Study information

Title	Description of Relugolix Use in Patients with Prostate Cancer: An Analysis of National Veterans Affairs Health Care Network Data
Protocol number	C4751009
Protocol version identifier	Version 1.0
Date	06 May 2024
Active substance	Relugolix (ATC code: L02BX04)
Medicinal product	Orgovyx
Research question and objectives	This study aims to achieve the following objectives: • Primary objective: 1. To describe demographics and clinical characteristics of patients with prostate cancer (PC) who initiated relugolix • Exploratory objectives: 2. To assess treatment patterns among patients with PC who initiated relugolix 3. To estimate adherence and persistence with relugolix among patients with PC who initiated relugolix 4. To assess testosterone suppression and prostate-specific antigen responses among androgen deprivation therapy (ADT) naïve patients with PC who initiated relugolix 5. To describe and compare demographics and clinical characteristics between Black and non-Hispanic White patients with PC who initiated relugolix 6. To describe and compare time to treatment changes between Black and non-Hispanic White patients with PC who initiated relugolix 7. To estimate and compare adherence and persistence with relugolix between Black and non-Hispanic White patients with PC who initiated relugolix

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1. CONTENTS

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ACS	American Cancer Society
ADT	Androgen Deprivation Therapy
ARPI	Androgen Receptor Pathway Inhibitor
ATC	Anatomical Therapeutic Chemical
CA	California
CCI	Charlson Comorbidity Index
CDC	Centers for Disease Control and Prevention
CDW	Corporate Data Warehouse
CIRCL	Center for Integrated Research in Cancer and Lifestyle
CPT	Current Procedural Terminology
dL	Deciliter
DOI	Digital Object Identifier
FDA	Food and Drug Administration
GnRH	Gonadotropin-Releasing Hormone
GPI	Generic Product Identifier
HCPCS	Healthcare Common Procedure Coding System
ICD	International Classification of Diseases
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
ICD-10-CM	International Classification of Diseases, 10th Revision, Clinical Modification
ICD-10-PCS	International Classification of Diseases, 10th Revision, Procedures
IEC	Independent Ethics Committee
IRB	Institutional Review Board
LHRH	Luteinizing Hormone–releasing Hormone

MA	Massachusetts
MPR	Medication Processing Ratio
NAACCR	North American Association of Central Cancer Registries
NC	North Carolina
NCCN	National Comprehensive Cancer Network
NCI	National Cancer Institute
ng	Nanogram
NHT	Novel Hormonal Therapy
NJ	New Jersey
NSAA	Non-Steroidal Anti-Androgen
NY	New York
NYC	New York City
PASS	Post-Authorization Safety Study
PC	Prostate Cancer
PDC	Proportion of Days Covered
PH	Proportional Hazards
PMCID	PubMed Central Identifier
PMID	PubMed Identifier
PSA	Prostate-Specific Antigen
SMD	Standardized Mean Difference
SMPA	Sumitomo Pharma America, Inc
US	United States
VA	Veterans Affairs

3. RESPONSIBLE PARTIES

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4. ABSTRACT

Title: Description of Relugolix Use in Patients with Prostate Cancer: An Analysis of National Veterans Affairs Health Care Network Data

Version: 1.0

Date of Protocol: 6 May 2024

Author: PPD

Rationale and Background: Prostate cancer (PC) is the most common cancer and the second leading cause of cancer death among men in the United States. Androgen deprivation therapy (ADT) such as injectable luteinizing hormone–releasing hormone (LHRH) agonists (e.g., leuprolide) is the standard of care for PC patients. ADT treatment can suppress testosterone level to castrate level and delay the progression of the disease. However, LHRH agonist can cause an initial surge of testosterone which results in a flare of symptoms including bone pain or obstructive urinary symptoms. In addition, LHRH agonist can increase the risk of cardiovascular events. As an alternative to LHRH, gonadotropin-releasing hormone (GnRH) antagonist can be considered. Relugolix is a recently approved oral GnRH antagonist, which can rapidly suppress testosterone level without the initial surge. The phase 3 HERO trial of relugolix in advanced PC patients has compared the efficacy and safety of oral relugolix with leuprolide and found that relugolix can achieve castration quicker and can better maintain castration than leuprolide. In addition, the incidence of major adverse cardiovascular events in the HERO trial was lower for relugolix than leuprolide (2.9% vs. 6.2%). Additionally, treatment was associated with a more rapid time to testosterone recovery. The positive results have led to the Food and Drug Administration (FDA) approval of relugolix in December 2020 for the treatment of adults with advanced PC. Currently, relugolix is the only ADT option available in oral form, distinguishing from the traditional injectable LHRH agonists. There are several studies in other diseases have shown that patients have a preference for oral medications due to cultural considerations, apprehension towards injections and needles, and concerns regarding incorrect administration. While the introduction of relugolix has offered a unique opportunity for patients with PC, it's vital to understand how it is being used in real-world. However, few studies have investigated this aspect.

Objectives: This study aims to achieve the following objectives:

- Primary Objective:
  1. To describe demographics and clinical characteristics of patients with PC who initiated relugolix
- Exploratory objectives:
  2. To assess treatment patterns among patients with PC who initiated relugolix
  3. To estimate adherence and persistence with relugolix among patients with PC who initiated relugolix
  4. To assess testosterone suppression and prostate-specific antigen (PSA) responses among ADT naïve patients with PC who initiated relugolix
  5. To describe and compare demographics and clinical characteristics between Black and non-Hispanic White patients with PC who initiated relugolix
  6. To describe and compare time to treatment changes between Black and non-Hispanic White patients with PC who initiated relugolix
  7. To estimate and compare adherence and persistence with relugolix between Black and non-Hispanic White patients with PC who initiated relugolix

Study Design: The current study will be a retrospective data analysis to describe patient characteristics, treatment patterns, adherence, and persistence among patients with PC who initiated relugolix. Adult (aged ≥18 years) male patients with PC who had relugolix (initiation date as the index date) will be selected from the National Veterans Affairs (VA) Health Care Network databases. Patients will be required to have continuous eligibility for at least 365 days prior to the index date and 90 days after the index date (unless died within 90 days). The baseline period will be the 365 days prior to the index date. The follow-up period will be from the index date to the earliest of death, end of continuous eligibility or end of data availability.

Population: The overall population will include PC patients who initiated relugolix. The following sample selection criteria will be used:

- Inclusion criteria
  - Male with ≥ 1 diagnosis for PC
  - Had ≥ 2 prescriptions of relugolix on or after the first observed PC diagnosis. The identification period for relugolix use will be from December 18, 2020 to December 31, 2023
    - Index date: the initiation date of relugolix
  - At least 18 years old at the index date
  - Had continuous activity in the data for at least 365 days before the index date and 90 days following the index date (unless died within 90 days)
- Exclusion criteria:
  - Had surgical castration (bilateral orchiectomy) any time before the index date
  - Participated in clinical trials within 30 days prior to or 90 days after the index date
  - Had any other primary cancer (excluding non-melanoma skin cancer) during the baseline period

Variables: Baseline demographics and clinical characteristics will include variables such as age, race/ethnicity, geographic regions, index year, previous treatment, Charlson Comorbidity Index score, and baseline comorbidities. Outcomes will include treatment patterns, adherence, and persistence with relugolix, and testosterone and PSA responses (if sample sizes allow).

Data Sources: January 1, 2006 to December 31, 2023 data from the National VA Health Care Network will be used.

Study Size: All eligible patients available for the analysis will be included.

Data Analysis: Descriptive analysis will be conducted for baseline demographics and clinical characteristics, and adherence/persistence to relugolix. Means, standard deviations, medians, and interquartile range will be estimated for continuous variables. Counts and percentages will be estimated for categorical variables. Treatment sequence will be described using a Sankey diagram. Kaplan-Meier analysis will be used to describe time to treatment changes. Adherence to relugolix will be calculated using medication processing ratio (MPR) and proportion of days covered (PDC). Persistence with relugolix will be analyzed using Kaplan-Meier analysis. If sample sizes are adequate, the counts and percentages of patients who had testosterone and PSA responses will be summarized. Unadjusted and adjusted comparisons of adherence/persistence to relugolix and time to treatment changes between Black and non-Hispanic White patients will be conducted using appropriate statistical models.

5. AMENDMENTS AND UPDATES

None.

6. MILESTONES

Milestone	Planned date
Approval of the National Veterans Affairs (VA) Health Care Network data application	November 30, 2023
Finalize Protocol	May 06, 2024
Final study report	May 31, 2025

7. RATIONALE AND BACKGROUND

Prostate cancer (PC) is the most common cancer and the second leading cause of cancer death among men in the United States.[1] The National Cancer Institute (NCI) estimated 299,010 new cases and 35,250 deaths of PC in 2024.[2] While the long-term outlook is positive for early-stage PC, survival rates drastically decrease once the disease has spread beyond the prostate gland (i.e., becoming metastatic) or when the disease becomes castration-resistant.[2]

Androgen deprivation therapy (ADT) is the standard of care for patients with PC, including such as injectable luteinizing hormone–releasing hormone (LHRH) agonists (e.g., leuprolide) and gonadotropin-releasing hormone (GnRH) antagonist. ADT treatment can suppress testosterone level to castrate level and delay the progression of the disease. LHRH agonist use can cause an initial surge of testosterone which results in a flare of symptoms including bone pain or obstructive urinary symptoms. In addition, LHRH agonist is associated with an increased risk of cardiovascular events.[3] As an alternative to LHRH, GnRH antagonist can be considered, which does not cause the initial surge in testosterone level.

Relugolix is a recently approved GnRH antagonist, which can rapidly suppress testosterone level without the initial surge. The phase 3 HERO trial of relugolix in advanced PC patients has compared the efficacy and safety of oral relugolix with leuprolide and has found that relugolix can achieve castration quicker and can better maintain castration than leuprolide.[4] In addition, the incidence of major adverse cardiovascular events in the HERO trial was also lower for relugolix than leuprolide (2.9% vs. 6.2%).[4] The positive results have led to the Food and Drug Administration (FDA) approval of relugolix in December 2020.[5]

Relugolix is the only ADT option available in oral form, distinguishing from the traditional injectable LHRH agonists.[6] While many factors could influence patients' treatment preferences, a

[1] American Cancer Society (ACS), the Centers for Disease Control and Prevention (CDC), the North American Association of Central Cancer Registries (NAACCR), and the NCI. Annual Report to the Nation 2022. https://seer.cancer.gov/report_to_nation. Accessed on May 1, 2023.

[2] NCI. Cancer Stat Facts: Prostate Cancer. https://seer.cancer.gov/statfacts/html/prost.html. Accessed on May 1, 2023.

[3] Davey P, Alexandrou K. Assessment and mitigation of cardiovascular risk for prostate cancer patients: a review of the evidence. International Journal of Clinical Practice. 2022 May 17;2022.

[4] Shore ND, Saad F, Cookson MS, George DJ, Saltzstein DR, Tutrone R, Akaza H, Bossi A, van Veenhuyzen DF, Selby B, Fan X. Oral relugolix for androgen-deprivation therapy in advanced prostate cancer. New England Journal of Medicine. 2020 Jun 4;382(23):2187-96.

[5] The United States Food and Drug Administration. FDA approves relugolix for advanced prostate cancer. https://www.fda.gov/drugs/resources-information-approved-drugs/fda-approves-relugolix-advanced-prostate-cancer#:~:text=On%20December%2018%2C%202020%2C%20the,patients%20with%20advanced%20prostate%20cancer. Accessed on August 24, 2023.

[6] Cordes LM, Karzai F, Figg WD, Madan RA. Relugolix in Clinical Practice: The Best Route for All? Oncologist. 2023 Aug 3;28(8):647-650. doi: 10.1093/oncolo/oyad099. PMID: 37162497; PMCID: PMC10400131.

few studies in other diseases have shown patients have a strong preference for oral medications due to cultural considerations, apprehension towards injections and needles, and concerns regarding incorrect administration.[7,8] Moreover, as noted from the HERO trial, there are other potential benefits to relugolix such as rapid testosterone level decline and improved testosterone recovery with potential for mitigation of major adverse cardiovascular events. As such, as an effective oral treatment, relugolix can potentially help address an unmet need in PC.

While the introduction of relugolix has offered a unique opportunity for patients with PC, it's vital to understand treatment patterns and the combination use of relugolix with other commonly employed drugs in PC treatment. However, few studies have looked into this aspect. Our study aims to bridge this gap by evaluating real-world treatment patterns involving relugolix to understand how it is being used in real-world, including whether it is used as monotherapy or combination therapy, adherence, persistence, and potentially treatment response.

This protocol is not designated as a post-authorization safety study per CT34 Post-Authorization Safety Studies (PASS), nor is it a commitment or requirement to any regulatory authority.[6]

[7] Boye, K., Ross, M., Mody, R., Konig, M., & Gelhorn, H. (2021). Patients' preferences for once-daily oral versus once-weekly injectable diabetes medications: The REVISE study. *Diabetes, obesity & metabolism*, *23*(2), 508–519. https://doi.org/10.1111/dom.14244

[8] Fayad F, Ziade NR, Merheb G, Attoui S, Aiko A, Mroue K, Masri AF. Patient preferences for rheumatoid arthritis treatments: results from the national cross-sectional LERACS study. Patient Prefer Adherence. 2018 Aug 31;12:1619-1625. doi: 10.2147/PPA.S168738. PMID: 30214164; PMCID: PMC6124803.

8. RESEARCH QUESTION AND OBJECTIVES

Using data from the National VA Health Care Network databases, the study will retrospectively analyze data to describe patient characteristics and the treatment patterns of relugolix among patients with PC who initiated relugolix.

Table 1. Objectives and endpoints

Objectives	Endpoints
1. (Primary) To describe demographics and clinical characteristics of patients with PC who initiated relugolix	• Patient baseline demographics and clinical characteristics
2. (Exploratory) To assess treatment patterns among patients with PC who initiated relugolix	• Index treatment regimen distribution • Treatment sequence presented by Sankey diagram • Time to treatment changes by Kaplan-Meier analysis
3. (Exploratory) To estimate adherence and persistence with relugolix among patients with PC who initiated relugolix	• Adherence to relugolix defined by medication processing ratio (MPR) • Adherence to relugolix defined by proportion of days covered (PDC) • Persistence with relugolix by Kaplan-Meier analysis
4. (Exploratory) To assess testosterone suppression and prostate-specific antigen (PSA) responses among ADT naïve patients with PC who initiated relugolix	• Testosterone suppression • PSA response
5. (Exploratory) To describe and compare demographics and clinical characteristics between Black and non-Hispanic White patients with PC who initiated relugolix	• Patient baseline demographics and clinical characteristics by race
6. (Exploratory) To describe and compare time to treatment changes between Black and non-Hispanic White patients with PC who initiated relugolix	• Time to treatment changes by Kaplan-Meier analysis by race
7. (Exploratory) To estimate and compare adherence and persistence with relugolix between Black and non-Hispanic White patients with PC who initiated relugolix	• Adherence to relugolix defined by MPR by race • Adherence to relugolix defined by PDC by race • Persistence with relugolix by Kaplan-Meier analysis by race

9. RESEARCH METHODS

9.1. Study design

This is a retrospective, observational study using January 1, 2006 – December 31, 2023 data from the National VA Health Care Network databases. PC patients who initiated relugolix will be selected based on diagnosis codes, age, treatment received, and continuous activity in the health care network. The identification period for relugolix use will be from December 18, 2020 to December 31, 2023. December 18, 2020 is the approval date for relugolix in the US, and December 31, 2023 is the end of available data. The index date will be defined as the initiation date of relugolix. The baseline period will be 365 days prior to the index date (hence the start of the study period is December 18, 2019). The follow-up period will be from the index date to the earliest of death, end of continuous eligibility or end of data availability. Most of the patient characteristics will be described during the baseline period. Certain patient characteristics will be described using all data available prior to the index date (i.e., data prior to December 18, 2019 will also be used if available; see more details in Table 2). Treatment patterns, adherence, and persistence with relugolix, and PSA and testosterone responses (if sample size allows) will be assessed during the follow-up period.

9.2. Setting

The National VA Health Care Network data will be used for the current analysis. PC patients initiated relugolix will be selected for analysis based on inclusion and exclusion criteria below.

9.2.1. Inclusion criteria

Patients who met all of the following sample selection criteria will be included:

- Male with ≥1 diagnosis of PC (International Classification of Diseases, 10th Revision, Clinical Modification [ICD-10-CM] C61)
- Had ≥2 prescriptions of relugolix on or after the first observed PC diagnosis. The initiation date of relugolix will be selected as the **index date**
- At least ≥18 years old as of the index date
- Had continuous activity in the data for ≥365 days prior to the index date and ≥90 days since the index date (unless died within 90 days). The **baseline period** will be defined as the 365-day period prior to the index date. The **follow-up period** will be from the index date to the end of continuous eligibility, data availability, or death, whichever happened first

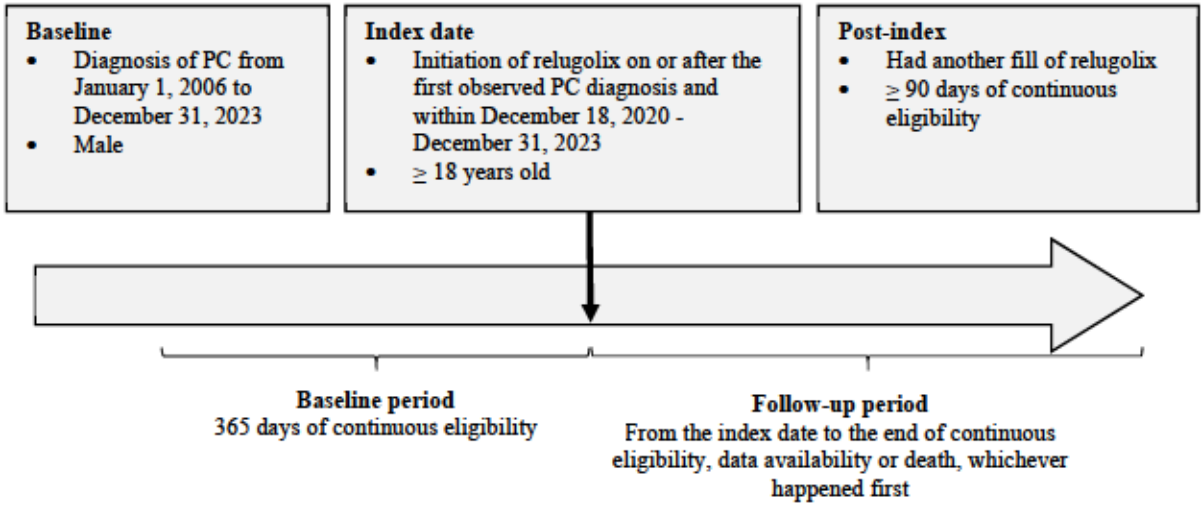
9.2.2. Exclusion criteria

Patients will not be included from the study if they:

- Had surgical castration (bilateral orchiectomy) any time before the index date

- Had evidence of clinical trial participation within 30 days prior to the index date or within 90 days since the index date
- Had any other primary cancer (excluding non-melanoma skin cancer) during the baseline period

Figure 1. Sample selection for PC patients initiated relugolix



9.3. Variables

Baseline variables (Table 2) will be measured during the baseline period (365 days prior to the index date). Treatment patterns, adherence and persistence, and clinical variables (Table 3) will be measured during the follow-up period.

Table 2. Baseline demographic and clinical characteristic variables

Variable	Operational definition
Age	Age will be defined as of the index date and retained in the dataset as a continuous variable and a categorical variable (e.g., ≤59, 60-69, 70-79, ≥80 years old).
Race/ethnicity	Proportion of patients that were non-Hispanic White, Black, Hispanic, other or unknown will be summarized.
Geographic regions	Proportion of patients that lived in Northeast, Midwest, South and West areas will be summarized.
Index year	A categorical variable for the index calendar year will be summarized.
Site of metastasis	Proportion of patients that had a metastatic diagnosis at the following sites: bone only, bone and node only, node

Variable	Operational definition
	only, viscera and other, will be summarized among patients with metastatic PC. All data available prior to the index date will be used.
Treatment history	Proportion of patients who had each of the following treatments in the baseline period will be evaluated: • Prostatectomy • Chronic oral corticosteroid use • Pain medication (opioids) • ADT treatment (leuprolide, degarelix, goserelin, histrelin, triptorelin) • Androgen receptor pathway inhibitor (ARPI; abiraterone, apalutamide, darolutamide, enzalutamide) • Non-steroidal anti-androgen (NSAA; bicalutamide, nilutamide, flutamide) • Chemotherapy (docetaxel, cabazitaxel, carboplatin, oxaliplatin, cisplatin, mitoxantrone) • Immunotherapy (sipuleucel-T, pembrolizumab) • Radium 223 • Systemic ketoconazole • Olaparib • Rucaparib • Talazoparib • Niraparib • Lutetium Lu 177 vipivotide tetraxetan • Radiotherapy Treatments considered as a part of index treatment regimen will not be flagged as baseline treatments if received within 30 days prior to index date.
Time from first observed PC diagnosis date to the index date	Time from the first observed PC date in the data to the index date will be evaluated. All data available prior to the index date will be used.
NCI Charlson Comorbidity Index (CCI) score	The NCI version of the CCI score will be created during the baseline period.

Variable	Operational definition
Comorbidities	A binary variable (yes/no) will be created for patients with a diagnosis of each of the following comorbidities during the baseline period: • Hypertension • Hyperlipidemia • Diabetes • Urinary tract infection • Chronic obstructive pulmonary disease • Arrhythmia • Congestive heart failure • Myocardial infarction • Stroke • Angina pectoris • Inflammatory bowel disease • Acute coronary syndrome • Sexual dysfunction • Depression • Anxiety • Hot flashes • Cognitive impairment • Major adverse cardiovscaular event (defined by any evidence of cardiomyopathy, heart failure, ischemic heart disease, myocardial infarction, pulmonary embolism, or stroke)
PSA	Baseline PSA value (among available) based on the PSA value closest to the index date during the 90-day window (or 180-day, to be finalized based on the number of patients with non-missing PSA value in these time frames) on or prior to the index date will be evaluated.
Testosterone	Baseline testosterone value (among available) based on testosterone value closest to the index date during the 90-day window (or 180-day; will be consistent with the time window for baseline PSA) on or prior to the index date will be evaluated.
Metastatic vs. non-metastatic PC	A binary variable for patients with metastatic vs. non-metastatic PC will be created. Metastatic PC will be

Variable	Operational definition
	defined as having evidence of metastasis during the baseline period or within 90 days since the index date.
ADT naïve vs. ADT experienced	A binary variable for patients who were ADT naïve vs. ADT experienced will be created. ADT naïve will be defined as having no records of any systemic ADT treatment ever based on all available data prior to the index date (i.e., including baseline period data and any available data prior to the baseline period). Systemic ADT treatment includes LHRH agonists and GnRH antagonists (i.e., degarelix, relugolix, goserelin, histrelin, leuprolide, triptorelin)

Table 3. Treatment patterns, adherence, persistence, and clinical variables during the follow-up period

Variable	Operational definition
Index treatment	Index treatment regimens include: • Relugolix monotherapy • Relugolix + NSAA only (at least 90 days of NSAA use) • Relugolix + ARPI +/- NSAA (no chemotherapy) • Relugolix + ARPI + chemotherapy • Relugolix + chemotherapy +/- NSAA (no ARPI) • Relugolix + other (no ARPI, no chemotherapy) Index treatment regimen will be defined based on treatments received within 30 days before the index date and within 90 days after the index date. Specific treatments included in each treatment category (i.e., ADT, NSAA, ARPI, chemotherapy, immunotherapy) are described in "Treatment history" in Table 2. Other treatments include immunotherapy, radium 223, olaparib, rucaparib, talazoparib, niraparib and lutetium Lu 177 vipivotide tetraxetan. Number of patients who received any radiotherapy during the index treatment will be summarized.

Variable	Operational definition
Treatment patterns of relugolix	Treatment patterns of relugolix include: • Continued relugolix as in the index treatment (regardless of discontinuation of concomitant medications) • Continued relugolix with a new add-on systemic PC treatment (excluding ADT) • Discontinued relugolix and switched to another ADT treatment • Discontinued relugolix without switching to another ADT treatment Add-on systemic PC treatments include: • ARPI • NSAA • Chemotherapy • Immunotherapy • Radium 223 • Ketoconazole • Olaparib • Rucaparib • Talazoparib • Niraparib • Lutetium Lu 177 vipivotide tetraxetan Add-on therapy will be evaluated from 90 days after the index period to the end of the follow-up period.
Time to treatment changes	The time to treatment changes of interest include: • Time to discontinuation of relugolix • Time to switching to a different ADT treatment • Time to add a new systemic PC treatment to relugolix
Treatment adherence	Adherence to relugolix post the index date will be described using both MPR and PDC: • MPR: Sum of the days of supply divided by the number of days between the first fill and the end of the last refill (i.e., including the days of supply from the last refill) • PDC: Sum of the non-overlapping (i.e., not double counting of overlaps) days of supply covered

Variable	Operational definition
	divided by a pre-determined period following treatment initiation (e.g., 6 and 12 months) Adherence will be described as a continuous variable and as a binary variable (<0.80: non-adherent, ≥0.80: adherent)
Treatment persistence	Persistence to relugolix will be described as the proportion of patients who did not discontinue relugolix (i.e., with a treatment gap, switch to another ADT, or death; the minimum days of treatment gap, e.g., 45 or 60 days, will be finalized based on sample size and clinical input) during the follow-up period. Treatment gaps will be assessed from the end of the days of supply of the previous prescription to the earliest of the next prescription or the end of data availability.
PSA response	Only if sample size is sufficient and among patients with at least one baseline and one follow-up period PSA measure: • The number and percentage of patients with ≥50% and ≥90% decline from the baseline PSA to any PSA measurement during the follow-up period and while on relugolix • The number and percentage of patients with the nadir PSA value during the follow-up period and on treatment of relugolix < 0.01, 0.1, and 0.2 ng/mL
Testosterone response	Only if sample size is sufficient and among patients with at least one follow-up period testosterone measure: • The number and percentage of patients with at least one testosterone value of <50ng/dL and <20 ng/dL during the follow-up period and while on relugolix If sample size is sufficient, the analysis above may be conducted among patients with at least one baseline and one follow-up period testosterone measure

9.4. Data sources

January 1, 2006 to December 31, 2023 data from the National VA Health Care Network will be used for this study. This network is the US's largest integrated health care system with over 1,700 sites of care, serving approximately 8.76 million veterans each year. The VA Health System Corporate Data Warehouse (CDW) includes all medical encounter information in the VA, comprised of medical centers, community-based outpatient clinics, community-living centers, veteran centers, and domiciliaries. The VA CDW stores data in separate databases, one for each type of clinical information - inpatient medication, inpatient laboratory, inpatient admission, outpatient medication, outpatient laboratory, outpatient visits, etc. The databases provide demographic information and contain comprehensive services, including primary care, specialty care, inpatient care, rehabilitation, long-term care, home care, and other services, to military veterans. The database also includes date of death. The date of death is extracted from the VA electronic health record systems and verified by official sources, including VA facilities, death certificates, and National Cemetery Administration. Information on CDW, including date of death, is updated on a daily base. Cause of death is not available on CDW.

9.5. Study size

As no priori hypotheses are specified, sample size calculations are not applicable. The number of patients eligible for the study will be determined in accordance with the sample selection conducted per the criteria described in Section 9.2.

9.6. Data management

A clean, patient-level dataset will be generated for use throughout the study. This process will entail basic exploratory checks to ensure data integrity; cleaning and reformatting the raw data as needed; and creating variables for all key study measures, including patient characteristics, treatment start and end dates, and classification of treatments and medication. All data will be stored and maintained on a secure encrypted non-cloud-based server and accessed over a secure internal private wide area network. The data will be made accessible only to individuals working on the current study. No attempt will be made to identify individual patients, hospitals, or physicians. Analyses will be conducted using SAS 9.4 (SAS Institute, Cary NC).

9.7. Data analysis

9.7.1. Data analysis for Objective 1: To describe demographics and clinical characteristics of patients with PC who initiated relugolix

Descriptive analysis will be conducted for baseline demographics and clinical characteristics. Means, standard deviations, medians, and interquartile range will be estimated for continuous variables. Counts and percentages will be estimated for categorical variables. If the sample sizes allow, standardized mean difference (SMD) will be calculated to compare the patient baseline characteristics between metastatic vs. non-metastatic PC cohorts. For each variable, the SMD will be calculated as the difference in mean between two cohorts divided by the standard

deviation of the two cohorts pooled together. The absolute value of a SMD > 10% will be considered as an indicator for significant imbalance.

9.7.2. Data analysis for Objective 2: To assess treatment patterns among patients with PC who initiated relugolix

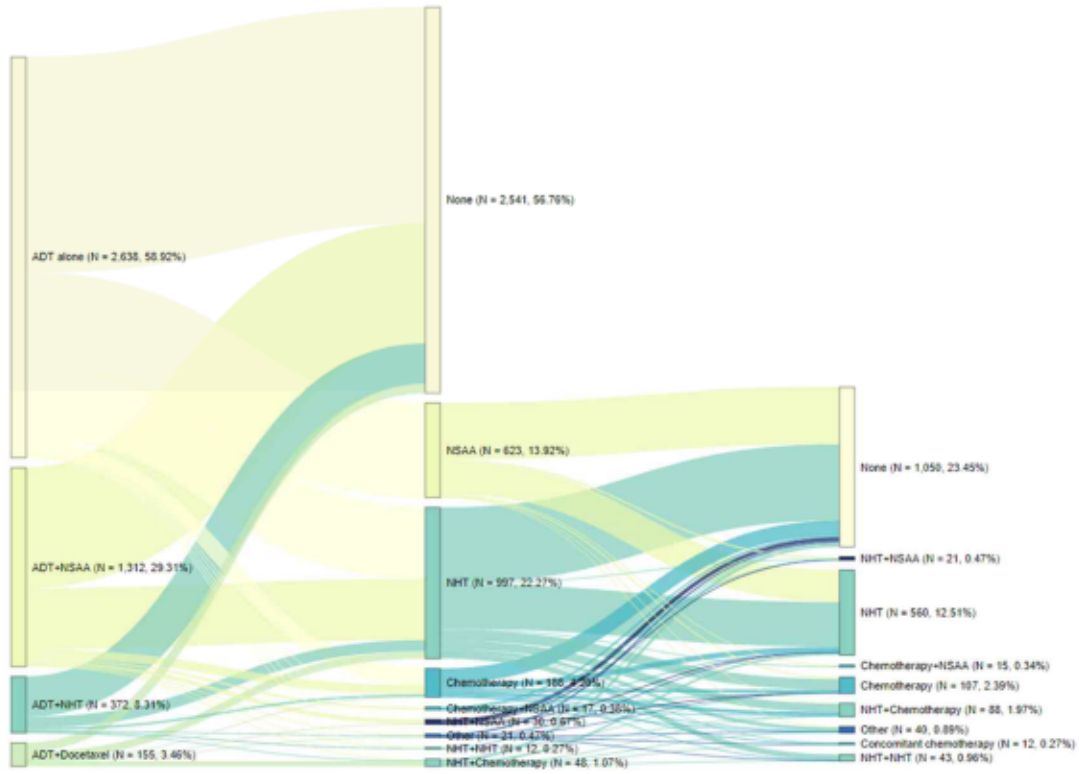
9.7.2.1. Index treatment distribution

The distribution of the index treatment will be described using counts and percentages. Index treatment will be defined based on treatments received within 30 days before the index date and within 90 days after the index date.

9.7.2.2. Treatment patterns of relugolix

Treatment patterns of relugolix will be analyzed and presented using Sankey diagrams (see an example in Figure 2). The four treatment patterns described in Table 3 will be considered. The number and proportion of patients with each of the four treatment patterns will be summarized.

Figure 2. Example of a Sankey diagram (for illustration purpose)



9.7.2.3. Time to treatment changes

Kaplan-Meier analysis will be conducted to describe the following time-to-event outcomes for the treatment patterns as listed in Table 3:

- Time to discontinuation of relugolix
- Time to switching to a different ADT treatment
- Time to add a new systemic PC treatment to relugolix

The number and proportion of patients with the corresponding event will be plotted over time and the number at risk table over time will be presented. The median time to event will be calculated.

9.7.3. Data analysis for Objective 3: To estimate adherence and persistence with relugolix among patients with PC who initiated relugolix

Adherence to relugolix as defined in Table 3 will be described. MPR will be summarized over the entire exposure to relugolix during the follow-up period. PDC will be summarized within the 6, 12, and 18 months (tentatively, pending on the final length of follow-up) since the index date. Means, standard deviations, medians, and interquartile range will be estimated for adherence as a continuous variable. Counts and percentages will be estimated for adherence as a binary variable. Patients will be required to have complete follow-up data during the time to be included in each adherence calculation.

Persistence to relugolix as defined in Table 3 will be described using Kaplan-Meier analysis since the index date. The number and proportion of patients persistent to relugolix will be plotted over time and the number at risk table over time will be presented.

9.7.4. Data analysis for Objective 4: To assess testosterone suppression and PSA responses among ADT naïve patients with PC who initiated relugolix

If sample size is sufficient, the count and percentage of patients with testosterone responses as defined in Table 3 will be calculated among ADT naïve patients with at least one testosterone measure during the follow-up period. Similarly, if sample size is sufficient, the count and percentage of patients with PSA responses as defined in Table 3 will be calculated among ADT naïve patients with at least one baseline and one follow-up period PSA measure.

9.7.5. Data analysis for Objective 5: To describe and compare demographics and clinical characteristics between Black and non-Hispanic White patients with PC who initiated relugolix

The same descriptive analysis described in Section 9.7.1 will be conducted in Black and non-Hispanic White patients separately. If the sample sizes allow, SMD will be calculated to compare the patient baseline characteristics between Black vs. non-Hispanic White cohorts. Additionally, p-values from appropriate statistical tests (e.g., t-tests or rank-sum tests for continuous variables and chi-square tests for categorical variables) comparing Black vs. non-Hispanic White cohorts will be reported.

9.7.6. Data analysis for Objective 6: To describe and compare time to treatment changes between Black and non-Hispanic White patients with PC who initiated relugolix

The same descriptive analyses described in Section 9.7.2.3 will be conducted in Back and non-Hispanic White patients separately. Unadjusted and adjusted comparisons between the two race groups will be conducted. Cox proportional hazards (PH) regressions will be used to compare the time to treatment changes between the two race groups. Patient characteristics to be included in the adjusted models will be selected based on findings in Section 9.7.5 and clinical input.

9.7.7. Data analysis for Objective 7: To estimate and compare adherence and persistence with relugolix between Black and non-Hispanic White patients with PC who initiated relugolix

The same descriptive analyses described in Section 9.7.3 will be conducted in Back and non-Hispanic White patients separately. Unadjusted and adjusted comparisons between the two race groups will be conducted. Generalized linear models will be used to compare adherence to relugolix between the two race groups. Cox PH regressions will be used to compare persistence between the two race groups. Patient characteristics to be included in the adjusted models will be selected based on findings in Section 9.7.5 and clinical input.

9.8. Quality control

Best practice guidelines will be followed to ensure project quality, including structured organization of project materials (e.g., data extracts, statistical software programs, output tables) and standard internal audit process. The audit process both confirms the validity of the analytical approach and ensures that all programs and results are accurate.

9.9. Limitations of the research methods

The analyses conducted as part of this study are subject to the following limitations, which will be addressed in any write-up of the study:

- As this study will be conducted among veterans, its findings may not be generalizable to other populations
- Certain assumptions will be made in order to depict treatment patterns. However, the definition of treatment patterns will nevertheless be subject to assumptions that may not match up to the prescribing physicians' intent
- Data are subject to inaccuracies in coding of diagnoses. The presence of a diagnosis code in the data does not necessarily mean the presence of disease. The disease may be incorrectly coded, or the code was included as a rule-out criterion
- The presence of a prescription does not necessarily mean the medication was consumed as prescribed. In addition, prescriptions filled over the counter or provided as samples by the physician are not included in the data

- The fact that our entry criteria is at least 2 subscriptions of relugolix means we are selecting patients who were able to tolerate the first month and followed up to receive a second month. How this cohort relates to all patients given relugolix is unknown.

9.10. Other aspects

Not applicable.

10. PROTECTION OF HUMAN SUBJECTS

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.1. Patient information

This study involves data that exist in anonymized structured format and contain no patient personal information.

10.2. Patient consent

As this study involves anonymized structured data, which according to applicable legal requirements do not contain data subject to privacy laws, obtaining informed consent from patients by Pfizer is not required.

10.3. Institutional review board (IRB)/Independent ethics committee (IEC)

An IRB waiver was received.

10.4. Ethical conduct of the study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society for Pharmacoepidemiology.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

This is a retrospective analysis using anonymized National VA Health Care Network database. In the data, individual patient data are not retrieved or validated, and it is not possible to link (i.e., identify a potential 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) cannot be met.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

In the event of any prohibition or restriction imposed (e.g., clinical hold) by an applicable competent authority in any area of the world, or if the investigator is aware of any new information which might influence the evaluation of the benefits and risks of a Pfizer product, Pfizer should be informed immediately.

13. LIST OF TABLES

14. LIST OF FIGURES

ANNEX 1. LIST OF STAND-ALONE DOCUMENTS

None.

ANNEX 2. ADDITIONAL INFORMATION

Appendix Table 1. Codes for PC treatments

	GPI	HCPCS/CPT	ICD
ADT			
Orchiectomy		CPT 54520, 54522, 54530, 54535, 54690	ICD-10-CM Z90.79 ICD-10-PCS 0V590ZZ, 0V593ZZ, 0V594ZZ, 0V5B0ZZ, 0V5B3ZZ, 0V5B4ZZ, 0V5C0ZZ, 0V5C3ZZ, 0V5C4ZZ, 0VT90ZZ, 0VT94ZZ, 0VTB0ZZ, 0VTB4ZZ, 0VTC0ZZ, 0VTC4ZZ
LHRH agonists/antagonists			
Degarelix	2140552510	J9155	
Goserelin	21405005	J9202	
Histrelin	2140500710	J1675, J9225, J9226, S0133	
Leuprolide	21405010	J1950, J9217, J9218, J9219, Q0057	
Relugolix	21405570000320, 24993503800320		
Triptorelin	21405050	J3315	
ARPI			
Apalutamide	2140241000		
Abiraterone	2140601020		
Darolutamide	2140242500		
Enzalutamide	2140243000		
NSAA			
Bicalutamide	2140242000		
Flutamide	2140244000		
Nilutamide	2140246000		
Chemotherapy		HCPCS	ICD
Cabazitaxel	2150000300	C9276, J9043	
Docetaxel	2150000500	J9170, J9171	
Carboplatin	2110001500	J8530, J9070, J9080, J9090, J9091, J9092, J9093, J9094, J9095, J9096, J9097	

Cisplatin	2110002000	J9045	
Oxaliplatin	2110002800	J9263	
Mitoxantrone	2120005500	J9293	
Immunotherapy		HCPCS	ICD
Sipuleucel-T	2165107000	Q2043, C9273	
Pembrolizumab	21357953002	J9271, C9027	
Others		HCPCS	ICD
Radium-223	2160005500	A9606	
Ketoconazole	1140404000, 9630106400, 9015404500		
Olaparib	21535560		
Lutetium Lu 177 vipivotide tetraxetan	21600045802020	A9607	
Niraparib	21535550200, 21409902120		
Talazoparib	215355804001		
Niraparib	21535550200, 21409902120		
Rucaparib	21535570		

Abbreviations: ADT: androgen deprivation therapy; ARPI: androgen receptor pathway inhibitor; CTP: Current Procedural Terminology; GPI: Generic Product Identifier; HCPCS: Healthcare Common Procedure Coding System; ICD: International Classification of Diseases; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification; ICD-10-PCS: International Classification of Diseases, 10th Revision, Procedures; LHRH: luteinizing hormone–releasing hormone; NSAA: non-steroidal anti-androgen

Appendix Table 2. Diagnosis codes for comorbidities

Conditions and comorbidities	ICD-10-CM
NCI comorbidity index[1]	
Cerebrovascular disease	G45, G46, H34.0, I60–I69
Chronic pulmonary disease	I27.8, I27.9, J40–J47, J60–J67, J68.4, J70.1, J70.3
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5–I42.9, I43, I50, P29.0
Dementia	F00–F03, F05.1, G30, G31.1
Diabetes with chronic complication	E10.2–E10.5, E10.7, E11.2–E11.5, E11.7, E12.2–E12.5, E12.7, E13.2–E13.5, E13.7, E14.2–E14.5, E14.7
Diabetes without chronic complication	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1,

	E14.6, E14.8, E14.9
Hemiplegia or paraplegia	G04.1, G11.4, G80.1, G80.2, G81, G82, G83.0–G83.4, G83.9
Mild liver disease	B18, K70.0–K70.3, K70.9, K71.3–K71.5, K71.7, K73, K74, K76.0, K76.2–K76.4, K76.8, K76.9, Z94.4
Moderate or severe liver disease	I85.0, I85.9, I86.4, I98.2, K70.4, K71.1, K72.1, K72.9, K76.5, K76.6, K76.7
Peripheral vascular disease	I70, I71, I73.1, I73.8, I73.9, I77.1, I79.0, I79.2, K55.1, K55.8, K55.9, Z95.8, Z95.9
Renal disease	I12.0, I13.1, N03.2–N03.7, N05.2–N05.7, N18, N19, N25.0, Z49.0–Z49.2, Z94.0, Z99.2
Individual conditions	

Hypertension	H35.039, I10–I13, I15–I16, I67.4
Hyperlipidemia	E78.00, E78.01, E78.1, E78.2, E78.3, E78.41, E78.49, E78.5
Type II diabetes	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9
Urinary tract infection	
Chronic obstructive pulmonary disease	J40, J41, J42, J43, J47, J44.9
Arrhythmia	I47.0, I47.2, I49.0, I46, I49.3, I49.49, I47.9, I49.40, I49.5, I49.8, I49.9
Congestive heart failure	I09.9, I11.0, I13.0, I13.2, I25.5, I42.0, I42.5-I42.9, I43, I50, P29.0
Myocardial infarction	I21, I22, I25.2

Stroke	I60, I61, I62, I64, I65, I67, H34.1, H34.23, H34.21, H34.0
Angina pectoris	I20
Inflammatory bowel disease	K50, K51
Acute coronary syndrome	I24, I21
Sexual dysfunction	F52.21, N52
Depression	F20.4, F31.3-F31.5, F32, F33, F34.1, F41.2, F43.2
Anxiety	F06.4, F41, F43.22, F43.23, F93.0
Cognitive impairment	G30, G31.0, F01, F05, R41.0, R41.82, F10.1, F10.2, G31.2, G31.83, F02, F03, G31.1, G31.84, F06.7, R41.3, R41.81, R41.840
Hot flashes	R23.2
Primary cancers	C00-C21, C22.1-C22.7, C23-C76, C80.1, C80.2, C81-C96, C7A

Abbreviations: ICD-9-CM: International Classification of Diseases, 9th Revision, Clinical Modification; ICD-10-CM: International Classification of Diseases, 10th Revision, Clinical Modification; NCI: National Cancer Institute

[1] Source: Quan, Hude, et al. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. Medical care (2005): 1130-1139. Adapted using codes found in NCI Comorbidity Index Overview: https://healthcaredelivery.cancer.gov/seermedicare/considerations/comorbidity.html

Appendix Table 3. Codes for corticosteroids and pain medications

Treatment	GPI	HCPCS
Corticosteroids	22, 8910, 8915	C9256, J0702, J0704, J1020, J1030, J1040, J1094, J1100, J1700, J1710, J1720, J2650, J2920, J2930, J3300, J3301, J3302, J3303, J7312, J7506, J7509, J7510, J7512, J7624, J7626, J7627, J7633, J7634, J7637, J7638, J7683, J7684, J8540
Pain medications (analgesics)		
Opioids	65	

Abbreviations: GPI: Generic Product Identifier; HCPCS: Healthcare Common Procedure Coding System