NON-INTERVENTIONAL (NI) STUDY REPORT

PASS information

Title	A Population-Based Cohort Study Using an Existing Database to Evaluate the Association Between Latanoprost Use and Primary Malignant Ocular Melanoma And Facial Cutaneous Melanoma
Protocol number	A6111157
Version identifier of the final study report	1.0
Date of last version of the final study report	19 August 2016
EU Post Authorisation Study (PAS) register number	ENCEPP/SDPP/8241
Active substance	Latanoprost (ATC: S01EE01)
Medicinal product	XALATAN® (LATANOPROST)
Product reference	PN-174912
Procedure number	Not applicable
Marketing Authorisation Holder (MAH)	Pfizer Limited Ramsgate Road, Sandwich, Kent CT130 NJ United Kingdom

Joint PASS	No
Research question and objectives	**RESEARCH QUESTION** To examine the potential risk of primary malignant ocular melanoma (OM) and facial cutaneous melanoma (CM), respectively, associated with latanoprost and other topical prostaglandin analogues (PGAs) among patients with glaucoma or ocular hypertension. **Primary Objective:** To examine the potential association between latanoprost use and risk of OM and facial CM. **Secondary Objective:** To examine the potential association between use of PGAs and risk of OM and facial CM.
Country(-ies) of study	Sweden
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1. ABSTRACT (STAND-ALONE DOCUMENT)

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
AE	Adverse event
ACME	Automated Classification of Medical Entities
ATC	Anatomical Therapeutic Chemical
CDR	Causes of Death Register
CHMP	Committee for Medicinal Products for Human Use
CM	Cutaneous Melanoma
DDD	Defined Daily Doses
e-HRD	Electronic Health Related Databases
EMA	European Medicines Agency
EU	European Union
HR	Hazard Ratio
ICD-9/10	The International Classification of Diseases Ninth/Tenth Revision
ICD-O-2/3	The International Classification of Diseases for Oncology Second/Third Revision
ICH GCP	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice
IQR	Interquartile Range
IOP	Intraocular Pressure
IRB/IEC	Institutional Review Board/Independent Ethics Committee
IR	Incidence rate
IRR	Incidence Rate Ratio
LPREIW	Longitudinal Population Register on Education, Income and Work
MAH	Marketing Authorisation Holder
MHRA	Medicines and Healthcare products Regulatory Agency
NCSP	Nordic Medico-Statistical Committee Classification of Surgical Procedures

NI	Non-Interventional
NMSC	Non-melanoma skin cancer
NSAIDs	Nonsteroidal anti-inflammatory drugs
NPR	National Patient Register
OH	Ocular Hypertension
OM	Ocular Melanoma
OTC	Over-the-counter
PASS	Post-Authorization Safety Study
PDR	Prescribed Drug Register
PhVWP	Pharmacovigilance Working Party
PGA	Prostaglandin analogue
PV	Pharmacovigilance
RR	Relative Risk
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedures
SCR	Swedish Cancer Register
SNOMED	Systematized Nomenclature of Medicine

3. INVESTIGATORS

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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Date of Independent Ethics Committee (IEC) or Institutional Review Board (IRB) approval of protocol	16 April 2014	16 April 2014	
Start of data collection	15 May 2015	15 May 2015	
End of data collection	11 September 2015	11 September 2015	
Registration in the EU PAS register	01 December 2014	01 December 2014	
Final report of study results	11 September 2016	09 September 2016	Planned date of September 11, 2016 is a Sunday, therefore, date was moved up to Friday September 9, 2016

6. RATIONALE AND BACKGROUND

6.1. Background

Medical treatment for glaucoma includes use of systemic and topical intraocular pressure-lowering medications. Xalatan® (latanoprost ophthalmic solution 0.005%) is a prostaglandin $F_{2\alpha}$ analogue that has been developed for the reduction of intraocular pressure (IOP) in patients with glaucoma and is delivered as a single liquid drop to the surface of the eye, with a serum half-life of 17 minutes. Xalatan was approved for the reduction of elevated IOP in adult patients with glaucoma and ocular hypertension (OH) in the European Union (EU) in 1996 and was approved for similar indications worldwide. It was also approved for the reduction of elevated IOP in paediatric patients with glaucoma or elevated IOP in the EU in 2010. Xalatan no longer has patent exclusivity in European countries as of 2012 and non-branded latanoprost has become available to patients. Xalacom® is the fixed combination of latanoprost and timolol maleate (beta-blocking agent). It was approved for the reduction of IOP in adult patients with open angle glaucoma and OH who are insufficiently responsive to topical beta-blockers or prostaglandin analogues (PGA) in the EU in 2000. Other topical PGAs available in the majority of EU markets include bimatoprost, travoprost, tafluprost and their fixed combinations with timolol.

A potential signal of an increased risk of malignant melanoma with latanoprost treatment was raised at the June 2009 Pharmacovigilance Working Party (PhVWP) of the Committee for Medicinal Products for Human Use (CHMP) meeting. In order to assess the potential association between the use of latanoprost and malignant melanoma, the Marketing Authorisation Holder (MAH) submitted a cumulative review to the European Medicines Agency (EMA) in August 2009, including data from in vitro and in vivo studies, data from MAH-sponsored clinical trials (November 1992 to November 2007), and spontaneous non-trial-related clinical reports from MAH's safety database (13 years for latanoprost and 9 years for latanoprost/timolol).

Among 12,880 latanoprost-treated patients in clinical trials, no cases of ocular melanoma and three cases of cutaneous melanoma were identified. Of 19,940 spontaneously reported adverse events among latanoprost users outside of clinical trials recorded in the safety database, eleven were ocular melanomas and six were cutaneous melanomas. Possible association with latanoprost use could not be excluded in three ocular and one periorbital melanoma events, but was excluded for all six reports of cutaneous melanoma. In a 5-year randomized open-label study of latanoprost and usual care[1] and a 5-year open-label uncontrolled safety study of latanoprost[2] conducted to address long-term safety including possible malignant transformation within the ocular structures due to its administration, no ocular or cutaneous melanoma cases were observed. Non-clinical data supports the hypothesis that latanoprost is not carcinogenic and does not promote proliferation of melanocytes.[3] The increase in iris pigmentation observed with latanoprost treatment results from stimulation of melanin synthesis by induction of tyrosinase transcription without increasing mitotic activity[4,5,6], and appears to be a class effect for PGAs[6]. Further, published literature showed no correlation between induced iris darkening or periocular skin pigmentation and the length of time a patient was exposed to latanoprost and PGAs.[6]

Therefore, there is insufficient evidence to support a causal link between latanoprost or latanoprost/timolol use and ocular or cutaneous melanoma.

6.2. Ocular and cutaneous melanoma

Malignant ocular melanoma (OM) is a rare type of cancer with an estimated annual incidence of 2 to 9 per million in European general populations[7] and approximately 5 per million in the US general population[8]. Annual incidence of OM among patients with glaucoma is unknown; however one study suggested that the annual incidence may be lower than 30 per million.[9] Uveal melanoma, which is located in the iris, ciliary body and choroid of the eye, accounts for the majority (85%) of OM in adults.[10] Other less common locations include the orbit, lacrimal gland, and conjunctiva, cornea or other unspecified ocular sites.[10]

Malignant cutaneous melanoma (CM) is uncommon but deadly.[11] A wide range of incidence rates are reported due to varying geography and ultraviolet (UV) exposure patterns.[12] In Europe, the highest incidence rates have been reported in Scandinavia (about 15 cases per 100,000 inhabitants per year) and the lowest in the Mediterranean countries (about 5-7 cases per 100,000 inhabitants per year).[13] The incidence in the US is reported to be 10-20 cases per 100,000 inhabitants per year and in Australia 40-60 cases per 100,000 inhabitants per year.[13] From 1973 to 1981, the estimated incidence of CM on the face in the US general population was 2.0 per 100,000 person-years in males and 1.3 per 100,000 person-years in females.[14] The incidence of CM on the face among glaucoma patients has not been reported in the literature.

The developing consensus shows considerable differences between CM and OM in terms of etiology, molecular biology and clinical behavior, and these two cancers require distinct consideration. Cutaneous melanocytes are derived from a different cell line than are uveal melanocytes. The former are derived from neuro-ectoderm and the latter from neural crest.[3] Another significant difference is that the periocular darkening process involves the production of many new melanin granules, whereas in induced iris darkening the increase in granule size is the predominating factor.[6] Additionally, the metastatic behavior of the two melanomas and tumor cytogenetics are distinctly different.[15] Epidemiological findings also support the distinction between CM and OM as separate disease entities. The incidence of OM has been notably stable over the last five decades[16,17,18], while there has been a continuous increase of CM incidence rates over the last 60 years in white populations, primarily due to increased UV exposure[11,12,15,17]. In contrast to the known contribution of UV radiation exposure to CM[15,17], the etiological role of UV radiation exposure is equivocal in the case of OM[15,19,20,21]. OM more often affects older aged individuals whereas CM is often a disease of younger aged individuals.[15]

6.3. Rationale

As described earlier, a potential signal of an increased risk of malignant melanoma with latanoprost exposure was raised in June 2009 at the CHMP meeting. Based on a feasibility assessment that was submitted to the MHRA[22] (Pfizer Inc. 2011), it was concluded that an existing database (ie, Swedish national health care register) can be used for an adequately powered study for OM and facial CM associated with latanoprost use.[22]

This non-interventional study was designated as a Post-Authorisation Safety Study (PASS) and was a commitment to the Medicines and Healthcare products Regulatory Agency (MHRA).

7. RESEARCH QUESTION AND OBJECTIVES

The primary objectives were to estimate the hazard ratios of primary OM and facial CM among patients with glaucoma or OH,

- By comparing users of latanoprost with users of topical non-PGAs
- By comparing users of latanoprost with users of other topical PGAs

The secondary objectives were to estimate the hazard ratios of primary OM and facial CM among patients with glaucoma or OH,

- By comparing users of other topical PGAs with users of topical non-PGAs
- By comparing users of topical PGAs with users of topical non-PGAs

An additional objective was to describe, over time, the clinical characteristics and the use of latanoprost, other topical PGAs and topical non-PGAs in glaucoma/OH patients. Descriptions for exposure drug groups are found in section 9.4.1.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

9.1. Study design

This was a cohort study using existing data from the Swedish National Health Registers.

9.1.1. Study strengths

One of the major advantages of a using a cohort study utilizing an existing database was that the incidence of primary ocular and facial cutaneous melanoma in glaucoma/OH patients receiving latanoprost and PGAs could be estimated and compared with glaucoma/OH patients who did not receive latanoprost and PGAs. The characteristics of the two groups such as demographic variables and concomitant medication use could also be estimated. Further, it was possible to study two endpoints (OM and facial CM) in the same study using a retrospective cohort study design.

Second, the Swedish national register database covers the entire population of Sweden (9.1 million) and provided a relatively large sample size to study rare events. Recall bias and outcome misclassification would be minimized due to the mandatory reporting and verification procedure of cancer cases in Sweden. Third, the national register system allowed for a continuous and long follow-up period for majority of patients. Finally, a unique personal identity number of each patient allowed for the data linkage between prescription drugs, the outcome, and the covariates.

9.2. Setting

The study was conducted in Sweden using data from the Swedish national health care registers. A unique personal registration number is issued to all residents in Sweden upon birth or immigration and is used throughout life. The unique personal registration number is used to link patients' data from the different registers. The primary sources of data include the following registers and are described in Section 9.5:

- the Swedish Prescribed Drug Register (PDR),
- the Swedish Cancer Register (SCR),
- the National Patient Register (NPR),
- the Causes of Death Register (CDR), and
- the Population Registers of Statistics Sweden

9.3. Subjects

The source population for this study constituted all patients with either a recorded diagnosis of glaucoma or ocular hypertension, or a procedure code for glaucoma surgery or at least one filled prescription of a medication approved exclusively for glaucoma or ocular hypertension. They were identified from the NPR (1997-2012) and from the PDR (2006-2012) through diagnosis (International Classification of Diseases [ICD] codes), performed procedures (Nordic Medico-Statistical Committee Classification of Surgical Procedures [NCSP 2002] codes) and/or filled prescriptions (Anatomical Therapeutic Chemical [ATC] classification codes).

9.3.1. Inclusion criteria

The study population for the primary and secondary objectives consisted of patients with at least one dispensing of topical drugs for glaucoma or OH between 01 July 2006 and 31 December 2012. To be eligible for the study, the individuals had to have at least 12 months database membership prior to inclusion and no history of malignant ocular or cutaneous melanoma at inclusion.
Cohort inclusion date was the date of a first filled prescription of any topical drugs for glaucoma or OH. Index date was the same as inclusion date plus the lag time. Information regarding lag times is described in section 9.3.3. Follow-up started at index date and continued until the earliest occurrence of one of the following events:

- First occurrence of the endpoint under study. If a patient develops both OM and facial CM, the patient was censored at the date of the first malignancy.
- Death
- Emigration
- End of the study follow-up at 31 December 2012.

Patients in the identified study population who had a filled prescription of topical drugs for glaucoma or OH between 01 July 2005 and 30 June 2006 (i.e., prior to entry in the study cohort) were considered as prevalent users. For sensitivity analyses, incident PGA users were selected by excluding patients with a dispensing of any PGA between 01 July 2005 and 30 June 2006. The Swedish Prescribed Drug register included all drugs dispensed since 01 July

2005 and as treatment with PGAs is expected to be a continuous treatment, those with a first prescription of PGA after 30 June 2006 are considered to be incident users.

9.3.2. Exclusion criteria

To ensure the melanoma cases ascertained during the study period represented incident malignant melanoma, patients with a previous diagnosis of malignant melanoma between 1958 (when the cancer register was established) and the date of study inclusion were excluded from the study.

9.3.3. Characterizing exposure for person-time

Since the possible pathogenesis of cancer in connection with latanoprost and other topical PGAs are unknown, two different exposure definitions were used: ever exposure and real-time exposure. In addition, the induction time for the occurrence of malignant OM and facial CM potentially associated with the use of latanoprost and other topical PGAs is unknown. Therefore, lag times were incorporated into the exposure definitions.

9.3.3.1. Defining Lag times

Since induction time is unknown, a lag time of 6 months was considered as a minimum between start of drug prescription and occurrence of melanoma cases.[23] For example, 6 months lag time meant follow-up of a patient occurred 6 months after the date of the prescription drug. Therefore, any malignant OM and facial CM cases that occurred within the interval of the 6 months since start of prescription were excluded.

9.3.3.2. Defining Ever Exposure

An ever exposure definition assumed that exposure to latanoprost or other topical PGAs will result in a lifetime change in risk associated with the drug. If a patient was exposed to latanoprost or other topical PGAs, the status of exposure was maintained until censoring, regardless of subsequent dispensing patterns (Figure 1). The person-time of follow-up in ever exposure to latanoprost or another topical PGA started at index date (i.e., first dispensing + lag time) and continued to the end of the follow-up period.

If the first drug being dispensed was a topical non-PGA, the person-time of exposure to the topical non-PGA started at index date (first dispensing + lag time) and continued to the earliest of the following dates: date of the first dispensing (+ lag time) of latanoprost or other topical PGAs, or the end of follow-up period. If a patient used both non-PGA and PGA simultaneously, then the follow up time was counted only as PGA exposure time, i.e. concurrent use was handled in a hierarchical manner with latanoprost>other PGA>non-PGA. Time on topical non-PGAs after dispensing of a topical PGA or latanoprost was ignored.

For the main analyses: A lag time of 6 months between the start of treatment and the occurrence of the study endpoints was applied. As the induction time for the occurrence of malignant OM and facial CM potentially associated with the exposures is unknown, sensitivity analyses to address the impact of a lag time of zero (i.e. no lag time) and of 12 months on the study endpoints were conducted.

9.3.3.3. Defining Real-time Exposure

In contrast to the ever exposure definition, the real-time exposure definition considered the drug exposure as a time-varying exposure. The real time exposure definition classified a user as exposed to a drug cohort starting at each dispensing and continuing until a) estimated end of supply, b) a filled prescription of another drug, or c) where appropriate, censoring. For an illustration of real time exposure definition see Figure 2. If the first drug being dispensed was a topical non-PGA followed by a topical PGA, the time of exposure started at the date of the dispensing of the topical non-PGA and continued to the date of the dispensing of the topical PGA.

Overlapping time with both non-PGA and PGA exposure was counted only as PGA exposure time. Thus, simultaneous exposure drug use was handled in a hierarchical manner with latanoprost>other PGA>non-PGA (Figure 2: Scenario 1 and 2). If a new prescription was filled for the same drug (latanoprost, other PGA or non-PGA) while the supply of the previous filling was still ongoing, then the start of the next dispensing was moved to the end of the previous filling (Figure 2: Scenario 3). Overlapping use not defined as simultaneous use was regarded as switching. Dispensing a different drug within 14 days of another drug was considered a switch and the first drug was disregarded. Therefore, when exposure drug switching occurred the ongoing exposure was cut short and the exposure was then attributed to the newly dispensed drug (Figure 2: Scenario 4).

For the main analyses: A zero month lag time (i.e. no lag time) between the start of drug and the occurrence of the study endpoints was applied. Since the real time exposure definition was utilized to estimate the actual exposure, the optimal choice for lag time in the main analysis was zero months. Introducing lag time other than zero months may lead to difficulties in interpreting the results such as several exposure episodes introducing repeated shifts. For this definition, sensitivity analyses were conducted using 6 months lag time.

9.4. Variables

9.4.1. Exposures

Exposure to four groups of topical drugs for glaucoma and OH were studied:

1. Latanoprost – Latanoprost and Latanoprost/Timolol.
2. Other topical PGAs – Bimatoprost, Travoprost, Tafluprost, and combinations of these with Timolol.
3. PGAs – Latanoprost and other topical PGAs.
4. Topical non-PGAs – Acetazolamide, Apraclonidine, Betaxolol, Brimonidine, Brinzolamide, Dipivefrine, Dorzolamide, Carbachol, Pilocarpine, Acetylcholine, and combinations of these with Timolol.

To identify the study drugs of interest, ACT codes obtained from the PDR were used (01 July 2005-31 December 2012). The information on codes of topical drugs of glaucoma, the classification of topical drugs for glaucoma and OH (PGAs and non-PGAs) substances of the drugs, recommended dosage and constraints for duration are found in Table 1 and Table 2. Data on topical drugs for glaucoma and OH were available during the entire study period. The NPR was used to identify the recorded diagnosis of glaucoma/OH and co-morbidity

(except for cancer). The codes used were ICD-10 codes available from 1997, and surgical procedures performed for glaucoma (NCSP codes from 2002 and onwards) (Table 3).

9.4.2. Outcomes

The two primary outcomes were:

- Diagnosis of a primary (i.e., not recurrent or secondary) OM
- Diagnosis of a primary facial CM

All outcome events were identified from the SCR, included only histologically verified melanoma, using ICD-O-3 codes. The codes used to identify the endpoints are described in Table 4.

9.4.3. Confounders and/or Effect Modifiers

Information on risk factors for the outcomes of interest and confounding variables are listed in Table 5. Variables were classified as either time-fixed or time-varying.

Time-fixed covariates included: age, sex, country of birth, place of residency, occupational history, and diagnosis of diabetes.

Time-varying covariates included:

- Variables associated with studied indication or exposure (explicit diagnosis of glaucoma or ocular hypertension and use of nonsteroidal anti-inflammatory drugs [NSAIDs]),
- Diagnoses that alters the risk of cutaneous malignant melanoma (diagnosis of atopic dermatitis, diagnosis of psoriasis and diagnosis of dysplastic naevus syndrome)
- Drugs that may alter the risk of cutaneous malignant melanoma (use of immune-suppressants and/or biological agents and use of cytostatics)
- Cancer diagnoses (diagnosis of non-melanoma skin cancer, diagnosis of non-facial cutaneous melanoma, and diagnosis of any cancer (except non-facial cutaneous melanoma or non-melanoma skin cancer)

9.5. Data sources and measurement

The data sources used in this study were linked by use of the personal registration number, a unique identifier assigned to all Swedish residents at birth or upon immigration and kept throughout life. All linkage between data sources occurred within the Swedish National Board of Health and Welfare, and anonymized data were delivered to the Karolinska Institute's Centre for Pharmacoepidemiology (CPE).

9.5.1. Swedish Prescribed Drug Register (PDR)

The PDR has been functioning since July 2005 and contains data with unique patient identifiers for all filled prescriptions to the whole population of Sweden (9.2 million inhabitants). The register is complete for the entire Swedish population (patient identity data are missing for <0.3% of all items). All drugs are classified according to the ATC classification system. Measurement units of utilization are prescriptions, Defined Daily Doses (DDDs) and expenditures. The register does not include data on over-the-counter

(OTC) medications. Furthermore, it holds incomplete data on drugs administrated during in- and out-patient hospital visits and drugs administrated in nursing homes.

9.5.2. National Patient Register (NPR)

The NPR contains data from all hospital admissions in Sweden. From 1987 it covers all public inpatient care and since 2001 all outpatient visits. The medical data includes main and secondary diagnoses and surgical procedures. Main diagnosis, secondary diagnosis and procedures from public and private service providers are included in the NPR. A quality control of the NPR is performed on the register, and in 2006 the main diagnosis was missing in 1.0%.[24]

9.5.3. Swedish Cancer Register (SCR)

The Swedish Cancer Register (SCR) covers the whole Swedish population. Approximately 50,000 neoplasms are registered every year in Sweden. It is compulsory for every health care provider to report new cases to the registry. The report informs about every cancer diagnosed at clinical, morphological, or other laboratory examinations, as well as cases diagnosed at autopsy. Since 2005, the site and histological type of the cases have been coded in ICD-O-3 codes. A quality study published in Acta Oncologica in 2009 estimated that underreporting was 3.7%.[25]

9.5.4. Causes of Death Register (CDR)

The CDR comprises all deaths among Swedish residents, whether occurring in Sweden or abroad. The causes of death are coded according to the international (English) version of ICD-10. The register is updated yearly. In 2006, the non-reporting rate was 0.7% of all deaths.[26]

9.5.5. The Population Registers of Statistics Sweden

Population registers from Statistics Sweden holds individual information on region of residency, occupation, emigration and immigration.

9.6. Bias

- Even though data was available on the exposure groups from the PDR which holds almost complete data on all filled prescriptions of drugs in the Swedish population, a filled prescription does not necessarily imply the use of the drug by the patient. This could have resulted in misclassification of drug exposure.

- Misclassification of exposure is a possibility. When using register based data, misclassification may occur if coding is not correct. However, exposure misclassification is expected to be non-differential in this study.

- Protopathic bias may occur since glaucoma/OH could be the first sign of OM, and the drug exposure may incorrectly be associated with an increased risk of OM. Protopathic bias, thus, reflects a reversal of cause and effect.[27] This is particularly a problem in studies of drug-cancer associations. In this study, 58% of OM was diagnosed within 6 months after the first filled prescription of a topical glaucoma/OH drug, than later (i.e., greater than 6 months) during follow-up. This may be consistent with protopathic bias. In

order to handle this matter the study included a lag-time of 6 months in the main analyses, and added different lag times to the sensitivity analyses.

- Surveillance (detection) bias is a potential bias in this study. For instance, if the patients in one exposure group have a higher probability of initiating their treatment by ophthalmologists, who are more likely to have an ophthalmoscopy compared to a general practitioner, then this may increase the possibility to identify an OM. The study adjusted for a diagnosis of glaucoma recorded in the NPR to handle potential surveillance bias.

- The results of the study may be influenced to some extent by unmeasured confounding due to UV exposure, e.g. life-style factors, travelling to warmer countries or time spent outdoor. It was not possible to address these factors in this study setting. In addition, the PDR does not include information on drugs purchased OTC. It is possible to purchase NSAIDs OTC, and thus, the information of exposure to NSAIDs is not complete in the PDR. Some drugs, such as infusions, antibiotics and analgesics administered during hospitalization, day-care at hospital and in nursing homes are not recorded in the PDR, and thus, not possible to be captured in this study.

9.7. Study Size

Sample size calculations were conducted during protocol development to estimate the minimum number of patients needed to address the primary study objectives. Incidence rates (IR) of OM and facial CM in glaucoma population, the loss-to-follow up rate, and the true exposed versus unexposed hazard ratios (HRs) are unknown and were estimated based on the data obtained from the preliminary feasibility assessment. Based on standard Cox proportional hazard model, assuming the incidence rate of a given melanoma in glaucoma population of 150 per million-year, a latanoprost exposed-to-unexposed ratio of 1:2, a total study duration and recruitment period of 6.5 years, a loss-to-follow rate of 3% per year and the minimum detectable HR of 2.0 with 80% power at a 5% significance level, the total number of glaucoma/OH patients required for the study was 116,172.

9.8. Data transformation

Raw data obtained from the National Board of Health and Welfare (NBHW) and Statistics Sweden were transformed into a common data model developed at the Centre for Pharmacoepidemiology, Karolinska Institutet (CPE). Analysis data sets were derived from these data.

The raw data was “verticalized” (i.e. one column for diagnose code, one for code system, one for start and stop dates etc.) and concepts were matched on from a concept dictionary. A basic analysis dataset (one record per subjects) was then created by adding protocol defined dates, demographic event dates (e.g. death, emigration) for censoring purpose and event dates and analysis flags for exposure, outcome and confounders in relation to the index date(s).

9.9. Statistical methods

Detailed information on the statistical methods was documented in the Statistical Analysis Plan (SAP) in Appendix 4. Any deviations from the SAP and/or additional analyses are documented in this report (section 9.9.5).

9.9.1. Main summary measures

Descriptive statistics were presented to describe patient characteristics such as age, sex, country of birth, occupation, geographical location of residence, glaucoma diagnosis, pharmacological and surgical treatments used in the latanoprost, other topical PGA and topical non-PGA cohorts at study entry. Frequencies and proportions were used to describe categorical variables (e.g., diabetes yes/no) and means and standard deviations (or median with inter quartile range (IQR), where appropriate) were calculated for continuous variables (e.g., age).

Baseline characteristics of the study population of PGA users, prevalent and incident, at the time of cohort entry, and by treatment cohorts were summarized, including demographic information, comorbidities and use of co-medications. The patterns of drug use over time were described using the following measures:

- Duration of exposure (accumulated time) at censoring
- Time from first filled prescription to censoring
- Time since last filled prescription to censoring

The crude incidence rates (IR) were calculated as number of events per 100,000 person-years of OM and facial CM. Hhazard ratios (HR) were estimated by comparing different exposure groups for both study endpoints.

9.9.2. Main statistical methods

Cox regression with time varying covariates was used for all analyses of time to facial CM and OM, respectively. Each patient's follow-up time was split into non-overlapping time-intervals; within each interval all covariates values remained constant. Consequently, the Cox regression was a counting process approach. For classification of whether covariates are time-varying or constant see Section 9.4. The proportional hazards assumption was assessed by using Kaplan-Meier curves and by the log-rank test. Hazard ratios with corresponding confidence intervals were estimated from the cox regressions. The main analyses were conducted on ever exposure with 6 months lag time and real-time exposure using zero lag time for each of the 3 models described below.

- Model 1: A minimal Cox regression model that adjusted only for sex and age.
- Model 2: A full Cox regression models that adjusted for all covariates.
- Model 3: A change in estimate model where each potential covariate was tested for inclusion by comparing the model adjusted for sex, age and the current covariate to Model 1. The tested covariate was included if the relative change in HR was more than 1%.

All results are given in aggregated form. Analyses were carried out using SAS® version 9.4, SAS Institute, Cary, NC, USA.

Person-time at risk

In this study, a patient may contribute person-time to different exposures, based on drug exposure during follow-up. Two different exposure definitions were used: ever exposure and real-time exposure (see section 9.3). Observed person-time was calculated as the sum of years during the follow-up period. The underlying time scale for the Cox regressions was time since index date (first dispensing + lag time).

Duration of use was defined as the total time of use of the drug during follow-up. For each patient, duration of use was accumulated daily according to the assumed duration of prescriptions. Durations were calculated as number of bottles times 28 days, since each bottle is estimated to cover 28 days of treatment. For single dose packages (unit dose), duration was set to the number of unit doses dispensed multiplied by the number of filled prescriptions.

Gaps are periods in which no medication was available to the patient. For each period of 28 days covered, a gap of 7 days was allowed, i.e. counted as continuous exposure despite the gap. For example, when a patient had filled a prescription of 3 bottles at one time, a gap of 21 days between previous dispensing's last date of supply and the next filling was permitted. Thus, if the patient filled a new prescription within the 21-day time period, the therapy was still considered as continuous. Overlaps (filling of prescriptions before estimated end of supply) of the same substance was shifted forward in time.

Simultaneous exposure drug use

Simultaneous drug use was defined as dispensing of more than one drug within one week in the PDR.

- In the ever exposure definition, simultaneous use was classified according to the hierarchy: latanoprost and other topical PGAs > topical non-PGAs. If patients were exposed to latanoprost or other PGAs, with simultaneous exposure of a topical non-PGA, then they only contributed person-time to the latanoprost or the other PGAs group, and the exposure of the topical non-PGAs was ignored. For simultaneous use of latanoprost and other topical PGAs, person-time was exclusively contributed to the first dispensed group (latanoprost or other PGAs), and the exposure to the other drug was ignored.

- In the real-time exposure definition, simultaneous use was classified according to the hierarchy: latanoprost > other PGAs > non PGAs. Patients, who were exposed to latanoprost or other PGAs with simultaneous exposure of a topical non-PGA, contributed person-time to the latanoprost or the other PGAs group, while the exposure of the topical non-PGAs was ignored. For simultaneous use of latanoprost and other topical PGAs, the exposure to other PGAs was ignored and person-time was exclusively contributed to the latanoprost group. Overlapping use not defined as simultaneous use was regarded as switching treatment. When a switch occurred the ongoing exposure was stopped and the newly dispensed drug became the drug of exposure.

9.9.2.1. Primary analyses

The primary analyses compared:

- Latanoprost exposed time to event vs. topical non-PGAs exposed time to event, and
- Latanoprost exposed time to event vs. other topical PGA exposed time to event.

The primary analyses utilized two exposure definitions, ever and real time exposure.

9.9.2.2. Secondary analyses

The secondary analyses compared:

- Other topical PGA exposed time to event vs. topical non-PGAs exposed time to event, and
- Topical PGA (latanoprost or other topical PGAs) exposed time to event vs. topical non-PGAs exposed time to event.

The secondary analyses utilized two exposure definitions, ever and real time exposure.

9.9.3. Missing values

As a general rule, subjects with missing values of a covariate did not contribute to the analyses. This was a limited problem since missing information was rare on the key variables such as: malignant melanoma, prescribed drugs and place of residency in the registers used. Age and sex were never missing since these are derived from the unique personal identifier. As a register-based study, if a patient did not have a diagnosis or drug code recorded, it was assumed that the patient did not have the disease or used the drug and no missing values were involved. A very small fraction of dates were imprecise with only year or only year and month given. Imprecise dates were imputed. A missing category is presented in the descriptive tables for variables with missing values.

9.9.4. Sensitivity analyses

The following sensitivity analyses were performed:

9.9.4.1. Subgroup analysis on incident users

In order to assess the potential associations of interest among incident users, the same analytical approach as described for the main analysis (full and minimal model for both ever use with 6 months lag time and real time use with zero lag time) was repeated among incident users of PGAs. Incident users in the study cohort were defined as users with no dispensing of any PGA between 01 July 2005 and 30 June 2006. The Swedish Prescribed Drug register included all drugs dispensed since 01 July 2005 and as treatment with PGAs was expected to be a continuous treatment; those with a first dispensing of PGAs after 01 July 2006 were considered to be incident users.

9.9.4.2. Use of different lag times by exposure definitions

Furthermore, sensitivity analyses were performed with 0 and 12 months lag time in the ever exposure analyses and with 6 months lag time in the real-time exposure analyses. This was done to minimize the risk of potential detection bias and protopathic bias, and also to account for a possible induction time in a potential association between the exposures and outcomes.

9.9.5. Amendments to the statistical analysis plan

9.9.5.1. Addition of variable to the model: non-facial CM

In the SAP, non-facial CM was not a variable considered as a confounder or as an effect modifier. However, this variable was added as a time-varying covariate in the analyses since it is an important risk factor for subsequent facial CM.[28]

9.9.5.2. Full model change in estimate

In the SAP, the change in estimate model was not included, but in order to handle the possible convergence problems that may occur within a limited sample it was added to the main analyses. The change in estimate method reduces the number of covariates in the models. Starting from the minimal Cox model (sex and age were already included) each covariate was tested, and included, if the relative change in HR was more than 1%.

9.9.5.3. Drop occupational history due to missing values

In the SAP, occupational history was a variable of importance as a proxy of sun exposure. However since a high proportion of the study population were missing this value (>50%), this variable was not used in the analyses.

9.10. Quality control

Security processes were in place to ensure the safety of all systems and data and that data could not be accessed by anyone except selected study staff.
Appropriate data storage and archiving procedures were followed, with periodic backup of files to tape. Standard procedures to restore files in the event of a hardware or software failure were in place.

CPE conducted quality control for data management and statistical analysis by following its internal guideline, “QC of data and Analysis & Reporting.” The guideline covers verification of data sets delivered from the National Board of Health and Welfare and from Statistics Sweden, checks of inclusion and exclusion criteria when preparing the analysis data set, and plausibility and consistency checks of output. All programs were checked and issues resolved. Senior team members from CPE conducted the final quality control for the deliverables. The programs, data sets, logs, and lists associated with this study, as well as all study deliverables, have been archived by CPE.

9.11. Protection of human subjects

9.11.1. Subject information and consent

Not Applicable.

9.11.2. Independent Ethics Committee (IEC)/ Institutional Review Board (IRB)

The study was approved by the Regional Ethical Review Board at Karolinska Institute on the 16 April 2014 (2014/509-31/2)

9.11.3. Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor, and followed generally accepted research practices described in Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on

Methodological Standards in Pharmacoepidemiology, and Food and Drug Administration (FDA) Guidance for Industry: Good Pharmacovigilance and Pharmacoepidemiologic Assessment, FDA Draft Guidance for Industry and FDA Staff: Best Practices for Conducting and Reporting of Pharmacoepidemiologic Safety Studies Using Electronic Healthcare Data Sets.

10. RESULTS

10.1. Participants

A total of 231,760 individuals with at least one filled prescription of a topical drug for glaucoma or OH between 1 July 2006 and 31 December 2012 were identified (Figure 3). Of those, 3,897 individuals were not eligible to be included in the study due to a history of melanoma prior to the first dispensing of a topical drug. The study population consisted of 227,863 patients with a first dispensing of a topical drug for glaucoma or OH between the study period without history of any cancer at the time of cohort entry. The contribution of person-time included in the analyses depended on the definition of exposure (ever or real-time exposure), study cohort (all users or incident users) and lag time. Hence, a patient may have contributed time to more than one exposure drug group during the follow up period.

10.2. Descriptive data

Patient characteristics at cohort entry date are presented for the different exposure groups in Table 6. A total of 123,235 individuals contributed person-time to the latanoprost cohort, 73,974 to the other PGA and 169, 873 to the non-PGA cohort during the follow-up. The median age among latanoprost users was 76 years and among those exposed to other PGAs and to non-PGAs, the median ages were 73 years and 75 years, respectively. The proportion of females in the treatment cohorts varied between 56.9% and 57.9 %. The proportions of individuals with diabetes, atopic eczema, a recorded diagnosis of glaucoma and OH, dysplastic naevus syndrome, psoriasis, any cancer and individuals born in Sweden were similar in the different exposure cohorts. Furthermore, the use of immunosuppressant and cytostatic were similar between the exposures. The recorded use of oral NSAIDs was more common among other PGA users compared to latanoprost and non-PGA users (34.6% versus 30.8% and 31.2%, respectively). Latanoprost exposed were more often residents of the northern region of Sweden (18.9 %) than other PGA exposed (15.3%). Information about outdoor work, which was a predefined covariate, had an unexpectedly high proportion of missing values (47%-55%).

Prevalent and incident PGA users

Among PGA users 47.1% of the patients were classified as prevalent users, i.e. who had a filled a prescription of any PGA between 1 July 2005 and 30 June 2006 (Figure 4). A total of 73.5% of the prevalent PGA users were treated with latanoprost at cohort entry, 15.2% with other PGAs, and 11.3 % entered the study with a non-PGA treatment. The incident users started latanoprost treatment in 40.1% of the cases, with other PGAs in 23.5% and with a topical non-PGA in 36.5%. The median age at cohort entry was 78 years among the prevalent PGA users and 73 years among incident users (Table 7). Females comprised 59.1% of the cohort of prevalent users and 55.7% of the incident users.

10.3. Outcome data

10.3.1. Duration of exposure (i.e. time of exposure during follow-up) and distribution of events

Ever exposure, 6 months lag time

Overall, 112,341 individuals contributed a total of 541,584 person-years of follow-up for assessment of OM among latanoprost treatment, on median 5.2 years follow-up per patient (Table 8). For other PGA treatment, 46,115 users contributed 179,831 person-years (median 3.5 years of follow-up per patient) and for non-PGA treatment, 95,777 users contributed 285,474 person-years (median 2.2 years of follow-up per patient). Median time since last date of dispensed supply to censoring was similar in the cohorts ranging from 0.0-0.3 years. For facial CM, similar number of individuals and median follow-up time were observed in the ever exposure analyses with a lag time of 6 months.

The total number of first events of OM and facial CM among those exposed to any topical drug for glaucoma or OH, were 21 and 151, respectively (Table 10). A larger proportion (58.3%) of OM was diagnosed among latanoprost and non PGA exposed within six months after a first filled prescription of a topical glaucoma /OH drug, than later during follow-up (Table 11). The corresponding frequency among other PGA exposed within 6 months was 25%.

Real-time exposure, zero month lag time

A total of 123,235 individuals contributed 382,996 person-years of follow-up for the assessment of OM among latanoprost exposed, on median 2.8 years follow-up per patient (Table 9). For other PGA treatment, 73,974 users contributed 163,323 person-years (median 1.8 years of follow-up per person). For non-PGA treatment, 169,869 individuals contributed person-time with a median follow-up of 1.1 years. In addition, 150,527 individuals were categorized with unexposed time. Time since last date of dispensed supply to censoring was similar in the cohorts, ranging from 0.7 to 1.0 years per person. For facial CM, similar number of individuals and median follow-up time were observed in the real-time exposure analyses with a lag time of zero months.

The total number of first events for OM and facial CM among those exposed to any topical drug for glaucoma or OH with, were 40 and 141, respectively (Table 10).

10.4. Main results

10.4.1. Crude incidence rates

OM

- In the ever exposure analyses, there were 10 OM events among latanoprost exposed patients, 6 among other PGAs and 5 among non-PGA exposed patients (Table 12). The incidence rates per 100,000 person-years were 1.8 among latanoprost exposed, 3.3 among other PGA exposed and 1.8 among those exposed to non-PGAs in the ever exposure analyses.
- In the real-time exposure analyses, there were 18 events among latanoprost exposed patients, 7 among other PGAs and 15 among non-PGA exposed patients (Table 13).

The corresponding incidence rates per 100,000 person-years were 4.7, 4.3 and 5.0, respectively.

Facial CM

- In the ever exposure analyses, there were a total of 70 facial CM events among the latanoprost exposed patients, which yielded an incidence rate of 12.9 per 100,000 person-year; a total of 31 (17.2 per 100,000 person-years) and 50 (17.5 per 100,000 person-years) among other PGAs and non-PGAs exposed patients, respectively (Table 14).
- In the real-time analyses, the lowest rate was for the latanoprost exposed patients (14.9 per 100,000 person-years) and the highest for those exposed to non-PGAs (18.6 per 100,000 person-years) (Table 15).

10.4.2. Primary objectives (Fully adjusted model results shown below [Model 2])

Latanoprost versus Non-PGAs

- Ever exposure (6 months lag time): When compared to non-PGAs, no associated risk of OM (HR 0.82; 95% CI: 0.27 - 2.49) or facial CM (HR: 0.71; 95% CI: 0.48 - 1.03) were observed among latanoprost users in the fully adjusted model (Table 16).
- Real time-exposure exposure (0 months lag time): When compared to non-PGAs, no associated risk of OM (HR 1.07; 95% CI: 0.53-2.16) or facial CM (HR: 0.79; 95% CI: 0.54-1.16) were observed among latanoprost users in the fully adjusted model (Table 16).

Latanoprost versus Other PGAs

- Ever exposure (6 months lag time): No associated risks were found for OM or facial CM among latanoprost exposed compared to other PGA exposed (HR: 0.52; 95% CI: 0.19-1.48) and (HR: 0.71; 95% CI: 0.46-1.10), respectively (Table 17).
- Real time-exposure exposure (0 months lag time): No associated risks were found for OM or facial CM among latanoprost exposed compared to other PGA exposed (HR 1.17; 95% CI: 0.48-2.85) and (HR: 0.84; 95% CI: 0.52-1.35), respectively (Table 17).

10.4.2. Secondary Objectives (Fully adjusted model results shown below [Model 2])

Other PGAs versus non-PGAs

- Ever exposure (6 months lag time): Compared to non-PGA users, the corresponding HRs for OM and facial CM among PGA users were 1.58 (95% CI: 0.47-5.32) and 1.03 (95% CI: 0.64-1.64), respectively (Table 18).
- Real time-exposure exposure (0 months lag time): Compared to non-PGA users the corresponding HRs for OM and facial CM among other PGA users were 0.72 (95% CI: 0.29-1.80) and 0.97 (95% CI: 0.60-1.57), respectively (Table 18).

PGAs versus non-PGAs

- Ever exposure (6 months lag time): When compared to non-PGA users, no associated risks were found for OM and facial CM among PGA users (HR: 1.02; 95% CI: 0.36-2.84) and (HR: 0.79; 95% CI: 0.55-1.13) respectively (Table 19).

- Real time-exposure exposure (0 months lag time): When compared to non-PGA users, no associated risks for OM and facial CM were found among PGA users (HR: 0.98; 95% CI: 0.51-1.90) and (HR: 0.84; 95% CI: 0.59-1.20) respectively (Table 19)

10.5. Other analyses

Results of Cox regression sensitivity analyses of incident users and for different lag times are presented in Table 20 through Table 29.

When sensitivity analysis was conducted for the ever exposure definition with lag time of zero months, the hazard ratio for the fully adjusted model showed borderline statistical significance for a lower risk of facial CM among latanoprost users compared to non-PGA users (HR: 0.69; 95% CI: 0.48 - 0.99) (Table 22).

In general, no increased risks were found with use of latanoprost or PGAs among incident users in the analyses, regardless of exposure category. No associations were found for latanoprost or PGA exposure on OM or facial CM, when using different exposure lag times.

10.6. Adverse events / adverse reactions

This study used patient-level electronic health related databases (e-HRD), in which the minimum criteria for reporting an adverse event (ie, identifiable patient, identifiable reporter, a suspect product, and event) are not available. Thus, adverse events are not reportable as individual adverse event reports.
According to the EMA *Guideline on Good Pharmacovigilance Practices (GVP), Module VI – Management and Reporting of Adverse Reactions to Medicinal Products*,

> "For non-interventional study designs which are based on secondary use of data, adverse reactions reporting is not required. All adverse events/reactions should be summarized in the final study report." (EMA, 2012a)

Module VIII – Post-Authorisation Safety Studies, of the same document echoes this approach (EMA, 2012b). The new legislation further states that for certain study designs such as retrospective cohort studies, particularly those involving electronic health care records, it may not be feasible to make a causality assessment at the individual case level.

11. DISCUSSION

11.1. Key results

This retrospective cohort study utilized the Swedish health registers to examine the potential association between latanoprost use and ocular or cutaneous melanoma among patients with glaucoma or OH. After controlling for potential confounders (i.e. socio-demographic factors, clinical characteristics, comorbidities, and concomitant drugs), no associations were found between the risk of primary OM or of facial CM, and latanoprost utilization compared to topical non-PGAs or other topical PGAs. Also, no associations were observed between the risk of primary OM and facial CM, respectively and PGAs compared to non-PGAs.

Results showed a larger proportion of OM was diagnosed within six months after a first filled prescription of a topical drug of glaucoma or OH than later during follow-up, which may be consistent with protopathic bias or surveillance bias. However, different lag time seemed to have no substantial impact on the risks, since the results of the cox regressions were consistent regardless of applied lag time.

Although the validity of the source of information from the Swedish registries used for the analysis has been documented over a long time to be accurate, it is possible the results may have been influenced by unmeasured confounders. Geographical location of residence was used as a proxy of recreational UV exposure; residency was considered to be an appropriate proxy of sun exposure, which was adjusted for in the cox regressions. Residency in the northern region of Sweden was associated with a lower rate of facial CM than residency in the southern or coastal region. This is in accordance with previous findings and that a lower rate of OM is associated with less sun exposure in northern Sweden. Data on occupational UV exposure was not available and therefore, residual confounding due to sun exposure is a possibility.

In general, results were consistent across the analyses of different exposure definitions (ever or real-time exposure), incident PGA use versus prevalent PGA use, and across different lag times. Even though the study used a large national health care register which comprised nearly all users of topical PGAs and topical non-PGAs in Sweden, the outcomes of interest, especially OM were uncommon. Thus, the risk estimates have rather wide confidence intervals.

11.2. Limitations

Rare outcomes
One of the main limitations of this study is the rarity OM and CM, as evidenced by the wide confidence intervals in the results.

Unmeasured and residual confounding
Information on patient characteristics such as smoking and obesity was not captured. Information on dispensed prescriptions does not include dose or instructions for use. Thus, duration of exposure was estimated from the total amount of substance in the prescription, as recorded in the Prescribed Drug Register, and the DDD. The DDD is defined by the World Health Organization as the assumed average maintenance dose per day for a drug used for its main indication in adults. A filled prescription of a drug does not necessarily imply use of the drug, and it is not possible to address this issue. The variable of occupational history to assess sun exposure was not included in the analysis due to the large amount of missing values. Although geographical location of residence was available as a proxy for sun exposure, residual confounding due to sun exposure is possible.
This study attempted to assess and control for the potential effect of age, sex, country of birth (a proxy of race/ethnicity), geographical location of residence (a proxy of sun exposure), co-morbidities and concomitant medications on the associations of interest. These are either known or potential risk factors of the outcomes or the factors that may be associated with exposures of interest. Information on other risk factors of melanoma (e.g. light skin and eye

color) was not recorded in the database and therefore cannot be adjusted for. However, there is no evidence that these factors are associated with latanoprost prescription and thus are unlikely to confound the associations of interest in this study.

Misclassification of exposure
The primary analysis which was conducted among prevalent glaucoma/OH patients and latanoprost use before the Swedish Prescription Drug Database was available (1 July 2005) may not be captured. If a patient used latanoprost before 2005 but not thereafter, this patient may be misclassified as unexposed. This is likely to be a non-differential misclassification as there is no reason to believe that this misclassification is related to the outcomes of interest.

11.3. Interpretation

The analyses from this study indicate that latanoprost exposure was not associated with higher risks of OM or facial CM compared to use of other other PGAs or non-PGAs. This study attempted to control for confounding variables including socio-demographic factors, clinical characteristics, comorbidities, and concomitant drug use. The results were consistent across the analyses on different exposure definitions (ever or real-time exposure), prevalent and incident use, and across different lag times.

11.4. Generalisability

Generalizations from these findings are possible to make on all users of the study drugs of interest in the Swedish population, since almost all users in Sweden are captured and followed. However, the study population may not be representative in other parts of the world which may limit the generalizability of the findings to populations with similar health systems, economy and social conditions.

12. OTHER INFORMATION

None.

13. CONCLUSIONS

No associated risk of OM or facial CM was found among latanoprost exposed patients compared to non-PGA exposed patients, or when comparing latanoprost exposure with other PGAs. In addition, there were no associated risks of OM and facial CM among PGA exposed (latanoprost + other PGAs) compared to non-PGAs. The findings were consistent when varying type of exposure (ever and real time exposure), restricted to incident PGA use, using different models in the cox regression, and when using different lag times.

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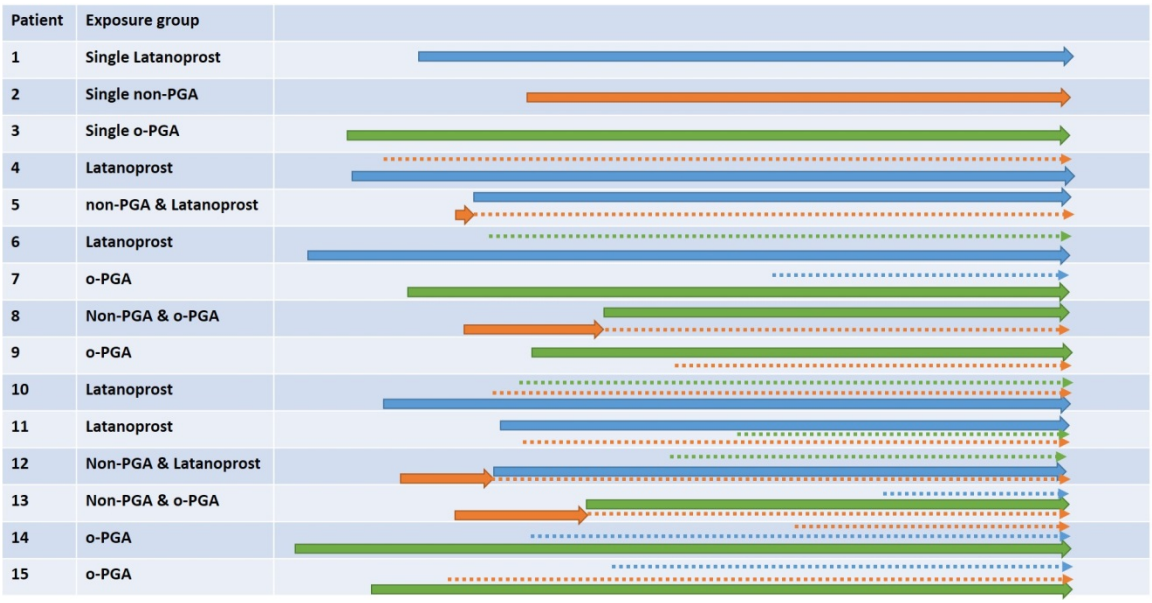
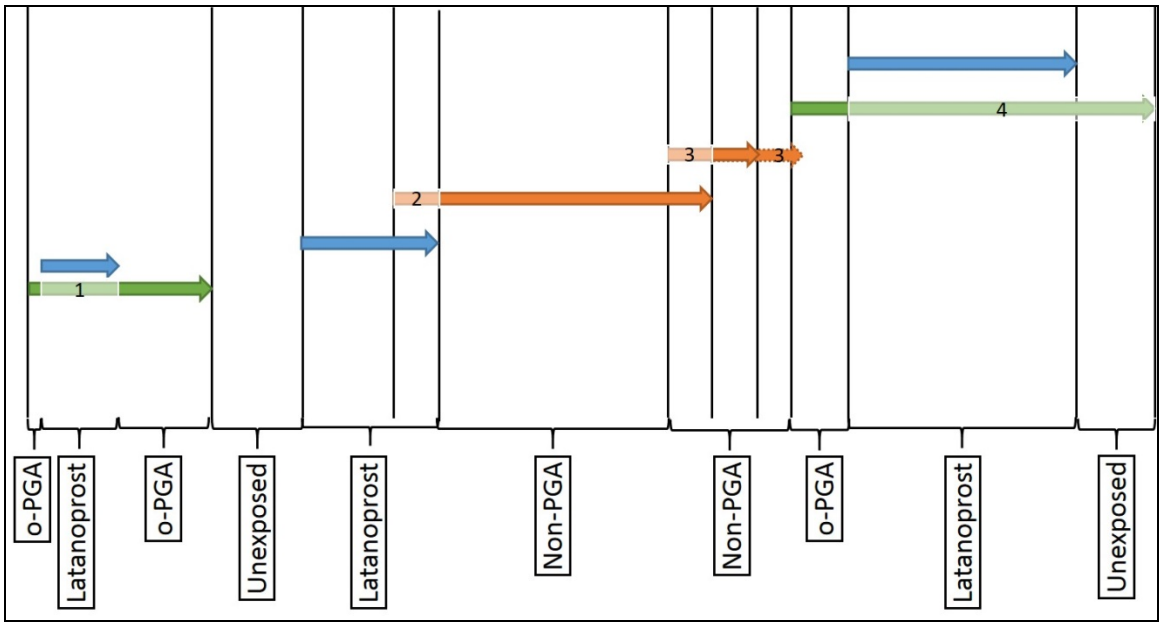
Table 10. Distribution of first events during follow-up, by ever exposure with 6 months lag time and real-time exposure with 0 months lag time, all users

Figure 1. Illustration of ever exposure definition



Blue = Latanoprost, Orange = non-PGA, Green = other PGA
Exposure time on non-PGA is ignored if there is simultaneous supply of latanoprost or other PGA.
Exposure, which contributes time to the analyses, is labelled as a filled arrow.
Exposure (overlapping) time that was ignored is labelled with a dotted arrow.

Figure 2. Illustration of real-time exposure definition



Blue = Latanoprost, Orange = non-PGA, Green = other PGA

1) Simultaneous use of latanoprost and other PGA was attributed to latanoprost
2) Exposure time on non-PGA was ignored if there was simultaneous supply of latanoprost or other PGA
3) If a new prescription was filled for the same drug group (latanoprost, other PGA or non-PGA) while the supply of the previous filling still lasts, the start of the next dispensing was moved to the end of the previous filling
4) A filled prescription of an additional drug later than 7 days after the previous filling is considered as a switch, the supply of the first drug is disregarded from that date and only the exposure of the additional drug contributed exposure time onwards.

Figure 3. Flow chart of study population inclusion

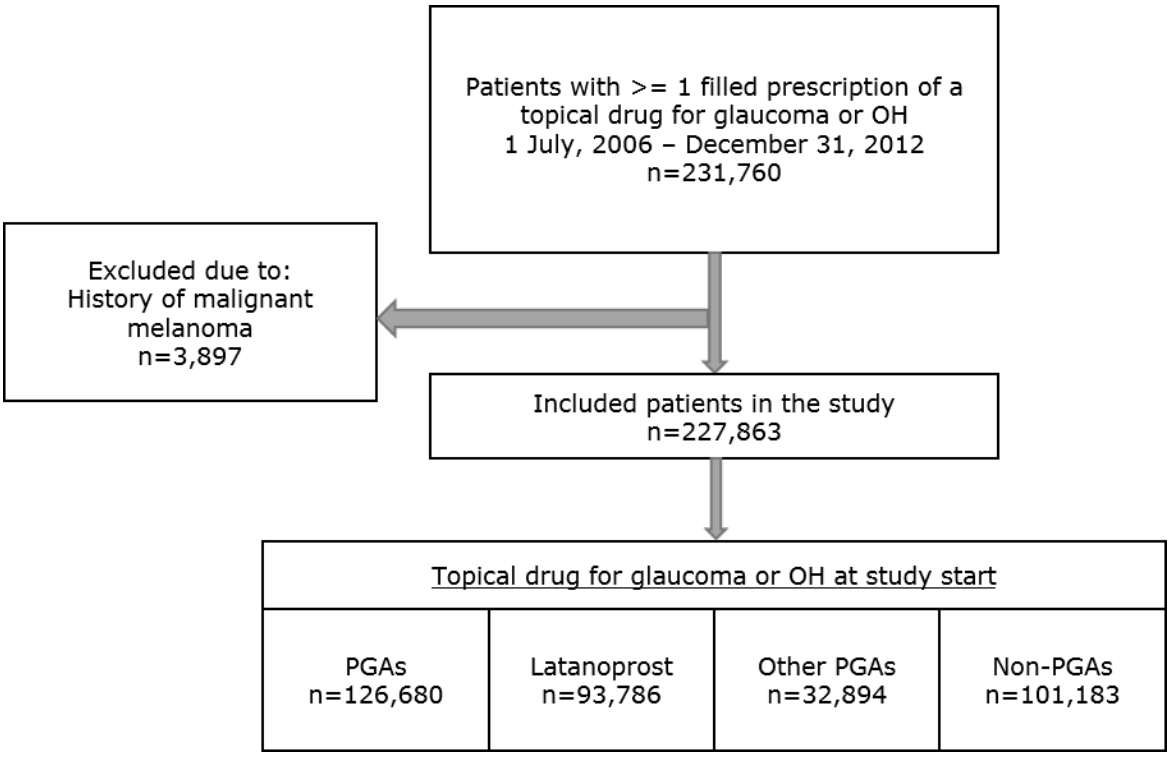


Figure 4. All PGA users during the study period, prevalent and incident use of topical drug use at study entry

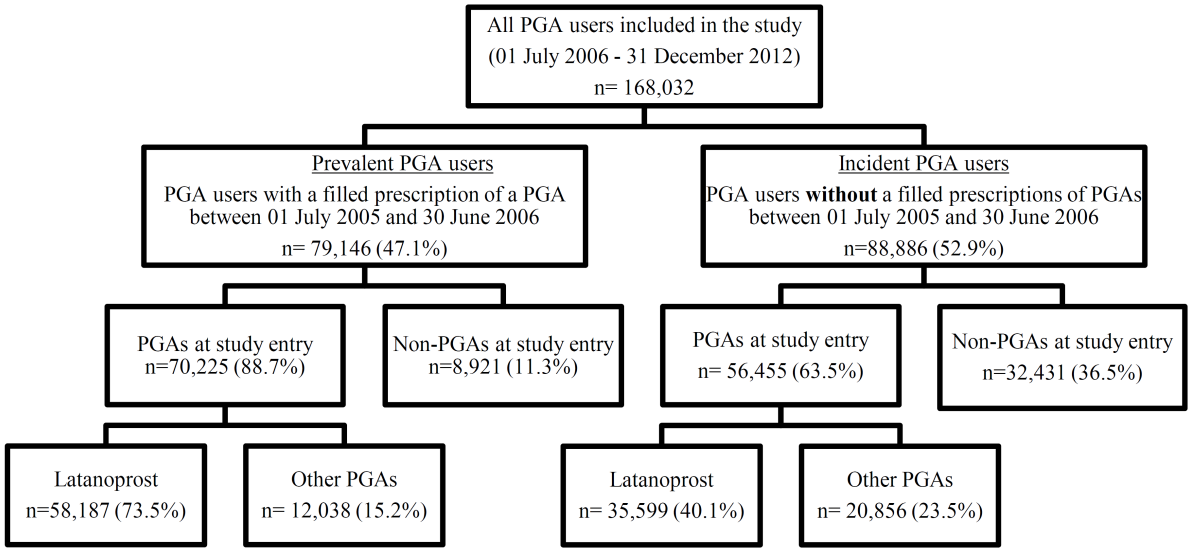


Table 1. ACT codes and classification of topical drugs for glaucoma and OH

ACT code	Drug	Latanoprost	Other PGA	Non-PGA
S01EA03	Apraclonidine			X
S01EA05	Brimonidine			X
S01EB01	Pilocarpine			X
S0EB02	Carbachol			X
S01EB09	Acetylcholine			X
S01EB51	Pilocarpine, combinations			X
S01EC01	Acetazolamide			X
S01EC03	Dorzolamide			X
S01EC04	Brinzolamide			X
S01ED01	Timolol			X
S01ED02	Betaxolol			X
S01ED51	Timolol+nonPGA			X
S01ED51	Timolol+other PGA		X	
S01ED51	Timolol+latanoprost	X		
S01EE01	Latanoprost	X		
S01EE03	Bimatoprost		X	
S01EE04	Travoprost		X	
S01EE05	Tafluprost		X	

Table 2. Drugs used to identify glaucoma/OH treatment in the study; substances, recommended dosage and constraints for duration

ATC, chapter S01E	Substance	Recommended dosage (drops per day)	Sustainability opened bottle/ foil pouch
S01EA03	Apraclonidine	3	4 weeks
S01EA05	Brimonidine	2	4 weeks
S01EB01	Pilocarpine	1-3	4 weeks
S01EB51 (Fotil)	Pilocarpine, combinations	2	4 weeks
S01EC03	Dorzolamide	3	4 weeks
S01EC04	Brinzolamide	2-3	4 weeks
S01ED01	Timolol	1	1 month/4 weeks
S01ED01	Timolol	1	N.A
S01ED02	Betaxolol		4 weeks
S01ED51	Timolol, combinations		4 weeks
S01EE01	Latanoprost	1	4 weeks
S01EE03	Bimatoprost	1	4 weeks
S01EE04	Travoprost	1	4 weeks
S01EE05	Tafluprost	1	4 weeks

Table 3. ICD-codes, procedure codes, and ATC- codes used to identify glaucoma or OH and covariates

Covariate	ICD-10 codes	ATC-codes	Procedure codes
Diagnosis of glaucoma or ocular hypertension	ICD-10: H40, H42 ICD-9: 365 ICD-8: 375 ICD-7: 387	S01E	ICD-10:CHD ICD-9:1460, 1461, 1462, 1490, 1491, 1492, 1493,1499, 1570, 1571, 1572, 1580, 1581, 1599
History of diabetes	E10, E11	A10A, A10B	
History of atopic dermatitis	L20		
History of psoriasis	L40		
Diagnosis of dysplastic naevus syndrome	D48.5C		
Exposure to NSAIDs		M01A	
Exposure to cytostatic		L01	
Exposure to immunosuppressant		L04	
Skin cancer	C44 (except facial cutaneous malignant melanoma)		
Cancer (except skin cancer)	C00-C09, C10-C19, C20-C26, C30-C34, C37-C39, C40, C41, C45-C49, C50-C58, C60-C68, C70-C76, C77, C78, C79, C80- C85, C88, C90-C97		

Table 4. Diagnosis codes used for identification of facial cutaneous melanoma and ocular melanoma endpoints

Cancer description	ICD-O-3 codes
Melanoma Cutaneous (facial)	**C.44.0, C44.1, C44.2, C44.3, C44.4**
	Morphology ICD-O/3 codes
Malignant melanoma, NOS (except juvenile melanoma M-8770/0)	M 8720/3
Nodular melanoma	M 8721/3
Balloon cell melanoma	M 8722/3
Malignant melanoma, regressing	M 8723/3
Amelanotic melanoma	M 8730/3
Malignant melanoma in junctional naevus	M 8740/3
Malignant melanoma in precancerous melanosis	M 8741/3
Lentigo maligna melanoma	M 8742/3
Superficial spreading melanoma	M 8743/3
Acral lentiginous melanoma, malignant	M 8744/3
Desmoplastic melanoma, malignant	M 8745/3
Mucosal lentiginous melanoma	M 8746/3
Malignant melanoma in giant pigmented nevus, Malignant melanoma in congenital melanocytic nevus	M 8761/3
Mixed epithelioid and spindle cell melanoma	M 8770/3
Epithelioid cell melanoma	M 8771/3
Spindle cell melanoma, NOS	M 8772/3
Blue nevus, malignant	M 8780/3
Melanoma Ocular	**C.69**
	Morphology ICD-O/3 codes
Malignant Melanoma NOS	M8720/3
Melanoma epithelioid type A	M8773/3
Melanoma epithelioid type B	M8774/3

Table 5. Definitions and data sources of potential confounders and/or effect modifiers

Variable	Role	Data Source/Definition
Age	Socio-demographic factor	Population Registers of Statistics Sweden; Fixed at inclusion; Defined as <18, 18-34, 35-44, 45-64, 65-74, 75-84, 85+
Sex	Socio-demographic factor	Population Registers of Statistics Sweden; Fixed at inclusion; Defined as Male/Female
Country of birth	Socio-demographic factor	Population Registers of Statistics Sweden; Fixed at inclusion; Defined as Sweden, other Nordic countries (Sweden excluded), EU-countries (Sweden, other Nordic countries excluded), other (Sweden, Nordic and EU countries excluded)
Place of residency	Socio-demographic factor	Population Registers of Statistics Sweden; Fixed at inclusion; Defined as the northern region; the central region; the southern or coastal region in Sweden
Occupational history^	Socio-demographic factor	Population Registers of Statistics Sweden; Fixed at inclusion; Defined as Never/Ever outdoor work
Use of NSAIDs	Concomitant drugs	PDR; Time varying; Used ATC codes to identify drugs. Defined as Yes/No
Use of immunosuppressant and/or biological agents	Concomitant drugs	PDR; Time varying; Used ATC codes to identify drugs. Defined as Yes/No
Use of cytostatic	Concomitant drugs	PDR; Time varying; Used ATC codes to identify drugs. Defined as Yes/No
Diagnosis of diabetes	Comorbidity	NPR; Fixed at inclusion; Defined as Yes/No
Diagnosis of glaucoma/ocular hypertension	Clinical characteristic	NPR; Time varying; ICD-10 codes that were available (1997- 2012) and surgical procedures performed for glaucoma (NCSP 2002 codes) were utilized. Defined as Yes/No
Diagnosis of atopic dermatitis	Comorbidity	NPR; Time varying; Defined as Yes/No
Diagnosis of psoriasis	Comorbidity	NPR; Time varying; Defined as Yes/No
Diagnosis of dysplastic naevus syndrome	Comorbidity	NPR; Time varying; Defined as Yes/No
Diagnosis of NMSC	Comorbidity	SCR; Time varying; Defined as Yes/No
Diagnosis of non-facial CM	Comorbidity	SCR; Time varying; Defined as Yes/No
Diagnosis of any cancer*	Comorbidity	SCR; Time varying; Defined as Yes/No

*except NMSC and non-facial cutaneous melanoma
^occupational history was excluded from the analyses due to a large proportion of missing values.
NSAID= Nonsteroidal anti-inflammatory drugs; NMSC= Non-melanoma skin cancer; CM= cutaneous melanoma; PDR=Prescribed Drug Register; NPR=National Patient Register; SCR=Swedish Cancer Register; EU= European Union; ATC= Anatomical Therapeutic Chemical; ICD= International Classification of Diseases;NCSP= Nordic Medico-Statistical Committee Classification of Surgical Procedures

Table 6. Patient baseline characteristics at cohort inclusion date, presented by drug group^ defined at real-time exposure with no lag time

Characteristic	Latanoprost	Other PGAs	PGAs	Non-PGAs
Total, N (%)	123,235 (100)	73,974 (100)	168,032 (100)	169,873 (100)
Age, median (IQR)	76 (67.0 - 83.0)	73 (65.0 - 80.0)	75 (67.0 - 82.0)	75 (66.0 - 82.0)
Females, N (%)	71,321 (57.9)	42,185 (57)	96,312 (57.3)	96,618 (56.9)
Drug exposure group at 1st entry, n (%)				
Latanoprost	93,786 (76.1)	18,931 (25.6)	93,786 (55.8)	51,496 (30.3)
Other PGAs	2,996 (2.4)	32,894 (44.5)	32,894 (19.6)	17,194 (10.1)
Topical non-PGAs	26,453 (21.5)	22,149 (29.9)	41,352 (24.6)	101,183 (59.6)
Country of birth, n (%)				
Sweden	111,949 (90.8)	67,004 (90.6)	152,450 (90.7)	153,659 (90.5)
Other Nordic countries	4,733 (3.8)	2,882 (3.9)	6,495 (3.9)	6,332 (3.7)
Other EU countries	4,039 (3.3)	2,530 (3.4)	5,629 (3.3)	5,745 (3.4)
Countries outside EU	2,408 (2)	1,482 (2)	3,362 (2)	3,962 (2.3)
Missing	106 (0.1)	76 (0.1)	156 (0.1)	175 (0.1)
Region of residency, n (%)				
Northern	23,348 (18.9)	11,289 (15.3)	29,431 (17.5)	29,230 (17.2)
Central	28,126 (22.8)	18,900 (25.5)	39,628 (23.6)	41,489 (24.4)
Southern or coastal	64,013 (51.9)	39,059 (52.8)	87,416 (52)	89,941 (52.9)
Missing	7,748 (6.3)	4,726 (6.4)	11,617 (6.9)	9,213 (5.4)
Ever outdoor work, n (%)				
Yes	3,875 (3.1)	2,703 (3.7)	5,512 (3.3)	5,462 (3.2)
No	51,730 (42.0)	36,425 (49.2)	73,583 (43.8)	73,542 (43.3)
Missing	67,630 (54.9)	34,846 (47.1)	88,997 (52.9)	90,869 (53.5)
Inclusion year, median (IQR)**	2006 (2006 – 2008)	2006 (2006 – 2009)	2006 (2006 – 2009)	2006 (2006 – 2008)
Comorbidity, n (%)				
Diabetes	11,745 (9.5)	6,286 (8.5)	15,842 (9.4)	16,526 (9.7)
ICD record of glaucoma/OH	88,305 (71.7)	51,378 (69.5)	118,448 (70.5)	114,012 (67.1)
Atopic dermatitis	290 (0.2)	234 (0.3)	430 (0.3)	475 (0.3)
Psoriasis	1,647 (1.3)	1,087 (1.5)	2,356 (1.4)	2,344 (1.4)
Dysplastic naevus	2 (0)	2 (0)	3 (0)	4 (0)
Non-facial cutaneous melanoma	0 (0)	0 (0)	0 (0)	0 (0)
Non-melanoma skin cancer	0 (0)	0 (0)	0 (0)	0 (0)
Any cancer*	13,650 (11.1)	7,818 (10.6)	18,706 (11.1)	18,300 (10.8)
Concomitant Medication, n (%)				
NSAID medication	37,910 (30.8)	25,624 (34.6)	54,207 (32.2)	53,066 (31.2)
Immunosuppressant and/or biological medication	2,113 (1.7)	1,404 (1.9)	3,000 (1.8)	3,110 (1.8)
Cytostatic medication	1,188 (1)	775 (1)	1,710 (1)	1,676 (1)

^ Note that patients may be included in more than one drug group during follow-up, therefore, groups will not add up to the total study population.
*except non-melanoma skin cancer and non-facial cutaneous melanoma
** the inclusion year was defined as the year of when the patient first was exposed to the specific drug group
n=Number; IQR=interquartile range ; EU=European Union; PGA=prostaglandin analogue ; OH=ocular hypertension; NSAID= Nonsteroidal anti-inflammatory drugs

Table 7. Baseline characteristics at date of study inclusion: All PGA users, prevalent PGA users and incident PGA users

Characteristics	All PGA users	Prevalent PGA users	Incident PGA users
Total, N (%)	168,032 (100)	79,146 (100)	88,886 (100)
Age, median (IQR)	75 (67.0 - 82.0)	78 (70.0 - 84.0)	73 (64.0 - 80.0)
Females, n (%)	96,279 (57.3)	46,768 (59.1)	49,511 (55.7)
Treatment group at 1st entry, n (%)			
Latanoprost	93,786 (55.8)	58,187 (73.5)	35,599 (40.1)
Other PGAs	32,894 (19.6)	12,038 (15.2)	20,856 (23.5)
Topical non-PGAs	41,352 (24.6)	8,921 (11.3)	32,431 (36.5)
Country of birth, n (%)			
Sweden	152,396 (90.7)	72,936 (92.2)	79,460 (89.4)
Other Nordic countries	6,493 (3.9)	2,871 (3.6)	3,622 (4.1)
Other EU countries	5,626 (3.3)	2,168 (2.7)	3,458 (3.9)
Countries outside EU	3,361 (2)	1,127 (1.4)	2,234 (2.5)
Missing	156 (0.1)	44 (0.1)	112 (0.1)
Region of residency, n (%)			
Northern	29,420 (17.5)	15,084 (19.9)	14,336 (17.8)
Central	39,622 (23.6)	19,820 (26.2)	19,802 (24.6)
Southern or coastal	87,377 (52)	40,885 (53.9)	46,492 (57.7)
Missing	11,613 (6.9)	3,357 (4.2)	8,256 (9.3)
Ever outdoor work, n (%)			
Yes	5,512 (3.4)	2,308 (7.6)	3,204 (6.6)
No	73,561 (43.8)	27,995 (35.4)	45,566 (51.3)
Missing	88,959 (52.9)	48,843 (61.7)	40,116 (45.1)
Inclusion year, median (IQR)**	2006 (2006 - 2009)	2006 (2006 – 2006)	2008 (2007 – 2010)
Comorbidity, n (%)			
Diabetes	15,836 (9.4)	7,406 (9.4)	8,430 (9.5)
ICD record of glaucoma/OH	118,410 (70.5)	60,843 (76.9)	57,567 (64.8)
Atopic dermatitis	430 (0.3)	142 (0.2)	288 (0.3)
Psoriasis	2,355 (1.4)	838 (1.1)	1,517 (1.7)
Dysplastic naevus	3 (0)	0 (0)	3 (0)
Non-facial cutaneous melanoma	0 (0)	0 (0)	0 (0)
Non-melanoma skin cancer	0 (0)	0 (0)	0 (0)
Any cancer*	18,702 (11.1)	8,729 (11)	9,973 (11.2)
Concomitant Medication, n (%)			
NSAID medication	54,179 (32.2)	18,096 (22.9)	36,083 (40.6)
Immunosuppressant and/or biological medication	2,998 (1.8)	1,017 (1.3)	1,981 (2.2)
Cytostatic medication	1,710 (1)	585 (0.7)	1,125 (1.3)

*except non-melanoma skin cancer and non-facial cutaneous melanoma
** the inclusion year was defined as the year of when the patient first was exposed to the specific drug group
n=Number; IQR=interquartile range; EU=European Union; PGA=prostaglandin analogue; OH=ocular hypertension; NSAID= Nonsteroidal anti-inflammatory drugs

Table 8. Duration of exposure by number of individuals and person-time for ocular melanoma and facial cutaneous melanoma: Ever Exposure with lag time of 6 months

Ocular Melanoma	Latanoprost	Other PGA	PGAs	Non-PGA	Unexposed [α]
Total number of individuals contributing person-time	112,341	46,115	158,456	95,777	-
Total person-time in years	541,584	179,831	721,415	285,474	-
Median follow-up in years (IQR)	5.2 (2.4–6.0)	3.5 (1.6–5.8)	4.7 (2.1–6.0)	2.2 (0.5–5.1)	-
Time since last date of dispensed supply to censoring in years	69,753	33,408	53,429	88,538	-
Time since last date of dispensed supply to censoring in years**, median (IQR)	0.0 (0.0-0.7)	0.0 (0.0-0.3)	0.0 (0.0-0.1)	0.3 (0.0-2.3)	-
Facial Cutaneous Melanoma	**Latanoprost**	**Other PGA**	**PGAs**	**Non-PGA**	**Unexposed [α]**
Total number of individuals contributing person-time	112,341	46,115	158,456	95,762	-
Total person-time in years	542,065	180,135	722,200	285,698	
Median follow-up in years (IQR)	5.2 (2.4–6.0)	3.5 (1.6–5.8)	4.7 (2.1–6.0)	2.2 (0.5–5.1)	-
Time since last date of dispensed supply to censoring in years	69,753	33,408	53,429	88,538	-
Time since last date of dispensed supply to censoring in years, median (IQR)	0.0 (0.0-0.6)	0.0 (0.0-0.3)	0.0 (0.0-0.1)	0.3 (0.0-2.3)	-

[α] Unexposed is period when the patient is not exposed to any treatment of a topical drug for glaucoma or OH.
PGA=prostaglandin analogue; IQR=interquartile range

Table 9. Duration of exposure by number of individuals and person-time for ocular melanoma and facial cutaneous melanoma: Real time exposure with lag time of 0 months

Ocular Melanoma	Latanoprost	Other PGA	PGAs	Non-PGA	Unexposed [α]
Total number of individuals contributing person-time	123,235	73,974	168,032	169,869	150,527
Total person-time in years	382,996	163,323	546,319	300,977	310,551
Median follow-up in years (IQR)	2.8 (1.0-5.0)	1.8 (0.6-3.6)	3.1 (1.2-5.1)	1.1 (0.3-2.9)	1.4 (0.3-3.5)
Time since last date of dispensed supply to censoring in years	112,524	55,104	167,628	96,483	225,443
Time since last date of dispensed supply to censoring in years, median (IQR)	0.9 (0.2-3.4)	0.7 (0.2-2.0)	0.8 (0.2-2.7)	1.0 (0.2-3.8)	2.3 (0.8-4.0)
Facial Cutaneous Melanoma	**Latanoprost**	**Other PGA**	**PGAs**	**Non-PGA**	**Unexposed [α]**
Total number of individuals contributing person-time	123,235	73,974	168,032	169,861	150,521
Total person-time in years	382,892	163,268	546,160	300,868	310,469
Median follow-up in years (IQR)	2.8 (1.0-5.0)	1.8 (0.6-3.6)	3.1 (1.2-5.1)	1.1 (0.3-2.9)	1.4 (0.3-3.5)
Time since last date of dispensed supply to censoring in years	112,559	55,112	167,671	96,531	225,394
Time since last date of dispensed supply to censoring in years, median (IQR)	0.9 (0.2-3.4)	0.7 (0.2-2.0)	0.8 (0.2-2.7)	1.0 (0.2-3.8)	2.3 (0.8-4.0)

[α] Unexposed is period when the patient is not exposed to any treatment of a topical drug for glaucoma or OH.
PGA=prostaglandin analogue; IQR=interquartile range

Table 10. Distribution of first events during follow-up, by ever exposure with 6 months lag time and real-time exposure with 0 months lag time, all users

Lag time (months)	Exposure Group	Ever exposure		Real-time exposure	
		OM	Facial CM	OM	Facial CM
0	Latanoprost	-	-	18	57
	Other PGA	-	-	7	28
	All PGA	-	-	25	85
	Non PGA	-	-	15	56
	Unexposed	-	-	4	24
	Total	-	-	40	141
6	Latanoprost	10	70	-	-
	Other PGA	6	31	-	-
	All PGA	16	101	-	-
	Non PGA	5	50	-	-
	Unexposed	N/A	N/A	-	
	Total	21	151	-	-

N/A=not applicable; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue

Table 11. Distribution of OM and facial CM events during follow-up: Number and proportion of events within 6 months of first filled prescription or later during follow-up, by drug exposure group using ever exposure definition

Exposure groups	OM			Facial CM		
	0-6 months follow-up	>6 months follow-up	Total follow-up	0-6 months follow-up	>6 months follow-up	Total follow-up
Latanoprost, N (%)	14 (58.3%)	10 (41.7%)	24 (100%)	6 (7.9%)	70 (92.1%)	76 (100%)
Other PGA, N (%)	2 (25.0%)	6 (75.0%)	8 (100%)	2 (6.1%)	31 (93.9%)	33 (100%)
PGA, N (%)	16 (50.0%)	16 (50.0%)	32 (100%)	8 (7.3%)	101 (92.7%)	109 (100%)
Non-PGA, N (%)	7 (58.3%)	5 (41.7%)	12 (100%)	6 (10.7%)	50 (89.3%)	56 (100%)
Total	23 (52.3%)	21 (47.7%)	44 (100%)	14 (8.5%)	151 (91.5%)	165 (100%)

N=number

Table 12. Number of events, total number of person-years of ever exposure and number of first events of ocular melanoma per 100,000 person-years by treatment groups stratified by patient characteristics, unadjusted: Ever exposure using 6 months lag time.

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Total	10	541,584	1.8 (1.0 - 3.4)	6	179,831	3.3 (1.5 - 7.4)	16	721,415	2.2 (1.4 - 3.6)	5	285,474	1.8 (0.7 - 4.2)
Age, years												
<18	0	1,268	0 (-)	0	520	0 (-)	0	1,788	0 (-)	0	2,279	0 (-)
18-34	0	2,517	0 (-)	0	1,066	0 (-)	0	3,583	0 (-)	0	4,544	0 (-)
35-44	0	6,207	0 (-)	1	2,084	48 (6.8 - 340.7)	1	8,291	12.1 (1.7 - 85.6)	0	7,118	0 (-)
45-64	3	98,696	3 (1.0 - 9.4)	0	37,605	0 (.)	3	136,301	2.2 (0.7 - 6.8)	0	63,699	0 (-)
65-74	5	148,297	3.4 (1.4 - 8.1)	2	55,600	3.6 (0.9 - 14.4)	7	203,897	3.4 (1.6 - 7.2)	1	70,314	1.4 (0.2 - 10.1)
75-84	2	206,411	1 (0.2 - 3.9)	3	63,870	4.7 (1.5 - 14.6)	5	270,282	1.8 (0.8 - 4.4)	3	92,944	3.2 (1.0 - 10.0)
85+	0	78,187	0 (-)	0	19,086	0 (-)	0	97,273	0 (-)	1	44,576	2.2 (0.3 - 15.9)
Females	3	315,619	1 (0.3 - 2.9)	5	102,065	4.9 (2.0 - 11.8)	8	417,684	1.9 (1.0 - 3.8)	2	163,455	1.2 (0.3 - 4.9)
Males	7	225,965	3.1 (1.5-6.5)	1	77,766	1.3 (0.2-9.1)	8	303,731	2.6 (1.3-5.3)	3	122,020	2.5 (0.8-7.6)
Country of birth												
Sweden	10	494,136	2 (1.1 - 3.8)	4	163,257	2.5 (0.9 - 6.5)	14	657,393	2.1 (1.3 - 3.6)	5	255,705	2 (0.8 - 4.7)
Other Nordic countries	0	20,526	0 (-)	2	6,883	29.1 (7.3 - 116.2)	2	27,409	7.3 (1.8 - 29.2)	0	10,962	0 (-)
Other EU-countries	0	17,057	0 (-)	0	6,296	0 (-)	0	23,353	0 (-)	0	10,905	0 (-)
Countries outside EU	0	9,438	0 (-)	0	3,238	0 (-)	0	12,677	0 (-)	0	7,573	0 (-)
Region of residency												
Northern	3	100,665	3 (1.0 - 9.2)	0	24,010	0 (-)	3	124,675	2.4 (0.8 - 7.5)	0	42,848	0 (-)

Table 12. Number of events, total number of person-years of ever exposure and number of first events of ocular melanoma per 100,000 person-years by treatment groups stratified by patient characteristics, unadjusted: Ever exposure using 6 months lag time.

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Central	1	122,161	0.8 (0.1 - 5.8)	2	46,450	4.3 (1.1 - 17.2)	3	168,611	1.8 (0.6 - 5.5)	3	68,822	4.4 (1.4 - 13.5)
Southern or coastal	5	286,387	1.7 (0.7 - 4.2)	4	98,661	4.1 (1.5 - 10.8)	9	385,048	2.3 (1.2 - 4.5)	2	154 371	1.3 (0.3 - 5.2)
Comorbidity												
Glaucoma/OH diagnosis	9	464,616	1.9 (1.0 - 3.7)	6	152,400	3.9 (1.8 - 8.8)	15	617,016	2.4 (1.5 - 4.0)	4	205,117	2 (0.7 - 5.2)
Diabetes	0	44,961	0 (-)	0	13,957	0 (-)	0	58,918	0 (-)	0	27,019	0 (-)
Any cancer	0	83,633	0 (-)	1	27,733	3.6 (0.5 - 25.6)	1	111,367	0.9 (0.1 - 6.4)	0	41,244	0 (-)
Non-facial cutaneous melanoma	0	1,673	0 (-)	0	536	0 (-)	0	2,209	0 (-)	0	790	0 (-)
Non-melanoma skin cancer	0	8,542	0 (-)	0	2,681	0 (-)	0	11,222	0 (-)	0	3,819	0 (-)
Psoriasis	0	11,707	0 (-)	0	4,147	0 (-)	0	15,854	0 (-)	0	6,259	0 (-)
Atopic dermatitis	0	2,319	0 (-)	0	870	0 (-)	0	3,189	0 (-)	0	1,373	0 (-)
Dysplastic naevus	0	37	0 (-)	0	24	0 (-)	0	61	0 (-)	0	29	0 (-)
Concomitant Medication												
NSAID	4	268,502	1.5 (0.6 - 4.0)	2	91,898	2.2 (0.5 - 8.7)	6	360,400	1.7 (0.7 - 3.7)	2	137,558	1.5 (0.4-5.8)
Immunosuppressor biological	0	14,203	0 (-)	0	4,762	0 (-)	0	18,965	0 (-)	0	8,003	0 (-)
Cytostatic	0	11,918	0 (-)	1	3,861	25.9 (3.6 - 183.9)	1	15,779	6.3 (0.9 - 45.0)	0	5,952	0 (-)

PY=person years; PGA=prostaglandin analogue; EU=European Union; OH=ocular hypertension; NSAID= Nonsteroidal anti-inflammatory drugs

Table 13. Number of events, total number of person-years of ever exposure and number of first events of ocular melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Real-time exposure using 0 months lag time

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Total	18	382,996	4.7 (3.0 - 7.5)	7	163,323	4.3 (2.0 - 9.0)	25	546,319	4.6 (3.1 - 6.8)	15	300,977	5 (3.0 - 8.3)
Age, years												
<18	0	496	0 (-)	0	311	0 (-)	0	807	0 (-)	0	1,441	0 (-)
18-34	1	1,099	91 (12.8 - 645.9)	0	592	0 (-)	1	1,691	59.1 (8.3 - 419.8)	0	1,959	0 (-)
35-44	1	3,139	31.9 (4.5 - 226.1)	0	1,508	0 (-)	1	4,647	21.5 (3.0 - 152.8)	2	3,629	55.1 (13.8 - 220.4)
45-64	2	61,295	3.3 (0.8 - 13.0)	1	32,858	3 (0.4 - 21.6)	3	94,153	3.2 (1.0 - 9.9)	7	52,045	13.4 (6.4 - 28.2)
65-74	8	99,565	8 (4.0 - 16.1)	3	50,572	5.9 (1.9 - 18.4)	11	150,137	7.3 (4.1 - 13.2)	1	72,234	1.4 (0.2 - 9.8)
75-84	3	150,646	2 (0.6 - 6.2)	3	59,215	5.1 (1.6 - 15.7)	6	209,861	2.9 (1.3 - 6.4)	4	108,452	3.7 (1.4 - 9.8)
85+	3	66,755	4.5 (1.4 - 13.9)	0	18,266	0 (-)	3	85,021	3.5 (1.1 - 10.9)	1	61,216	1.6 (0.2 - 11.6)
Females	8	228,328	3.5 (1.8 - 7.0)	4	93,421	4.3 (1.6 - 11.4)	12	321,749	3.7 (2.1 - 6.6)	6	180,296	3.3 (1.5 - 7.4)
Males	10	154,668	6.5 (3.5-12.0)	3	69,902	4.3 (1.4-13.3)	13	224,569	5.8 (3.4 – 10.0)	9	120,681	7.5 (3.9-14.3)
Country of birth												
Sweden	18	352,288	5.1 (3.2 - 8.1)	6	149,843	4 (1.8 - 8.9)	24	502,131	4.8 (3.2 - 7.1)	14	274,858	5.1 (3.0 - 8.6)
Other Nordic countries	0	14,243	0 (-)	1	6,219	16.1 (2.3 - 114.2)	1	20,462	4.9 (0.7 - 34.7)	1	10,713	9.3 (1.3 - 66.3)
Other EU-countries	0	10,800	0 (-)	0	4,870	0 (-)	0	15,669	0 (-)	0	9,592	0 (-)
Countries outside EU	0	5,446	0 (-)	0	2,276	0 (-)	0	7,722	0 (-)	0	5,588	0 (-)
Region of residency												
Northern	7	74,661	9.4 (4.5 - 19.7)	0	24,500	0 (-)	7	99,161	7.1 (3.4 - 14.8)	1	49,420	2 (0.3 - 14.4)

Table 13. Number of events, total number of person-years of ever exposure and number of first events of ocular melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Real-time exposure using 0 months lag time

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Central	3	88,944	3.4 (1.1 - 10.5)	3	43,641	6.9 (2.2 - 21.3)	6	132,586	4.5 (2.0 - 10.1)	3	74,016	4.1 (1.3 - 12.6)
Southern or coastal	8	194,515	4.1 (2.1 - 8.2)	4	86,224	4.6 (1.7 - 12.4)	12	280,739	4.3 (2.4 - 7.5)	10	158,750	6.3 (3.4 - 11.7)
Comorbidity												
Glaucoma/OH	11	320,433	3.4 (1.9 - 6.2)	6	136,982	4.4 (2.0 - 9.7)	17	457,415	3.7 (2.3 - 6.0)	9	358,688	2.5 (1.3- 4.8)
Diabetes	0	32,918	0 (-)	1	12,520	8 (1.1 - 56.7)	1	45,438	2.2 (0.3 - 15.6)	0	36,935	0 (0)
Cancer	2	49,835	4 (1.0 - 16.0)	0	21,385	0 (-)	2	71,220	2.8 (0.7 - 11.2)	1	57,214	1.7 (0.2- 12.4)
Malignant melanoma of skin excl. face	0	503	0 (-)	0	249	0 (-)	0	752	0 (. - .)	0	781	0 (0)
Non-melanoma skin cancer	0	2,673	0 (-)	0	1,209	0 (-)	0	3,882	0 (. - .)	0	3,827	0 (0)
Psoriasis	0	6,239	0 (-)	0	2,868	0 (-)	0	9,107	0 (. - .)	0	7,828	0 (0)
Atopic dermatitis	0	1,052	0 (-)	0	610	0 (-)	0	1,662	0 (. - .)	0	1,647	0 (0)
Dysplastic naevus	0	22	0 (-)	0	13	0 (-)	0	35	0 (. - .)	0	77	0 (0)
Concomitant Medication												
NSAID	4	159,483	2.5 (0.9 - 6.7)	2	75,080	2.7 (0.7 - 10.7)	6	234,563	2.6 (1.1 - 5.7)	5	191,778	2.6 (1.1- 6.3)
Immunosuppressant/ biological medication	0	7,371	0 (-)	0	3,499	0 (-)	0	10,870	0 (. - .)	0	9,784	0 (0)
Cytostatic	0	5,882	0 (-)	1	2,714	36.8 (5.2 - 261.5)	1	8 ,596	11.6 (1.6 - 82.6)	0	7,315	0 (0)

PY=person years; PGA=prostaglandin analogue; EU=European Union; OH=ocular hypertension; NSAID= Nonsteroidal anti-inflammatory drugs

Table 14. Number of events, total number of person-years of ever exposure and number of first events of facial cutaneous melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Ever exposure using 6 months lag time.

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Total	70	542,065	12.9 (10.2 - 16.3)	31	180,135	17.2 (12.1 - 24.5)	101	722,200	14 (11.5 - 17.0)	50	285,698	17.5 (13.3 - 23.1)
Age, years												
<18	0	1,268	0 (-)	0	520	0 (-)	0	1,788	0 (-)	0	2,279	0 (-)
18-34	0	2,517	0 (-)	0	1,066	0 (-)	0	3,583	0 (-)	0	4,544	0 (-)
35-44	0	6,207	0 (-)	0	2,135	0 (-)	0	8,342	0 (-)	0	7,118	0 (-)
45-64	2	98,848	2 (0.5 - 8.1)	2	37,605	5.3 (1.3 - 21.3)	4	136,453	2.9 (1.1 - 7.8)	2	63,695	3.1 (0.8 - 12.6)
65-74	18	148,541	12.1 (7.6 - 19.2)	7	55,700	12.6 (6.0 - 26.4)	25	204,242	12.2 (8.3 - 18.1)	9	70,353	12.8 (6.7 - 24.6)
75-84	28	206,503	13.6 (9.4 - 19.6)	12	64,025	18.7 (10.6 - 33.0)	40	270,528	14.8 (10.8 - 20.2)	27	93,093	29 (19.9 - 42.3)
85+	22	78,180	28.1 (18.5 - 42.7)	10	19,085	52.4 (28.2 - 97.4)	32	97,265	32.9 (23.3 - 46.5)	12	44,617	26.9 (15.3 - 47.4)
Females	36	315,758	11.4 (8.2 - 15.8)	20	102,319	19.5 (12.6 - 30.3)	56	418,076	13.4 (10.3 - 17.4)	29	163,537	17.7 (12.3 - 25.5)
Males	34	226,307	15.0 (10.7-21.0)	11	77,816	14.1 (7.8-25.5)	45	304,123	14.8 (11.0-19.8)	21	122,161	17.2 (11.2-26.4)
Country of birth												
Sweden	65	494,620	13.1 (10.3 - 16.8)	29	163,458	17.7 (12.3 - 25.5)	94	658,078	14.3 (11.7 - 17.5)	48	255,932	18.8 (14.1 - 24.9)
Other Nordic countries	1	20,526	4.9 (0.7 - 34.6)	1	6,987	14.3 (2.0 - 101.6)	2	27,512	7.3 (1.8 - 29.1)	0	10,962	0 (-)
Other EU-countries	4	17,054	23.5 (8.8 - 62.5)	0	6,296	0 (-)	4	23,349	17.1 (6.4 - 45.6)	1	10,901	9.2 (1.3 - 65.1)
Countries outside EU	0	9,438	0 (-)	1	3,237	30.9 (4.4 - 219.3)	1	12,676	7.9 (1.1 - 56.0)	1	7,573	13.2 (1.9 - 93.7)
Region of residency			()									
Northern	6	100,806	6 (2.7 - 13.2)	2	24,010	8.3 (2.1 - 33.3)	8	124,817	6.4 (3.2 - 12.8)	4	42,846	9.3 (3.5 - 24.9)

Table 14. Number of events, total number of person-years of ever exposure and number of first events of facial cutaneous melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Ever exposure using 6 months lag time.

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Central	15	122,209	12.3 (7.4 - 20.4)	7	46,553	15 (7.2 - 31.5)	22	168,762	13 (8.6 - 19.8)	14	68,974	20.3 (12.0 - 34.3)
Southern or coastal	43	286,633	15 (11.1 - 20.2)	20	98,865	20.2 (13.1 - 31.4)	63	385,499	16.3 (12.8 - 20.9)	29	154,447	18.8 (13.0 - 27.0)
Comorbidity												
Glaucoma/OH	60	465,063	12.9 (10.0 - 16.6)	26	152,709	17 (11.6 - 25.0)	86	617,772	13.9 (11.3 - 17.2)	34	205,305	16.6 (11.8 - 23.2)
Diabetes	7	44,961	15.6 (7.4 - 32.7)	4	13,957	28.7 (10.8 - 76.4)	11	58,918	18.7 (10.3 - 33.7)	6	27,015	22.2 (10.0 - 49.4)
Cancer	13	83,631	15.5 (9.0 - 26.8)	10	27,780	36 (19.4 - 66.9)	23	111,411	20.6 (13.7 - 31.1)	7	41,233	17 (8.1 - 35.6)
Malignant melanoma of skin excl. face	0	1,673	0 (-)	0	536	0 (-)	0	2,209	0 (-)	0	790	0 (-)
Non-melanoma skin cancer	1	8,542	11.7 (1.6 - 83.1)	0	2,681	0 (-)	1	11,222	8.9 (1.3 - 63.3)	0	3,819	0 (-)
Psoriasis	1	11,707	8.5 (1.2 - 60.6)	0	4,147	0 (-)	1	15,854	6.3 (0.9 - 44.8)	2	6,255	32 (8.0 - 127.9)
Atopic dermatitis	0	2,319	0 (-)	1	870	114.9 (16.2 - 815.9)	1	3,189	31.4 (4.4 - 222.6)	0	1,373	0 (-)
Dysplastic naevus	0	37	0 (-)	0	24	0 (-)	0	61	0 (-)	0	29	0 (-)
Concomitant Medication												
NSAID	31	268,695	11.5 (8.1 - 16.4)	18	91,995	19.6 (12.3 - 31.1)	49	360,690	13.6 (10.3 - 18.0)	22	137,654	16 (10.5 - 24.3)
Immunosuppressant/ biological medication	6	14,200	42.3 (19.0 - 94.1)	1	4,762	21 (3.0 - 149.1)	7	18,962	36.9 (17.6 - 77.4)	2	7,999	25 (6.3 - 100.0)

Table 14. Number of events, total number of person-years of ever exposure and number of first events of facial cutaneous melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Ever exposure using 6 months lag time.

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Cytostatic	4	11,918	33.6 (12.6 - 89.4)	2	3,911	51.1 (12.8 - 204.5)	6	15,829	37.9 (17.0 - 84.4)	2	5,947	33.6 (8.4 - 134.5)

PY=person years; PGA=prostaglandin analogue; EU=European Union; OH=ocular hypertension; NSAID= Nonsteroidal anti-inflammatory drugs

Table 15. Number of events, total number of person-years of ever exposure and number of first events of facial cutaneous melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Real-time exposure using 0 months lag time

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Total	57	382,892	14.9 (11.5 - 19.3)	28	163,268	17.1 (11.8 - 24.8)	85	546,160	15.6 (12.6 - 19.2)	56	300,868	18.6 (14.3 - 24.2)
Age, years												
<18	0	496	0 (-)	0	311	0 (-)	0	807	0 (-)	0	1,441	0 (-)
18-34	0	1,099	0 (-)	0	592	0 (-)	0	1,691	0 (-)	0	1,959	0 (-)
35-44	0	3,140	0 (-)	0	1,508	0 (-)	0	4,648	0 (-)	0	3,630	0 (-)
45-64	1	61,300	1.6 (0.2 - 11.6)	2	32,850	6.1 (1.5 - 24.3)	3	94,150	3.2 (1.0 - 9.9)	3	52,046	5.8 (1.9 - 17.9)
65-74	16	99,539	16.1 (9.8 - 26.2)	3	50,569	5.9 (1.9 - 18.4)	19	150,108	12.7 (8.1 - 19.8)	12	72,209	16.6 (9.4 - 29.3)
75-84	26	150,593	17.3 (11.8 - 25.4)	15	59,190	25.3 (15.3 - 42.0)	41	209,783	19.5 (14.4 - 26.5)	21	108,407	19.4 (12.6 - 29.7)
85+	14	66,725	21 (12.4 - 35.4)	8	18,248	43.8 (21.9 - 87.7)	22	84,973	25.9 (17.0 - 39.3)	20	61,176	32.7 (21.1 - 50.7)
Females	25	228,275	11 (7.4 - 16.2)	17	93,393	18.2 (11.3 - 29.3)	42	321,668	13.1 (9.6 - 17.7)	33	180,224	18.3 (13.0 - 25.8)
Males	32	154,617	20.7 (14.6 – 29.3)	11	69,875	15.7 (8.7 – 28.4)	43	224,492	19.2 (14.2 – 25.8)	23	120,643	19.1 (12.7 – 28.7)
Country of birth												
Sweden	54	352,190	15.3 (11.7 - 20.0)	26	149,787	17.4 (11.8 - 25.5)	80	501,977	15.9 (12.8 - 19.8)	52	274,756	18.9 (14.4 - 24.8)
Other Nordic countries	1	14,243	7 (1.0 - 49.8)	1	6,220	16.1 (2.3 - 114.1)	2	20,463	9.8 (2.4 - 39.1)	0	10,714	0 (-)
Other EU-countries	2	10,796	18.5 (4.6 - 74.1)	0	4,870	0 (-)	2	15,665	12.8 (3.2 - 51.1)	3	9,587	31.3 (10.1 - 97.0)
Countries outside EU	0	5,446	0 (-)	1	2,275	44 (6.2 - 312.0)	1	7,721	13 (1.8 - 91.9)	1	5,585	17.9 (2.5 - 127.1)
Region of residency												

Table 15. Number of events, total number of person-years of ever exposure and number of first events of facial cutaneous melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Real-time exposure using 0 months lag time

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Northern	7	74,663	9.4 (4.5 - 19.7)	2	24,496	8.2 (2.0 - 32.6)	9	99,159	9.1 (4.7 - 17.4)	5	49,409	10.1 (4.2 - 24.3)
Central	13	88,918	14.6 (8.5 - 25.2)	6	43,631	13.8 (6.2 - 30.6)	19	132,549	14.3 (9.1 - 22.5)	14	73,995	18.9 (11.2 - 31.9)
Southern or coastal	32	194,441	16.5 (11.6 - 23.3)	18	86,186	20.9 (13.2 - 33.1)	50	280,628	17.8 (13.5 - 23.5)	33	158,680	20.8 (14.8 - 29.3)
Comorbidity												
Glaucoma/OH	48	320,341	15 (11.3 - 19.9)	24	136,936	17.5 (11.7 - 26.1)	72	457,277	15.7 (12.5 - 19.8)	45	245,120	18.4 (13.7 - 24.6)
Diabetes	6	32,910	18.2 (8.2 - 40.6)	4	12,511	32 (12.0 - 85.2)	10	45,421	22 (11.8 - 40.9)	6	28,694	20.9 (9.4 - 46.5)
Cancer	12	49,807	24.1 (13.7 - 42.4)	9	21,361	42.1 (21.9 - 81.0)	21	71,168	29.5 (19.2 - 45.3)	7	39,478	17.7 (8.5 - 37.2)
Malignant melanoma of skin excl. face	0	503	0 (-)	0	249	0 (-)	0	752	0 (-)	0	413	0 (-)
Non-melanoma skin cancer	1	2,670	37.5 (5.3 - 265.9)	0	1,207	0 (-)	1	3,877	25.8 (3.6 - 183.1)	0	2,157	0 (-)
Psoriasis	1	6,239	16 (2.3 - 113.8)	0	2,868	0 (-)	1	9,106	11 (1.5 - 78.0)	0	4,907	0 (-)
Atopic dermatitis	0	1,052	0 (-)	1	608	164.4 (23.2 - 1167)	1	1,660	60.2 (8.5 - 427.6)	0	997	0 (-)
Dysplastic naevus	0	22	0 (-)	0	13	0 (-)	0	35	0 (-)	0	37	0 (-)
Concomitant Medication												
NSAID	24	159,431	15.1 (10.1 - 22.5)	16	75,052	21.3 (13.1 - 34.8)	40	234,483	17.1 (12.5 - 23.3)	20	122,129	16.4 (10.6 - 25.4)

Table 15. Number of events, total number of person-years of ever exposure and number of first events of facial cutaneous melanoma per 100,000 person-years by treatment groups, stratified by patient characteristics, unadjusted: Real-time exposure using 0 months lag time

Characteristic	Latanoprost			Other PGAs			PGAs			Non-PGAs		
	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)	Number of events	PY	Events per 100,000 PY (95% CI)
Immunosuppressant/ biological medication	6	7,364	81.5 (36.6 - 181.4)	1	3,497	28.6 (4.0 - 203.0)	7	10,862	64.4 (30.7 - 135.2)	1	6,469	15.5 (2.2 - 109.7)
Cytostatic	4	5,875	68.1 (25.6 - 181.4)	2	2,714	73.7 (18.4 - 294.6)	6	8,589	69.9 (31.4 - 155.5)	1	4,797	20.8 (2.9 - 148.0)

PY=person years; PGA=prostaglandin analogue; EU=European Union; OH=ocular hypertension; NSAID= Nonsteroidal anti-inflammatory drugs

Table 16. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Latanoprost versus Non-PGAs: Main Analyses Ever Exposure (6 months lag time) and Real time (0 months lag time)

Exposure definition	Outcome	Latanoprost		Non-PGAs		Model 1	Model 2	Model 3
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	10	1.8	5	1.8	1.02 (0.34 - 3.00)	0.82 (0.27 - 2.49)	0.82 (0.27 - 2.52)[a]
	Facial CM	70	12.9	50	17.5	0.7 (0.48 - 1.00)	0.71 (0.48 - 1.03)	0.71 (0.49 - 1.03)[b]
Real-time exposure (0 month lag time)	OM	18	4.7	15	5	0.99 (0.50 - 1.98)	1.07 (0.53 - 2.16)	1.08 (0.54 - 2.19)[c]
	Facial CM	57	14.9	56	18.6	0.79 (0.55 - 1.14)	0.79 (0.54 - 1.16)	0.79 (0.54 - 1.16)[d]

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, diagnosis of atopic dermatitis, diagnosis of psoriasis, diagnosis of dysplastic naevus syndrome, diagnosis of non-melanoma skin cancer and diagnosis of any cancer except malignant melanoma or non-melanoma skin cancer.
Model 3: Change-in-estimate method
[a]Model 3 for OM was additionally adjusted by diabetes, explicit diagnosis of glaucoma or ocular hypertension and country of birth
[b]Model 3 for facial CM was additionally adjusted by explicit diagnosis of glaucoma or ocular hypertension and place of residency
[c]Model 3 for OM was additionally adjusted by explicit diagnosis of glaucoma or ocular hypertension and place of residency
[d]Model 3 for facial CM was additionally adjusted by place of residency

Table 17. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Latanoprost versus Other PGAs: Main Analyses Ever Exposure (6 months lag time) and Real time (0 months lag time)

Exposure definition	**Outcome**	**Latanoprost**		Other PGAs		Model 1	Model 2	Model 3
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	10	1.8	6	3.3	0.59 (0.22 - 1.63)	0.52 (0.19 - 1.48)	0.53 (0.19 - 1.49)[a]
	Facial CM	70	12.9	31	17.2	0.70 (0.46 - 1.07)	0.71 (0.46 - 1.10)	0.70 (0.46 - 1.07)[b]
Real-time exposure (0 month lag time)	OM	18	4.7	7	4.3	1.17 (0.48 - 2.83)	1.17 (0.48 - 2.85)	1.18 (0.49 - 2.87)[c]
	Facial CM	57	14.9	28	17.1	0.85 (0.54 - 1.35)	0.84 (0.52 - 1.35)	0.84 (0.52 - 1.36)[d]

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, diagnosis of atopic dermatitis, diagnosis of psoriasis, diagnosis of dysplastic naevus syndrome, diagnosis of non-melanoma skin cancer and diagnosis of any cancer except malignant melanoma or non-melanoma skin cancer .
Model 3: Change-in-estimate method
[a]Model 3 for OM was additionally adjusted by place of residency
[b]Model 3 for facial CM was additionally adjusted by place of residency
[c]Model 3 for OM was additionally adjusted by explicit diagnosis of glaucoma or ocular hypertension and place of residency
[d]Model 3 for facial CM was additionally adjusted by place of residency

Table 18. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Other PGAs versus non-PGAs: Main Analyses Ever Exposure (6 months lag time) and Real-time (0 months lag time)

Exposure definition	**Outcome**	Other PGAs		Non-PGAs		Model 1	Model 2	Model 3
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	6	3.3	5	1.8	1.89 (0.57 - 6.31)	1.58 (0.47 - 5.32)	1.6 (0.48 - 5.37)[a]
	Facial CM	31	17.2	50	17.5	1.02 (0.65 - 1.60)	1.03 (0.64 - 1.64)	1.02 (0.64 - 1.64)[b]
Real-time exposure (0 month lag time)	OM	7	4.3	15	5	0.7 (0.28 - 1.75)	0.72 (0.29 - 1.80)	0.72 (0.29 - 1.81)[c]
	Facial CM	28	17.1	56	18.6	0.98 (0.61 - 1.55)	0.97 (0.60 - 1.57)	0.96 (0.59 - 1.55)[d]

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diabetes, all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, diagnosis of atopic dermatitis, diagnosis of psoriasis, diagnosis of dysplastic naevus syndrome, diagnosis of non-melanoma skin cancer and diagnosis of any cancer except malignant melanoma or non-melanoma skin cancer.
Model 3: Change-in-estimate method
[a]Model 3 for OM was additionally adjusted by Diagnosis of diabetes, explicit diagnosis of glaucoma or ocular hypertension, country of birth and place of residency
[b]Model 3 for facial CM was additionally adjusted by explicit diagnosis of glaucoma or ocular hypertension and place of residency
[c]Model 3 for OM was additionally adjusted by country of birth
[d]Model 3 for facial CM additionally adjusted by place of residency

Table 19. Adjusted hazard ratios (HR) with 95% confidence intervals (CI) for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to PGAs versus non-PGAs: Main Analyses Ever Exposure (6 months lag time) and Real time (0 months lag time)

Exposure definition	**Outcome**	PGAs		Non-PGAs		Model 1	Model 2	Model 3
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	16	2.2	5	1.8	1.23 (0.45 - 3.39)	1.02 (0.36 - 2.84)	1.04 (0.37 - 2.90)[a]
	Facial CM	101	14	50	17.5	0.79 (0.56 - 1.11)	0.79 (0.55 - 1.13)	0.8 (0.57 - 1.13)[b]
Real-time exposure (0 month lag time)	OM	25	4.6	15	5	0.92 (0.48 - 1.75)	0.98 (0.51 - 1.90)	0.99 (0.51 - 1.92)[c]
	Facial CM	85	15.6	56	18.6	0.84 (0.60 - 1.18)	0.84 (0.59 - 1.20)	0.84 (0.59 - 1.19)[d]

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and any cancer except malignant melanoma or non-melanoma skin cancer.
Model 3: Change-in-estimate method
[a]Model 3 for OM was additionally adjusted by diabetes, explicit diagnosis of glaucoma or ocular hypertension
[b]Model 3 for facial CM was additionally adjusted by explicit diagnosis of glaucoma or ocular hypertension and place of residency
[c]Model 3 for OM was additionally adjusted by explicit diagnosis of glaucoma or ocular hypertension
[d]Model 3 for facial CM was additionally adjusted by place of residency

Table 20. Distribution of first events during follow-up: Sensitivity Analyses. Different lag times for ever exposure with 0 and 12 months and real-time exposure 6 months

Lag time (months)	Exposure group	Ever exposure		Real-time exposure	
		OM	Facial CM	OM	Facial CM
0	Latanoprost	24	76	-	-
	Other PGA	8	33	-	-
	All PGA	32	109	-	-
	Non PGA	12	56	-	-
	Unexposed	N/A	N/A	-	-
	Total	44	165	-	-
6	Latanoprost	-	-	8	50
	Other PGA	-	-	3	25
	All PGA	-	-	11	75
	Non PGA	-	-	5	62
	Unexposed	-	-	7	20
	Total	-	-	16	137
12	Latanoprost	10	62	-	-
	Other PGA	5	27	-	-
	All PGA	15	89	-	-
	Non PGA	3	43	-	-
	Unexposed	N/A	N/A	-	-
	Total	18	132	-	-

N/A=not applicable; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue

Table 21. Distribution of first events during follow-up, by ever and real-time exposure and lag times: Sensitivity Analyses for Incident PGA Users

Lag time (months)	Exposure groups	Ever exposure		Real-time exposure	
		OM	Facial CM	OM	Facial CM
0	Latanoprost	-	-	13	12
	Other PGA	-	-	4	13
	All PGA	-	-	17	26
	Non PGA	-	-	12	44
	Unexposed	-	-	6	27
	Total	-	-	**29**	**71**
6	Latanoprost	1	17	-	-
	Other PGA	3	16	-	-
	All PGA	4	33	-	-
	Non PGA	5	49	-	-
	Unexposed	N/A	N/A	-	-
	Total	**9**	**82**	-	-

N/A: not applicable OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue;

Table 22. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Latanoprost versus Non- PGAs: Sensitivity Analyses for different time lags

Exposure definition	Outcome	Latanoprost		Non-PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (0 month lag time)	OM	24	3.9	12	3.7	1.66 (0.81 - 3.37)	1.63 (0.79 - 3.36)
	Facial CM	76	12.2	56	17.3	0.67 (0.47 - 0.95)	0.69 (0.48 - 0.99)
Ever exposure (12 month lag time)	OM	10	2.1	3	1.2	1.7 (0.46 - 6.25)	1.41 (0.37 - 5.36)
	Facial CM	62	13.3	43	17.3	0.71 (0.48 - 1.06)	0.72 (0.48 - 1.09)
Real-time exposure (6 months lag time)	OM	8	6.3	5	4.3	1.6 (0.9-2.7)	1.5 (0.9-2.7)
	Facial CM	50	12.2	62	12.4	0.7 (0.5 - 1.1)	0.7 (0.5 - 1.1)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 23. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Latanoprost versus Other PGA:, Sensitivity Analyses for different time lags

Exposure definition	Outcome	Latanoprost		Other PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (0 month lag time)	OM	24	3.9	8	3.8	1.11 (0.50 - 2.49)	1.05 (0.47 - 2.36)
	Facial CM	76	12.2	33	15.6	0.73 (0.49 - 1.11)	0.73 (0.48 - 1.12)
Ever exposure (12 month lag time)	OM	10	2.1	5	3.3	0.69 (0.24 - 2.03)	0.61 (0.20 - 1.82)
	Facial CM	62	13.3	27	17.9	0.69 (0.44 - 1.09)	0.68 (0.43 - 1.08)
Real-time exposure (6 months lag time)	OM	8	6.3	3	4.7	0.6 (0.2 - 1.9)	0.7 (0.4 - 1.0)
	Facial CM	50	12.2	25	15.6	1.3 (0.6-2.8)	1.3 (0.6-2.7)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 24. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Other PGAs versus Non-PGAs: Sensitivity Analyses for different time lags

Exposure definition	Outcome	Other PGAs		Non-PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (0 month lag time)	OM	8	3.8	12	3.7	1.24 (0.50 - 3.07)	1.16 (0.46 - 2.91)
	Facial CM	33	15.6	56	17.3	0.93 (0.60 - 1.44)	0.96 (0.61 - 1.51)
Ever exposure (12 month lag time)	OM	5	3.3	3	1.2	2.22 (0.53 - 9.33)	1.95 (0.46 - 8.34)
	Facial CM	27	17.9	43	17.3	1.05 (0.65 - 1.71)	1.11 (0.67 - 1.83)
Real-time exposure (6 months lag time)	OM	3	4.3	5	4.1	1.2 (0.5-2.6)	1.2 (0.5-2.6)
	Facial CM	25	15.4	62	15.6	1.5 (0.8-2.8)	1.6 (0.8-2.9)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 25. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to PGAs versus Non-PGAs: Sensitivity Analyses for different time lags

Exposure definition	Outcome	PGAs		Non-PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (0 month lag time)	OM	32	3.8	12	3.7	1.54 (0.78 - 3.03)	1.51 (0.76 - 3.02)
	Facial CM	109	13.1	56	17.3	0.74 (0.54 - 1.02)	0.76 (0.54 - 1.07)
Ever exposure (12 month lag time)	OM	15	2.4	3	1.2	1.8 (0.52 - 6.26)	1.52 (0.43 - 5.38)
	Facial CM	89	14.4	43	17.3	0.81 (0.56 - 1.17)	0.82 (0.56 - 1.21)
Real-time exposure (6 months lag time)	OM	11	5.9	5	1.3	1.6 (0.8-2.5)	1.6 (0.9-2.7)
	Facial CM	75	13.1	62	17.2	1.1 (0.8-1.5)	1.4 (1.0-1.9)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 26. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Latanoprost versus Non-PGAs, Sensitivity Analyses for incident users

Exposure definition	**Outcome**	Latanoprost		Non-PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	1	0.6	5	1.8	0.34 (0.04 - 2.90)	0.35 (0.04 - 3.02)
	Facial CM	17	9.9	49	17.4	0.57 (0.33 - 1.00)	0.56 (0.31 - 1.01)
Real-time exposure (0 month lag time)	OM	13	3.4	13	4.3	0.84 (0.39 - 1.83)	0.81 (0.37 - 1.77)
	Facial CM	12	3.1	44	14.6	0.21 (0.11 - 0.40)	0.21 (0.11 - 0.42)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 27. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Latanoprost versus Other PGAs: Sensitivity Analyses for incident users

Exposure definition	**Outcome**	Latanoprost		Other PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	1	0.6	3	3.2	0.18 (0.02 - 1.77)	0.17 (0.02 - 1.62)
	Facial CM	17	9.9	16	16.8	0.59 (0.30 - 1.18)	0.6 (0.29 - 1.26)
Real-time exposure (0 month lag time)	OM	13	3.4	4	2.4	1.42 (0.45 - 4.43)	1.42 (0.45 - 4.45)
	Facial CM	12	3.1	14	8.6	0.44 (0.20 - 0.96)	0.47 (0.21 - 1.08)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 28. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to Other PGAs versus Non-PGAs: Sensitivity Analyses for incident users

Exposure definition	Outcome	Other PGAs		Non-PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	3	3.2	5	1.8	1.88 (0.44 - 7.98)	1.64 (0.38 - 7.05)
	Facial CM	16	16.8	49	17.4	0.99 (0.56 - 1.75)	0.94 (0.51 - 1.73)
Real-time exposure (0 month lag time)	OM	4	2.4	13	4.3	0.49 (0.16 - 1.51)	0.44 (0.14 - 1.39)
	Facial CM	14	8.6	44	14.6	0.56 (0.31 - 1.04)	0.53 (0.27 - 1.02)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer

Table 29. Adjusted hazard ratios (HR) with 95% confidence intervals for ocular melanoma (OM) and facial cutaneous melanoma (CM) with exposure to PGAs versus Non-PGAs: Sensitivity Analyses for incident users

Exposure definition	Outcome	PGAs		Non-PGAs		Model 1	Model 2
		N of events	Events per 100,000 PY	N of events	Events per 100,000 PY	HR (95% CI)	HR (95% CI)
Ever exposure (6 months lag time)	OM	4	1.5	5	1.8	0.88 (0.23 - 3.32)	0.81 (0.21 - 3.06)
	Facial CM	33	12.4	49	17.4	0.72 (0.46 - 1.13)	0.69 (0.43 - 1.11)
Real-time exposure (0 month lag time)	OM	17	3.1	13	4.3	0.75 (0.36 - 1.54)	0.71 (0.34 - 1.47)
	Facial CM	26	4.8	44	14.6	0.31 (0.19 - 0.51)	0.31 (0.19 - 0.52)

PY=person years; OM=ocular melanoma; CM=cutaneous melanoma; PGA=prostaglandin analogue; N=Number; HR=hazard ratio; CI=confidence interval
Model 1: adjusted for age and sex measured at inclusion date.
Model 2: Fully adjusted for following variables:
Time fixed: age, sex, country of birth, place of residency, and diagnosis of diabetes all measured at inclusion date
Time-varying: ICD diagnosis code of glaucoma or OH, exposure to NSAIDs, exposure to immunosuppressant and/or biological agents, exposure to cytostatic, atopic dermatitis, psoriasis, dysplastic naevus syndrome, non-melanoma skin cancer and diagnosis of any cancer, except malignant melanoma or non-melanoma skin cancer