Pooled Analysis Protocol and Statistical Analysis Plan

Pan European Multi-Database Bladder Cancer Risk Characterisation Study

Pooled Analysis Based On Individual Patient Level Data

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1 APPROVALS

I have carefully read this document and agree to its terms.

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2 LIST OF ABBREVIATIONS

ACE inhibitor	Angiotensin converting enzyme inhibitor
ARB	Angiotensin receptor blockers
ATC code	Anatomical therapeutic chemical classification system code
BPH	Benign prostatic hypertrophy
CHMP	Committee for Medicinal Products of Human Use
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CPRD	Clinical Practice Research Datalink Group
DDD	Defined daily dose
EMA	European medical agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FIN	Finland
GP	General practitioner
HR	Hazard ratio
ICD-9; ICD-10	International classification of diseases, 9th revision; 10th revision
ICD-O-3	International classification of diseases for oncology, 3rd edition
ICPC	International classification of primary care
ISPE	International Society for Pharmacoepidemiology
KI	Karolinska Institute
NCSP	NOMESCO classification of surgical procedures code
NL	The Netherlands
NL GP	PHARMO General Practice Dataset
PASS	Post authorisation safety study
PHARMO	Pharmo Institute for Drug Outcomes Research
PUNLMP	Papillary urothelial neoplasia of low malignant potential

SWE	Sweden
UK	United Kingdom

3 RATIONALE

The Medicinal Products of Human Use Committee (CHMP) of the European Medicines Agency (EMA) recently finalized its review on pioglitazone use and occurrence of bladder cancer. Evidence from several recent epidemiological studies suggests a small increased risk of bladder cancer with pioglitazone use in patients with type 2 diabetes (Lewis *et al*. 2011; CNAMTS 2011). In the 4th interim analysis (8-years follow-up) of the Kaiser Permanente Northern California Study cohort, the hazard ratio (HR) of ever vs. never use of pioglitazone was 1.07 (95% CI 0.87-1.30) and a non-significant elevated risk among patients with longest >4 years duration of therapy (HR=1.30, 95% CI 0.91-1.86) (Lewis *et al.* 2012). In the French CNAMTS study a similar risk for pioglitazone use was observed (HR=1.22, 95% CI 1.05-1.43), and a significant risk with cumulative doses over 28 000 mg (HR=1.75, 95% CI 1.22-2.50), and with duration of therapy between 12 to 23 months (HR=1.34, 95% CI 1.02-1.75) or over 24 months (HR=1.36, 95% CI 1.04-1.79) (CNAMTS 2011).

The CHMP agreed that further evidence is still needed and has requested Takeda Global Research & Development Centre Europe Ltd (Takeda) to conduct a Pan European post-authorisation safety study (PASS) on pioglitazone use and occurrence of bladder cancer.

In order to fulfil the imposed request by CHMP, an observational study was designed and started to further assess the association between pioglitazone use and bladder cancer risk among patients with type 2 diabetes mellitus in four European countries: Finland (FIN), the Netherlands (NL), Sweden (SWE), and United Kingdom (UK). The study protocol has been reviewed and approved by the EMA and has been registered on March 7 2013 in the EU PAS register and the protocol serves as a common protocol for all countries with the acknowledgement that country specific adaptations may be required. The record of the registration can be found at http://encepp.eu/encepp/viewResource.htm?id=3627.

The participating centres responsible for conducting the study are EPID Research (Finland), Karolinska Institutet (KI, Sweden), Pharmo Institute for Drug Outcomes Research (PHARMO, Netherlands) and the Clinical Practice Research Datalink Group (CPRD, UK). Each centre will conduct the study, collect and analyse data and report the country specific results as described in the protocol. EPID Research will further perform a pooled analysis using individual patient data from each country.

This pooled analysis protocol and statistical analysis plan describes the process and analysis principles used in the pooled analysis and refers to the common study protocol as appropriate.

4 OBJECTIVES OF THE STUDY

The objective of this study is to assess the association between pioglitazone use and bladder cancer risk among patients with type 2 diabetes mellitus through pooled patient level analysis using data from Finland, the Netherlands, Sweden, and United Kingdom.

4.1 Primary objectives

The primary objectives of the study are:

1. To estimate and compare the absolute and relative risk of bladder cancer in patients with type 2 diabetes with ever exposed to pioglitazone vs. never exposed to pioglitazone,
2. To estimate and compare the absolute and relative risk of bladder cancer in patients with type 2 diabetes with increasing duration of pioglitazone treatment,
3. To estimate and compare the absolute and relative risk of bladder cancer in patients with type 2 diabetes with increasing cumulative dose of pioglitazone treatment,
4. To examine the association between pioglitazone exposure and risk of bladder cancer with respect to possible channelling bias, detection bias and other sources of confounding.
5. To characterize the stage and grade of the bladder cancer cases at the time of diagnosis in patients with type 2 diabetes who are ever exposed to pioglitazone vs. who are never exposed to pioglitazone, and
6. To characterize all-cause mortality and bladder cancer-specific mortality pattern amongst patients ever exposed to pioglitazone vs. never exposed to pioglitazone.

4.2 Exploratory objectives

The exploratory objective of this study is to estimate and compare the absolute and relative risk of bladder cancer in patients with type 2 diabetes with time since the last dose of pioglitazone use.

5 PARTICIPATING CENTRES AND DATA SOURCES

5.1 Participating centres

Principal investigator Pasi Korhonen, PhD; Adj. Professor Chief Executive Officer EPID Research Oy Tekniikantie 12 FI-02150 Espoo Finland	Co-Investigator Edith M. Heintjes, PhD Scientific Research Manager Pharmo Institute for Drug Outcomes Research (PHARMO) Van Deventerlaan 30-40 3528 AE Utrecht The Netherlands
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Other co-investigators who have contributed to the design of the study protocol:

Shahram Bahmanyar, Associate Professor, KI; Paul Dolin, Director Epidemiology, Takeda; Susan Eaton, MSPH, CPRD; Fabian Hoti, PhD, EPID Research; Leanne Houweling, MSc, PHARMO; Marie Linder, PhD, KI; Timothy Williams, Dr, CPRD; Helen Strongman, MSc, CPRD

5.2 Data sources/pooled analysis datasets

The country specific studies will be undertaken in FIN, NL, SWE, UK using linkage of drug prescribing/dispensing databases to country-specific selected databases including (i) cancer registries, (ii) general practitioner (GP) records and/or hospital discharge records, (iii) death records, (iv) reimbursement decisions, and (v) immigration and emigration records.

As some countries only have hospital-discharge morbidity databases while other have GP-based records, the datasets are categorized according to source of morbidity covariate data:

- 4 hospital-based morbidity datasets (FIN dataset, SWE dataset, NL Pharmacy-Hospital dataset, UK CPRD GOLD-HES dataset) and
- 2 GP-based morbidity datasets (NL GP dataset, UK CPRD GOLD dataset)

Detailed descriptions of each of the six dataset can be found from the main study protocol, version 2.0, dated 20th June 2013.

The study will contain three pooled analyses, a primary pooled analysis and two sensitivity pooled analysis. In the primary pooled analysis all datasets are combined into a single Pan European meta-analysis dataset containing common variables from all datasets. In the second pooled analysis only the 4 hospital-based datasets are utilized. In the third pooled analysis datasets with information on smoking, BMI, HbA1C and urinary/renal marker information available will be used. The third pooled analysis will include datasets from UK, NL and SWE. (see section 12.1, pooled datasets).

6 STUDY POPULATION

The target population consists of patients with type 2 DM whose antidiabetic treatment at cohort entry is modified to include pioglitazone or another antidiabetic medication. In each dataset these patients are identified with the following inclusion / exclusion criteria.

Inclusion criteria:

- Treatment with any oral antidiabetic drugs at any time in the available medication records.
- Baseline is modified (cohort entry point) to include pioglitazone (exposure group) or another antidiabetic medication (reference group).
- Age ≥ 40 years at cohort entry.
- At least 12 months of medication database membership during baseline period prior to cohort entry.

Exclusion criteria:

- Diagnosis of type 1 diabetes, gestational diabetes, or secondary and other types of diabetes mellitus prior to cohort entry using available data sources. For detailed ICD-10, ICD-9, ICPC and READ codes see Appendix 3. ,
- Patients who are entitled to special reimbursement for type 1 diabetes, diabetes with malnutrition, other diabetes or gestational diabetes, respectively (specific to FIN dataset only), and
- Diagnosis or history of bladder cancer, in-situ bladder cancer or benign neoplasm of bladder prior to cohort entry.
- Diagnosis of secondary malignant neoplasm of bladder prior to cohort entry
- Diagnose of neoplasms of uncertain or unknown behaviour of bladder prior to cohort entry
- History of cystectomy at cohort entry
- History of resection or removal of bladder tumour (benign or malignant) at cohort entry
- History of biopsy of bladder tumour or lesion a cohort entry

6.1 Study cohorts

The previously observed weak association between long term pioglitazone use and risk of bladder cancer could in part be due to channelling bias because pioglitazone is more likely to be prescribed to patients with more advanced diabetes or who are obese. Advanced diabetes and obesity are both independent risk factors for developing bladder cancer, and the preferential prescribing of pioglitazone to such patients could lead to biased estimates of risk.

To minimize channelling bias, each pioglitazone-exposed patient (exposure group) will be matched (Li et al 2012; Spreeuwenberg 2010) with up to 10 pioglitazone-unexposed diabetic patients (reference group). Each country will perform matching of the country specific datasets according to the main study protocol, version 2.0, dated 20th June 2013 and the country specific statistical analysis plans. In the pooled analysis the post-matched country specific datasets will be transferred to EPID Research, where they will be combined into pooled datasets.

6.2 Cohort entry date and start of follow-up

Cohort entry date and start of follow-up is defined as the date when the baseline therapy (including no pharmacotherapy) was modified to include pioglitazone (exposure group) or another antidiabetic medicine (reference group).

6.3 Baseline observation period

Each patient must have at least one year of membership in the relevant study database prior to cohort entry. This period is used to characterise baseline therapy, baseline medical history, and baseline covariates. This baseline observation period will start from 1.1.1998 onwards in Finland, from 1.7.2005 onwards in Sweden, and from start of database membership for the NL and UK datasets. In the Finnish and Swedish datasets the coverage for each patient is assured by verifying the place of domicile not being abroad 12 months prior to the index date (FIN, SWE).

6.4 End of follow-up

In the bladder cancer analyses, each patient will be followed-up from cohort entry until the date of diagnosis of the first incident bladder cancer, date of first diagnosis of secondary malignant neoplasm of bladder, start of other thiazolidinediones (other than pioglitazone) at or after cohort entry, end of membership of the database, end of database coverage, death or 30 June 2011, whichever occurs first.

In the bladder cancer mortality and the all-cause mortality analyses, each patient will be followed-up from cohort entry until death, start of other thiazolidinediones (other than pioglitazone) at or after cohort entry, end of membership of the database, end of database coverage, or 30 June 2011, whichever occurs first.

6.5 Censoring of follow-up

The NL GP, NL Pharmacy-Hospital, UK CPRD GOLD and UK CPRD GOLD-HES datasets have definable entry and exit dates for each person. Exit date will be used as a follow-up censoring date. The FIN Population Information System register and the SWE Total Population Register (maintained by Statistics Sweden) contain immigration and emigration date information and will be used to censor follow-up. In addition date of death will be used as a censoring event in the bladder cancer incidence analyses, and as an endpoint for the mortality analyses.

7 STUDY VARIABLES

7.1 Outcome variables

Bladder cancer

Date of diagnosis of the first incidence of bladder cancer after the entry into the study cohort will be used as the primary outcome date. The bladder cancer definition will include

- malignant neoplasm of the bladder and
- carcinoma in situ of the bladder.

Sensitivity analysis will also look the following additional outcomes:

- neoplasm of uncertain or unknown behaviour of the bladder.

In the FIN, SWE and CPRD GOLD-HES datasets information from cancer registries will used to define incident bladder cancers. Other datasets will use hospital discharge and GP records to find incident bladder cancers. The CPRD GOLD-HES dataset will use the registry diagnosis date as the gold standard, and diagnosis dates recorded in other sources only if there is no record in the registry. In the cancer registries, malignant bladder cancer is coded to ICD-O-3 code C67 with behaviour code "3". In the Hospital discharge data, malignant bladder cancer is coded to ICD-9-CM 188 or ICD-10 code C67. In NL GP, bladder cancer is coded to ICPC code U76, and in the UK CPRD malignant bladder cancer is coded to READ codes B49, 7B2C700 and 7B2CE00.
The specific codes malignant neoplasm of the bladder, carcinoma in situ of the bladder and neoplasm of uncertain or unspecified behaviour of the bladder are given in the following table.

Table 1: Bladder cancer codes

	ICD-10 CM	ICD-9 CM	ICD-O-3	ICPC	READ
Malignant neoplasm of the bladder	C67	188	C67 with behaviour code "3"	U76	B49, 7B2C700, 7B2CE00
Carcinoma in situ of the bladder	D09.0	233.7	C67 with behaviour code "2"	*	B837, selected BB4 codes
Neoplasm of uncertain or unknown behaviour of the bladder	D41.4	236.7 239.4	C67 with behaviour code "1" (PUNLMP with morphology code M-8130/1	U79	B917, BA04

* Text mining of the database contents used to identify in situ carcinomas and neoplasms of uncertain or unknown behaviour of the bladder

In the FIN, SWE and UK CPRD GOLD-HES datasets, there is 100% linkage to cancer registries. The data collection on all cancer cases is compulsory and the informants submitting data on cancer patients to the registry include all hospitals, physicians, pathological, cytological and haematological laboratories, and dentists. The data collected by these registers include demographic information on the patient, medical data such as the primary site of the tumour (International Classification of Diseases for Oncology code), date of diagnosis, and tumour type and grade. In the FIN, SWE and UK CPRD GOLD-HES datasets, bladder cancer will be based on cancer registry-based information.

The NL Pharmacy-Hospital and NL GP datasets only have partial linkage to the cancer registry data (20-30% in NL Pharmacy-Hospital and 10% NL GP datasets). It is thus not possible to use cancer registry-based diagnosis for all subjects. GP records data (NL GP dataset) and Hospital discharge data (NL Pharmacy-Hospital dataset) will be used to identify bladder cancers. For patients living in geographical areas that can be linked to the cancer registry, this method of outcome detection will be validated using the cancer registry data.

The CPRD GOLD dataset is not linked to the cancer registry data. Diagnosis of bladder cancer will be based on GP records data only.

All cause mortality and bladder cancer mortality

Information on date of all deaths among cohort members, and deaths where bladder cancer is recorded as the cause of death will be obtained from the national death registries for FIN, SWE, and UK CPRD GOLD-HES datasets. A recent validation study in the UK CPRD Gold demonstrated 99% concordance between GP's mortality record and national death registry entries. Cause-specific mortality is not available for the two NL datasets or the UK CPRD GOLD dataset. Bladder cancer deaths will be identified as deaths with malignant bladder cancer (e.g. ICD-10 code C67) as the underlying cause of death.

7.2 Exposure variables

Continuous drug use periods are constructed for the following drug groups. A detailed list of the diabetes drugs (ATC codes) within each group is given in **Appendix 1.**

Table 2 Diabetes drugs

Group number	Group name*
1	Pioglitazone
2	Other thiazolidinediones (including rosiglitazone)
3	Biguanides/Metformin
4	Sulphonylureas
5	DDP-4 inhibitors
6	Alpha glucosidase inhibitors
7	GLP-1 agonists
8	Meglitinides
9	Amylin analogues
10	Other oral diabetic medications
11	Insulin

** ATC codes given in Appendix 1. Combination products included into multiple groups.*

The following time dependent variables will be calculated for each of the diabetes drug groups of interest at any given time during the follow-up:

- Current exposure indicating whether the patient is in the treatment group at the current time point.(needed for all drug groups to identify changes in treatment)
- Ever vs. never exposure taking the value 1 (ever) as soon as one prescription of the treatment group has been purchased / prescribed, and 0 (never) otherwise.
- Duration of exposure indicating how long the patient has been exposed to a treatment group at the current time point (only for pioglitazone and insulin group).
- Cumulative dose indicating the cumulated dose the patient has been exposed to at the current time point (only for pioglitazone group).
- Time since last exposed to treatment group (only for pioglitazone group).

For other drugs of interest (Appendix 4) only the date of the first purchase / prescription will be used to define the time dependent ever vs. never exposure variable. Detailed instructions for calculating the different exposure variables for diabetes drug groups is given in Appendix 2. Especially, for pioglitazone the exposure variables listed) are constructed.

Table 3 Pioglitazone exposure variables

Pioglitazone exposure variable (T = time dependent)	**Description**
Current exposure (T)	Indicator of current pioglitazone use either used alone or as a combination. This variable is not in the statistical analysis but only used in the calculation of duration of exposure and time since last dose.
Ever vs. never use (T)	Taking the value 1 (ever) as soon as one prescription with pioglitazone has been purchased, and 0 (never) otherwise.
Duration of exposure (T)	Time-dependent cumulative sum of durations of previous pioglitazone exposure periods. The duration of exposure categories will be identical to those used in the KPNC final (10-year follow-up) analysis. A secondary analysis will use the duration of exposure category from the KPNC 3rd interim (5-year) analysis: Never, <12 months, 12-24 months, and more than 24 months.
Cumulative dose (T)	Time-dependent cumulative sum of drug consumption based on the daily dosage of pioglitazone containing prescriptions or dispensings

	since entry into the cohort. The cumulative dose categories will be identical to those used in the KPNC final (10-year follow-up) analysis. A secondary analysis will use the exposure category from the KPNC 3rd interim (5-year) analysis: Never, 1-10,500mg, 10,501-28,000mg, and more than 28,000mg.
Time since last dose (T)	Current time minus the time of the end of last current exposure to pioglitazone containing prescriptions since entry into the study cohort. Categorised into Current, <1 year, 1-2 years, 2-3 years, 3-4 years, 4+ years, Never†
† The category levels are preliminary, and will be based on the actual exposure distribution	

Further details about calculation of the exposure are given in Appendix 2.

7.3 Cohort matching variables

The following variables are used in constructing the country specific matched populations. Dataset specific definitions of the variables are given in **Appendix 4.**

Table 3: Matching variables

Variable (F= Fixed at cohort entry, T = time dependent)	**Description**
Propensity score variables	
Duration of treated diabetes mellitus at cohort entry (F)	Duration (years) of treated diabetes mellitus is approximated as the interval between the first diabetes therapy in the prescription records, and date of cohort entry.
History of diabetic complications at cohort entry (F)	History of any of the following (N/Y): • Diabetic retinopathy or maculopathy (N/Y) • Ketoacidosis (N/Y) • Diabetic coma (N/Y) • Diabetic lower limb severe complications (N/Y) • Diabetic renal complications (N/Y). Definitions of the individual variables are given in Appendix 3.
History of myocardial infarction or stroke at cohort entry (F)	Classified as (Y/N), for detailed definition see Appendix 3.
History of congestive heart failure at cohort entry (F)	Classified as (Y/N), for detailed definition see Appendix 3.
Year of cohort entry (F)	Calendar year of cohort entry

Duration of database membership before cohort entry (F)	Duration (years) of membership in medication database prior to cohort entry.
Number of different antidiabetic drug classes prior to cohort entry (F)	Score from 0 to 10 with one point from each of the following classes used prior to cohort entry: metformin, sulphonylureas, other TDZs, alphaglucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, meglitinides, amylin analogues, insulin, other. Combination products contribute separately to each drug class based on the active substances included in the product.
Other matching variables	
Use of other TDZs prior to cohort entry (F)	Use of other thiazolidinediones (other than pioglitazone) prior to cohort entry (N/Y)
Type of antidiabetic treatment prior to cohort entry (F)	Type of antidiabetic medication immediately prior to cohort entry classified as: • No pharmacotherapy • Metformin only • Sulphonylurea only • Metformin + sulphonylureas only • Insulin with or without other antidiabetic medications • Any other antidiabetic medications or combinations
Type of modification in baseline therapy (F)	Type of modification in baseline antidiabetic therapy at cohort entry classified as treatment switch or addition of new treatment to all prior treatment (if any existed). See Appendix 2.
Geographical area (F)	Living in geographical area for which cancer data are available (Y/N, used in the Netherlands only)

7.4 Other relevant covariates

Further details of the variable definitions for each dataset are given in Appendix 3 and Appendix 4.

Table 4: Other relevant covariates

Covariates (F = fixed at cohort entry, T = time dependent)	**Description**
Dataset identifier (F)	**Dataset membership categorized as: FIN, SWE, CPRD GOLD, CPRD GOLD HES, NL GP, NL Pharmacy-Hospital**

Gender (F)	M/F
Age (F)	Age at cohort entry
Cigarette smoking (F)	Cigarette smoking status at cohort entry. If not available before cohort entry the first available record after cohort entry is adopted. If no cigarette smoking data available, coded as 'unknown'. No smoking data is available in FIN & NL Pharmacy-Hospital datasets. Categorized into: Never, Ever (current or former), Unknown
Body Mass Index at cohort entry (F)	Classified as missing, <30, 30-34.9 and ≥ 35. Used in those datasets where information available, for detailed definition see Appendix 3. If not available at baseline, the first record within 12 months of cohort entry is adopted. If no BMI data is available, coded as 'missing'. No BMI data is available in FIN & NL Pharmacy-Hospital datasets.
HbA1C (F, T)	Classified as missing, <7.5%, 7.5-8.9%, ≥9.0%. Baseline HbA1C measurement will be most recent record within 6 months prior to cohort entry. Persons with no baseline HbA1C will be coded as 'missing'. HbA1C will also be measured as a time varying covariate, using the most recent HbA1C record at a point in time. No HbA1C data is available in FIN & NL Pharmacy-Hospital datasets
PSA elevated (T)	PSA elevated at any given time during the follow-up. Classified as Never vs. ever elevated; and Never elevated vs. Elevated vs. Not elevated. No PSA data in FIN, SWE & NL Pharmacy-Hospital datasets.
Number of PSA tests (T)	Cumulative number of PSA tests during the follow-up period.
Number of urine protein tests (T)	Cumulative number of urine protein tests during the follow-up period
History of diabetic complications (For details see Appendix 3)	
Diabetic retinopathy or maculopathy (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Ketoacidosis (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Diabetic coma (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.

Diabetic lower limb complications (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Diabetic Renal complications (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
History of relevant comorbidities (For details see Appendix 3)	
Other urinary tract cancers (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Other cancers, excluding urinary tract (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Myocardial infarction or stroke (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Peripheral vascular disease (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Congestive heart failure (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Chronic pulmonary obstructive disease (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
History of relevant medications (for details see Appendix 4)	
Statin use (T)	Prior use of statins or statin combinations Classified as never (0) or ever (1) use evaluated at any given time during the follow-up; Starting at 1 if prior use at cohort entry, 0 otherwise.
ARB use (T)	Prior use of angiotensin receptor blockers (ARB) Classified as never (0) or ever (1) use evaluated at any given time during the follow-up; Starting at 1 if prior use at cohort entry, 0 otherwise.
ACE use (T)	Prior use of angiotensin converting enzyme (ACE) inhibitors Classified as never (0) or ever (1) use evaluated at any given time during the follow-up; Starting at 1 if prior use at cohort entry, 0

	otherwise.
BPH drug use (T)	Prior use of drug for benign prostatic hypertrophy (BPH) Classified as never (0) or ever (1) use evaluated at any given time during the follow-up; Starting at 1 if prior use at cohort entry, 0 otherwise.
Use of other diabetic medications (T)	A separate variable for each of the following classes: metformin, sulphonylureas, other thiazolidinediones, alpha-glucosidase inhibitors, DPP-4 inhibitors, GLP-1 agonists, meglitinides, amylin analogues, insulins and other oral antidiabetic medications. Classified as never (0) or ever (1) use evaluated at any given time during the follow-up; Starting at 1 if prior use at cohort entry, 0 otherwise.
History of bladder comorbidities (For details see Appendix 3)	
Urinary incontinence (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Urinary tract infection (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Pyelonephritis (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Urolithiasis (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Hematuria (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Urinary Retention (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Neurogenic bladder (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at cohort entry, 0 otherwise.
Catheterization (T)	Classified as never (0) or ever (1) with the condition evaluated at any given time during the follow-up; Starting at 1 if condition exists at

	cohort entry, 0 otherwise.

8 CHANGES COMPARED TO STUDY PROTOCOL

The following changes to the exclusion criteria have been made compared to the study protocol version 2.0 dated 20th June 2013:

- "Diagnosis of secondary malignant neoplasm of bladder prior to cohort entry" has been added as a cohort entry exclusion criterion.
- "Diagnoses of neoplasms of uncertain or unknown behaviour of bladder prior to cohort entry" has been added as a cohort entry exclusion criterion.
- "Diagnoses of benign neoplasm of bladder prior to cohort entry" has been added as a cohort entry exclusion criterion.
- "History of cystectomy at cohort entry" has been added as a cohort entry exclusion criterion.
- "History of resection or removal of bladder tumour (benign or malignant)" at cohort entry has been added as a cohort entry exclusion criterion.
- "History of biopsy of bladder tumour or lesion a cohort entry" has been added as a cohort entry exclusion criterion.

The following changes to the censoring of follow-up criteria have been made compared to the study protocol version 2.0 dated 20th June 2013:

- "Diagnosis of secondary malignant neoplasm of bladder " has been added as a censoring criterion to the bladder cancer analysis.

The following changes in the study variables have been done compared to the study protocol version 2.0 dated 20th June 2013:

- "Diabetic lower limb severe complications" has been added (replaces the dropped variable "Peripheral neuropathy")
- "Diabetic renal complications" has been added (includes the dropped variables: "Chronic kidney disease" and "Diabetic nephropathy" and "Proteinuria (micro and macro)")
- "Other cancers" has been replaced with "Other urinary tract cancers" and "Other cancers, excluding urinary tract"
- "Other vascular diseases" has been dropped.

The following changes in the bladder cancer outcome definition have been done compared to the study protocol version 2.0 dated 20th June 2013:

- ICPC code U79 has been added for Neoplasm of uncertain or unknown behaviour of the bladder

9 DATA DEIDENTIFICATION

Prior to transferring the data to EPID Research, the following precautionary measures are taken by each country to ensure non-identifiably of study individuals in the pooled analysis.

- Patients are anonymised and assigned a dummy study identification number (SID)
- Dates of birth are coded at year level only
- For each individual the cohort entry time is taken as time zero
- All other event times are defined relatively to cohort entry time
- The actual cohort entry time is coded at year level only
- Country specific dataset will not include within country location information (e.g. address, postal code, municipality)
- Reporting of the results is done on aggregated level only, according to the study protocol

10 TRANSFER OF THE COUNTRY SPECIFIC DATASETS FOR POOLED ANALYSIS

The transfer of the datasets to EPID Research in Finland will be done in the following steps:

1. Each of the four participating centres will prepare country specific datasets according to the main study protocol and the country specific statistical analysis plan (Matched data sets). The datasets will be saved as tab-separated text files (.csv). A list of the study variables with operational definitions will be prepared by EPID Research and provided to each country before transferring the data.
2. The country specific post-matched datasets are transferred from each centre to EPID Research on a CD via courier mail as follows:
    a. The information on the CD must be encrypted and password protected.
    b. A separate document is prepared that includes the password for the CD.
    c. Each participating centre also prepares a document with the following summary statistics from the data on the CD
        - Total number of rows in the dataset
        - Number of patients per treatment group in the dataset
        - Descriptive statistics for each variable in the dataset
    d. The CD containing the data and the summary statistics document is delivered to EPID Research using courier mail.
    e. The password document is delivered to EPID Research by email.
3. After the receipt of the CD, the summary statistics, and the password EPID Research will transfer the country specific data into its computational environment and derive from the received dataset the following summary statistics
    - Total number of rows in the data set
    - Number of patients per treatment group
    - Descriptive statistics for each variable

and compare the results with the summary statistics document received from the centre. Any problems identified in the delivery process or data checking process are documented and addressed accordingly.

4. Steps 2-3 above are tested first with a random sample of data from each centre (about 10% of the final data). These steps are repeated until all possible problems have been corrected. Thereafter EPID Research requests the full country specific datasets following Steps 1-3.

5. Once EPID Research has received all country specific datasets, the data will be merged and the pooled analyses will be performed and reported according to this protocol.

11 DATA STORAGE

The datasets will only be used for the analysis outlined in the protocol. The datasets will be retained at EPID Research until the study report is finalized and the main results have been published. This is to ensure comments raised by the referees in the submission phase can be addressed in a timely fashion.

The country specific components of the datasets will be preserved by each country and in case new analyses of the pooled datasets is required a new request for the use of the data will be made according to the data source specific requirements.

12 DATA ANALYSIS

The pooled datasets will be analysed using the methods and approaches described here. The analyses are similar to those used in the analyses of the individual data sets. The Cox proportional hazards models will include a dataset identifier as a categorical covariate.

12.1 Pooled datasets

The following three pooled datasets will be constructed (see table 5 for an overview)

Primary pooled dataset

The primary pooled analysis will include the largest number of patients as possible with common variables from all datasets. This analysis will not include information on smoking, BMI, HbA1C and urinary/renal markers.

For FIN and SWE the hospital-based morbidity data sets will be utilized.

For UK the GP-based morbidity dataset CPRD GOLD will be used. When possible data will be complimented with data from the linked data set CPRD GOLD-HES.

For NL both the hospital-based morbidity dataset (Pharmacy-Hospital dataset) and the GP-based morbidity dataset (NL GP) will be used. In non-overlapping geographical areas either of the data sources is utilized. For overlapping geographical areas all information regarding diagnoses is utilized, but for exposure only community pharmacy records are utilized.

Second pooled dataset (sensitivity analysis)

The second pooled analysis will utilize the 4 hospital-based morbidity datasets only.

For FIN and SWE the hospital based morbidity datasets will be included. For NL the Pharmacy-Hospital dataset will be used, and for UK the CRPD GOLD-HES data set will be used.

This analysis will not include information on smoking, BMI, HbA1C and urinary/renal markers.

Third pooled dataset (sensitivity analysis)

The third pooled analysis will utilize datasets containing information on smoking, BMI, HbA1C and urinary/renal markers

For FIN no dataset is included.

For SWE the hospital-based morbidity dataset is complimented with data from the National Diabetes Register.

For UK the GP-based morbidity dataset CPRD GOLD will be used. When possible data will be complimented with data from the linked data set CPRD GOLD-HES.

For NL the GP-based morbidity dataset is used and when there is overlap with the Pharmacy- Hospital dataset, the two datasets will be combined with exposure measured in the community pharmacy records.

Table 5: Pooled datasets

Country	**Primary pooled analysis**	**Second pooled analysis**	**Third pooled analysis**
	Including data from as many patients, and the greatest number of sources for these patients. The limitation is that we will not include variables that are missing from some data sets (e.g. BMI)	Restricted to patients with hospital data available. The limitations are the reduction in sample size, and again only using the common variables	Restricted to patients with the extra variables (e.g. BMI) available, but using the maximum number of sources for these patients
UK	CPRD-GOLD-HES (linkage dataset) CPRD-GOLD (for unlinked practices / patients)	CPRD-GOLD-HES	CPRD-GOLD-HES (linkage dataset) CPRD-GOLD (for unlinked practices / patients)

NL	Pharmacy-Hospital dataset NL GP Where there is overlap, the two datasets will be combined with exposure measured in the community pharmacy records	Pharmacy-Hospital	NL GP Where there is overlap with the Pharmacy- Hospital dataset, the two datasets will be combined with exposure measured in the community pharmacy records
Sweden	Hospital based morbidity	Hospital based morbidity	Hospital based morbidity complimented with information from the National Diabetes
Finland	Hospital based morbidity	Hospital based morbidity	

12.2 Statistical hypothesis

With regard to the bladder cancer incidence the formal statistical hypothesis between any two treatment groups is as follows:

$$H_0 : HR = Incidence_{PioGroupX} / Incidence_{REF} = 1$$

against the alternative

$$H_1 : HR = Incidence_{PioGroupX} / Incidence_{REF} \neq 1$$

where

HR denotes the hazard ratio,

$Incidence_{PioGroupX}$ denotes the bladder cancer incidence rate in a specific group of pioglitazone exposure for example in the group of ever exposed to pioglitazone or in the group of <18 months of exposure to pioglitazone, and

$Incidence_{REF}$ denotes the bladder cancer incidence rate in the reference group of patients never exposed to pioglitazone.

12.3 Sample size

The estimated number of patients who were ever exposed and who were never exposed to pioglitazone and estimates number of bladder cancers expected during the follow-up are presented in the Table below for each dataset.

Power calculations for pooling all morbidity datasets for meta-analysis are presented for the comparison of ever vs. never exposed to pioglitazone.

In pooling of all datasets, the overlap between the UK CPRD GOLD-HES and UK CPRD GOLD dataset will be removed as discussed in section 11.1. In addition overlap of the NL datasets must be removed (~10%). Power calculations for the cohort study (1 to 10 matching) are presented. For individual datasets the data specific background rates and follow-up times given in table 2 and for pooled datasets the average values provided in Table 3 are applied.

For the cohort study the power is calculated for the effect sizes 1.2 – 2.0 on the relative risk scale. A two sided type 1 error rate of 5% is used. Calculations were carried out using the cpower function of the Hmisc package in the R-program (R Development Core Team 2008; Peterson et al. 1993; Lachin and Foulkes 1986; Schoenfeld 1983).

Table 6 Estimated number of patients exposed and unexposed to pioglitazone

	Finland	**Sweden**	**NL Pharmacy-Hospital***	**UK CPRD GOLD-HES subset**	**NL GP**	**UK CPRD GOLD (minus overlap with GOLD-HES dataset)**
Ever exposed to pioglitazone	4 021	4 067	10 680	17152	2 276	14 033
Never exposed to pioglitazone (10:1 matched)	40 210	40 670	106 800	17 1520	22 760	140 330
Mean follow-up time (years)	10.5	4	5.2	5.2	5.2	5.2
Total person years	464 426	178 948	610 896	981 094	130 187	802 688
Annual Incidence rate (Incidence / 100 000)	30.6	50.5	33.5	32.8	33.5	32.8
Cancer cases (total)	142	90	205	322	44	263

*** Approx. 10% overlap with NL GP**

Table 6 Power calculations with the pooled meta-analysis dataset

	Pooled dataset
Follow-up time[1] t (years)	5.5
Annual incidence rate[2] λ (Incidence/100 000)	33.7
Cumulative probability of developing bladder cancer[3] (%)	0.19
Power (%) **Cohort studies** RR=1.2 RR=1.3 RR=1.4 RR=1.5 RR=2.0	 **34.4** **58.0** **76.3** **87.8** **99.7**

12.4 Missing data

If a variable (for example smoking and BMI) is not available in an individual data set, which is included in the pooled data set, the missing variable is excluded from the analysis of that pooled database. If a variable is missing only for some patients in an individual data set, a missing data category is added and used in the analysis of the pooled data set.

12.5 Population summary

The characteristics of the post-matching pooled study population will be described with descriptive statistics at the entry into the study cohort. The following baseline variables will be included in the population summary: country, age, gender, year of entry, duration of treated diabetes mellitus, history of relevant diabetic medications, history of other relevant medications, history of diabetic complications, history of bladder comorbidities and history of other relevant comorbidities.

The population summary will be stratified according to pioglitazone exposure using ever vs. never exposure variable. Table templates are provided in appendix7.

12.6 Descriptive evaluation

Comparisons for the various pioglitazone exposure definitions will be performed. Crude bladder cancer incidence and mortality rates with 95% confidence intervals (CI) will be estimated for each pioglitazone exposure definition separately within the strata of gender, age, year of entry, duration of treated diabetes, history of relevant diabetic medications, history of relevant concomitant medications, history of diabetic complications, history of bladder comorbidities and history of other relevant comorbidities. Table templates are provided in appendix 7.

12.7 Formal evaluation

The hazard ratio (HR) estimates with 95% CIs for each pioglitazone exposure definition will be estimated using the conventional Cox's proportional hazards model with a counting process approach which enables the follow-up time of each patient to be split into several periods and thus allows adjustments for relevant baseline and time-dependent covariates in the model specification. Separate analyses of bladder cancer incidence, bladder cancer mortality and all-cause mortality will be performed.

In the matched cohort analysis three models will be used: i) the crude model with pioglitazone exposure as ever vs. never exposed included only, ii) the base model with age at cohort entry, sex and use of metformin, sulphonylureas, insulins or other antibiabetic drugs each classified as never vs. ever exposed added to the crude model, and iii) the adjusted model created by using the following forward and backward selection procedure:

1. Identify candidate covariates as those covariates with at least 5% prevalence in pioglitazone or reference group and with the p-value of the univariate association between the covariate and bladder cancer incidence <0.1.
2. Start with the base model
3. For each candidate covariate produce a new adjusted model with the candidate covariate one at a time added in the base model.
4. Consider each candidate covariate as a potential confounder if the relative change in the HR of pioglitazone exposure is at least a 10% relative when comparing to the base model. This process will generate a set of potential confounders.
5. Add all potential confounders simultaneously in the base model
6. Remove each potential confounder one at a time from the model and see if this results in a 10% relative change in the HR of pioglitazone exposure. If any potential confounder does not fulfil the 10% threshold, drop the one with the smallest relative change in HR. Repeat the process until no further changes are needed. This will be the adjusted model.

The covariates included in adjusted model will be used in the analysis of the effect of different pioglitazone exposure definitions (never/ever exposed; duration of exposure; cumulative dose; time since last dose) on bladder cancer incidence, all cause mortality and bladder cancer mortality as well as in the sensitivity analyses.

The crude, base and adjusted models will include as covariates the study cohort dataset identifier and all matching variables (Bland 1994, Stuart 2010). The propensity score (at start of follow-up) will be included as a categorical variable based on quintiles (5-quantiles). Especially, the Cox's proportional hazards models will not be stratified using the matching sets (Austin 2013). Table templates are provided in appendix 7.

12.8 Stratified analysis

The risk models will be presented stratified, if there are sufficient event, by the following baseline variables used in the matching or propensity score:

- Duration of treated diabetes
- Use of other TZDs (other than pioglitazone) prior to cohort entry
- History of Chronic Kidney disease or renal impairment
- History of diabetic renal complications

12.9 Sensitivity analysis and heterogeneity checks

As sensitivity analysis to the primary pooled analysis a meta-analysis of the country specific adjusted analysis will be performed (Viechtbauer, 2010). The meta-analysis will be done using the random effect model, where the assumption is that each datasets has it's own effect and the model provides a mean estimate of these. The random effect model provides information on the between study variability and sampling variability.

The hazard ratio estimates for the country specific analysis, the primary pooled analysis and the meta-analysis will be presented and compared using a forest plot (Blettner 1999).

For comparison and to control for heterogeneity that originates from the use of different covariates in the country specific models, the country specific analysis and the meta-analysis will be redone using the covariates chosen in the adjusted pooled analysis. The results will be presented using forest plots.

In addition to the forest plots the heterogeneity captured by the random effect models will be quantified using the I^2 statistic. The I^2 statistic estimates (in percentages) how much of the total variability in the effect size estimates (which is composed of heterogeneity and sampling variability) can be attributed to heterogeneity among the true effects.

13 COMMUNICATION OF STUDY RESULTS

The principal and co-investigators will write the study reports. The report is delivered to the Sponsor. Based on these results the principal and co-investigators will co-author scientific manuscript(s) of the results to be published. The publication strategy has been defined in the research agreement between the principal investigators and the Sponsor. The publications will include a large group of co-authors and each country can decide which contributors need to be included.

The study has been registered to the ENCePP's E-register with ENCePP Seal of Approval (http://encepp.eu/encepp/viewResource.htm?id=3627). The results will also be published on the same site. The criteria and process for sharing the analytical country specific datasets and meta-analysis dataset for third parties are described in Appendix 5. According to the ENCePP Code of Conduct, the principal investigator is responsible for publication of the results.

A summary of the main results of the study, whether positive or negative and including results from prematurely terminated studies, will always be made available to the public. An abstract of the study findings will be provided through the ENCePP E-register of studies within three months following the final study report. The principal investigator may ask the ENCePP Secretariat to delay the publication of this abstract for a limited period pending response to peer-review comments. The outcome of a study will always be presented in an objective and truthful manner providing a comprehensive and accurate

description of the findings. In no way shall the interpretation and presentation of the results be aimed towards any commercial, financial or personal interests.

The study Sponsor is entitled to view the final results and interpretations thereof prior to submission for publication and to comment in advance of submission as agreed in the research contract and without unjustifiably delaying the publication.

14 APPENDICES

- **Appendix 1. Antidiabetic medications** (version 1.0 dated 12 February 2014)
- **Appendix 2. Calculation of exposure** (version 1.0 dated 12 February 2014)
- **Appendix 3. Variable definitions** (version 1.0 dated 12 February 2014)
- **Appendix 4. Other medications** (version 1.0 dated 12 February 2014)
- **Appendix 5. Criteria and process for sharing the analytical country specific datasets and meta-analysis dataset for third parties** (version 1.0 dated 12 February 2014)
- **Appendix 6. List of planned analyses** (version 1.0 dated 12 February 2014)
- **Appendix 7. Table templates** (version 1.0 dated 12 February 2014)

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