PROTOCOL AMENDMENT

An observational study of patient cohorts who previously received long-term treatment with pioglitazone or placebo in addition to existing anti diabetic medications.

Sponsor:	**Takeda Global R&D Centre (Europe) Ltd** **Arundel Great Court, 2 Arundel Street** **London, WC2R 3DA United Kingdom**		
Study Number:	**EC-445**		
IND Number:	**N/A**	**EudraCT Number:**	**N/A**
Investigational Medicinal Product:	**AD-4833**		
Amendment Number:	**2**		

Global Amendment ☒ **Amendment applicable to all sites**

Local Amendment ☐

Countries Affected by this Local Amendment:

Amendment Date: **11 January 2007**

APPROVAL SIGNATURES

Representatives of Takeda Global R&D Centre (Europe) Ltd

I agree to conduct this trial in accordance with the requirements of this Clinical Trial Protocol and also in accordance with the following:

- World Health Organisation (WHO) Declaration of Helsinki (2000)
- Respective local laws and regulations

1/12/07
Dr. Alfonso Perez, MD Date
Vice-President, Clinical Science
Takeda Global R&D Center Inc

P.R. 15th Jan 2007
Mr. Paul Worthington, MSc BSc C. Stat Date
Senior Manager, Statistics
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Mr. Karl Redhead, BSc (Hons) RN MICR Date
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A.R. van Troostenburg 15 Jan 07
Dr. Anne-Ruth van Troostenburg de Bruyn Date
tGP MFPM Dip. Pharm. Med. (RCP)
Medical Director, Pharmacovigilance
Takeda Global R&D Centre (Europe)

Investigator Agreement

I confirm that I have read and understand this protocol. I agree to conduct this trial in accordance with the requirements of this protocol, and also in accordance with the following:

- WHO Declaration of Helsinki (2000)
- Respective local laws and regulations

Signature of Investigator	Date
Investigator Name (print or type)	
Investigator Title	
Name of Facility	
Location of Facility (City)	

DESCRIPTION OF PROTOCOL AMENDMENTS

Amendment 2 - Global Protocol Amendment

The purpose of amendment number 2 is:

Protocol EC-445 outlines an investigation into the effects of prolonged peroxisome proliferator-activated receptor (PPAR) agonist therapy on mortality, macrovascular morbidity and incidence of malignancy in high-risk patients with diabetes mellitus. In particular, as an observational follow-up study to the PROACTIVE study, EC-445 provides an important opportunity to address these important matters in a study population where there was a placebo-treated control group.

In line with the intention to minimize complexity of this observational follow up study, basic data were specified for collection in the original version of the study protocol. However, it is now considered that this study data would be enhanced by the collection of additional information on cases of reported malignancies and thiazolidinedione therapy.

PROPOSED AMENDMENTS

Page 15, 16.2.4 Malignancy

Existing Text

Details *(site of primary malignancy, histological classification and date of diagnosis)* of any malignancies diagnosed since the last assessment will be recorded at each assessment.

Revised Text

Details (site of primary malignancy, histological classification and date of diagnosis, **additional information for bladder cancer (as detailed in appendix 1) and additional information for other malignancies (as detailed in appendix 2)** of any malignancies diagnosed since the last assessment will be recorded at each assessment.

This expanded list of details will be collected for all cases of malignancy which have been reported since study start.

Consideration may be given to the need for further information to be requested from the investigator, in the follow up of individual cases of reported malignancy.

Rationale for Amendment

This amendment will permit the collection of more comprehensive data for analysis of reported malignancies.

Page 15, 16.2.5 Anti-diabetic Medication and Concomitant Medication

Existing Text

Details of patient's current anti-diabetic, lipid, cardiovascular and anti-platelet medication will be recorded at each assessment *(drug class only).*

Revised Text

Details of patient's current anti-diabetic **(For thiazolidinediones, additional information will be collected as detailed in appendix 3)**, lipid, cardiovascular and anti-platelet medication will be recorded at each assessment

Rationale for Amendment

This amendment will permit the collection of more comprehensive data for analysis of concomitant medication usage.

Appendix 1 - Additional Information: Bladder Cancer

The following additional information will be collected for reported cases of bladder cancer:

- cancer staging
- smoking history
- exposure to industrial carcinogenic agents
- exposure to potentially carcinogenic drugs
- history of chronic irritation of bladder
- history of schistosomiasis (Bilhazia)
- family history of bladder cancer
- histological type of bladder cancer
- history of haematuria

Appendix 2 - Additional Information: Malignancies

The following additional information will be collected for reported cases of malignancies:

- cancer staging
- smoking history
- alcohol history
- exposure to industrial carcinogenic agents
- exposure to potentially carcinogenic drugs
- history of the same or other malignancies
- history of chronic local inflammations
- family history of malignancy

Appendix 3 - Additional Information: Thiazolidinedione use

The following additional information will be collected for all reported thiazolidinedione use:

- Drug Name
- Total Daily Dose
- Start and Stop Dates