



EUROPEAN MEDICINES AGENCY  
SCIENCE MEDICINES HEALTH

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Final study protocol  
for service contract

EMA/2011/38/CN - PIOGLITAZONE

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## Table of contents

<b>DOCUMENT INFORMATION</b> .....	<b>3</b>
<b>DOCUMENT HISTORY</b> .....	<b>3</b>
<b>DEFINITIONS</b> .....	<b>4</b>
<b>1. BACKGROUND AND RATIONALE</b> .....	<b>5</b>
<b>2. OBJECTIVES</b> .....	<b>5</b>
<b>3. METHODS</b> .....	<b>6</b>
<b>3.1 SOURCE POPULATION AND STUDY POPULATION</b> .....	<b>6</b>
<b>3.2 STUDY DESIGN AND STUDY PERIOD</b> .....	<b>6</b>
<b>3.3 EXPOSURE</b> .....	<b>6</b>
<i>3.3.1 Initiation, use, and termination of pioglitazone-containing products</i> .....	<i>6</i>
<b>3.4 ENDPOINTS</b> .....	<b>9</b>
<i>3.4.1 Utilization patterns</i> .....	<i>9</i>
<i>3.4.2 Patient-level endpoints</i> .....	<i>11</i>
<b>3.5 ANALYSIS PLAN</b> .....	<b>12</b>
<b>4. SOURCE OF BIAS AND LIMITATIONS</b> .....	<b>12</b>
<b>5. QUALITY ASSURANCE, FEASIBILITY AND REPORTING</b> .....	<b>13</b>
<b>5.1 DATA STORAGE</b> .....	<b>13</b>
<b>5.2 METHODS FOR QUALITY ASSURANCE</b> .....	<b>13</b>
<b>5.3 DATA QUALITY</b> .....	<b>14</b>
<b>5.4 FEASIBILITY AND TIMELINES</b> .....	<b>14</b>
<b>5.5 REPORTING AND DISSEMINATION OF RESULTS</b> .....	<b>14</b>
<b>5.6 AMENDMENTS</b> .....	<b>15</b>
<b>5.7 INDEPENDENT REVIEW OF STUDY RESULTS</b> .....	<b>15</b>
<b>6. ETHICAL ISSUES</b> .....	<b>15</b>
<b>7. DATA SOURCES</b> .....	<b>16</b>
<b>8. REFERENCES</b> .....	<b>17</b>
<b>9. APPENDICES</b> .....	<b>18</b>
<b>9.1 APPENDIX 1. PROPOSED TABLES/FIGURES FOR UTILIZATION ANALYSIS</b> ..	<b>18</b>
<b>9.2 APPENDIX 2. PROPOSED TABLES FOR PATIENT-LEVEL OUTCOMES</b> .....	<b>29</b>
<b>9.3 APPENDIX 3. ALGORITHMS USED TO IDENTIFY STUDY VARIABLES</b> .....	<b>35</b>
<b>9.4 APPENDIX 4. LIST OF PLANNED TABLES AND FIGURES</b> .....	<b>36</b>

## DOCUMENT INFORMATION

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## DOCUMENT HISTORY

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Vera Ehrenstein, Ángel Honrado	20/06/2012	4.0	Final version
Vera Ehrenstein, Susan Jick, Lin Li , Sinna Pilgaard Ulrichsen, Jørgen Rungby, Ingrid Leal, Daniel Weibel, Peter Rijnbeek, Ángel Honrado	23/10/2012-11/7/2012		Internal review and amendments

## DEFINITIONS

- Participants in this tender are referred to herein according to the following codes:
  - **AUH-AS** Aarhus University Hospital (Denmark).Contractor
  - **BCDSP** Boston Collaborative Drug Surveillance Program (USA). Subcontractor
  - **EMC** Erasmus University Medical Center (Netherlands). Subcontractor
  - **SYNAPSE** Synapse Research Management Partners S.L. (Spain). Subcontractor
  
- **Contract:** Legal document signed between the Contractor and the European Medicines Agency for the undertaking of the tender.
- **Contractor:** A tenderer to which a framework contract has been awarded and signed with the EMA. It is responsible before the EMA of the right execution of the tender and of the delivery of the results in due time and form according to the Contract.
- **EMA:** European Medicines Agency.
- **Subcontractor:** Organisation supporting the Contractor in the fulfilment of the tender objectives and technical execution.
- **Technical specifications:** Official document generated by the EMA for the tender that includes a detailed description of all technical requirements, contractual arrangements, and price, that enables the EMA to specify and acquire services provided by resources not employed directly by the EMA.
- **Tender:** Public (or restrictive) offer made by the EMA to specific providers to enter into the contract of transaction of services at certain specified cost.
- **Work plan:** Schedule of tasks, deliverables, efforts, dates and responsibilities corresponding to the work to be carried out, as specified in the Contract.

## 1. BACKGROUND AND RATIONALE

Pioglitazone belongs to the drug class thiazolidinediones and is used as a second-line therapy in patients with type 2 diabetes mellitus.<sup>1</sup> Pioglitazone was approved for use in the European Union in 2000. The drug controls type 2 diabetes in certain patients in whom traditional glucose-lowering drugs are not effective. Evidence suggests that the drug is associated with a slightly increased risk of bladder cancer.<sup>2</sup> Based on that evidence, on 21 July 2011, the EMA's Committee for Medicinal Products for Human Use (CHMP), concluded that 'although there is a small risk of bladder cancer with pioglitazone, its benefits continue to outweigh its risks in a limited population of type 2 diabetes patients'.<sup>3</sup> The Committee recommended discontinuation of pioglitazone in patients with bladder cancer or uninvestigated haematuria and in patients not deriving sufficient therapeutic benefit from pioglitazone; there is also a recommendation for consideration of patients' risk factors for bladder cancer, such as age and smoking, before initiating pioglitazone treatment; and for prescribing the lowest possible dose to elderly patients.<sup>3</sup> Following the CHMP recommendation, Takeda UK Ltd., the marketing authorization holder for pioglitazone, issued a "Dear Health Professional" communication (DHPC), detailing the labelling amendments.

This study was commissioned by the EMA. EMA wishes to assess, in two or more European Union Member States, changes in pioglitazone utilization and patient-level outcomes following the DHPC, including size and composition of the treated patient population. On the patient level, EMA wishes to assess diabetes control among patients who remained on or discontinued pioglitazone drug after the DHPC.

## 2. OBJECTIVES

The four objectives of this study, listed below, relate to the effects of pioglitazone DHPC on the utilization of pioglitazone-containing products (Objective 1) and on patient-level diabetes control (Objective 2). Objective 3 and Objective 4 relate to interpretation and reporting of results obtained by addressing Objective 1 and Objective 2. Fulfilment of Objective 3 and Objective 4 is described in **Section 5.5 Reporting and dissemination of results**.

- **Objective 1:** To provide observational data on drug utilisation patterns of pioglitazone-containing products in the European Union (EU) and to study associations between changes in drug utilisation patterns and the regulatory decisions in the form of DHPC.
- **Objective 2a:** To analyse events in patients discontinuing pioglitazone after the DHPC, including adverse drug events, alterations in glycaemic control, and modification of other objective parameters of disease.
- **Objective 2b:** To analyse contraindications and events in patients continuing or starting pioglitazone, including adverse drug events, alterations in glycaemic control, and modification of other objective parameters of disease.

- **Objective 3.** To evaluate effectiveness of risk minimisation measures recommended by CHMP based on results obtained for Objective 1 and Objective 2.
- **Objective 4.** To provide practical recommendations for improving effectiveness of risk minimisation measures.

### 3. METHODS

#### 3.1 SOURCE POPULATION AND STUDY POPULATION

The source population for this study will be residents of three EU Member States covered by relevant medical databases (described in **Section 7 Data sources**). In Denmark, the source population for the analysis of utilization will include the entire Danish population from 2004 to 2011; for the analysis of laboratory data, the analysis will be restricted to residents of the North and the Central Denmark regions, represented by the Aarhus University Research Database (AU), which includes information on laboratory data<sup>4,5</sup>; in the Netherlands, residents treated by general practitioners participating in the Integrated Primary Care Information (IPCI); and in the United Kingdom, patients treated by general practitioners participating in the Clinical Practice Research Datalink (CPRD), formerly known as the General Practice Research Database (GPRD).<sup>6,7</sup>

The study population will be members of the source population with an identifiable record of use of pioglitazone-containing products. Hereafter 'pioglitazone use' refers to use of all pioglitazone-containing products, unless stated otherwise. Only patients with at least one year of recorded data in the database before the first time pioglitazone use (as defined in current protocol) will be included in the study.

#### 3.2 STUDY DESIGN AND STUDY PERIOD

For Objective 1, we will examine utilization of pioglitazone over time, and changes in utilization patterns in relation to DHPC. For Objectives 2a and 2b, we will use the historical cohort design to provide descriptive analysis of the occurrence of potential adverse events and changes in objective parameters of disease among pioglitazone users.

The study period will begin on 1.1.2000 in CPRD, on 1.1.2004 in AU, and on 1.1.2007 in IPCI, reflecting availability of prescription data. The end of observation will be determined by the status of database updates (see **Section 7 Data sources**) and will vary by country.

**Data cut:** the final report will contain data updated and available in the three databases as of 1 August 2012. On that date, all three databases are expected to have data on pioglitazone utilization at least through the end of 2011.

#### 3.3 EXPOSURE

##### 3.3.1 *Initiation, use, and termination of pioglitazone-containing products*

**DHPC baseline (or DHPC)** is the calendar date of the “Dear Health Professional” communication (**DHPC**). This date will be used as the baseline date of utilization patterns among prevalent users of pioglitazone at the time of DHPC. The country-specific **DHPC** baselines are:

DENMARK	11 August 2011
NETHERLANDS	05 August 2011
UNITED KINGDOM	29 July 2011

These dates were communicated in an email from 20 February 2012 by the following official:

Sarah Harding  
Medical Director, Pharmacovigilance  
Takeda Global R & D Centre (Europe) Ltd.,  
61 Aldwych,  
London WC2B 4AE  
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Fax: +44 (0)20 7242 1820

**New user of pioglitazone** will be defined as a person with the first recorded prescription for a pioglitazone-containing product in the absence of such prescriptions at least 180 days before the date of the first pioglitazone prescription within the study period. The date of the first-recorded pioglitazone prescription will be the date of the initiation of pioglitazone. This date will be used as baseline for ascertaining baseline characteristics among new users of pioglitazone.

**Prevalent user of pioglitazone** is a pioglitazone user who had initiated pioglitazone before a given date and continues to be on the drug, as evidenced by the date of the most recent prescription and the estimated prescription length.

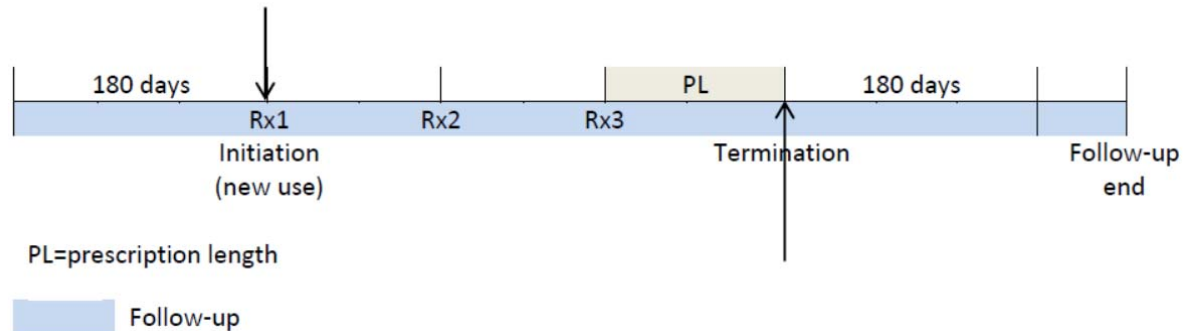
**Prescription length** will be defined separately in each database, based on prescribing practices and the best available data. In the AU databases the prescription length for each prescription will be the number of days supplied based on the number of defined daily doses (DDD) in a dispensed prescription. In the IPCI database, prescribed dose will be used whenever recorded; if not recorded, DDD will be used. In the CPRD, prescription length for pioglitazone, based on recommendation and actual use.

**Last prescription** for pioglitazone will be defined as the prescription for pioglitazone product followed by absence of a new prescription for a pioglitazone for 180 days, or end of the patient record, whichever comes first. The end of patient record occurs by death, migration from the database catchment area, or end of study.

**Termination** of pioglitazone will be defined as the date of the last estimated drug intake, calculated by adding the estimated prescription length to the date of the last prescription for a pioglitazone-containing product. If death, emigration, or the end of the follow-up occurs before the end of the estimated prescription length plus 180 days (see last

prescription definition), the date of death, emigration, or end of follow-up will not be considered as date of termination of pioglitazone, but follow-up will be censored at this time.

Thus, according to these definitions, it is possible for a person to be initiate or terminate pioglitazone use more than once during the study period. The definitions are presented in the figure below:



For patients whose use of pioglitazone continues beyond DHCP, a modified definition of termination will be applied in order to accommodate unavailability of full 180 days of follow-up in the databases after DHCP. This definition will be based on estimated date of switching from pioglitazone to another oral hypoglycemic agent (OHA) among pioglitazone terminators who have  $\geq 180$  days of follow-up available after termination date (termination date = date of last prescription + prescription length). In this group of people, we will:

- Find the date of the first OHA prescription after termination of pioglitazone
- calculate 'time to switch, defined as number of days from the termination date until the date of the first post-termination OHA prescription
- obtain median time to switch', defined as median number of days in the population of switchers to other OHAs with  $\geq 180$  days of follow-up
- use the 'median time to switch' instead of 180 days to define termination of pioglitazone for those whose pioglitazone use extends beyond DHCP date. The 'median time to switch' will be estimated separately in each database, so termination definition will depend on prescription patterns in each database.

The new definition will apply to data reported in Tables 6, 7, 14, 16.



## 3.4 ENDPOINTS

### 3.4.1 Utilization patterns

Changes in utilization of pioglitazone over time will be reported for the number of new users, prevalent users, and the number of prescriptions during the study period. First, we will report baseline characteristics of new users of pioglitazone containing products before and after the country-specific date of DHPC. The data will include type of first pioglitazone-containing product prescribed; calendar year of pioglitazone initiation; sex; age at pioglitazone initiation, contraindications (heart failure, hepatic impairment, diabetic ketoacidosis, bladder cancer, any recorded haematuria); diabetes-related characteristics (glycated haemoglobin A [HbA1c]; fasting plasma glucose [FPG]; duration of type 2 diabetes); overall comorbidity (measured by Charlson comorbidity index); history of medication use (lipid-lowering agents, antihypertensive agents, diuretics; nitrates; antiplatelet agents); and lifestyle factors whenever available (obesity, defined as body mass index  $\geq 30$  kg/m<sup>2</sup> or a relevant diagnostic codes; smoking, alcohol use).

The look-back period for assessment of the baseline covariates will be based on the period covered by each database and by clinical relevance. History of cancer, and Charlson comorbidity index, medication use, obesity, smoking and alcoholism will be assessed using the entire period available in each database. Diabetes-related characteristics will be assessed within up to 24 months before the baseline. Measurable characteristics will be database-specific. Duration of diabetes will be defined as the time from diabetes onset until pioglitazone initiation date. Diabetes onset will be defined as the date of the first prescription for an oral hypoglycaemic agent or the date of the first-recorded diabetes diagnosis.

Concomitant treatment of pioglitazone with other glucose lowering agents will be assessed among new users of pioglitazone before and after DHPC. Among the new users, we will define the on-treatment period starting from the date of the first prescription of pioglitazone and ending at the end of the last prescription for pioglitazone (or end of the follow-up). Presence of concomitant treatment with glucose-lowering agents will be defined as at least one prescription for a given agent recorded during the on-treatment period. Pioglitazone combination preparation with metformin, glimepiride or alogliptin will be reported as concomitant treatment with the respective oral glucose lowering agent.

To assess switching to and from alternative therapies, among all new users of pioglitazone, we will report distribution of last glucose-lowering agent(s) prescribed before the initiation of pioglitazone. Among patients who terminate pioglitazone not as a result of death emigration or end of follow-up, we will report the distribution of the first glucose-lowering agent(s) prescribed after termination of pioglitazone.

To examine changes in pioglitazone utilization around the time of DHPC, we will identify a cohort of prevalent users of pioglitazone, i.e. those who started the drug before the DHPC date and a cohort of new pioglitazone users, ie those who started the drug on or after the DHPC date. The baseline among the prevalent users will be the DHPC date. The baseline for the new users will be the initiation date. We will examine:

- Prevalence of contraindications and risk factors for bladder cancer separately for the prevalent users and for the new users, by calendar month starting in July 2011 and until the end of the follow-up.
- To examine how investigation of haematuria affected utilization of pioglitazone, we will report the number and the proportion of the prevalent pioglitazone users with a haematuria record after DHPC, and among those, the number and proportion of patients subsequently terminating pioglitazone. Among patients initiating pioglitazone after DHPC, we will examine the proportion of those with haematuria recorded after DHPC but before pioglitazone initiation.
- To assess whether periodic reviews of treatment took place, we will count, for each of the cohort members, the number of HbA1c measurements recorded from DHPC and until the end of the follow-up (for prevalent users) or from the first pioglitazone prescription until the end of the follow-up (for new users initiating after DHPC). We will report the distribution of the total number of the post-DHPC/post-initiation HbA1c measurements in this cohort (0, 1, >1).
- To assess outcomes of periodic treatment reviews we will identify patients failing to derive sufficient benefit from treatment. Failure to derive treatment benefit will be defined as at least one measurement of HbA1c  $\geq 7.5\%$  recorded after DHPC (for prevalent users) or the initiation of pioglitazone (for new users). Among the patients identified as failing to derive sufficient treatment benefit, we will report the proportion receiving at least one prescription for pioglitazone after the date of the recorded HbA1c  $\geq 7.5\%$ . We will also assess the proportion of prevalent (as of DHPC date) pioglitazone users who discontinue pioglitazone treatment after DHPC date in the absence of evidence of insufficient treatment benefit (patients without data on HbA1c or patients with HbA1c  $< 7.5\%$ ).

To compare prescribing patterns in the elderly before and after DHPC, we will compare new users of pioglitazone before DHPC with new users of pioglitazone after DHPC with respect to

- Age distribution at the start of pioglitazone therapy;
- First prescribed dose, stratified by age group. In Denmark and in the Netherlands, an **estimated first prescribed dose** will be calculated by dividing the total amount of pioglitazone dispensed at the initiation date by the time between the first and the second prescription for pioglitazone. The total amount dispensed will be calculated by multiplying the number of pills by pill strength. In the CPRD, the **actual first prescribed dose** is recorded and will be reported. To account for uncertainty about inter-prescription intervals, first-prescribed pill strength will also be reported.
- Prevalence of concomitant use of pioglitazone with insulin by age group. Concomitant use with insulin will be defined as record of at least one prescription

for insulin between the first-recorded and the last-recorded prescription for pioglitazone.

### **3.4.2 Patient-level endpoints**

Patient-level outcomes will be examined in the following two groups of patients: 1) all users of pioglitazone on/after DHPC (new and prevalent users combined); and 2) persons terminating pioglitazone after DHPC (group 2 is a subset of group 1).

For the analysis of the prevalent/new users, baseline will be defined as the date of DHPC (for prevalent users) or date of the first prescription for pioglitazone after DHPC (for new users). For the analysis of terminating patients, baseline will be defined as the date of termination of pioglitazone (date of the last prescription + prescription length).

#### Potential adverse events

We will examine occurrence of the following potential adverse events during the relevant follow-up, separately for prevalent/new and for pioglitazone users with last prescription for pioglitazone after DHPC:

- Death from all causes;
- Diabetes complications, defined as a compound outcome of acute renal failure, diabetic coma, or diabetic acidosis;
- Cardiovascular events, specifically:
  - a. acute myocardial infarction,
  - b. acute coronary syndrome,
  - c. haemorrhagic stroke,
  - d. ischemic stroke.

The follow-up will start on the date of the relevant baseline and will end at the earliest of 45 days, emigration, or death. For pioglitazone users who terminate the drug after DHPC, only diabetes complications will be examined. Other events (death and cardiovascular events) will not be examined, since conditioning of pioglitazone termination on absence of future use requires that patients survive until the termination definition is fulfilled. This requirement may not be tenable for death and cardiovascular outcomes, which have high mortality.

#### Measures of diabetes control

This analysis will be conducted using available data on laboratory tests in the three databases. In AU, laboratory data analysis will be restricted to users of pioglitazone in northern Denmark, the area covered by the clinical laboratory information systems (the LABKA database<sup>4</sup>).

Glycated haemoglobin A (HbA1c) and fasting plasma glucose (FPG) will serve as measures of glycaemic control. Whenever available, renal function will be measured using estimated glomerular filtration rate (eGFR), calculated based a standard formula using serum creatinine, age and sex (Appendix). Lipids will be measured by fasting serum concentrations of total cholesterol, LDL cholesterol, HDL cholesterol, and triglycerides.

Baseline and post-baseline values in these parameters will be compared for all users of pioglitazone who filled a prescription post-DHPC (prevalent and new users) and again for all for all pioglitazone users who stopped use after DHPC (post-DHPC terminators). For prevalent users, the baseline value of each laboratory parameter will be the value recorded before or on, and most proximal in time, to the DHPC date. For new users, who started pioglitazone after the DHPC date, the baseline will be the date of the first pioglitazone prescription. To identify the baseline values the look-back period of 24 months before the baseline will be used.

For the comparison of lab values before and after the termination of pioglitazone, the baseline date will be the estimated date of termination (date of the last prescription plus the estimated prescription length).

Changes relative to a baseline will be assessed at 3, and 6 months post-baseline for all laboratory parameters, except eGFR. These periods will be defined to provide non-overlapping, all-inclusive continuity of observation, with each period continuing until the time accumulated for the next period, as follows: >0-3 months=day 1 post-baseline through day-89 post-baseline; >3-6 months=day 90-post-baseline through day 180 post-baseline. Within each period, the earliest available post-baseline measurement will be used as the follow-up value. Estimated glomerular filtration rate (eGFR) will be calculated at the first available relevant measurement of serum creatinine during the follow-up. Relevant measurements of serum creatinine for calculating eGFR are measurements taken on day 1 though day 365 post-baseline.

### 3.5 ANALYSIS PLAN

We will report prevalences and distributions of variables in the descriptive utilization tables (e.g., prevalence of users with history of bladder cancer, distribution of age groups). For adverse events, we will report incidence rates with 95% confidence intervals. For changes in the laboratory parameters, we will report means or medians, or both, as appropriate based on underlying distributions; with appropriate measures of spread. This report will contain descriptive analyses. No hypothesis will be tested. Appendix 1 and Appendix 2 list suggested tables and figures to be included in the report.

## 4. SOURCE OF BIAS AND LIMITATIONS

The main types of systematic error in epidemiologic studies include selection bias, information bias and confounding. Because of routine data collection in the data sources involved, selection bias is expected to be negligible. Information bias may stem from inability to ascertain the actual drug intake from prescription issue or dispensation data; however, because diabetes is a chronic condition requiring treatment – including

pioglitazone - high compliance with all glucose-lowering drugs will be assumed. It is acknowledged that exact timing of start and end of medication intake will inevitably be misclassified to a certain extent. This is general limitation of drug safety studies. These sources of bias will be explicitly discussed in study reports and will be considered when interpretation of the study findings.

Uninvestigated haematuria is an important DHPC contraindication for continuing or starting pioglitazone. We will not be able to quantify this in these databases. We will, however, be able to capture the presence of haematuria though with unknown completeness. It can be indirectly inferred that for patients with a haematuria record, in whom pioglitazone was stopped, the haematuria was significant and considered a potential early sign of bladder cancer. However, in these patients, termination of pioglitazone for other – possibly unmeasured reasons – cannot be ruled out based on the available data.

While results of this investigation may be assumed generalisable to the populations of pioglitazone users in Denmark, the Netherlands, and the United Kingdom, generalisability to the entire EU population is less clear. To assess generalisability, we obtain all published data on pioglitazone utilization in other EU Member States and use that information when interpreting results of the present study.

## **5. QUALITY ASSURANCE, FEASIBILITY AND REPORTING**

### **5.1 DATA STORAGE**

Due to the differences in the statistical software and analytical capabilities across the institutions, a distributed network approach will be adopted in this project. JERBOA © is custom built JAVA-based software created in the EU-ADR project<sup>9</sup> (FP7-ICT-215847) and that has been used in other European funded projects (i.e. VAESCO, SOS) will be used. Each database owner will locally create standardized input files (patients, events and prescriptions). JERBOA © aggregates, anonymises the information in those files and produce encrypted output files that will be shared and stored centrally for further analysis.

### **5.2 METHODS FOR QUALITY ASSURANCE**

The core research team will consist of epidemiologists and biostatisticians with experience in drug safety studies; for clinical and laboratory data extraction, and results' interpretation, an experienced diabetologist will be consulted. Data linkage, extraction, coding, and management will be conducted by experienced statisticians and data managers, using established institutional facilities, including secure servers. The milestones for data collection, analysis, and final report submission have been established and agreed upon with the Agency. A professional project managing company will provide administrative and communication support. A built-in quality assurance method is use of different databases to provide estimates of the same population parameters (drug utilization patterns, incidence rates of adverse events). Although certain level of inter-database variation is expected based on the true differences in the underlying population and in recording practices, overt discrepancies in results stemming from different databases will be flagged and investigated to assure quality.

### 5.3 DATA QUALITY

There were several validation studies of Danish registries, demonstrating adequacy of data quality for epidemiologic research.<sup>5,10,11</sup> Likewise, the CPRD has been demonstrated to contain high-quality data.<sup>6,7</sup> The IPCI database has been validated and for its use in post-marketing surveillance, has proven to be useful for post-marketing surveillance, that purpose and has been used in other European funded projects (i.e. SOS - FP7-HEALTH-223495).<sup>12</sup>

### 5.4 FEASIBILITY AND TIMELINES

In Denmark, pioglitazone has been available since 2000 as a single-substance preparation (source: Danish Medicines Agency, [www.dkma.dk](http://www.dkma.dk)). In The Netherlands, and in the United Kingdom, pioglitazone has been marketed as a single-substance preparation and in combination with glimepiride and/or metformin (sources: Medicines Evaluation Board, Medicines and Healthcare Products Regulatory Agency <http://www.mhra.gov.uk>). Based on this information, it is feasible to conduct this study using the listed databases.

The project will be implemented according to the following milestones/timelines:

MILESTONE	DATE OF COMPLETION
D4.a: Preliminary study protocol submitted to the Agency for a 15-day consultation period	20/05/2012
D4.b: Final study protocol revised after consideration of Agency's comments; the final study protocol shall be subject of an ENCePP seal application.	20/06/2012
D5.a: Interim report on study results of the epidemiological study, submitted to the Agency for a 15-day consultation period	20/11/2012
D5.b: Final report on study results of the epidemiological study.	20/02/2013
D3: Report with an evaluation of the impact of the recent regulatory decisions on the utilisation patterns of this drug and other anti-diabetic medications.	20/03/2013

### 5.5 REPORTING AND DISSEMINATION OF RESULTS

Reporting and dissemination of results will fulfil Objective 3 and Objective 4 of this study.

**Objective 3** is provision of comprehensive and judicious interpretation of findings obtained while achieving Objective 1 and Objective 2. The findings will be presented in the form of a formal epidemiologic study report, and interpretation of results is an integral part of such a report. Effectiveness of risk minimisation on the population level will be evaluated by the proportion of persons with contraindications among pioglitazone users in relation to the timing of DHPC. Effectiveness of risk minimisation measures on individual level will be evaluated based on stability of diabetes and by occurrence of potential acute adverse events in persons terminating and continuing pioglitazone after the DHPC. Precision of the



estimates, risk of systematic error, and clinical significance of results will be considered when interpreting the findings.

**Objective 4** is provision of practical recommendations for improving effectiveness of risk minimisation measures. Based on findings obtained while achieving Objective 1 and Objective 2 and their interpretation (Objective 3), practical recommendations will be formulated, in liaison with EMA, for improving effectiveness of risk minimisation measures in Europe. Particular care will be taken to interpret the data while weighing strengths and limitations of each piece of evidence, and accounting for potential sources of bias.

## 5.6 AMENDMENTS

An amendment of the existing contract becomes necessary anytime any of the contractual terms need to be changed (e.g., delivery dates of deliverables, modification of the contractor's address, etc.) without any constraint on either the time or the quantity. Amendments always should be requested based on reasoned justification that will be included in an email to be sent to the EMA, together with the proposed modifications.

The EMA gives its initial response by email. Time required for response will depend on the nature, complexity and scope of the proposed amendment. Once it has become clear that the amendment is necessary, the EMA drafts the 'contract amendment' reflecting the amendments to the existing contract and transmits the draft to the contractor for review; once agreed, the EMA prepares two copies of the amendment which are signed by the Agency's representative, and then transmitted to the contractor for counter-signature. One original copy remains with the contractor, the other original is returned to the Agency.

## 5.7 INDEPENDENT REVIEW OF STUDY RESULTS

Following ENCePP policies, the protocol of this study will be used to apply for an ENCePP seal. The Interim Report and the Final Report will be available in open-access format on the EMA's ENCePP register of studies.

As mandated by the ENCePP, interim and final reports of this investigation will be published in the ENCePP register of studies. Subsequently, reports will be submitted to appropriate peer reviewed journals.

## 6. ETHICAL ISSUES

This final study protocol will be submitted for an approval to the appropriate authorities: the Danish Data Protection Agency (Datatilsynet) for the AU database; the "Raad van Toezicht van IPCI" (Board of Supervisors) for the IPCI database, and by the Independent Scientific Advisory Committee of the CPRD (ISAC).

## 7. DATA SOURCES

The following table provides brief description of the three automated databases in the European Union that will be used to in this project.

CHARACTERISTIC	DATABASE		
	AU	IPCI	CPRD
Type of database	Population-based medical registries	GP database	GP database
Coding system for drugs	ATC	ATC	READ
Coding system for events	ICD-8, ICD-10	ICPC 1	READ
Free text	No	Yes	Available on request
Availability of FU years	Drugs 2003-2011; hospital visits 1977-2011, including outpatient visits since 1995	2007 up to date	1990 to 2011
Patient identifier used for linkage	The Danish Civil Registration System	Patient file	The CPRD administrative file
Deaths	The Danish Civil Registration system	Patient file	The CPRD event file plus death registry data where available.
Prescription medication	Aarhus University Prescription Database; reimbursed prescriptions filled in outpatient pharmacies	Prescriptions file: issued prescriptions	The CPRD drug file: issued prescriptions
Diagnoses	Inpatient and outpatient hospital-based diagnoses, recorded in the Danish National Registry of Patients	Diagnosis file (ICPC) and Journal (free text)	The CPRD event file
Laboratory tests	The Laboratory Information Systems research database	Measurements file and Journal (free text)	The CPRD laboratory file
Smoking, alcohol use body mass index	Hospital codes for obesity and alcohol use will be used	Diagnosis file and Measurements file	The CPRD registration file



## 8. REFERENCES

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## 9. APPENDICES

### 9.1 APPENDIX 1. PROPOSED TABLES/FIGURES FOR UTILIZATION ANALYSIS

*Figure 1. New users of pioglitazone-containing products over calendar time, by database.*

*Figure 2. Prevalent users of pioglitazone-containing products over calendar time, by database.*

*Figure 3. Prescriptions of pioglitazone-containing products over calendar time, by database.*

**Table 1. Baseline characteristics of the new users of pioglitazone who initiate pioglitazone before DHPC (baseline=initiation date).**

CHARACTERISTIC	DATABASE		
	AU (Northern Denmark)	IPCI (Netherlands)	CPRD (United Kingdom)
All new users in period	N		
Type of pioglitazone preparation			
All preparations	N (XX.X%)		
Pioglitazone			
Pioglitazone and glimepiride			
Pioglitazone and metformin			
Pioglitazone and alogliptin			
Calendar year of pioglitazone initiation (all preparations)			
2000			
2001			
...			
2011			
Sex			
Men			
Women			
Age at initiation of pioglitazone-containing products, years			
<18			
18-35			
35-44			
45-54			
55-64			
65-74			

75-84			
≥85			
History of potential contraindications any time before initiation			
Any contraindication			
Bladder cancer			
Haematuria			
Mild hepatic impairment			
Moderate to severe hepatic impairment			
Diabetic ketoacidosis			
Heart failure			
Diabetes-related history in 24 months before initiation			
Glycated haemoglobin A (HbA1c), %, mean (SD)	XX.X (X.X)		
Inadequate glycaemic control (HbA1c ≥ 7.5%)			
Fasting plasma glucose, mmol/L, mean (SD)	XX.X (X.X)		
Duration of type 2 diabetes, months, mean (SD)			
Charlson comorbidity index any time before initiation			
Low (0)			
Medium (1-2)			
High (>2)			
History of medication use any time before initiation			
Lipid-lowering agents			
Antihypertensive agents			
Diuretics			
Nitrates			
Antiplatelet agents			
Lifestyle factors (whenever available)			
Obesity/ BMI			
Smoking			



Alcoholism				
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***Table 2. Baseline of the new users of pioglitazone who initiate pioglitazone on/after DHPC (baseline=initiation date).***  
SAME ROWS AND COLUMNS AS TABLE 1

**Table 3. Concomitant treatment of pioglitazone with other antidiabetic drugs before DHPC (new users starting before DHPC).**

CHARACTERISTIC	ATC CODE	DATABASE		
		AU (Northern Denmark)	IPCI (Netherlands)	CPRD (U. Kingdom)
Insulins and analogues	A10A	XXX (XX.X%)		
Biguanides	A10BA			
<b>**list specific drugs in each category</b>				
Sulfonamides, urea derivatives	A10BB			
Sulfonamides (heterocyclic)	A10BC			
Combinations of oral blood glucose lowering drugs	A10BD			
Alpha glucosidase inhibitors	A10BF			
Thiazolidinediones	A10BG			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Alpha glucosidase inhibitors	A10BF			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Other blood glucose lowering drugs, excl. insulins	A10BX			

**Table 4. Concomitant treatment of pioglitazone with other antidiabetic drugs on/after DHPC (new users starting on/after DHPC).**  
 SAME ROWS AND COLUMNS AS TABLE 3.

**Table 5. Distribution of last antidiabetic drugs prescribed before the initiation pioglitazone (all new users).**  
 SAME ROWS AND COLUMNS AS TABLE 3.

**Table 6. Distribution of first antidiabetic drugs prescribed on/after termination of pioglitazone before and on/after DHPC. (This table includes persons switching to other OHAs from pioglitazone and those in whom pioglitazone was removed from the treatment regimen.)**

CHARACTERISTIC	ATC CODE	DATABASE		
		AU (Northern Denmark)	IPCI (Netherlands)	CPRD (U. Kingdom)
	Termination before DHPC			
Insulins and analogues	A10A	XXX (XX.X%)		
Biguanides	A10BA			
**list specific drugs in each category				
Sulfonamides, urea derivatives	A10BB			
Sulfonamides (heterocyclic)	A10BC			
Combinations of oral blood glucose lowering drugs	A10BD			
Alpha glucosidase inhibitors	A10BF			
Thiazolidinediones	A10BG			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Alpha glucosidase inhibitors	A10BF			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Other blood glucose lowering drugs, excl. insulins	A10BX			
	Termination on/after DHPC			
Insulins and analogues	A10A	XXX (XX.X%)		
Biguanides	A10BA			
**list specific drugs in each category				



Sulfonamides, urea derivatives	A10BB			
Sulfonamides (heterocyclic)	A10BC			
Combinations of oral blood glucose lowering drugs	A10BD			
Alpha glucosidase inhibitors	A10BF			
Thiazolidinediones	A10BG			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Alpha glucosidase inhibitors	A10BF			
Dipeptidyl peptidase 4 (DPP-4) inhibitors	A10BH			
Other blood glucose lowering drugs, excl. insulins	A10BX			



**Table 7. Termination of pioglitazone among prevalent users with contraindications\* and risk factors\* for bladder cancer.**

	Pioglitazone users with contraindication as of 30 June 2011	MONTH, 2011 Number of terminators among those with contraindications/risk factors						Total number of terminators with contraindication/risk factor
		July	August	September	October	November	December*	
Contraindication								
Heart failure	N	n1 (%=n1/N)	n2 (%=n2/N)	n3 (%=n3/N)	n4 (%=n4/N)	n5 (%=n5/N)	n6 (%=n6/N)	Sum(n1 to n6)
Mild hepatic impairment								
Moderate or severe hepatic impairment								
Diabetic ketoacidosis								
History of bladder cancer								
Haematuria								
Risk factors for bladder cancer								
Age								
History of smoking								

\*Contraindications and risk factors assessed before 30 June 2011.

**Table 8. Prevalence of contraindications\* and risk factors for bladder cancer\* among users of pioglitazone who start pioglitazone on/after DHCP.**

	MONTH					
	July N=number of new users	August N=number of new users	September N=number of new users	October N=number of new users	November N=number of new users	December* N=number of new users
Contraindication						
Heart failure	n with contraindication (%=n/N)					
Mild hepatic impairment						
Moderate or severe hepatic impairment						
Diabetic ketoacidosis						
History of bladder cancer						
Haematuria						
Risk factors for bladder cancer						
Age at first pioglitazone prescription (categories)						
History of smoking						

\*Contraindications and risk factors for bladder cancer measured before the first pioglitazone prescription.

**Table 9. Estimated first prescribed dose/dispensed strength among new users of pioglitazone before DHPC, by age group**

	AU	IPCI	CPRD
	N=		
	Estimated* first prescribed dose, median (quartiles)		
Age group, years			
<50	Median (quartiles)		
50-<55			
55-<60			
60-<65			
65-<70			
70-<75			
75-<80			
	First prescribed pill strength median (quartiles)		
<50			
50-<55			
55-<60			
60-<65			
65-<70			
70-<75			
75-<80			

\*Actual prescribed dose will be reported for CPRD

**Table 10. Estimated first prescribed dose among new users of pioglitazone, on/after DHPC, by age group**  
 SAME ROWS AND COLUMNS AS TABLE 9

**Table 11. Prevalence of concomitant use with insulin, new users before DHPC, by age group**

	AU	IPCI	CPRD
N=			
Number (%)			
Age group, years			
<50	N (%)		
50-<55			
55-<60			
60-<65			
65-<70			
70-<75			
75-<80			

**Table 12. Prevalence of concomitant use with insulin, new users on/after DHPC, by age group**  
 SAME ROWS AND COLUMNS AS TABLE 11

## 9.2 APPENDIX 2. PROPOSED TABLES FOR PATIENT-LEVEL OUTCOMES

**Table 13. Potential adverse events and among prevalent and new users of pioglitazone on/after DHPC within 45 days of baseline. Baseline=DHPC/initiation date.**

ADVERSE EVENT	DATABASE								
	AU			IPCI			CPRD		
	N at risk	Events	Risk (95% CI)	N at risk	Events	Risk (95% CI)	N at risk	Events	Risk (95% CI)
Death of all causes									
Diabetes complications									
Acute myocardial infarction									
Acute coronary syndrome									
Haemorrhagic stroke									
Ischemic stroke									

**Table 14. Diabetes related adverse events among persons who have the last pioglitazone prescription on/after DHPC, within 45 days of termination, by database/country. Baseline = termination date.**

ADVERSE EVENT	DATABASE								
	AU			IPCI			CPRD		
	N at risk	Events	Risk (95% CI)	N at risk	Events	Risk (95% CI)	N at risk	Events	Risk (95% CI)
Diabetes complications									

**Table 15. Changes in laboratory parameters before and on/after DHPC among prevalent and new users of pioglitazone at DHPC (Baseline=DHPC/initiation date).**

	AU		IPCI		CPRD	
	3 months	6 months	3 months	6 months	3 months	6 months
HbA1c, %						
N with both measurements	XX					
Baseline mean (SD)	Xx (xx)					
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
FPG, mmol/L						
N with both measurements						
Baseline mean (SD)						
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
Total cholesterol, mmol/L						
N with both measurements						
Baseline mean (SD)						
Follow-up mean (SD)						
Change from baseline, mean (95% CI)						
HDL cholesterol, mmol/L						
N with both measurements						

Baseline mean (SD)			
Follow-up mean (SD)			
Change from baseline, mean (95% CI)			
LDL cholesterol, mmol/L			
N with both measurements			
Baseline mean (SD)			
Follow-up mean (SD)			
Change from baseline, mean (95% CI)			
Triglycerides mmol/L			
N with both measurements			
Baseline mean (SD)			
Follow-up mean (SD)			
Change from baseline, mean (95% CI)			
	First measurement after baseline up to 12-months post-baseline	First measurement after baseline up to 12-months post-baseline	First measurement after baseline up to 12-months post-baseline
eGFR			
N with both measurements			
Baseline mean (SD)			
Follow-up mean (SD)			
Change from baseline, mean (95% CI)			





D4.a Preliminary Study Protocol  
for Service Contract EMA/2011/38/CN PIOGLITAZONE  
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***Table 16. Changes in laboratory parameters before and after pioglitazone termination among patients terminating pioglitazone on/after DHPC. Baseline=date of termination.***

SAME ROWS AND COLUMNS AS TABLE 15

**Table 17. Periodic treatment reviews among prevalent users of pioglitazone as of DHPC**

	AU	IPCI	CPRD
Prevalent users of pioglitazone as of DHPC	N1=	N2=	N3=
Total of HbA1c measurements taken after DHPC			
0			
1			
>1			
Patients with evidence of insufficient benefit*	X	Y	Z
Patients with prescription for pioglitazone after evidence of insufficient benefit**	A (A/X)	B (B/Y)	C (C/Z)

\*Defined as patient with at least one measurement of HbA1c $\geq$ 7.5% **after** DHPC

\*\*Defined as patients with evidence of insufficient benefit who receive at least one pioglitazone prescription after the earliest HbA1c HbA1c $\geq$ 7.5% measurement recorded after DHPC

**Table 18. Periodic treatment reviews among new user of pioglitazones on/after DHPC**

	AU	IPCI	CPRD
Total number of new users after DHPC	N1=	N2=	N3=
Total of HbA1c measurements taken after first pioglitazone prescription			
0			
1			
>1			
Patients with evidence of insufficient benefit*	X	Y	Z
Patients with prescription for pioglitazone after evidence of insufficient benefit**	A (A/X)	B (B/Y)	C (C/Z)

\*Defined as patient with at least one measurement of HbA1c $\geq$ 7.5% **after** first prescription for pioglitazone

\*\*Defined as patients with evidence of insufficient benefit who receive at least one pioglitazone prescription after the earliest HbA1c $\geq$ 7.5% measurement recorded after the first prescription for pioglitazone



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### 9.3 APPENDIX 3. ALGORITHMS USED TO IDENTIFY STUDY VARIABLES

TBA to the final protocol (currently kept as a separate document)

#### 9.4 APPENDIX 4. List of planned tables and figures

Figure 1. New users of pioglitazone-containing products over calendar time, by database.

Figure 2. Prevalent users of pioglitazone-containing products over calendar time, by database.

Figure 3. Prescriptions of pioglitazone-containing products over calendar time, by database.

Table 1. Baseline characteristics of the new users of pioglitazone who initiate pioglitazone before DHPC (baseline=initiation date).

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Table 10. Estimated first prescribed dose among new users of pioglitazone, on/after DHPC, by age group

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Table 13. Potential adverse events and among prevalent and new users of pioglitazone on/after DHPC within 45 days of baseline. Baseline=DHPC/initiation date.

Table 14. Diabetes related adverse events among persons who have the last pioglitazone prescription on/after DHPC, within 45 days of termination, by database/country. Baseline = termination date.

Table 15. Changes in laboratory parameters before and on/after DHPC among prevalent and new users of pioglitazone at DHPC (Baseline=DHPC/initiation date).

Table 16. Changes in laboratory parameters before and after pioglitazone termination among patients terminating pioglitazone on/after DHPC. Baseline=date of termination.

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Table 18. Periodic treatment reviews among new user of pioglitazones on/after DHPC