



Pharmacoepidemiological Study Report

The risk of developing prostate cancer in entacapone and levodopa/DDCI users compared to levodopa/DDCI users without entacapone - A nation-wide retrospective register-based study

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1 Abbreviations, tables, and figures

1.1 List of abbreviations

The following abbreviations have been used in the following text.

ATC	Anatomical therapeutic chemical
BPH	Benign prostatic hypertrophy
CI	Confidence interval
COMT inhibitor	Catechol-O-methyl transferase inhibitor
DA	Dopamine agonist
DDCI	Dopa decarboxylase inhibitor
DDD	Defined daily dose
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
FCDR	Finnish Causes of Death Register
FCR	Finnish Cancer Register
FDA	The U.S. Food and Drug Administration
FPR	Finnish Prescription Register
FRM	Finnish Registry for Reimbursed Medications
HR	Hazard ratio
ICD-10	International classification of diseases, 10th revision
MAO-B	Monoamine oxidase B
OR	Odds ratio
PCA	Prostate cancer
PD	Parkinson's disease
PID	Personal identification number
SID	Study identification number
SII	Social Insurance Institute
SF	Statistics Finland
TNM classification	Classification for malignant tumors (T = size of the tumor, N = lymph nodes involved, M = distant metastasis)

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2 Executive summary

Background: A potential new safety signal for Stalevo was detected in the STRIDE-PD study: Prostate cancer (PCA) was reported in 9 and 2 males randomized to Stalevo (levodopa/carbidopa/entacapone) and Sinemet (levodopa/carbidopa), respectively. The U.S. Food & Drug Administration (FDA) is currently evaluating whether patients taking entacapone (Comtess/Comtan or Stalevo) for the treatment of Parkinson's disease are at an increased risk of PCA. Evaluation of a rare event such as PCA in a clinical trial setting in Parkinson's disease (PD) would not be feasible as prolonged follow-up would be required in order to have a sufficient number of cancer cases for a reliable comparison between various treatments used in PD. Use of population-wide health care registers provides an alternative approach. This retrospective study was designed to investigate the possible increased risk of PCA with entacapone use by linkage of the nation-wide health care registers in Finland.

Design: The study was conducted as a nation-wide retrospective register-based cohort study with an embedded nested case-control study. Information on purchased PD treatment prescriptions, notifications of new PCA cases and deaths from the Finnish health care databases during the follow-up period 1998-2009 were collected. The study cohort included all male patients entitled to special reimbursement for PD and who had purchased at least one prescription of levodopa/dopa decarboxylase inhibitor (DDCI), dopamine agonist (DA) or monoamine oxidase B (MAO-B) inhibitor within 180 days prior to start of follow-up. Patients with prior cancer history were excluded.

Primary objectives: The primary objectives of the study were to compare the PCA incidence rates between patients on levodopa/DDCI with entacapone +/- dopamine agonists (DA) and/or monoamine oxidase B (MAO-B) inhibitors (group 1) and patients on levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitors (group 2).

Definition of exposure: PD prescriptions were converted into continuous drug use periods by means of the defined daily doses (DDD) contained in each prescription. The length of each prescription was defined as DDD plus an additional exposure extension period of 30 days and subsequently current exposure and cumulative exposure to each treatment was calculated. The following categories were used for the cumulative exposure: non-use, short-term use (< 180 days), intermediate-term use (180-360 days) and long-term use (> 360 days).

Outcome measures: The outcome variables used in survival analysis were defined as the time from the start of follow-up to the first PCA detected and death caused by PCA.

Statistical analysis: The hazard ratio (HR) estimates with 95% confidence intervals (CI) were estimated using Cox's proportional hazards model with adjustments for relevant baseline and time-dependent variables. The robustness of the findings was evaluated in sensitivity analyses.

Results: The study population comprised 11 396 male Parkinson's disease patients. A total of 359 PCA cases occurred during a mean follow-up time of 4.6 years and 89 PCA deaths during a mean follow-up time of 4.7 years. Current exposure to levodopa/DDCI with add-on entacapone (group 1) was not associated with an increased risk of PCA (HR=1.046, 95% CI 0.761-1.437, p-value 0.782) or PCA death (HR=0.927, 95% CI 0.434-1.981, p-value 0.846) when compared to exposure to levodopa/DDCI without add-on entacapone (group 2). Similarly, the longer cumulative exposure to entacapone was not associated with an increased risk of PCA or PCA death. The HR estimates with the long cumulative exposure were 0.815 (95% CI 0.562-1.182, p-value 0.281) for PCA incidence and 1.271 (95% CI 0.595-2.716, p-value 0.535) for PCA mortality, respectively. For details see the EXECUTIVE SUMMARY TABLE.

Conclusions: Current exposure to treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) was not associated with increased prostate cancer risk or an increased prostate cancer mortality risk when compared to current treatment with levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2). Cumulative exposure to entacapone during the follow-up was not

associated with increased prostate cancer risk or increased prostate cancer mortality. In various sensitivity analyses the results remained virtually unchanged.

EXECUTIVE SUMMARY TABLE. Summary of the results for PCA incidence and PCA mortality - Complete follow-up period analysis where all continuous drug use periods are used from each patient						
Outcome :	Prostate cancer incidence			Prostate cancer mortality		
Exposure comparison	Events Rate per 1000 years	Hazard Ratio (95% CI)	P-value	Events Rate per 1000 years	Hazard Ratio (95% CI)	P-value
Current exposure to add-on treatment group						
Group 1	78 6.69	1.046 (0.761 – 1.437)	0.782	11 0.91	0.927 (0.434 – 1.981)	0.846
Group 2	205 7.39	Reference	-	41 1.45	Reference	-
Cumulative exposure to entacapone						
No	252 7.35	Reference	-	65 1.86	Reference	-
Short	20 4.56	0.625 (0.379 – 1.031)	0.066	6 1.34	1.220 (0.492 – 3.026)	0.668
Intermediate	28 6.10	0.792 (0.509 – 1.232)	0.301	6 1.27	1.275 (0.503 – 3.235)	0.609
Long	59 6.76	0.815 (0.562 – 1.182)	0.281	12 1.32	1.271 (0.595 – 2.716)	0.535
Data 10 May, 2012 Group 1 – Treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor Group 2 – Treatment with levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor Cumulative exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days)						

3 Background

3.1 Rationale

Entacapone is a selective and reversible, peripherally-acting catechol-*O*-methyltransferase (COMT) inhibitor, which is always administered as an adjuvant to levodopa/dopa decarboxylase inhibitor (DDCI). Entacapone is indicated in the treatment of idiopathic Parkinson's disease (PD) patients experiencing the signs and symptoms of end-of-dose wearing-off. Levodopa/DDCI is indicated in early PD and entacapone is started only when levodopa/DDCI does not offer sufficient symptom control in wearing-off patients. In other words, entacapone is second-line treatment to levodopa/DDCI. The most common adverse reactions of entacapone include e.g., dyskinesia, nausea, diarrhea, and benign urine discoloration that is due to entacapone's chemical structure (PSG 1997; Rinne et al. 1998). Entacapone is available as a separate tablet (Comtess[®]/Comtan[®]) or in combination tablet with levodopa/carbidopa (Stalevo[®]).

Entacapone has also been studied in early PD without motor complications (such as dyskinesia and wearing-off symptoms). The STRIDE-PD study was a randomized, double-blind study comparing levodopa/carbidopa/entacapone (Stalevo[®]) and levodopa/carbidopa (Sinemet[®]) in PD patients requiring initiation of levodopa. The mean age of the study subjects was approximately 60 years and 58% of the subjects were already on dopamine agonists at the time of randomization. Approximately 65% and 60% of the study population were males in Stalevo and Sinemet arms, respectively in STRIDE-PD. Follow-up lasted up to 4 years; the mean being approximately 2.5 years. The primary end-point (time to development of dyskinesia) failed and the study demonstrated that Stalevo did not offer clinically significant advantages over Sinemet in early PD. In terms of tolerability and safety, a potential new safety signal for Stalevo was detected in the STRIDE-PD study. Prostate cancer (PCA) was reported in 9 and 2 males randomized to Stalevo and Sinemet, respectively (Stocchi et al. 2010).

The U.S. Food and Drug Administration (FDA) is currently evaluating whether patients taking entacapone (Comtess/Comtan or Stalevo) for the treatment of Parkinson's disease are at an increased risk for developing PCA. Evaluation of a rare event such as PCA in a clinical trial setting in PD would not be feasible because of the prolonged follow-up which would be needed in order to have a sufficient number of cancer cases for a reliable comparison between various treatments used in PD. Population-wide health care registers with patient level linkage can be used for such a purpose.

The present retrospective study was designed to investigate whether there is an increased risk of PCA with entacapone use by linkage of the nation-wide health care registers in Finland. The current treatment guidelines of PD are very similar in the US and in Europe including Finland. These guidelines generally recommend starting PD pharmacotherapy with either a dopamine agonist (DA) or a monoamine oxidase B (MAO-B) inhibitor. Levodopa/DDCI is recommended to be started only after treatment with DA or MAO-B inhibitor is shown to no longer provide satisfactory benefit. The primary comparisons in the current study were performed between current use of levodopa/DDCI with entacapone and current use of levodopa/DDCI without entacapone with possibly concurrent treatment with DA and/or MAO-B inhibitor because this approach reflects most realistically current PD treatment practices as well as representing the patient population in the STRIDE-PD study, from which the safety signal for prostate cancer originated. This kind of comparison also provides a larger patient pool and thus more statistical power for the evaluation of prostate cancer risk associated with entacapone.

3.2 Study hypothesis

The purpose of the study was to evaluate whether treatment with entacapone as add-on to levodopa/DDCI increases the risk of developing prostate cancer when compared to levodopa/DDCI without entacapone among male PD patients in Finland.

4 Treatment comparison groups

Following time dependent treatment groups were used in the main analysis of the study:

- **Group 1:** Treatment with levodopa/DDCI **with** entacapone +/- DA and/or MAO-B inhibitor, and
- **Group 2:** Treatment with levodopa /DDCI **without** entacapone +/- DA and/or MAO-B inhibitor.

Due to the definition of exposure it was possible that at any given time a patient did not belong to group 1 nor group 2 in which case the patient was allocated to group 5 (i.e., not group 1 and not group 2).

In addition, following additional treatment groups were used in the exploratory analysis

- **Group 3:** Treatment with add-on entacapone to levodopa/DDCI without other add-on treatments. Note that with this definition, current or prior use of DA and/or MAO-B inhibitors is not allowed.
- **Group 4:** Treatment with add-on DA and/or MAO-B inhibitor to levodopa/DDCI, or add-on levodopa/DDCI to DA and/or MAO-B inhibitor. Note that with this definition, current or prior use of entacapone is not allowed.

5 Study objectives

5.1 Primary objective

The primary objective of this study was:

- to compare the incidence rates of developing prostate cancer between group 1 and group 2 by using the current exposure to each of the treatment group as the definition for exposure.

5.2 Secondary objectives

The secondary objectives of this study were:

- to compare the incidence rates of developing prostate cancer between group 1 and group 2 by using the time-varying cumulative exposure to each of the treatment group as the definition for exposure, and
- to compare the prostate cancer mortality rates between group 1 and group 2 by using the current and the time-varying cumulative exposure to each of the treatment group as the definition for exposure.

5.3 Exploratory objectives

The exploratory objectives of this study were:

- to compare the incidence rates of developing prostate cancer between treatment group 3 and treatment group 4 by using the current and time-varying cumulative exposure to each of the treatment groups as the definition for exposure, and
- to compare the prostate cancer mortality rates between treatment group 3 and treatment group 4 by using the current and the time-varying cumulative exposure to each of the treatment group as the definition for exposure.

5.4 Analysis of study objectives

The above primary and secondary objectives were evaluated by two different analysis strategies:

- the primary analysis by using all continuous drug use periods from each patient, and
- the secondary analysis by using the first continuous add-on drug use period from each patient.

The primary analysis strategy is referred to as the "complete follow-up period analysis" and the secondary analysis strategy as the "first drug use period analysis".

The exploratory objectives are evaluated only in the secondary analysis by using the first continuous add-on drug use period from each patient.

6 Material and methods

6.1 Study population

The broad study population included all males in Finland who have purchased at least one prescription of any Parkinson's disease medication (Anatomical Therapeutic Chemical (ATC) codes N04BA03, N04BX02, N04BA02, N04BD and N04BC), including entacapone, levodopa/DDCI, monoamine oxidase B (MAO-B) inhibitors, and dopamine agonists (DA) during 1998 – 2009.

Inclusion criteria

The following inclusion criteria were applied to the broad study population for the definition of the study population:

- subjects who were entitled to special reimbursement for Parkinson's disease according to the Register of Reimbursement Medications (special refund category 110 for all PD drugs excluding rasagiline and 193 for rasagiline in PD), and
- subjects who had at least one prescription of levodopa/DDCI or DA or MAO-B inhibitor within 180 days prior to index date. (Note: For all valid index dates the 180 day criteria is fulfilled by default.)

Exclusion criteria

The following exclusion criteria were applied to the broad study population for the definition of the study population:

- subjects with International Classification of Diseases (ICD-10) diagnosis codes G23 (other degenerative diseases of basal ganglia), G24.1 (idiopathic familial dystonia), G24.8 (other dystonia), and G90.3 (multi-system degeneration) in the special refund category 110 when information on these ICD-10 codes was available, and
- subjects with any cancer diagnoses before index date as indicated by data from the Finnish Cancer Registry (FCR).

Nested case-control study

A nested case-control study design was used as the sensitivity analysis for the evaluation of the association between the treatment groups of interest and the risk of developing prostate cancer. For each incident prostate cancer case within the study population of the cohort study, 4-5 individually matched male PD controls were randomly selected using the following criteria when comparing with the respective prostate cancer case:

- the control was alive and at risk for developing prostate cancer at the time of the prostate cancer diagnosis of the cancer case,
- age within ± 3 years at the time of the prostate cancer case,
- duration of earlier levodopa/DDCI treatment within ± 6 months at the time of the prostate cancer diagnosis of the cancer case.

Note: The nested case control analysis was not performed for prostate cancer mortality due to the limited number of deaths in the register.

6.2 Exposure variables

Continuous drug use periods were constructed according to the principles presented by Nielsen et al. (Nielsen et al. 2008 and 2009). Drug use periods create time-varying exposure to various treatments meaning that the exposure to any particular treatment group can change during the follow-up period. Based on the defined daily dose (DDD) information each prescription was modified into a drug use period in a prospective manner by defining the length of the prescription as the DDD plus an additional exposure extension period of 30 days. This extension period was included to avoid unnecessary breaks between consecutive prescriptions. The resulting consecutive overlapping drug use periods were combined to form a continuous drug use period. The effect of the length of the exposure extension period was further evaluated in the sensitivity analysis.

Based on the continuous drug use periods the following exposure variables were calculated for each of the treatment groups of interest at any given time during the follow-up:

- Current exposure indicating whether the patient was in the treatment group at the current time point.
- Time-varying cumulative exposure indicating how long the patient has been in the treatment group at the current time point. The following categories were used for the cumulative exposure: non-use, short-term use, intermediate-term use and long-term use. Cut-off points were defined based on the distribution of the duration of drug use data from the cohort analyzed.
- Exposure history indicating whether the patient has been in the treatment group earlier during the follow-up period. The following categories were used for the exposure history: recent exposure within 6 months, exposure over 6 months ago and no previous exposure.

The current exposure was used for the evaluation of the primary objectives. In addition, the time-varying cumulative exposure was used for the evaluation of the secondary objectives. Exposure history was used as an adjustment variable in the statistical models as appropriate.

6.3 Outcome measures

The following outcome variables were used as end-point events in the survival analysis:

- time from the start of follow-up (index date) to the first prostate cancer detected, and
- time from the start of follow-up (index date) to death caused by prostate cancer.

6.4 Follow-up period

The **index date (i.e., the start of follow-up)** is defined as follows. The first date of a new prescription of

- entacapone or another add-on therapy to levodopa/DDCI, or
- add-on levodopa/DDCI to DA or add-on levodopa/DDCI to MAO-B inhibitor or add-on levodopa/DDCI to the combination of DA and MAO-B inhibitor during 1998-2009.
- For individuals with only levodopa/DDCI purchases the index date is the date of the first purchase + 180 days.

The following additional clarifying criteria were used in the definition of a valid index date:

1. The purchase had to occur within 180 days of the previous purchase to be considered an add-on therapy.
2. Multiple purchases during the same day were considered valid add-on treatments.

3. A purchase of Stalevo (levodopa/DDCI + entacapone) was considered as valid add-on.
4. For individuals with only levodopa/DDCI purchases, the first purchase could have been in 1997 as long as the index date was within year 1998-2009.
5. Individuals with no levodopa/DDCI purchases had no index date.

Regarding **prostate cancer incidence** the follow-up started in the complete follow-up period analysis from the index date and ended at date of first cancer diagnosis, death or end of study period (31-12-2009), whichever came first. In the first drug use period analysis the follow-up started from the index date and ended at date of first cancer diagnosis, death, end of the first continuous add-on drug use period or end of study period (31-12-2009), whichever came first. **Note:** Censoring was changed from “**date of prostate cancer**” to “**date of first cancer**” which is in line with the exclusion criteria.

Regarding **prostate cancer mortality** the follow-up started in the complete follow-up period analysis from the index date and ended at date of death or end of study period (31-12-2009), whichever came first. In the first drug used period analysis the follow-up started from the index date and ended at date of death, end of the first continuous add-on drug use period or end of study period (31-12-2009), whichever came first.

6.5 Background variables

The following baseline explanatory variables were treated as fixed, i.e., their values did not change during follow-up period:

- age at the index date (5 year age groups),
- time since PD diagnosis at the index date which was approximated using the prescription and special reimbursement data available after 1994 and categories defined as (0-1] years, (1-2] years, (2-5] years, (5-10] years, and over 10 years,
- PD treatments used before the index date defined as prior DA use (yes/no), prior MAO-B inhibitor use (yes/no), prior levodopa use (yes/no), and prior entacapone use (yes/no),
- use of benign prostatic hyperthrophy (BPH) treatment (G04C) before the index date (yes/no), and
- hospital district where the first PD prescription during the follow-up was purchased was used as region indicator at index date.

The following explanatory variables were treated as time dependent variables:

- current age using 5 year age groups,
- recent use of BPH treatment (including finasteride) during the follow-up period classified as no previous use, use within the previous 6 months, and use over 6 months ago,
- duration of earlier levodopa/DDCI treatment classified as non-use, short-term use (< 180 days), intermediate-term use (180 – 360 days), and long-term use (>360 days), and
- recent change in PD add-on treatments during the follow-up period classified as no change within the previous 6 months, DA added within the previous 6 months, MAO-B inhibitor added within the previous 6 months, entacapone added within the previous 6 months or levodopa/DDCI started within the previous 6 months.

The above baseline and time-dependent variables were considered as potential confounders in the statistical analyses.

6.6 Data sources and data requests

6.6.1 Prescription register and registry for reimbursed medication

The Finnish Prescription Register (FPR) contains information on all medications purchased provided that their cost exceeds the threshold for basic reimbursement that applies to all prescribed medications. The Finnish Registry for Reimbursed Medications (FRM) identifies patients who are receiving reimbursement based on certain specific diseases like Parkinson's disease. These registries are held by the Social Insurance Institution (SII). The prescription data in the FPR includes the generic name of the drug, the Anatomical Therapeutic Chemical (ATC) classification system code, the brand name, the formulation and package, the amount in defined daily doses (DDD), the date of purchase, the prescribing practice (primary vs. secondary health care), and the prescribing physician's area of specialization.

Due to the threshold for basic reimbursement the prescription register may not have complete information for very inexpensive medicines. However, patients with PD are all eligible for reimbursement (special refund category 110) and thus the prescription databases contain reliable and up to date information on the use of PD treatments enabling the identification of the study population. It should also be noted that prescription databases do not include data on drugs used in hospitals or nursing homes, neither drugs bought over-the-counter. This may have caused some underestimation of the underlying exposure.

Data on purchased prescriptions for the following PD treatments and BPH treatments were obtained from the FPR (with the ATC codes in the parenthesis):

- entacapone (N04BA03 Stalevo and N04BX02 for Comtess),
- levodopa/DDC inhibitors (N04BA02),
- MAO-B inhibitors (N04BD),
- dopamine agonists (N04BC), and
- drugs used in benign prostatic hyperthrophy (G04C).

Information on patients receiving special reimbursement for Parkinson's disease was obtained from the FRM for the special refund category 110 for all PD drugs excluding rasagiline and for the category 193 for rasagiline in PD. Category 110 includes the ICD-10 code G20 for Parkinson's disease and codes G23 for other degenerative diseases of basal ganglia, G24.1 for idiopathic familial dystonia, G24.8 for other dystonia, and G90.3 for multi-system degeneration. Apart from patients with PD (G20), all patients with other ICD-10 diagnosis codes listed above were excluded. This was possible because special reimbursement applications written by the treating physicians require the ICD-10 code.

Data on purchased prescriptions and special reimbursements were requested from the study period 1998 – 2009 and also from the time 1994 – 1997 before the study period in order to obtain treatment history information.

6.6.2 Cancer register

The Finnish Cancer Register (FCR) covers the whole of Finland. It collects data on all cancer cases and the collected information includes the primary site of the tumor, time of diagnosis, malignancy, and histology. The informants submitting data on cancer patients to the registry include all hospitals, physicians, pathological, cytological and haematological laboratories, and dentists. Data are also obtained through death certificates from Statistics Finland. The coverage, accuracy and reporting delay of the register data are considered good for scientific research (Teppo et al. 1994; Korhonen et al. 2002). For example, for prostate cancer the primary site is correct in 96.8% of the cases (Korhonen et al. 2002).

The following data regarding prostate cancers during the study period 1998 – 2009 were obtained from the FCR:

- the primary site and date of diagnosis,
- tumor staging: localised, regional metastases, or distant metastases,
- malignancy,
- histology and cell type,
- TNM classification (TNM is available in about one third of the cancer cases), and
- time and cause of death.

Data on other cancers prior to the study period and during 1998 – 2009 at the FCR was also obtained in order to exclude patients with earlier cancer history from the study population.

6.6.3 Causes of death register

The Finnish Causes of Death Register (FCDR), maintained by the Statistics Finland (SF), provides data on dates and causes of death and also stores death certificates. A large validation study came to the conclusion that none of the personal identification codes in the FCDR was incomplete (Pajunen et al. 2005). The register includes the personal identification number of each deceased person, sex, age, place of residence and principal, underlying and contributory causes of death and the date of death. The routine validation of death certificates means that the accuracy of the registers is good by international standards (Lahti and Penttilä 2001).

Data on deaths includes the causes of death along with the date of death.

6.7 Construction of study database

The data between 1998 and 2009 for the study population were extracted from the registers. The extraction process was as follows. First, data from SII were extracted to define the broad study population and a unique dummy study identification number (SID) was created for each personal identification number (PID). The list with the PID-SID pairs was provided by SII to the other register holders. Subsequently, each register holder extracted the relevant data according to the study protocol by linking the data to the PID-SID list and de-coded the data by destroying the key between the PID and SID permanently. Finally, each register holder provided the de-identified study data to EPID Research. Thus, only de-identified data was provided to EPID Research for performing the analysis of the study data.

6.8 Statistical methods

6.8.1 Descriptive analyses

Crude prostate cancer incidence rates and prostate cancer mortality rates with 95% confidence intervals (CI) were estimated within each treatment group. The estimates were stratified by the above baseline variables and in addition by initial treatment for PD at index date (DA yes/no, MAO-B inhibitor yes/no, levodopa yes/no, entacapone yes/no). Stratification by the following time-dependent variables was also performed: by recent use of BPH medication (no previous use, use over 6 months ago, use within previous 6 months) and by duration of earlier levodopa/DDCI treatment (non-use, short-term use, intermediate-term use, and long-term use).

6.8.2 Conventional Cox's proportional hazards model

Adjusted hazard ratio (HR) estimates with 95% CIs were estimated using Cox's proportional hazards model with a counting process approach (Andersen and Gill 1982) for prostate cancer incidence and prostate cancer mortality. Adjustments were made for the following baseline variables and time-dependent variables in the analyses:

- current age using 5 year age groups,
- time since PD diagnosis at the index date,
- prior DA use (yes/no) and prior MAO-B inhibitor use (yes/no) at the index date,

- prior BPH treatment use (yes/no) at the index date,
- hospital district at index date (used as strata in the model).
- recent use of BPH treatment (no previous use, use within the previous 6 months, and use over 6 months ago),
- duration of earlier levodopa/DDCI treatment (non-use, short-term use (< 180 days), intermediate-term use (180 – 360 days), and long-term use (>360 days), and
- recent change in PD add-on treatments during the follow-up period classified as no change within the previous 6 months, DA added within the previous 6 months, MAO-B inhibitor added within the previous 6 months, entacapone added within the previous 6 months or levodopa/DDCI started within the previous 6 months.

6.8.3 Sensitivity analysis

To evaluate the robustness of the results the association between the treatment groups of interest with the risk of developing prostate cancer was further analysed using several sensitivity analyses.

First, the effect of the length of the exposure extension period (i.e., 30, 60 or 90 days) on the prostate cancer risk (group 1 vs group 2) was investigated using the complete follow-up period analysis strategy.

Second, alternative strategies for the exposure definition were employed with the complete follow-up period analysis strategy. These included the comparison of the prostate cancer risk

- between the current treatment on entacapone vs. not on entacapone,
- between group 1 and group 2 where treatment periods with entacapone but without levodopa/DDCI were allocated to group 5 (i.e. not group 1 or group 2), and
- between group 1 and group 2 where those treatment periods which start in group 5 (i.e. not group 1 or group 2) at the index date were censored.

Third, the set and definitions of the time-dependent covariates included in the model were modified in the analysis the prostate cancer risk (group 1 vs group 2) using the complete follow-up period analysis strategy. The models employed included

- a model where the recent add-on indicator variables for levodopa/DDCI, DA and MAO-B inhibitor use were removed from the model and cumulative exposure to DA and MAO-B inhibitor were added in the model,
- a model where the recent add-on indicator variables for levodopa/DDCI, DA and MAO-B inhibitor use were removed from the model and current exposure (yes/no) to DA and MAO-B inhibitor were added in the model,
- a model where variables prior BPH treatment use and recent BPH treatment use were replaced by prior use of finasteride and time since last finasteride purchase, and
- a model where prior and recent BPH use were combined into a single time-dependent covariate.

Fourth, a marginal structural models (Hernán et al. 2000) approach was used to estimate the probability of receiving entacapone on the index date conditionally on age, time since diagnose, cumulative exposure to levodopa/DDCI, cumulative exposure to DA, cumulative exposure to MAO-B inhibitor, and prior use of BPH medication. In the analysis the prostate cancer risk (group 1 vs group 2) using the complete follow-up period analysis strategy patients were then assigned a weight as the inverse of this probability, thus correcting for confounding due to differences at time of index date between those who received entacapone and who did not receive entacapone.

Fifth, the association between the treatment groups of interest with the risk of developing prostate cancer was analysed from the nested case-control study. For each prostate cancer case 5 randomly chosen controls were selected according to the criteria given in section 6.1. In one case a patient was assigned the same control twice, otherwise all cases were assigned with 5 different controls. The current exposure to

the group 1 or group 2 at the time of the prostate cancer diagnosis was used as the exposure variable. The adjusted odds-ratios (OR) with 95% CIs were calculated using the conditional logistic regression modelling with adjustments for relevant baseline variables, exposure history and other time dependent variables.

The results of the sensitivity analyses are presented in section 8.9.

6.9 Ethical considerations

The study was conducted as specified in the protocol. All revisions to the protocol were properly documented as protocol amendments and such protocol amendments were delivered to register holder(s) whenever amendment(s) to the data permissions were required.

The study protocol was written by following the the Code of Conduct by the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) that provides a set of rules and principles for post-authorization studies with regard to the best practices and transparency, thereby promoting scientific independence of such studies (ENCePP Code of Conduct, 2011). The ENCePP is a project led by the European Medicines Agency to further strengthen the post-authorization monitoring of medicinal products in Europe by facilitating the conduct of multi-centre, independent, post-authorization studies focusing on safety and on benefit – risk evaluation. The parties involved in this study committed to adhere to the rules of the ENCePP Code of Conduct in their entirety. The study was registered to the ENCePP's E-register of studies and the results will also be published on the same site. The study protocol also followed the recent draft Guidance for Industry and FDA Staff "Best Practices for Conducting and Reporting Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets" (FDA, February 2011).

6.10 Study organization and timelines

EPID Research Oy carried out the study and had full access to the de-identified data. Orion Corporation Orion Pharma funded the study and had access to the study report, but not to the original data.

As this was a fully register-based study, patients were not contacted in any way in any phase of the study. All patient data was anonymous ensuring data protection. All data analysis and reporting was carried out according to the research protocol and amendments. The timelines related to the various steps within the study conduct are given in Table 1.

Table 1 Timelines of the study

Action	Date	Note
Contract signed	21.2.2011	
Study protocol Version 5.0 dated May 4 2011 approved	4.5.2011	EPID Research and Sponsor approvals First protocol submitted to the FDA
Ethics committee approval	14.6.2011	Ethical Review Board of HUS District Reference: 148/13/03/00/2011
Data permits	Causes of death data 19.5.2011	Reference: TK-53-617-11
	Cancer data 27.6.2011	Reference: THL/769/5.05.00/2011
	Prescription data 14.9.2011	Reference: Kela 32/522/2011
Data received	Prescription data 1.12.2011	
	Causes of death data 7.12.2011	
	Cancer data 13.12.2011	
Amendment 1	19.4.2012	EPID Research and Sponsor approvals Revised protocol dated FEB 8, 2012 submitted to the FDA
FDA additional analysis request	24.10.2012	
Study protocol Version 6.0 dated Feb 8 2012 approved	11.6.2013	EPID Research and Sponsor approvals after FDA had approved the protocol on 10 May 2013
Statistical analysis plan approved	10.5.2012	EPID Research internal approval
ENCePP registration	29.5.2012	http://www.encepp.eu/encepp/viewResource.htm?id=2279
Ethics committee approval of Amendment 1	19.6.2012	Ethical Review Board of HUS District Reference: 148/13/03/00/2011
Full study report	25.6.2013	EPID Research and Sponsor approvals

7 Changes to the original study protocol

7.1 List of amendments to the original study protocol

The following amendments have been done to the original Pharmacoepidemiological Study Protocol ER11-9411 (version 5.0, dated May 4th, 2011) based on the comments and request for information received on Oct 20, Nov 14 and Dec 2, 2011 from the US Food and Drug Administration (FDA) and the subsequent responses on Nov 7 and Dec 14, 2011 to the FDA.

Amendment 1 (dated April 19, 2012)

- **Description:** The primary treatment comparison groups were changed as follows to group 1: treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor, and group 2: treatment with levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor.
- **Reason for change:** The FDA was concerned about the power for the comparison between the earlier group 1 (treatment with add-on entacapone to levodopa/DDCI) and group 2 (treatment with add-on dopamine agonists (DA) and/or add-on monoamine oxidase B (MAO-B) inhibitor to levodopa/DDCI, or add-on levodopa/DDCI to DA monotherapy) definitions. The power calculations of the protocol were originally made for the comparison of treatment with entacapone against treatment without entacapone treatment. It was discussed with the FDA that these groups would be used as the primary treatment comparison groups because they reflect better the current real-life PD treatment practices and also provide a larger patient pool and higher power for the evaluation of prostate cancer risk associated with entacapone.

Study protocol Version 6.0 (dated Feb 08, 2012)

- **Description:** Amended protocol written based on Amendment 1.

7.2 Changes from the planned analysis

Statistical analysis of the time-varying cumulative exposure within the treatment group 1 was only performed for the complete follow-up period analysis of prostate cancer incidence and prostate cancer mortality. This analysis was not performed for the first drug use period analyses using the first continuous add-on drug use period from each patient. The time-varying cumulative exposure to each treatment (i.e., levodopa/DDCI, DA, MAO-B inhibitor or entacapone) separately was used throughout in the statistical analysis because it provides more natural interpretation of the cumulative exposure.

In the secondary analysis of the primary and secondary objectives, the statistical analysis of prostate cancer mortality was not performed for the time-varying cumulative exposure because of low number of prostate cancer deaths.

All BPH treatments were considered as a group in the statistical analyses. This group included also finasteride. A further sensitivity analysis was performed where finasteride was used instead of all PHB treatments.

The analysis of exploratory objectives was performed only using the first drug use period analysis. Statistical analysis was not performed for the time-varying cumulative exposure to each of the treatment group as the definition for exposure because in many cases the number of events was low.

Regarding the prostate cancer incidence the definition of censoring has been changed from “date of prostate cancer” to “date of first cancer”.

The sensitivity analysis with the nested case control design was not performed for prostate cancer deaths because of small number events.

7.3 Additional analyses

The following additional analyses were performed in response to the recommendations stated in FDA letter received 24 October 2012 regarding the Postmarketing Requirements (PMRs) for entacapone and new safety signals of prostate cancer and myocardial infarction detected from the STRIDE-PD trial.

The additional analyses are described below and referred as analysis #01 – analysis #09. The results of these additional analyses are reported as a separate section of the study report (see section 8.11).

Analysis #01

FDA requested additional analyses on prostate cancer incidence and prostate cancer mortality using the following group definitions:

- group 1*: patients treated with levodopa/DDCI (with or without prior exposure to DA and/or MAO-B inhibitor) who receive new add-on entacapone, against
- group 2*: patients treated with levodopa/DDCI with new add-on DA and/or MAO-B inhibitor (without prior exposure to entacapone or to DA and/or MAO-B inhibitor).

These group definitions require that patients have been treated previously with levodopa/DDCI before they receive add-on entacapone (group 1*) or add-on DA and/or MAO-B inhibitor (group 2*), respectively. Patients in group 1* may have been exposed to DA and/or MAO-B inhibitor earlier before they start add-on entacapone. In group 2* prior exposure to entacapone or to DA and/or MAO-B inhibitor is not allowed. In the analysis the first continuous drug use period is used and the follow-up time is censored as soon as patients switch to any treatment which is not compatible with these group definitions.

Analysis #02

FDA requested additional analyses on prostate cancer incidence and prostate cancer mortality with the following group definitions:

- group 1**: patients treated with levodopa/DDCI with a new add-on entacapone (without prior exposure to entacapone, DA or MAO-B inhibitor), against
- group 2**: patients treated with levodopa/DDCI with a new add-on DA and/or MAO-B inhibitor (without prior exposure to entacapone, DA or MAO-B inhibitor).

These group definitions are otherwise the same as in analysis #01 but in group 1** prior exposure to entacapone, DA or MAO-B inhibitor is not allowed.

Analysis #03

FDA requested an additional sensitivity analysis of possible immortal-bias by assessing the distribution of the length of time (i.e., number of days) from the first prescription of levodopa until the first prescription of entacapone in the study arm (sub-groups 1a-1d as described on pages 11-12 of protocol Version 6.0 dated Feb 08 2012). FDA was concerned that valid unexposed person time by design may have been excluded from the comparison group (group 2).

It should be noted that the group definitions for group 1 and group 2 used in the main analysis of the study, i.e.

- **Group 1:** Treatment with levodopa/DDCI **with** entacapone +/- DA and/or MAO-B inhibitor, and
- **Group 2:** Treatment with levodopa /DDCI **without** entacapone +/- DA and/or MAO-B inhibitor,

are time-dependent and patients potentially contribute their follow-up time to both groups based on what treatments they are receiving at any given point in time. Therefore all person time without entacapone but with levodopa /DDCI +/- DA and/or MAO-B inhibitor at any time has been accounted to the comparison group 2.

Analysis #04

FDA requested additional analyses of prostate cancer incidence and prostate cancer mortality with adjustment for the age at disease onset.

Analysis #05

FDA requested an additional analysis of prostate cancer incidence by excluding patients who switch Parkinson's disease medications over follow-up even this is based on future event of switching.

Analysis #06

FDA requested an additional analysis of prostate cancer incidence where the follow-up time after switching will be censored.

Analysis #07

FDA requested an additional analysis by evaluating the extent of switching using descriptive statistics (n, %) in each treatment group (group 1 and group 2) and by further describing the distribution of the remaining follow-up time after the switch.

Analysis #08

FDA requested an additional analysis of prostate cancer incidence by investigating how lagging the exposure by for example 1, 2, or 3 years impact the results.

Analysis #09

Investigators suggested an additional analysis of prostate cancer incidence with a time-dependent exposure definition ever exposed to entacapone during the follow-up which can be considered as a very-long exposure lag-time.

8 Results

In this section we summarize results of the analyses. For full results, see Appendices.

8.1 Study population characteristics

The broad study population consisted of 30 235 males who had purchased at least one prescription of any PD medication. Of these, 13 598 were entitled to special reimbursement for drugs used in Parkinson's disease (special refund categories 110 or 193). Out of these 134 patients with ICD-10 diagnosis codes G23, G24.1, G24.8, and G90.3 in the special refund category 110 were excluded.

Valid index date could not be found for 1299 patients. Of these, 1158 patients had no levodopa/DDCI purchases. The index date occurred after the end of follow-up in 344 patients. In addition, 444 patients had a cancer diagnosis prior to their index date. These patients were subsequently excluded from the study population.

The resulting study population consisted of 11 396 male PD patients. The schematic description of study population is shown in Figure 1.

The characteristics of the study population by treatments are described in Table 2. The mean age of the study population was 70.1 years and 59.3% of patients were older than 70 years. The time from PD diagnosis at index date was more than 5 years for 19.4% of patients. Dopamine agonists were used by 22.5% and MAO-B inhibitors by 39.5% of the patients prior to the index date. Prior use of BPH medications occurred in 28.6% and prior finasteride use in 13.0% of patients, respectively.

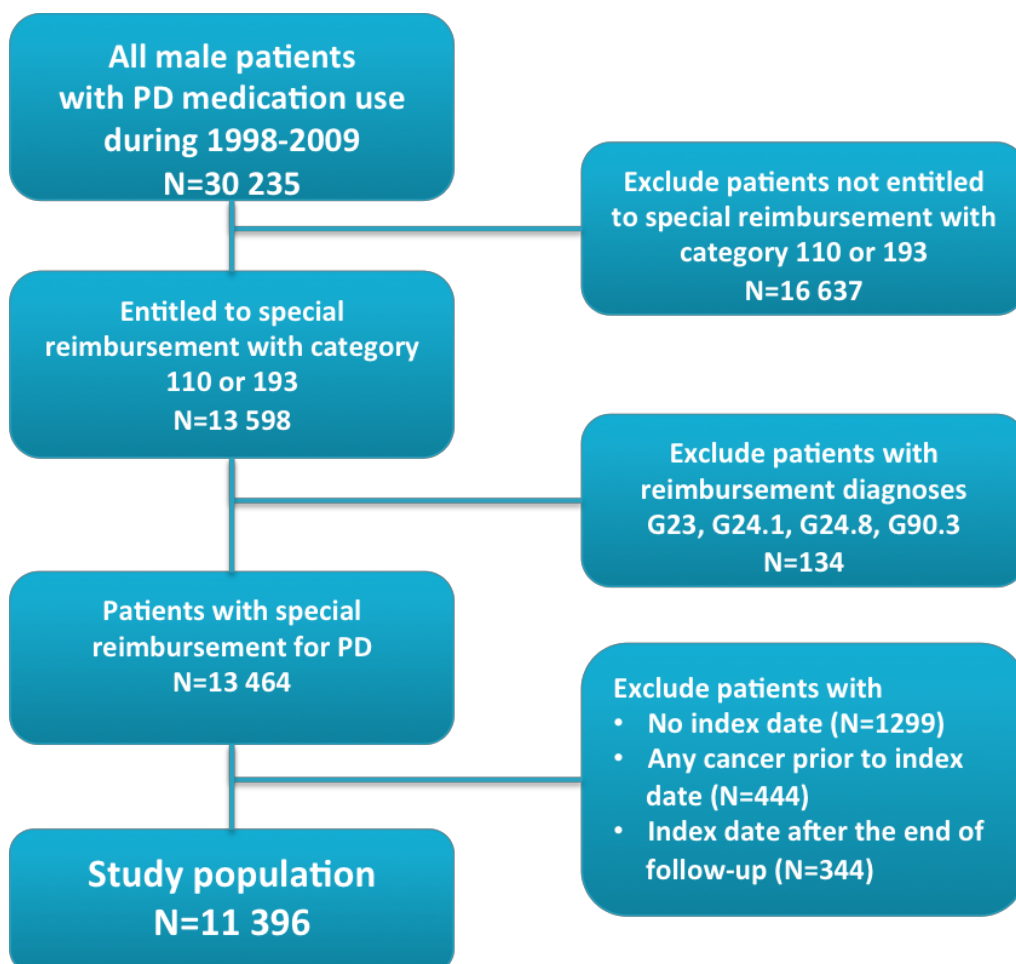


Figure 1 Construction of the study population

Table 2 Characteristics of the study population by treatment group at the index date

	G1 (with entacapone)		G2 (without entacapone)		G5		Total	
	N	%	N	%	N	%	N	%
N (% of Total N)	1141	10.0%	8482	74.4%	1773	15.6%	11396	100%
Mean age (yrs)	71.6		70.6		72.6		70.1	
Age 0-59 yrs	141	12.4	1174	13.8	181	10.2	1496	13.1
Age 60-64 yrs	118	10.3	975	11.5	158	8.9	1251	11.0
Age 65-69 yrs	171	15.0	1470	17.3	249	14.0	1890	16.6
Age 70-74 yrs	245	21.5	1868	22.0	379	21.4	2492	21.9
Age 75-79 yrs	256	22.4	1697	20.0	421	23.7	2374	20.8
Age 80-84 yrs	153	13.4	926	10.9	278	15.7	1357	11.9
Age 85- yrs	57	5.0	372	4.4	107	6.0	536	4.7
Time since diagnosis 0-1 yrs	421	36.9	4286	50.5	875	49.4	5582	49.0
Time since diagnosis 1-2 yrs	185	16.2	958	11.3	150	8.5	1293	11.3
Time since diagnosis 2-5	294	25.8	1714	20.2	306	17.3	2314	20.3
Time since diagnosis 5-10	152	13.3	1058	12.5	276	15.6	1486	13.0
Time since diagnosis 10-	89	7.8	466	5.5	166	9.4	721	6.3
Prior DA use	211	18.5	2144	25.3	206	11.6	2561	22.5
Prior MAO-B inhibitor use	224	19.6	3612	42.6	670	37.8	4506	39.5
Prior BPH drug use	429	37.6	2353	27.7	482	27.2	3264	28.6
Prior Finasteride use	173	1.5	1074	12.7	229	12.9	1476	13.0
Data 10 May, 2012 G1 : levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor G2 : levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor G5 : not G1 and not G2 at index date Source: Appendix 1 - Table 7, Table 9, Table 13 - Table 16.								

8.2 Presentation of the analysis of the primary and secondary objectives

The results of the analysis for each outcome variable in the primary and secondary objectives are all presented in similar fashion in the following sequence:

1. The results for the complete follow-up period analysis strategy using all continuous drug use periods from each patient are presented first with comparisons between the current exposure to the treatment groups.
2. Thereafter the results for the complete follow-up period analysis strategy are presented using the time-varying cumulative exposure to each treatment.
3. Then the results for the first drug use period analysis strategy using only the first continuous drug use period from each patient are presented with comparisons between the current exposure to the treatment groups.
4. Last the results for the first drug used period analysis strategy using the time-varying cumulative exposure to each treatment are presented.

For each analysis, the number of patients and events, and crude incidence rates per 1000 person years are presented in tabular format along with the adjusted hazard ratio estimates for the treatment comparisons from the Cox proportional hazards models.

The hazard ratio estimates with 95% CIs for the each variable in the Cox model are also presented in graphical format. The reference groups for each variable used in the Cox model are indicated with red color in Figure 2.

Finally the crude incidence rates stratified by selected baseline variables are presented graphically. The variables include age at index date and prior use of levopoda, DA, MAO-B inhibitor, entacapone, finasteride or any BPH medication at the index date. The treatment group specific total incidence rates are drawn in horizontal lines. The stratified incidence rates are not presented for the time-varying cumulative exposure treatments, see Figure 3.

8.3 Complete follow-up period analysis of prostate cancer incidence - comparisons between current exposure to group 1 and group 2

Table 3 Analysis of the prostate cancer incidence – Complete follow-up period analysis – Current exposure to group 1 and group 2

Current treatment	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
G1 – with entacapone	4404	78	6.69 (5.36, 8.35)	1.046 (0.761, 1.437)	0.782
G2 – without entacapone	10613	205	7.39 (6.45, 8.48)	Reference value	-
G5 : other	10331	76	6.04 (4.82, 7.56)	0.795 (0.596, 1.060)	0.118

Data 10 May, 2012
 G1 : group 1 - levodopa/DDCI **with** entacapone +/- DA and/or MAO-B inhibitor
 G2 : group 2 - levodopa/DDCI **without** entacapone +/- DA and/or MAO-B inhibitor
 G5 : group 5 - not G1 and not G2 at a given point during the follow-up
 Source: Appendix 2 – Table 1, Table 14

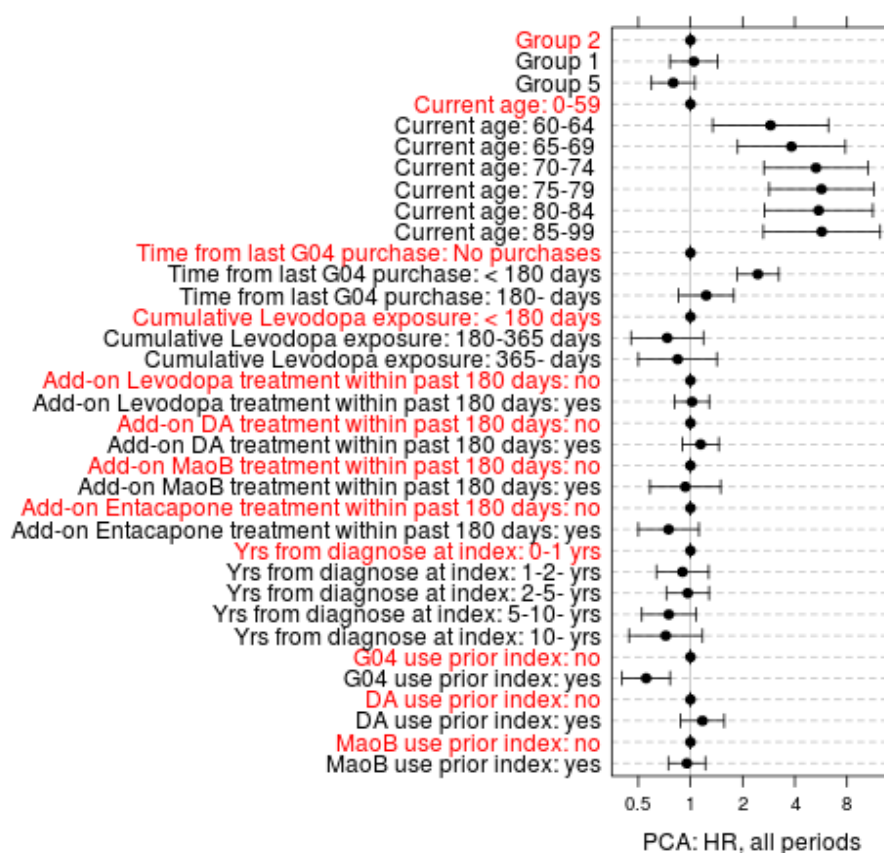


Figure 2 Prostate cancer (PCA) incidence – Primary analysis - Current exposure to group 1 and group 2. Hazard ratios estimates and the respective 95% CIs. Reference values indicated with red.

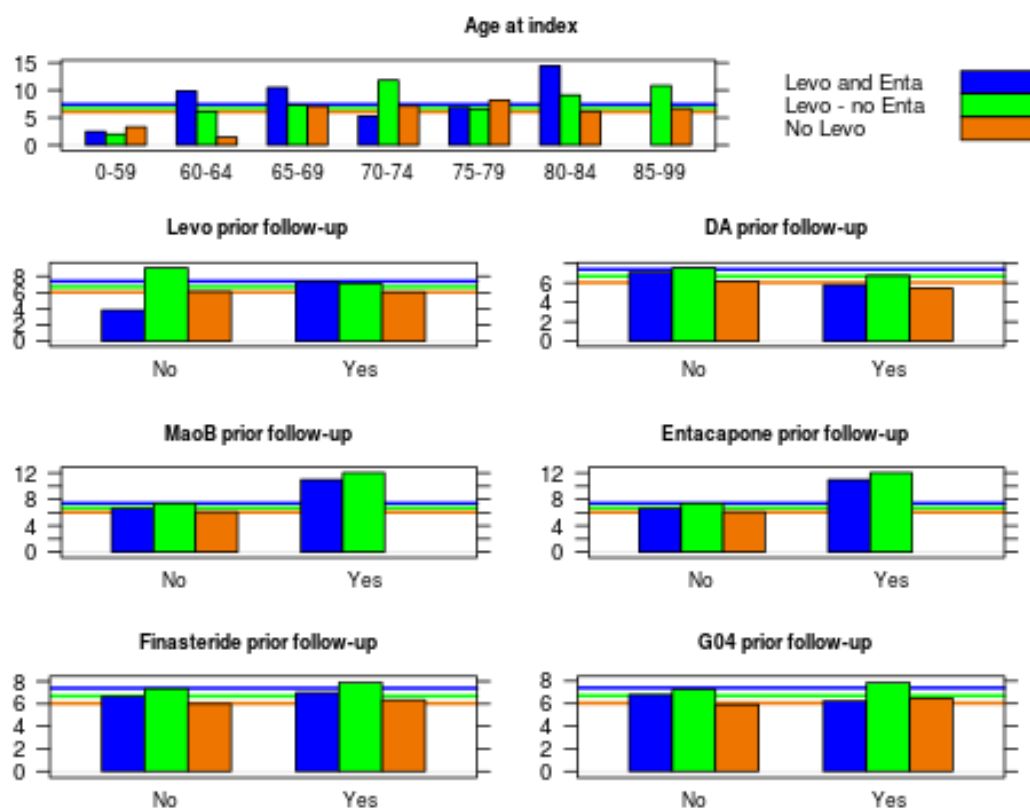


Figure 3 Prostate cancer (PCA) incidence – Complete follow-up period analysis - Current exposure to group 1 and group 2. Crude prostate cancer incidence rates (per/1000) by current use of treatment and stratified by selected baseline variables. The treatment group specific total incidence rates are drawn in horizontal lines.

For the evaluation of the primary objective of the study a total of 359 prostate cancer cases occurred during a mean follow-up time of 4.6 years. The crude prostate cancer incidence rate per 1000 yrs (95% CI) was 6.69 (5.36 - 8.35) for group 1 with entacapone and 7.39 (6.45, 8.48) for group 2 without entacapone. Treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor had a 4.6% (-23.9% - 43.7%) higher but not statistically significant (p-value 0.782) prostate cancer risk when compared to treatment with levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor. (Appendix 2 – Table 1, Table 14)

The prostate cancer risk increased with age and was significantly lower if BPH treatments had been used at baseline (HR=0.555, 95% CI 0.403 - 0.762, p-value <0.001). The prostate cancer risk also increased if BPH treatments had recently been used (i.e., time from last purchase < 180 days) during the follow-up period (HR=2.449, 95% CI 1.854 - 3.234, p-value <0.001). (Appendix 2 – Table 14)

8.4 Complete follow-up period analysis of prostate cancer incidence - comparisons between the categories of time-varying cumulative exposure to entacapone

Table 4 Analysis of the prostate cancer incidence – Complete follow-up period analysis – Time-varying cumulative exposure to entacapone

Cumulative entacapone exposure	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
No exposure	10508	252	7.35 (6.50, 8.32)	Reference value	-
Short exposure	4396	20	4.56 (2.94, 7.06)	0.625 (0.379, 1.031)	0.066
Intermediate	3471	28	6.10 (4.21, 8.83)	0.792 (0.509, 1.232)	0.301
Long exposure	2509	59	6.76 (5.24, 8.72)	0.815 (0.562, 1.182)	0.281
Data 10 May, 2012 Exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) Source: Appendix 2 – Table 19, Table 82					

The crude prostate cancer incidence rates per 1000 yrs (95% CI) varied from 7.35 with no exposure to entacapone to 6.76 with long exposure to entacapone. Short treatment with entacapone had a 37.5% (-62.1% - 3.12%) lower (p-value 0.066) prostate cancer risk when compared to no exposure to entacapone. The risk attenuated with longer cumulative exposure. (Appendix 2 – Table 19, Table 82)

The prostate cancer risk increased with age and with longer cumulative exposure to DA (HR=1.821, 95% CI 1.236-2.682, p-value 0.002 for long exposure vs. no exposure to DA). The risk was again significantly lower if BPH treatments had been used at baseline (HR=0.550, 95% CI 0.400 - 0.756, p-value <0.001) and higher if BPH treatments had recently been used (i.e., time from last purchase < 180 days) during the follow-up period (HR=2.441, 95% CI 1.848 - 3.226, p-value <0.001). (Appendix 2 – Table 82)

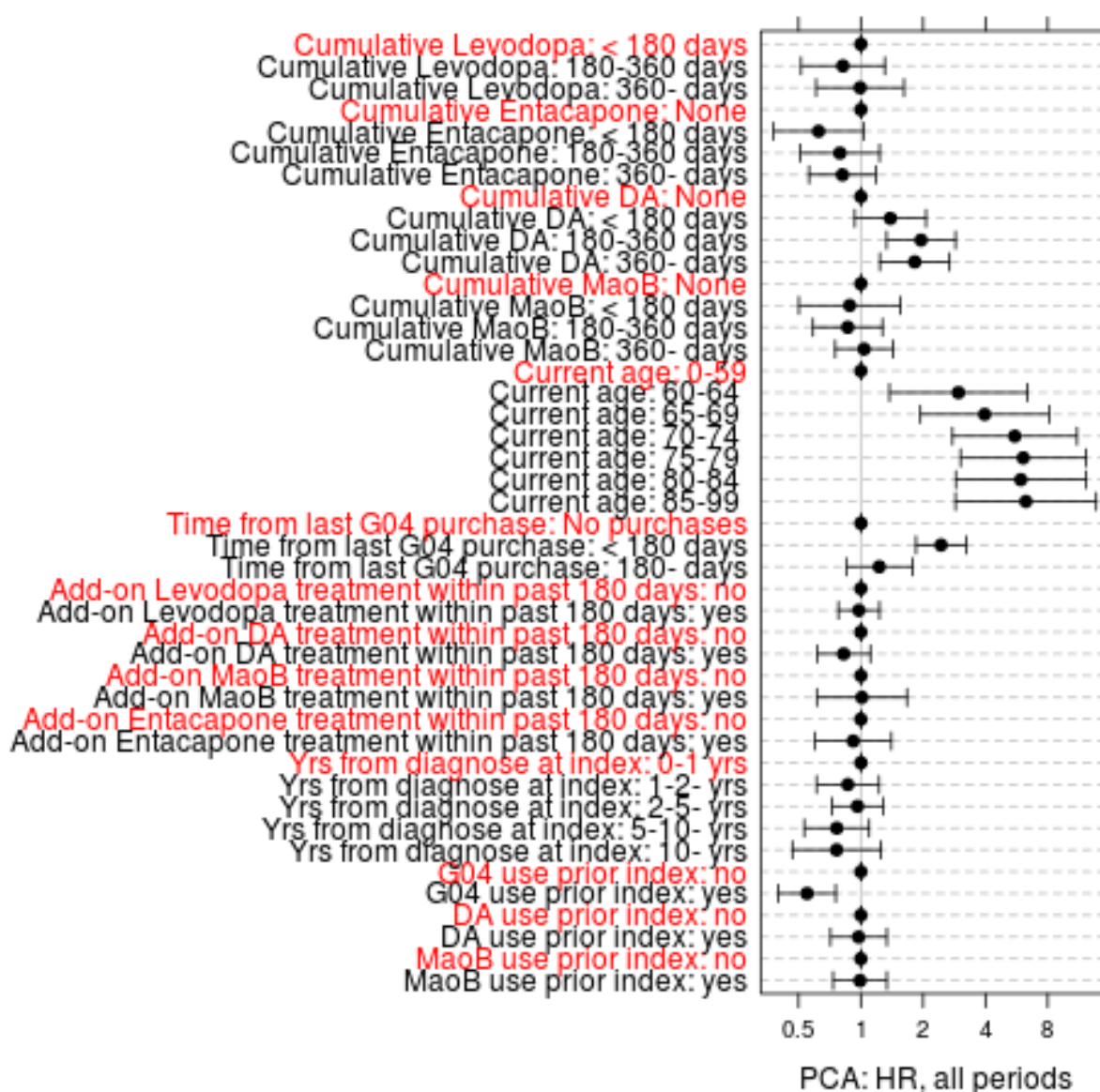


Figure 4 Prostate cancer (PCA) incidence – Complete follow-up period analysis – Time-varying cumulative exposure to entacapone and other PD treatments. Hazard ratios estimates and the respective 95% CIs. Reference values indicated with red.

8.5 Complete follow-up period analysis of prostate cancer incidence - comparisons between the categories of time-varying cumulative exposure to treatment group 1 with entacapone

Table 5 Analysis of the prostate cancer incidence – Complete follow-up period analysis – Time-varying cumulative exposure within group 1 (levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor)

Cumulative exposure within G1	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
No exposure	10547	252	7.33 (6.48, 8.30)	Reference value	-
Short exposure	4379	21	4.52 (2.95, 6.94)	0.610 (0.374, 0.994)	0.047
Intermediate	3400	30	6.63 (4.64, 9.49)	0.879 (0.570, 1.354)	0.558
Long exposure	2450	56	6.62 (5.09, 8.60)	0.798 (0.548, 1.163)	0.240
Data 10 May, 2012 G1 : group 1 - levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor Exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) Source: Appendix 2 – Table 25, Table 81					

The crude prostate cancer incidence rates per 1000 yrs (95% CI) varied from 7.33 with no exposure within group 1 to 6.62 with long exposure within group 1. Short treatment within group 1 with entacapone had a 39.0% (0.6% - 62.6%) lower (p-value 0.047) prostate cancer risk when compared to no exposure within group 1 with entacapone. The risk attenuated with longer cumulative exposure. (Appendix 2 – Table 25, Table 81)

The prostate cancer risk increased with age and with longer cumulative exposure to DA (HR=1.821, 95% CI 1.236 - 2.683, p-value 0.002 for long exposure vs. no exposure to DA). The risk was significantly lower if BPH treatments had been used at baseline (HR=0.549, 95% CI 0.399 - 0.755, p-value <0.001) and higher if BPH treatments had recently been used (i.e. time from last purchase < 180 days) during the follow-up period (HR=2.445, 95% CI 1.850 - 3.230, p-value <0.001). (Appendix 2 – Table 81)

These results are similar to the results when the time-varying cumulative exposure to entacapone was used as exposure in section 8.4 and therefore no further details are presented here.

8.6 Complete follow-up period analysis of prostate cancer mortality - comparisons between current exposure to group 1 and group 2

Table 6 Analysis of the prostate cancer mortality – Complete follow-up period analysis – Current exposure to group 1 and group 2

Current treatment	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
G1 – with entacapone	4470	11	0.91 (0.51, 1.65)	0.927 (0.434, 1.981)	0.846
G2 – without entacapone	10623	41	1.45 (1.07, 1.97)	Reference value	-
G5 : other	10356	37	2.87 (2.08, 3.96)	1.508 (0.924, 2.461)	0.101

Data 10 May, 2012

G1 : group 1 - levodopa/DDCI **with** entacapone +/- DA and/or MAO-B inhibitor

G2 : group 2 - levodopa /DDCI **without** entacapone +/- DA and/or MAO-B inhibitor

G5 : group 5 - not G1 and not G2 at a given point during the follow-up

Source: Appendix 3 – Table 1, Table 14

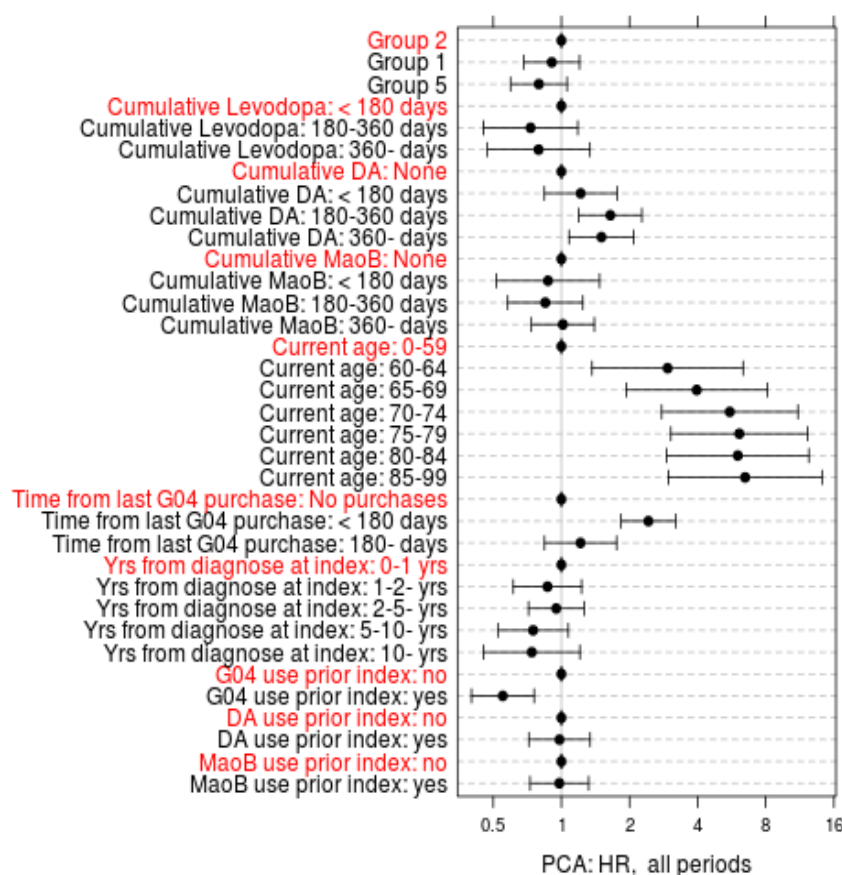


Figure 5 Prostate cancer (PCA) mortality – Complete follow-up period analysis - Current exposure to group 1 and group 2. Hazard ratios estimates and the respective 95% CIs. Reference values indicated with red.

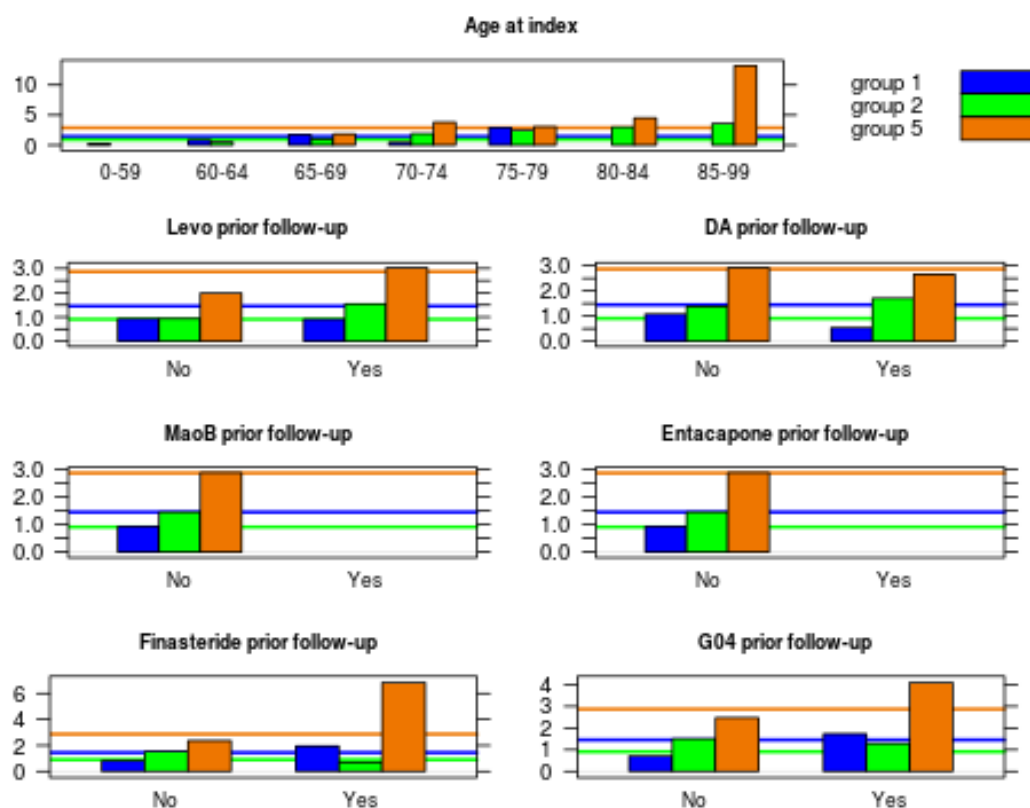


Figure 6 Prostate cancer (PCA) mortality – Complete follow-up period analysis - Current exposure to group 1 and group 2. Crude prostate cancer incidence rates (per/1000) by current use of treatment and stratified by selected baseline variables. The treatment group specific total incidence rates are drawn in horizontal lines.

For the evaluation of the secondary objective of the study a total of 89 prostate cancer deaths occurred during a mean follow-up time of 4.7 years. The crude prostate cancer mortality rate per 1000 yrs (95% CI) was 0.91 (0.51, 1.65) for group 1 with entacapone and 1.45 (1.07, 1.97) for group 2 without entacapone. The prostate cancer mortality increased with age. Treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor had a 7.3% (-56.6% - 98.1%) lower but statistically non-significant (p-value 0.846) prostate cancer mortality rate when compared to treatment with levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor. (Appendix 3 – Table 1, Table 14)

8.7 Complete follow-up period analysis of prostate cancer mortality - comparisons between the categories of time-varying cumulative exposure to entacapone

Table 7 Analysis of the prostate cancer mortality – Complete follow-up period analysis – Time-varying cumulative exposure to entacapone

Cumulative entacapone exposure	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
No exposure	10508	65	1.86 (1.46, 2.37)	Reference value	-
Short exposure	4462	6	1.34 (0.60, 2.99)	1.220 (0.492, 3.026)	0.668
Intermediate	3537	6	1.27 (0.57, 2.83)	1.275 (0.503, 3.235)	0.609
Long exposure	2576	12	1.32 (0.75, 2.33)	1.271 (0.595, 2.716)	0.535
Data 10 May, 2012 Exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) Source: Appendix 3 – Table 19, Table 82					

The crude prostate cancer mortality rates per 1000 yrs (95% CI) varied from 1.86 with no exposure to entacapone to 1.32 with long exposure to entacapone. There was no statistically significant association between duration of entacapone exposure and prostate cancer mortality risk.

The prostate cancer mortality risk increased with age and with prior use of DA (HR=2.274, 95% CI 1.181 - 4.382, p-value 0.014). There was a tendency of decreased mortality risk with longer cumulative exposure to DA. The prostate cancer mortality risk tended to decrease if BPH treatments had recently been used (i.e., time from last purchase < 180 days) during the follow-up period (HR=0.490, 95% CI 0.227 - 1.055, p-value 0.068). (Appendix 3 – Table 82)

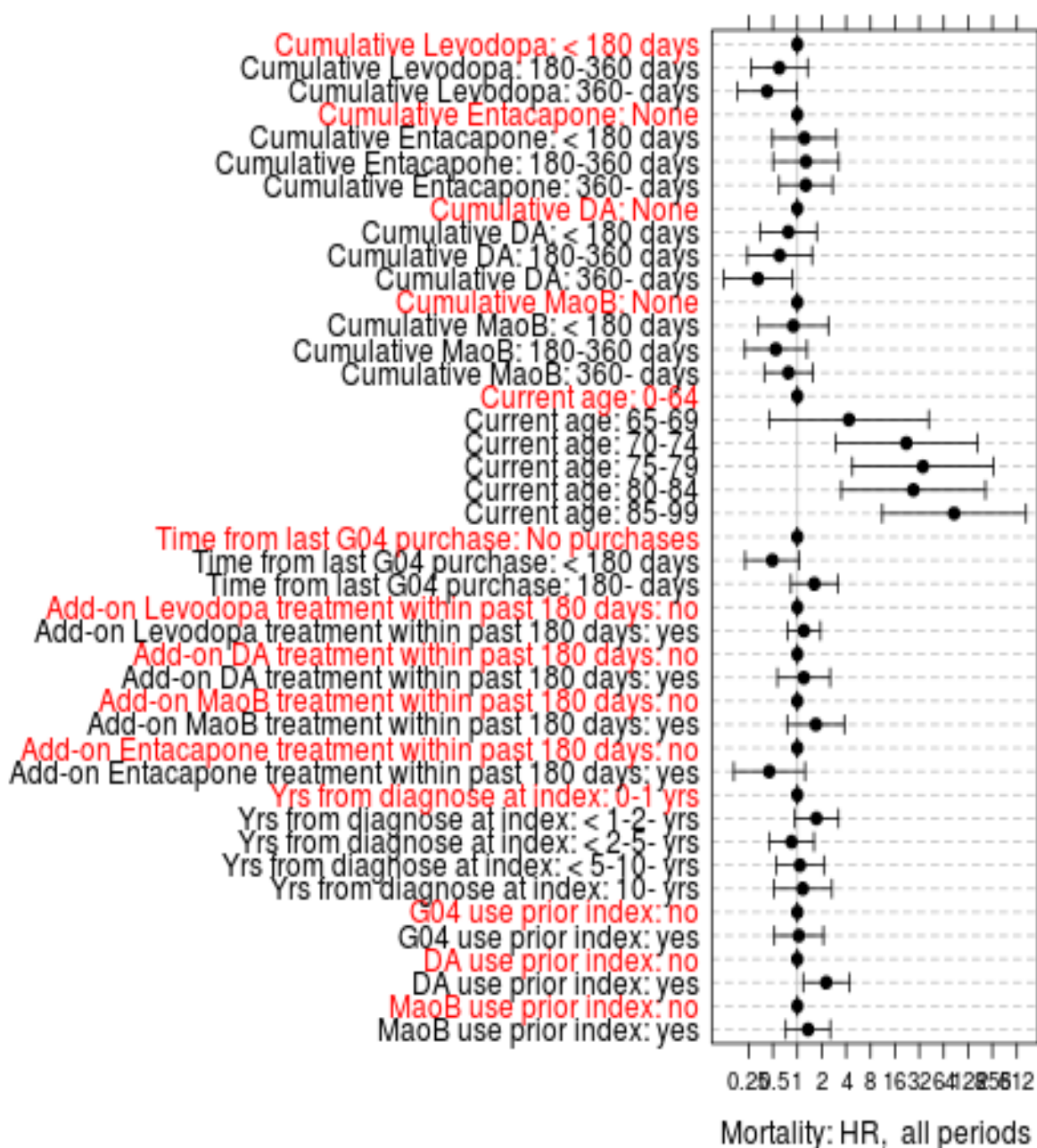


Figure 7 Prostate cancer (PCA) mortality – Complete follow-up period analysis – Time-varying cumulative exposure to entacapone and other PD treatments. Hazard ratios estimates and the respective 95% CIs. Reference values indicated with red.

8.8 First drug use period analysis of prostate cancer incidence and prostate cancer mortality

In this section the first drug use period analysis of the primary and secondary objectives are presented. The first drug use period analyses utilises only the first continuous add-on drug use period from each patient. Only tabular presentation of the crude incidence rates with adjusted hazard ratio estimates are given. For more detailed results references to the Appendices are given.

Table 8 Analysis of the prostate cancer incidence – First drug use period analysis – Current exposure to group 1 and group 2

Current treatment	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
G1 – with entacapone	1141	3	3.67 (1.18, 11.36)	0.558 (0.125, 2.497)	0.446
G2 – without entacapone	8482	36	6.22 (4.49, 8.62)	Reference value	-
G5 : other	1773	8	5.98 (2.99, 11.97)	0.710 (0.187, 2.695)	0.615
Data 10 May, 2012 G1 : group 1 - levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor G2 : group 2 - levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor G5 : group 5 - not G1 and not G2 at a given point during the follow-up Source: Appendix 4 – Table 1, Table 14					

Table 9 Analysis of the prostate cancer incidence – First drug use period analysis – Time-varying cumulative exposure to entacapone

Cumulative entacapone exposure	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
No exposure	10194	44	6.21 (4.62, 8.34)	Reference value	-
Short exposure	1178	1	3.00 (0.42, 21.30)	0.523 (0.015, 17.95)	0.719
Intermediate	416	1	3.83 (0.54, 27.22)	0.430 (0.047, 3.942)	0.456
Long exposure	172	1	3.87 (0.54, 27.47)	0.578 (0.065, 5.134)	0.623
Data 10 May, 2012 Exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) Source: Appendix 4 – Table 19, Table 68					

The total follow-up time during the first continuous add-on drug use period was 7943 person years, which was 15.3% of the respective follow-up time of the complete follow-up period analysis. A total of 47 prostate cancer cases occurred during a mean follow-up time of 0.7 years. Neither the crude event rates nor the adjusted hazard ratios showed increased risk with current exposure to group 1 nor with longer duration of exposure to entacapone. (Appendix 2 – Table 1, Appendix 4 – Table 1)

Table 10 Analysis of the prostate cancer mortality – First drug use period analysis – Current exposure to group 1 and group 2

Current treatment	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
G1 – with entacapone	1141	1	1.22 (0.17, 8.63)	0.927 (0.100, 8.600)	0.947
G2 – without entacapone	8482	12	2.06 (1.17, 3.62)	Reference value	-
G5 : other	1773	3	2.23 (0.72, 6.91)	0.805 (0.082, 7.914)	0.852
Data 10 May, 2012 G1 : group 1 - levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor G2 : group 2 - levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor G5 : group 5 - not G1 and not G2 at a given point during the follow-up Source: Appendix 5 – Table 1, Table 14					

Table 11 Analysis of the prostate cancer mortality – First drug use period analysis – Time-varying cumulative exposure to entacapone

Cumulative entacapone exposure	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
No exposure	10194	15	2.10 (1.26, 3.48)	Reference value	-
Short exposure	1178	1	3.00 (0.42, 21.30)	NA	NA
Intermediate	416	0	0 (0,∞)	NA	NA
Long exposure	173	0	0 (0,∞)	NA	NA
Data 10 May, 2012 Exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) The statistical analysis has not been performed due to limited number of events in the exposure categories Source: Appendix 5 – Table 19					

The total follow-up time during the first continuous add-on drug use period was 8007 person years, which was 15.0% of the respective follow-up time of the complete follow-up period analysis. A total of 16 deaths due to prostate cancer occurred during a mean follow-up time of 0.7 years. The low number of events does not provide a solid basis for meaningful statistical analyses and therefore only crude incidence rates have been reported for the cumulative exposure to entacapone. (Appendix 3 – Table 1, Appendix 5 – Table 1)

8.9 Sensitivity analyses

A summary of the results from the sensitivity analyses of prostate cancer incidence (for methodological details see section 6.8.3) is given in Table 12. The results are robust to the various analysis strategies.

Table 12 List of different models and their description used in the sensitivity analysis of the prostate cancer incidence. Cox proportional hazards model of the complete follow-up period analysis strategy.

Model	Model description	Hazard ratio (95% CI)	P-value
Model 1	Original Cox proportional hazards model of the primary analysis – Current treatment G1 vs. G2 comparison	1.046 (0.761, 1.437)	0.782
Model 2	60 days exposure extension period – Current treatment G1 vs. G2 comparison	0.976 (0.729, 1.307)	0.872
Model 3	90 days exposure extension period – Current treatment G1 vs. G2 comparison	0.929 (0.697, 1.236)	0.612
Model 4	Current treatment on entacapone vs. not on entacapone comparison	1.171 (0.863, 1.589)	0.310
Model 5	Treatment periods with entacapone but without levodopa/DDCI are moved to G1 – Current treatment G1 vs. G2 comparison	1.089 (0.794, 1.492)	0.597
Model 6	Treatment periods starting at index date with G5 censored – Current treatment G1 vs. G2 comparison	1.048 (0.762, 1.441)	0.773
Model 7	Recent add-on indicator variables (levodopa, DA, MAO-B inhibitor) have been removed and cumulative exposure variables (DA, MAO-B inhibitor) added – Current treatment G1 vs. G2 comparison	0.907 (0.683, 1.203)	0.496
Model 8	Recent add-on indicator variables (levodopa, DA, MAO-B inhibitor) have been removed and current exposure variables (DA, MAO-B inhibitor) added – Current treatment G1 vs. G2 comparison	0.937 (0.703, 1.249)	0.659
Model 9	Variables i) BPH (G04) prior to follow-up and ii) time since last BPH (G04) purchase are replaced with i) use of finasteride prior to follow-up and ii) time since last finasteride purchase – Current treatment G1 vs. G2 comparison	1.051 (0.765, 1.442)	0.760
Model 10	Variables i) BPH (G04) prior to follow-up and ii) time since last BPH (G04) purchase are combine into a single variable – Current treatment G1 vs. G2 comparison	1.045 (0.760, 1.436)	0.786
Model 11	IPW weighted model with 1% truncation of weights – Current treatment G1 vs. G2 comparison	1.026 (0.730, 1.440)	0.884
Model 12	Conditional logistic regression model of the nested case-control design – Current treatment G1 vs. G2 comparison at the time of the prostate cancer diagnosis	0.878 (0.652, 1.181)	0.389
Data 10 May, 2012 G1 : levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor G2 : levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor G5 : not G1 and not G2 at a given point during the follow-up Source: Appendix 7 – Table 1 - Table 12			

For the risk of prostate cancer mortality less sensitivity analyses were performed which are reported in Table 13.

Table 13 . List of different models and their description used in the sensitivity analysis of prostate cancer mortality. Cox proportional hazards model of the complete follow-up period analysis strategy.

Model	Model description	Hazard ratio (95% CI)	P-value
Model 1	Original Cox proportional hazards model of the primary analysis – Current treatment G1 vs. G2 comparison	0.927 (0.434, 1.981)	0.846
Model 2	Current treatment on entacapone vs. not on entacapone comparison	0.755 (0.361, 1.579)	0.455
Model 3	Recent add-on indicator variables (levodopa, DA, MAO-B inhibitor) have been removed and cumulative exposure variables (DA, MAO-B inhibitor) added – Current treatment G1 vs. G2 comparison	0.794 (0.395, 1.599)	0.519
Model 4	Recent add-on indicator variables (levodopa, DA, MAO-B) have been removed and current exposure variables (DA, MAO-B inhibitor) added – Current treatment G1 vs. G2 comparison	0.748 (0.368, 1.519)	0.422
Data 10 May, 2012 G1 : levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor G2 : levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor G5 : not G1 and not G2 at a given point during the follow-up Source: Appendix 7 – Table 13 - Table 16			

8.10 First drug use period analysis of prostate cancer incidence – exploratory analysis of comparisons between group 3 and group 4

In this section the first drug use period analyses of the exploratory objective for the comparison of the prostate cancer incidence rates between treatment groups 3 and 4 are presented. These analyses contain those patients who started their first add-on treatment either within group 3 or within group 4. Tabular presentation of the crude incidence rates with adjusted hazard ratio estimates are given for the current exposure. For more detailed results references to the Appendices are given.

Table 14 Analysis of the prostate cancer incidence – First drug use period analysis – Current exposure to treatment group 3 or group 4

Current treatment	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
Group 3	800	3	5.46 (1.76, 16.94)	0.764 (0.118, 4.955)	0.778
Group 4	5894	16	5.54 (3.40, 9.05)	Reference value	-
Data 10 May, 2012 Group 3 - treatment with add-on entacapone to levodopa/DDCI without other add-on treatments Group 4 - treatment with add-on DA and/or MAO-B inhibitor to levodopa/DDCI, or add-on levodopa/DDCI to DA and/or MAO-B inhibitor. Source: Appendix 6 – Table 1, Table 14					

Table 15 Analysis of the prostate cancer incidence – First drug use period analysis – Time-varying cumulative exposure to entacapone

Cumulative entacapone exposure	Npat	# Events	Rate per 1000 (95% CI)	Hazard Ratio (95% CI)	P-value
No exposure	5894	16	5.54 (3.40, 9.05)	Reference value	-
Short exposure	796	1	4.43 (0.62, 31.45)	NA	NA
Intermediate	270	1	5.83 (0.82, 41.40)	NA	NA
Long exposure	99	1	6.58 (0.93, 46.72)	NA	NA
Data 10 May, 2012 Exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) Source Appendix 6 – Table 19					

The total follow-up time during the first continuous add-on drug use period was 3436 person years from 6694 patients in the analysis population. A total of 19 prostate cancer cases occurred during a mean follow-up time of 0.5 years. The low number of events does not provide a solid basis for meaningful statistical analyses and therefore only crude incidence rates have been reported for the cumulative exposure to entacapone. Statistical analysis was not performed for prostate cancer mortality because there were only 6 prostate cancer deaths within this analysis population. They all occurred during the

treatment with add-on DA and/or MAO-B inhibitor to levodopa/DDCI, or add-on levodopa/DDCI to DA and/or MAO-B inhibitor.

8.11 Additional analyses requested by FDA

The results of the additional analyses in response to the recommendations stated in FDA letter received 24 October 2012 are given in detail in Table 1 – Table 14 of Appendix 8. Summary of the findings from these analyses are presented below.

Analysis #01

The definitions for group 1* and group 2* require specific temporal order between initiation of levodopa/DDCI, entacapone, DA and MAO-B inhibitor. The follow-up is censored as soon as patient switch to treatment which is not compatible with these group definitions. Due to these reasons number of prostate cancer events was 6 and number of prostate cancer deaths was 3 and thus insufficient for performing further statistical analysis (Appendix 8, Table 1 – Table 2). The crude event prostate cancer incidence rates were 2.67 vs. 4.70 (group 1* vs. group 2*) per 1000 person years (Appendix 8, Table 1). Similarly crude event prostate cancer mortality rates were 1.33 vs. 2.34 (group 1* vs. group 2*) per 1000 person years (Appendix 8, Table 2).

Analysis #02

The definitions for group 1** and group 2** are otherwise the same as in analysis #01 but in group 1** prior exposure to entacapone, DA or MAO-B inhibitor was not allowed. Again, the follow-up is censored as soon as patient switch to treatment which is not compatible with these group definitions. Due to these reasons number of prostate cancer events was 6 and number of prostate cancer deaths was 2 and thus insufficient for performing further statistical analysis (Appendix 8, Table 3 – Table 4). The crude event prostate cancer incidence rates were 3.75 vs. 4.70 (group 1** vs. group 2**) per 1000 person years (Appendix 8, Table 3). Similarly crude event prostate cancer mortality rates were 0 vs. 2.34 (group 1** vs. group 2**) per 1000 person years (Appendix 8, Table 4).

Analysis #03

The distribution of the length of time (i.e. number of days) between the first prescription of levodopa/DDCI and the first prescription of entacapone in the study arm (sub-groups 1a-1d) is given in Table 5 of Appendix 8. There is a clear trend towards longer time between the first levodopa and entacapone prescriptions depending how many other add-on treatments have been used earlier in their disease history. This is not a sign of survival bias, however, because definitions for group 1 and group 2 used in the main analysis of the study are time-dependent and patients potentially contribute their follow-up time to both groups based on what treatments they are receiving at any given point in time. Therefore all person time without entacapone but with levodopa /DDCI +/- DA and/or MAO-B inhibitor at any time has been accounted to the comparison group 2.

Analysis #04

The analysis of prostate cancer incidence with adjustment for the age at disease onset resulted in HR of 1.041 (95% CI 0.757 – 1.430, p-value 0.805) when comparing treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) to treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2), Appendix 8 – Table 6.

The analysis of prostate cancer mortality with adjustment for the age at disease onset resulted in HR of 1.088 (95% CI 0.510 – 2.325, p-value 0.827) when comparing treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) to treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2), Appendix 8 – Table 7.

Analysis #05

The analysis of prostate cancer incidence by excluding patients who switch Parkinson's disease medications at any time over follow-up resulted in HR of 0.582 (95% CI 0.275 – 1.233, p-value 0.158) when comparing treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) to treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2), Appendix 8 – Table 8.

The switch was defined either as

- a switch from group 2 (without entacapone) to group 1 (with entacapone) at any given time,
- a switch from group 1 to group 2 with at least 180 days without entacapone prescriptions before entering into group 2,
- a switch from group 1 to group 5 (i.e. not group 1 or group 2) with at least 180 days in group 5 after the switch, or
- a switch from group 2 to group 5 (i.e. not group 1 or group 2) with at least 180 days in group 5 after the switch.

Analysis #06

The analysis of prostate cancer incidence by censoring follow-up time after switching resulted in HR of 0.824 (95% CI 0.376 – 1.804, p-value 0.628) when comparing treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) to treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2), Appendix 8 – Table 9.

Analysis #07

Descriptive statistics for evaluating the extent of switching in treatment group 1 and group 2 and describing the distribution of the remaining follow-up time after the switch is given in Table 10 of Appendix 8. Approximately 32% of patients switched at some point from group 1 (treatment with entacapone) and similarly 46% of patients switched at some point from group 2 (treatment without entacapone).

The median durations of remaining follow-up time after switches from group 1 were 1082 days and 691 days towards groups 2 and 5, respectively. For the switches from group 2 these durations were 1402 towards group 1 and 990 days towards group 5.

Analysis #08

In the analysis of prostate cancer incidence with lagging exposure the lag was defined as an extension of exposure up to 1, 2 or 3 years.

Analysis with lags of 1, 2 and 3 years resulted in HRs of 0.993 (95% CI 0.727 – 1.356, p-value 0.966), 0.933 (95% CI 0.688 – 1.265, p-value 0.656), and 0.957 (95% CI 0.710 – 1.291, p-value 0.776), respectively when comparing treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) to treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2), Appendix 8 – Table 11 – Table 13.

Analysis #09

The analysis of prostate cancer incidence with a time-dependent exposure definition ever vs. never exposed to entacapone resulted in HR of 0.817 (95% CI 0.603 – 1.108, p-value 0.194) when comparing treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) to treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2), Appendix 8 – Table 14.

None of the above additional analyses requested by FDA suggested a significant increase in the risk of prostate cancer incidence or mortality when comparing add-on treatment with entacapone to other add-on treatments without entacapone.

8.12 Description of the prostate cancer cases

From the 359 patients diagnosed with prostate cancers, 78 (21.7%), 205 (57.1%) and 76 (21.2%) were classified at the time of diagnosis into group 1 (with entacapone), group 2 (without entacapone), and group 5, respectively. The age distribution within the groups at the time of diagnosis was similar with 98% within the age range 60 to 90 years (Appendix 1, Table 18).

For group 2 (without entacapone) the year of diagnosis was evenly distributed on the follow-up range 1998-2009, but for group 1 (with entacapone) a doubling of the yearly cases after year 2004 was observed (Appendix 1, Table 23). This is in line with the doubling of the number of patients starting their follow-up in group 1 one year earlier (Appendix 1, Table 8), which most probably is due to Stalevo being launched in Finland in 2003.

The distribution of the time from start of follow-up to date of prostate cancer diagnosis differed between group 1 and group 2. In group 1, in 55.1% of the prostate cancers this time exceeded 5 years while in group 2 the respective percentage was only 22.0% (Appendix 1, Table 27). Also, the percentage for the time shorter than 1 year differed among the groups being 5.1% and 22.0% for group 1 and group 2, respectively. The duration from starting to use levodopa/DDCI, DA, and MAO-B inhibitor until the prostate cancer diagnosis the percentage of times was exceeding 5 years in 75.6% vs. 40.0% patients regarding levodopa/DDCI, in 41.0% vs 10.7% patients regarding DA, and in 57.7% vs. 29.8% patients regarding MAO-B inhibitor in groups 1 and 2, respectively. This reflects the fact that entacapone is only used as a second-line treatment to levodopa/DDCI (Appendix 1, Table 28, Table 30, Table 31).

In group 1 in 93.6% of the prostate cancer cases the cumulative exposure to levodopa/DDCI exceeded 1 year, compared to only 69.8% in the group 2 (Appendix 1, Table 19). A similar pattern of longer exposure in group 1 compared to group 2 was observed in the use of MAO-B inhibitor and DA. For MAO-B inhibitor the percentages for the cumulative exposure exceeding 1 year were 57.7% and 43.4% for group 1 and group 2, respectively (Appendix 1, Table 21), and for DA the percentages were 50.0% and 21.5%, respectively (Appendix 1, Table 22). For entacapone in group 1 in 64.1% of the cancer cases the cumulative exposure exceeded 1 year and in group 2 only 2% and 9.3% of patients in group 2 had earlier entacapone exposure (Appendix 1, Table 20), which suggest that patients in group 2 at the time of prostate cancer diagnosis have not frequently been exposed to entacapone.

Of the prostate cancer cases 33 (42.3%) in group 1 and 106 (51.7%) in group 2 died during follow-up (Appendix 1, Table 24). From prostate cancer cases diagnosed before 2005, 47.1% (16/34) and 49.6% (70/141) survived for more than 5 years in group 1 and group 2, respectively (Appendix 1, Table 26). The percentage of deaths caused by prostate cancer was 18.2% (6/33) for group 1 and 26.4% (28/106) for group 2 (Appendix 1, Table 32).

From the tumor diagnoses 93% were based on histology of main tumor. No differences between group 1 and group 2 were observed in tumor staging summary and TNM staging (Appendix 1, Table 33).

9 Discussion

This study represents a comparative safety study where treatment with levodopa/DDCI **with** entacapone +/- DA and/or MAO-B inhibitor (group 1) was compared with treatment with levodopa /DDCI **without** entacapone +/- DA and/or MAO-B inhibitor (group 2) in a large unselected population of male Parkinson's disease patients in a real-life setting in Finland. We did not find statistically significant differences in the adjusted relative risks for the prostate cancer incidence rates or the prostate cancer mortality rates when the current exposure to these two treatment groups or the cumulative exposure to entacapone was considered. We performed several sensitivity analyses and statistical modeling strategies and found that the main results remained virtually unchanged. These analyses included e.g., nested case-control design.

Several general limitations must be kept in mind when evaluating the results from observational study that is based on record linkage of healthcare registers.

First, the exposure and use of specific PD treatments was derived from prescription data by use of defined daily doses, which may have caused some miss-classification of the exposure. To partly overcome these biases, a sensitivity analysis was performed where the exposure extension period was varied between 30 and 90 days with practically unchanged results. Prostate cancer mortality seemed higher for group 5 (HR=1.508, 95% CI 0.924-2.461, p-value 0.101, Appendix 3 – Table 14) when compared to group 2 without entacapone. This may reflect the fact that some older patients were in long-term care facilities and their exposure was not known. Therefore they were classified as not being in either group 1 or group 2.

Second, adjustment for confounding factors is important in observational studies. We did not have information on important risk factors such as life style factors, which are generally not captured in population-based registers. However, our analysis was adjusted for time since diagnosis, age, previous and concurrent use of PD treatments, previous and concurrent use of BPH treatments and hospital district. These factors were available in the registers and were potential confounders in the pathway between entacapone exposure and prostate cancer risk.

Third, there are many alternative statistical modeling approaches that could be applied to the data with different choices for the statistical model and variables included in the model. Several sensitivity analyses and statistical modeling strategies were performed with main findings remaining virtually unchanged. In addition, none of the additional analyses requested by FDA suggested a significant increase in the risk of prostate cancer incidence or mortality when comparing add-on treatment with entacapone to other add-on treatments without entacapone.

10 Conclusions

In the study population of 11 396 male Parkinson's disease patients a total of 359 prostate cancer cases occurred during a mean follow-up time of 4.6 years and 89 prostate cancer deaths occurred during a mean follow-up time of 4.7 years. Table 16 gives a summary of the study results in terms of the adjusted hazard ratio estimates when all continuous drug use periods are used from each patient.

Table 16 Summary of the results for prostate cancer incidence and prostate cancer mortality – Complete follow-up period analysis where all continuous drug use periods are used from each patient

Outcome	Prostate cancer incidence			Prostate cancer mortality		
Exposure comparison	Events Rate per 1000	Hazard Ratio (95% CI)	P-value	Events Rate per 1000	Hazard Ratio (95% CI)	P-value
Current exposure to add-on treatment group						
Group 1	78 6.69	1.046 (0.761 – 1.437)	0.782	11 0.91	0.927 (0.434 – 1.981)	0.846
Group 2	205 7.39	Reference	-	41 1.45	Reference	-
Cumulative exposure to entacapone						
No	252 7.35	Reference	-	65 1.86	Reference	-
Short	20 4.56	0.625 (0.379 – 1.031)	0.066	6 1.34	1.220 (0.492 – 3.026)	0.668
Intermediate	28 6.10	0.792 (0.509 – 1.232)	0.301	6 1.27	1.275 (0.503 – 3.235)	0.609
Long	59 6.76	0.815 (0.562 – 1.182)	0.281	12 1.32	1.271 (0.595 – 2.716)	0.535
Data 10 May, 2012 Group 1 – Treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor Group 2 – Treatment with levodopa /DDCI without entacapone +/- DA and/or MAO-B inhibitor Cumulative exposure categories: No (0 days), short (<180 days), intermediate (180 – 360 days), long (> 360 days) Source: Table 3, Table 4, Table 6, Table 7						

The following conclusions can be drawn from the analyses of the study:

- Current exposure to treatment with levodopa/DDCI with entacapone +/- DA and/or MAO-B inhibitor (group 1) was not associated with increased prostate cancer risk or increased prostate cancer mortality risk when compared to current treatment with levodopa/DDCI without entacapone +/- DA and/or MAO-B inhibitor (group 2).
- Cumulative exposure to entacapone during the follow-up was not associated with increased prostate cancer risk or an increased prostate cancer mortality risk.
- The main results remained virtually unchanged in various sensitivity and additional analyses.
- The results strongly suggest that entacapone does not increase the risk of prostate cancer in PD.

11 References

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12 Appendices

12.1 Appendix 1 Data summary

12.2 Appendix 2 Complete follow-up period analysis of prostate cancer incidence

12.3 Appendix 3 Complete follow-up period analysis of prostate cancer mortality

12.4 Appendix 4 First drug use period analysis of prostate cancer incidence

12.5 Appendix 5 First drug use period analysis of prostate cancer mortality

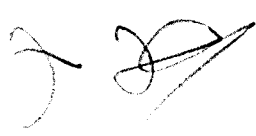
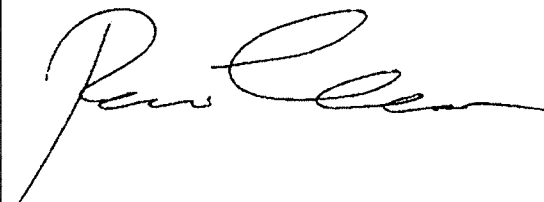
12.6 Appendix 6 Analysis of exploratory objectives

12.7 Appendix 7 Sensitivity analyses

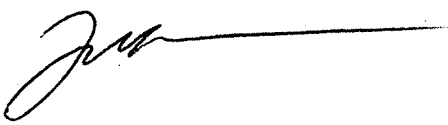
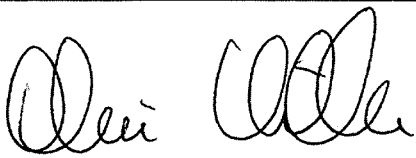
12.8 Appendix 8 Additional sensitivity analysis as recommended by FDA

APPROVALS

We have reviewed this pharmacoepidemiological study report (ER11-9411, version 1.0, dated 25 June, 2013) and accept it by signing it.

On behalf of EPID Research Oy		
Principal investigator	Signature	Date
Jari Haukka, PhD Adjunct Professor of Epidemiology Chief Scientific Officer		25 JUNE 2013
Pasi Korhonen, PhD Adjunct Professor of Biostatistics CEO		25 JUNE 2013

We have reviewed this pharmacoepidemiological study report (ER11-9411, version 1.0, dated 25 June, 2013) and accept it by signing it.

On behalf of Orion Corporation Orion Pharma		
Name and title	Signature	Date
Jukka Pesonen Director Drug Safety and Qualified Person Responsible for Pharmacovigilance (QPPV)		25/06/2013
Olavi Kilkku Director Biostatistics and Support Functions		25/06/2013