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**AMENDMENT 4 TO VERSION 1.1 OF THE
CLINICAL TRIAL PROTOCOL DATED 28 JANUARY 2001**

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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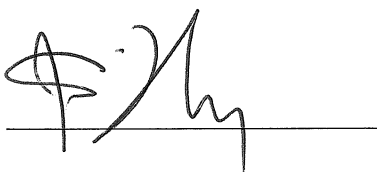
Appendix 1 Example Investigator Acknowledgement

SIGNATURES

The undersigned agree to the changes to Version 1.1 of the Clinical Trial Protocol as described in this Amendment Number 4:

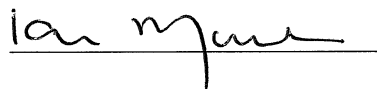
Name**Signature****Date**

Prof J A Dormandy
Study Chairman



28/10/04

Mr I Moules
European Development Director
(Takeda Europe R&D Centre Limited)



27.10.04

Dr B Voet
Director of IT, Biometrics and
Data Management
(Takeda Europe R&D Centre Limited)



27/10/2004

Note

Each investigator will sign a copy of the Investigator Acknowledgement for this Amendment, a copy of which is given in Appendix 1.

1 INTRODUCTION

In the time since the original protocol and the first three amendments, a further issue has arisen which necessitates amendment 4 to the protocol.

2 AMENDMENT TO THE DEFINITION OF SILENT MYOCARDIAL INFARCTION (MI)

In section 6.4.1 the following change will be made:

Change in definition of Silent myocardial infarction

Old text:

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.

New text:

New Q waves on two contiguous leads or R wave reduction in the precordial leads without a change in axis deviation. The date of the event will be set to the date of the ECG where evidence of the silent MI was first discovered.

Reason for change:

It is now generally agreed, that a definite diagnosis of myocardial infarction from the electrocardiogram can be only made on the basis of abnormalities of the QRS-complex. These diagnostic abnormalities are: Q-waves either 0,04 sec or longer in duration or QS-complexes (equals R-wave reduction in the precordial leads (excluding AVR and III)).

Additional features frequently associated with myocardial infarctions include ST-segment and T-wave changes and also the development of left bundle branch block. These changes are, however, not necessarily indicative of MI. Therefore, in the light of many patients with diabetes and polyneuropathy, only the definite diagnosis of MI should be accepted. These diagnostic criteria have been used by most recent publications in this field (Aguilar et al., Am J. Cardiol. 94 (2004) 337-9; Davis et al, Diabetologia 47 (2004) 395-9). Therefore, we suggest to change the original protocol of the PROactive Study to comply with the international recent literature based on new findings with relevance to our results.

The task force on the management of acute myocardial infarction of the European Society of Cardiology (Europ. H. J. 2003, 24, 28-66) defines acute myocardial

infarction also with ECG signs, specifically ST- and T-changes. This, however, applies only to acute myocardial infarction. As silent myocardial infarction, diagnosed retrospectively will always be non acute, only the narrow definition as mentioned above should be taken.

Appendix 1

PROactive Study

Investigator Acknowledgement (Protocol Amendment 4)

I acknowledge receipt of the above Protocol Amendment and will ensure that its contents are communicated to and observed by personnel involved in the study at my centre.

Name

Signature

Date

Centre Number: _____

Original: To study masterfile

NCR Copy: File with protocol in Investigator Site File

Do not delete!