§ Anticipated to be required approximately 48 months after start of the study; sites will be advised when to schedule final visits

(1) Review of local ALT result only

(2) A sample for local determination of ALT must be taken at this visit; an historical value must not be used

(3) Required only if there is no historical value from a sample taken within the previous two months

(4) Sample(s) to be sent to the ICON Central Laboratory

(5) Required for women of child-bearing potential

3 BACKGROUND AND RATIONALE

3.1 Product Summary

Pioglitazone is a thiazolidinedione compound, discovered by Takeda Chemical Industries Limited, with a mode of action as a PPAR γ agonist³. Activation of this receptor causes increased transcriptional activity at a number of locations that are important to carbohydrate and lipid metabolism⁴. Insulin resistance is reversed by enhancing the action of insulin, thereby promoting glucose utilisation in peripheral tissues, suppressing gluconeogenesis in the liver, and reducing lipolysis at the adipocyte. Pioglitazone lowers HbA_{1C}, fasting plasma glucose and fasting plasma insulin levels in type 2 diabetic patients. It also increases HDL-cholesterol and reduces triglycerides.

The clinical development programme for pioglitazone has involved more than 5,500 subjects in 47 studies, including 28 clinical pharmacology studies. Pioglitazone has been administered to more than 3,500 patients with type 2 diabetes in clinical studies conducted in the United States, Europe, and Japan using doses up to 60 mg/day.

Pioglitazone has been approved in the United States, Japan, the European Union, Switzerland, Norway, Iceland, Russia, Canada, Mexico, Colombia, Brazil, Argentina, South Africa, Australia and Thailand. Since approval, over one million patients have been prescribed pioglitazone.

3.2 Efficacy

Significant hypoglycaemic effects are obtained with monotherapy at doses of 15 mg, 30 mg and 45 mg in a dose dependent manner. The magnitude of the glycaemic response is in the range of 20-70 mg/dl (1-4 mmol/l) for fasting plasma glucose and 0.5-2.0% for HbA_{1C}. Analysis of all the studies shows that there are no major differences in efficacy with age, BMI or baseline HbA_{1C}, but prior antidiabetic therapy does seem to influence response. No prior therapy is associated with a better glycaemic response, and females appear to have greater mean reductions in glycaemic variables than males. There is also a suggestion from the pharmacokinetic studies that plasma concentrations are somewhat higher in females, however, there is no need to modify the dose of pioglitazone according to gender.

In patients with abnormal lipids at baseline, pioglitazone shows a clear improvement in triglycerides (reduced by 21-32%) and HDL-cholesterol (increased by 10-12%). Total and LDL-cholesterol were not influenced in any study.

In combination with sulphonylureas, pioglitazone has shown dose dependent efficacy at 15 mg and 30 mg (HbA_{1C} reduced by 1.22% with 30 mg) as well as reductions in fasting insulin and C-peptide. HDL-cholesterol and triglycerides were improved and LDL-cholesterol did not change in comparison with placebo. In combination with metformin, after 16 weeks treatment there was an improvement of glycaemic control (both HbA_{1C} and FPG) as well as fasting insulin, triglycerides and HDL-cholesterol. Again, LDL-cholesterol did not change compared to metformin treatment alone.

3.3 Safety

Most of the adverse events which have been reported to date are expected in clinical trials in this population. Withdrawal rates due to adverse events have been similar in pioglitazone and placebo treated groups.

Oedema appears to be a dose dependent phenomenon with pioglitazone. In placebo controlled monotherapy trials in the USA and Europe, oedema was seen with a frequency of 3.2% compared with 0.6% on placebo and is reported more by females than males. As oedema is sometimes seen in diabetic patients after the administration of insulin; this may be viewed as an expected pharmacological effect of an insulin sensitiser. Oedema caused patients to withdraw from clinical studies only rarely and was not related to reports of right or left ventricular failure, shortness of breath or angina, although patients with significant cardiac decompensation have been excluded from these studies. Of the other adverse events reported in these studies, none showed a clear relationship to dose.

Open, long-term monotherapy studies with pioglitazone did not reveal any increase in incidence of adverse events over time or new adverse events suggestive of a cumulative toxic effect. The pattern of adverse events by age and gender were similar in long-term and short-term studies.

In general, combination therapy showed a similar adverse event profile to monotherapy with the exception of hypoglycaemia (which does not occur with pioglitazone as monotherapy). When pioglitazone was given in combination with sulphonylurea or insulin there were reports of hypoglycaemia (sulphonylurea + placebo 0.5%, sulphonylurea + pioglitazone 1.9%, insulin + placebo 4.8%, insulin + pioglitazone 11.6%). However, when pioglitazone was given in combination with metformin there was no increase in the reporting of hypoglycaemia over that seen with metformin alone.

Small decreases in haemoglobin, haematocrit and red cell count have been seen during treatment with pioglitazone, which probably simply reflects modest fluid retention. Increases in LDH (by approximately 10%) and CPK (by approximately 15%) compared to placebo have also been observed which may be a reflection of increased muscle formation⁵, possibly resulting from improved insulin sensitivity. None of these changes are of clinical significance. There was careful investigation of specific issues, and in particular of liver function, cardiac size and changes in the bladder epithelium. No effects were detectable.

Analysis of left ventricular structure and function using echocardiography showed no difference between pioglitazone and placebo in a study where treatment was continued for six months. Pioglitazone was continued in an open extension for up to two and a half years. Even at higher doses (maximum 60 mg) than currently recommended (maximum 45 mg), there were still no clinically relevant changes in any echocardiographic variables.

3.4 Rationale

Diabetes mellitus is one of the most common non-communicable diseases globally. In the European region of the International Diabetes Federation there are over 22 million persons with diabetes. Complications of diabetes, both microvascular and macrovascular, are resulting in increased disability and reduced life expectancy¹. A major problem of diabetes is the associated macrovascular morbidity and mortality which results from disease of the coronary, cerebral and peripheral vascular beds. The macrovascular risk of diabetes is 3-5 times that of the matched non-diabetic population. The underlying disease process appears to be accelerated atherosclerosis to which the patient with diabetes is especially prone. Whilst microvascular complications can be controlled through management of glycaemia, the aetiology and management of macrovascular disease in diabetes is more complicated. Conventional agents used to treat diabetes have not shown an improvement in macrovascular outcomes in the way that they have for microvascular complications.

Insulin resistance is central to the genesis of both atherosclerosis and diabetes mellitus. For diabetes to result, insulin resistance needs to be coupled with beta cell dysfunction. In atherosclerosis, insulin resistance may have a direct effect on the cardiovascular system as well as additional indirect effects through the modification of blood sugar, lipids, clotting factors and endothelial function amongst other variables. There is now much indirect evidence that PPAR agonists may favourably influence macrovascular outcome, either through modification of risk factors (such as lipids) or through direct effects on the vessel wall².

Pioglitazone is a newly developed PPAR- γ agonist for the treatment of type 2 diabetes mellitus. It acts by reducing insulin resistance. Pioglitazone improves the metabolic state of animals with diabetes and also improves the vascular state in various models of vascular damage. In patients with diabetes, there is an overall improvement in metabolic control; as well as improved glycaemic control, the dyslipidaemia associated with diabetes is improved, with increased HDL and reduced triglycerides. LDL-cholesterol (the concentration of which is not notably abnormal in patients with diabetes) remains unchanged after treatment with pioglitazone. Whilst body weight increases with pioglitazone, this is associated with a redistribution of body fat, with a reduction of visceral, intra-abdominal stores and an increase in subcutaneous depots. This redistribution is associated with an improved cardiovascular risk profile. This overall pattern of changes induced by pioglitazone suggests a general amelioration of the metabolic syndrome which should result in reduced macrovascular morbidity.

The present study will examine whether the incidence of macrovascular events is reduced in patients receiving pioglitazone in combination with their usual medication for glycaemic management compared with a control group of patients who will receive placebo in combination with their usual treatment. Using pioglitazone as 'add-on' medication allows the use of a double-blind placebo-controlled design whilst not denying patients the best therapy that is currently available. Patients at high risk of macrovascular events have been chosen since this is likely to give the earliest answer to the question posed. This approach has been used successfully in the past, most notably with HMGCoA reductase inhibitors (4S study⁶), fibrates (VA HIT

study⁷) and ACE inhibitors (HOPE study⁸). It is estimated that between 2.5 and 4 years treatment in 5,000 patients will be required to demonstrate the benefit of pioglitazone in this study.

3.5 Justification of Dose

Pioglitazone is licensed in Europe at a dose of 15 to 30 mg in combination therapy and further safety data are available from open studies using 45 mg. In other parts of the world, pioglitazone is also registered for use as monotherapy at a dose range of 15 to 45 mg, with further data from open studies using 60 mg. There is, therefore, controlled clinical trial data regarding efficacy with doses up to 45 mg and data regarding safety in man at doses up to 60 mg. In this study, patients are to be titrated from 15 to 45 mg unless limited by tolerability or safety considerations in the individual patient. This should allow maximum efficacy to be achieved in each patient without there being undue risk.

4 TRIAL OBJECTIVES AND ENDPOINTS

4.1 Objectives

- To demonstrate that pioglitazone reduces total mortality and macrovascular morbidity in high-risk patients with type 2 diabetes mellitus
- To further characterise the safety of pioglitazone in this group of type 2 diabetes patients

4.2 Endpoints

4.2.1 Efficacy

Primary endpoint

The primary endpoint variable will be the time from randomisation to the first occurrence of any of the events in the following composite:

- all-cause mortality
- non-fatal myocardial infarction (including silent myocardial infarction)
- acute coronary syndrome
- cardiac intervention including coronary artery bypass graft or percutaneous coronary intervention
- stroke

- major leg amputation (above the ankle)
- bypass surgery or revascularisation in the leg

(See section 6.4.1 for definitions)

Secondary endpoints

- Individual components of the primary endpoint
- Cardiovascular mortality

Other measurements of interest

- Cause of death
- Time to start of permanent insulin use (in patients not receiving insulin at the time of randomisation)
- Transient ischaemic attack (TIA)
- Treatment with retinal photocoagulation
- Carotid intervention
- Number of days of hospitalisation for any cause
- Usage of:
 - antihypertensive medication
 - lipid-lowering medication
 - oral antidiabetic medication

(See section 6.4.1 for definitions)

4.2.2 Safety

Incidence of:

- serious adverse events
- non-serious adverse events

(See section 8.1 for definitions of serious and non-serious adverse events)

5 PATIENT SELECTION

5.1 Trial Population

The trial population will consist of patients with type 2 diabetes mellitus who are at increased risk of cardiovascular complications.

5.2 Inclusion Criteria

Patients with type 2 diabetes mellitus are potentially eligible for entry into the study if each of the following is met:

- Male or female patients, aged 35-75 years inclusive
- HbA_{1C} above the upper limit of normal (i.e. the local equivalent of 6.5% for a DCCT traceable assay) as determined by the local laboratory at screening or at any time in the previous two months
- Established history of macrovascular disease, defined as one or more of:
 - myocardial infarction at least 6 months before entry into the study (as documented in the patient's medical record or a discharge summary)
 - stroke at least 6 months before entry into the study
 - (acute focal neurological deficit lasting more than 24 hours which was diagnosed as being due to a cerebral lesion of vascular origin but excluding known subarachnoid haemorrhage. Wherever possible, diagnosis should have been made on the basis of diagnostic neuro-imaging but in instances where this was not performed, a clinical diagnosis may be accepted)
 - PCI or CABG at least 6 months before entry into the study
 - acute coronary syndrome at least 3 months before entry into the study
 - (treatment in a hospital setting as a consequence of one or more episodes of ischaemic discomfort at rest and characterised by ECG changes and/or an elevation of a cardiac serum marker to an extent *not* indicative of myocardial infarction)
 - objective evidence of coronary artery disease including any one of the following: a positive exercise test, angiography showing at least one lesion of $\geq 50\%$ stenosis or positive scintigraphy at any time prior to entry into the study
 - peripheral arterial obstructive disease
 - (current symptoms of intermittent claudication confirmed by an ankle brachial pressure index (ABPI) or toe brachial pressure index (TBPI) of < 0.90 obtained at any time in the previous 12 months); or
 - (a healed amputation of the leg(s) at any level above the ankle which was performed for documented peripheral arterial obstructive disease as defined above)

- Patient is willing and able to give written informed consent

5.3 Exclusion Criteria

Patients should be excluded from the study if any of the following criteria apply:

- Signs of type 1 diabetes (including any history of ketoacidosis or requirement for insulin within 1 year of first diagnosis)
- Patients prescribed insulin as sole therapy for glycaemic control of diabetes for two weeks or more at any time in the previous three months
- Myocardial infarction, stroke, CABG or PCI in the six months prior to enrolment
- Acute coronary syndrome (see definition in section 5.2) in the three months prior to enrolment
- Heart failure at entry defined as patient having an NYHA functional score of II or above
- Patient has an appointment for a coronary angiogram or endovascular or surgical intervention
- Leg ulcers, gangrene or ischaemic rest pain [Note: previous ulceration which has healed or rest pain which has resolved are not considered to be grounds for exclusion of the patient]
- Patient has an appointment for an angiogram or endovascular or surgical intervention for leg ischaemia
- Patient has undergone a major operation (defined as a surgical procedure lasting for more than 30 minutes) at any time in the previous four weeks
- Significantly impaired hepatic function, defined as ALT > 2.5 x ULN [Note: Local measurement of ALT is required at the time of screening to confirm eligibility for entry into the study]
- Familial polyposis coli
- Patient requires dialysis
- History of alcohol or drug abuse
- Any other intercurrent disease believed to be likely to have a significant impact on the patient's life expectancy during the course of the study (e.g. cancer)
- Patient is undergoing follow-up as part of another clinical trial or less than three months has elapsed since the last dose of an investigational drug or procedure
- Hypersensitivity to pioglitazone or other thiazolidinediones

- Current use of pioglitazone or other thiazolidinediones
- Patient is known to be infected with HIV or is known to have viral hepatitis
- Women who are any of the following:
 - pregnant
 - breast feeding
 - may wish to become pregnant during the course of the study
 - of child-bearing potential and not planning to use a reliable method of contraception (i.e. oral contraceptives or an IUD) throughout the study

[Note: Women of child-bearing potential (i.e. who are not postmenopausal, hysterectomised or surgically sterilised) must have a negative pregnancy test (blood or urine) prior to entry into the study.]

- Any other condition or circumstance which, in the opinion of the Investigator, would compromise the patient's ability to comply with the study protocol

6 TRIAL DESIGN

6.1 Design Overview

The overall design of this study is defined as follows:

- Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study
- Phase IIIb, intention to treat analysis
- Treatments:
 - Pioglitazone (15 mg, 30 mg or 45 mg; titrated)
 - Matching placebo

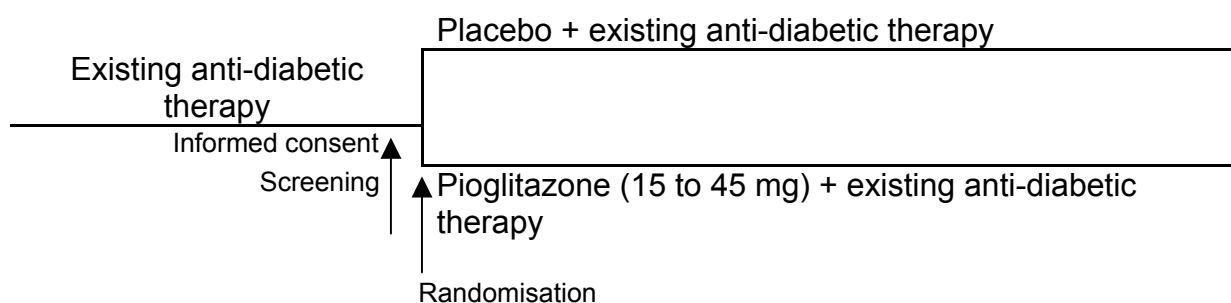
A total of 5,000 patients will be randomised to treatment with equal allocation to the two treatment groups. The study will be conducted in 300-500 centres in Europe.

Recruitment is anticipated to be completed within 18 months. All patients will continue in the study until the final patient recruited has been followed for a minimum of 2.5 years (30 months). However, in order to maintain 90% power to detect a 20% reduction in the primary event rate, endpoint events must be observed for at least 760 patients. Blinded follow-up of all patients will continue, therefore, until both of the following targets are achieved:

- Last patient recruited is followed for at least 30 months

- The number of patients with one or more endpoint events is at least 760

Patients giving informed consent will be screened for eligibility to enter the treatment phase of the study.



6.2 Titration of Study Medication

PROactive has been designed as a forced titration study with the objective of maintaining patients on the maximum tolerated dose of study medication. During the first three months of a patient's participation, the study medication should be increased stepwise from 15 mg to 30 mg to 45 mg. It is envisaged that this will be achieved in the majority of patients by increasing the dose to 30 mg at Visit 2 (Month 1) and to 45 mg at Visit 3 (Month 2). At any time during this period and during the remainder of the study, the dose may be increased or decreased within the range 15 to 45 mg based on tolerability. [Note: all medication will need to be dispensed using the central telephone randomisation service (IVRS) details of which are given in section 7.6.]

Specific guidance regarding the management of study medication in the event of known possible side effects is summarised as follows:

- If a patient has episodes of hypoglycaemia, this should be managed by reducing the dose of other antidiabetic therapy (sulphonylurea or insulin) and the dose of study medication should be maintained or upward titration towards 45 mg continued.
- If troublesome oedema develops, consideration should be given to managing this with a loop diuretic, e.g. frusemide before changing the dose of study medication.
- In the case of problematic weight gain, more intensive dietary counselling should be given where possible before reducing the dose of study medication.
- In the event of other troublesome side effects, consideration should be given to reducing the dose of study medication.

Where adverse events are believed to be associated with concomitant medication, (e.g. gastrointestinal upset in a patient taking metformin) consideration should be given to modifying the treatment thought to be responsible for the event before altering the dose of the study medication.

6.3 Trial Procedures

6.3.1 Medical History

A comprehensive medical history will be obtained at Visit 1a as part of patient screening.

6.3.2 Physical Examination

A physical examination will be performed at Visit 1a (baseline) and again at the Final Visit. The examination at baseline will be conducted with the aim of:

- confirming that the patient meets the inclusion criteria and has none of the exclusion criteria
- characterising the patient population with particular reference to: diabetic retinopathy, neuropathy, nephropathy and diabetic foot

Both examinations will be carried out by the Investigator or a suitably trained health professional designated by the Investigator.

6.3.3 Body Weight

Body weight will be measured at Visit 1b prior to randomisation and at every visit thereafter up to and including the final visit. Measurements should be taken whilst the patient is wearing indoor clothes without shoes.

6.3.4 Waist Circumference

Waist circumference will be measured at Visit 1b prior to randomisation and every six months thereafter up to and including the final visit. Waist is defined as the midpoint between the lower rib margin and the iliac crest.

6.3.5 Blood Pressure

Blood pressure will be measured at all visits throughout the study (patient in sitting position after 5 minutes rest).

6.3.6 12-Lead Electrocardiograms

Standard twelve-lead electrocardiograms (ECGs) will be recorded at Visit 1b prior to randomisation and at twelve-monthly intervals thereafter. A final twelve-lead ECG will be performed at the final visit.

Copies of all the ECGs obtained during the course of the study will be submitted to NCRL for central reading. The purpose of central review will be to identify ECG changes suggestive of silent myocardial infarction as per the definition given in section 6.4.1.

6.3.7 Laboratory Tests

At the time of screening (Visit 1a), local laboratory assessment of ALT will be carried out to confirm the patient's eligibility for entry into the treatment phase. In addition, if a value for HbA_{1c} has not been obtained in the previous two months, a local assessment should be made to confirm that the patient meets this entry criterion.

Prior to randomisation (Visit 1b) a urine pregnancy test will be performed for women of child-bearing potential to confirm the absence of pregnancy. Also at this visit, blood samples will be drawn from all patients to permit central laboratory assessment of the following:

Glycaemic control:

- HbA_{1c} [Note: the value obtained from this first central laboratory sample will not be used to verify the patient's eligibility for entry into the study]

Lipids:

- Triglycerides
- HDL cholesterol
- LDL cholesterol (direct)

Liver function:

- ALT
- AST
- Total bilirubin
- Alkaline phosphatase

Renal function:

- Creatinine

Thereafter, HbA_{1c}, lipids and creatinine will be measured at six-monthly intervals and at the final visit. Samples to measure liver function will be drawn at months 1, 2, 4, 6, 8, 10 and 12, at six-monthly intervals thereafter and again at the final visit.

Blood samples for lipid assessments should be taken under fasting conditions unless, in the judgement of the investigator, it would be inappropriate for the patient to be asked to provide a fasting sample. Samples drawn prior to randomisation must only be obtained following informed consent. Thereafter, blood samples may be collected within 7 days before or after the visit at which they are due to be taken.

As the assay of the blood samples by the Central Laboratory has to be performed as soon as possible after sampling, the Investigator should inform the courier company immediately to arrange the shipment. The Central Laboratory will provide detailed instructions concerning blood sampling and shipment procedures to each investigator.

All materials needed for blood sampling will be supplied by the Central Laboratory, packed into boxes by patient and per visit.

For each patient, the amount of blood required to be collected will be approximately 80 ml in the first year and 25 ml in each of the subsequent years.

6.4 Study Endpoints

6.4.1 Definitions

The following definitions will be used when classifying endpoint events:

Non-fatal myocardial infarction (MI)

Patient survives more than 24 hours from onset of symptoms and:

1) In the absence of PCI or CABG in previous 72 hours:

At least two of:

- Symptoms suggestive of MI (ischaemic chest pain or discomfort) lasting ≥ 30 minutes
- ECG evidence of MI, defined as major new Q waves (≥ 30 ms), or deepening Q waves in two or more contiguous leads or new left bundle branch block
- Elevation of a serum marker (obtained from a sample taken after the onset of the event and prior to any subsequent coronary revascularisation or bypass graft), defined as any of:
 - CK-MB $> 6\%$ of total CK; or
 - CK-MB $> 2 \times$ ULN in the absence of a corresponding value for total CK; or
 - Troponin I or T $> 2 \times$ ULN; or
 - Total CK $> 2 \times$ ULN (provided that the ECG criteria above are also met)

[Note: Serum marker results obtained after a cardiac intervention performed subsequent to a suspected myocardial infarction may not be used as evidence to support a diagnosis of myocardial infarction.]

2) Following PCI or CABG in the previous 72 hours:

- ECG evidence of MI, defined as major new Q waves (≥ 30 ms), or deepening Q waves in two or more contiguous leads or new left bundle branch block

Where death occurs within 24 hours of ischaemic symptoms, the ischaemic event will be assessed as having a fatal outcome. In this circumstance the Investigator will be asked to record the most likely cause of death on the basis of the information available. Myocardial infarction is thus defined as non-fatal myocardial infarction together with those deaths where MI was the most likely cause of death.

Silent myocardial infarction

The appearance on any ECG of new Q waves in any two contiguous leads or any new LBBB or loss of R wave progression or T wave inversion in a patient who has not suffered an overt MI since the previous ECG. The date of the event will be set to the date of the ECG where evidence of the silent MI was first discovered.

Acute coronary syndrome

Treatment in a hospital setting as a consequence of one or more episodes of ischaemic discomfort at rest lasting at least 5 minutes and supported by one or more of:

- ST depression of > 0.5 mm
- ST elevation > 0.5 mm
- Persistent (> 30 minutes) ST elevation < 0.5 mm
- Elevation of CK or CK-MB to above the ULN
- Positive Troponin T or I

[Note: If an event meets both the definition of acute coronary syndrome and myocardial infarction, the event will be classified as a myocardial infarction]

Coronary revascularisation

Patient has undergone percutaneous transluminal coronary intervention (e.g. angioplasty, stenting, atherectomy, laser ablation) or CABG.

Stroke

Acute focal neurological deficit lasting for more than 24 hours or resulting in death within 24 hours of the onset of symptoms which is diagnosed as being due to a cerebral lesion of vascular origin but excluding subarachnoid haemorrhage. Wherever possible, diagnosis should be made on the basis of diagnostic neuro-imaging but in instances where this was not performed, a clinical diagnosis may be accepted.

Major leg amputation

All amputations of the leg above the ankle, that is, a standard below-knee, through knee or above knee amputation. The definition excludes through-ankle (Syme's) amputation.

Bypass surgery or revascularisation in the leg

Patient has undergone any of:

- Surgical bypass
- Atherectomy
- Angioplasty
- Thrombolysis

Cause of death

All fatal events will be classified as cardiovascular unless there is a clear non-cardiovascular cause, for example, trauma, cancer or suicide.

Cardiovascular deaths will be classified as:

- Myocardial infarction
- Other cardiac
- Cerebrovascular
- Other

Permanent insulin use

Daily insulin use for a period of at least three months (90 days) for glycaemic control in patients not using insulin at entry into the study. The date of this event will be taken as the first day of any period of insulin use exceeding 90 days and the analysis of this endpoint will consider only those patients not taking insulin on entry.

Transient ischaemic attack

Focal neurological deficit which resolves spontaneously without any evidence of residual deficit 24 hours after the onset of symptoms.

6.4.2 Central Adjudication

Clinical events identified by NCRL as possibly constituting a primary or secondary study endpoint will pass through a central adjudication process, which will be blinded

regarding treatment allocation. Details of the adjudication process are given in the Endpoint Adjudication Charter.

6.4.3 Data Capture

On entry to the study each patient will receive a Patient Medical Notebook which he/she will be asked to maintain for the duration of the study. This booklet will explain that the patient is being followed as part of a clinical trial and will provide a facility for health professionals who treat the patient to record any period of hospitalisation, emergency treatment or procedure. For each hospitalisation or visit, the date and reason will be recorded by the attending health professional, along with contact details. If this is not possible, the entries may be made by the patient.

At each follow-up visit, in addition to asking the patient to report any events which have occurred since his/her last study visit, the Investigator should review with the patient the entries made in the Notebook for the period since the previous visit. The Notebook is not a source document but is intended to serve as a prompt to the Investigator to identify potential SAEs and potential primary or secondary endpoints which will require the retrieval of full and complete information in order that the event may be reported to NCRL. Any event which meets the definition of a serious adverse event (see section 8.1) or is possibly a primary or secondary endpoint must be documented using an Alert Report Booklet and faxed to NCRL within one working day.

Detailed instructions as to which events must be reported in this manner are given in the Alert Report Booklet. All such events which occur between the time of randomisation and the final follow-up visit for the patient including all events which occur following a patient's permanent cessation of study treatment should be reported.

6.5 Patient Management

Throughout the study, all patients should be managed in accordance with current International Diabetes Federation Guidelines for the management of type 2 diabetes, copies of which will be supplied separately.

To aid the regular monitoring of blood glucose, whenever needed, the Sponsor will supply blood glucose meters and testing strips to the centre for use by patients participating in the study.

6.6 Visit Schedule

Patients will attend visits as follows:

- Baseline (Month 0 - screening and randomisation)
- Month 1 (± 5 days)
- Month 2 (± 5 days)

- Every 2 months (± 7 days) thereafter until Month 12
- Every 3 months (± 14 days) thereafter until the final visit

The organisation of the baseline visit(s) may be arranged to suit usual site practice and applicable laws, regulations and guidelines. When a potentially eligible patient is identified, the nature and purpose of the study must be discussed with the patient to ensure that informed consent can be obtained. The patient should be given a sufficient opportunity to consider their participation. Informed consent is required before any assessments to confirm eligibility are performed. When a patient is finally confirmed to be eligible for participation and before formally randomising the patient via the central telephone randomisation service (IVRS), the Investigator should be satisfied that the patient is still willing to participate in the study.

For the purpose of the visit schedule, a month is defined as having 30 days with timing determined relative to the date of randomisation. If any visit date does not conform to the planned schedule, the timing of subsequent visits should be planned to maintain the visit structure relative to randomisation. Where there is any departure from the schedule, the Investigator must ensure that the patient has sufficient medication to cover the period to the next assessment. The visit schedule is not affected by unscheduled visits.

If a patient permanently ceases treatment with study drug, details of the circumstances should be documented. The Investigator should make every effort to ensure that the patient attends all remaining study visits until termination of the study.

If the patient is unwilling or unable to attend scheduled visits, the Investigator should encourage the patient to agree to telephone or written contacts or other visits as appropriate in accordance with the patient's originally anticipated visit schedule for the study.

Baseline Visit 1a (Screening)

The following procedures or determinations will be performed for part 1a:

- Written informed consent
- Verification of entry criteria
- Demographic data (gender, date of birth, ethnic origin)
- Medical History (including relevant previous disease and history of type 2 diabetes mellitus and its treatment)
- Physical examination
- Blood sampling for local assessment of ALT and HbA_{1c} (HbA_{1c} required only if there is no value available from the previous two months. The central laboratory sample for HbA_{1c} obtained at visit 1b will not be used to verify patient eligibility.)

Baseline Visit 1b (Randomisation)

The following procedures or determinations will be performed for part 1b:

- Review of ALT result obtained from the local laboratory
- Concomitant medications
- Blood sampling for central laboratory evaluation of HbA_{1c}, lipids, liver function tests and creatinine
- Body weight
- Waist measurement
- Blood pressure
- 12-lead ECG
- Drug dispensing (via the IVRS)

Study medication will only be dispensed after all other procedures scheduled for the Baseline visit(s) have been completed. If the patient's eligibility can be confirmed, the patient will be randomised and the study medication will be dispensed. To do this, the Investigator will telephone the central telephone randomisation service (IVRS) to report the new patient. The Investigator will then be told which of the study treatment kits on-site should be dispensed to the patient.

Visits 2, 3, 4, 6 and 7 (Months 1, 2, 4, 8 and 10) – Follow-up visit Type A

The following procedures or determinations will be performed:

- Documentation of serious adverse events
- Documentation of potential study endpoints
- Documentation of non-serious adverse events
- Concomitant medication
- Blood sampling for central laboratory assessment of liver function
- Body weight
- Blood pressure
- Retrieval and dispensing of study medication

Visit 5 (Month 6) – Follow-up visit Type B

The following procedures or determinations will be performed:

- Documentation of serious adverse events
- Documentation of potential study endpoints
- Documentation of non-serious adverse events
- Concomitant medication
- Blood sampling for central laboratory assessment of HbA_{1c}, lipids, liver function and creatinine
- Body weight
- Waist measurement
- Blood pressure
- Retrieval and dispensing of study medication

Visits 8, 12, 16 (Months 12, 24, and 36) – Follow-up visit Type C

The following procedures or determinations will be performed:

- Documentation of serious adverse events
- Documentation of potential study endpoints
- Documentation of non-serious adverse events
- Concomitant medication
- Blood sampling for central laboratory assessment of HbA_{1c}, lipids, liver function and creatinine)
- Body weight
- Waist measurement
- Blood pressure
- 12-lead ECG
- Retrieval and dispensing of study medication

Visits 9, 11, 13, 15, 17, 19 (Months 15, 21, 27, 33, 39 and 45) – Follow-up visit Type D

The following procedures or determinations will be performed:

- Documentation of serious adverse events
- Documentation of potential study endpoints
- Documentation of non-serious adverse events
- Concomitant medication
- Body weight
- Blood pressure
- Retrieval and dispensing of study medication

Visits 10, 14 and 18 (Months 18, 30 and 42) – Follow-up visit Type E

The following procedures or determinations will be performed:

- Documentation of serious adverse events
- Documentation of potential study endpoints
- Documentation of non-serious adverse events
- Concomitant medication
- Blood sampling for central laboratory assessment of lipids, liver function and creatinine
- Body weight
- Waist measurement
- Blood pressure
- Retrieval and dispensing of study medication

Final Visit – Follow-up visit Type F

Sites will be advised when to schedule final visits. This information will be available at least six months prior to the projected end of follow-up. It is anticipated that no extra visits will be required beyond that implied by the regular visit schedule.

The following procedures or determinations will be performed:

- Documentation of serious adverse events
- Documentation of potential study endpoints
- Documentation of non-serious adverse events

- Concomitant medication
- Physical examination
- Blood sampling for central laboratory assessment of HbA_{1c}, lipids, liver function and creatinine
- Body weight
- Waist measurement
- Blood pressure
- 12-lead ECG
- Retrieval of study medication

6.7 Unscheduled Visits

Unscheduled (additional) visits may take place at any time during the study in cases of medical emergencies, or if the Investigator considers this to be appropriate for patient care, or to modify the patient's dose of study medication outside the visit schedule. Additional study medication at the same dose or at an altered dose can be obtained at any time using the 'request maintenance medication' or the 'request replacement medication' options of the central telephone randomisation service (IVRS) as appropriate. In all circumstances, the patient's original protocol visit schedule should be maintained.

6.8 Hospitalisations

Each period of hospitalisation should be documented including any hospitalisation occurring after a patient has permanently ceased to take study medication. The following information will be captured:

- Date of admission
- Date of discharge
- Reason(s) for admission
- Days in coronary care/high dependency unit
- Investigations and procedures

In addition, events which lead to hospital admission require reporting as serious adverse events unless the reason for admission is an elective procedure. An elective procedure is defined as any diagnostic or therapeutic procedure (including surgery) which has not been prompted by a new or worsening adverse event or which was otherwise already planned at the time the patient was randomised.

6.9 Visits Following Premature Discontinuation of Study Drug

Following permanent cessation of medication, patients are required to continue to attend all remaining study visits until termination of the study. Assessments at each such visit will be unchanged from those scheduled for patients continuing on medication without exception.

7 STUDY TREATMENT

Pioglitazone and placebo will be indistinguishable from each other on the basis of all directly observable characteristics such as shape, size, appearance, weight, taste, odour, finish and dissolution characteristics. The study medication will be taken in addition to the patient's usual treatment with diet, exercise, antidiabetic drug treatment (except other thiazolidinediones) and any other required medication.

7.1 Test Preparation

Code name (INN): AD-4833 (pioglitazone)
Chemical name: (\pm)-5-[p-[2-(5-ethyl-2-pyridyl)ethoxy]benzyl]-2,4-thiazolidinedione hydrochloride
Dosage form: Tablet
Strength: 15, 30, or 45 mg
Blinded batch no.: E4833444
Expiry date: See Takeda Europe R&D Centre Limited study file
Manufacturer: Takeda Ireland Limited
Packaging and release: Brecon Pharmaceuticals Limited

7.2 Reference Preparation

Code name: Placebo
Dosage form: Tablet
Blinded batch no.: E4833444
Expiry date: See Takeda Europe R&D Centre Limited study file
Manufacturer: Takeda Ireland Limited
Packaging and release: Brecon Pharmaceuticals Limited

7.3 Drug Packaging

Each study treatment kit will comprise a card folder in which there is a blister strip containing 35 tablets (either pioglitazone or matching placebo).

7.4 Drug Labelling

The card folder of each treatment kit will have a multilingual label which meets the regulatory requirements for the countries participating in the study. The label will include the following information:

- Sponsor details
- Name of drug
- Study number
- Dosage form
- Strength
- Number of tablets
- Batch number
- Directions for use
- Storage conditions
- Expiry date
- Pack number
- “Keep out of reach of children”
- “For clinical trial use only”

After a treatment kit has been allocated to a patient by the central telephone randomisation service (IVRS), the Investigator or specifically designated other person(s) will stick the detachable part of the two-part label on the appropriate field of the Treatment Kit Dispensing Log.

7.5 Storage of Drug Supplies

The Investigator or site pharmacy will be responsible for ensuring that all study medication is stored in a dry location, below 25°C, protected from exposure to any environmental changes and in a locked facility. Only the Investigator and specifically designated staff will have access to the drug supplies.

7.6 Study Drug Dispensing (IVRS)

In order to monitor and control the use of study medication, a central telephone randomisation service (IVRS) will be employed to assign medication to patients at all visits. All instances of dispensing (scheduled visits and any unscheduled dose adjustments) will require a telephone call to the central telephone randomisation

service (IVRS). In addition, any instance of a patient permanently ceasing to take medication (including death) will be reported to the central randomisation service so that adjustments can be made to the quantities of treatment kits to be included in subsequent deliveries to the site.

7.7 Study Drug Administration

One tablet (either pioglitazone or matching placebo) is to be taken with water in the morning with breakfast.

7.8 Overdose

Deliberate or accidental drug overdose should be treated symptomatically. Hypoglycaemia should be treated in the conventional manner.

7.9 Patient Compliance

All empty blisters and/or unused tablets will be returned to the Investigator at every scheduled visit after commencing treatment. Study drug compliance will be assessed by the Investigator according to a scale of poor, satisfactory or good without the necessity to count returned tablets.

7.10 Concomitant Medication

7.10.1 Permitted Concomitant Medication

Any other medication required (including non-thiazolidinedione oral anti-diabetic agents) may be administered concomitantly. Patients should be managed according to the IDF (Europe) guidelines for the management of type 2 diabetes mellitus, including control of blood pressure and lipids where applicable.

If a patient treated with a sulphonylurea or insulin develops hypoglycaemia, the dose of sulphonylurea or insulin should be reduced.

7.10.2 Prohibited Concomitant Medication

No thiazolidinedione will be allowed concomitantly with the study medication.

7.11 Randomisation and Unblinding Procedures

7.11.1 Randomisation and Dispensing Procedures

Each patient will be randomly allocated to one of the two treatment groups (either pioglitazone or placebo) at baseline. Randomisation will be done centrally via a telephone randomisation service (IVRS) to achieve equal allocation of patients between pioglitazone and placebo. The Investigator will place a telephone call to the

IVRS using a country-specific toll-free telephone number to report a new eligible patient and in turn will receive instructions as to which one of the study treatment kits on-site should be dispensed to the patient. Each treatment kit will be identified by a unique kit number.

Dispensing of further medication to the patient is achieved via calls to the central telephone randomisation service (IVRS) at each follow-up visit.

7.11.2 Emergency Unblinding

In the event of a medical emergency where management of a patient's condition requires knowledge of the study medication, the randomisation code may be broken by calling the 24-hour special assistance facility provided as part of the central telephone randomisation service (IVRS) (see section 1.2).

Reasons for breaking a code should be clearly explained and justified in writing. The date on which the code was broken together with the identity of the person responsible should also be documented.

7.12 Drug Accountability

Whenever study medication is dispensed to the patient, the detachable part of the treatment kit label should be stuck to the appropriate field of the Treatment Kit Dispensing Log.

Upon each delivery of study medication, the Investigator or delegate will call the central telephone randomisation service (IVRS) to register the arrival of the study medication by quoting the reference number on the shipping note. This call has the effect of making the contents of the shipment available for use in subsequent dispensing calls to the IVRS.

All unused supplies and any empty or part-used treatment kits returned by the patient should be retained for inspection. Drug accountability will be documented at the level of the monthly treatment kit. Counting of individual tablets is not required. The site will be provided with documentation in order to maintain a drug inventory throughout the study which will be signed by the Investigator at study end. Sites will be instructed as to how to dispose of any unused medication and should not destroy or ship any medication prior to receiving these instructions.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event

An adverse event (AE) is any unintended or unfavourable sign, symptom or disease occurring during the course of the study, whether or not believed to be causally related to study medication. This definition includes:

- Any worsening of conditions which were present at the time of entry into the study
- Accidents
- Clinically significant change in laboratory values
- Withdrawal effects
- Drug interactions
- Effects due to overdose, abuse or dependence

This definition applies throughout the period from randomisation until the final visit and includes periods of placebo treatment or periods when the patient is not receiving study medication.

8.1.2 Serious Adverse Events

A serious adverse event (SAE) is an adverse event which falls in any of the following categories:

- Results in death
- Is life-threatening
- Requires in-patient hospitalisation or occurs while in hospital and prolongs hospital stay
- Results in persistent or significant disability or incapacity
- Is a congenital anomaly/birth defect
- Is an important medical event which requires intervention to prevent one of the above

When deciding whether an adverse event meets any of the above, consideration should be given to the following notes:

A 'life-threatening' event is one where the patient was at increased risk of death at the time of the event. The definition does not apply if the event is one which would have increased the risk of death had the event been more severe.

Hospital admission is usually interpreted as requiring at least one overnight stay unless the reason for admission is an elective procedure. An elective procedure is defined as any diagnostic or therapeutic procedure (including surgery) which has not been prompted by a new adverse event or worsening of a previous event/condition or which was otherwise already planned at the time the patient was randomised. A requirement for out-patient treatment in an emergency room is not, of itself, an SAE although the event requiring treatment may be.

Adverse events as a consequence of drug misuse or drug overdose should be reported as SAEs even if the definition is not met.

8.1.3 Adverse Events of Special Interest

In this study the following events are defined as being of special interest:

- Hypoglycaemia
- New or worsening heart failure
- Oedema
- Any event resulting in the permanent cessation of study medication

8.2 Adverse Event Reporting

All serious and non-serious adverse events which occur between randomisation and close of the study must be reported.

8.2.1 Serious Adverse Event Reporting

Legislation requires that serious adverse events be reported to the appropriate authorities in a timely manner. As soon as an investigator becomes aware of an adverse event which meets the definition of 'serious' this should be documented using the Alert Report Booklet, to the extent that information is available, and this report faxed immediately to NCRL. Details are given in section 1.2 of this protocol. The minimum information required is: identity of investigator, centre number, patient number, treatment kit number, a description of event, the reason why the event is considered to be serious and an assessment of the relationship of the event to study medication. This first report should be submitted within one working day of the Investigator becoming aware of the event.

In all cases, the Investigator should continue to monitor the situation and report to NCRL all material facts relating to the progression or outcome of the event. Furthermore, the Investigator may be required to provide supplementary information as requested by any of: NCRL, the site monitor or the Sponsor.

Each Alert Report Booklet will bear a unique number. SAEs are thus reported in the Case Report Form (CRF) by referencing the Alert Report number. Repetition of event details is not required, but original top copies of Alert Report Booklet pages must be submitted along with CRF pages.

When reporting serious adverse events, the following additional points should be noted:

- Where possible, describe the event in terms of a diagnosis or syndrome rather than as signs or symptoms. Signs and symptoms may form part of the narrative.
- Give consideration to the number of SAE reports which are necessary. Repeated events which are closely linked both in type and time may be described in a single report. Similarly, events which form a well-recognised 'cascade' may be described in a single report. A specific instance of a cascade is the situation where the patient's heart failure worsens. At first, the event does not meet the definition of 'serious' but subsequently the definition does apply. This should be reported as a single SAE with the original date of onset and a comment in the narrative indicating when the event became serious. However, SAEs which are clearly distinct must be reported separately using separate Alert Report Booklets.
- Cause of death is required whenever known. Thus, death should usually be reported as the outcome of a specific serious adverse event.

8.2.2 Reporting of All Other Adverse Events

All other adverse events which do not meet the definition of serious should be documented in the CRF.

8.3 Other Safety Considerations

All laboratory data obtained during the course of the study, comprising both those central laboratory assessments required by this protocol and any other clinical investigation, should be reviewed. Any abnormal value which is considered to be of clinical significance should be reported as an adverse event or serious adverse event as appropriate, unless this value is consistent with the patient's present disease state (e.g. diabetes mellitus) or is consistent with values obtained prior to entry into the study.

Pregnancy is an exclusion criterion and patients of child-bearing potential who are eligible to enter the study will have agreed to use a method of contraception throughout the course of the study. However, should a patient become pregnant, study medication must be stopped immediately and the pregnancy monitored throughout its course. The Investigator must inform the Sponsor of the pregnancy. Any birth defect or congenital anomaly must be reported as a serious adverse event and any other untoward events occurring during the pregnancy must be reported as adverse events or serious adverse events, as appropriate.

8.4 Safety Monitoring

8.4.1 Safety Reviews by the Data and Safety Monitoring Committee

Throughout the study, an independent Data and Safety Monitoring Committee (DSMC) will receive end-point, serious adverse event and laboratory data. The DSMC will review these data with the primary aim of protecting the interests of patients and if necessary will recommend to the ISC any changes in the protocol or the premature termination of the study if this is required to maintain patient safety. (See section 1.3.7 for further information concerning the membership and operation of the DSMC.)

8.4.2 Unblinding for Regulatory Authorities and Ethical Committees

Bearing in mind the existence and responsibilities of the DSMC and the necessity for study medication in individual patients to remain blinded in order to maintain the integrity of the study, SAEs which are also endpoints will not be unblinded individually or reported as individual events to any regulatory authority or ethical committee, regardless of the investigator's assessment of causality. SAEs which are not endpoints will only be unblinded as individual events if the reporting investigator considers it possible that there is a causal relationship between the SAE and the study drug and the occurrence of such an SAE if caused by the study drug would change the known risk associated with pioglitazone therapy.

9 ENDPOINT REPORTING

During the study, all events which are possible primary or secondary endpoints must be reported to NCRL in an expedited manner. This is necessary to permit timely review of the accumulating safety data by the DSMC and to allow the central adjudication of endpoint data to proceed without undue delay.

All possible primary and secondary endpoint events will be reported using the Alert Report Booklet using the same time limits as for serious adverse events. For certain primary and secondary endpoint events, additional information will be required to permit central adjudication. This information will be collected via supplementary pages in the Alert Report Booklet.

The large majority of possible primary and secondary endpoints will be serious adverse events and so the completion of a single Alert Report Booklet will satisfy the reporting requirement for both SAE and endpoint purposes. However, there are some events which are primary or secondary endpoints but are not SAEs, for example, elective coronary revascularisation. Such events must still be reported via an Alert Report Booklet. Details of all events which must be reported by an Alert Report are given in the Alert Report Booklet.

10 DISCONTINUATION OF STUDY DRUG

Patients are free to stop taking study medication or to discontinue their participation in the study at any time without prejudice to further treatment. In addition, a patient's study medication may be temporarily suspended or permanently ceased at any time at the discretion of the Investigator, however, treatment with the study drug must be permanently discontinued in the following cases:

- Anaphylaxis
- Patient develops ketoacidosis
- Patient develops elevated liver tests (defined as ALT > 3 x ULN) on two consecutive occasions that cannot be explained by a concomitant disease
- Patient becomes pregnant

Following a temporary suspension of study medication, every possible effort should be made to restart double-blind treatment provided that there is no clinical contraindication and the patient has not withdrawn his/her consent. In the case of permanent cessation of study drug, the Investigator should notify the central telephone randomisation service (IVRS) and the patient should continue to be followed-up until the termination of the study. All patients withdrawn from study drug treatment should not be included in any other study until the PROactive Study has been completed.

11 STATISTICAL CONSIDERATIONS

The primary objective of this study is to compare the effect of pioglitazone with placebo on the occurrence of events within a composite of death, non-fatal myocardial infarction (including silent MI), acute coronary syndrome, coronary intervention, stroke, or revascularisation or amputation of the leg (see sections 4.2.1 and 6.4.1). Specifically, the primary endpoint variable will be the event-free interval (days) from randomisation to the first occurrence of any event within the composite. All patients will be followed from randomisation until the end of the study. Patients not experiencing an event within the primary endpoint composite will be administratively censored at their final visit. It is anticipated that the total duration of the study from first patient recruited until study end will be up to four years, subject to the requirement that all patients must be followed for at least 2.5 years. However, in order to maintain the statistical power of the study, follow-up under double-blind conditions will continue beyond the point where the last patient recruited completes 2.5 years of follow-up, if this is necessary to achieve the required minimum number of patients with primary endpoint events.

11.1 Interim Analyses

Safety aspects of the study will be monitored by the DSMC throughout the study. In addition, two interim analyses are planned so that the study can stop early if the

benefits of pioglitazone are clear and unambiguous. The analyses will occur when approximately 50% and 75% of the anticipated (projected) final number of endpoint events have occurred. These analyses will be conducted by the Independent Statistical Centre and then reported to the DSMC. (The DSMC Charter gives administrative details of the function of the Independent Statistical Centre and its role in support of the DSMC.) Each interim analysis for efficacy will consider the one-sided logrank test for the superiority of pioglitazone.

The precise timing of each interim analysis will be determined by projecting when the required number of endpoint events are likely to have occurred. A meeting of the DSMC will then be scheduled to occur shortly thereafter. Once a meeting date has been arranged, a “cut-off” date will be set two weeks in advance of the date of the meeting. At the “cut-off” date, all patients for whom NCRL have not been notified of an endpoint event will be censored at the “cut-off” date. Following review of each interim analysis, the DSMC will recommend that the study should stop early on the grounds of proven efficacy if the observed significance level is less than that specified by the following criteria:

- Total (one-sided) alpha of 0.025
- Lan-DeMets alpha spending function
- O’Brien-Fleming boundary

The use of a Lan-DeMets alpha spending function allows some flexibility with respect to the timing of the interim analyses. However, assuming that the interim analyses take place as scheduled, the study will stop early if the observed significance level for the analysis at 50% of endpoints is less than 0.0015 or the observed significance level at 75% of endpoints is less than 0.0081. Both interim analyses will use adjudicated data where this is available but will otherwise include those endpoints awaiting adjudication which have been identified by the Investigator as meeting the endpoint definition.

Assuming that the second interim analysis occurs as scheduled, the final analysis for efficacy will require the observed significance level for the one-sided test to be less than 0.0154 for the result to be declared significant overall at the 0.025 level.

There will be no analysis for futility.

11.2 Sample Size

The proposed recruitment of 2,500 patients per treatment group (that is, a total of 5,000 patients who successfully complete the screening period and are randomised to study medication) reflects the following assumptions and considerations:

- The annual event rate for the primary endpoint composite will be 6% in the placebo group
- Sites will join the study uniformly over the first nine months of recruitment and all sites will recruit uniformly

- Sufficient sites will be recruited to ensure that recruitment of patients is completed within 18 months of first patient
- The study should be completed in approximately four years
- Pioglitazone will effect a reduction in the primary endpoint event rate of 20% or greater
- The overall probability of a type I error for the analysis of the primary endpoint is limited to 0.05, two-sided (0.025 for superiority of pioglitazone)

It follows that:

- Average follow-up will be a little over three years
- The placebo event rate at average follow-up will be 17%; a 20% reduction in this event rate gives a pioglitazone event rate of 13.6%
- A total of 5,000 patients will ensure an overall power of 91% to detect a difference between the treatments of this magnitude (logrank test; alpha=0.025, one-sided)
- Assuming that the interim analyses take place as planned, but the study proceeds to full follow-up, 5,000 patients will give at least 88% power that the final analysis will declare that pioglitazone is superior to placebo at the 0.025 level of significance

In order to maintain the power of the study to detect a 20% lowering of the primary endpoint event rate, at least 760 patients must report a primary endpoint event. If the assumptions above prove correct, then this target will have been reached at the time the last patient recruited completes 2.5 years of follow-up. The earliest that the interim analyses can be scheduled is thus at 380 and 570 patients with a primary endpoint event, respectively.

11.3 Patient Populations

The statistical analysis will identify the following populations:

Safety:

The analysis of safety will include all patients who take at least one dose of study medication. If there is any error in treatment assignment, patients who receive the wrong treatment will be analysed in the safety analysis according to the treatment actually received.

Where patients permanently cease study medication prior to their final visit, adverse events identified during the 28 days following last tablet will be included in the analysis. The safety profile of pioglitazone is well characterised by previous studies and so no further adverse event reporting will be required for patients who stop study medication at their final visit.

Intention-to-treat:

The intention-to-treat population will include all patients randomised to treatment according to the treatment assigned by the central telephone randomisation service (IVRS) with the exception of those patients who withdraw without having taken any study medication. The statistical analysis for all primary, secondary and other endpoints of interest will consider this group of patients.

11.4 General Principles of Data Management and Statistical Analysis

Study data will be captured via a case record form (CRF), additional Alert Report Booklets used for the expedited reporting of serious adverse events or potential primary or secondary endpoint events or via the electronic transfer of laboratory data from the Central Laboratory. A CRF and Alert Report Booklet(s), as required, must be completed for every patient randomised. Patients entering the screening phase who do not subsequently qualify for randomisation require limited documentation which will be collected via a single page report.

Any 'printouts' giving the results of investigations or local laboratory measurements, etc. are source documents and must be retained in the patient's medical record. All data recorded in the CRF or an Alert Report Booklet must be able to be referenced to a source document forming part of the patient's medical record.

Management of the study database will be carried out without access to knowledge of treatment allocation. When all the data have been checked for plausibility, corrected to the extent possible and all coding and assessments have been completed, the database will be locked. Prior to the release of the treatment codes, patient membership of each of the safety and intention-to-treat populations will be determined and documented. Thereafter, the treatment codes will be revealed and the database will be made available for the statistical analysis.

Following database lock, NCRL will provide a copy of the database to the Sponsor. The statistical analysis will then be completed both by the Sponsor and NCRL each acting independently and in parallel. Subsequent comparison and reconciliation of the two analyses will ensure the overall accuracy of the statistical analysis.

As a general principle, the statistical analysis will follow the pre-specified Statistical Analysis Plan. The Analysis Plan will be prepared and agreed during a period of three months following the completion of recruitment, subject always in the case of premature termination of the study to the requirement that the Analysis Plan be finalised prior to revealing the treatment codes. During the course of recruitment, aggregated baseline data will be inspected for the purposes of determining the appropriate methodology for summarising the baseline data and the comparison of treatment groups at baseline. The Analysis Plan will specify also which subgroup analyses will be undertaken of the primary and secondary endpoints, the feasibility of such analyses having been determined after inspection of the aggregated baseline data. The Analysis Plan will address the methods to be used to handle missing data.

Where aspects of the data indicate that a departure from the plan is appropriate, the change to the plan will be documented, together with the reason for the change. The Analysis Plan will reflect the following:

- Where a primary or secondary endpoint of the study contains components which are the subject of central review, the final statistical analysis will consider the adjudicated data.
- Given the number of sites and the fact that each site will contribute a very small fraction of total recruitment, analysis of the primary endpoint will employ a logrank test without stratification for centre. If there are grounds for believing that the treatment groups are not directly comparable at baseline, the sensitivity of the inference based on the logrank test will be investigated using Cox model regression with the introduction of those covariates thought to be prognostically important. The same methodology will be used for all secondary endpoints which involve time to event measurements. Given the number of patients per treatment group, parametric methods will be used for all other analysis of efficacy endpoints.
- For the purpose of accommodating interim analysis rules, the analysis of the primary endpoint is viewed as two one-sided hypotheses, each with a significance level of 0.025. All other hypothesis testing to determine differences between treatments will be two-sided, with differences being declared statistically significant if the observed significance level is less than 0.05. The analysis described for the primary endpoint is confirmatory, with the overall probability of a type I error controlled to 0.05. All other analysis is secondary and will be reported without adjustment of significance levels. Treatment effects and treatment differences will be reported as point estimates with 95% confidence intervals.
- Incidence and type of adverse events will be summarised by treatment. Such summaries will allow for length of exposure. Laboratory parameters will be summarised both by mean values and the number of patients moving in and out of normal range. Where appropriate, alternative robust measures of location and scale will be used to characterise trends where means and standard deviations are sensitive to outlying observations.

11.5 Patient Numbering, Treatment Assignment and Use of the IVRS

All patients entering the screening phase will be assigned the next available patient number by the Investigator. Within a site, the first patient screened should be given the number 001. Thereafter, patients should be numbered consecutively without any gaps in the numbering sequence. The patient number, together with the pre-assigned centre (site) number, uniquely identifies each patient in the study. The patient number must be notified to the central telephone randomisation service (IVRS) at the time of randomisation and, thereafter, when each additional request is made for the assignment of further study treatment.

Where a patient is found to be eligible for the treatment phase, the Investigator will call the central telephone randomisation service (IVRS). Treatment assignment (active or placebo) will be on the basis of a separate pre-defined randomisation list

for each site created using the method of randomised permuted blocks. The kit number assigned by the system for the first month's treatment and, thereafter, for every follow-on kit will be chosen at random from the applicable kits of the correct type and dose which are known to be at the site, subject only to the fact that kits with an earlier expiry date will be assigned before kits with a later expiry date and will not be dispensed at all if the expiry date is likely to be exceeded within the period that the contents of the kit are to be consumed.

In addition to contacting the central telephone randomisation service (IVRS) for the purposes of randomising and assigning treatment kits to patients, the Investigator or designate will be required to report changes in a patient's requirement for further medication (i.e. at the point a patient dies or permanently ceases medication). The system will also provide the facility to assign replacement treatment kits (in the event that the previously assigned kit is missing or damaged) together with special assistance and demonstration options.

12 ETHICAL CONSIDERATIONS

The study will be conducted in accordance with the principles stated in the Declaration of Helsinki, as given in Appendix 3.

For each study site, this study protocol together with the Patient Information Sheet and Consent Form to be used at the site must be approved by an appropriately constituted Ethics Committee(s) as required by applicable laws, regulations and guidelines.

All Ethics Committee opinions should be given in writing and be signed and dated. A list of those persons attending the meeting at which the opinion is given (names and positions) must also be obtained. All correspondence with the Ethics Committee(s) should be filed by the Investigator. Copies of all relevant opinions and membership lists for a given site must be received by ICON before approval will be granted for the release of trial supplies for that site.

When instructed by the Sponsor or ICON, the Investigator must inform the relevant Ethics Committee(s) of any material change to the safety profile of the study medication.

12.1 Informed Consent

It is the responsibility of the Investigator to ensure that the patient is given full and adequate verbal and written information about the nature, purpose, benefit and the possible risks of the trial. Patients should be informed that they are free to discontinue their participation in the study at any time without giving a reason and without prejudice to the quality of their continuing care. The Investigator should ensure that there is sufficient time between the giving of consent and the commencement of study medication to allow the patient to reconsider his/her decision to enter the study. As a minimum, this period should be that specified under the applicable local laws or regulations.

Master versions of the Patient Information Sheet and Consent Form are given in Appendix 2. These will be modified and translated as required for individual sites. Should any modifications to the content of either document be required to meet local requirements, these changes must be approved by the Sponsor or one of its representatives (Senior Project Manager of ICON).

12.2 Patient Data Protection

All data received and processed by NCRL will be identified by patient number only. Patient identity will remain unknown to NCRL and the Sponsor.

Patients will be informed that the data which they provide will be stored and managed on computer in accordance with the applicable Data Protection legislation for the participating countries.

Patients should also be informed in writing that authorised representatives of any of the Sponsor, regulatory authorities and Ethics Committees may require access to those parts of their hospital records which are relevant to the study for the purposes of data verification. The Consent Form will ask the patient to grant permission for this access.

The Investigator must maintain a Patient Identification Log of all patients admitted to the screening phase whereby patient identity can be determined from a study number. As an added precaution, this log should also record the patient's initials in the same manner as they are recorded in the CRF.

12.3 Insurance

The Sponsor carries insurance for the study to compensate patients in the event of a trial-related injury except for claims that arise from malpractice or negligence. Insurance details will be provided by the Sponsor.

13 ADMINISTRATIVE ISSUES

13.1 Investigator Responsibilities

Investigators are required to undertake the following administrative responsibilities:

- The Investigator must ensure that patient management throughout the course of the study is fully documented in the patient's medical record. This record must include full details of procedures, investigations and tests carried out as part of the study as well as the patient's usual management. The Investigator will review all entries in the Patient Medical Notebooks to identify potential SAEs and potential primary or secondary endpoints for which more detailed information will need to be obtained in order to enable the Investigator to report the event to NCRL.

- Whenever the Investigator learns that the patient has been admitted to hospital or is otherwise treated at an Institution or in a Department which is distant from the Investigator, the Investigator will make every effort to recover those data necessary for completion of the CRF or an Alert Report Booklet. Proforma letters and additional data capture forms will be made available to the Investigator to help with this task.
- The Investigator or an appropriately qualified member of staff will ensure that all appropriate CRF pages and Alert Report Booklets are completed in full and in a timely manner and are consistent with source documents. Initial reports of serious adverse events must be notified to NCRL within one working day of the Investigator becoming aware of the event. The Investigator or delegate will assist the site monitor with the management of these data sheets and any reconciliation of these data with source documents. The Investigator will ensure that any data enquiries arising from the data cleaning process will be answered promptly.
- In order to permit the central adjudication of coronary ischaemic events, copies of relevant ECGs will be required to be submitted along with the CRF. The Investigator's responsibility in this respect extends to obtaining ECGs from remote sites.
- The Investigator will maintain the Investigator Site File and the logs therein as instructed by the site monitor.

Following completion of the study, the Investigator will be responsible for archiving the Investigator Site File and other documentation relating to the study until further notice. In particular, it is essential that the Patient Identification Log which provides the link between a patient study number and the patient's identity be maintained for a period of at least two years following the date of the final amendment to any regulatory approval notice in any jurisdiction. The Sponsor will advise the Investigator in this respect.

Original patient medical records should be maintained for the longest possible time consistent with standard practice at the site. If, at any time, there is a possibility that effective archiving of study documents may be compromised, the Investigator must inform the Sponsor.

13.2 Monitoring, Quality Assurance and Inspection by Authorities

This study will be conducted in accordance with the ICH Harmonised Tripartite Guideline for Good Clinical Practice. Each site will have an assigned site monitor who will conduct regular visits to the site and assist or advise the site on all aspects of their duties and responsibilities. Details of monitoring duties will be described in a Manual of Operations (Monitoring).

Throughout the study, the Sponsor may, at its discretion, require a site audit to be conducted either by a member of their own staff, an auditor from NCRL or by an independent auditor as part of an overall programme of quality assurance. The site Investigator is requested to cooperate fully with any such audit.

If, at any time during or after the study, a site receives a request to conduct an audit from any regulatory authority, the Sponsor must be informed immediately.

13.3 Protocol Amendments

Any changes to the design or conduct of the study or any new practices or decisions which are inconsistent with this protocol must be documented as written protocol amendments and approved by the ISC. Any amendments that affect the patient must be appropriately reviewed by the relevant Ethics Committee(s) as required by applicable laws, regulations and guidelines. These committees will also be advised of any amendments of a purely administrative nature.

13.4 Publication Policy

Following closure of the study database and the final statistical analysis, the EC will prepare a manuscript for publication. Prior to submission, the manuscript will be reviewed by the ISC, DSMC, EAC and the Sponsor and approved by the ISC. The manuscript will be submitted for publication on behalf of the 'PROactive Study Investigators'.

Conduct of the study and publication of the results will comply with the new "Uniform Requirements for Manuscripts Submitted to Biomedical Journals: Writing and Editing for Biomedical Publication". The role of the Sponsor in the study design, collection, analysis and interpretation of the data; the writing of the report; the decision to submit the report for publication will be specifically detailed. Furthermore, the Executive Committee, on behalf of the International Steering Committee, will have full access to the data and ultimately will be responsible for the integrity of the data and the accuracy of the data analysis.

Subsequent derivative publications may have individual authorship but require the prior approval of the EC. The Sponsor retains the right to comment on all publications prior to their submission and will respond in all cases within 90 days.

The study database is the commercial property of the Sponsor and the Sponsor reserves the right to undertake analysis of study data and initiate publication or distribution of the data at its own discretion.

14 REFERENCES

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Appendix 1
PROactive Study
Investigator Statement

I agree to conduct the PROactive clinical trial (Takeda study code: AD-4833/EC444) in accordance with the requirements of this Protocol and also in accordance with the following:

- Declaration of Helsinki (Edinburgh, Scotland, October 2000)
- Good Clinical Practice of the European Community, CPMP/ICH/135/95
- Applicable laws and regulations
- Regulatory requirements for reporting of serious adverse events defined in section 8 of the study protocol

Name

Signature

Date

Original: To study masterfile

NCR Copy: File with protocol in Investigator Site File

[Note for revised study protocol incorporating amendments 1, 2 & 3 (02-May-2003): Investigator Statements have been signed each time an amendment has been produced. There is therefore no requirement to sign this page in version 1.2 of the study protocol dated 02-May-2003.]

Appendix 2

Patient Information Sheet and Informed Consent Form (Master version)

Note to Ethics Committees

The sample Patient Information Sheet and Informed Consent Form contained in this appendix form the master versions only and are not intended to form part of an application for the Ethic's Committee permission to conduct the study. When considering an application from an investigator, reference should be made to the Patient Information Sheet and Consent Form that will have been submitted separately.

[To be on hospital headed paper, if applicable]

Patient Information Sheet (Master Version)

Version 1.0 (28 January 2001)

5 PROactive: A macrovascular outcome study in type 2 diabetic patients comparing pioglitazone with placebo in addition to existing therapy

10 You are being invited to take part in a medical research study, which is being
sponsored by Takeda Europe R&D Centre Ltd. Before you decide whether you are
willing to take part, it is important for you to understand why the research is being
done and what it will involve. The purpose of this information sheet is to provide you
with details about the study. It is important that you understand the possible risks
and benefits, so please take time to read it carefully and discuss it with friends,
relatives and your GP as you wish. Please ask the study doctor if there is anything
15 you don't understand or if you would like more information.

*[Refer to country-specific guidelines that provide patients with information about
medical research, if applicable.]*

What is the purpose of the study and why have I been chosen?

20 You are being asked to take part in this research study because you have a condition
called type 2 diabetes mellitus. Patients with type 2 diabetes can develop
cardiovascular complications including heart attacks, strokes and poor circulation to
the legs. You already have or have had one of these complications and the purpose
of this study is to determine whether pioglitazone can prevent further episodes. The
study will involve 5,000 patients in 15 countries and will last for approximately 4 years
25 although some patients may be treated for a shorter period of time.

What is the drug that is being tested?

Pioglitazone is a drug that is used to treat diabetes and is approved and available in
some countries. It lowers increased blood sugar levels and it may also lower some
of the fats that circulate in the blood. These properties should be beneficial in
30 reducing the cardiovascular complications of diabetes but this has not yet been
proven. *[State if pioglitazone has been approved in appropriate country and/or
extent to which the drug has been prescribed, if applicable.]*

What will happen to me if I take part?

35 If you decide to take part, the study doctor will take a medical history and perform a
physical examination and a blood test in order to check your eligibility for the study.
If the blood test results show that you are eligible, the study doctor will take additional
blood samples and perform a tracing of your heart (electrocardiogram, ECG). The

study doctor will then prescribe your study medication. At the end of this visit, you will be given a patient-held record (patient medical notebook) containing details of this study and pages to be completed by any medical professionals (doctors/nurses) you may be treated by between your study visits. It is important that you bring your notebook to all your visits so that the study doctor can review it.

It is planned that you will be followed up in the study for at least two and a half years, and depending on your entry in to the study, up to a maximum of approximately four years. During this time you will need to see your study doctor on a regular basis. Your first visit will be after one month, followed by two-monthly visits during the first year and three-monthly visits during the following years. At these visits the assessments may include:

- Measurement of weight, waist circumference, and blood pressure (at every visit)
- Blood samples (at every visit during the first year and every 6 months subsequently)

These are taken to make sure that there are no unwanted effects of the study drug, and to check that your diabetes is under control. In the first year of the study blood will be drawn at each visit and in the following years blood will be drawn every other visit. The amount of blood drawn at each of these visits will be approximately 2 to 3 teaspoonsful.

- Heart tracing (electrocardiogram, ECG) (once per year)

During the study, in addition to your regular anti-diabetic treatment (diet, tablets or insulin), you will receive either the active study medication (pioglitazone) or a dummy substance (placebo), which contains no active drug. Whether you receive the active or inactive drug will be determined by chance. There is an equal chance of receiving either active or inactive drug. Neither you nor the study doctor will know which type of medication you are taking, but if the study doctor needs to find out he/she will be able to do so.

During the first three months, the dose of the active drug, if you are on active medication, will be increased in two steps to a maximum of 45mg. This will be done to achieve the best possible control of your blood sugar. The study doctor will explain any change and will make sure that it is safe and appropriate for the dose to change. If you suffer from symptoms of low blood sugar or if the study doctor thinks your blood sugar should not be lowered any further, he/she may decide not to increase or even to decrease the dose of the study medication. **The study doctor might also tell you to reduce the dose of your usual anti-diabetes treatment.**

To allow you to measure your blood sugar at home, the study doctor will give you a glucose meter, if you do not already have one. The study doctor or his/her staff will show you how to use it.

What do I have to do?

For some of the visits, you must not have any food or drink (except water) for 12 hours before you come to the clinic. The appointment schedule in your patient

medical notebook will make it clear for which visits this applies and you will be told by the study doctor or his/her nurse at the previous visit.

At each visit, you will receive enough study medication to last you until your next visit. You have to take one tablet (with water) with breakfast, every day. You must return unused study medication to the study doctor at your next visit.

5

At each visit, the study doctor will also ask you if you have had any side effects to the medications you are taking. It is also important that you inform the study doctor of any medications you are taking other than the study medication. Except for drugs belonging to the same class as pioglitazone, your GP will be able to prescribe any treatment that is clinically necessary for you.

10

You should keep your patient medical notebook with you at all times and always show it when being treated by medical professionals. This will inform them that you are taking part in a research study and allow them to record any treatment you receive.

15 If you decide to take part in this study, you cannot take part in any other clinical trial until 30 days after the end of this study.

What are the possible side effects?

To date, more than 3,500 patients with type 2 diabetes have received pioglitazone in clinical studies and more than 1 million patients have received pioglitazone in normal clinical practice. In the clinical studies, the most commonly occurring side-effects thought to be due to the study drug were fluid retention (e.g. ankle swelling) and weight gain. Because another drug of a similar nature had problems with damaging the liver, although no such effects have been seen with pioglitazone, the study doctor will not let you take part in the study if you have a history of liver problems or if your liver enzymes are too high at the first visit. Throughout the study, your liver enzymes will be monitored closely and if they are too high, study medication will be stopped. Please inform the study doctor by or on the next working day if you experience any of the following symptoms without any obvious other reason: nausea (feeling sick), vomiting, abdominal pain, tiredness, loss of appetite, or dark urine. The study doctor will then perform the necessary tests to find out whether this is due to a liver problem and will ask you to stop taking the study medication if this is the case. If you develop jaundice (your skin or eyes turn yellow) you should stop taking the tablets immediately and inform the study doctor by or on the next working day.

20

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When selecting you for this study, the study doctor will have made sure that you do not have serious heart failure causing breathlessness, which would make it inappropriate for you to take the study medication. However, as fluid retention may sometimes occur with this drug, you should inform the study doctor about any symptoms you notice (e.g. swelling of the feet or legs or shortness of breath). The study doctor will then monitor you closely and, if appropriate, ask you to stop taking the study medication or give you another medicine to counteract these effects.

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What are the other possible disadvantages and risks?

5 The blood sampling done during this study involves minimal risk but it may be associated with discomfort, redness or bruising where the skin is punctured. If you have private medical insurance, you should contact your insurance company, if necessary, before agreeing to take part in this study. You need to check this to ensure that your taking part does not affect your medical insurance.

Special note to females

10 It is possible that if the study medication is given to a pregnant woman it will harm the unborn child. Pregnant women or breast-feeding women must therefore not take part in the study; neither should women who plan to become pregnant during the study. Women who could become pregnant during the study must be planning to use an effective contraceptive during the course of this study. Any woman who finds that she has become pregnant while taking part in the study should take no further dose of the study medication and should inform the study doctor by the next day.

15 What are the possible benefits?

Taking the study medication together with your regular treatment may prevent or reduce the occurrence of cardiovascular complications. However, this cannot be guaranteed. The information we get from this study may help make the treatment of patients with type 2 diabetes better in the future.

20 What if new information becomes available?

25 Sometimes during the course of a study new information becomes available concerning the drug that is being studied. If this happens, the study doctor will tell you about it and discuss with you whether you want to continue taking the study drug. If you decide to withdraw, the study doctor will make arrangements for your care to continue. Also on receiving new information the study doctor or the organisers of the study might consider it to be in your best interests to stop taking study drug. He/she will explain the reasons and arrange for your care to continue.

What happens when the research study stops?

30 [At the end of the study, the doctor responsible for managing your diabetic treatment will prescribe the appropriate available medication. This might include pioglitazone. At all times throughout the study if the study doctor is not your GP, the study doctor will remain in contact with your GP.](#)

What if something goes wrong?

[Provide details of country-specific compensation guidelines and procedures.]

35 Will my taking part in this study be kept confidential?

If you consent to take part in the study you have a right to privacy. Personal data that may be sensitive will be collected and processed but only for research purposes

in connection with this study. The study data will be sent around the world but you will not be referred to by name or identified in any report or publication nor could the data be traced back to you. Takeda Europe R&D Centre Ltd (who will control the use of the data) will take steps to ensure that your personal data is protected. It is a requirement that your involvement in this study is noted in your medical records. Direct access to your records will be required by authorised representatives of Takeda Europe R&D Centre Ltd to check the information collected for the study. Your medical records may also be reviewed by the independent ethics committee members or by the regulatory authorities to check that the study is being carried out correctly.

If the study doctor is not your GP, he/she will, on your behalf, inform your GP that you are taking part in this study.

What will happen to the results of the research study?

When the results of the study have become available to Takeda Europe R&D Centre Ltd, the findings of the research will be published in a medical journal. At this time the study doctor will be able to let you know what medication you were taking during the study.

Who is organising and funding the research?

The sponsors of the study, Takeda Europe R&D Centre Ltd, will contribute a study grant to the study doctor or his/her hospital to fund the conduct of this study. *[State whether the study doctor will receive personal payment for being involved in the study.]* You will not receive personal payment for being involved in the study. However, your reasonable travel expenses to attend study visits will be reimbursed.

What happens if I do not want to take part, or if I wish to withdraw from the study?

It is up to you to decide whether or not to take part. The study doctor will answer any questions you might have concerning the study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form. Even if you decide to take part, you are still free to withdraw at any time and without giving a reason. This will not affect the standard of your future medical care. If you discontinue study medication, the study doctor will ask to remain in contact with you for the rest of the study and for you to continue the regular follow-up visits. This is to ensure that you are well and to continue to record information about your state of health as part of the study.

What are the alternatives for treatment?

If you decide not to take part, you will continue to be treated with the standard medical treatment for type 2 diabetes. *[State if Pioglitazone is available as standard therapy in specific country.]* The study doctor will be happy to explain the alternatives to you.

Contact for further information

If you would like more information or if you have any problems, concerns or questions about this study please ask the study doctor. The numbers to call are given below.

Name

**Telephone
Number**

5

[If required, insert contact details for organisation(s) who can provide information to the patient regarding his/her rights as research subject and any mandatory information concerning complaints procedures.]

Centre Number: _____
 Study Number: AD-4833/EC444
 Patient Identification Number: _____

Informed Consent Form (Master Version)

Title of Project: PROactive: A macrovascular outcome study in type 2 diabetic patients comparing pioglitazone with placebo in addition to existing therapy

A randomised, double-blind, parallel-group, multi-centre study

Name of Researcher: _____

- 1) I confirm that I have read and understand the information sheet dated [date of country specific version] (Version [country specific version number]) for the above study and have had the opportunity to ask questions.
- 2) I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected.
- 3) I understand that sections of my medical notes may be looked at by representatives of Takeda Europe R&D Centre Ltd, independent ethics committee members or regulatory authorities. I give permission for these individuals to have access to my records.
- 4) By taking part in this study I agree to the transfer of my personal data to other Takeda companies and to medicines regulatory authorities both within and outside Europe and I agree not to restrict the use of these data even if I withdraw.
- 5) I agree to take part in the above study.

A copy of the information sheet and signed consent form will be given to you to keep.

Name of Patient	Date (DD/MM/YYYY)	Signature
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Name of Person taking Consent (if different from Researcher)	Date (DD/MM/YYYY)	Signature
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Top Copy - patient's notes

Second Copy - patient

Third Copy – researcher's study file

Appendix 3

Declaration of Helsinki (Edinburgh, Scotland, October 2000)

WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI

Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly,
Helsinki, Finland, June 1964

and amended by the

29th WMA General Assembly, Tokyo, Japan, October 1975

35th WMA General Assembly, Venice, Italy, October 1983

41st WMA General Assembly, Hong Kong, September 1989

48th WMA General Assembly, Somerset West, Republic of South Africa, October
1996

and the

52nd WMA General Assembly, Edinburgh, Scotland, October 2000

A. INTRODUCTION

1. The World Medical Association has developed the Declaration of Helsinki as a statement of ethical principles to provide guidance to physicians and other participants in medical research involving human subjects. Medical research involving human subjects includes research on identifiable human material or identifiable data.

2. It is the duty of the physician to promote and safeguard the health of the people. The physician's knowledge and conscience are dedicated to the fulfilment of this duty.

3. The Declaration of Geneva of the World Medical Association binds the physician with the words, "The health of my patient will be my first consideration," and the International Code of Medical Ethics declares that, "A physician shall act only in the patient's interest when providing medical care which might have the effect of weakening the physical and mental condition of the patient."

4. Medical progress is based on research which ultimately must rest in part on experimentation involving human subjects.

5. In medical research on human subjects, considerations related to the well-being of the human subject should take precedence over the interests of science and society.

6. The primary purpose of medical research involving human subjects is to improve prophylactic, diagnostic and therapeutic procedures and the understanding

of the aetiology and pathogenesis of disease. Even the best proven prophylactic, diagnostic, and therapeutic methods must continuously be challenged through research for their effectiveness, efficiency, accessibility and quality.

7. In current medical practice and in medical research, most prophylactic, diagnostic and therapeutic procedures involve risks and burdens.

8. Medical research is subject to ethical standards that promote respect for all human beings and protect their health and rights. Some research populations are vulnerable and need special protection. The particular needs of the economically and medically disadvantaged must be recognized. Special attention is also required for those who cannot give or refuse consent for themselves, for those who may be subject to giving consent under duress, for those who will not benefit personally from the research and for those for whom the research is combined with care.

9. Research Investigators should be aware of the ethical, legal and regulatory requirements for research on human subjects in their own countries as well as applicable international requirements. No national ethical, legal or regulatory requirement should be allowed to reduce or eliminate any of the protections for human subjects set forth in this Declaration.

B. BASIC PRINCIPLES FOR ALL MEDICAL RESEARCH

10. It is the duty of the physician in medical research to protect the life, health, privacy, and dignity of the human subject.

11. Medical research involving human subjects must conform to generally accepted scientific principles, be based on a thorough knowledge of the scientific literature, other relevant sources of information, and on adequate laboratory and, where appropriate, animal experimentation.

12. Appropriate caution must be exercised in the conduct of research which may affect the environment, and the welfare of animals used for research must be respected.

13. The design and performance of each experimental procedure involving human subjects should be clearly formulated in an experimental protocol. This protocol should be submitted for consideration, comment, guidance, and where appropriate, approval to a specially appointed ethical review committee, which must be independent of the Investigator, the sponsor or any other kind of undue influence. This independent committee should be in conformity with the laws and regulations of the country in which the research experiment is performed. The committee has the right to monitor ongoing trials. The researcher has the obligation to provide monitoring information to the committee, especially any serious adverse events. The researcher should also submit to the committee, for review, information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest and incentives for subjects.

14. The research protocol should always contain a statement of the ethical considerations involved and should indicate that there is compliance with the principles enunciated in this Declaration.

15. Medical research involving human subjects should be conducted only by scientifically qualified persons and under the supervision of a clinically competent medical person. The responsibility for the human subject must always rest with a medically qualified person and never rest on the subject of the research, even though the subject has given consent.

16. Every medical research project involving human subjects should be preceded by careful assessment of predictable risks and burdens in comparison with foreseeable benefits to the subject or to others. This does not preclude the participation of healthy volunteers in medical research. The design of all studies should be publicly available.

17. Physicians should abstain from engaging in research projects involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed. Physicians should cease any investigation if the risks are found to outweigh the potential benefits or if there is conclusive proof of positive and beneficial results.

18. Medical research involving human subjects should only be conducted if the importance of the objective outweighs the inherent risks and burdens to the subject. This is especially important when the human subjects are healthy volunteers.

19. Medical research is only justified if there is a reasonable likelihood that the populations in which the research is carried out stand to benefit from the results of the research.

20. The subjects must be volunteers and informed participants in the research project.

21. The right of research subjects to safeguard their integrity must always be respected. Every precaution should be taken to respect the privacy of the subject, the confidentiality of the patient's information and to minimize the impact of the study on the subject's physical and mental integrity and on the personality of the subject.

22. In any research on human beings, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail. The subject should be informed of the right to abstain from participation in the study or to withdraw consent to participate at any time without reprisal. After ensuring that the subject has understood the information, the physician should then obtain the subject's freely-given informed consent, preferably in writing. If the consent cannot be obtained in writing, the non-written consent must be formally documented and witnessed.

23. When obtaining informed consent for the research project the physician should be particularly cautious if the subject is in a dependent relationship with the physician or may consent under duress. In that case the informed consent should be obtained by a well-informed physician who is not engaged in the investigation and who is completely independent of this relationship.

24. For a research subject who is legally incompetent, physically or mentally incapable of giving consent or is a legally incompetent minor, the Investigator must obtain informed consent from the legally authorized representative in accordance with applicable law. These groups should not be included in research unless the research is necessary to promote the health of the population represented and this research cannot instead be performed on legally competent persons.

25. When a subject deemed legally incompetent, such as a minor child, is able to give assent to decisions about participation in research, the Investigator must obtain that assent in addition to the consent of the legally authorized representative.

26. Research on individuals from whom it is not possible to obtain consent, including proxy or advance consent, should be done only if the physical/mental condition that prevents obtaining informed consent is a necessary characteristic of the research population. The specific reasons for involving research subjects with a condition that renders them unable to give informed consent should be stated in the experimental protocol for consideration and approval of the review committee. The protocol should state that consent to remain in the research should be obtained as soon as possible from the individual or a legally authorized surrogate.

27. Both authors and publishers have ethical obligations. In publication of the results of research, the Investigators are obliged to preserve the accuracy of the results. Negative as well as positive results should be published or otherwise publicly available. Sources of funding, institutional affiliations and any possible conflicts of interest should be declared in the publication. Reports of experimentation not in accordance with the principles laid down in this Declaration should not be accepted for publication.

C. ADDITIONAL PRINCIPLES FOR MEDICAL RESEARCH COMBINED WITH MEDICAL CARE

28. The physician may combine medical research with medical care, only to the extent that the research is justified by its potential prophylactic, diagnostic or therapeutic value. When medical research is combined with medical care, additional standards apply to protect the patients who are research subjects.

29. The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic, and therapeutic methods. This does not exclude the use of placebo, or no treatment, in studies where no proven prophylactic, diagnostic or therapeutic method exists.

30. At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.

31. The physician should fully inform the patient which aspects of the care are related to the research. The refusal of a patient to participate in a study must never interfere with the patient-physician relationship.

32. In the treatment of a patient, where proven prophylactic, diagnostic and therapeutic methods do not exist or have been ineffective, the physician, with informed consent from the patient, must be free to use unproven or new prophylactic, diagnostic and therapeutic measures, if in the physician's judgement it offers hope of saving life, re-establishing health or alleviating suffering. Where possible, these measures should be made the object of research, designed to evaluate their safety and efficacy. In all cases, new information should be recorded and, where appropriate, published. The other relevant guidelines of this Declaration should be followed.

Appendix 4

NYHA Classification

- I Patients with cardiac disease but without resulting limitation of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or anginal pain.
- II Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
- III Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea or anginal pain.
- IV Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.