Janssen Research & Development

Observational Study Protocol

Post Authorization Safety Study to Characterize the Risk of SPM Including MDS/AML Among Metastatic Prostate Cancer Patients Exposed to AKEEGA

Protocol PCSONCA0485**; [Version: 1.2 Revised Protocol]**

CJNJ-67652000 (niraparib/abiraterone acetate fixed dose combination)

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STUDY INFORMATION

Title: Post Authorization Safety Study to Characterize the Risk of SPM Including MDS/AML Among Metastatic Prostate Cancer Patients Exposed to AKEEGA

Protocol version: 1.2

Date of last version of the protocol: 04 March 2024

Active substances (INN common name): Niraparib, Abiraterone Acetate

Pharmaco-therapeutic group (ATC Code): L01XK

Medicinal product(s): Niraparib/Abiraterone Acetate Fixed-Dose Combination plus Prednisone/Prednisolone

Product reference: EU/1/23/1722/001-2

Procedure number: EMEA/H/C/005932/MEA/001

Name of Marketing Authorization Holder(s): Janssen-Cilag International N.V.

Joint PASS: No

Research question and objectives: What is the risk of second primary malignancy among patients exposed to AKEEGA® (niraparib/abiraterone acetate) in a real-world setting? The primary objectives of this study are to estimate the incidence of myelodysplastic syndrome / acute myeloid leukemia and other second primary malignancies among patients exposed to AKEEGA and in comparison to BRCA1/2 mutated patients exposed to androgen-receptor pathway inhibitors (ARPIs) indicated for metastatic castrate resistant prostate cancer (mCRPC).

Country(-ies) of study: Sweden, United States

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2. LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Description of Abbreviated Term
AA	Abiraterone Acetate
AAP	Abiraterone Acetate and Predniso(lo)ne
AE	Adverse Event
AML	Acute Myeloid Leukemia
ARPI	Androgen-receptor Pathway Inhibitor
CDM	Clinformatics® Data Mart
CHMP	Committee For Medicinal Products for Human Use
CI	Confidence Interval
EAP	Early Access Program
EC	European Commission
ECOG PS	Eastern Cooperative Oncology Group Performance Status
EDC	Electronic Data Capture
EHR	Electronic Health Records
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
FDC	Fixed-dose Combination
GePaRD	German Pharmacoepidemiological Research Database
GVP	Good Pharmacovigilance Practices
HIPAA	Health Insurance Portability and Accountability Act
HR	Hazard Ratio
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IQR	Interquartile Range
IRB	Institutional Review Board
MAA	Marketing Authorisation Application
MAH	Marketing Authorisation Holder
mCRPC	Metastatic Castration-resistant Prostate Cancer
MDS	Myelodysplastic Syndrome
Optum	Optum De-identified Clinformatics® Data Mart Database – Date of Death (DOD)
OS	Overall Survival
PARP	Poly Adenosine Diphosphate-ribose Polymerase
PASS	Post-authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
rPFS	Radiographic Progression-free Survival

SAP	Statistical Analysis Plan
SEER	Surveillance, Epidemiology and End Results Program
SHI	Statutory Health Insurance
SIR	Standardized Incidence Ratio
SmPC	Summary of Product Characteristics
SPM	Second Primary Malignancy
TCC	Time to Cytotoxic Chemotherapy
TSP	Time to Symptomatic Progression
US	United States

Definition of Term(s)

Study	The term "study" indicates the collection of data for research purposes only. The use of this term in no way implies that any treatments or procedures outside clinical practice, planned or otherwise, have been provided or performed.
Retrospective non-interventional study	A study that has all information collected from source data or a retrospective database. Normally, there is no new collection of information for a patient, although this may be required to address specific questions. Studies/Programs/Related Research Activities with only one visit can be considered prospective or retrospective bearing in mind this definition and the source of information.

3. RESPONSIBLE PARTIES

Principal Participating Physician: Peter Francis, MD, Senior Global Medical Affairs Lead, Janssen Global Services LLC

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4. SYNOPSIS

Protocol Title: Post Authorization Safety Study to Characterize the Risk of SPM Including MDS/AML Among Metastatic Prostate Cancer Patients Exposed to AKEEGA

Sponsor's Responsible Party: Janssen-Cilag International N.V.
NOTE: The term "sponsor" used throughout this document refers to the entities listed in the Contact Information page(s), which will be provided separately.

The objective of this Post-Authorisation Safety Study is to assess the incidence of and risk factors for SPM including MDS/AML among prostate cancer patients exposed to AKEEGA in the routine clinical setting.

This PASS will be conducted as a retrospective, noninterventional, study including patients who receive AKEEGA in routine clinical practice, using data from the Swedish Medical Registries. Additionally, a complementary study will be conducted utilizing the US based Optum Clinformatics DOD database. The study period for both analyses will be five years following study initiation, with interim descriptive reports provided annually describing outcomes among AKEEGA exposed patients and a final comparative safety analysis including BRCA1/2 carriers exposed to ARPIs indicated for mCRPC implemented and reported five years following study initiation. The category of ARPIs is inclusive of abiraterone, enzalutamide, darolutamide and apalutamide.

5. AMENDMENTS AND UPDATES

Version	Date	Rationale
1.	October 2023	Original protocol
1.1	March 2024	Revised protocol
1.2	June 2024	Revised protocol

6. RATIONALE AND BACKGROUND

6.1. Background

Prostate cancer is the most common cancer in men in Europe, and the sixth-highest cause of cancer-related death worldwide[1,2]. Despite treatment advances, metastatic castration-resistant prostate cancer (mCRPC) remains an incurable, deadly disease [5,6]. BRCA1/2 gene mutations have been identified in approximately 10-15% of mCRPC patients [7,8] and are associated with aggressive disease, poor outcomes, and a shorter survival time [9-12].

Niraparib is a highly selective poly adenosine diphosphate-ribose polymerase (PARP) inhibitor [13]. PARP1 belongs to a family of 17 enzymes that catalyze the ADP-ribosylation reaction and plays a versatile role in various DNA metabolism [14,15]. PARP1 is the primary target in causing cytotoxicity in BRCA1/2 mutant cancers [16]. When treated with PARP inhibitor, the BRCA1/2 deficient tumors experience intolerable replication stress at multiple difficult-to-replicate loci, which then leads to cell death [17]. Abiraterone acetate (AA) is an orally administered androgen biosynthesis inhibitor. As a fixed-dose combination (FDC) tablet combining niraparib and AA, AKEEGA plus predniso(lo)ne targets the androgen receptor axis, which remains the key oncogenic driver in mCRPC, and induces synthetic lethality in tumors that harbor BRCA1/2 gene mutations by potent inhibition of PARP activity[13,18,19].

In the randomised, double-blind, placebo controlled, Phase 3 MAGNITUDE study (64091742PCR3001) [20], a total of 765 mCRPC patients were enrolled. The study includes patients with specific HRR gene alterations (biomarker positive: ATM, BRCA1, BRCA2, BRIP1, CDK12, CHEK2, FANCA, HDAC2, PALB2) and without HRR gene alterations (biomarker negative), who were randomised 1:1 to receive niraparib once daily plus abiraterone acetate and predniso(lo)ne (AAP) or placebo plus AAP [21,22]. Among the total of 765 patients enrolled, 423 patients had HRR gene alterations, 225 (53.2%) of whom had BRCA mutations [21,22]. Additionally in an open-label cohort of HRR-positive patients, 95 patients received the FDC formulation of niraparib and AA, plus predniso(lo)ne [22]. The primary endpoint of the MAGNITUDE study was radiographic progression-free survival (rPFS), and the key secondary endpoints included time to symptomatic progression (TSP), time-to-initiation of cytotoxic chemotherapy (TCC), and overall survival (OS) [21,22].

The MAGNITUDE trial results showed that niraparib plus AAP significantly improved rPFS in HRR-positive patients (Hazard Ratio [HR] 0.73; 95% Confidence Interval [CI], 0.56 to 0.96; p=0.022) [7]. This improvement was most pronounced in patients with BRCA1/2 gene mutations, where a statistically significant 47% risk reduction in rPFS was observed (Hazard ratio [HR], 0.53; p=0.001) [7]. At IA2 (17 Jun 2022) after a median follow-up of 24.8 months in the BRCA subgroup, a consistent and clinically meaningful treatment effect favouring niraparib plus AAP was observed, with a median rPFS of 19.5 months compared with 10.9 months for placebo plus AAP [23].

The incidence of grade ≥ 3 adverse events (AEs) was 67.0% with niraparib + AAP and 46.4% with placebo + AAP [24]. The most commonly observed grade 3 AEs were anemia (28.3% vs 7.6%) and hypertension (14.6% v 12.3%) with niraparib + AAP versus placebo + AAP, respectively [24]. Other grade 3/4 AEs of note include thrombocytopenia (6.6% v 2.4%) and neutropenia (6.6% v 1.4%) with niraparib + AAP versus placebo + AAP, respectively [24]. A total of 38 patients died during study treatment, with 19 from each group [24]. In patients who died due to AEs, infections (e.g., COVID-19 and pneumonia) were the leading cause of death in the niraparib + AAP group; cardiac disorders were the leading cause of death in the placebo + AAP group [24]. Patients with niraparib drug interruptions or dose reductions had comparable rPFS benefit from niraparib + AAP compared with the observed benefit in the overall HRR-positive population (HR, 0.72; 95% CI, 0.53 to 0.97 and HR, 0.70; 95% CI, 0.46 to 1.08, respectively) [24].

Second Primary Malignancies

Second primary malignancies (SPMs) are cancers that develop after a primary cancer is diagnosed and treated in the same individual. Population-based studies in several tumor types including prostate cancer show that patients with metastatic disease are at an increased risk for SPMs. Based on a study using information from the United States (US) Surveillance, Epidemiology and End Results Program (SEER) database collected from 1992 to 2010, among 441,504 men who were diagnosed with prostate cancer, a total of 44,310 men developed at least one SPM during the study [25]. Risk was significantly lower for leukemia and for cancers of the oral cavity and pharynx, esophagus, stomach, colon and rectum, liver, gallbladder, pancreas, lung and bronchus, and larynx among men with prostate cancer compared with the general population [25]. Conversely, there was a significantly higher risk for cancers of soft tissue including heart, bladder, kidney, and endocrine system among men with prostate cancer [25]. In a more recent analysis of SEER data, conducted between the years 2000 through 2016, 3.9% of patients with prostate cancer developed at least one SPM during the study period.

As a specific SPM, myelodysplastic syndrome (MDS) is a group of bone marrow failure disorders characterized by ineffective haematopoiesis in one or more of the lineages of the bone marrow [26]. MDS can evolve from a refractory anemia to acute myeloid leukemia (AML), which is associated with a decrease in intramedullary apoptosis and a block in myeloid differentiation. In the general population, the incidence of MDS is 5 per 100,000 and increases to 21 per 100,000 among persons aged 70 or older [27]. The association of MDS with age suggests genetic damage caused by hazardous exposure or inherited susceptibility, or accumulation of genetic damage. The diagnostic classification currently in use by the World Health Organization recognizes six distinct entities of MDS based on morphologic quantitative and qualitative evaluation of the peripheral blood and bone marrow using basic haematological techniques [28]. MDS and AML have been found to be associated with PARP inhibitor therapy in some clinical trials and real-world data [29-33]. Additionally, in some studies BRCA1/2 carriers have been found to have an increased risk of several cancers, including breast, prostate, pancreatic, gastric, esophageal, and biliary cancer, with suggested evidence for potential increased risk of colorectal cancer, melanoma, and MDS/AML.

As part of post-approval commitments, the MAH is requested to conduct a voluntary Category 3 Post authorization safety study to characterize the risk of SPM including MDS/AML among metastatic prostate cancer patients exposed to AKEEGA, with a final study report to be submitted five years following study initiation.

7. OBJECTIVES

Objective(s) and Outcome(s)/Measure(s) of Interest

The objective of this Post-Authorisation Safety Study is to assess the incidence of and risk factors for MDS/AML and other SPMs among prostate cancer patients exposed to AKEEGA in the routine clinical setting.

The specific objectives are as follows:

Primary objective

1) To estimate the incidence rate of (a) MDS/AML and (b) other SPMs in a cohort of adult patients with mCRPC and treated with AKEEGA.
2) To compare the incidence of (a) MDS/AML and (b) other SPMs in a cohort of adult male patients with mCRPC and treated with AKEEGA with a clinically comparable cohort of BRCA-mutated patients treated with ARPIs indicated for mCRPC.

Secondary objective:

1) To assess clinical characteristics and characterize potential risk factors among patients with mCRPC who develop MDS/AML or other SPMs in a cohort of adult male patients with mCRPC and treated with AKEEGA.

8. RESEARCH METHODS

8.1. Study Design

This PASS will be conducted as a retrospective, noninterventional, study including patients who receive AKEEGA in routine clinical practice captured by selected real world databases.

The study period will range from EMA approval of the study protocol through five years following study initiation, with interim descriptive reports annually describing outcomes among patients exposed to AKEEGA and final comparative safety analysis demonstrating relative risk in comparison to clinically comparable BRCA-mutated patients exposed to ARSIs indicated for mCRPC available at that time which will be implemented and reported five years following study initiation.

In this study, data collected will be de-identified data drawn from the Swedish Medical Registries and the US based Optum Clinformatics database. Analyses will be conducted separately for each database.

8.2. Setting and Study Population

8.2.1. Study Setting

Data will be drawn from the Swedish Medical Registries and the Optum DOD Clinformatics database. Further details of data sources are provided in Section 8.4.

8.2.2. Patient Selection Criteria

All patients with mCRPC, who have documented exposure to AKEEGA in selected databases as part of routine clinical practice and following the approved label in the region, are eligible to be included in the study.

8.2.2.1. Inclusion Criteria

The population under study will consist of individuals meeting the following criteria:

1. Aged 18 years or older.
2. Patients with mCRPC.
3. Received (1) AKEEGA, or (2) ARPI after patients were identified with mCRPC.
4. Had a 6-month prior observation before being identified as patients with mCRPC.
5. Patients with BRCA1/2 mutation.

8.2.2.2. Exclusion Criteria

Patients who meet any of the following criteria will not be eligible for this study:

1. Patients who received AKEEGA for use that is not according to the authorized indication in the region.
2. Patients with prior history of MDS/AML.

8.2.2.3. Patient Selection: Matching and Other Sampling Techniques

Patients that meet the inclusion criteria will be considered for analysis. For the comparative analysis, propensity scores will be utilized to match BRCA1/2 mutated patients treated with ARPIs indicated for mCRPC to patients treated with AKEEGA. Given the comparative analysis will be conducted five years following study initiation to allow for uptake of AKEEGA post-approval, potential comparators in the same indicated patient population will be evaluated at this time for inclusion in this study. Comparative therapies that will be evaluated via propensity score matching will include ARPIs indicated for mCRPC with documentation of mutated BRCA1/2 status. Further discussion related to the propensity score matching method is included in Section 8.2.2.3. and will be further detailed in the statistical analysis plan (SAP).

8.2.2.4. Calculation of Time-at-Risk

An intent-to-treat analysis will be utilized, in which patients will be followed from their first exposure through the occurrence of an outcome, death, disenrollment from the database, or the end of the study period, whichever comes first.

8.2.3. Duration of Study Period(s) and Follow-Up

Patients' baseline data will be collected in the 6-month time period (or earlier, as available) prior to their first documented exposure to AKEEGA. The follow-up period will be from the first documented exposure to AKEEGA through the outcome of interest, death, disenrollment from the database, or the end of the study period, whichever comes first.

Descriptive interim analysis including baseline information on AKEEGA exposed patients as well as counts of the occurrence of second primary malignancy will be reported annually. The comparative cohort study comparing AKEEGA to clinically comparable alternate therapies such as ARPIs indicated for mCRPC with documented BRCA mutations will be conducted 5 years following study initiation.

8.3. Variables

Variables of interest are listed in Sections 8.3.1. to 8.3.4. Data listed below can be obtained within both data sources, however some variables, such as family history, smoking, stop dates of treatment, may be limited and need to be defined using algorithms and/or proxies. Details of operationalization of each definition within each database including phenotype algorithms will be included in the SAP.

8.3.1. Baseline Information

- Demographic data including age
- Diagnosis and medical history, including age at treatment initiation, comorbidities, concomitant medications, family history of cancer, as available
- Treatment history, including start and stop dates, dose and duration as available
- Genetic information, including BRCA1/2 gene mutations as available

8.3.2. Exposure

Exposures of interest include AKEEGA and ARPIs indicated for mCRPC, and concomitant prednisone/prednisolone as indicated in the product labels. Of note, due to the nature of secondary observational data, exposure is captured as treatment as prescribed in the data sources.

- Treatment history, dose, and duration as available

8.3.3. Outcomes

Outcomes of interest include MDS/AML and other second primary malignancies. Second primary malignancy outcomes will be defined according to ICO criteria mapped to local diagnostic codes

(Full list appended in ANNEX 1). All malignancy outcomes within the Swedish Registries are identified directly from the linked Swedish Cancer Registry.

8.3.4. Other Variables

Other variables of interest include potential risk factors for second primary malignancy, including but not limited to age at initial prostate cancer diagnosis, stage/disease severity at diagnosis, ECOG performance status at diagnosis, comorbidities at diagnosis including immunosuppressive conditions, medications, cancer treatments, start and stop dates for prior treatment, reason for discontinuation of cancer treatment, and history of smoking (when available).

8.4. Data Sources

The primary data sources for this study are the Swedish Medical Registries. Additionally, a complementary study will be conducted using Optum Clinformatics DOD database given the large sample size and additional coverage of geographic region. Details of the full feasibility assessment can be found in Section 8.4.1.

In Sweden, the nationwide registries are population-based with virtually complete follow-up, continuously updated information, and exact censoring information throughout entire lifespan. Sweden has well-established cancer registries with data on incident malignancies, which receive information from multiple sources, including hospitals, outpatient clinics, primary care physicians, pathology and cytology laboratories, and death certificates. Cancer reporting is mandatory in Sweden, and cancer registries include high quality data in terms of completeness and validity [35]. In addition, microscopic verification of the cancers is frequent [36]. The validity of the cancer registries is fortified by manual quality control routines and notifications from different data sources, which also secures high completeness. Sweden has a nationwide prescription registry containing electronically submitted information on prescriptions dispensed by pharmacies [37,38]. The registries are valuable data sources for drug utilization studies or pharmacoepidemiological research on the effectiveness or safety of medical drugs.

Optum's Clinformatics® Data Mart (CDM) is derived from a database of administrative health claims for members of large commercial and Medicare Advantage health plans. The database includes data over a 14-year period (1/2007 through 12/2021). Clinformatics® Data Mart is statistically de-identified under the Expert Determination method consistent with the Health Insurance Portability and Accountability Act (HIPAA) and managed according to Optum® customer data use agreements. CDM administrative claims submitted for payment by providers and pharmacies are verified, adjudicated and de-identified prior to inclusion. This data, including patient-level enrollment information, is derived from claims submitted for all medical and pharmacy health care services with information related to health care costs and resource utilization. The population is geographically diverse, spanning all 50 states in the US.

8.4.1. 'Fit-for-Purpose' and Data Feasibility Assessment(s)

After reviewing regulatory guidance documents and peer-reviewed publications, including Pacurariu A, et al [39], on the advantages and limitations of existing real world database such as cancer registries and other secondary data sources in the EU and US, a total of nine real-world databases were selected for inclusion in a feasibility assessment to determine which data source may be fit-for-purpose for this PASS (sections 13.1., and 13.2.). Data sources evaluated included Optum de-identified Clinformatics® Data Mart Database - Date of Death (Optum DOD), IBM MarketScan databases, Swedish Medical Registries, PHARMO network database, Flatiron Oncology electronic health records (EHR), ConcertAI, Tempus, COTA, and German Pharmacoepidemiological Research Database (GePaRD).

The feasibility of each database was assessed by (1) total number of patients diagnosed with prostate cancer, (2) total number of patients with exposure to abiraterone acetate plus prednisone, (3) duration of follow-up, (4) availability of genetic information, and (5) availability of the following critical variables: initial prostate cancer diagnosis, initial diagnosis date, stage/disease severity at diagnosis, ECOG performance status at diagnosis and during follow-up at month 12, comorbidities at diagnosis and follow-up including immunosuppressive conditions, concomitant medications, cancer treatments, start and stop dates for prior treatment, reason for discontinuation of cancer treatment, complete response and other effectiveness outcomes, second primary malignancy occurrence (type and diagnosis date), age at diagnosis, and history of smoking (sections 13.1. and 13.2.).

The majority of data providers demonstrated sufficient capture of prostate cancer patients in general and patients exposed to abiraterone acetate plus prednisone annually, with the exception of the COTA database (section 13.3.). Length of follow-up varied, with the Swedish Medical Registries demonstrating longest follow-up. Capture of critical variables also varied across databases. Despite having large sample sizes, the US based Oncology EHR data sources, Tempus, Flatiron and ConcertAI, demonstrated a lack of capture of non-cancer related comorbidity and concomitant medications, which would be necessary for propensity score matching as well as identification of potential risk factors. Some genetic data are available in each of the data sources, with the exception of GePaRD.

Based on the MAH's assessment of the data sources, the EMA accepted that this Category 3 Post-Authorization Safety Study for the evaluation of second malignancies among patients exposed to AKEEGA be conducted using data captured from the Swedish Medical Registries and complimented by the Optum database. The primary analysis will be the study utilizing the Swedish Medical Registries, given the longitudinal nature of the databases, ability to link national registries for complete capture of critical variables and established track record for Post-Authorisation Safety Studies as well as second primary malignancy outcomes. The Optum DOD database will be complimentary in that it is a large database representing another region with wide use of both therapies. Both of these data sources have been used widely to study prostate cancer therapies as well as malignancy outcomes.

8.5. Study Size

The following sample size estimation was calculated for the study design of a prospective cohort study with comparison to a historic and/or contemporaneous control cohort for the outcome of second primary malignancy. Assuming a background incidence rate for subsequent malignancy of 3% in prostate cancer patients, an alpha of 0.05, and 80% power, approximately 746 patients will be required for a minimally detectable increased relative risk among AKEEGA patients of 2.0 [34]. A broader range of potential background incidence values and relative risks are provided below.

Table 1. Sample size (per cohort) for range of incidence values and relative risks

	P=0.01	P=0.02	P=0.03	P=0.04	P=0.05
RR=2	2316	1139	**746**	550	432
RR=3	766	373	243	177	138
RR=4	422	204	131	95	73
RR=5	282	135	86	61	47

8.6. Data Analysis

Statistical analyses will be performed by or under the authority of the sponsor. A general description of the planned statistical methods to be used to analyze the data collected in this study is presented in the following subsections. Details of the data analysis methods presented below will be provided in the study's SAP. A change to data analysis methods described in the protocol will require a protocol amendment only if it alters a principal feature of the protocol.

8.6.1. Descriptive Analysis

The analysis population will include all patients who meet the inclusion criteria in the data sources.

Analyses reported annually will be descriptive, and no hypothesis will be tested. Distributions of patient and disease characteristics will be summarized. A descriptive comparison of the baseline demographic and clinical characteristics of patients for the AKEEGA and ARPIs cohorts will be included in the final analysis. Incidence rates of MDS/AML and other SPMs and their respective 95% CIs per 100 person-time units will be estimated. For calculation of incidence rates, the number of events, the total time-at-risk, and the incidence rate per person-time within each database separately will be reported for the cohort of patients exposed to AKEEGA, as well as for the comparable cohort of BRCA-mutated patients treated with ARPIs indicated for mCRPC.

Potential risk factors for MDS/AML and SPMs within each cohort will be described, such as age, anticancer chemotherapy and radiotherapy received, history of other cancers, family history of

cancers, and use of tobacco as available (for a complete explanation of variables analyzed during the study, see Section 8.3.). Standardized mean differences will be calculated to explore patient characteristics among patients who experience a second primary malignancy or AML/MDS event compared to those who do not.

8.6.2. Comparative analysis

8.6.2.1. Model Specification

The comparative safety study will be conducted five years following study initiation at which time a sufficient number of patients are anticipated to have accrued within the databases that allows for a comparative analysis.

For the purpose of contextualizing the event rates and quantifying relative risk while controlling for potential confounding factors, a new user cohort design will be used to conduct comparative analyses if the exposed (AKEEGA) population can be appropriately matched to selected comparator populations using propensity score matching. Propensity scores will be used as an analytic strategy to reduce potential confounding due to imbalance between the target and comparator cohorts in baseline covariates. The propensity score is the probability of a patient being classified in the target cohort vs. the comparator cohort, given a set of observed covariates. Comparative analyses will only be run in the case that feasibility assessments show appropriate comparable clinical cohorts can be generated based on diagnostics (see section 8.6.2.2. evaluation of cohorts and modeling below). Further details will be outlined within the SAP.

Cox proportional hazards will be used to estimate the hazards of each outcome for patients exposed to AKEEGA, relative to patients exposed to identified clinically comparable comparator therapies. The final outcome model will be summarized by providing the hazard ratio and associated 95% confidence interval. The number of persons at-risk, amount of time-at-risk, time-to-outcome, and number of outcomes in each cohort will also be reported. Additionally, a Kaplan-Meier plot will be generated to characterize the contour of risk over time for the outcome(s) of interest.

8.6.2.2. Evaluation of Cohorts and Modeling

Covariate balance will be summarized in tabular form by showing the mean value for all baseline covariates in AKEEGA exposed patients and BRCA1/2 mutated patients exposed to ARPIs indicated for mCRPC, with the associated standardized mean difference computed for each covariate. Once the propensity score model is fit, the propensity score distribution of each cohort will be plotted to evaluate the comparability of the two cohorts. Missingness of key variables will be described. Variables with a high degree of missingness will not be included in the propensity score matching models for the comparative analysis.

8.6.3. Strata Analyses

As feasible, comparative analyses will be stratified on known and potential risk factors for second malignancies.

8.7. Quality Control

8.7.1. Quality Assurance and Quality Control of the Database

Standard operating procedures or internal process guidance will be adhered to for the conduct of the study. These procedures include internal quality audits, rules for secure and confidential data storage, methods to maintain and archive project documents, quality-control procedures for programming, standards for writing analysis plans, and other relevant process documents.

8.8. Milestones

Table 2. Detailed Study Milestones

Milestone	**Planned Date**
Registration in the European Union electronic Register of Post-Authorisation Studies	Q2 2024
Start of data collection	Q3 2024
Interim report	Q3 2025 Q3 2026 Q3 2027 Q3 2028
End of data collection, and start of final data analysis	Q2 2029
Final report of study results	Q4 2029

Abbreviations: Q1, first quarter; Q2, second quarter; Q3, third quarter; Q4, fourth quarter.

8.9. Strengths and Limitations of the Research Methods

Limitations inherent to the use of administrative databases for epidemiological research are applicable to this study.

The proposed study design is subject to limitations due to the secondary use of health care data/registries. Data-related limitations include dependency on the accuracy of codes and algorithms to identify at risk conditions, professions or living circumstances, limited information on prior enrolment in randomized controlled trials, and potential bias associated with missing or underreporting of genetic information (e.g., BRCA1/2 gene mutations) in the earlier part of the study period within the data sources. Exposure ascertainment may be based on pharmacy dispensing records, general practice records, immunization registers, medical records, or other electronic data sources. In addition, dates of events may be missing or not correspond exactly to the onset date of the event.

9. PROTECTION OF HUMAN SUBJECTS

The use of the Optum database and the Swedish Medical Registries have been reviewed by respective Institutional Review Boards (IRB) and are determined to be exempt from broad IRB approval. Confidentiality of patient records will be maintained at all times. All study reports will contain aggregate data only and will not identify individual patients or physicians. At no time during the study will the sponsor receive patient identifying information except when it is required by regulations in case of reporting adverse events.

10. COLLECTION AND REPORTING OF SAFETY DATA

This study uses coded data that already exist in an electronic database. In this type of database, it is not possible to link (i.e., identify a potential causal association between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available, and adverse events are not reportable as individual case safety reports [EMA GVP 2017]. Further, analysis of AEs is not intended to be carried out as part of the study. The study results will be assessed for medically important results.

11. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The results of the study will be reported in a clinical study report generated by the sponsor. Patient identifiers will not be used in the publication of results. The sponsor will register and/or disclose the existence of and the results of clinical studies as required by law.

Any work created in connection with performance of the study and contained in the data that can benefit from copyright protection (except any publication by the participating physician) shall be the property of the sponsor as author and owner of copyright in such work.

12. REFERENCES

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13. ADDITIONAL INFORMATION

13.1. General feasibility counts including capture of prostate cancer patients, exposure to abiraterone acetate, duration of follow up, and genetic information

Table 3. General feasibility counts including capture of prostate cancer patients, exposure to abiraterone acetate, duration of follow up, and genetic information

	Number of patients with prostate cancer	Number of patients with exposure to abiraterone	Duration of follow-up (range, mean, median)	Genetic information (yes/no)
Swedish registries	Prevalence 122,000 (2019), incidence 10,000/year	2015: 469 2016: 324 2017: 494 2018: 572	All prostate cancer patients followed from diagnosis (from earliest 1958) to death or end of follow-up (March 2023)	Can be determined via proxy variables, linkages, and/or chart review
PHARMO	The 10-year prevalence increased from about 31,500 men in 1999 to more than 92,000 in 2022	~4,000 overall 2017: 660 2018: 860 2019: 1120 2020: 1300 2021: 1880	On average 12 years	Yes
ConcertAI	10,683	~4,100 overall	Median follow-up ~2,100 days. 99% follow-up≤30 days 98% follow-up≤90 days 97% follow-up≤180 days 93% follow-up≤360 days	Yes
COTA	2,700	384 overall	4.6 years (average)	Available for ~25% of records
GePaRD	Total 177915. 2004: 9928 2005: 9658 2006: 10544 2007: 11324 2008: 11106 2009: 11217 2010: 10754 2011: 10891 2012: 10569 2013: 9902 2014: 9596 2015: 10163 2016: 11101 2017: 12655 2018: 13768 2019: 14739	Total: 19,956 overall 2011: 408 2012: 1215 2013:2272 2014: 2431 2015: 2194 2016: 2132 2017: 2515 2018: 3136 2019: 3653	Data not provided	No
Tempus	65,000+	8,000+ overall	Data not provided	Available for ~40% of records
Flatiron	~20,500 patients overall Metastatic diagnosis by year: 2018: ~2,160 2019: ~2,330 2020: ~2,080 2021: ~2,080 2022: ~1,830 2023: ~230	~8,290 patients overall 2018: 1,170 2019: 1,215 2020: 1,020 2021: 1,070 2022: 1,110 2023: 215	Data not provided	Available for ~50% of patients
Optum	~900,000 prostate cancer patients overall	~15,800 patients overall	~3 years, range up to 10 years	Available for subset of patients
MarketScan	~500,000 prostate cancer patients overall	~4,400 patients overall	~2-3 years, range up to 10 years	No

13.2. Availability of critical variables including patient characteristics, potential risk factors for second malignancy, and outcomes

Table 4. Availability of critical variables including patient characteristics, potential risk factors for second malignancy, and outcomes

Variable	Swedish registries	PHARMO	ConcertAI	COTA	Flatiron	GePaRD	Tempus	Optum DOD	Marketscan
Prostate cancer diagnosis	Y	Y	Y	Y	Y	Y	Y	Y	Y
Initial diagnosis date	Y	Y	Y	Y	Y	Y	Y	Y	Y
Stage/disease severity at diagnosis	Y	Y	Y	Y	Y	With limitations	Y	Proxy algorithm	Proxy algorithm
ECOG at diagnosis	Can be accessed in linked sources	Y	Y	Y	Limited %	N	Y	N	N
ECOG during follow-up at month 12	N	N	Y	Y	N	N	Y	N	N
Comorbidities at diagnosis and follow-up (with focus on immunosuppressive conditions)	Y	Y	Y	Limited %	Limited %	Y	Y	Y	Y
Treatment	Y	Y	Y	Y	Y	Y	Y	Y	Y
Surgical history	Y	Y	Y	Y	Y	Y	Y	Y	Y
Concomitant medications including immunosuppressive medications	Y	Y	Y	Limited %	Limited %	Y	Y	Y	Y
Prior cancer treatments (including hormone therapy, chemotherapy, radiation therapy, immunotherapy)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Start and stop dates for prior treatment	Y	Y	Y	Y	Y	Y	Y	Y	Y
Reason for discontinuation	Can be accessed in linked sources	N	Y	Y	N	N	Y	N	N
Complete response	N	N	Y	Y	Y	N	Y	N	N
Outcomes including any second primary malignancy (type and diagnosis date)	Y	Y	Y	Y	Y	Y	Y	Y	Y
Effectiveness measures such as progression free survival, time to next treatment, response rate	Can be accessed in linked sources	Y	Y	Y	Y	N	Y	Proxy algorithm	Proxy algorithm
Survival status	Y	Y	Y	Y	Y	Y	Y	Limited %	Limited %
Age at diagnosis	Y	Y	Y	Y	Y	Y	Y	Y	Y
Smoking status	Can be accessed in linked sources	Y	Limited %	Limited %	Limited %	N	N	Limited %	Limited %

13.3. Summary of advantages and limitations of included data sources

Table 3: Summary of advantages and limitations of included data sources

	Advantages	Limitations
Swedish registries (Sweden)	• Provides population-based, routine, and prospective data on individuals lives and health • Adequate sample size • Includes all data from diagnosis (since 1958) to death or end of follow-up • Virtually complete follow-up and exact censoring information • Availability of most critical variables via registry linkages	• Sample size is lower than some other data sources • Linkages required to obtain some variables
PHARMO (Netherlands)	• Provides population-based, routine, and prospective data on individuals lives and health • Duration of follow-up • Availability of most critical variables	• Duration of follow-up and completeness is less comprehensive than Sweden • Sample size is lower than some other data sources
ConcertAI (US)	• Low rate of loss to follow-up: from diagnosis through outcome for >90% of patients • Availability of most critical variables • Linkage to claims data capability in near future	• Currently missing some comorbidity and concomitant medication information that is needed for risk factor identification • Follow-up for adverse events is currently limited
COTA (US)	• Geographic representation of patients accessible through mix of academic and community networks (1:1) in the US • Capture of relevant cancer diagnosis disease characteristics	• Very small sample size • Short duration of follow-up • Currently missing comorbidity and concomitant medication data that is needed for risk factor identification
GePaRD (Germany)	• Large sample size	• No genetic information • No length of follow-up information provided • Missing critical variables
Tempus (US)	• Includes comprehensive genetic data	• Small sample size • Lack of capture of critical variables
Flatiron (US)	• Availability of data pertinent to cancer diagnosis and treatment • Effectiveness outcomes captured well	• Currently missing comorbidity and concomitant medication data that is needed for risk factor identification
Optum (US)	• Large sample size • Availability of critical variables including risk comorbidities and concomitant medications • Includes some genetic data • If needed can access medical charts	• Duration of follow-up not as long as existing registries • Genetic data only available for small subset of patients • Survival data available for a subset of patients
MarketScan (US)	• Large sample size • Availability of critical variables including risk comorbidities and concomitant medications	• Smaller sample size than Optum • Duration of follow-up not as long as existing registries • Survival not captured

13.4. Title of Annex

ANNEX 1: ICD-O- Third Edition, Second Revision Morphology

14. ENCEPP CHECKLIST FOR STUDY PROTOCOLS

ANNEX 2: ENCEPP CHECKLIST FOR STUDY PROTOCOLS

Section 1: Research question	Yes	No	N/A	Page Number (s)
1.1 Does the formulation of the research question clearly explain:				10
1.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	X	☐	☐	
1.1.2 The objectives of the study?	X	☐	☐	
1.2 Does the formulation of the research question specify:				11
1.2.1 The target population? (i.e. population or subgroup to whom the study results are intended to be generalized)	X	☐	☐	
1.2.2 Which formal hypothesis(-es) is (are) to be tested?	X	☐	☐	
1.2.3 if applicable, that there is no a priori hypothesis?	X	☐	☐	

Comments:

Section 2: Source and study populations	Yes	No	N/A	Page Number (s)
2.1 Is the source population described?	☐	☐	☐	13
2.2 Is the planned study population defined in terms of:				12
2.2.1 Study time period?	X	☐	☐	
2.2.2 Age and sex?	X	☐	☐	
2.2.3 Country of origin?	X	☐	☐	
2.2.4 Disease/indication?	X	☐	☐	
2.2.5 Co-morbidity?	X	☐	☐	
2.2.6 Seasonality?	☐	☐	X	
2.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	X	☐	☐	11

Comments:

Section 3: Study design	Yes	No	N/A	Page Number (s)
3.1 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	X	☐	☐	12
3.2 Is the study design described? (e.g. cohort, case-control, randomized controlled trial, new or alternative design)	X	☐	☐	10
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	X	☐	☐	15-16
3.4 Is sample size considered?	X	☐	☐	15
3.5 Is statistical power calculated?	X	☐	☐	15

Comments:

Section 4: Data sources	Yes	No	N/A	Page Number (s)
4.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				12-13
4.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc)	X	☐	☐	
4.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, participant interview including scales and questionnaires, vital statistics, etc)	X	☐	☐	
4.1.3 Covariates?	X	☐	☐	
4.2 Does the protocol describe the information available from the data source(s) on:				12-13
4.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	X	☐	☐	
4.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	X	☐	☐	
4.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co- morbidity, co-medications, life style, etc.)	X	☐	☐	
4.3 Is the coding system described for:				12-13
4.3.1 Diseases? (e.g. International Classification of Diseases (ICD)- 10)	X	☐	☐	
4.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities (MedDRA) for adverse events)	X	☐	☐	
4.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	X	☐	☐	
4.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	X	

Comments: ATC classification not yet available for AKEEGA

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number (s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorizing exposure)	X	☐	☐	12
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	X	☐	☐	12
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	X	☐	☐	12
5.4 Is exposure classified based on biological mechanism of action?	☐	☐	X	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	X	☐	☐	12

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number (s)
6.1 Does the protocol describe how the endpoints are defined and measured?	X	☐	☐	12-13
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	X	☐	☐	12-13

Comments:

Section 7: Biases and Effect modifiers	Yes	No	N/A	Page Number (s)
7.1 Does the protocol address: 7.1.1 Selection biases? 7.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	 X X	 ☐ ☐	 ☐ ☐	17-18
7.2 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	X	☐	☐	16-18
7.3 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	X	☐	☐	16-18
7.4 Does the protocol address other limitations?	X	☐	☐	17-18

Comments:

Section 8: Analysis plan	Yes	No	N/A	Page Number (s)
8.1 Does the plan include measurement of absolute effects?	X	☐	☐	16
8.2 Is the choice of statistical techniques described?	X	☐	☐	15-16
8.3 Are descriptive analyses included?	X	☐	☐	15-16
8.4 Are stratified analyses included?	X	☐	☐	16
8.5 Does the plan describe the methods for identifying: 8.5.1 Confounders? 8.5.2 Effect modifiers?	 X X	 ☐ ☐	 ☐ ☐	16
8.6 Does the plan describe how the analysis will address: 8.6.1 Confounding? 8.6.2 Effect modification?	 X X	 ☐ ☐	 ☐ ☐	16

Comments:

Section 9: Quality assurance, feasibility and reporting	Yes	No	N/A	Page Number (s)
9.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	X	☐	☐	17
9.2 Are methods of quality assurance described?	X	☐	☐	17
9.3 Does the protocol describe quality issues related to the data source(s)?	X	☐	☐	17
9.4 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, participant recruitment)	X	☐	☐	14
9.5 Does the protocol specify timelines for				17
9.5.1 Start of data collection?	X	☐	☐	
9.5.2 Any progress report?	X	☐	☐	
9.5.3 End of data collection?	X	☐	☐	
9.5.4 Reporting? (i.e. interim reports, final study report)	X	☐	☐	
9.6 Does the protocol include a section to document future amendments and deviations?	X	☐	☐	7
9.7 Are communication methods to disseminate results described?	X	☐	☐	18
9.8 Is there a system in place for independent review of study results?	X	☐	☐	18

Comments:

Section 10: Ethical issues	Yes	No	N/A	Page Number (s)
10.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	X	☐	☐	18
10.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	X	
10.3 Have data protection requirements been described?	X	☐	☐	18

Comments: