



Takeda Europe R&D Centre Limited  
Savannah House  
11-12 Charles II Street  
London SW1Y 4QU  
United Kingdom  
Tel.: +44 (0)20 7484 9000  
Fax: +44 (0)20 7484 9060

## STATISTICAL ANALYSIS PLAN

Version 1.3 (FINAL) / 12 May 2005

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**

### Confidentiality Statement

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## 1. INTRODUCTION

This document describes the Statistical Analysis Plan for the PROactive Study, a multicentre randomised double-blind, parallel-group study to compare the effect on mortality and morbidity of pioglitazone with placebo in addition to existing therapies in patients with Type II Diabetes.

The PROactive Study design is described in detail in the Study Protocol, Version 1.2, dated 2nd May 2003, (incorporating protocol amendments 1, 2 and 3) together with protocol amendment 4 dated 26<sup>th</sup> October 2004. The following plan has been determined following the close of recruitment but prior to database lock.

### 1.1 Objectives

The overall objectives of the PROactive Study are as follows:

- 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 patients

### 1.2 Design

Brief details of the study design are as follows:

- Multi-centre, randomised, double-blind, placebo-controlled, parallel-group study
- Phase IIIb
- Treatments
  - Pioglitazone (15 mg, 30 mg or 45 mg; forced titration)
  - Matching placebo

The study protocol indicated that 5,000 patients would be randomised with equal allocation to the two treatment groups. In the event, the first patient was randomised on 28<sup>th</sup> May 2001 and recruitment was closed on 30<sup>th</sup> April 2002, at which time 5,238 patients had entered the study and had received study medication. Patients were recruited in 19 countries in Europe, with 321 centres contributing patients.

The PROactive Study is a forced titration study, with the objective of maintaining patients on the maximum tolerated dose of study medication. All patients commenced treatment at the 15mg dose (active or matching placebo) and then, for the large majority of patients, the dose was increased stepwise to 30 mg at Visit 2 (Month 1) and 45 mg at Visit 3 (Month 2). However, upward titration could proceed at a slower rate if tolerability problems were observed. Throughout the treatment period, the dose could be increased or decreased within the range 15 to 45 mg as tolerability allowed.

### **1.3 Time Course**

The study protocol provides a rationale for the choice of sample size. In order that the study retain a power of at least 90% to detect a 20% reduction in the primary endpoint event rate for pioglitazone relative to placebo at average follow-up, the protocol stated that the study should continue until primary endpoint events have been observed for at least 760 patients.

During initial planning, it was estimated that follow-up of all patients would continue until at least April 2005. As the study progressed it became clear that endpoint events for 760 patients would be reached during the early part of 2004. One consequence of stopping follow-up at this time is that the mean duration of exposure to treatment would have been shorter than originally anticipated.

Protocol amendment 3 was therefore introduced stating that follow-up of all patients would continue until both of the conditions following were satisfied:

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

Both conditions were satisfied by 31<sup>st</sup> October 2004. The Executive Committee, therefore, instructed all investigators to schedule a final visit for each subject within the period 1<sup>st</sup> November 2004 and 31<sup>st</sup> January 2005. It is anticipated that data cleaning will be completed during the second half of May 2005.

### **1.4 Responsibilities**

The statistical analysis of the PROactive Study will be conducted by Nottingham Clinical Research Limited (NCRL) on behalf of the PROactive Study Steering Committee and the Sponsor, Takeda Europe R&D Centre Limited (Takeda).

### **1.5 Scope**

This Plan describes the intended analysis which will be carried out to address the objectives of the study as stated in the protocol. However, the PROactive Study is a major study in patients with type II diabetes and the database will provide numerous additional opportunities to address questions of scientific or clinical interest. This Plan does not preclude any additional exploratory analyses as may be requested by the Executive Committee, the Sponsor or Regulatory Authorities. Additional analyses requested by the Steering Committee or other parties will also be considered, subject to approval of the Executive Committee.

## **2 PROTOCOL CONSIDERATIONS**

The following sections summarise key definitions and other aspects of the study, which are given in the protocol and are relevant to the statistical analysis. Where necessary, these definitions provide additional detail beyond that provided in the study protocol.

### **2.1 Study Populations**

The trial population consists of patients with type II diabetes mellitus who are at increased risk of cardiovascular complications. Specifically, patients are required to meet all of the inclusion criteria and meet none of the exclusion criteria. See sections 5.2 and 5.3 of the Study Protocol.

#### **Efficacy Analysis**

All efficacy analyses will consider the intention to treat population (ITT), defined as follows: all patients who are randomised (i.e., assigned to a treatment group via a telephone call to the central randomisation facility) and who subsequently take at least one dose of study medication. Patients who receive study medication through a prescription error, either initially or during the course of follow-up, which is not consistent with the treatment group to which they were assigned, will be included in the analysis according to treatment assigned.

It is argued that restricting the intention to treat analysis to patients who receive at least one dose of treatment is appropriate in the context of this study. Patients considering entry to the study are given clear information as to the nature of the study and the extent of the commitment necessary. Patients are encouraged to review their willingness to participate and thus the taking of the first dose indicates that both physician and patient have the intent to proceed with the course of treatment.

No Per-Protocol analysis is planned. The number of patients entered into the study in violation of the inclusion or exclusion criteria and having a significantly altered potential to benefit from study medication will be small in number. Such patients will be identified prior to study treatment unblinding and will be described in a separate table and listing, but will be included in the ITT population.

#### **Safety Analysis**

The safety analysis will also consider all patients who receive at least one dose of study medication. If, at baseline, a subject received a treatment kit other than that assigned by the randomisation service and the error was notified to the Coordination Centre prior to the month 1 follow-up call, the IVRS, thereafter, assigned study medication to be consistent with the actual medication used during the first month. Any such subject will be included in the safety analysis in the treatment group according to the medication used. All other subjects will be analysed according to the medication assigned, even if a prescription error at some point during follow-up results in the subject being swapped temporarily to the opposite treatment.

In some circumstances the safety analysis will be restricted to those data obtained while the subject was continuing to take study medication (defined as data recorded at any visit prior to or at the time of the date of permanent cessation of study medication, without consideration of compliance or temporary cessation). Referring to any such analysis as 'on treatment' analysis, in contrast to analysis of the ITT population, the following table summarises the circumstances where each approach will be used.

| Variable                               | ANALYSIS  |
|--|---|
| All efficacy variables                 | ITT   |
| Serious and non-serious adverse events | Both ITT and on treatment (see also additional groupings of interest specified in sections 6.2 – 6.5) |
| HbA1c and Lipid parameters             | Both  |
| Laboratory safety data                 | Both  |
| Blood pressure                         | Both  |
| Measures of body size                  | Both  |

## 2.2 Primary Endpoint

The primary endpoint for the study is the following composite; see section 2.6 of the study protocol:

- All-cause mortality
- Non-fatal myocardial infarction (including silent MI)
- Acute coronary syndrome
- Cardiac intervention including coronary artery bypass graft (CABG) or percutaneous coronary intervention (PCI)
- Stroke
- Major leg amputation (above ankle)
- Bypass surgery or revascularisation in the leg

Study treatments will be compared using a time to event analysis (see section 3.2) and so the primary endpoint variable will be the number of days from the date of randomisation to the date of first occurrence of any of the components of the composite (the 'event-free' time) or the number of days from the date of randomisation to the date of the end of study if the patient does not suffer any of the events in the composite. In the latter case, the event-free time will be treated as a censored observation.

Precise definitions are given in the study protocol for each of the components of the primary endpoint; see protocol section 6.4. All events which might potentially constitute an event within the primary endpoint composite are adjudicated centrally. Details of the adjudication process are given in the PROactive Study Endpoint Adjudication Charter. Analysis of the primary endpoint will only consider endpoints confirmed through the Endpoint Adjudication Process. An analysis based on investigator diagnosis is not planned.

### **2.3 End of study date**

All patients who do not die during the course of the study will be followed up to the end of study, whether or not the patient has previously ceased study medication. After the first year of follow-up, all patients attend clinic visits at three-monthly intervals.

The study protocol identifies a final visit or telephone contact for each patient at which a number of additional assessments are completed. As indicated above, the Executive Committee has informed all investigators that from 1<sup>st</sup> November 2004 all further study visits should be treated as final and that all final assessments must be completed by 31<sup>st</sup> January 2005. For each patient, therefore, the *end of study date* will be the date at which the final visit or telephone contact takes place. Any event occurring prior to, or on the date of, the final visit or contact will be included in the efficacy and safety analyses as appropriate. Any data after the final contact will be excluded from the analyses.

Where a patient dies prior to 1<sup>st</sup> November 2004, the end of study date will be the date of death.

Where a patient is lost to follow-up (see below), the end of study date will be the date at which the patient is considered to be lost to follow-up.

Where a subject dies during the period from 1<sup>st</sup> November 2004 to 31<sup>st</sup> January 2005 (inclusive) without a final visit, the date of death will be taken as the end of study date and thus the death will be included in the analysis together with any other events prior to death.

### **2.4 Loss to follow-up**

Some patients will not reach a final visit having been permanently lost to follow-up at some previous time. The number of such patients is anticipated to be small, however, all such patients will be described and the reason for being permanently lost to follow-up will be tabulated/listed. It is very unlikely that loss to follow-up is related to study treatment, nevertheless, this assertion will be checked. For all such patients, a *lost to follow-up date* will be determined, this being the date beyond which no further data relating to endpoint events is available. The lost to follow-up dates will be agreed for all such patients prior to treatment unblinding. For these patients, the loss to follow-up date will be used as the end of study date for the purpose of time to event calculations.

The only exception to the above is the case where the death of a patient previously lost to follow-up becomes known. This death will count as an endpoint event if the date of death is prior to 31<sup>st</sup> January 2005.

## 2.5 Secondary endpoints

The study protocol identifies the following as secondary endpoints:

- The individual components of the primary endpoint
- Cardiovascular mortality

In addition, at the time of preparation of this plan, it was decided to add one further composite endpoint to the list of secondary endpoints, namely, all-cause mortality, acute myocardial infarction (excluding silent MI) and stroke. The reason for this addition is so that the analysis can report the extent of treatment effects with respect to an endpoint which is also used commonly in large cardiovascular outcome studies.

All secondary endpoints will be analysed using time to event methodology. In the analysis of each component of the primary endpoint, subjects who die without having reached an event of the type under consideration will be censored at the date of death.

In each case, the event times will be calculated in a manner analogous to that used for the primary endpoint and will be subject to the definitions given in sections 2.3 and 2.4, above.

All fatal events will be classified as cardiovascular unless there is a clear non-cardiovascular cause. This classification will be carried out through the Endpoint Adjudication Process. For the analysis of cardiovascular mortality, time to death for a non-cardiovascular death will be treated as a censored observation.

## 2.6 Additional measures of interest

The following measures of interest are believed, *a priori*, to be variables where differences between the study treatments may be observed:

- The composite endpoint of cardiovascular death, acute myocardial infarction (excluding silent MI), and stroke
- The composite endpoint of cardiovascular death and non-fatal MI (excluding silent MI)
- Time to MI (excluding silent MI)
- 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
- Glycaemic control: HbA<sub>1c</sub>
- Degree of micro-albuminuria
- Lipids: HDL cholesterol, LDL cholesterol, triglycerides
- LDL cholesterol / HDL cholesterol

## **2.7 Safety Analysis**

The study protocol identifies the following measures of interest

- Serious adverse events
- Non-serious adverse events of special interest:
  - Hypoglycaemia
  - New or worsening heart failure
  - Oedema
  - Any event leading to permanent cessation of study medication
- Laboratory measures:
  - Liver function: ALT, AST, Total bilirubin, Alkaline phosphatase
  - Renal function: creatinine
- Blood pressure
- Weight, waist circumference

In addition, all other non-serious adverse events are collected.

## 2.8 Interim Analysis

Throughout the study, safety aspects of the study have been monitored by a Data and Safety Monitoring Committee (DSMC). In addition, two interim efficacy analyses have been carried out, these analyses being conducted out by an Independent Statistical Centre (ISC) reporting to the DSMC alone. Details of the roles and responsibilities of both the DSMC and ISC with respect to interim analyses are given in the DSMC Charter.

The interim analyses were conducted when approximately 50% and 75% of the target number of endpoints had been reached. For the purposes of early stopping, the formal statistical analysis considered the primary endpoint alone and the analysis followed the same rules as described in this document for the final analysis of the primary endpoint, with the following exceptions:

- The analysis employed a one-sided logrank test for the superiority of pioglitazone
- Data relating to silent myocardial infarctions were not considered as these will not be available until the end of the study.
- When determining whether or not a patient has reached the primary endpoint, adjudicated data were used where these were available. However, all other potential endpoints were reviewed against the definitions by NCRL and all events that were identified as endpoints by this process were also considered.

Following review of each interim analysis the DSMC had the opportunity to recommend that the study be stopped early providing that the observed significance level was less than the threshold defined by the following criteria:

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

The use of the Lan-DeMets alpha spending function allows some flexibility with respect to the timing of the interim analyses. The study protocol specified the significance levels to be used at the interim analyses planned when 50% and 75% of the target number of endpoints had been reached. However, the values stated in the protocol represent the incremental alpha spent at each interim rather than the nominal critical significance level to be used. The following table summarizes the cumulative alpha level spent and the correct nominal critical significance level for the interim and final analyses. These values were computed using the East® software for group sequential designs and interim monitoring of clinical trials (Cytel Software Corporation).

|           | <i>Information Fraction</i> | <i>Incremental Alpha Spent</i> | <i>Cumulative Alpha Spent</i> | <i>Nominal Critical Significance Level</i> |
|-----------|-----------------------------|--------------------------------|-------------------------------|--|
| Interim 1 | 50%                         | 0.00153                        | 0.00153                       | 0.00153                                    |
| Interim 2 | 75%                         | 0.00812                        | 0.00965                       | 0.0092                                     |
| Final     | 100%                        | 0.01535                        | 0.02500                       | 0.022                                      |

Each interim analysis took place as scheduled; therefore, the final analysis will be performed using a nominal critical significance level of 0.022.

No interim analysis for futility was considered.

## 2.9 Impact of interim analysis on final analysis of the primary endpoint

Given interim analyses for efficacy, which involve one-sided hypothesis tests, it is convenient to consider the final analysis of the primary endpoint as two one-sided tests.

If the observed significance level is less than 0.025 with the benefit in favour of placebo, the analysis will conclude that pioglitazone is inferior to placebo with respect to the incidence of primary endpoint events,  $p < 0.025$ , one-sided (equivalently;  $p < .05$ , two-sided).

As both interim analyses have occurred as planned, the overall superiority of pioglitazone over placebo can be claimed providing the observed significance level for the one-sided test for superiority is less than 0.022. This procedure ensures that the overall type I error for rejecting the null hypothesis of no treatment difference at either the interim or final analysis is no greater than 5%.

## 3 STATISTICAL METHODS

### 3.1 Statistical Principles

#### Data summaries and analysis tables

Data summaries and tables describing the output of each aspect of the statistical analysis will be presented.

#### Interpretation of multiple hypothesis tests

Control of the type I error for the analysis of the primary endpoint is given above in section 2.9. The analysis described for the primary endpoint is confirmatory. All other analysis is secondary and findings of hypothesis tests will be summarised by citing the observed significance level (p-value) without any attempt to adjust for the multiplicity of tests. Observed significance levels which achieve conventional levels of significance will be annotated using '\*' (  $p < 0.05$  ), '\*\*' (  $p < 0.01$  ) or '\*\*\*' (  $p < 0.001$  ). Observed significance levels are provided as an aid to the interpretation of individual parameter estimates or treatment contrasts. Overall interpretation of findings will be given in the text of the report.

## **Missing data**

All incomplete dates will be entered on the database as they are recorded in the CRF. Thereafter, incomplete dates are completed using the following rules:

- Patient history: If a day or month is recorded as UNK (unknown) or NA (not available) it is replaced by 01 or JAN respectively, provided this does not contradict any other dates recorded.
- Adverse events: Where an onset date is required, a missing date will be replaced by the date one day following the day the patient was last known to be event free. A partial date will be replaced with either the earliest complete date consistent with the partial date or the day following the last day the patient is known to be event free if later.

In all other circumstances missing data will be treated as missing and not imputed.

## **Patients withdrawing consent to follow-up**

Where a patient has withdrawn consent to any form of follow-up, any data that relates to the period after the date of withdrawal of consent will be ignored, with the exception of date of death, which is considered to be in the public domain.

## **Use of centre as a covariate**

The number of sites recruiting at least one patient during the course of the study is 321. The largest number of patients recruited at a single site is 252 representing 4.8% of the total recruitment. Although randomisation is stratified by site, the number of sites is too numerous to consider including site as a covariate.

## **Excluded data**

Clinical events that occur following the end of study date and which become known to the database will be listed separately, but not otherwise considered. Events which meet the definition of an adverse event but which occur prior to first dose will also be listed but will not, otherwise, be included in the comparative summaries of safety.

Patients who were randomised into the study but did not receive any study medication will be listed in a separate table along with the reason for not starting medication, but will not otherwise be considered.

## **Concomitant medications**

The study design specifies that study medication is given in addition to existing medications, but should adjustment of diabetic medications be necessary for disease management or should tolerability issues arise, adjustments to concomitant medications should be considered prior to any down-titration of study medication. As pioglitazone is a proven compound for the management of blood glucose levels in diabetic patients some changes in concomitant diabetic medications are anticipated.

Diabetic medications are recorded at baseline and at each subsequent visit by class (insulin, metformin, sulphonylureas, others), type (where applicable) and dose. The

CRF records concomitant treatment on the day of the visit, i.e. a 'snapshot', but does not record dates of medication changes or dose adjustments, nor any short term changes occurring between study visits. Statistical methods for summarising concomitant diabetic medications will therefore consider the proportion of patients receiving each type of medication and mean dose levels by visit, together with changes from baseline (number of patients with dose increase or newly starting, continuing and stopping or dose reduction). Estimates of the total burden of concomitant medication use over time will be constructed using area under the curve methods, employing linear interpolation.

Use of concomitant medications, other than diabetic medications, is also recorded by visit. Again, the snapshot method is used, but the detail collected is restricted. Specific drugs and doses are not recorded, with treatments being classified according to the table in Appendix 1.

Summaries will consider the proportion of patients taking any specific concomitant medication by visit together with changes from baseline.

### **3.2 Statistical Methods**

As indicated above, the analysis of the primary and secondary endpoints is exclusively an analysis of time to events. All other statistical analysis of additional measures of efficacy or health resource utilisation will employ statistical models and methods as appropriate.

#### **Time to event analyses**

In each case the comparative effect of the study treatments will be examined initially using a logrank test without covariates. Equivalently, a Cox proportional hazards model will be fitted with treatment as the only independent variate to obtain an estimate of the hazard ratio and a 95% confidence interval for this parameter. Kaplan-Meier estimates of the survival functions will be displayed in order to characterise treatment effects. Plots of the empirical cumulative hazard function will be used to assess, informally, whether the hazard function for each treatment is constant. If so, annualised event rates will be estimated. Where there is evidence of a non-constant hazard, one-year event rates and event rates at average follow-up will be quoted.

Where appropriate, additional exploratory analysis will be carried out using the proportional hazards model and incorporating covariates in addition to the term for treatment effects. The purpose of this analysis is to characterise the magnitude of treatment differences relative to the effects of factors known to be predictive of cardiovascular morbidity in patients with type II diabetes. Variables to be considered will include:

- Age
- Gender
- Insulin use at baseline (yes/no)

- Oral antidiabetic medication at baseline (none, metformin, sulphonylureas, both)
- Established history of macrovascular disease (defined as the number of criteria which the patient satisfies, as identified by inclusion condition 3)
- Body mass index at baseline
- Smoking history (non-smoker/ any smoking history )
- HbA1c at baseline

Baseline lipids (each of: LDL cholesterol, HDL cholesterol, triglycerides and the ratio of LDL/HDL cholesterol)

### **Continuous variables**

Linear models will be used as appropriate. Given the overall sample size, large sample properties of estimates will be used to establish confidence intervals.

### **Binary variables**

Standard methods for the analysis of 2 x 2 contingency tables will be used without correction for continuity. Where covariates are considered, logistic regression models will be used

### **Ordinal scale variables**

Given the sample size, ordinal scale data will be summarised as (multi-way) tables of counts and chi-squared tests and loglinear models used as appropriate. Logistic regression models for ordinal data will be used to investigate location and scale effects.

### **Repeated measures**

Follow-up data not relating to specific events is concerned principally with safety (e.g. laboratory data, haemodynamic data, weight, waist circumference), compliance, or use of concomitant medications and will be analysed by visit. Formal methods for repeated measures will not be used, but univariate measures which aggregate data from multiple visits will be used as part of the exploratory analysis where this aids interpretation.

### **Graphical displays**

Time to event analysis will be supported by Kaplan-Meier plots of the empirical functions for each treatment. As such plots can be misleading at the extreme where the number of patients at risk becomes small, the plots will be truncated at the time fewer than 100 subjects remain at risk in each group. All events occurring after this time will, however, still be included in the time to event analysis.

Analysis of endpoint events by subgroups will be summarised graphically, by displaying 95% confidence interval estimates of the hazard ratio for each subgroup

(so-called Oxford plots) to allow visual comparison of treatment differences across subgroups.

Additional histogram and boxplots will be used where appropriate to show distributions or aid interpretation of analysis results.

### **3.3 Visit Alignment**

The study protocol specifies that follow-up visits be conducted to a strict schedule and that following any departure from the schedule, subsequent visits should revert to the original schedule. The intention, therefore, is to analyse data collected at follow-up visits by nominal visit. However, prior to revealing the treatment codes, each case will be examined to determine those visits where the date is substantially from the scheduled date (i.e. those visits where the date of the visit is closer to the scheduled date for another visit than the date of this visit). These visits will be reassigned to a different nominal visit or ignored for the purpose of analysis, as appropriate. All such decisions will be documented.

Unscheduled visits will be considered only to the extent that they provide information as to the need for changes in dose of study medication outside of the regular visit schedule. Data from unscheduled visits will only be included in listings.

### **3.4 Data Listings**

Full data listings with annotations as given on the case report form will be prepared and supplied as an electronic appendix to the statistical report.

### **3.5 Computer programs**

All calculations and figures will be produced using SAS Version 8.2 or S-Plus 6.0.

## **4 DESCRIPTION OF STUDY POPULATION**

### **4.1 Source of Patients**

A summary of the total number of patients randomised will be presented, listing numbers of patients randomised, who received at least one dose of study medication and those for whom follow-up information is available by treatment group, centre, country and overall.

### **4.2 Baseline Characteristics**

The following summaries of baseline characteristics will be presented by treatment group and overall for the intention to treat population.

### **4.2.1 Demography**

Baseline demography data is recorded at the pre-randomisation visit. The following baseline demographic parameters will be summarised:

- Age (years, also categorised as < 65, ≥ 65)
- Gender (male, female)
- Race (White, Black, Asian/Oriental, other)
- Cigarette Smoking (Current smoker, previous smoker, never)

Race, gender and smoking status will be summarised by counts and percentages. Age will be summarised by mean, standard deviation, median, minimum and maximum and also by counts and percentages for the categorised groups.

### **4.2.2 Diabetes history and current treatment**

This section will consider:

- Time since diagnosis of type 2 diabetes (years)

Current treatment (at time of pre-randomisation visit):

- Use of Insulin (yes/no). If yes, number of injections per day and total daily dose
- Use of Metformin or Sulphonylureas (both (distinguishing subjects using fixed combinations from subjects using other dual therapy), metformin alone, sulphonylureas alone, neither). If yes, total daily dose by subgroup
- Use of other antidiabetic treatment (yes/no). If yes, name of treatment and total daily dose

### **4.2.3 Patient medical history**

Summary tables will be presented by treatment group and overall for the following medical history variables as recorded at the baseline visit.

#### **Macrovascular history**

- Cardiovascular
  - Myocardial Infarction
  - Acute coronary syndrome
  - History of angina pectoris
  - Confirmed coronary artery disease

- Percutaneous coronary intervention
- Coronary artery bypass graft
- History of hypertension
- Peripheral vascular
  - Claudication
  - Leg revascularisation
  - Amputation
- Cerebrovascular
  - Stroke
  - Transient ischaemic attack
- Other vascular
  - Carotid surgery

Patients entering into the study are required to have an established history of macrovascular disease, defined as one or more of the following:

- Myocardial infarction at least six months before entry into the study
- Stroke at least six months before entry into the study
- PCI or CABG at least six months before entry into the study
- Acute coronary syndrome at least three months before entry into the study
- Objective evidence of coronary artery disease
- Peripheral arterial obstructive disease

Study treatment groups will also be summarised with respect to the incidence of each of these specific conditions and with respect to the number of such conditions that apply.

#### **Microvascular history**

- Retinopathy. If yes, incidence of previous photocoagulation therapy
- Nephropathy
- Neuropathy

Full details of medical history for each patient will be available in the individual patient listings.

#### **4.2.4 Baseline medication record**

Treatment groups will be summarised with respect to the use of concomitant medications at the time of the baseline visit. This summary will consider both the major and minor classification drug classes, as given in Appendix 1.

#### **4.2.5 Physical Examination**

The following clinical examination variables were assessed prior to randomisation

- Systolic BP (mm Hg)
- Diastolic BP (mm Hg)
- Ankle systolic BP (mm Hg)
- MICRAL-TEST (negative / circa 20mg/l / circa 50mg/l / circa 100mg/l)
- Weight (kg)
- Waist circumference (cm)
- Height (cm), permitting the calculation of Body mass index (Kg/m<sup>2</sup>)
- Presence of abnormalities at Physical examination (Eyes, Ears, nose, throat, Skin, Musculoskeletal system, Central & Peripheral nervous system, Gastrointestinal tract, Endocrine & Lymphatic system, Respiratory, Other)

Summaries will be presented by treatment group and overall using standard methods.

#### **4.2.6 Laboratory parameters**

The following laboratory measures are obtained centrally from samples drawn prior to randomisation:

- Glycaemic control: HbA<sub>1c</sub>
- Lipids: HDL cholesterol, LDL cholesterol, triglycerides
- ALT, AST, total bilirubin, alkaline phosphatase
- Creatinine

Each measure will be summarised by treatment, giving mean levels and the number of patients outside of normal range. Where necessary, boxplots and/or histograms will be used to display overall distributions or the distribution of extreme observations.

#### **4.2.7 Further Comparisons at Baseline**

Patients who are included in the intention-to-treat population but have entered the study after failing an inclusion criterion or after an exclusion criterion is noted will be listed by treatment. Elapsed time between date of randomisation and date of first tablet will be presented by treatment group

#### **4.3 Titration progress**

Patient progress with titration will be summarised for each treatment group via a schematic which gives the proportion of patients at each dose level at each nominal visit and the transition rates between dose levels from visit to visit over the first year of follow-up. Thereafter, the proportion of patients undergoing changes of dose level of study medication at any time will be identified along with the reasons for such changes

#### **4.4 Cessation of Study Medication**

The numbers and reasons for permanent cessation of study medication will be summarised by treatment. Reasons will be grouped as follows:

- Patient withdraws consent
- A condition has developed or been discovered such that it is now considered that study treatment should be discontinued for reasons of safety
- Patient's failure or inability to comply with protocol requirements
- Pregnancy
- Adverse event
- Other

Treatment groups will be summarised with respect to:

- Proportion of patients permanently withdrawing from the use of study medication
- Reasons for cessation of study medication
- Mean exposure to treatment

More generally, the analysis will show the distribution of treatment exposure times by treatment as a basis for discussion of adverse event incidence.

#### **4.5 Compliance**

Patient compliance is assessed at each visit through discussion with the patient. The CRF records whether compliance was poor (< 50% of full dose schedule), satisfactory (50% – 75%), or good (> 80%). Compliance data will be summarised by

treatment, visit and in total, the latter using an area under the curve calculation per month on treatment.

## 5 EFFICACY EVALUATION

### 5.1 Primary endpoint

The sole primary endpoint for this study is the composite defined in section 2.2. Treatment groups will be compared using a time to event analysis (see section 3.2), with a treatment difference being asserted if the observed significance level is less than the appropriate boundary value, as given in section 2.9. As part of the exploratory analysis, treatment effects with respect to the primary endpoint will be estimated in the following subgroups:

- Gender
- Age (< 65 years / ≥ 65 years)
- Number of macrovascular disease conditions (defined as the number of criteria which the patient satisfies, as identified by inclusion condition 3) (1/ 2 / > 2)
- Myocardial infarction at least 6 months before entry into the study (yes / no)
- Stroke at least 6 months before entry into the study (yes / no)
- PCI or CABG at least 6 months before entry into the study (yes / no)
- Acute coronary syndrome at least 3 months before entry into the study (yes / no)
- Objective evidence of coronary artery disease (yes / no)
- Peripheral arterial obstructive disease (yes / no)
- Duration of diabetes history (< 5 years / ≥ 5-10 years / ≥ 10 years )
- Baseline Micral test strip results (+ve / -ve)
- Metformin or sulphonylureas at baseline (both (including fixed combinations), metformin alone, sulphonylureas alone, neither)
- Insulin as part of standard therapy at baseline (yes / no)
- Body Mass Index (< 30 / ≥ 30 kg/m<sup>2</sup>)
- Serum triglycerides (low risk (< 1.7 mmol/l) / at risk (1.7-2.2 mmol/l) / high risk (> 2.2 mmol/l))
- Serum HDL cholesterol (low risk (> 1.2 mmol/l) / at risk (1.0-1.2 mmol/l) / high risk (< 1.0 mmol/l))

- Serum LDL cholesterol (low risk (< 3.0 mmol/l) / at risk (3.0 – 4.0 mmol/l) / high risk (> 4.0 mmol/l))
- HbA<sub>1c</sub> (DCCT standardized) (< 7.5 %Hb) / ≥ 7.5 %Hb)
- Creatinine (< 130 umol/l / ≥ 130 umol/l)
- Combined blood pressure (low risk / high risk). “High Risk” defined as Systolic BP at “High Risk” (≥ 140mmHg) and/or Diastolic BP at “High Risk” (≥ 85mmHg)
- Metabolic syndrome at baseline (present/absent) “present” defined as two or more of the following: hypertension (≥ 130/85 or a history of hypertension), increased triglycerides (≥ 1.7 mmol/L), decreased HDL (< 1.0 mmol/L for men or < 1.3 mmol/L for women), central obesity (≥ 100 cm for men or ≥ 88 cm for women)
- Use of statins (Yes / No)
- Use of Thiazide or loop diuretics (Yes / No)
- Use of ACE or ARB inhibitors (Yes / No)
- Use of beta blockers (Yes / No)

In all cases the subgroups are defined using measurements taken at baseline.

In each case the analysis will examine the plausibility of a treatment by subgroup interaction via a Cox regression model, but the primary purpose of this analysis is to examine consistency of benefit. Any conclusion that the magnitude of the difference between treatments depends on subgroup will acknowledge the multiplicity of tests for interaction central to this aspect of the analysis.

## 5.2 Secondary endpoints

Secondary endpoints are identified and analysed as described in section 2.5 above, with the following order representing the priority of each secondary endpoint

- Time to the first occurrence of any of: death from any cause, acute myocardial infarction (excluding silent MI), stroke
- Time to cardiovascular death
- The individual components of the primary endpoint:
  - Time to all-cause death
  - Time to non-fatal MI (including silent MI)
  - Time to acute coronary syndrome
  - Time to cardiac intervention

- Time to stroke
- Time to major leg amputation
- Time to bypass surgery or revascularisation of leg

In addition, the primary endpoint composite, excluding silent MI, will be examined using the same methods.

Subgroup analysis of secondary endpoints is not envisaged, however, the following comparisons are of interest:

Treatment differences by prior history of AMI (yes / no) for the endpoints

- Time to the first occurrence of any of: cardiovascular death, acute myocardial infarction (excluding silent MI), stroke
- Time to the first occurrence of any of: cardiovascular death, acute myocardial infarction (excluding silent MI)
- Time to the first occurrence of any fatal or non-fatal myocardial infarction (excluding silent MI)

Treatment differences by prior stroke (yes / no) for the endpoints

- Time to the first occurrence of any of: cardiovascular death, acute myocardial infarction (excluding silent MI), stroke
- Time to the first occurrence of any of: cardiovascular death, stroke
- Time to the first occurrence of any stroke

### **Additional analysis of mortality**

All reports of death require the investigator to state the likely primary cause of death. Treatment groups will be compared to determine whether there is evidence of a difference between treatments as to the cause of death.

## **5.3 Additional measures of interest**

Treatment groups will be compared with respect to those measures identified in section 2.6. The following sections provide additional detail of the intended analysis as necessary.

### **5.3.1 Hospitalisations**

Study treatments will be compared with respect to:

- Number of hospitalisations (hospitalisation for any cause except compassionate stay)

- Total number of days in hospital (hospitalisation for any cause except compassionate stay)
- Number of days in high dependency units

If the treatment groups differ with respect to time to death or the pattern of lost to follow-up, each analysis will be adjusted to accommodate the differing observation periods

### **5.3.2 Permanent insulin use**

The study protocol defines permanent insulin use as daily insulin use for a period of at least 90 days. This definition does not allow for the possibility that a subject commenced on permanent insulin may die / attend their final visit within the first 90 days. Two analyses will therefore be carried out. The first will compare treatments using a time to event analysis where the date of the event will be the start of the first period of insulin use to exceed 90 days. Shorter periods of treatment will not count as an event. The second analysis will include as an event any shorter periods of insulin treatment that end with death / final visit. Both analyses will be restricted to those subjects who are not receiving insulin at baseline.

### **5.3.3 Retinal photocoagulation**

At each visit, the CRF records whether or not the patient has received retinal photocoagulation treatment at any time since the previous visit. Treatment groups will be compared with respect to:

- Total number of visits at which retinal photocoagulation is reported
- Total number of patients for whom retinal photocoagulation is reported
- Time from randomisation to first report of retinal photocoagulation treatment (time to event analysis, with date of event taken as the date of the visit at which the event is reported)

If necessary, previous photocoagulation treatment (prior to entry into the study) and baseline HbA1c will be used as a covariate.

### **5.3.4 Concomitant medications**

#### **Diabetic Concomitant Medications**

Diabetic concomitant medications will be summarised by visit, and treatment group. Changes in diabetic concomitant medications from baseline will be compared by treatment group.

#### **Other Concomitant Medications**

Use of other concomitant medications will be summarised by major drug classification (major and minor at final visit), visit and study treatment. Change in use

from baseline will also be summarised. Particular attention will be given to the use of:

- Antihypertensive medication
- Lipid-lowering medication

### **5.3.5 HbA1c**

For HbA<sub>1c</sub> (%) differences between treatment groups will be examined by visit together with changes from baseline. An area under the curve measure (linear interpolation, together with adjustment for duration of exposure) will be used as an aggregate measure of HbA<sub>1c</sub> for the study as a whole.

### **5.3.6 Lipids**

For each of the following lipid parameters, differences between treatment groups will be examined by visit, and through both change from baseline and percentage change from baseline.

- Triglycerides (mmol/l)
- HDL cholesterol (mmol/l)
- LDL cholesterol (mmol/l)
- The ratio of LDL cholesterol to HDL cholesterol

## **6 ANALYSIS OF SAFETY**

### **6.1 Exposure to study drug**

Extent of exposure (in days) will be calculated as date of the last study tablet minus the date of the first study tablet +1. No allowance for breaks in therapy will be made. For patients who die on treatment, the day of last dose will be taken as the day prior to death. Additional tabulations will be provided by dose.

### **6.2 Serious adverse events (SAEs)**

There is no reconciliation between investigator-reported serious adverse events and adjudicated events. Serious adverse events will thus be presented as the investigator reported. (For example, an episode of unstable angina reported by the investigator as an SAE but adjudicated as an AMI will appear as unstable angina in the safety summaries.)

SAEs summaries will be presented as follows

- Events occurring during the period of the study, i.e. between date of first dose and the end of study date

- Events occurring whilst on treatment, i.e. between date of first dose and date of last dose.

Pre-treatment events and post-study emergent events will be listed separately, but not considered otherwise.

The following variables will be included in the tabulations of serious adverse events:

- Study treatment dose at onset of adverse event
- Preferred term of adverse event according to MedDRA version 8.0
- Body system (System Organ Class) of adverse event according to MedDRA version 8.0
- Relationship of adverse events to study medication (definite, probable, possible, unlikely or not related)
- Action taken (none, dose reduced, dose temporarily ceased, study medication permanently ceased, not applicable, permanently ceased prior to event)
- Outcome (resolved, fatal, permanent sequelae, ongoing, unknown or lost to follow-up)

The number of patients reporting serious adverse events following start of treatment will be reported by preferred term (incidence > 1.0%), system organ class, treatment group, and relationship to study medication. In addition, there is interest in the incidence of TIAs, carotid intervention, malignancies and the number of patients reporting at least one SAE in each of the following event classes:

| Class                    | Preferred term  |
|--------------------------|---|
|                          |   |
| Oedema                   | Gravitational oedema, Localised oedema, Neck oedema, Oedema abdomen NOS, Oedema NOS, Oedema peripheral, Orbital oedema, Pitting oedema.   |
| Cardiac ischaemic        | Myocardial infarction, Acute myocardial infarction, Angina pectoris, Angina unstable, Myocardial ischaemia, Acute coronary syndrome.  |
| Hypertension             | Accelerated hypertension, Diastolic hypertension, Essential hypertension, Hypertension NOS, Hypertensive crisis, Hypertensive emergency, Hypertensive encephalopathy, Labile hypertension, Malignant hypertension NOS, Malignant secondary hypertension NOS, Postoperative hypertension, Renal hypertension NOS, Renovascular hypertension, Secondary hypertension NOS, Systolic hypertension   |
| Cerebrovascular          | Brain stem haemorrhage, Brain stem infarction, Carotid arterial embolus, Carotid artery thrombosis, Cerebellar artery thrombosis, Cerebellar haemorrhage, Cerebral artery embolism, Cerebral artery occlusion, Cerebral artery thrombosis, Cerebral haemorrhage, Cerebral infarction, Cerebral thrombosis NOS, Cerebrovascular accident, Embolic stroke, Haemorrhagic cerebral infarction, Haemorrhagic stroke, Intracranial haemorrhage NOS, Ischaemic stroke NOS, Thalamus haemorrhage, Thromboembolic stroke, Thrombotic stroke, Vertebral artery thrombosis |
| Congestive Heart Failure | Cardiac failure NOS, Cardiac failure acute, Cardiac failure aggravated, Left ventricular failure, Cardiac failure congestive, Congestive cardiac failure aggravated, Cardiac failure chronic, Pulmonary oedema NOS, Acute pulmonary oedema, Pulmonary oedema aggravated.  |

(Ongoing review of blinded data may identify preferred terms which should be added to the classes above. All such additions will be identified and documented prior to database unblinding.)

For commonly occurring events or event classes differences between the treatments will be assessed using the chi-square test.

In counting the number of events reported, non-continuous adverse events reported several times by the same patient will be counted as multiple events. If there are

differences between groups with respect to exposure adjusted rates (rates *per annum*) will be used, together with Kaplan–Meier plots as appropriate.

### **6.3 Non-serious events of special interest**

Non-serious events of special interest (hypoglycaemia, new or worsening heart failure, oedema, malignancy or any other event leading to permanent cessation of study medication) will be summarised and the treatment groups compared in a manner identical to that described for serious adverse events. Aggregate tables combining both SAEs and AEs of special interest will also be produced.

It is noted that new or worsening CHF is a clinically serious event typically necessitating inpatient evaluation and treatment and thus interpretation of treatment effects will rely principally on those CHF events reported as SAEs

### **6.4 Additional summaries of SAEs and AEs of special interest**

Additional summaries of SAEs and AEs of special interest will be provided as follows:

- Events occurring in the first six months and subsequently
- Events occurring in patients grouped according to baseline anti-diabetic medication (insulin (yes / no))
- Events occurring in patients grouped according to baseline anti-diabetic medication (metformin alone, sulphonylureas alone, both, neither)

In each case the summary will allow direct comparison of the study treatments.

### **6.5 Other non-serious adverse events**

Other non-serious adverse events are stated at each visit without details as to onset date or severity of outcome. These events will be coded according to the MedDRA version 8.0 classifications and the treatment groups compared with respect to the number of patients reporting each common term in the periods:

- Start of treatment to visit 5 (six months)
- At any time beyond visit 5 until and including the first visit report following permanent cessation of treatment.

### **6.6 Laboratory safety data**

For each of the laboratory measures below, data will be summarised by treatment group and visit. Where appropriate, boxplots will be used to highlight the pattern of outlying observations.

- Aspartate aminotransferase (U/l)
- Alanine aminotransferase (U/l)
- Bilirubin ( $\mu\text{mol/l}$ )
- Alkaline phosphatase (U/l)
- Creatinine ( $\mu\text{mol/l}$ )

Summary tables (by visit and at any time during the study) will also give the number of patients by treatment with markedly abnormal lab values as indicated in the table below.

|                                  |                           |
|----------------------------------|---------------------------|
| Aspartate aminotransferase (U/l) | > 3 x ULN                 |
| Alanine aminotransferase (U/l)   | > 3 x ULN                 |
| Bilirubin ( $\mu\text{mol/l}$ )  | > 34.2 $\mu\text{mol/l}$  |
| Alkaline phosphatase (U/l)       | > 3 x ULN                 |
| Creatinine ( $\mu\text{mol/l}$ ) | > 176.8 $\mu\text{mol/l}$ |

Mean changes from baseline will be summarised and shift tables detailing changes in normality/abnormality status in relation to the normal range will be generated.

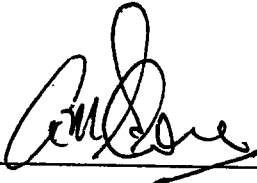

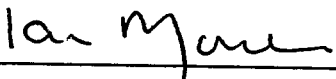
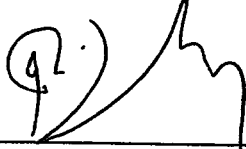
## 6.7 Blood pressure and measures of body size

Changes in systolic and diastolic blood pressure, weight, waist circumference and body mass index, from baseline to each subsequent visit will be summarised by treatment group to the extent that the data are available.

## 7 REFERENCES

- (1) SAS Institute Inc. *The SAS System, Version 8.2.* Cary, NC, SAS Institute Inc. 2001.
- (2) S-PLUS 6 *User's Guide for Windows, Insightful Corporation, Seattle, WA, 2001.*

## 8 SIGNATURES

| Name  | Signature  | Date       |
|---|--|------------|
| Dr A Skene<br>Managing Director<br>(Nottingham Clinical Research Limited)             |    | 12-05-2005 |
| Dr Shawn Yu<br>Associate Director<br>(Takeda Global Research &<br>Development Center) |    | 5-13-05    |
| Mr I Moules<br>European Development Director<br>(Takeda Europe R&D Centre Limited)    |   | 13.5.05    |
| Prof J A Dormandy<br>Study Chairman   |  | 13/5/05    |

## Appendix 1

### Concomitant Medications

The following table summarises concomitant medications recorded on the PROactive Study case report form:

|   |                                     |
|---|-------------------------------------|
| <b>Cardiovascular medications</b>         | <b>Gastrointestinal medications</b> |
| Beta blockers                             | H <sub>2</sub> receptor antagonists |
| ACE inhibitors                            | Proton pump inhibitors              |
| Calcium channel blockers                  | Antidiarrhoeals                     |
| Nitrates                                  | Anticonstipation                    |
| Angiotensin II antagonists                | Antiemetics                         |
| Alpha blockers                            | Other gastrointestinal medication   |
| Thiazide diuretics                        |                                     |
| Loop diuretics                            | <b>Hormones</b>                     |
| Potassium sparing diuretics               | Thyroid                             |
| Cardiac glycosides                        | HRT or contraceptive pill           |
| Antiarrhythmics                           | Other hormone                       |
| Other cardiovascular medication           |                                     |
|   | <b>Nervous system medications</b>   |
| <b>Antiplatelet medications</b>           | Antidepressants                     |
| Acetylsalicylic Acid                      | Antipsychotics                      |
| Ticlopidine/Clopidogrel                   | Hypnotics                           |
| Oral anticoagulants                       | Anticonvulsants                     |
| Other antiplatelet medication             | Antiparkinsonism                    |
|   | Other nervous system medication     |
| <b>Lipid lowering medications</b>         |                                     |
| Statins                                   | <b>Other medications</b>            |
| Fibrates                                  | NSAIDs                              |
| Other lipid lowering medication           | System corticosteroids              |
|   | Immunomodulators                    |
| <b>Respiratory medications</b>            | Antiinfectives                      |
| Beta <sub>2</sub> adrenoreceptor agonists | Xanthine oxidase inhibitors         |
| Antimuscarinic bronchodilators            | Any other important medication      |
| Phosphodiesterase inhibitors              |                                     |
| Inhaled corticosteroids                   |                                     |
| Other respiratory medication              |                                     |
|   |                                     |

## Appendix 2

### List of Tables

The following listing identifies those tables which will form Section 15 of the final study report.

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|            |  |
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|            |  |
|------------|--|
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Table 3.5 Descriptive statistics and classification by reference ranges and critical values: Total Bilirubin

### **15.3.3 Physical Examination, Vital Signs and Body Measurements**

Table 1 Physical examination at final visit  
Table 2.1 Time course of systolic blood pressure  
Table 2.2 Time course of diastolic blood pressure  
Table 2.3 Time course of body weight  
Table 2.4 Time course of waist circumference  
Table 2.5 Time course of BMI  
Table 3 Ankle systolic blood pressure at final visit