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Global Medical Affairs, Evidence Generation

Non-Interventional Study Protocol (PASS) with Secondary Use of Data

Redacted Protocol

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Title	Understanding drug utilisation, treatment patterns, clinical outcomes, and profile of the patients receiving lutetium (^{177}Lu) vipivotide tetraxetan for the treatment of metastatic prostate cancer: a multicountry, AI-powered registry (PULSE)
Protocol version number	v00 (original protocol)
Content final date	27 November 2025
EU PAS register number	None (Voluntary PASS)
Active substance	lutetium-177 (ATC code: V10XX05)
Medicinal product	lutetium (^{177}Lu) vipivotide tetraxetan 1 000 MBq/mL solution for injection/infusion
Product reference	EU/1/22/1703/001
Procedure number	Not applicable
Name of marketing authorization holder(s)	Novartis Europharm Limited Vista Building Elm Park, Merrion Road Dublin 4 Ireland
Joint PASS	No
Research question and	The overarching research question for the study is “What are the demographic and clinical characteristics profiles, drug utilisation,

objectives	treatment patterns, and associated clinical outcomes among adults with metastatic prostate cancer (mPC) who are treated with lutetium (^{177}Lu) vipivotide tetraxetan over a five-year follow-up period?" The primary objective of the study is to describe real-world drug utilisation of lutetium (^{177}Lu) vipivotide tetraxetan among mPC patients. Secondary objectives of the study are as follows: 1. To understand the profiles (in terms of demographic and clinical characteristics) of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan 2. To evaluate survival outcomes of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan 3. To estimate treatment response of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan 4. To describe adverse events of special interest (AESIs) in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan 5. To assess changes in drug utilisation and treatment patterns in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan 6. To examine profiles (defined in terms of demographic and clinical characteristics) and clinical outcomes of patients who receive sequential treatment of lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel
Country (-ies) of study	Canada, Germany, Portugal, Switzerland, and Italy, with the potential to expand to other countries
Authors	PPD , Novartis Pharma AG, 4002 Basel, Switzerland PPD

Marketing authorization holder(s)

Marketing authorization holder(s)	Novartis Europharm Limited Vista Building Elm Park, Merrion Road, Dublin 4 Ireland
MAH contact person	PPD

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List of abbreviations

1L	First line
ADT	Androgen deprivation therapy
AESI	Adverse event of special interest
AI	Artificial intelligence
ARPI	Androgen receptor pathway inhibitors
ASR	Age-standardised incidence rate
ATC	Anatomical therapeutic chemical
BMI	Body mass index
CI	Confidence interval
cNLP	Clinical natural language processing
CRPC	Castration-resistant prostate cancer
CSPC	Castration-sensitive prostate cancer
EAP	Expanded access program
EHR	Electronic health record
GPP	Good Pharmacoepidemiological Practices
HMAC	Hash-based message authentication code
HR	Hazard ratio
HSPC	Hormone-sensitive prostate cancer
ICD	International Classification of Diseases
IEC	Independent ethics committee
IQR	Interquartile range
IRB	Institutional review board
IT	Information technology
IV	Intravenous
LOINC	Logical Observation Identifiers Names and Codes
mCRPC	Metastatic castration-resistant prostate cancer
mHSPC	Metastatic hormone-sensitive prostate cancer
ML	Machine learning
mPC	Metastatic prostate cancer
MRI	Magnetic resonance imaging
NER	Named-entity recognition
NEL	Named-entity linking
NLP	Natural-language processing
OS	Overall survival
PARPi	Poly(ADP-ribose) polymerase inhibitor
PC	Prostate cancer
PCDP	Prostate cancer disease panel
PFS	Progression-free survival
PIO	Population, intervention, outcomes
PSA	Prostate-specific antigen
PSMA	Prostate-specific membrane antigen
PULSE	Pluvicto Utilization and Long-term Study of Effectiveness

Q	Quarter
rPFS	Radiographic progression-free survival
RWD	Real-world data
RWE	Real-world evidence
rwOS	Real-world overall survival
rwPFS	Real-world progression-free survival
SAP	Statistical analysis plan
SD	Standard deviation
SLiCE	Sampling for large-scale information extraction and classification evaluation
SNOMED CT	Systematized Nomenclature of Medicine—Clinical Terminology
US	United States

1 Responsible parties

Table 1-1 Responsible parties

Role	Person
Main protocol author	PPD Novartis Pharma AG 4002 Basel, Switzerland
Principal investigator (PI)	Not applicable
MAH contact person	PPD

2 Abstract/study summary

This section contains a summary of the study information. Additional details can be found in each subsequent section of the protocol.

Title

Understanding drug utilisation, treatment patterns, clinical outcomes, and profile of the patients receiving lutetium (^{177}Lu) vipivotide tetraxetan for the treatment of metastatic prostate cancer: a multicountry, AI-powered registry (PULSE)

Protocol version and release date

v00; 24-NOV-2025

Name and affiliation of main author

PPD

Novartis Pharma AG

Rationale and background

With a worldwide incidence of approximately 7.3% in 2022 (Bray et al., 2024), prostate cancer (PC) is the second most commonly diagnosed cancer and the fifth leading cause of cancer death among men worldwide (Bray et al., 2024). An estimated 1.5 million men worldwide were diagnosed with and 396,000 died because of PC in 2022 (Bray et al., 2024). By 2040, the worldwide PC burden is projected to increase to approximately 2.4 million cases and 712,000 deaths due to the ageing global population (Schafer et al., 2025).

Most patients with PC initially present with localised disease and initially undergo surgery and/or local radiotherapy with concomitant or subsequent use of androgen deprivation therapy (ADT; chemical castration) (McKay et al., 2020; Shore 2020; Zaorsky et al., 2020). Despite initial response rates of 80% to 90% (Ahmad and Raghavan, 2018), nearly all patients with PC subsequently develop progressive disease, even while receiving ADT therapy. Metastatic PC (mPC) includes different disease states, classified based on their response to ADT. These classifications consist of metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC) (Borque-Fernando et al., 2025).

Over the past two decades, management of mHSPC and mCRPC has shifted from monotherapy with ADT to intensified combination regimens, as monotherapy with the former has been found to typically result in progression within a year of therapy initiation (Kostos and Murphy, 2022). Given the number of options currently available for mPC, patients often undergo multiple treatment sequences; the timing of receipt of these various regimens may impact oncological outcomes (Wenzel et al., 2024).

Based on current guidelines (Cornford et al., 2024; Fizazi et al., 2023; Parker et al., 2020; Saad et al., 2022), mCRPC should be treated with lifelong ADT and systemic therapy because of demonstrated survival benefits: first-line systemic therapies include androgen receptor pathway inhibitors (ARPIs) such as enzalutamide and abiraterone, the taxane docetaxel in select cases, or the poly(ADP-ribose) polymerase inhibitor (PARPi) olaparib for patients with homologous recombination repair mutation or *BRCA1/2* mutations (the latter in Europe). Options for second-line therapy include ARPIs, taxanes (e.g., cabazitaxel and docetaxel), bone-directed radiopharmaceutical therapy (radium-223), olaparib, and, most recently (as of 2022), the radioligand therapy lutetium (^{177}Lu) vipivotide tetraxetan® (Lowrance et al., 2023). Third-line treatment options include cabazitaxel, radium-223, olaparib, and lutetium (^{177}Lu) vipivotide tetraxetan (Parker et al., 2020).

Lutetium (^{177}Lu) vipivotide tetraxetan is a beta-particle emitter that binds with high affinity to prostate-specific membrane antigen (PSMA), resulting in internalisation and apoptosis of targeted PC cells (Benesová et al., 2015; Sartor et al., 2021). It is administered via intravenous infusion every 6 weeks (±1 week) for up to six cycles, with each dose of lutetium (^{177}Lu) vipivotide tetraxetan containing 7.4 GBq (200 mCi).

The Phase III VISION trial demonstrated that lutetium (^{177}Lu) vipivotide tetraxetan significantly improved overall survival (OS) and radiographic progression-free survival (rPFS) in PSMA-positive mCRPC patients in the post-taxane setting compared with best standard of care (Sartor et al., 2021). Results of this study, along with others, informed its regulatory approval in 2022 for adult patients with PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy. This was approved in the United States, Canada, and Europe as the first therapy in its class. In the more recent PSMAfore (NCT04689828) Phase III trial (Fizazi et al., 2025), lutetium (^{177}Lu) vipivotide tetraxetan improved rPFS in taxane-naive patients with mCRPC compared with a change in ARPI. The safety profile of lutetium (^{177}Lu) vipivotide tetraxetan was favourable, with no new safety signals identified. The Phase II TheraP trial showed a higher prostate-specific antigen (PSA) response rate and fewer adverse events among mCRPC patients who received lutetium (^{177}Lu) vipivotide tetraxetan compared with cabazitaxel, highlighting the potential of the former as an effective treatment in this indication (Hofman et al., 2024). Furthermore, in terms of relative long-term efficacy and safety, the TheraP trial demonstrated comparable OS between groups, and no new safety concerns were reported (Hofman et al., 2024). In June 2025, Novartis announced that the PSMAddition trial (NCT04720157; Sartor et al., 2022; Novartis, 2025), a Phase III study, demonstrated that Pluvicto™ (lutetium [^{177}Lu] vipivotide tetraxetan) combined with standard hormone therapy significantly improved rPFS in patients with PSMA-positive mHSPC compared with hormone therapy alone, based on interim analysis results. The trial also showed a positive trend in OS.

However, real-world data on the effectiveness and safety of lutetium (^{177}Lu) vipivotide tetraxetan among patients with mCRPC remain limited. Although available studies (Assadi et al., 2020; Khreish et al., 2022; Moradi Tuchayi et al., 2024) report findings consistent with the VISION and TheraP trials, their generalizability is limited owing to small sample sizes, single-centre designs, and short follow-up periods. These limitations underscore the need for broader real-world evidence (RWE) on lutetium (^{177}Lu) vipivotide tetraxetan, particularly its long-term effectiveness and safety among a larger and more diverse population of patients with mPC. Expanding insights into the profiles (in terms of demographic and clinical characteristics) of patients with mPC who receive such therapy, along with detailed information on their drug utilisation, treatment patterns and clinical outcomes, will be crucial for advancing research, optimising treatment strategies, and improving care for this patient population.

Large-scale clinical registries have become essential tools in biomedical research to address such knowledge gaps, replacing smaller (e.g., single-centre) studies with more comprehensive, generalisable data. The artificial intelligence (AI)-powered Pluvicto Utilization and Long-term Study of Effectiveness (PULSE) Registry described below is designed as a global, multicentre, AI-enhanced digital registry that will leverage advanced data extraction technologies to efficiently generate RWE on mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan from multiple countries (Canada, Germany, Portugal, Switzerland, and Italy, with the potential to expand to other countries).

Research question and objectives

The overarching research question for the study is "What are the patient demographic and clinical characteristics profiles, drug utilisation, treatment patterns, and associated clinical outcomes among adults with mPC who are treated with lutetium (^{177}Lu) vipivotide tetraxetan over a five-year follow-up period?"

The primary objective of the study is to describe real-world drug utilisation of lutetium (^{177}Lu) vipivotide tetraxetan among mPC patients.

The secondary objectives of the study are as follows:

1. To understand the profiles (in terms of demographic and clinical characteristics) of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
2. To evaluate survival outcomes of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
3. To estimate treatment response of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
4. To describe adverse events of special interest (AESIs) in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
5. To assess changes in drug utilisation and treatment patterns in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
6. To examine profiles (defined in terms of demographic and clinical characteristics) and clinical outcomes of patients who receive sequential treatment of lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel

Study design

This study is planned as a multicountry, non-interventional, longitudinal registry. The AI-powered PULSE Registry will use EHRead® (Medsavana S.L., Spain), a clinical natural language processing (cNLP) technology, to periodically (quarterly) extract and structure clinical data documented in electronic health records (EHR) of patients with mPC who are treated with lutetium (^{177}Lu) vipivotide tetraxetan as part of routine clinical care. EHRead directly analyses the free-text content of clinical reports extracted from patients' EHR using machine learning models trained on clinical texts and curated by medical research experts. Use of EHRead to enable creation of the PULSE Registry requires the a priori implementation of a validated and scalable prostate cancer disease panel (PCDP). Using PCDP-defined terms, specific cNLP filters will identify patients with mPC and select those who meet the inclusion criteria. An initial data extraction will be conducted at registry outset, followed by scheduled extractions once every calendar quarter to capture the following: (1) incremental information on patients with mPC who are treated with lutetium (^{177}Lu) vipivotide tetraxetan and who had been previously identified and included in the registry; and (2) information on "new" (i.e., newly initiated on lutetium [^{177}Lu] vipivotide tetraxetan at some point subsequent to the last extraction). No additional clinical activity (e.g., assessments, measurement, prescribing or administering treatment[s]) will be conducted as part of this research study beyond what was already done by the care providers (i.e., usual care).

Data extraction will begin on 25 August 2021 and continue until the earliest of the last available EHR record, patient's death, or end of the PULSE Registry (31 July 2031).

The following timeframes will be considered for inclusion of data for this study:

Study timeframes:

- **Study period** will span from 25 August 2021 to 31 July 2031 (inclusive of the start and end dates)
- **Patient selection period** will begin on 25 August 2022 and extend to 31 July 2029
- **Preselection period** will last from 25 August 2021 to 24 August 2022 (inclusive of the start and end dates)
- **Postselection period** will extend from 01 August 2029 to 31 July 2031 (inclusive of the start and end dates)

Patient timeframes:

- **mPC diagnosis date** will be defined as the first date when a patient meets the definition of mPC diagnosis
- **Index date** will be defined as the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan on or after mPC diagnosis date
- **Preindex period** will be defined as the period beginning 365 days prior to the index date and extending up to (but not including) the index date
- **Follow-up period/Postindex period** will begin on the index date and continue until the earliest of death, five years, end of study, or last available EHR record

A medical and technical feasibility assessment will be conducted as a preamble to the registry. This assessment will evaluate each site identified as a possible candidate for inclusion, focusing on the following aspects:

- **Medical**, including the site's interest and commitment in participation, operational capacity, suitability of available EHR data (i.e., presence of clinically relevant information in a format and level of detail [and quantity] amenable to automated extraction by means of cNLP techniques), and the anticipated timing of data availability
- **Technical**, which refers to the site's ability to extract and contribute EHR data at scheduled intervals

Information on both aspects of feasibility will be obtained directly from relevant personnel at each identified site through a structured technical viability questionnaire. Findings from this assessment will inform the selection of participating sites, along with potential refinement of the criteria used to guide operational definitions and optimisation of the data collection strategy.
Following feasibility (at the selection of relevant sites in each country of interest), but prior to data collection, the study will be submitted for review or notification to the appropriate national or central institutional review board (IRB) or independent ethics committee (IEC), in accordance with local regulations. Regional and site-specific IRBs or IECs will also be notified or consulted, as required by local laws or institutional policies.

Setting and study population

Up to 40 sites across Canada, Germany, Portugal, Switzerland, and Italy (with the potential to expand to other sites and countries) will be selected for inclusion in this study. Study sites will be hospitals equipped with nuclear medicine and/or oncology departments.
A screening set will first be generated, when feasible, to include all EHRs from patients with PC attended at participating sites during the study period. Specific cNLP filters based on a predefined set of terms from the PCDP will then be applied to define and select the source population (i.e., patients with mPC). The study population will include at least 564 patients selected from the source population who meet the selection criteria outlined below. To comply with the principle of data minimisation, only patients who fulfil these selection criteria will be included in the final study database; information contained and maintained within the final

study database will serve as the foundation for subsequent descriptive and statistical analyses focused on addressing the research questions specified above.

Inclusion criteria

- Age ≥ 18 years at index date
- Diagnosis of mPC
- PSMA positive
- Received at least one dose of lutetium (^{177}Lu) vipivotide tetraxetan on or after mPC diagnosis date

Exclusion criterion

- Current or prior participation in an investigational study within the 30-day period immediately prior to and including the index date, or within five half-lives of the investigational product (whichever is longer)

Variables

The exposure of interest for this study is treatment with lutetium (^{177}Lu) vipivotide tetraxetan. The primary outcome of interest for the study is the number of patients who receive any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles. Secondary outcomes will describe the profile (i.e., demographic and clinical characteristics) of patients who receive lutetium (^{177}Lu) vipivotide tetraxetan, survival outcomes, treatment responses, AESIs, changes in drug utilisation, and treatment patterns with lutetium (^{177}Lu) vipivotide tetraxetan.

Data sources

The data sources for this study are the EHRs of patients with mPC who receive treatment with lutetium (^{177}Lu) vipivotide tetraxetan, as "hosted" within sites from the countries of interest. All information (i.e., unstructured and structured data) from the EHRs of selected patients will be automatically extracted at periodic intervals (i.e., quarterly) for the duration of the follow-up period.

Data processing

Data acquisition will be carried out by each participating site, guided by the study team with regard to required data sources. These include data types (i.e., structured, semi-structured, free text), relevant clinical areas (e.g., emergency, inpatient, outpatient), report types (e.g., discharge summaries, clinical notes, imaging, pathology, laboratory). Prior to automated extraction, sites must pseudonymise personal data in order to conform to relevant privacy laws and standards. Data will then be securely transferred to a dedicated data lake using secure file transfer protocol. Once in the data lake, all further data integration and processing will be performed by Medsavana. The pseudonymised data from participating sites are expected to be heterogeneous because of differences in information systems, local customisations, clinical workflows, and variability in documentation practices. To address this heterogeneity and to ensure that available data are suitable for cNLP with EHRead, a standardised data integration process will be carried out for each data extract. This process will involve standardisation, cleaning, and quality assessment of the extract. An initial data quality report will be generated to assess the completeness of the data, focusing on key hospital departments (e.g., oncology, nuclear medicine) and report types. Data extracts and integrations will be repeated at regular intervals (i.e., once quarterly) over the duration of the study, ultimately resulting in the capture of clinical information from the EHRs of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan from the index date through the end of follow-up, (i.e., a minimum of two years and a maximum

of five years of information for each patient, beginning with the initial date of treatment with lutetium (^{177}Lu) vipivotide tetraxetan.
The first AI-powered data extraction and integration will occur upon site activation, capturing all available and relevant historical data, to ensure accurate patient selection and development of comprehensive medical histories therefor. Subsequent data extractions will be conducted once every calendar quarter, incorporating new and updated data.
The cNLP will be applied to the pseudonymised data extract to identify clinical variables necessary to address the registry's objectives and research questions. As part of this process, data will be fully anonymised, and the extracted information will be structured into a dedicated anonymised database that contains only clinically relevant terms required to construct study variables. This database will serve as the basis for generating "analysis-ready" variables that will feed the study registry. The registry will be updated regularly with new data integrations, increasing both the number of relevant patients and the richness of available information. This approach will result in comprehensive capture of each patient's experience following initiation of treatment with lutetium (^{177}Lu) vipivotide tetraxetan, thereby enabling examination of all study objectives.

Validation processing

To ensure the precision and reliability of the data extracted and analysed in this study, a three-tier validation approach will be conducted, addressing different levels of validation:

- **Term validation**, defined as the evaluation of reading performance at the term level: This validation assesses the ability of EHRead to accurately capture and extract clinical terms from EHRs. It includes the following:
  - Internal validation: Performed by Medsavana annotators for each relevant language
  - External validation: Carried out by clinical investigators at each participating hospital
- **Patient-level verification**, defined as the evaluation of the precision of natural language processing (NLP)-based rules in identifying patients with mPC treated with lutetium (^{177}Lu) vipivotide tetraxetan, through manual review of full EHRs by Medsavana annotators. False positives will be removed from the analytical dataset.
- **Indirect epidemiological comparisons**, defined as evaluation of the plausibility of the source population (mPC patients) identified by cNLP rules from the screening population (PC patients). To do this, key epidemiological indicators (e.g., age at mPC diagnosis) will be calculated and compared with published data, when available.

Study size

We anticipate that a minimum sample size of 564 patients will be selected for inclusion in this study. As this is a descriptive study with no planned statistical significance testing, the study sample was estimated based on calculations of precision around the proportion receiving all six currently indicated cycles of lutetium (^{177}Lu) vipivotide tetraxetan (European Medicines Agency, 2022; Novartis, 2022a). In the VISION study (Canadian Agency for Drugs and Technologies in Health, 2023), 46.5% of participants randomised to lutetium (^{177}Lu) vipivotide tetraxetan completed all six cycles of such therapy, whereas the comparable estimate reported in a subsequent study based on a retrospective cohort design was 34% (Desai et al., 2024). Using PASS 2024 version 24.0.1 and the Clopper-Pearson exact formula, we estimated 95% confidence intervals (CIs) for six-cycle completion rates of 34%, 46.5%, and 59%, respectively (the third estimate was selected as a "best case" scenario). Should 34% of patients ultimately included in this study complete all six cycles of therapy, as reported in the aforementioned

retrospective study, the corresponding 95% CI is calculated to range between 30.1% and 38.1%, resulting in a margin of error (calculated as the 95% CI/2) of 4.0%.

Table 2-1 Precision achieved under different proportions of patients receiving all six cycles of lutetium (^{177}Lu) vipivotide tetraxetan

N	Six-cycle completion (%)	95% CI lower limit	95% CI upper limit	Margin of error (95% CI/2)
564	34.0%	30.1%	38.1%	4.0%
564	46.5%	42.3%	50.7%	4.2%
564	59.0%	54.8%	63.1%	4.1%

Abbreviation: CI, confidence interval.

Data analysis

All analyses will be performed by PPD. This study will be descriptive only, with no comparisons or tests of statistical significance planned (although standard errors and 95% CIs will be presented).

Continuous variables will be summarised using the number of non-missing observations, mean, standard deviation (SD), 95% CIs, median, minimum, maximum, and interquartile range (IQR). Categorical data will be presented as counts and percentages. The number of non-evaluable outcomes and missing data will also be reported, with missing data excluded from relevant percentage calculations.

The number and proportion of patients with any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles (e.g., one cycle, two cycles, ..., six cycles) will be described using counts and percentages. Patient profiles (in terms of demographic and clinical characteristics) will be summarised by the number of non-missing observations: mean, SD, median, minimum, maximum, 95% CI, and IQR for continuous variables, and by counts and percentage for categorical variables. Survival outcomes (real-world overall survival [rwOS], median rwOS, five-year rwOS, real-world progression-free survival [rwPFS], median rwPFS, five-year rwPFS), will be assessed using time-to-event Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median [IQR] time to event) with accompanying 95% CIs. Hazard ratios from Cox proportional hazards regression will be presented with 95% CIs. A p-value of less than 0.05 will be considered significant. Treatment response-related outcomes based on PSA level cutoffs will be reported as counts and percentages. Time to treatment response will be assessed Kaplan-Meier methodology. Best overall response and duration of response will be described by reporting the number of non-missing observations, mean, SD, 95% CI, median, minimum, maximum, and IQR for continuous variables. The overall response rate (complete response + partial response) will be presented as a rate with 95% CIs. AESIs will be reported as counts and percentages. Changes in drug utilisation and treatment patterns will be described by reporting the number of non-missing observations: mean, SD, 95% CI, median, minimum, maximum, and IQR for continuous variables, and counts and percentages for categorical variables. Time to next treatment, time to treatment initiation, persistence, and time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan outcomes will be analysed using Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median time to event, IQR, mean, SD) with 95% CI. Sankey diagrams or sunburst plots will be developed to visualise treatment pathways and sequencing.

Milestones

Table 2-2 Planned dates of study milestones

Milestone	Planned date
Study start date (data extraction start)	Q1-Q2 2026
Study end date (data extraction end)	Q3 2031
Annual interim analysis (n=7)	Q4 of each year, from 2026 to 2031
Completion of the study (final study report)	Q3 2032
Primary publication date	Q4 2032

Abbreviation: Q, quarter.

3 Amendments and updates

None.

Table 3-1 Study protocol amendments and updates

Version date	Version number	Section of protocol	Substantial amendment or update	Reason
n/a	n/a	n/a	n/a	n/a

Abbreviation: n/a, not applicable.

4 Milestones

Table 4-1 Planned dates of study milestones*

Milestone	Planned date
Study start date (data extraction start)	Q1-Q2 2026
Study end date (data extraction end)	Q3 2031
Annual interim analysis (n=7)	Q4 of each year, from 2026 to 2031
Completion of the study (final study report)	Q3 2032
Primary publication date	Q4 2032

*All milestone dates are estimates and are subject to change, pending timing of study start-up.
Abbreviation: Q, quarter.

5 Rationale and background

With a worldwide incidence rate in 2022 of approximately 7.3% (Bray et al., 2024), prostate cancer (PC) is the second most commonly diagnosed cancer and the fifth leading cause of cancer mortality among men worldwide (Bray et al., 2024). In 2022, an estimated 1.5 million men worldwide were diagnosed with and 396,000 died because of PC (Bray et al., 2024). By 2040, the worldwide burden of PC is projected to increase to approximately 2.4 million cases and 712,000 deaths due to the expected growth of a relatively aged global population (Schafer et al., 2025).

In Europe, PC incidence rates vary across countries but are generally high, making it the most frequently diagnosed cancer among men. According to the Global Cancer Observatory, the age-standardised incidence rate (ASR) of PC in Europe was 59.9 cases per 100,000 men in 2022, whereas the ASR for mortality in the same year was 11.2 per 100,000 men (Schafer et al., 2025). ASRs per 100,000 men for PC vary across Europe, ranging from 51.9 in Italy to 78.1 in

Switzerland (it is 62.6 in Portugal and 65.0 in Germany; all values per 100,000 men). Data from EUROCARE-5 reveal that the overall five-year relative survival rate for PC in Europe is 83% overall, with a higher survival rate of 90% for men diagnosed between the ages of 55 and 64 years. Geographic differences are notable, with the highest five-year survival rate of 92.8% in Northern Europe and the lowest of 80.1% in Eastern Europe (Marhold et al., 2022).

In Canada, PC is the most commonly diagnosed cancer among men. The ASR in Canada is approximately 64.9 cases per 100,000 men (Schafer et al., 2025), with a five-year survival rate of approximately 93% (Ellison & Saint-Jacques, 2023).

Both Europe and Canada have seen improvements in survival rates due to early detection through prostate-specific antigen (PSA) testing and associated advancements in medical treatments; however, the burden of PC remains significant across these and other countries, necessitating continued efforts in research, prevention, and healthcare strategies to manage the disease effectively (Vakili et al., 2025; Marhold et al., 2022; van Poppel et al., 2007).

PC remains a major health issue, with several established risk factors influencing its development and progression to metastatic disease. Age is a significant determinant, with the likelihood of diagnosis increasing substantially in men aged > 50 years (Rawla, 2019). Genetic factors, including family history (first-degree relative) and mutations in genes such as *BRCA1* and *BRCA2*, are critical in assessing the risk (Cancer Council, 2025; CDC, 2024a). Ethnicity also plays a role, with men of African descent exhibiting higher incidence rates than their European or Asian counterparts (Rebbeck, 2017). Smoking, environmental, infectious, lifestyle, and dietary factors elevate the risk (Bergengren et al., 2022). Furthermore, obesity and related metabolic conditions have been linked to a greater risk of aggressive disease (Perez-Cornago et al., 2017).

PC is typically diagnosed through a combination of screening tests and diagnostic procedures (Benelli et al., 2020; Litwin and Tan, 2017). The initial screening often involves measuring the levels of PSA in the blood, as elevated PSA levels can indicate the presence of PC. Additionally, a digital rectal examination may be performed to detect any abnormalities in the prostate gland. Further diagnostic procedures may include transrectal ultrasound-guided biopsies, where tissue samples are extracted from the prostate and examined histologically for cancerous cells. Magnetic resonance imaging can also be used to provide detailed images of the prostate and surrounding tissues, aiding in the detection and staging of the cancer (Benelli et al., 2020; Litwin and Tan, 2017).

Most patients with PC initially present with localised disease and undergo initial surgical and/or local radiotherapy with concomitant or subsequent use of androgen deprivation therapy (ADT; chemical castration). Despite initial response rates of 80% to 90% (Ahmad and Raghavan, 2018), nearly all patients subsequently develop progressive disease, even while receiving ADT therapy. Metastatic prostate cancer (mPC) includes different disease states, classified based on their response to ADT. These classifications consist of metastatic hormone-sensitive prostate cancer (mHSPC) and metastatic castration-resistant prostate cancer (mCRPC) (Borque-Fernando et al., 2025). The mean age at diagnosis of mHSPC is approximately 69 years (ASCO, 2025), and the median age at diagnosis of mCRPC is 70 years (Shore et al., 2021).

Over the past two decades, management of mHSPC and mCRPC has shifted from ADT to intensified combination therapies (Kostos and Murphy, 2022) as progression typically occurs within a year of starting ADT. As more treatment options become available for mPC, patients may undergo multiple treatment sequences, which may impact oncological outcomes (Wenzel et al., 2024). Current guidelines for mCRPC from various scientific societies recommend

combination treatment with lifelong ADT and systemic therapy because of demonstrated survival benefits (Cornford et al., 2024; Fizazi et al., 2023; Parker et al., 2020; Saad et al., 2022). First-line (1L) systemic therapies include androgen receptor pathway inhibitors (ARPIs) such as enzalutamide and abiraterone, the taxane docetaxel (in specific subgroups of patients), or the poly(ADP-ribose) polymerase inhibitor (PARPi) olaparib for patients with homologous recombination repair mutation or *BRCA1/2* mutations (the latter in Europe). Second-line therapy includes ARPIs, taxanes (e.g., cabazitaxel and docetaxel), bone-directed radio pharmaceutical therapy (radium-223), olaparib, and, most recently (as of 2022), the radioligand therapy [^{177}Lu] Lu-PSMA-617 (lutetium [^{177}Lu] vipivotide tetraxetan) (Lowrance et al., 2023). Third-line treatments include cabazitaxel, radium-223, olaparib, and lutetium (^{177}Lu) vipivotide tetraxetan (Parker et al., 2020).

Prostate-specific membrane antigen (PSMA), also known as folate hydrolase or glutamate carboxypeptidase II, is a transmembrane protein that is highly overexpressed in nearly all PCs. Its expression in normal tissues is significantly lower and restricted to areas such as the duodenal mucosa, proximal renal tubules, and salivary glands (Bostwick et al., 1998; Ghosh and Heston, 2004; Mannweiler et al., 2009). The overexpression of PSMA is further associated with advanced, high-grade, metastatic, and androgen-independent PC (Ross et al., 2003). This differential expression between tumour and non-tumour tissues has led to the development of numerous targeted strategies for disease localisation using radioactive imaging and therapeutic interventions. As a result, PSMA has become an attractive target for the treatment of men with mPC.

Lutetium (^{177}Lu) vipivotide tetraxetan is indicated for the treatment of adult patients with progressive PSMA-positive mCRPC who have been treated with ARPI and taxane-based chemotherapy. Lutetium (^{177}Lu) vipivotide tetraxetan received a marketing authorisation in Canada on 25 August 2022 and throughout the European Union on 09 December 2022. Lutetium (^{177}Lu) vipivotide tetraxetan is a beta-particle emitter that binds with high affinity to PSMA overexpressed in the prostate tumour tissue. The binding results in internalisation and retention within the targeted PC cells (Benesová et al., 2015; Sartor et al., 2021), leading to their death. As PSMA is minimally expressed in non-prostatic tissues, it exhibits very low background accumulation in healthy tissue, thereby minimising severe side effects and ensuring a relatively safe therapy with low toxicity. Unlike chemotherapy, lutetium (^{177}Lu) vipivotide tetraxetan is highly specific to the disease, limiting damage to surrounding tissues (Hennrich et al., 2022). Lutetium (^{177}Lu) vipivotide tetraxetan is administered via intravenous (IV) injection or infusion, approximately once every six weeks for up to six cycles, with one dose of lutetium (^{177}Lu) vipivotide tetraxetan containing 7.4 GBq (200 mCi).

The VISION trial, a prospective, open-label, multicentre, randomised, Phase III study of lutetium (^{177}Lu) vipivotide tetraxetan for the treatment of patients with progressive PSMA-positive mCRPC who had received at least one ARPI and one, but not more than two, taxanes, was pivotal to inform regulatory approvals in 2022 in the United States (US; Novartis, 2022b), Canada, and Europe as the first therapy in its class. In 2021, the VISION trial inferred that lutetium (^{177}Lu) vipivotide tetraxetan treatment demonstrated statistically significantly greater overall survival (OS) and radiographic progression-free survival (rPFS) benefits in the posttaxane setting versus the best standard of care (excluding cabazitaxel, immunotherapy, and radium-223) (Sartor et al., 2021).

In the PSMAfore (NCT04689828) open-label, international, randomised Phase III trial (Fizazi et al., 2025), lutetium (^{177}Lu) vipivotide tetraxetan improved rPFS with a median of 9.30 months

(95% CI 6.77–not estimable) versus 5.55 months (95% CI 4.04–5.95 months) with ARPI change (hazard ratio [HR] 0.41, 95% CI 0.29–0.56) in taxane-naive patients with mCRPC compared with a change in ARPI. The median OS was 24.48 months for lutetium (^{177}Lu) vipivotide tetraxetan versus 23.13 months for ARPI change, with no statistically significant difference (HR 0.91, p=0.20). The safety profile of lutetium (^{177}Lu) vipivotide tetraxetan was favourable, showing lower incidences of severe adverse events (AEs) compared with ARPI change. These results demonstrated that lutetium (^{177}Lu) vipivotide tetraxetan could be used as an alternative treatment option to ARPI change for patients with PSMA-positive mCRPC who have experienced disease progression after a previous ARP and are suitable candidates for delaying taxane-based chemotherapy. The interim analyses from June 2025 of the PSMAddition trial (NCT04720157; Sartor et al., 2022; Novartis, 2025), a Phase III open-label, randomised 1:1 study, demonstrated that lutetium (^{177}Lu) vipivotide tetraxetan combined with standard hormone therapy significantly improved rPFS in patients with PSMA-positive mHSPC compared with hormone therapy alone. The trial also showed a positive trend in OS, demonstrating potential for patients with mHSPC.

The Phase II TheraP trial demonstrated a higher PSA response rate and fewer AEs among mCRPC patients who received lutetium (^{177}Lu) vipivotide tetraxetan compared with cabazitaxel, highlighting its potential as an effective treatment (Hofman et al., 2024). Furthermore, for long-term efficacy and safety, the TheraP trial demonstrated comparable OS between groups and reported no new safety concerns (Hofman et al., 2024).

Several studies have investigated the real-world effectiveness and safety of lutetium (^{177}Lu) vipivotide tetraxetan as treatment for patients with mCRPC (Assadi et al., 2020; Khreish et al., 2022; Moradi Tuchayi et al., 2024), with results similar to those reported by the VISION and TheraP trials (Sartor et al., 2021; Hofman et al., 2024). However, while results have been promising, data related to lutetium (^{177}Lu) vipivotide tetraxetan administration and long-term outcomes in real-world settings are limited. An in-depth understanding of lutetium (^{177}Lu) vipivotide tetraxetan drug utilisation and patient profiles and clinical outcomes in routine care is important for informing decisions concerning the treatment and management of patients with mPC.

PULSE Registry

Clinical registries have transformed the conduct of clinical and biomedical research. National and international collaborations that enable the creation of large registries based on “all comers” across many sites are replacing smaller studies with limited sample sizes and low external validity. The PULSE Registry is conceptualised as a global multicentre artificial intelligence (AI)-powered study that will enhance our understanding of real-world lutetium (^{177}Lu) vipivotide tetraxetan drug utilisation, treatment patterns, and characteristics of patients treated with this therapy in clinical practice. Unlike traditional registries that rely on manual, time-intensive data entry, the PULSE Registry will leverage AI-powered clinical and multilingual natural language processing (NLP) and machine learning (ML) technologies to efficiently extract, clean, and analyse large volumes of both structured and unstructured clinical data from electronic health records (EHRs) of patients with mPC treated with lutetium (^{177}Lu) vipivotide tetraxetan. Patients will be followed for a minimum potential period of two years and up to five years. Related processes will enable the collection and analysis of clinical information from the EHRs of patients with mPC (both mHSPC and mCRPC) to evaluate real-world treatment patterns, patient characteristics, and clinical outcomes, thus unlocking valuable insights from narrative content that extend beyond the limitations of structured data alone.

6 Research question(s) and objectives

6.1 Research question(s)

The research question of this non-interventional, longitudinal study is "What are the patient demographic and clinical characteristics profiles, drug utilisation, treatment patterns, and clinical outcomes among adults with mPC who are treated with lutetium (^{177}Lu) vipivotide tetraxetan over a five-year follow-up period?"

It is anticipated that this study will generate real-world evidence that may address existing knowledge gaps regarding lutetium (^{177}Lu) vipivotide tetraxetan as a treatment for patients diagnosed with mPC.

6.2 Study objectives

6.2.1 Primary objective

The primary objective (Table 6-1) of the study is to describe the real-world drug utilisation of lutetium (^{177}Lu) vipivotide tetraxetan in patients diagnosed with mPC. It involves exposure to lutetium (^{177}Lu) vipivotide tetraxetan in eligible mPC patients in Canada, Germany, Portugal, Switzerland, Italy, and any other countries where the study may be expanded.

Table 6-1 Primary objective

Objective	To describe real-world drug utilisation of lutetium (^{177}Lu) vipivotide tetraxetan among mPC patients
Rationale	The real-world drug utilisation of lutetium (^{177}Lu) vipivotide tetraxetan in mPC patients may differ from the approved labels, which reflects the variable practice in clinical care influenced by several factors
Outcomes	The proportion and number of patients who receive any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles (e.g., one cycle, two cycles, …, six cycles)
Timeframe	From the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the end of follow-up
Main measure of effect	Descriptive statistics

Abbreviation: mPC, metastatic prostate cancer.

6.2.2 Secondary objectives

Secondary objectives are presented in Table 6-2, Table 6-3, Table 6-4, Table 6-5, Table 6-6, and Table 6-7. All secondary objectives involve exposure to lutetium (^{177}Lu) vipivotide tetraxetan in eligible mPC patients in Canada, Germany, Portugal, Switzerland, Italy, and any other countries where the study may be expanded. For secondary objective 6 in Table 6-7, exposure includes both lutetium (^{177}Lu) vipivotide tetraxetan and docetaxel.

Table 6-2 Secondary objective 1

Objective	To understand the profiles (in terms of demographic and clinical characteristics) of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
Rationale	mPC patients receiving lutetium (^{177}Lu) vipivotide tetraxetan in clinical practice may differ in baseline demographic and clinical characteristics profile from the population studied in clinical trials, and from the intended target population for which lutetium (^{177}Lu) vipivotide tetraxetan is authorised and reimbursed (as applicable).
Outcomes	1. Profile of patient demographics (e.g., age, race, and ethnicity [as allowed per local country regulations], country, prescriber type, insurance type, COVID-19 vaccination status) 2. Profile of clinical characteristics (vital signs, anthropometrics, symptoms/physical signs of PC and metastasis, mPC tumour characteristics, lab and imaging parameters, other prior antineoplastic treatments, performance scales, comorbidities, CCI, and prior prescription drugs for chronic conditions, risk factors for PC, metastasis location/characteristics and treatment, and additional primary malignancies)
Timeframe	Patient demographics and clinical characteristics profile will be measured as of index date, using the closest date prior to the index date. Select demographic and clinical characteristics will be assessed at PC diagnosis or mPC diagnosis. Comorbidities will be measured within the 365 days prior to the index date (preindex)
Main measure of effect	Descriptive statistics

Abbreviations: CCI, Charlson comorbidity index; mPC, metastatic prostate cancer; PC, prostate cancer.

Table 6-3 Secondary objective 2

Objective	To evaluate survival outcomes of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
Rationale	To contextualise survival outcomes observed in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan in real-world settings with those from literature, including RCTs and other RWE studies
Outcome	1. rwOS, median rwOS, and five-year rwOS 2. rwPFS, median rwPFS, and five-year rwPFS
Timeframe	From the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the earliest of end of follow-up or last available EHR record, or the event date (date of death due to any cause for rwOS or the earliest of date of documented disease progression or death from any cause for rwPFS) For the five-year rwOS and rwPFS, patients will be censored at five years from the index date
Main measure of effect	Median survival times, five-year survival, and rwOS will be reported using Kaplan-Meier methodology. Hazard ratios from Cox proportional hazards regression will be calculated.

Abbreviations: EHR, electronic health record; mPC, metastatic prostate cancer; RCT, randomised controlled trial; RWE, real-world evidence; rwOS, real-world overall survival; rwPFS, real-world progression-free survival.

Table 6-4 Secondary objective 3

Objective	To estimate treatment response of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
Rationale	To contextualise treatment response observed in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan in a real-world setting with that from the literature, including RCTs and other RWE studies
Outcome	1. PSA 30 response rate (≥ 30% decrease in PSA from date of lutetium (^{177}Lu) vipivotide tetraxetan initiation [index date]) 2. PSA 50 response rate (≥ 50% decrease in PSA from index date) 3. PSA 90 response rate (≥ 90% decrease in PSA from index date) 4. Time to treatment response for PSA 30, PSA 50, and PSA 90 5. BOR 6. ORR 7. DOR
Timeframe	From the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the end of follow-up
Main measure of effect	Response outcomes using PSA levels above a cutoff, BOR, and DOR will be reported with descriptive statistics. ORR will be reported as a rate of CR and PR with 95% CIs. Time to response for PSA 30, 50, and 90 will be reported using Kaplan-Meier methodology.

Abbreviations: BOR, best overall response; CI, confidence interval; CR, complete response; DOR, duration of response; mPC, metastatic prostate cancer; ORR, overall response rate; PR, partial response; PSA, prostate-specific antigen; RCT, randomised controlled trial; RWE, real-world evidence.

Table 6-5 Secondary objective 4

Objective	To describe AESIs in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
Rationale	Clinical trials are conducted in controlled environments with specific inclusion and exclusion criteria. Evaluating if lutetium (^{177}Lu) vipivotide tetraxetan has a reasonably well-tolerated safety profile in real-world setting, based on clinical trial data, will provide a more comprehensive understanding of its safety.
Outcome	Patients with evidence of AESIs, including, but not limited to, renal events, myelosuppression (cytopenia, bone marrow failure), dry eye, dry mouth, and second primary malignancies (malignancies other than the primary prostate cancer, including haematological and solid malignancies)
Timeframe	From the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the end of follow-up
Main measure of effect	Descriptive statistics

Abbreviations: AESI, adverse event of special interest; mPC, metastatic prostate cancer.

Table 6-6 Secondary objective 5

Objective	To assess changes in drug utilisation and treatment patterns in mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan
Rationale	Variations in dosing and treatment patterns observed in real-world clinical care are influenced by multiple factors, reflecting the dynamic nature of clinical practice
Outcome	1. Time interval between two consecutive cycles of lutetium (^{177}Lu) vipivotide tetraxetan (i.e., between first and second, second and third, third and fourth, fourth and fifth, and fifth and sixth cycles) 2. Number and proportion of patients with a change in lutetium (^{177}Lu) vipivotide tetraxetan dose (increase in dose or decrease in dose) 3. Number and proportion of patients with a change in frequency of lutetium (^{177}Lu) vipivotide tetraxetan cycles relative to the recommended frequency in the label

	4. Time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan relative to the recommendations in the label 5. Persistence (time to discontinuation): time from the index date until the date of last dose of lutetium (^{177}Lu) vipivotide tetraxetan administration 6. Number and proportion of newly diagnosed mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 1L 7. Number and proportion of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 2L or 2L+ 8. TTI: time from diagnosis of mPC to the index date 9. TTNT: time from index date until the start date of the next treatment 10. TFI: aggregate time between the end date of one regimen/treatment and the start date of the next regimen/treatment for all treatments 11. Duration of treatment: aggregate time of all treatment patterns from treatment/line initiation to discontinuation within each treatment (mean time on a given treatment for all patients) 12. Number and proportion of patients discontinuing lutetium (^{177}Lu) vipivotide tetraxetan documented by physician in the medical charts as discontinued. 13. Number and proportion of patients switching treatment, defined as discontinuation of lutetium (^{177}Lu) vipivotide tetraxetan and initiation of new drug(s) 14. Number and proportion of patients who received each treatment prior to lutetium (^{177}Lu) vipivotide tetraxetan administration since diagnosis of mPC 15. Number and proportion of patients who received each treatment following initiation of lutetium (^{177}Lu) vipivotide tetraxetan
Timeframe	All of the outcomes will be measured from the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the end of follow-up, except for: the number and proportion of newly diagnosed mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 1L, the number and proportion of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 2L or 2L+, TTI, and the number and proportion of patients receiving each treatment prior to lutetium (^{177}Lu) vipivotide tetraxetan administration since diagnosis of mPC. These parameters will be measured from mPC diagnosis to the index date whenever possible.
Main measure of effect	Descriptive statistics. TTNT, TTI, persistence, and time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan outcomes will be analysed using Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median time to event, IQR, mean, SD) with 95% CI. Sankey diagrams or Sunburst plots to visualise treatment pathways and sequencing.

Abbreviations: 1L, first line; 2L, second line; CI, confidence interval; mPC, metastatic prostate cancer; TFI, treatment-free interval; TTI, time to treatment initiation; TTNT, time to next treatment.

Table 6-7 Secondary objective 6

Objective	To examine profiles (defined in terms of demographic and clinical characteristics) and clinical outcomes of patients who receive sequential treatment of lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel
Rationale	mPC patients receiving lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel may have distinct patient profiles and clinical outcomes
Outcome	1. Patient profile (patient demographics [e.g., age, race, and ethnicity (as allowed per local country regulations), country, prescriber type, insurance type, COVID-19 vaccination status] and clinical characteristics [vital signs, anthropometrics, symptoms/physical signs of PC and metastasis, mPC tumour characteristics, lab and imaging parameters, other prior antineoplastic treatments, performance scales, comorbidities, CCI, and prior prescription drugs for chronic conditions, risk factors for PC, metastasis location/characteristics and treatment, and additional primary malignancies]) 2. Clinical outcomes (rwOS, median rwOS, five-year rwOS, rwPFS, median rwPFS, five-year rwPFS, treatment response, and AESIs)

Timeframe	Patient profiles (as defined above) will be measured as of index date (or closest date to index date where relevant information is identified). Select demographic and clinical characteristics will be assessed at PC diagnosis or mPC diagnosis. Comorbidities will be measured within the 365 days prior to the index date (preindex). Survival outcomes will be measured from the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the earliest of end of follow-up or last available EHR record, or the event date (date of death due to any cause for rwOS, or the earliest of date of documented disease progression or death from any cause for rwPFS). For the five-year rwOS and rwPFS, patients will be censored at five years from the index date. Response will be measured from the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the end of follow-up. AESIs will be measured from the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) until the end of follow-up.
Main measure of effect	Patient demographics and clinical characteristics profile using descriptive statistics Survival outcomes will be analysed using Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median time to event, IQR) with 95% CI. Hazard ratios will be calculated from Cox proportional hazards regression. Response outcomes using PSA levels above a cutoff, BOR, and DOR will be reported with descriptive statistics. ORR will be reported as a rate of CR and PR with 95% CIs. Time to response for PSA 30, 50, and 90 will be reported using Kaplan-Meier methodology. AESIs will be reported using descriptive statistics.

Abbreviations: AESI, adverse event of special interest; BOR, best overall response; CCI, Charlson comorbidity index; CI, confidence interval; CR, complete response; DOR, duration of response; EHR, electronic health record; IQR, interquartile range; mPC, metastatic prostate cancer; PC, prostate cancer; PR, partial response; PSA, prostate-specific antigen; rwOS, real-world overall survival; rwPFS, real-world progression-free survival.

7 Research methods

7.1 Study design

This multicountry, non-interventional, longitudinal study will establish an AI-powered registry using EHR data from participating sites treating patients with mPC using lutetium (^{177}Lu) vipivotide tetraxetan. Patients will be selected from 25 August 2022 to 31 July 2029 (selection period). The start of the selection period corresponds to the approval date of the treatment in the participating countries (Canada: 25 August 2022; Europe: 9 December 2022). The AI-powered PULSE Registry will extract clinical data from structured and unstructured fields in EHRs during the study period (25 August 2021 to 31 July 2031), with quarterly extractions from 2026 to 2031, using clinical natural language processing (cNLP) and ML (EHRead®, Medsavana S.L., Spain). A preselection "clean" period will be established to ensure that lutetium (^{177}Lu) vipivotide tetraxetan initiation occurs within the selection period. Similarly, a postselection period will be defined to minimise cohort effects on censoring for the primary outcome analysis during follow-up. No additional clinical activity (assessments/measurement/prescriptions, etc.) will be initiated as part of this research study beyond what was already done by healthcare providers as part of routine care (i.e., this study will be based on activities that happen in routine clinical practice [and not protocol-specified activities]). Novartis will not have access to individual patient-level data.

An operational and technical feasibility assessment will be conducted as a preamble to the study. This assessment aims to evaluate the readiness and capability of each site identified as a potential candidate for inclusion. The evaluation will focus on two main dimensions:

- **Medical,** including the site's interest and commitment in participation, operational capacity, suitability of available EHR data (i.e., presence of clinically relevant information in a format and level of detail [and quantity] amenable to automated extraction by means of cNLP techniques), and the anticipated timing of data availability
- **Technical,** which refers to the site's ability to extract and contribute EHR data at scheduled intervals, assessed using a structured technical viability questionnaire designed to capture information on data infrastructure, interoperability capabilities, and the use of automated data extraction tools

Information on both aspects of feasibility will be obtained directly from relevant personnel at each identified site through a structured technical viability questionnaire. Findings from this assessment will inform the selection of participating sites, along with potential refinement of the criteria used to guide operational definitions and optimisation of the data collection strategy.
EHRead is a powerful cNLP pipeline capable of processing multilingual free text and analysing and meaningfully interpreting clinical records, regardless of the EHR system used. For EHRead to help inform the generation of the PULSE Registry on mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan, a validated and scalable prostate cancer disease panel (PCDP)—defined as a structured list of standardised clinical terms associated with PC—will be implemented to both screen patients for inclusion in the registry and, for those who meet relevant selection criteria, characterise them. Refer to Sections 7.5.3 and 7.5.4 for details.
A cross-sectional analysis of all patients will be conducted at the time of their inclusion in the study, defined as the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan (index date) during the selection. Periodic analyses will be performed during follow-up to assess treatment patterns, patients' clinical characteristics profiles, and outcomes related to effectiveness and safety. Important study timeframes are detailed in section 7.1.1, and the study design diagram is presented as Figure 7-1.

Data extraction will begin on 25 August 2021 and continue until the earliest of the last available EHR record, patient's death, or end of the PULSE Registry (31 July 2031).

7.1.1 Study design diagram

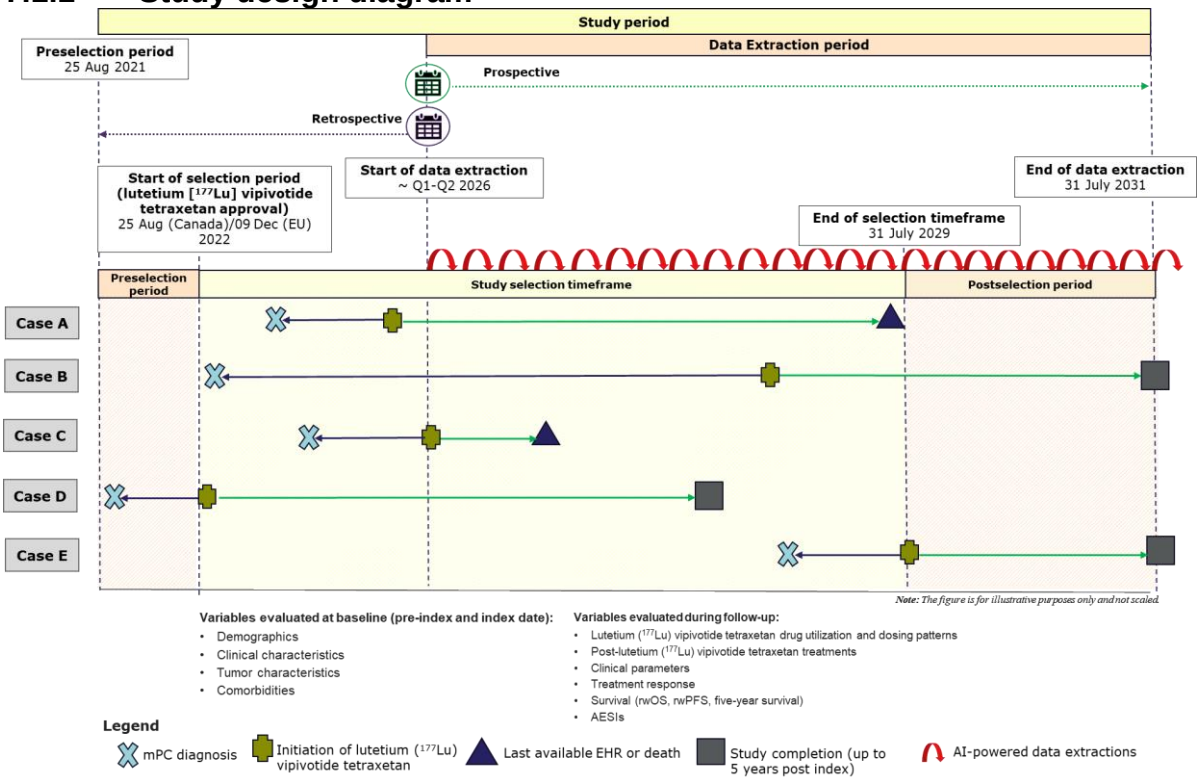

Figure 7-1 Study design diagram

Abbreviations: AESI, adverse event of special interest; AI, artificial intelligence; CCI, Charlson comorbidity index; EHR, electronic health record; EU, European Union; mPC, metastatic prostate cancer; PC, prostate cancer; Q, quarter; rwOS, real-world overall survival; rwPFS, real-world progression-free survival.

7.2 Setting and study population

Up to 40 sites across Canada, Germany, Portugal, Switzerland, and Italy (with the potential to expand to other sites and countries) will be selected for inclusion in this study. Study sites will be hospitals equipped with nuclear medicine and/or oncology departments.

A screening set will first be generated, when feasible, to include all EHRs from patients with PC attended at the participating sites during the study period. This initial selection will not involve the use of NLP; instead, it will rely on structured or administrative filters as agreed upon with each site (see section 7.5.1 for details). From this initial set, the source population will be defined by applying clinical NLP-specific filters designed to identify cases of mPC. These filters are guided by key terms (see section 7.5.4 for details) from the previously defined PCDP. The study population will include at least 564 patients from the source population who meet the selection criteria outlined below (Figure 7-2).

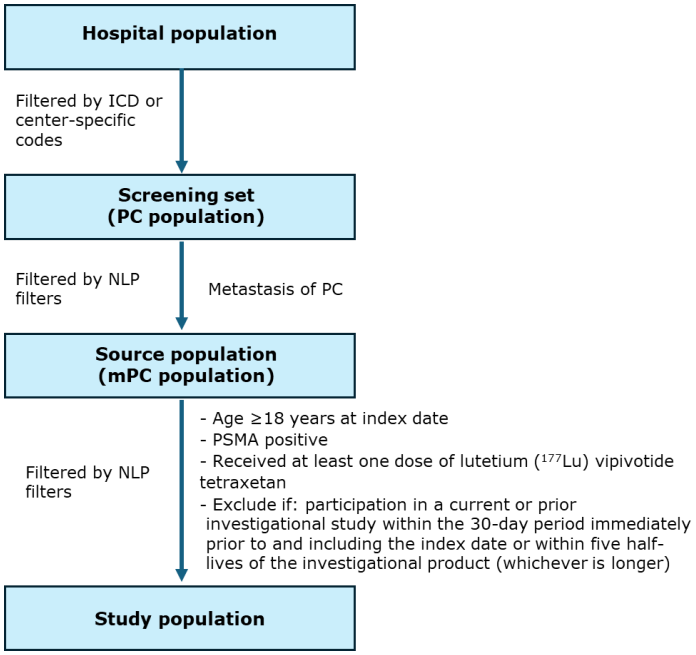

Figure 7-2 Flowchart of planned population selection

PC cases will be identified using ICD or centre-specific codes. Metastatic cases will be selected via NLP filters, and the final study cohort will include adults with PSMA-positive mPC treated with at least one dose of lutetium (^{177}Lu) vipivotide tetraxetan.

Abbreviations: ICD, International Classification of Diseases; mPC, metastatic prostate cancer; NLP, natural language processing; PC, prostate cancer; PSMA, prostate-specific membrane antigen.

Although only patients who meet the predefined selection criteria will be included in the final study database, participating sites will be asked to provide data on all PC patients who meet the general inclusion conditions (e.g., diagnosis, time period, hospital settings; see Section 7.5.1). This broader data set is essential for the following reasons: 1) to ensure a robust and homogeneous application of cNLP-based filters across all sites, allowing consistent selection of the final study population and decreasing the risk of selection biases, and 2) to enable the evaluation of the plausibility of the source population generated through filtering, which serves as the basis for the definition of the study population. Importantly, data from patients who do not meet the specific selection criteria will only be used for the filtering and validation process and will not be retained, stored, or processed further. This approach complies with the principle of data minimisation, which requires that personal data be adequate, relevant, and limited to what is necessary to meet the study objectives, in line with ethical and data protection standards, ensuring that only the data strictly necessary for achieving the study objectives are ultimately included in the analysis. In practice, although participating hospitals may initially provide a larger dataset, only data from patients meeting the predefined study selection criteria will be included in the final database. Information contained and maintained within the final database will serve as the foundation for subsequent descriptive and statistical analyses of lutetium (^{177}Lu) vipivotide tetraxetan and the patients with mPC who received it.

7.2.1 Timeframes considered for the study

The following study timeframes will be considered for inclusion of data for this study:

- **Study period** will span from 25 August 2021 to 31 July 2031 (inclusive of the start and end dates)
- **Patient selection period** will begin on 25 August 2022 and extend to 31 July 2029
- **Preselection period** will last from 25 August 2021 to 24 August 2022 (inclusive of the start and end dates)
- **Postselection period** will extend from 01 August 2029 to 31 July 2031 (inclusive of the start and end dates)

The following patient timeframes will be considered for this study:

- **Index date** will be defined as the date of the first administration of lutetium (^{177}Lu) vipivotide tetraxetan
- **Preindex period** will be defined as the period beginning 365 days prior to the index date and extending up to (but not including) the index date
- **Follow-up period/Postindex period** will begin on the index date and continue until the earliest of death, five years, end of study, or last available EHR record

7.2.2 Context and rationale for Time 0 and other primary time anchors for each study population

As the PULSE Registry intends to assess the profile (demographic and clinical characteristics) of, and selected outcomes in, patients with mPC who receive lutetium (^{177}Lu) vipivotide tetraxetan, the index date (i.e., date of first administration of lutetium (^{177}Lu) vipivotide tetraxetan) will serve as the primary time anchor, or Time 0, for this study. This ensures that only patients who have received lutetium (^{177}Lu) vipivotide tetraxetan are enrolled. To minimise the potential for bias, no postindex information will be used to determine the index date.

7.2.2.1 Operational definition of Time 0 (index date) and other primary time anchors

The operational definition of Time 0 (index date) is presented in Table 7-1.

Table 7-1 Definition of Time 0 and other primary time anchors

Study population name(s)[1]	Time anchor description (e.g., Time 0)	Number of entries	Type of entry	Washout window[2]	Care setting	Code type	Diagnosis position	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
PC population	Date of diagnosis of metastasis	Single entry	Incident	[1,∞]	IP, OP, and OT	ICD-9, or ICD-10 or ICD-O-3 or others centre-specific[3]	Primary	Diagnosis of metastasis	No validation study. Patients with PC will first be identified through structured data using ICD-9, ICD-10, or local coding systems. This initial cohort will constitute the screening set. Within this set, cases of mPC will be defined based on the earliest evidence fulfilling at least one of the following criteria: • At least one record from the medical oncology, radiation oncology, or urology departments indicating a direct mention in free text detected by cNLP of metastatic prostate cancer (e.g., “metastatic prostate cancer,” “mPC,” “prostate cancer with metastasis,” “M1 disease,” “prostate cancer stage IV”) • Evidence of metastatic disease in imaging reports detected by ICD code or cNLP in free text (e.g., “bone metastasis,” “lymph node involvement,” “visceral metastasis”) with mention of e.g., prostate cancer diagnosis	PC population

									• Evidence of a structured diagnosis of metastatic prostate cancer recorded using ICD-O-3 codes (e.g., C61 with M8000/6)	

Abbreviations: cNLP, clinical natural language processing; ICD, International Classification of Diseases; IP, inpatient; mPC, metastatic prostate cancer; OP, outpatient; OT, other; PC, prostate cancer.

[1]The definitions of the study populations are described in Figure 7-1.

[2] The preindex lookback period is 365 days before the index date. However, the washout window uses a lower bound of -∞ to capture all relevant events, i.e., if there is a reference to an event more than 365 days before the index date in the source documents.

[3] ICD-9, ICD-10, ICD-O-3, and other centre-specific codes will be used to identify patients with a diagnosis of prostate cancer, depending on data availability and local coding practices at each participating centre. ICD-O-3 refers to the *International Classification of Diseases for Oncology*, used to capture tumour site (e.g., C61.9, prostate) and morphology (e.g., M-8140/3, adenocarcinoma, not otherwise specified). “Other centre-specific codes” refer to local hospital coding systems used for diagnostic classification or case identification within each institution.

7.2.3 Context and rationale for study inclusion criteria

The study will enrol only mPC patients receiving treatment with lutetium (^{177}Lu) vipivotide tetraxetan within the selection period. While lutetium (^{177}Lu) vipivotide tetraxetan is indicated for mCRPC, to understand the real-world usage of lutetium (^{177}Lu) vipivotide tetraxetan, we will include both mHSPC and mCRPC patients (at least to the extent that such patients are treated with lutetium [^{177}Lu] vipivotide tetraxetan at participating sites).

The inclusion criteria designed to enrol patients for the study are listed below:

- Age ≥ 18 years at index date
- Diagnosis of mPC
- PSMA positive
- Received at least one dose of lutetium (^{177}Lu) vipivotide tetraxetan

7.2.3.1 Operational definitions of inclusion criteria.

The operational definitions for the inclusion criteria are presented in Table 7-2.

Table 7-2 Operational definitions of inclusion criteria

Criterion	Details	Order of application	Assessment window	Care settings	Code type	Diagnosis position	Applied to study populations[1]	Measurement characteristics/ validation	Source for algorithm
Observable time	Longitudinal secondary data	Before	[-365, 0]	n/a	n/a	n/a	PC population	n/a	n/a
mPC diagnosis	Patients with an mPC diagnosis on or after the primary PC diagnosis date	1 (Before)	[-PC diagnosis, 0]	IP, OP, OT	ICD-9, or ICD-10 or ICD-O-3 or centre-specific	Any	PC population	No validation study Details about the criterion used for the mPC diagnosis definition are provided in Table 7-1	n/a
Age	Patients ≥ 18 years of age at index date	2 (Before)	[-∞, 0]	n/a	n/a	n/a	mPC population	At least one record of age indicating age ≥ 18 years at index date or Year of index date - Year birth date ≥ 18 years, Both based on administrative structured data	n/a
PSMA positive	Patients positive for PSMA	3 (Before)	[-PC diagnosis, 0]	IP, OP, OT	n/a	n/a	mPC population	At least one record from the medical oncology, radiation oncology, urology or nuclear medicine departments with any one of the following: • Direct mention of PSMA positivity detected by cNLP in free text (e.g., "PSMA expression detected,"	n/a

								"positive for PSMA expression," "PSMA +") • Reference to intention to treat with PSMA-targeted therapies (e.g., "PSMA radioligand therapy indicated," "PSMA-targeted treatment planned," "PSMA-targeted treatment administered") detected by cNLP in free text	

Exposure to treatment	Patients who received at least one dose of lutetium (^{177}Lu) vipivotide tetraxetan on or after mPC diagnosis date	4 (Before)	[0]	IP, OP, OT	n/a	n/a	mPC population	First exposure to lutetium (^{177}Lu) vipivotide tetraxetan: Patients who received at least one dose of lutetium (^{177}Lu) vipivotide tetraxetan during selection period and had no evidence of lutetium (^{177}Lu) vipivotide tetraxetan administration during preselection period. • At least one record from the Medical Oncology, Radiation Oncology, Urology or Nuclear Medicine Departments with direct mention of lutetium (^{177}Lu) vipivotide tetraxetan administration in free text (e.g., "lutetium [^{177}Lu] vipivotide tetraxetan dispensed," or" "Pluvicto administered," "lutetium (^{177}Lu) vipivotide tetraxetan prescribed") detected by cNLP in free text. • Pharmacy records documenting the administration of lutetium (^{177}Lu) vipivotide tetraxetan or structured encounter records	n/a

								including relevant procedure or billing codes (e.g., ICD 10-PCS, CPT/HCPCS, or national/local procedure coding systems) indicating (^{177}Lu) vipivotide tetraxetan administration	

Abbreviations: cNLP, clinical natural language processing; CPT, Current Procedural Terminology; HCPCS, Healthcare Common Procedure Coding System; ICD, International Classification of Diseases; IP, inpatient; mPC, metastatic prostate cancer; n/a, not applicable; NLP, natural language processing; OP, outpatient; OT, other; PC, prostate cancer; PCS, Procedure Coding System; PSMA, prostate-specific membrane antigen.

[1] The definitions of the study populations are described in Figure 7-1.

7.2.4 Context and rationale for study exclusion criteria

The study will enrol mPC patients only. The exclusion criterion designed for the study is listed below.

- Participation in a current or prior investigational study within the 30-day period immediately prior to and including the index date or within five half-lives of the investigational product (whichever is longer)

7.2.4.1 Operational definitions of exclusion criteria

The operational definition of the exclusion criterion is presented in Table 7-3.

Table 7-3 Operational definition of exclusion criterion

Criterion	Details	Order of application	Assessment window	Care settings	Code type	Diagnosis position	Applied to study populations[1]	Measurement characteristics/validation	Source for algorithm
Current or previous enrolment in investigational studies	Participation in a current or prior investigational study within the 30-day period immediately prior to and including the index date, or within five half-lives of the investigational product (whichever is longer)	5 (Before)	[-30, 0] (except for the inference of the exposure period, which will be assessed from the index date to start of the study period)	n/a	n/a	n/a	mPC population	At least one record from any department with direct mention detected by cNLP in free text of active participation in any interventional clinical trial (e.g., "currently enrolled in a clinical trial," "participating in an investigational study"). or Evidence of “study drug” administration recorded from either: Free-text mentions detected by cNLP with at least one entry (e.g., "first dose of study drug ABC on 14 March 2025," "second dose of study drug ABC administered on 21 March 2025") Pharmacy records confirming administration (e.g., "200 mg IV of study drug ABC, date of administration 2025-04-10").	n/a

Criterion	Details	Order of application	Assessment window	Care settings	Code type	Diagnosis position	Applied to study populations[1]	Measurement characteristics/validation	Source for algorithm
								Inference of exposure period: requires cNLP-detected mention of the investigational drug in clinical records and publicly available information on its half-life. Exposure is defined as index date minus five half-lives. If either drug mention or half-life information is not available, exposure will be defined using the rules mentioned above.	

Abbreviations: cNLP, clinical natural language processing; IV, intravenous; mPC, metastatic prostate cancer; n/a, not applicable.
[1] The definitions of the study populations are described in Figure 7-1.

7.3 Variables

Details on the exposure variables, outcome variables, and covariates are presented in the subsections below. The operational definitions presented for these variables have been developed theoretically but may require adjustment once the actual data are available, to ensure alignment with real-world clinical documentation. It should also be noted that, due to the methodology used, based on information extracted from EHRs, some variables may present a high proportion of missing data depending on real-world documentation practices at the participating sites.

7.3.1 Context and rationale for exposure(s) of interest

The exposure of interest for this study is lutetium (^{177}Lu) vipivotide tetraxetan. This is an IV (injection or infusion) medication administered every 6 weeks ± 1 week for up to six cycles with one dose of lutetium (^{177}Lu) vipivotide tetraxetan containing 7.4 GBq (200 mCi). Lutetium (^{177}Lu) vipivotide tetraxetan is a beta-particle emitter that binds to PSMA and kills the targeted PC cells (Benesová et al., 2015; Sartor et al., 2021). It is currently recommended among the six major treatment options of mCRPC (Lowrance et al., 2023). The exposure is chosen as lutetium (^{177}Lu) vipivotide tetraxetan to enrol only those patients who receive at least one dose of lutetium (^{177}Lu) vipivotide tetraxetan.
The index date for this study will be the date of first administration of lutetium (^{177}Lu) vipivotide tetraxetan on or after mPC diagnosis date.

7.3.1.1 Operational definitions of exposure

The operational definitions for the exposure of interest are presented in Table 7-4.

Table 7-4 Operational definitions of exposure

Exposure group name(s)	Details	Washout window[1]	Assessment window	Care Setting	Code type	Diagnosis position	Applied to study populations[2]	Incident with respect to…	Measurement characteristics/ validation	Source of algorithm
mPC patients who received lutetium (^{177}Lu) vipivotide tetraxetan	Lutetium (^{177}Lu) vipivotide tetraxetan after or on mPC diagnosis date	[-∞, -1]	[0, end of follow-up]	IP, OP, OT	n/a	n/a	Study population	First administration of lutetium (^{177}Lu) vipivotide tetraxetan on or after mPC diagnosis date	No validation study	n/a
mPC patients exposed to any antineoplastic systemic treatment before or after initiation of lutetium (^{177}Lu) vipivotide tetraxetan	Any anti-neoplastic systemic treatment given before or after lutetium (^{177}Lu) vipivotide tetraxetan	[-∞, PC diagnosis-1]	[PC diagnosis, end of follow-up]	IP, OP, OT	n/a	n/a	Study population	Any antineoplastic systemic treatment	No validation study	Treatment will be defined per the data collected on sequential exposures.
mPC patients who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	Lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	[-∞, -1]	[0, end of follow-up]	IP, OP, OT	n/a	n/a	Study population	Administration of docetaxel after lutetium (^{177}Lu) vipivotide tetraxetan on or after mPC diagnosis date	No validation study	n/a

Abbreviations: IP, inpatient; mPC, metastatic prostate cancer; n/a, not applicable; OP, outpatient; OT, other; PC, prostate cancer.

[1] The preindex lookback period is 365 days before the index date. However, the washout window uses a lower bound of -∞ to capture all relevant events, i.e., if there is a reference to an event more than 365 days before the index date in the source documents.

[2] The definitions of the study populations are described in Figure 7-1.

7.3.2 Context and rationale for outcome(s) of interest

The outcomes of the study are formulated to help answer questions for fulfilling evidence generation needs for facilitating access and authorisation of lutetium (^{177}Lu) vipivotide tetraxetan. The primary outcome of interest for the study is the number of patients who receive any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles. This will help understand the real-world use and prescription practices of the medication.

Secondary outcomes will describe patient profiles (in terms of demographic and clinical characteristics), survival outcomes, treatment responses, AESIs, changes in drug utilisation and treatment patterns, patient profiles, and clinical outcomes in patients who receive the treatment sequence of lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel. These outcomes will bridge currently identified evidence gaps related to profiling, effectiveness, and safety of lutetium (^{177}Lu) vipivotide tetraxetan.

7.3.2.1 Operational definitions of outcome

Operational definitions of the outcomes are presented in Table 7-5.

Table 7-5 Operational definitions of outcome

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Number of lutetium (^{177}Lu) vipivotide tetraxetan cycles	The number and proportion of patients who receive any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles (e.g., one cycle, two cycles... six cycles)	Yes	Categorical (count and percentage)	[-∞, -1]	IP, OP, OT	ICD-10-PCS, CPT/HCPCS, or national/ local procedure coding systems[3]	Any	Study population	No validation study Time frame for outcome will begin on index date and end on date of the last follow-up within five years post index. Any of the following conditions will define lutetium (^{177}Lu) vipivotide tetraxetan cycles: At least one record from the medical oncology, radiation oncology, urology or nuclear medicine departments with any of the following: • Direct mention in free text detected by cNLP with explicit reference to cycle numbers or sequence (e.g., "third lutetium (^{177}Lu) vipivotide tetraxetan cycle completed," "administered first cycle of lutetium (^{177}Lu) vipivotide tetraxetan ") or	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									• Direct mention in free text detected by cNLP with explicit mention of different dates of lutetium (^{177}Lu) vipivotide tetraxetan administration or • Pharmacy records documenting the administration of lutetium (177Lu) vipivotide tetraxetan or structured encounter records including relevant procedure or billing codes (e.g., ICD-10-PCS, CPT/HCPCS, or national/local procedure coding systems) indicating (177Lu) vipivotide tetraxetan administration, with associated dates Number of cycles categorised as < 6 cycles, 6 cycles, and > 6 cycles.	
Age at mPC diagnosis	Year of mPC diagnosis – Year of birth The number and	No	Continuous (mean, SD, median, IQR, minimum,	[mPC diagnosis date +1, study	n/a	n/a	n/a	Study population	No validation study. Age at mPC diagnosis, categorised as < 65 years, 65–74 years, and ≥ 75 years, assessed based on	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	proportion of patients in each age category at mPC diagnosis		maximum) and categorical (count and percentage)	period end date]					administrative structured data	
Age at index date	Year of index date – Year of birth The number and proportion of patients in each age category at index date	No	Continuous (mean, SD, median, IQR, minimum, maximum) and categorical (count and percentage)	[1, study end date]	n/a	n/a	n/a	mPC population	No validation study. Age at index date, categorised as < 65 years, 65–74 years, and ≥ 75 years, assessed based on administrative structured data	n/a
Race (if allowed per local country regulation)	The number and proportion of patients in each race category at index date	No	Categorical (count and percentage)	n/a	n/a	n/a	n/a	Study population	No validation study. Race at index date categorised as Asian, Black, Caucasian/White, Mixed/Other, assessed based on administrative structured data or mentions detected by cNLP in free text Race will be determined at the closest date to the index date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Ethnicity (if allowed per local country regulation)	The number and proportion of patients in each ethnicity category at index date	No	Categorical (count and percentage)	n/a	n/a	n/a	n/a	Study population	No validation study Ethnicity as assessed at index date categorised as Atlantic fringe (Celtic culture area, English culture area, French culture area, Netherlandish culture area, Scandinavian culture area), Mediterranean (Iberian culture area, Pyrenean culture area, Mediterraneo-Alpine culture area, Italic culture area, Balkan culture area), Carpatho-Alpine–West Plain Climax (German culture area, Baltic culture area, West Slavic culture area, West Ugric culture area), East Plain and the Caucasus (East Finno-Permian culture area, East Slavic culture area, Pre-Uralian Turko-Tatar culture area, Ponto-Caspian Turko-Tatar culture area, West Finno-Permian culture area, Samoyed culture area, Caucasian culture area, Sporadic ethnic units of extra-European origins),	(Poulsen et al., 2025)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									unknown, not reported, and other, assessed based on structured administrative text or mentions detected by cNLP in free text Ethnicity will be determined at the closest date to the index date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Prescriber type[&]	The number and proportion of patients in each lutetium (^{177}Lu) vipivotide tetraxetan prescriber type category at index date	No	Categorical (count and percentage)	[1, study end date]	n/a	n/a	n/a	Study population	No validation study Prescriber type at index date, categorised as academic institute, community practice, centre of excellence, former lutetium (^{177}Lu) vipivotide tetraxetan clinical trial investigator, and others, assessed based on structured administrative text or mentions detected by cNLP in free text Prescriber type will be determined at the closest date to the index date, among the study population and those who	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Insurance type[&]	The number and proportion of patients in each medical insurance type category at index date	No	Categorical (count and percentage)	[1, study end date]	n/a	n/a	n/a	Study population	No validation study Insurance type at index date, categorised as private health insurance, public health insurance, statutory health insurance, supplementary insurance, employer-sponsored insurance, social assistance, cross-border healthcare, out of pocket/none and others, assessed based on structured administrative text Insurance type will be determined at the closest date to the index date, among the study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Country[&]	The number and proportion of patients in each country	No	Categorical (count and percentage)	[1, study end date]	n/a	n/a	n/a	Study population*	No validation study Country at index date, categorised as Canada, Germany, Portugal, Switzerland, and Italy	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	category at index date								(plus any countries identified for future study expansion), assessed based on structured administrative text Country will be determined at the index date, among the study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
COVID-19 vaccination status	The number and proportion of patients in each COVID-19 vaccination status category at index date (preindex)	No	Categorical (count and percentage)	[-∞, -1]	n/a	n/a	n/a	Study population	No validation study. COVID-19 vaccination status at index date, categorised as: fully vaccinated, partially vaccinated, unvaccinated, and unknown assessed from free-text mentions detected by cNLP COVID-19 vaccination status will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Smoking status at mPC diagnosis	The number and proportion of patients in each smoking status category at mPC diagnosis The number of cigarettes smoked per day for current smoker (preindex)	No	Categorical (count and percentage) Continuous for the number of cigarettes smoked per day (mean, SD, median, IQR, minimum, maximum)	[mPC diagnosis+ 1, study period end date]	n/a	n/a	n/a	Study population	No validation study Smoking status at mPC diagnosis, categorised as prior smoker, current smoker, never smoker, or unknown, and number of cigarettes smoked per day assessed from free-text mentions detected by cNLP or from structured codes when available. Smoking status will be determined based on relevant information identified on the closest date to the mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Weight at mPC diagnosis	Weight at mPC diagnosis (preindex)	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[mPC diagnosis date +1, study period end date]	n/a	n/a	n/a	Study population	No validation study Weight in kilograms at mPC diagnosis assessed from free-text mentions detected by cNLP or from structured fields when available Weight will be determined at the closest date to the mPC diagnosis, among	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Weight at index date	Weight at index date	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[1, study end date]	n/a	n/a	n/a	Study population	No validation study Weight in kilograms at index date assessed from free-text mentions detected by cNLP or from structured fields when available Weight will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Height at index date	Height at index date	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[1, study end date]	n/a	n/a	n/a	Study population	No validation study Height in centimetres at index date assessed from free-text mentions detected by cNLP or from structured fields when available. Height will be determined at the closest date to the index date, among the study population, and in those who received	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
BMI at mPC diagnosis	BMI at mPC diagnosis (preindex) The number and proportion of patients in each BMI category at mPC diagnosis	No	Continuous (mean, SD, median, IQR, minimum, maximum) and categorical (count and percentage)	[mPC diagnosis date +1, study period end date]	n/a	n/a	n/a	Study population	No validation study BMI in kg/m^2 at mPC diagnosis, categorised as underweight (< 18.5), healthy (18.5–24.9), overweight (25.0–29.9), obese (≥ 30.0), or unknown, assessed from direct mentions in free-text detected by cNLP fields or calculated from reported weight and height at mPC diagnosis, as defined above BMI will be determined at the closest date to the mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	(CDC, 2024b)
BMI at index date	BMI at index date The number and proportion of patients in each BMI	No	Continuous (mean, SD, median, IQR, minimum, maximum) and categorical	[1, study end date]	n/a	n/a	n/a	Study population	No validation study BMI in kg/m^2 at index date, categorised as underweight (< 18.5), healthy (18.5–24.9), overweight (25.0–29.9), obese (≥ 30.0), or	(CDC, 2024b)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	category at index date		(count and percentage)						unknown, assessed from direct mentions in free-text detected by cNLP fields or calculated from reported weight at index date and height at mPC diagnosis BMI will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Genetic testing	The number and proportion of patients in each genetic testing category at index date	No	Categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study Genetic testing status at index date, categorised as yes, no, or unknown for each of the following genomic risk factors: DNA damage repair genes (e.g., *BRCA1/2*), *PTEN* loss, *TP53* mutation, and *RB1* mutation, assessed from free-text mentions detected by cNLP or structured genomic testing reports Genetic testing will be determined at the closest date to the index date in the study population and in those who received	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
History of sexually transmitted infections (STIs)	The number and proportion of patients in each STI history category at index date	No	Categorical (count and percentage)	[1, study end date]	IP, OP, OT	ICD-9 or ICD-10 when available	Any	Study population	No validation study STI history at index date, categorised as yes, no, or unknown, assessed from free-text mentions detected by cNLP, or, when available, from structured ICD-9 or ICD-10 diagnostic codes indicating a personal history or previous diagnosis of STIs (e.g., ICD-10 A50–A64 – syphilis and other STIs; or ICD-9 090–097 – syphilis and other venereal diseases; 098 – gonococcal infections) STI history will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Family history of PC	The number and proportion of	No	Categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	patients in each family history of PC category at index date								Family history of PC at index date, categorised as yes, no, or unknown, assessed from free-text mentions detected by cNLP Family history of PC will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Symptoms of PC and metastasis	The number and proportion of patients in each symptom of PC and metastasis category (preindex)	No	Categorical (count and percentage)	[mPC diagnosis date +1, study period end date]	IP, OP, and OT	ICD-9 or ICD-10 when availab le	Any	Study population	No validation study Symptoms of PC and metastasis, categorised as tired, increased/frequent urination, decrease force in the stream of urine/weak flow, bone pain, pain or burning during urination, pain in hips, pain in pelvis, nausea, vomiting, lower back pain, weight loss, inability to urinate or difficulty starting to urinate, changes in erectile function, lower body weakness or	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									numbness, other, assessed based on free-text mentions detected by cNLP, or, when available, from structured ICD-9 or ICD-10 diagnostic codes related to these symptoms (e.g., ICD-9 788.62 – straining on urination; 783.21 – loss of weight ; or ICD-10; R39.12 – weak urinary stream; R63.4 – abnormal weight loss) Symptoms of PC and metastasis will be determined at the closest date to PC or mPC diagnosis, respectively, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Physical signs of PC and metastasis	The number and proportion of patients in each physical signs of PC or metastasis category at mPC	No	Categorical (count and percentage)	[mPC diagnosis date +1, study period end date]	IP, OP, and OT	ICD-9 or ICD-10 when available	Any	Study population	No validation study. Physical signs of PC and metastasis categorised as blood in urine, blood in semen, elevated liver enzymes, swollen lymph nodes, other, assessed based on free-text mentions detected by cNLP or, when available, from structured ICD-9 or	Physical signs of PC and metastasis

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	diagnosis (preindex)								ICD-10 diagnostic codes indicating these clinical signs (e.g., ICD-9 599.7 – haematuria; 608.82 – haematospermia; 790.4 – abnormal liver function study; 785.6 – enlarged lymph nodes; or ICD-10 R31 – haematuria; R36 – urethral discharge including blood in semen; R74.0 – elevated liver enzymes; R59 – enlarged lymph nodes) Physical signs of PC and metastasis will be determined at the closest date to PC or mPC diagnosis, respectively, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Clinical subgroups (phenotypes)	Subgroups identified based on clinical profile and administered treatments	No	Categorical (count and percentage)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Clinical profiles will be evaluated based on the following: Hormone sensitivity (mHSPC) at mPC diagnosis (including high volume disease/low volume disease,	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									synchronous or metachronous metastatic disease), tumour characteristics at mPC diagnosis, PSA at mPC diagnosis, PSMA positivity at mPC diagnosis, antineoplastic interventions prior to systemic therapy at mPC diagnosis, ECOG performance scale at mPC diagnosis, comorbidities at index date, risk factors at index date, ARPI use prior to index date, treatment patterns/sequences received prior to index date, and additional primary malignancies prior to index date These will be determined at mPC diagnosis or index date (variable depending), using the closest date to it, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Hormone sensitivity	Hormone sensitivity at mPC diagnosis (preindex) Proportion of patients with mHSPC or mCRPC type of mPC at mPC diagnosis	No	Categorical (count and percentage)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	Validation by logical consistency based progression from mHSPC to mCRPC (i.e., mCRPC to mHSPC is invalid) Proportion of patients with mHSPC or mCRPC status at mPC diagnosis date and proportion of patients who progress from mHSPC to mCRPC between mPC and index date The hormone sensitivity status at mPC diagnosis will be determined based on mentions detected by cNLP in free-text notes at or near the index date, using the mention closest to the index. The proportion of patients who progressed from mHSPC to mCRPC prior to the index date will be assessed based on sequential documentation in free-text sources Hormone sensitivity will be determined at the closest date to the mPC diagnosis and progress from mHSPC to mCRPC will be	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									determined at closest date to index, both in the study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Time to mCRPC	Time to progress from mHSPC at mPC diagnosis to mCRPC (preindex)	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Time to progress from mHSPC at mPC diagnosis to mCRPC will be measured only among those patients who were diagnosed with mHSPC at mPC diagnosis date Time to mCRPC will be assessed at index date, using the closest date to it, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Biopsy	The number and proportion of patients with a biopsy performed for PC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Biopsy test performed at PC diagnosis based on mentions detected by cNLP in free-text notes Biopsy test will be determined at the closest date to PC diagnosis, among the study	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Disease stage	The number and proportion of patients with disease stage I, II, III and unknown at PC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Disease stage at PC diagnosis will be determined either by a direct mention of stage (e.g., "prostate cancer stage I") **or** by inference from reported TNM, both detected by cNLP. Tumour (T) stage will be categorised as 0, 1, 2, 3, 4, TX, or unknown. Node (N) stage will be categorised as 0, 1, NX, or unknown. Metastatic (M) stage will be categorised as M0, M1a/M1b/M1c (for validation in case the first PC diagnosis coincides with mPC diagnosis), or unknown. Stage grouping will follow the AJCC and UICC TNM guidance Disease stage will be determined at the closest date to PC diagnosis, among the study population and those who received lutetium (^{177}Lu)	(Amin et al., 2016; Brierley et al., 2016)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									vipivotide tetraxetan followed by docetaxel	
Site of primary tumour	The number and proportion of patients with primary tumour at each site category at PC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Site of primary tumour at PC diagnosis, categorised as peripheral zone, central zone, transition zone, anterior fibromuscular stroma, or unknown, assessed based on free-text mentions detected by cNLP Site of primary tumour will be determined at the closest date to the PC diagnosis in the study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	(Bhavsar et al., 2014)
Site(s) of secondary tumour(s)	The number and proportion of patients with secondary tumours at each site category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Site(s) of secondary tumour(s) at mPC diagnosis, categorised as bone, liver, lung, brain, other, or unknown, assessed based on free-text mentions detected by cNLP, according to the criteria described in the algorithm source either by	(Freedland et al., 2021)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									direct detection of body-part terms using the body parts model or by explicit mention of M1a, M1b, or M1c Site(s) of secondary tumour(s) will be determined at the closest date to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Number of secondary tumour(s)	The number and proportion of patients in each secondary tumour (bones involved and organs affected) category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Number of secondary tumours (bones involved and organs affected) at mPC diagnosis, calculated as the per-patient sum of the findings detected by cNLP in the prior outcome, categorised as 1, 2, 3, 4, 5, etc., and unknown Number of secondary tumour(s) will be determined at the closest date to mPC diagnosis, among the study population, and in those who received lutetium	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									(^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Tumour size	The size of (each) tumour at mPC	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	No validation study. Tumour size(s) at mPC will be defined hierarchically based on data availability. It will first be obtained from explicit mentions detected by cNLP in radical prostatectomy pathology reports. If unavailable, it will be extracted from clinical records following radical prostatectomy (e.g., “pathology revealed a 22 mm tumour in the left lobe,” “dominant lesion measured 2.1 cm on prostatectomy”). If no radical prostatectomy is documented, tumour size will be obtained from other pathology reports (partial prostatectomy or biopsy), clinical records, or imaging studies (e.g., “tumour measuring 18 mm in the left peripheral zone,” “dominant nodule of 23 mm at the prostate apex,” “lesion of 15 × 10 mm in the right lobe”).	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									Across all sources, the largest reported dimension will be used, and all values expressed in millimetres Tumour size(s) will be determined at the prostatectomy date when available, or otherwise from the mention closest to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Cell differentia-tion	The number and proportion of patients in each cell differentia-Tion category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Cell differentiation at mPC diagnosis, categorised as well-differentiated, undifferentiated, unclear, or unknown, based on free-text mentions detected by cNLP, according to the criteria described in the algorithm source Cell differentiation will be determined at the closest date to the mPC diagnosis in the study population, and in those who received lutetium (^{177}Lu) vipivotide	(Humphrey et al., 2017, Diaconescu et al., 2011)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									tetraxetan followed by docetaxel	
Cell histology	The number and proportion of patients in each cell histology category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Cell histology at mPC diagnosis, categorised as acinar adenocarcinoma, prostate intraepithelial neoplasia, intraductal carcinoma, ductal adenocarcinoma, urothelial carcinoma, squamous neoplasms (adenosquamous neoplasm, squamous cell carcinoma), basal cell carcinoma, adenocarcinoma with neuroendocrine differentiation, small cell carcinoma, others, or unknown, assessed based on free-text mentions detected by cNLP, according to the criteria described in the reference Cell histology will be determined at the closest date to the mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	(Humphrey et al., 2017, Diaconescu et al., 2011)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Perineural invasion	The number and proportion of patients in each perineural invasion category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Perineural invasion at mPC diagnosis, categorised as positive, negative, or unknown, based on free-text mentions detected by cNLP, according to the criteria described in the algorithm source Perineural invasion will be determined at the closest date to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	(Niu et al., 2022, Diaconescu et al., 2011)
Involvement of lymph nodes	The number and proportion of patients in each lymph node involvement category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Involvement of lymph nodes at mPC diagnosis, categorised as present with extracapsular extension, present without extracapsular extension, absent, or unknown, assessed based on free-text mentions detected by cNLP Involvement of lymph nodes will be determined	(Datta et al., 2010)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									at the closest date to mPC diagnosis, among the study population and for those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Lymphovascular space invasion	The number and proportion of patients in each lympho-vascular space invasion category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date-1]	IP, OP, OT	n/a	n/a	Study population	No validation study Lymphovascular space invasion at mPC diagnosis, categorised as positive, negative, or unknown, assessed based on free-text mentions detected by cNLP Lymphovascular space invasion will be determined at the closest date to mPC diagnosis, among the study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	(Diaconescu et al., 2011)
Involvement of margins	The number and proportion of patients in each margin's involvement category at	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Involvement of margins at mPC diagnosis, categorised as positive, negative, or unknown, assessed based on free-	(Iczkowski et al., 2011)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	mPC diagnosis (preindex)								text mentions detected by cNLP Involvement of margins will be determined at the closest date to mPC diagnosis , among the overall study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Visceral metastasis	The number and proportion of patients in each visceral metastasis category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	mPC population	No validation study. Visceral metastasis at mPC diagnosis, categorised as yes (documented visceral metastasis), no (absence of visceral metastasis), or unknown (insufficient information), assessed based on free-text mentions detected by cNLP either by direct detection in visceral organs using the body parts model (e.g., liver, lung, adrenal, spleen) or by explicit mention of M1c Visceral metastasis will be determined at the closest date to mPC diagnosis, among the study population, and in those	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Gleason score	The number and proportion of patients in each Gleason score category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis - 1]	IP, OP, OT	n/a	n/a	Study population	No validation study Gleason score at mPC diagnosis will be assessed based on free-text mentions detected by cNLP, according to the criteria described in the reference, either by direct mention (e.g., "Gleason 7") or by inference from reported Gleason patterns (e.g., "Gleason 3+4"). When possible, it will be categorised into grade groups as follows: • Grade Group 1: Gleason ≤ 6 (3+3) • Grade Group 2: Gleason 7 (3+4) • Grade Group 3: Gleason 7 (4+3) • Grade Group 4: Gleason 8 (4+4, 3+5, 5+3) • Grade Group 5: Gleason 9–10 (4+5, 5+4, 5+5)	(Scher & Eastham 2022)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									Gleason score will be determined at the closest date to mPC diagnosis, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
PSMA positivity	The number and proportion of patients in each PSMA result category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	mPC population	No validation study PSMA positivity at mPC diagnosis will be categorised as PSMA positive, PSMA negative, unknown, assessed based on free-text mentions detected by cNLP. Method categories: PET scan, PET-CT, PET-MRI Radiotracer categories: 68Ga-PSMA-11, 177Lu-PSMA,18F-PSMA, piflufolast F-18, 18F-DCFPyL PSMA positivity will be determined at the closest date to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
PSA levels at mPC diagnosis (in ng/mL)	PSA levels at mPC diagnosis (preindex) The number and proportion of patients in each PSA level category at mPC diagnosis	No	Continuous (mean, SD, median, IQR, minimum and maximum values), and categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study PSA levels at mPC diagnosis, categorised as < 5.0, 5.0 ≤ PSA < 10.0, 10.0 ≤ PSA < 20.0, 20.0 ≤ PSA < 50.0, 50.0 ≤ PSA < 100.0, ≥ 100.0, unknown, assessed based on free-text mentions detected by cNLP PSA levels will be determined at the closest date to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
PSA levels at index date (in ng/mL)	PSA levels at index date The number and proportion of patients in each PSA level category at index date	No	Continuous (mean, SD, median, IQR, minimum and maximum values), and categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study PSA levels at index date, categorised as < 5.0, 5.0 ≤ PSA < 10.0, 10.0 ≤ PSA < 20.0, 20.0 ≤ PSA < 50.0, 50.0 ≤ PSA < 100.0, ≥ 100.0, or unknown, assessed based on free-text mentions detected by cNLP	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									PSA levels will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Total blood testosterone at mPC diagnosis (ng/dL)	Total blood testosterone levels at mPC diagnosis (pre-index) Number and proportion of patients in each testosterone level category at mPC diagnosis	No	Continuous (mean, SD, median, IQR, minimum and maximum values), and categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Total blood testosterone levels at mPC diagnosis, categorised as: < 270, 270–1070, > 1070, unknown, assessed based on free-text mentions detected by cNLP Total blood testosterone levels will be determined at the closest date to the mPC diagnosis date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Total blood testosterone at index date (ng/dL)	Total blood testosterone levels at index date The number and	No	Continuous (mean, SD, median, IQR, minimum and maximum	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study Total blood testosterone levels at index date, categorised as < 270, 270–1070, > 1070, or unknown, assessed from	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	proportion of patients in each testosterone level category at index date		values), and categorical (count and percentage)						direct mentions in free-text detected by cNLP or from structured laboratory data. Total blood testosterone levels will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Operability	The number and proportion of patients in each operability category at mPC diagnosis date (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study. Operability at mPC diagnosis, categorised as operable, inoperable, or unknown, assessed based on free-text mentions detected by cNLP (e.g., “operable,” “inoperable,” “not a surgical candidate”) **or** inferred from the presence/absence of surgical treatment with curative intent Operability will be determined at the closest date to mPC diagnosis, in the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Previous prostatectomy	The number and proportion of patients in each previous prostatectomy category prior to mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis date -1]	IP, OP, OT	ICD-10 when available	Any	Study population	No validation study Previous prostatectomy prior to mPC diagnosis, categorised as yes (prostatectomy, radical prostatectomy, transurethral prostatectomy, cystoprostatectomy, retropubic prostatectomy), no, or unknown, assessed based on free-text mentions detected by cNLP or evidence of surgical procedures (e.g., prostatectomy surgery report), or, when available, from structured procedure codes indicating prostatectomy (e.g., ICD-10-PCS 0VT00ZZ – resection of prostate, open approach; CPT 55866 – laparoscopic radical prostatectomy; or national/local procedure coding systems) Previous prostatectomy will be determined between PC diagnosis and mPC diagnosis at the closest date prior to mPC diagnosis, among the study population, and in	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Imaging preindex	The number and proportion of patients with each imaging category performed between PC diagnosis and mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Imaging prior to mPC diagnosis, categorised as yes, no, or unknown. for each of the following: TRUS, CT scan report, MRI report, bone scan (technetium scintigraphy), 68Ga-PSMA-11 PET/CT scan, PSMA tracer, based on free-text mentions detected by cNLP Prior imaging will be determined between PC diagnosis and mPC diagnosis at the closest date prior to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Radiotherapy	The number and proportion of patients with each radiotherapy	No	Categorical (count and percentage)	[-∞, PC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Radiotherapy prior to mPC diagnosis, categorised as yes, no, or unknown for the following:	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	category administered between PC diagnosis and mPC diagnosis (preindex)								EBRT, SBRT, IMRT, IGRT, or unknown, assessed based on free-text mentions detected by cNLP Previous radiotherapy will be determined between PC diagnosis and mPC diagnosis at the closest date prior to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Bone marrow examination	The number and proportion of patients in each bone marrow examination category between PC diagnosis and mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Bone marrow examination prior to mPC diagnosis, categorised as yes, no, or unknown, categorised based on the findings, assessed based on free-text mentions detected by cNLP or procedure codes, if available Prior bone marrow examination will be determined between PC diagnosis and mPC diagnosis at the closest date prior to mPC diagnosis, among the	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Antineoplastic treatment before mPC diagnosis	The number and proportion of patients in each antineoplastic systemic treatment category given between PC diagnosis and mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Prior antineoplastic treatment prior to mPC diagnosis, categorised as ARPIs (e.g., enzalutamide, abiraterone acetate), taxanes (e.g., docetaxel, cabazitaxel), PARPi (e.g., olaparib), bone-directed radiopharmaceutical therapy, assessed based on free-text mentions detected by cNLP Prior antineoplastic treatment will be determined between PC diagnosis and mPC diagnosis at the closest date prior to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Antineoplastic treatment between mPC diagnosis and index date	The number and proportion of patients in each antineoplastic systemic treatment category given prior to index date, after mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, and OT	n/a	n/a	Study population	No validation study Antineoplastic treatment(s) after mPC and prior to index date, categorised as ARPIs (e.g., enzalutamide, abiraterone acetate), taxanes (e.g., docetaxel, cabazitaxel), PARPi (e.g., olaparib), bone-directed radiopharmaceutical therapy, assessed based on direct mention in free text detected by cNLP Antineoplastic treatment(s) will be determined between mPC diagnosis and index date at the closest date prior to index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Prior prescription drugs for chronic conditions	The number and proportion of patients in each prescription drugs category	No	Categorical (count and percentage)	[-∞, -366]	IP, OP, and OT	n/a	n/a	Study population	No validation study Prior prescription drugs for chronic conditions, e.g., medications for cardiovascular disease, diabetes, autoimmune disease, assessed based on free-text mentions	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	given for chronic conditions in the year prior to and including index date (preindex)								detected by cNLP or, when available, from structured ATC codes identifying the corresponding drug classes (e.g., C01–C10 for cardiovascular agents, A10 for drugs used in diabetes, L04 for immunosuppressants). Prior prescription drugs for chronic conditions will be determined in the 365 days prior to index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Vital signs at mPC diagnosis	Blood pressure (systolic/diastolic) pulse, respiratory rate, and body temperature at diagnosis of mPC (preindex)	No	Continuous (mean, SD, median, IQR, minimum and maximum values)	[-∞, mPC diagnosis date -1]	IP, OP, and OT	n/a	n/a	Study population	No validation study Vital signs at mPC diagnosis assessed based on free-text mentions detected by cNLP Vital signs will be determined at the closest date to mPC diagnosis, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Vital signs at index date	Blood pressure (systolic/diastolic) pulse, respiratory rate, and body temperature at index date	No	Continuous (mean, SD, median, IQR, minimum and maximum values)	[1, study end date]	IP, OP, and OT	n/a	n/a	Study population	No validation study Vital signs at index date assessed based on free-text mentions detected by cNLP Vital signs will be determined at the closest date to index date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
DRE	The number and proportion of patients in each DRE category at diagnosis of PC (preindex)	No	Categorical (count and percentage)	[-∞, PC diagnosis date -1]	IP, OP, and OT	n/a	n/a	Study population	No validation study DRE at diagnosis of PC, categorised as yes, no, and for those with yes, results categorised as enlargement of the prostate, presence of suspicious nodule(s), lobar asymmetry, a hard consistency, obliteration of the median groove, induration of a lobe or the whole prostate, palpable seminal vesicles, other, assessed based on free-text mentions detected by cNLP DRE will be determined at the closest date to PC	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									diagnosis, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
ECOG status at mPC diagnosis	The number and proportion of patients in each ECOG performance status category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study ECOG performance status at mPC diagnosis, categorised as 0–1, 2, 3+, or unknown, assessed from free-text mentions detected by cNLP ECOG performance status will be determined at the closest date to the mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
ECOG status at index date	The number and proportion of patients in each ECOG performance status category at index date	No	Categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study ECOG performance status at index date, categorised as 0–1, 2, 3+, or unknown, assessed from free-text mentions detected by cNLP ECOG performance status will be determined at the closest date to the index	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Karnofsky status at mPC diagnosis	The number and proportion of patients in each Karnofsky scale category at mPC diagnosis (preindex)	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Karnofsky performance status at mPC diagnosis, categorised as 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, or unknown, assessed from free-text mentions detected by cNLP Karnofsky scale will be determined at the closest date to mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Karnofsky status at index date	The number and proportion of patients in each Karnofsky scale category at index date	No	Categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study Karnofsky performance status at index date, categorised as 100, 90, 80, 70, 60, 50, 40, 30, 20, 10, or unknown, assessed from free-text mentions detected by cNLP	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									Karnofsky scale will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Comorbidity type	The number and proportion of patients with each comorbidity type at index date (preindex)	No	Categorical (count and percentage)	[1, study end date]	IP, OP, and OT	ICD-9 or ICD-10 when availab le	Any	Study population	No validation study Comorbidity type at index date, categorised as: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, AIDS/HIV, or others, assessed from free-text mentions detected by cNLP or, when available, from structured ICD-9 or ICD-10 diagnostic codes	(Breccia et al., 2011)

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									corresponding to these conditions (e.g., ICD-9 410 – acute myocardial infarction; 428 – heart failure; 250.0–250.9 – diabetes mellitus; 585 – chronic renal failure; or ICD-10 I21 – acute myocardial infarction; I50 – heart failure; E10–E14 – diabetes mellitus; N18 – chronic kidney disease) Comorbidity type will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Additional primary malignancies	The number and proportion of patients with each additional primary malignancy category prior to index date but after mPC	No	Categorical (count and percentage)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study Additional primary malignancies prior to index date, categorised as head and neck, digestive organs and peritoneum, respiratory and intra-thoracic organs, bone/connective tissue/skin/breast, genitourinary organs, lymphatic and hematopoietic tissues,	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	diagnosis (preindex)								neuroendocrine tumours, others and unspecified sites, no additional primary malignancy, or unknown, assessed from free-text mentions detected by cNLP Additional primary malignancies will be determined between mPC diagnosis and index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Charlson comorbidity index (CCI)	CCI score at index date	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study CCI at index date, assessed either from direct free-text mention or calculated based on the presence of comorbidities included in the CCI algorithm detected by cNLP. CCI will be measured at the closest date to the index, among the study population, and in those who received lutetium (^{177}Lu) vipivotide	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									tetraxetan followed by docetaxel	
ECG at index date	ECG at index	No	Categorical (count and percentage)	[1, study end date]	IP, OP, and OT	n/a	n/a	Study population	No validation study ECG at index date assessed based on free-text mentions detected by cNLP ECG will be determined at the closest date to index date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
LDL levels at index date (in U/L)	LDL levels at index date The number and proportion of patients in each LDL level category at index date	No	Continuous (mean, SD, median, IQR, minimum and maximum values), and categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study. LDL levels at index date, categorised as < 135, 135–225, > 225, or unknown, assessed from direct mentions in free-text detected by cNLP or from structured laboratory data LDL levels will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
ALP levels at index date (in U/L)	ALP levels at index date The number and proportion of patients in each ALP level category at index date	No	Continuous (mean, SD, median, IQR, minimum and maximum values), and categorical (count and percentage)	[1, study end date]	IP, OP, OT	n/a	n/a	Study population	No validation study ALP levels at index date, categorised as < 44, 44–147, > 147, or unknown, assessed from direct mentions in free-text detected by cNLP or from structured laboratory data ALP levels will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
rwOS	rwOS (median and five-year): Time from index date until death for any cause	No	Time to event (median, IQR)	[-∞, -1]	IP, OP, OT, ER	n/a	n/a	Study population	No validation study Death within five years post index, with median survival defined as the time from the index date at which point one-half of patients in the cohort remain alive The outcome time frame will be from index date up to the last follow-up within five years post index, and five-year survival will be estimated among patients with follow-up ≥five years	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									Patients lost to follow-up will be censored at the date of the last available EHR record, and all patients alive at the end of the study period will also be censored Death will be identified from free-text mentions detected by cNLP in any department, either by (1) direct documentation of death (e.g., "patient deceased," "death confirmed") or (2) terms that clearly imply death (e.g., "end-of-life situation," "comfort measures initiated," "palliative care only") rwOS will be determined among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
rwPFS	rwPFS (median and five-year): Time from index date to the earliest	No	Time to event (median, IQR)	[-∞,-1]	IP, OP, OT, ER	n/a	n/a	Study population	No validation study The time frame for rwPFS will be from index date up to the last follow-up within five years post index	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	date of documented disease progression, or death from any cause, whichever occurs first								Calculated time in years from the index date until the earliest occurrence of any of the following events: • Disease progression, defined as any of the following: ○ At least one record from the medical oncology, radiation oncology or urology departments with mention in free text detected by cNLP indicating disease progression (e.g., “tumour progression," “new metastatic lesions identified,” "PSA increase consistent with progression") ○ Imaging reports indicating progression (e.g., “new bone metastasis on	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									PET-CT) detected by cNLP ○ Biochemical progression, confirmed by two consecutive PSA measurements in laboratory records, showing a 25% increase from the nadir (the lowest PSA value recorded after lutetium (^{177}Lu) vipivotide tetraxetan initiation) and an absolute increase of at least 2 ng/mL, with measurements separated by a minimum of one week • Death, as defined previously Median rwPFS will be defined as the time from the index date at which half of the patients in the cohort remain free of progression or death, and five-year rwPFS will be	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									estimated among patients with follow-up up to five years Patients lost to follow-up will be censored at the date of last EHR record, and all patients alive or without progression at the end of the study period will also be censored rwPFS outcome will be determined among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
PSA response	PSA response (≥ 30%, ≥ 50%, ≥ 90%): The proportion of patients who achieve a reduction in PSA levels of at least 30%, 50%, or 90% after treatment with lutetium (^{177}Lu)	No	Binary (responder vs. non-responder)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for PSA response will be from the index date up to the last follow-up within five years postindex At least one record from the medical oncology, radiation oncology or urology departments with mentions in free text detected by cNLP indicating PSA reduction (e.g., "PSA reduced by 50%")	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	vipivotide tetraxetan								or Evidence of PSA level reduction, defined as a decrease from the baseline PSA level (measured closest prior to the index date). This reduction will be calculated using all PSA levels available. The reduction will be confirmed by at least two measurements PSA response will be determined among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Time to treatment response for PSA	Time to treatment response for PSA: time (in months) from the index date to achieving PSA response of 30%, 50%, or 90%	No	Time to event (median, IQR, mean, SD)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for time-to treatment response for PSA outcome will be from the index date up to the last follow-up within five years post index. Calculated as the time (in months) from the index date to the achievement of a PSA response rate of 30%, 50%, and 90%, as	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									identified following the criteria mentioned above Time to treatment response for PSA will be determined among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
BOR	BOR: Time interval to achieve CR or PR	No	Time-to-event (median, IQR)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for BOR will be from the index date up to the last follow-up within five years post index Time interval (in months) calculated from the index date to the achievement of either CR or PR, as defined by the criteria outlined below BOR will be measured among the overall study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
ORR	ORR: rate of CR and PR	No	Rate of CR and PR divided by	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
			the overall population (percentage and 95%CI)						The time frame for ORR will be from the index date up to the last follow-up within five years post index Percentage of cases with CR or PR, defined as follows: CR: Any of the following: • At least one record from the medical oncology, radiation oncology, or urology departments with mention in free text detected by cNLP indicating complete response (e.g., "no residual disease," "complete remission"). or • PSA measurements showing undetectable levels in at least two consecutive tests taken at least 4 weeks apart or • At least one imaging report from radiology (e.g., CT, MRI, PET-CT, bone scan) showing no detectable	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									by cNLP prostate lesions and no metastases related to prostate cancer PR: Any of the following: • At least one record from the oncology or urology departments with mentions in free text detected by cNLP indicating partial response (e.g., "partial reduction in tumour size," "PSA decreased by half") or • PSA response rate ≥ 50% reduction, following the criteria mentioned above Or • An imaging report showing a ≥ 30% reduction in measurable lesions compared to baseline. ORR will be determined among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
DOR	DOR: Time from date patient initially meets response criteria (CR or PR) until date of disease progression	No	Time to event (median, IQR)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for DOR will be from the index date up to the last follow-up within five years post index Time interval in months calculated from date patient initially meets response criteria (CR or PR) until date of disease progression, as previously defined DOR will be measured among the overall study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
AESIs	The number and proportion of patients AESIs, by category	No	Categorical (count and percentage)	[-∞, -1]	IP, OP, OT, ER	ICD-9 or ICD-10 when availab le	Any	Study population	No validation study The time frame for the outcome will be from index date up to the last follow-up within five years post index Potential AESIs will be identified based on the detection by cNLP of mentions in free text from a predefined list of AESIs.	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									These mentions must appear in at least one record from any department. Detection will be based on mentions recorded after the initiation of lutetium (^{177}Lu) vipivotide tetraxetan. When available, structured ICD-9 or ICD-10 diagnostic codes corresponding to these AESIs will also be used to support their identification Patients will be considered to have evidence of AESIs if there are mentions or structured diagnostic codes indicating any of the AESIs, including, but not limited to: renal events, myelosuppression (cytopenia, bone marrow failure), dry eye, dry mouth, and second primary malignancies (malignancies other than the primary prostate cancer, including haematological and solid malignancies) AESIs will be determined among the study	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Lutetium (^{177}Lu) vipivotide tetraxetan EAP	Ther number and proportion of patients in each lutetium (^{177}Lu) vipivotide tetraxetan EAP initiation category	No	Categorical (counts and percentage)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study. The time frame for the outcome will be from the index date up to the last follow-up within five years post index Categorised as yes, no, unknown, assessed based on free-text mentions detected by cNLP	n/a
Time interval between two consecutive lutetium (^{177}Lu) vipivotide tetraxetan cycles	Time interval between two consecutive cycles of lutetium (^{177}Lu) vipivotide tetraxetan (between first and second, second and third, third and fourth, fourth and fifth, and fifth and sixth)	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study. The time frame for the outcome will be from the index date up to the last follow-up within five years post index Number of days between the administration dates of two consecutive cycles, as identified following the definition described above for the primary outcome. Intervals will be calculated between the following pairs: first and second, second and third, third	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									and fourth, fourth and fifth, and fifth and sixth cycles (if more than six cycles are given, then this will also be reported) The outcome will be determined among the study population	
Change in lutetium (^{177}Lu) vipivotide tetraxetan dose	The number and proportion of patients with a change in lutetium (^{177}Lu) vipivotide tetraxetan dose: any adjustment (increase or decrease) in the lutetium (^{177}Lu) vipivotide tetraxetan dose compared with the recommended dose specified in the prescribing information	No	Binary (dose changed: yes/no)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study. The time frame for the outcome will be from the index date up to the last follow-up within five years post index • At least one record from the medical oncology, radiation oncology or urology or nuclear medicine departments with mentions in free text detected by cNLP indicating a change in dosage (e.g., "lutetium (^{177}Lu) vipivotide tetraxetan dose increased to 8 GBq," "dose reduced to 6 GBq") or • Pharmacy records documenting lutetium	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									(^{177}Lu) vipivotide tetraxetan administration that indicate a dose different from the standard recommended dose (e.g., "administered 5 GBq IV") The outcome will be determined among the study population	
Change in lutetium (^{177}Lu) vipivotide tetraxetan cycle frequency	The number and proportion of patients with a change in lutetium (^{177}Lu) vipivotide tetraxetan cycle frequency: Any adjustment (increase or decrease) in the frequency of lutetium (^{177}Lu) vipivotide tetraxetan cycle	No	Binary (frequency changed: yes/no)	[-∞, -1]	IP, OP, OT	ICD-10 when availab le	Any	Study population	No validation study The time frame for the outcome will be from index date up to the last follow-up within five years post index • Record from the medical oncology, radiation oncology or urology, or nuclear medicine departments with mentions in free text detected by cNLP indicating a change in administration frequency (e.g., "lutetium (^{177}Lu) vipivotide tetraxetan every 4 weeks instead of 6 weeks," "frequency increased	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	administrations compared with the recommended schedule specified in the relevant and applicable prescribing information								due to rapid progression") or derivation of time intervals from all available records of lutetium (^{177}Lu) vipivotide tetraxetan administration. or • Structured pharmacy records or structured encounter records including relevant procedure or billing codes (e.g., ICD-10-PCS, CPT/HCPCS, or national/local procedure coding systems) indicating administration dates of lutetium (^{177}Lu) vipivotide tetraxetan that differ from the recommended frequency (e.g., "administered on 2025-04-10 and again on 2025-05-01"), or derivation of time intervals from all available records of lutetium (^{177}Lu) vipivotide tetraxetan	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									The standard dosing interval is 6 weeks. A variation of up to ± 1 week (i.e., 5–7 weeks between cycles) will be considered within the acceptable clinical range and not treated as a formal "change in frequency." Any dosing interval shorter than 5 weeks or longer than 7 weeks will be classified as a change in administration frequency. The outcome will be determined among the study population	
Time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan	Time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan relative to the recommendations in the label	No	Time to event (median, IQR, mean, SD)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from index date up to the last follow-up within five years post index The time interval in months calculated from the index date to the earliest date where any change in lutetium (^{177}Lu) vipivotide tetraxetan dose or frequency is detected,	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									following the criteria described above The outcome will be determined among the study population	
Persistence	Persistence (time to discontinuation): time from index date until date of last dose of lutetium (^{177}Lu) vipivotide tetraxetan administration	No	Time to event (median, IQR, mean, SD)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up within five years post index The time interval in months calculated from the index date to the earliest date where the last dose administration is detected in the records as follows: • At least one record from the medical oncology, radiation oncology, or urology or nuclear medicine departments with mentions in free text detected by cNLP indicating end of treatment, switch or discontinuation (e.g., "lutetium (^{177}Lu) vipivotide tetraxetan or Pluvicto discontinued,"	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									"lutetium (^{177}Lu) vipivotide tetraxetan or Pluvicto treatment completed," or "homebrew radiopharmaceutical given"). or • Structured pharmacy records or structured encounter records, including relevant procedure or billing codes (e.g., ICD-10-PCS, CPT/HCPCS, or national/local procedure coding systems) documenting the last administration date of lutetium (^{177}Lu) vipivotide tetraxetan (e.g., "lutetium (^{177}Lu) vipivotide tetraxetan 7.4 GBq IV administered on 2025-06-15") in cases with active follow-up The outcome will be determined among the study population	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
Lutetium (^{177}Lu) vipivotide tetraxetan as 1L	The number and proportion of newly diagnosed mPC patients treated with lutetium (177Lu) vipivotide tetraxetan as 1L	No	Binary (1L: yes/no)	[-∞, mPC diagnosis date – 1]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from mPC diagnosis up to index date Calculated as the number of newly diagnosed mPC patients receiving lutetium (^{177}Lu) vipivotide tetraxetan as the 1L therapy divided by the total number of newly diagnosed mPC patients, expressed as a percentage Identification will be based on the following: • Detection of lutetium (^{177}Lu) vipivotide tetraxetan (Pluvicto) in free-text mentions detected by cNLP, pharmacy records, or structured encounter records including relevant procedure or billing codes **and** • Identification of treatment line (e.g., 1L, 2L) based on free-text mentions	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									detected by cNLP (e.g., "Pluvicto as first-line therapy") **or** from treatment sequences created using the results of free-text mentions and/or structured records The outcome will be determined among the study population	
Lutetium (^{177}Lu) vipivotide tetraxetan as 2L or later	The number and proportion of mPC patients who received lutetium (^{177}Lu) vipivotide tetraxetan as 2L or 2L+	No	Categorical (count and percentage) for 2L Categorical (count and percentage) for 2L+	[-∞, mPC diagnosis date – 1]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from mPC diagnosis up to index date Calculated as the number of mPC patients receiving lutetium (^{177}Lu) vipivotide tetraxetan as second-line or subsequent lines of therapy divided by the total number of mPC patients who progressed from 1L to 2L or 2L+, expressed as a percentage. Identification of lutetium (^{177}Lu) vipivotide tetraxetan and its treatment line will be based on free-text mentions detected by cNLP (e.g., "Pluvicto as	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									second-line therapy") or from treatment sequences created using the results of free-text mentions and/or structured records, including pharmacy data or encounter records with relevant procedure or billing codes, where lutetium (^{177}Lu) vipivotide tetraxetan appears as a second or later line of therapy. The outcome will be determined among the study population	
TTI	Time from diagnosis of mPC to date of first lutetium (^{177}Lu) vipivotide tetraxetan administration (index date)	No	Time to event (median, IQR, mean, SD)	[-∞, mPC diagnosis date -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from date of mPC diagnosis to index date TTI will be calculated as the difference (in months) between the mPC diagnosis date and the index date The outcome will be determined among the study population	n/a
TTNT	Time from index date until start	No	Time to event (median,	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	date of next line of treatment		IQR, mean, SD)						The time frame for the outcome will be from index date up to the last follow-up within five years post index TTNT will be calculated as the difference (in months) between the index date and the date of switch, following the criteria defined above The outcome will be determined among the study population	
TFI	Aggregate time between the end date of one treatment and the start date of the next treatment in patients with mPC	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date to the last follow-up within five years post index Calculated as the difference (in months) between the end date of one regimen and the start date of the next regimen The outcome will be determined among the study population	n/a
Duration of treatment	Aggregate time of all treatment	No	Continuous (mean, SD, median,	[-∞, – 1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	patterns from treatment/ line initiation to discontinuation within each treatment (mean time on a given treatment for all patients)		IQR, minimum, maximum)						outcome will be from the index date to the last follow-up within five years post index . Calculated as the difference (in days) between the initiation date and the discontinuation date for each detected line, with the mean time on a given treatment calculated for all patients receiving that line The outcome will be determined among the study population	
Proportion of patients discontinuing lutetium (^{177}Lu) vipivotide tetraxetan	The number and proportion of patients who permanently stop the lutetium (^{177}Lu) vipivotide tetraxetan during the follow-up period, limited to those who did not complete the	No	Binary (yes/no per patient; proportion)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up within five years post index Percentage of cases with evidence of lutetium (^{177}Lu) vipivotide tetraxetan discontinuation, defined as the earliest date of any of the following: • At least one record from the medical oncology, radiation	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	full six-cycle regimen								oncology, urology, or nuclear medicine departments with mentions in free text detected by cNLP indicating discontinuation, switch, or treatment cessation (e.g., "lutetium (^{177}Lu) vipivotide tetraxetan discontinued due to toxicity," "therapy switched to alternative regimen") or • Free-text mentions detected by cNLP of lutetium (^{177}Lu) vipivotide tetraxetan administration or pharmacy records or encounter records with relevant procedure or billing codes documenting the last administration date, followed by no subsequent mention of lutetium (^{177}Lu) vipivotide tetraxetan. The date of discontinuation will be defined as the last	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									documented administration date The outcome will be determined among the study population	
Proportion of treatment switching	The number and proportion of patients switching treatment, defined as discontinuation of lutetium (^{177}Lu) vipivotide tetraxetan and initiation of new drug(s), limited to those who did not complete the full six-cycle regimen	No	Binary (yes/no per patient; proportion)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up within five years post index Percentage of cases with evidence of treatment switching, defined as the discontinuation of lutetium (^{177}Lu) vipivotide tetraxetan followed by the initiation of a new drug, as identified by the earliest date of any of the following: • At least one record from the medical oncology, radiation oncology, urology, or nuclear medicine departments with mentions detected by cNLP in free text indicating treatment switch (e.g., "lutetium (^{177}Lu) vipivotide	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									tetraxetan discontinued, initiated docetaxel," "switched from lutetium (^{177}Lu) vipivotide tetraxetan to cabazitaxel") or • Pharmacy records or encounter records with relevant procedure or billing codes documenting the initiation of a new antineoplastic drug without subsequent records of lutetium (^{177}Lu) vipivotide tetraxetan administration within a 90-day period. A 90-day washout after the last administration of lutetium (^{177}Lu) vipivotide tetraxetan will be applied only when treatment switching is inferred from structured data gaps. When explicit evidence of progression or treatment change is present in free text, or when a new antineoplastic therapy	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									is initiated with no further lutetium (^{177}Lu) vipivotide tetraxetan administrations from that date, the switch will be recorded at the documented start of the new therapy irrespective of the 90-day interval The outcome will be determined among the study population	
Pre-lutetium (^{177}Lu) vipivotide tetraxetan systemic treatment	The number and proportion of patients who received each treatment prior to lutetium (^{177}Lu) vipivotide tetraxetan initiation since diagnosis of mPC	No	Categorical (count and percentage)	[-∞, mPC diagnosis date – 1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the date of mPC diagnosis to the last follow-up within five years post index Calculated as the number of patients who received a specific therapy before starting lutetium (^{177}Lu) vipivotide tetraxetan divided by the total number of patients receiving lutetium (^{177}Lu) vipivotide tetraxetan, expressed as a percentage, identified through treatment sequences where the therapy precedes lutetium	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									(^{177}Lu) vipivotide tetraxetan initiation. As identified in free-text mentions detected by cNLP and/or structured records. The outcome will be determined among the study population	
Post lutetium (^{177}Lu) vipivotide tetraxetan treatment lines	The number and proportion of patients who received each specific treatment after lutetium (^{177}Lu) vipivotide tetraxetan treatment	No	Categorical (count and percentage)	[-∞,– 1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will extend from the index date to the last follow-up within five years post index Calculated as the number of patients who received a specific therapy after lutetium (^{177}Lu) vipivotide tetraxetan treatment divided by the total number of patients receiving lutetium (^{177}Lu) vipivotide tetraxetan, expressed as a percentage, identified through treatment sequences where the therapy is initiated after lutetium (^{177}Lu) vipivotide tetraxetan initiation. As identified in free-text mentions detected by cNLP and/or structured records	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									The outcome will be determined among the study population	
Antineoplastic treatments post index	The number and proportion of patients in each antineoplastic systemic treatment category given during follow-up (preindex)	No	Categorical (count and percentage)	[-∞,– 1]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will extend from the index date to the last follow-up within five years post index Antineoplastic treatment(s) after index date, categorised as ARPIs (e.g., enzalutamide, abiraterone acetate), taxanes (e.g., docetaxel, cabazitaxel), PARPi (e.g., olaparib), bone-directed radiopharmaceutical therapy, assessed based on direct mention in free text detected by cNLP Antineoplastic treatment(s) will be determined during follow-up, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Bone	The number	No	Categorical	[-∞, -1]	IP, OP,	n/a	n/a	Study	No validation study	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
marrow examination post index	and proportion of patients in each bone marrow examination category during follow-up		(count and percentage)		OT			population	Bone marrow examination post index, categorised as yes, no, or unknown, categorised based on the findings, assessed based on free-text mentions detected by cNLP or procedure codes, if available Bone marrow examination will be determined during follow-up, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Imaging post index	The number and proportion of patients with each imaging category performed during follow-up	No	Categorical (count and percentage)	[-∞, -1]	IP, OP, OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up withing five years post index Imaging post index, categorised as yes, no, or unknown for each of the following: CT scan report, MRI report, bone scan (technetium scintigraphy), based on free-text mentions detected by cNLP, along with the results.	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									Imaging will be determined during follow-up, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Vital signs post index	Blood pressure (systolic/diastolic) pulse, respiratory rate, and body temperature during follow-up	No	Continuous (mean, SD, median, IQR, minimum and maximum values)	[-∞, -1]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up, assessed based on free-text mentions detected by cNLP Vital signs will be determined during follow-up, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
ECG readings post index	ECG results during follow-up	No	Categorical (count and percentage)	[-∞, -1]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up within five years post index ECG results will be determined during follow-up, among the study	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
									population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Urinalysis post index	Urine results post index	No	Continuous (mean, SD, median, IQR, minimum and maximum values)	[1, study end date]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up within five years post index Urinalysis results post index (urine pH, protein content, specific gravity, appearance and colour, glucose, ketones), assessed from direct mentions in free text detected by cNLP or from structured laboratory data. Urinalysis results will be determined during follow-up, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Laboratory assessments	Total bilirubin, direct bilirubin, indirect bilirubin,	No	Continuous (mean, SD, median, IQR, minimum and	[1, study end date]	IP, OP, and OT	n/a	n/a	Study population	No validation study Laboratory assessments post index assessed based on free-text	n/a

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	ALT, ALP, AST, total serum protein, serum albumin, prothrombin time, aPTT, international normalised ratio, serum creatinine, blood urea nitrogen, serum uric acid, serum sodium, serum potassium, serum chloride, blood haemoglobin, blood lymphocyte count, blood platelets, white blood cell count, ANC, serum bicarbonate, serum calcium, serum phosphorus, serum		maximum values)						mentions detected by cNLP Vital signs during follow-up will be determined among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	

Outcome name	Details	Primary outcome?	Type of outcome	Washout window[1]	Care settings	Code type	Diagnosis position	Applied to study populations[2]	Measurement characteristics/ validation	Source of algorithm
	glucose, LDH during follow-up									
Visit dates post index	Health encounter with HCPs during follow-up	No	Continuous (mean, SD, median, IQR, minimum, maximum)	[-∞, -1]	IP, OP, and OT	n/a	n/a	Study population	No validation study The time frame for the outcome will be from the index date up to the last follow-up within five years post index Health encounters with HCPs during follow-up, defined as the number and dates of hospital-based health encounters with HCPs occurring after the index date to the last follow-up within five years post index , assessed from administrative structured data	n/a

Abbreviations: 1L, first line; 2L, second line; AESI, adverse event of special interest; AJCC, American Joint Committee on Cancer; ALP, alkaline phosphatase; ANC, absolute neutrophil count; aPTT, activated partial thromboplastin time; ARPI, androgen receptor pathway inhibitor; ATC, anatomical therapeutic chemical classification system; BMI, body mass index; BOR, best overall response; CCI, Charlson Comorbidity Index; CI, confidence interval; cNLP, clinical natural language processing; CPT, Current Procedural Terminology; CR, complete response; CT, computed tomography; DOR, duration of response; DRE, digital rectal examination; EAP, expanded access program; ECG, electrocardiogram; EBRT, external beam radiotherapy; ECOG, Eastern Cooperative Oncology Group; EHR, electronic health record; ER, emergency room; HCP, healthcare provider; HCPCS, Healthcare Common Procedure Coding System; ICD, International Classification of Diseases; IGRT, image-guided radiotherapy; IMRT, intensity-modulated radiotherapy; IP, inpatient; IQR, interquartile range; IV, intravenous; LDH, lactate dehydrogenase; LDL, low-density lipoprotein; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; MRI, magnetic resonance imaging; OP, outpatient; ORR, overall response rate; OT, other; PARPi, poly(ADP-ribose) polymerase inhibitor; PC, prostate cancer; PET, positron emission tomography; PR, partial response; PSA, prostate-specific antigen PSMA, prostate-specific membrane antigen; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; SBRT, stereotactic body radiotherapy; SD, standard deviation; STI, sexually transmitted infection; TFI, treatment-free interval; TNM, Tumour, Node, Metastasis; TRUS, transrectal ultrasound; TTI, time to treatment initiation; TTNT, time to next treatment; UICC, Union for International Cancer Control.

[&] These outcomes can only be reported at the individual level when there are at least two participating centres per country.

[1] The preindex lookback period is 365 days before the index date. However, the washout window uses a lower bound of -∞ to capture all relevant events, i.e., if there is a reference to an event more than 365 days before the index date in the source documents.

[2] The definitions of the study populations are described in Figure 7-1.

[3] ICD-10-PCS refers to the International Classification of Diseases, 10th Revision, Procedure Coding System; CPT to the Current Procedural Terminology; HCPCS to the Healthcare Common Procedure Coding System; and national or local procedure coding systems to country- or institution-specific classifications used to code medical procedures (e.g., OPS in Germany, SwissDRG procedure codes in Switzerland)

7.3.3 Context and rationale for follow-up

The study will evaluate outcomes "anchored" to lutetium (^{177}Lu) vipivotide tetraxetan administration, such as real-world drug utilisation, survival outcomes (rwOS, median rwOS, and rwPFS, median rwPFS), treatment responses (PSA response rates, overall response), AESIs, and changes in drug utilisation and treatment patterns. Hence, the maximum follow-up for these outcomes, spanning from index date to a maximum of five years thereafter, allows for assessment of relatively long-term safety and effectiveness of lutetium (^{177}Lu) vipivotide tetraxetan.

7.3.3.1 Operational definitions of follow-up

The operational definitions for follow-up are presented in **Error! Not a valid bookmark self-reference.**.

Table 7-6 Operational definitions of follow-up

Follow-up start	n/a: race, ethnicity preindex (365 days prior to index date): comorbidities, CCI, history of STIs, family history of PC, symptoms/physical signs of PC and metastasis, clinical subgroups (phenotypes), prescription drugs for chronic conditions At PC diagnosis: biopsy, disease stage, site of primary tumour, previous prostatectomy, antineoplastic treatments, DRE At mPC diagnosis: age, smoking status, weight, height, BMI, hormone sensitivity, time to mCRPC, site(s) of secondary tumour(s), number of secondary tumour(s), tumour size, cell differentiation, cell histology, perineural invasion, involvement of lymph nodes, lymphovascular space invasion, involvement of margins, visceral metastasis, Gleason score, PSMA positivity, PSA levels, total blood testosterone level, operability, imaging, radiotherapy, bone marrow examination, antineoplastic treatments, ECOG status, Karnofsky status, additional primary malignancies, LDL levels, ALP levels, TTI, number and proportion of patients receiving each treatment line prior to lutetium (^{177}Lu) vipivotide tetraxetan administration, number and proportion of newly diagnosed patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 1L, 2L, or 2L+ At index: age, prescriber type, insurance type, country, COVID-19 vaccination status, weight, height, BMI, genetic testing, PSA levels, total blood testosterone level, vital signs, ECG, ECOG status, Karnofsky status, number and proportion of patients with each category of lutetium (^{177}Lu) vipivotide tetraxetan cycles, rwOS, median rwOS, rwPFS, median rwPFS, PSA response rate, time to treatment response for PSA, BOR, ORR, DOR, AESIs, number and proportion of patients in each lutetium (^{177}Lu) vipivotide tetraxetan EAP initiation category, time interval between two consecutive to lutetium (^{177}Lu) vipivotide tetraxetan cycles, number and proportion of patients with a change in to lutetium (^{177}Lu) vipivotide tetraxetan dose compared with the recommended dose specified in the prescribing information, number and proportion of patients with a change in lutetium (^{177}Lu) vipivotide tetraxetan cycle frequency compared with the recommended schedule specified in the relevant and applicable prescribing information, time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan relative to the recommendations in the label, persistence, TTNT, TFI, duration of treatment, number and proportion of patients discontinuing to lutetium (^{177}Lu) vipivotide tetraxetan, number and proportion of patients switching treatment, number and proportion of patients receiving each treatment post to lutetium (^{177}Lu) vipivotide tetraxetan administration, HCP health encounter visit dates

	At five-year post index: five-year rwOS, five-year rwPFS	
Follow-up end[1]		
	Select all that apply	**Specify**
Date of outcome	Yes	rwPFS, median rwPFS, discontinuation, switch, time to treatment response, time to mCRPC, TTNT, time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan, persistence (time to discontinuation), BOR, DOR
Date of death	Yes	Treatment patterns, changes in dosing and treatment patterns, rwOS, median rwOS, rwPFS, median rwPFS, AESIs, response rates, number and proportion of patients receiving each treatment line post lutetium (^{177}Lu) vipivotide tetraxetan administration
End of observation in data	Yes	Treatment patterns, response rate, rwOS, median rwOS, rwPFS, median rwPFS, AESIs, changes in treatment patterns, number and proportion of patients receiving each treatment line post lutetium (^{177}Lu) vipivotide tetraxetan administration
Five years following index date	Yes	Five-year rwOS, five-year rwPFS, all other survival outcomes, response outcomes, treatment patterns, changes in treatment patterns, number and proportion of patients receiving each treatment line post lutetium (^{177}Lu) vipivotide tetraxetan administration
End of study period	Yes	Treatment patterns, changes in treatment patterns, rwOS, rwPFS, median rwOS, median rwPFS, response outcomes, AESIs, number and proportion of patients receiving each treatment line post lutetium (^{177}Lu) vipivotide tetraxetan administration
End of exposure	Yes	Treatment patterns
Date of add to/switch from exposure	Yes	rwPFS, median rwPFS, switch, persistence, TTNT, TFI, discontinuation, duration of treatment, PSA response rate
Other date *(specify)*	n/a	Race, ethnicity (no follow up but measured at index date)
	Index date	Age at index date, prescriber type, insurance type, country, smoking status at index date, weight at index date, height at index date, BMI at index date, genetic testing, history of STIs, family history of PC, PSA levels at index date, total blood testosterone at index date, vital signs at index date, ECG at index date, ECOG status at index date, Karnofsky status at index date, comorbidity type, CCI, LDL levels at index date, ALP levels at index date, additional primary malignancies, TTI, patients receiving each treatment line prior to lutetium (^{177}Lu) vipivotide tetraxetan since mPC diagnosis, number and proportion of newly diagnosed mPC patients treated lutetium (^{177}Lu) vipivotide tetraxetan as 1L, 2L, or 2L+

	PC diagnosis	Biopsy, disease stage, imaging, radiotherapy, bone marrow examination, DRE, site of primary tumour
	mPC diagnosis	Time to mCRPC, site(s) of secondary tumour(s), number of secondary tumour(s), tumour size, cell differentiation, cell histology, perineural invasion, involvement of lymph nodes, lymphovascular space invasion, involvement of margins, visceral metastasis, Gleason score, PSA levels at mPC diagnosis Total blood testosterone at mPC diagnosis, operability, vital signs, ECOG status at mPC diagnosis, Karnofsky status at mPC diagnosis, age at mPC diagnosis, BMI at mPC diagnosis, smoking status at mPC diagnosis, hormone sensitivity, previous prostatectomy, radiotherapy, clinical subgroups (phenotypes), PSMA positivity

Abbreviations: 1L, first line; 2L second line; ALP, alkaline phosphatase; BMI, body mass index; BOR, best overall response; CCI, Charlson comorbidity index; DOR, duration of response; DRE, digital rectal examination; ECG, electrocardiogram; ECOG, Eastern Cooperative Oncology Group; EHR, electronic health record; HCP, healthcare professional; LDL, low-density lipoprotein; LVSI, lymph-vascular space invasion; mCRPC, metastatic castration-resistant prostate cancer; mPC, metastatic prostate cancer; n/a, not applicable; ORR, overall response rate; PC, prostate cancer; PSA, prostate-specific antigen; PSMA, prostate-specific membrane antigen; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; STI, sexually transmitted infection; TTI, time to treatment initiation; TTNT, time to next treatment.

[1] Follow-up ends at the first occurrence of any of the selected criteria that end follow-up.

7.3.4 Context and rationale for covariates (confounding variables and effect modifiers, e.g., risk factors, comorbidities, comedications)

The measured confounders or baseline covariates that could affect the exposure and outcome will be entered into a model (for example, the Cox proportional hazards model) along with other variables for analysis.

The covariates considered for the current study include patient demographic variables such as age, race, ethnicity; risk factors such as body mass index, smoking status, comorbidities, genetic testing, history of sexually transmitted infections, and family history of PC. Variable values within the assessment period will be used. However, there can be unmeasured confounders that cannot be captured within the study. Changes in the grouping of variables or recording of variables in different variables, if any, will be detailed in the statistical analysis plan.

7.3.4.1 Operational definitions of covariates

The covariates considered for the study, together with their operational definitions, are presented in Table 7-7.

Table 7-7 Operational definitions of covariates

Characteristics	Details	Type of variable	Assessment window	Care settings	Code type	Diagnosis position	Applied to study populations	Measurement characteristics/validation	Source of algorithm
Age at mPC diagnosis	Year of mPC diagnosis – Year of birth The number and proportion of patients in each age category at mPC diagnosis	Continuous (mean, SD, median, IQR, minimum, maximum) and categorical (count and percentage)	[-∞, mPC diagnosis date]	n/a	n/a	n/a	Study population*	No validation study Age at mPC diagnosis, categorised as < 65 years, 65-74 years, and ≥ 75 years, assessed based on administrative structured data	n/a
Race (if allowed per local country regulation)	The number and proportion of patients in each race category at index date	Categorical (count and percentage)	n/a	n/a	n/a	n/a	Study population*	No validation study Race at index date categorised as Asian, Black, Caucasian/White, Mixed/Other, assessed based on administrative structured data or mentions detected by cNLP in free text Race will be determined at the closest date to the index date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	n/a
Ethnicity (if allowed per	The number and	Categorical (count and	n/a	n/a	n/a	n/a	Study population	No validation study	n/a

local country regulation)	proportion of patients in each ethnicity category at index date	percentage)						Ethnicity as assessed at index date categorised as Hispanic or Latino, Non-Hispanic or Latino, unknown, not reported, and others., assessed based on structured administrative text or mentions detected by cNLP in free text Ethnicity will be determined at the closest date to the index date, among the study population and those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
BMI at mPC diagnosis	BMI at mPC diagnosis (preindex) The number and proportion of patients in each BMI category at mPC diagnosis	Continuous (mean, SD, median, IQR, minimum, maximum) and categorical (count and percentage)	[-365, mPC diagnosis]	n/a	n/a	n/a	Study population	No validation study BMI in kg/m^2 at mPC diagnosis, categorised as underweight (< 18.5), healthy (18.5–24.9), overweight (25.0–29.9), obese (≥ 30.0), or unknown, assessed from direct mentions in free text detected by cNLP fields or calculated from reported weight and height at mPC diagnosis, as defined above BMI will be determined at the closest date to the mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	(CDC, 2024b)
Smoking status at mPC diagnosis	The number and proportion of patients in each smoking	Categorical (count and percentage)	[-365, mPC diagnosis]	n/a	n/a	n/a	Study population	No validation study	n/a

	status category at mPC diagnosis (preindex)							Smoking status at mPC diagnosis, categorised as prior smoker, current smoker, never smoker, or unknown, assessed from free-text mentions detected by cNLP or from structured codes when available Smoking status will be determined based on relevant information identified on the closest date to the mPC diagnosis, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel.	
Comorbidity type	The number and proportion of patients with each comorbidity type at index date (preindex)	Categorical	[-365, 0]	IP, OP, and OT	ICD-9 or ICD-10 when available	Any	Study population	No validation study	n/a

								Comorbidity type at index date, categorised as: myocardial infarction, congestive heart failure, peripheral vascular disease, cerebrovascular disease, dementia, chronic pulmonary disease, rheumatic disease, peptic ulcer disease, mild liver disease, diabetes without chronic complications, diabetes with chronic complication, hemiplegia or paraplegia, renal disease, moderate or severe liver disease, AIDS/ HIV, or others, assessed from free-text mentions detected by cNLP or, when available, from structured ICD-9 or ICD-10 diagnostic codes corresponding to these conditions (e.g., ICD-9 410 – acute myocardial infarction; 428 – heart failure; 250.0–250.9 – diabetes mellitus; 585 – chronic renal failure; or ICD-10 I21 – acute myocardial infarction; I50 – heart failure; E10–E14 – diabetes mellitus; N18 – chronic kidney disease) Comorbidity type will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
Genetic testing	The number and proportion of patients in each	Categorical (count and percentage)	[-365,0]	IP, OP, OT	n/a	n/a	Study population	No validation study	n/a

	genetic testing category at index date							Genetic testing status at index date, categorised as yes, no, or unknown for each of the following genomic risk factors: DNA damage repair genes (e.g., *BRCA1/2*), *PTEN* loss, *TP53* mutation, and *RB1* mutation, assessed from free-text mentions detected by cNLP or structured genomic testing reports Genetic testing will be determined at the closest date to the index date in the study population and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel	
History of sexually transmitted infections (STIs)	The number and proportion of patients in each STI history category at index date	Categorical (count and percentage)	[-365,0]	IP, OP, OT	ICD-9 or ICD-10 when available	Any	Study population	No validation study STI history at index date, categorised as yes, no, or unknown, assessed from free-text mentions detected by cNLP, or, when available, from structured ICD-9 or ICD-10 diagnostic codes indicating a personal history or previous diagnosis of sexually transmitted infections (e.g., ICD-10 A50–A64 – syphilis and other sexually transmitted infections; or ICD-9 090–097 – syphilis and other venereal diseases; 098 – gonococcal infections). STI history will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel.	n/a

Family history of PC	The number and proportion of patients in each family history of PC category at index date	Categorical (count and percentage)	[-365,0]	IP, OP, OT	n/a	n/a	Study population	No validation study. Family history of PC at index date, categorised as yes, no, or unknown, assessed from free-text mentions detected by cNLP. Family history of PC will be determined at the closest date to the index date, among the study population, and in those who received lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel.	n/a

Abbreviations: BMI, body mass index; cNLP, clinical natural language processing; ICD, International Classification of Diseases; IP, inpatient; OP, outpatient; OT, other; PC, prostate cancer; mPC, metastatic prostate cancer; STI, sexually transmitted infection.

7.4 Data sources

Data sources for this study will be the EHRs maintained by sites participating in the registry that treat patients with mPC with lutetium (^{177}Lu) vipivotide tetraxetan, including outpatient clinic reports, discharge reports, emergency reports, prescriptions, and other medical reports (unstructured and structured information); images (e.g., hand-drawn pictures, scanned images) will not be extracted. No data entry by physicians or their delegates into an electronic data capture platform will be performed. Electronic data will be collected for the duration of the follow-up period using automated extraction at period intervals (i.e., quarterly) from all available services and departments in each participating site, including emergency, external consultations, and hospitalisation notes.

7.4.1 Context and rationale for the data sources

Reason for selection: Using real-world data (RWD) from EHRs, both structured and unstructured, offers valuable insights into actual clinical practices and patient outcomes. With EHRs, AI and NLP technologies can be leveraged to efficiently extract, clean, and analyse large volumes of both structured and unstructured clinical data.

Strengths of data source: EHRs capture routine clinical practice and include a wide range of medical reports such as outpatient clinic reports, discharge reports, emergency reports, prescriptions, and other structured and unstructured information. They capture detailed patient histories and treatment outcomes over time, allowing for long-term analysis of outcomes. Physicians or their delegates will not perform data entry into an electronic data capture platform, limiting site burden.

Limitations of data source: Refer to section 7.10 for details.

Data source provenance/curation: Employing AI and NLP technologies to extract and analyse unstructured data captures valuable narrative content beyond the confines of structured data in a maximally efficient manner. This approach (1) reduces the participation burden for sites by eliminating the need for manual data entry into an electronic data capture platform, (2) standardises data collection across centres, and (3) allows for continuous improvement in data extraction quality over the course of the registry, as methodological enhancements can be applied retrospectively to the entire dataset. Collectively, these aspects will increase internal validity through automation, as it will substantially reduce the risk of human error and the time required to update manual processes.

7.5 Data processing

This section outlines procedures for data acquisition and integration across participating sites, including identification of relevant data sources, timing of extractions, providing for secure transfer of pseudonymised data, and enabling centralised processing to maximise efficiency and ensure consistency and readiness for analysis (Figure 7-3).

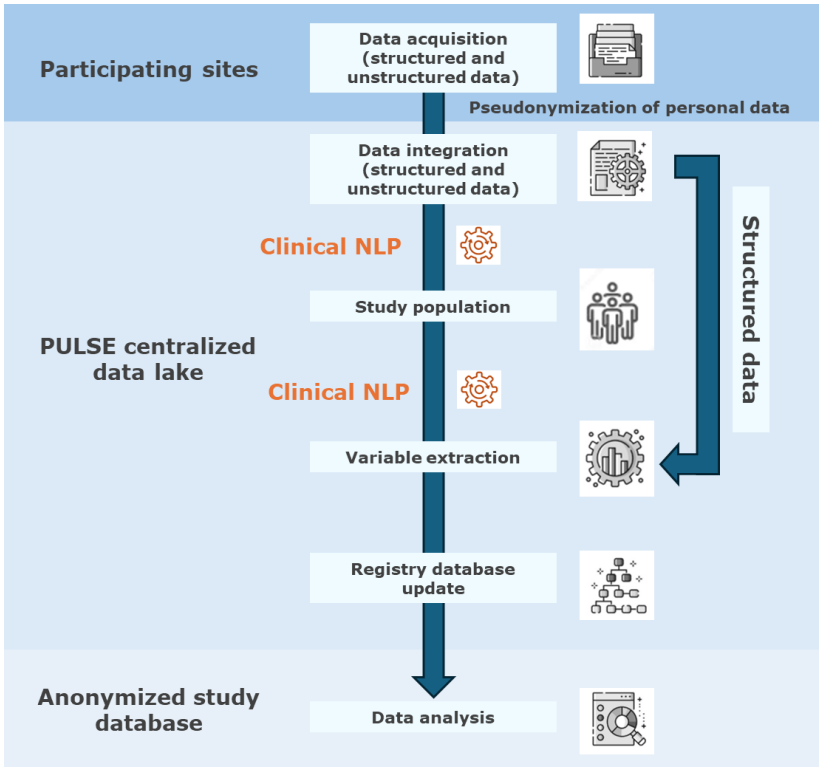

Figure 7-3 Overview of data flow in the PULSE Registry

Participating sites will perform an initial EHR data extract and pseudonymise the data before proceeding to secure transfer via sFTP. Once ingested, data will undergo standardisation, clinical NLP, and variable extraction to curate and create the patient-level longitudinal data files required for analysis.

Abbreviations: EHR, electronic health records; NLP, natural language processing; PULSE, Pluvicto Utilization and Long-term Study of Effectiveness; sFTP, secure file transfer protocol.

7.5.1 Data acquisition

Data acquisition will be carried out independently by each participating site (Figure 7-2), following detailed guidance provided by the study team regarding the specific data sources required. To standardise and facilitate the process, technical documentation will be developed based on this protocol that detail the data sources necessary to construct the study database. Briefly, the list of data sources will contain information on the necessary type of data (e.g., structured, semi-structured, free text) and the relevant hospital departments and hospital areas (e.g., oncology, nuclear medicine) at each participating site from which information needed to assess the objectives of the study is expected to be stored. Additionally, if required by participating hospitals, the list of data sources will include a comprehensive list of relevant coding taxonomies, such as International Classification of Diseases (ICD)-9/ICD-10 codes or other coding systems used in participant countries, corresponding to the patients with diseases of interest to the study. Data acquisition will begin between quarter (Q)1 and Q2 of 2026 and will conclude on 31 July 2031. For each participating site, the first data extraction will occur at site activation and will include, from the source population, all available historical data from the beginning of the study period up to the date of initial extraction. This will ensure accurate patient selection and the corresponding information required to develop a comprehensive

reconstruction of their medical history. Subsequent data extractions and integrations will be conducted quarterly throughout the study period, incorporating updated information from previously selected patients and available data from patients newly identified and selected after the initial integration. All data acquisition will be retrospective in nature, and no prospective or future data extractions are planned beyond the study end date.

7.5.2 Data integration

The study team, in close collaboration with each participating site's information technology (IT) service, will receive the EHR data from the participating sites (Figure 7-2). Prior to data transference, pseudonymisation of personal data must be performed by the participating sites (see details in section 8.1), which will then securely transfer the transformed data using a dedicated secure file transfer protocol utility, which will be exclusively available to each site.
Once transferred, the data will be integrated into a centralised data lake environment to enable standardised processing and preparation of the data for the NLP phase (using EHRead technology). This process will consist of the following phases:

- **Data completeness assessment:** Once participating sites have been signed and their data integrated, an initial data quality report will be generated to assess completeness of the integrated information, focusing especially on key site departments and report types. The total number of screened records and patients will be analysed per site, according to the primary data sources (admission, consultation, or emergency notes) and departments (oncology, urology, radiotherapy, nuclear medicine, emergency department, and others).
- **Standardisation:** EHR data are expected to come from heterogeneous sources, as each participating site may use different information systems. This variability complicates data integration and interpretation. To address this, all data will be converted into Medsavana's standardised data model.
- **Data cleaning:** In this phase, a quality check will be performed to identify inconsistent or incomplete records. Data that do not meet predefined minimum quality requirements will be cleaned or excluded, as appropriate.
- **Data quality assessment:** A standardised quality assessment will be conducted before the data integration is finalised, resulting in an internal data quality report.

This data integration process will be repeated quarterly during the study to include clinical information from the EHRs of patients with metastatic prostate cancer treated with lutetium (^{177}Lu) vipivotide tetraxetan from baseline to the date of the last data extraction.

7.5.3 Clinical NLP pipeline (EHRead)

Medsavana has developed EHRead technology, which uses a diverse suite of cNLP and ML techniques to capture and extract clinically relevant information from free text within EHRs (Arguello-Gonzales et al., 2023; Canales et al., 2021; Hernandez Medrano et al., 2018). EHRead is a powerful cNLP pipeline capable of multilingual free-text analysis by meaningful interpretation of the content included in clinical records, regardless of the EHR system. The cNLP models that capture and extract clinical terms from free text correspond to the named-entity recognition and named-entity linking (NER-NEL) modules. These modules detect the clinical terms and semantically map them to the corresponding concepts of the PCDP terminology. Once the NER-NEL modules detect the term, general and specific models are applied to provide contextual information.

General models are designed to enhance text interpretation and standardisation by identifying essential characteristics and relationships within the clinical data, regardless of the specific study context. These include models for negation detection (classifying clinical entities as "affirmative" or "non-affirmative"), copy-paste deletion (flagging duplicate text within patient documents for downstream analysis), section detection (categorising EHR content based on clinical context, such as family background or patient information obtained via encounter), temporality (linking clinical entities to time references, including explicit dates and relative time expressions), and measurable parameters (extracting and standardizing quantitative clinical data, such as laboratory results or biometric variables). These models can be further enhanced using large language models.

In contrast, specific models are customised according to the study's objectives and focus on extracting clinical entities and attributes deemed particularly relevant for answering specific research questions. Some of them—specifically, those needed for defining variables related to population, intervention, or outcomes (PIO-related variables)—will also be evaluated and adjusted based on site-level performance.

The same algorithms are used for all hospitals where EHRead technology is applied. Thereby, the criteria used for data extraction are unified and data extraction heterogeneity issues are avoided.

7.5.4 Terminology of the PCDP

The PCDP will be a comprehensive list of clinical terms associated with the clinical features of the disease. The Disease Panel will contain a combination of existing terminology standards, namely Systematized Nomenclature of Medicine—Clinical Terminology (SNOMED CT), anatomical therapeutic chemical (ATC), Logical Observation Identifiers Names and Codes (LOINC), and Medsavana's terminology. SNOMED CT terminology includes codes, concepts, synonyms, and definitions used in clinical documentation and is considered the most comprehensive terminology in the world (Benson, 2012). The ATC system categorises drugs based on the organ or system they act upon and their therapeutic, pharmacological, and chemical properties. LOINC uniquely codes laboratory tests across various domains, offering a standardised approach for reporting and exchanging results across different healthcare systems. Medsavana's terminology is a list of relevant terms used in clinical practice that are not included in any of the other standardised terminologies used (SNOMED CT, ATC, or LOINC). These terms are identified and refined by medical research experts from the study team with experience in NLP-based studies, in order to generate standardised complementary terms that enhance and complete the coverage of existing terminologies.

A multidisciplinary working group, including medical researchers and cNLP experts from the study team, will elaborate the initial list of clinical terms included on the PCDP. This list will be guided by the variables required to address the study objectives, and will include alternative expressions (e.g., names, abbreviations, acronyms) as well as classifications based on their relevance to the project and their use in clinical practice (e.g., clinical characteristics, treatments, outcomes). Terms will be classified into four categories: **key**, referring to those essential for defining the **Population**; **critical**, referring to those essential for defining the **Intervention** and **Outcomes**; **important**, referring to those needed to characterise the study population; and **nice-to-have**, referring to additional information that can enrich the analysis

but is not essential. The list will then be enriched through annotation projects that use a selected document corpus pre-annotated with NER-NEL predictions. Medical expert annotators will manually identify synonyms not pre-annotated by NER-NEL (false negatives) and remove incorrectly mapped tags (false positives). After completion, medical and terminology experts will evaluate and update the term alternatives based on joint review and consensus.

7.5.5 Validation processing

To ensure the accuracy and reliability of the data extracted and analysed in this study, a three-tier validation approach will be conducted, addressing different levels of validation.

7.5.5.1 Term validation

After the PCDP terminology is approved, the performance of NER-NEL for term capture will be evaluated for terms eligible for cNLP assessment, with particular emphasis on those classified as **key/critical**. This will include terms captured and extracted through direct cNLP detection. However, specific terms (important/nice-to-have) will not be included in the cNLP performance evaluation, as they are expected to be extracted from structured data (e.g., age, sex, specific drugs), analysed through the primary detection of their independent components (e.g., drug combinations), or require extraction using specific models with defined attributes. Some selected models (those required for PIO-related variables) will be evaluated in additional dedicated projects. Two separate annotation assessments will be launched to determine term-level precision, recall, and F1-score (please see below for definitions of each term). The first assessment will include a targeted selection of sentences for each alternative name, abbreviation, and acronym in the PCDP. The second assessment will involve a targeted selection of full documents sampled through sampling for large-scale information extraction and classification evaluation (SLiCE) based on the full set of key/critical terms (Canales et al., 2021). SLiCE will ensure the robustness and representativeness of performance metrics for cNLP system evaluations through a statistically robust gold standard.
Performance metrics will be calculated as follows:

- Precision (P)=tp/(tp + fp); indicates the proportion of retrieved information that is actually correct
- Recall (R) = tp/(tp + fn); indicates the amount of information the system retrieves
- F1-score =(2 × P ×R)/(P + R); overall performance indicator of information retrieval

In all cases, “tp” is the number of true positives (i.e., records correctly retrieved); “fn,” the number of false negatives (i.e., records incorrectly not retrieved); and “fp,” the number of false positives (i.e., records incorrectly retrieved).
Precision and F1-scores of 0.9 or higher will be considered acceptable for key/critical terms. If lower metric values are obtained, the annotation project will be re-executed until precision exceeds the acceptable threshold. This validation will be conducted only at the time of the first data extraction of each centre, as once performance is confirmed, no relevant changes in documentation habits are expected that could impact term-detection performance.

7.5.5.2 cNLP external validation

Clinical findings will be complemented with an evaluation of the performance of EHRead by external investigators, who will comprise physicians from participating sites involved in the study. This process is equivalent to internal validation but is conducted by external researchers. It will be carried out once, at the time of the initial data extraction by cNLP, at each participating

site of the study. A random sample of the EHRs annotated internally for performance evaluation (see section 7.5.6) will be selected and made available to local annotators at each participating site. Sampling will be performed through SLiCE, following the same procedure as in the internal validation.

Their workflow will be as follows:

- Two designated physicians (hereinafter referred to as "the annotators") at each participating site will annotate a set of randomly selected records from their site. These physicians will be selected by the principal investigator at each site. They will annotate clinical entities relevant to the study. The annotators will not be allowed to communicate with each other, as far as the annotation process is concerned (as needed, the study team will provide support to the annotators during the annotation process).
- Once the annotations are finalised, a third physician from the same site will review them and adjudicate discrepancies on an as-needed basis, serving as the final arbiter to evaluate the performance of EHRead (Figure 7-4).

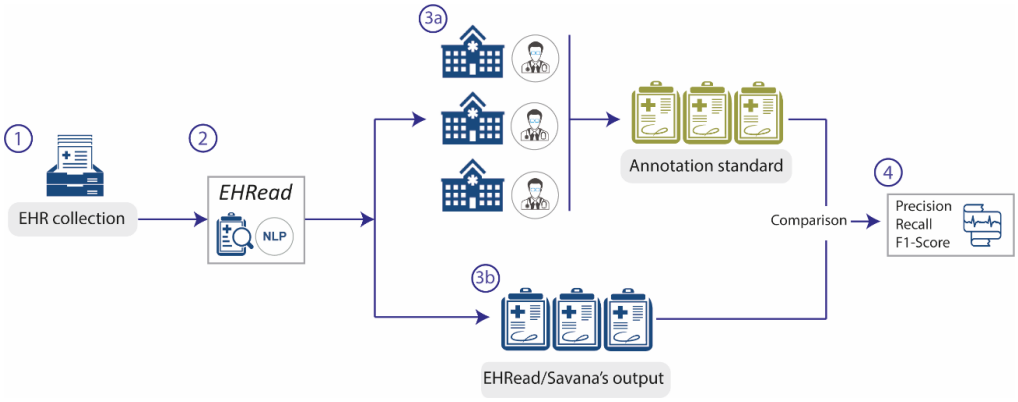

Figure 7-4 External validation process

A set of EHRs (1) collected via EHRead (2) is annotated by physicians to generate the annotation standard (3a) and compare it to the study results (3b), obtaining precision, recall, and F1-scores, to evaluate the quality of Medsavana' s output (4)

Abbreviations: EHR, electronic health record; NLP, natural language processing.

Results of this annotation process are the inter-annotator agreement and performance of the EHRead system, as reported using the aforementioned standard metrics of precision, recall, and F1-score. As in the internal validation, precision and F1-scores of 0.9 or higher will be considered acceptable for key or critical terms.

These metrics will be reported as an average across all participating sites. Should the external F1-score (the F1-score obtained from the evaluation described in this section) for any variable deviate by > 15% from the internal F1-score (the F1-score measured during the internal validation described in section 7.2), a dedicated investigation will be conducted to identify the cause(s) of the discrepancy. Annotated results from the internal performance validation project described in section 7.5.6 will serve as the reference for resolving such discrepancies.

7.5.5.3 Patient-level verification

The patient-level verification process will include the entire cohort of patients who meet all the inclusion criteria and not the exclusion criterion specified in sections 7.2.3 and 7.2.4. Medical

expert annotators will review the complete health records of these patients to verify both the mPC diagnosis and lutetium (^{177}Lu) vipivotide tetraxetan exposure. Any misclassified cases will be labelled as false positives and subsequently removed from the analytical dataset, ensuring that the study population only includes true positive cases. These misclassifications, if any, will be documented in the final study report. The verification process will be conducted at the time of the first data collection and repeated annually to ensure stability of the results throughout the study period, as changes in clinical practice may affect them.

7.5.5.4 Indirect epidemiological comparisons

This step will assess the plausibility of the source population (mPC patients), from which the study population is defined. This source population is derived from the broader screening population (PC patients, when available) using cNLP-based rules. This process aims to verify that the application of these rules yields a population with expected epidemiological patterns. To achieve this, selected epidemiological indicators will be calculated and compared against reference values reported in the literature.

Examples of epidemiological indicators include:

- The proportion of de novo mPC cases (i.e., those with PC and metastasis diagnosed within a short time window, e.g., ± two months)
- Prevalence of mPC in patients surviving ≥ five years after PC diagnosis
- Age at mPC diagnosis
- PSMA-positive rate
- The distribution of 1L systemic therapies used in mPC

The list of indicators may be refined during the analysis phase, depending on data availability. To evaluate reliability and rigor, the values of each indicator will be compared with those reported in the literature, considering the measures of central tendency and dispersion used. If the difference between the observed and reported indicators exceeds ±1 SD, an alert will be triggered and the findings should be re-examined; a difference of ±2 SDs indicates implausible results and warrants a more in-depth assessment, including a review of the operational definitions employed. As with the patient-level verification, this assessment will be performed at the time of the first data collection and repeated annually to ensure stability over the study period.

Table 7-8 NLP performance evaluation

Validation	What	Who	When
Internal term	Evaluation of reading performance at the term level	Medical annotators from study team	1st data extraction
External term	Evaluation of reading performance at the term level	Clinical investigators at participating sites	1st data extraction
Patient-level verification	Sensitivity and specificity of population, intervention, and outcome definitions at the patient level	Medical annotators from study team	1st data extraction and yearly
Indirect epidemiological comparisons	Evaluation of the reliability and robustness of the study population identified through the cNLP-based rules	Medical research experts from study team	1st data extraction and yearly

Abbreviations: cNLP, clinical natural language processing; NLP, natural language processing.

7.5.6 Metadata from data sources and software

Not applicable.

7.6 Study size/power calculation

We anticipate a minimum sample size of 564 patients. As the study is primarily descriptive, the sample size estimation is based on the precision around the proportion of patients receiving all six cycles of lutetium (^{177}Lu) vipivotide tetraxetan (European Medicines Agency, 2022; Novartis, 2022a). In the VISION study, 46.5% of patients received all six cycles of lutetium (^{177}Lu) vipivotide tetraxetan. In a retrospective observational study (Canadian Agency for Drugs and Technologies in Health, 2023), 34% of patients treated with lutetium (^{177}Lu) vipivotide tetraxetan completed six cycles (Desai et al., 2024). PASS 2024 version 24.0.1 was used to estimate the 95% CIs and precision (CI width/2) using frequencies of 34%, 46.5%, and 59% (the latter estimate selected in case there are more completers of all cycles), based on the Clopper-Pearson exact formula.

Table 7-9 shows that, assuming 34% of patients receive all six cycles of lutetium (^{177}Lu) vipivotide tetraxetan (as found in a retrospective study), with a sample size of 564 patients, the 95% CI ranges from 30.1% to 38.1% for a precision of 4.0%.

Table 7-9 Precision achieved under different proportions of patients receiving all six cycles of lutetium (^{177}Lu) vipivotide tetraxetan

N	Frequency	95% CI lower limit	95% CI upper limit	Precision (CI width/2)
564	34.0%	30.1%	38.1%	4.0%
564	46.5%	42.3%	50.7%	4.2%
564	59.0%	54.8%	63.1%	4.1%

Abbreviation: CI, confidence interval.

7.7 Data management

The data for this study will be retrieved from extracted from EHRs generated during routine clinical practice (i.e., secondary use of RWD).

7.8 Data analysis

The designated contract research organisation, PPD, will perform the analysis according to the contract agreement.

This study is observational, and all data analyses will be descriptive in nature as there are no prespecified hypotheses. Analyses will be performed using SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, US). Full details will be provided in a statistical analysis plan (SAP). The final SAP will include (empty) table and figure shells to be populated during the interim and final data analyses. It will also provide a description of the methods for dealing with missing and anomalous data. The SAP will be developed before the interim analyses and finalised before the end of data collection.

All analyses will be conducted in accordance with the study objectives, SAP, and applicable guidelines. Results will be rounded to one decimal place; therefore, percentages may not always sum to 100. Standard deviation and 95% CIs will be calculated when relevant.

The study population will be all patients who meet all inclusion criteria and not the exclusion criterion (refer to Figure 7-2).

The primary analysis is the number and proportion of patients with any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles (e.g., 1 cycle, two cycles, ... 6 cycles), described using counts and percentages.

Secondary analyses will be as follows:

- Patient profile (demographic and clinical characteristics), which will be reported as the number of non-missing observations, mean, SD, median, minimum, maximum, and IQR for continuous variables and counts and percentages for categorical variables.
- Survival outcomes (rwOS, median rwOS, five-year rwOS, rwPFS, median rwPFS, five-year rwPFS) will be assessed using time-to-event Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median time to event, IQR) with 95% CIs. Hazard ratio from Cox proportional hazards regression will be presented with 95% CIs. A p-value of less than 0.05 will be considered significant.
- Treatment response-related outcomes based on PSA level cutoffs will be reported as counts and percentages. Time to treatment response will be assessed using Kaplan-Meier methodology. Best overall response and duration of response will be described by reporting the number of non-missing observations, mean, SD, median, minimum, maximum, and IQR for continuous variables. The overall response rate (complete response + partial response) will be presented as a rate with 95% CIs.
- AESIs will be reported as counts and percentages.
- Changes in drug utilisation and treatment patterns will be described by reporting the number of non-missing observations, mean, SD, median, minimum, maximum, and IQR for continuous variables, and counts and percentages for categorical variables. TTNT, TTI, persistence and time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan outcomes will be analysed using Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median time to event, IQR, mean, SD) with 95% CI. Sankey diagrams or sunburst plots will be developed to visualise treatment pathways and sequencing.

The number of non-evaluable outcomes and missing data will also be reported, with missing data excluded from percentage calculations.

Subgroups (e.g., mCRPC and mHSPC or expanded access program [EAP] and non-EAP patients) will be described in the SAP, when applicable.

7.8.1 Context and rationale for analysis plan

The analysis plan was designed to fulfil the study objective and provide insights regarding the research question “What are the demographic and clinical characteristics profiles, drug utilisation, treatment patterns, and associated clinical outcomes among adults with mPC who are treated with lutetium (^{177}Lu) vipivotide tetraxetan over a five-year follow-up period?”. This study is single-arm by design, and the reporting of the key descriptive statistics for each objective, along with the time-to-event analysis and Cox proportional hazards regression, fulfils the study objectives.

Table 7-10 Primary analysis

Hypothesis	Not applicable (descriptive study)
Exposure contrast	Not applicable (descriptive study)
Outcome	Number and proportion of patients receiving any given number of lutetium (^{177}Lu) vipivotide tetraxetan cycles
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Descriptive statistics using counts and percentages
Confounding adjustment method	Not applicable (descriptive analysis)
Missing data methods	No imputations due to missing data will be performed. Missing data will be excluded from percentage calculations
Subgroup Analyses	Subgroups (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable

Abbreviations: EAP, expanded access program; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; SAP, statistical analysis plan.

Table 7-11 Secondary analysis 1

Hypothesis	Not applicable (descriptive analysis)
Exposure contrast	Not applicable (descriptive analysis)
Outcome	1. Profile of patient demographics (e.g., age, race, and ethnicity [as allowed per local country regulations], country, prescriber type, insurance type, COVID-19 vaccination status) 2. Profile of clinical characteristics (vital signs, anthropometrics, symptoms/physical signs of PC and metastasis, mPC tumour characteristics, lab and imaging parameters, other prior antineoplastic treatments, performance scales, comorbidities, CCI, and prior prescription drugs for chronic conditions, risk factors for PC, metastasis location/characteristics and treatment, and additional primary malignancies)
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Descriptive statistics for continuous variables (mean, SD, median, minimum, maximum, IQR) and categorical variables (counts and percentages)
Confounding adjustment method	Not applicable (descriptive analysis)
Missing data methods	No imputations due to missing data will be performed. Missing data will be excluded from percentage calculations
Subgroup Analyses	Subgroups (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable

Abbreviations: CCI, Charlson comorbidity index; EAP, expanded access program; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; SAP, statistical analysis plan; SD, standard deviation.

Table 7-12 Secondary analysis 2

Hypothesis	Not applicable (descriptive analysis)
Exposure contrast	Not applicable (descriptive analysis)
Outcome	1. rwOS, median rwOS, and five-year rwOS 2. rwPFS, median rwPFS, and five-year rwPFS
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Kaplan-Meier methodology for time-to-event data Cox proportional hazards regression for hazard ratios with 95% CIs

Confounding adjustment method	The measured confounders or baseline covariates that could affect the exposure and outcome will be entered into a model (for example, the Cox proportional hazards model) along with other variables for analysis.
Missing data methods	No imputations due to missing data will be performed
Subgroup Analyses	Subgroup (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable

Abbreviations: CI, confidence interval; EAP, expanded access program; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; SAP, statistical analysis plan.

Table 7-13 Secondary analysis 3

Hypothesis	Not applicable (descriptive analysis)
Exposure contrast	Not applicable (descriptive analysis)
Outcome	1. PSA 30 response rate (≥ 30% decrease in PSA from date of lutetium (^{177}Lu) vipivotide tetraxetan initiation [index date]) 2. PSA 50 response rate (≥ 50% decrease in PSA from index date) 3. PSA 90 response rate (≥ 90% decrease in PSA from index date) 4. Time to treatment response for PSA 30, PSA 50, and PSA 90 5. BOR 6. ORR 7. DOR
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Descriptive statistics for PSA response rates, BOR, and DOR (counts, percentages, mean, SD, median, minimum, maximum, IQR) Kaplan-Meier Methodology for time to treatment response
Confounding adjustment method	Not applicable (descriptive analysis)
Missing data methods	No imputations due to missing data will be performed. Missing data will be excluded from percentage calculations
Subgroup Analyses	Subgroups (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable

Abbreviations: BOR, best overall response; DOR, duration of response; EAP, expanded access program; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; SAP, statistical analysis plan.

Table 7-14 Secondary analysis 4

Hypothesis	Not applicable (descriptive analysis)
Exposure contrast	Not applicable (descriptive analysis)
Outcome	Patients with evidence of AESIs including, but not limited to, renal events, myelosuppression (cytopenia, bone marrow failure), dry eye, dry mouth, and second primary malignancies (malignancies other than the primary prostate cancer, including haematological and solid malignancies)
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Descriptive statistics using counts and percentages
Confounding adjustment method	Not applicable (descriptive analysis)
Missing data methods	No imputations due to missing data will be performed. Missing data will be excluded from percentage calculations.
Subgroup Analyses	Subgroups (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable.

Abbreviations: AESI, adverse event of special interest; EAP, expanded access program; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; SAP, statistical analysis plan.

Table 7-15 Secondary analysis 5

Hypothesis	Not applicable (descriptive analysis)
Exposure contrast	Not applicable (descriptive analysis)
Outcome	1. Time interval between two consecutive cycles of lutetium (^{177}Lu) vipivotide tetraxetan (i.e., between first and second, second and third, third and fourth, fourth and fifth, and fifth and sixth cycles) 2. Number and proportion of patients with a change in lutetium (^{177}Lu) vipivotide tetraxetan dose (increase in dose or decrease in dose) 3. Number and proportion of patients with a change in frequency of lutetium (^{177}Lu) vipivotide tetraxetan cycles relative to the recommended frequency in the label 4. Time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan relative to the recommendations in the label 5. Persistence (time to discontinuation): time from the index date until the date of last dose of lutetium (^{177}Lu) vipivotide tetraxetan administration 6. Number and proportion of newly diagnosed mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 1L 7. Number and proportion of mPC patients treated with lutetium (^{177}Lu) vipivotide tetraxetan as 2L or 2L+ 8. TTI: time from diagnosis of mPC to the index date 9. TTNT: time from index date until the start date of the next treatment 10. TFI: aggregate time between the end date of one regimen/treatment and the start date of the next regimen/treatment for all treatments 11. Duration of treatment: aggregate time of all treatment patterns from treatment/line initiation to discontinuation within each treatment (mean time on a given treatment for all patients) 12. Number and proportion of patients discontinuing lutetium (^{177}Lu) vipivotide tetraxetan documented by physician in the medical charts as discontinued. 13. Number and proportion of patients switching treatment, defined as discontinuation of lutetium (^{177}Lu) vipivotide tetraxetan and initiation of new drug(s) 14. Number and proportion of patients who received each treatment prior to lutetium (^{177}Lu) vipivotide tetraxetan administration since diagnosis of mPC 15. Number and proportion of patients who received each treatment following initiation of lutetium (^{177}Lu) vipivotide tetraxetan
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Descriptive statistics for continuous variables (mean, SD, median, minimum, maximum, IQR) and categorical variables (counts and percentages). TTNT, TTI, persistence and time to first change in dose or frequency of lutetium (^{177}Lu) vipivotide tetraxetan outcomes will be analysed using Kaplan-Meier methodology and will be reported as descriptive statistics (e.g., median time to event, IQR, mean, SD) with 95% CI. Sankey diagrams or sunburst plots to visualize treatment pathways and sequencing
Confounding adjustment method	Not applicable (descriptive analysis)
Missing data methods	No imputations due to missing data will be performed. Missing data will be excluded from percentage calculations.
Subgroup Analyses	Subgroups (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable.

Abbreviations: 1L, first line; 2L, second line; CI, confidence interval; EAP, expanded access program; IQR, interquartile range; KM, Kaplan-Meier; mCRPC, metastatic castration-resistant prostate cancer; mHSPC,

metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; SAP, statistical analysis plan; SD, standard deviation; TFI, treatment-free interval; TTI, time to index; TTNT, time to next treatment.

Table 7-16 Secondary analysis 6

Hypothesis	Not applicable (descriptive analysis)
Exposure contrast	Not applicable (descriptive analysis)
Outcome	In patients who receive sequential treatment of lutetium (^{177}Lu) vipivotide tetraxetan followed by docetaxel: 1. Patient profile (patient demographics [e.g., age, race, and ethnicity [as allowed per local country regulations], country, prescriber type, insurance type, COVID-19 vaccination status] and clinical characteristics [vital signs, ECG, anthropometrics, symptoms/physical signs of PC and metastasis, mPC tumour characteristics, lab and imaging parameters, other prior antineoplastic treatments, performance scales, comorbidities, CCI, and prior prescription drugs for chronic conditions, risk factors for PC, metastasis location/characteristics and treatment, and additional primary malignancies]) 2. Clinical outcomes (rwOS, median rwOS, five-year rwOS, rwPFS, median rwPFS, five-year rwPFS, treatment response, and AESIs)
Analytic software	SAS® Enterprise Guide 7.1 or higher (SAS Institute, Cary, NC, USA)
Model(s)	Patient demographics and clinical characteristics profile using descriptive statistics for continuous variables (mean, SD, median, minimum, maximum, IQR) and categorical variables (counts and percentages) Survival outcomes analysed using Kaplan-Meier methodology and reported as descriptive statistics (e.g., median time to event, IQR) with 95% CI; hazards ratio calculated from Cox proportional hazards regression Response outcomes using PSA levels above a cutoff, BOR, and DOR reported with descriptive statistics; ORR reported as a rate of CR and PR with 95% CIs; time to response for PSA 30, 50, and 90 reported using Kaplan-Meier methodology AESIs reported using descriptive statistics (counts and percentages)
Confounding adjustment method	Not applicable (descriptive analysis)
Missing data methods	No imputations due to missing data will be performed. Missing data will be excluded from percentage calculations.
Subgroup Analyses	Subgroup (e.g., mCRPC and mHSPC or EAP and non-EAP patients) will be described in the SAP, when applicable.

Abbreviations: AESI, adverse event of special interest; BOR, best overall response; CCI, Charlson comorbidity index; CI, confidence interval; CR, complete response; DOR, duration of response; ECG, electrocardiogram; EAP, Expanded Access Program; IQR, interquartile range; mCRPC, metastatic castration-resistant prostate cancer; mHSPC, metastatic hormone-sensitive prostate cancer; mPC, metastatic prostate cancer; ORR, objective response rate; PC, prostate cancer; PR, partial response; PSA, prostate-specific antigen; rwOS, real-world overall survival; rwPFS, real-world progression-free survival; SAP, statistical analysis plan; SD, standard deviation.

7.8.2 Sensitivity analyses—rationale, strengths, and limitations

Sensitivity analyses, if any, will be described in the SAP, when applicable.

7.9 Quality control

The following measures will be taken to ensure quality study execution.

The study will be conducted in accordance with the protocol and a prespecified SAP to ensure that the data are fit for purpose and that the analytical approach is systematic and transparent. Quality checks will cover three main areas: (i) designing a hospital-level data extraction strategy that guarantees completeness and consistency; (ii) developing and validating EHRead cNLP

through both internal and external performance evaluations; and (iii) carrying out the predefined analyses required to meet study objectives.
For analyses, an additional programmer will peer-review all source code and output, and any discrepancies or potential errors will be discussed and resolved. All programs will be saved, and the process will be tracked. All study documents will undergo review per standard operating procedures and practice-area specific processes and guidance to ensure continuous quality assurance of all methods and analyses used in this project.

7.10 Limitations of the research methods

As all data for this registry will be retrospectively extracted from EHRs generated during routine clinical practice (i.e., secondary use of RWD), analyses will be restricted to the information available in the EHRs.
The data utilised in this study will be derived from EHRs collected as part of routine clinical practice and not specifically for research purposes. Consequently, there is a risk of misclassification or incorrect coding, which can lead to information bias or measurement error arising from inaccuracies at the point of data entry. These errors and issues cannot be readily detected as they occur, let alone be corrected during the curation or analysis phase.
Routine clinical documentation may lead to incomplete or missing data, as not all clinically relevant information is consistently recorded, for any number of reasons. There may be missing or incomplete data across the different databases included in this study. Given that multiple databases from various hospitals will be incorporated, inconsistencies and gaps in medical data collection are likely to be encountered. This may affect the comprehensiveness and accuracy of the analysis.
Over time, changes in clinical practices, diagnostic criteria, and coding standards may occur, leading to temporal variations in the data.
The study population is limited to individuals whose data are recorded in the specific EHR system used. Therefore, findings may not be generalisable to populations outside of the relevant systems (or countries) or those who received comparable care in similar, albeit non-participating, healthcare settings (selection bias).
As the registry is technology-driven, certain limitations may arise, such as slow or incomplete adoption of the technology necessary to enable automated extraction, variable data lag between EHR extraction and electronic data collection tool data, and errors in NLP-based mapping of unstructured data.
The lack of standardisation in EHRs presents several challenges. Variations in the type of data collected across different disciplines, the use of standard versus “in-house” medical terminology, and the potential for omitted information or misuse of sections within the records are limitations that should be considered. These discrepancies can lead to difficulties in data integration and interpretation.
The use of NLP to extract data from EHRs may introduce additional limitations. NLP algorithms may not accurately capture the context or nuances of medical language, leading to potential misinterpretations or errors in data extraction. A limitation of this study is that the analyses planned are purely descriptive and do not account for potential confounding factors.

7.11 Other aspects

Database retention and archiving of study documents

The investigator must retain all study records and source documents for the maximum period required by applicable regulations and guidelines, institutional procedures, or for the period specified by the Sponsor, whichever is longest. The investigator must contact the Sponsor prior to destroying any records associated with the study.

8 Protection of human subjects

Individual patient data will be de-identified in accordance with legal, compliance, and regulatory standards. No efforts are made to re-identify the protected health information.

The study follows the ethical principles of the Declaration of Helsinki. The protocol is prepared as per the HARmonized Protocol Template to Enhance Reproducibility (HARPER) for capturing relevant details.

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE, 2016), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (von Elm et al., 2007), and with the ethical principles laid down in the Declaration of Helsinki.

This study will be executed with an anonymised database. To execute the anonymisation process, it is necessary to have access to the participating site's database, which requires a prior technical process of pseudonymisation of the EHRs performed by the participating site.

8.1 Submission process

For the purposes of this section, EHRs shall be those that the participating sites transfer to the centralised data lake administered by Medsavana according to the following: the structured data, including patient ID, episode ID, date of birth, and EHR number, shall be fully pseudonymised, to ensure that Medsavana cannot identify any individual patient. Given that each participating site will perform pseudonymisation of personal data prior to securely transferring relevant data, any additional information that could allow re-identification will be stored separately at the originating site and will not be accessible to Medsavana.

Thus, in accordance with the foregoing paragraph, the pseudonymisation process must ensure the suppression of the names and surnames of selected patients, as well as replacement of the patient ID with a randomly generated identifier that does not correspond to the ID used by the participating site. The method for transferring the pseudonymised personal data will be agreed upon by the parties.

The conversion table (i.e., the crosswalk between original patient ID and the study-specific pseudonymised ID) will be securely stored at each participating site. It will not be shared with the study team. Each site is responsible for retaining and managing this table throughout the duration of the study and for any additional period required to comply with applicable legal and regulatory obligations, including enabling any necessary data extractions.

8.1.1 Anonymisation process

Once in the centralised data lake, cNLP techniques will be applied to the pseudonymised data to find and extract the clinical variables described in the Study Protocol that will subsequently be structured, resulting in a database that only contains clinical terms (based on the SNOMED

CT ontology) and that therefore no longer contains pseudonymised free text. This database, which only contains variables in numeric format, will then have anonymisation techniques applied to the following identifiers:

- Patient identifier (an internal system for sample naming which is not related with the patient or EHR number) called patient_client_id
- Document identifier
- Episode identifier
- Hospital identifier
- Date of birth

These anonymisation techniques to be applied will consist of the following:

- The date of birth will be replaced with the 15th of the month for all records
- For the rest of the identifiers described (i.e., patient identifier, patient-client identifier, document identifier, episode identifier, hospital identifier), a one-way hash function will be applied that converts original values into a unique code with different digits.

Specifically, a "hash with salt" method will be used. This is a type of keyed hash algorithm that is generated from a specific hash function and is used as a hash-based message authentication code (HMAC). The HMAC process mixes a secret key with the message data, hashes the result with the hash function, re-mixes that hash value with the secret key, and applies the hash function a second time.

An HMAC can be used to determine whether a message sent through a non-secure channel has been manipulated, provided that the sender and receiver share a secret key. The sender calculates the hash value of the original data and sends the original data and the hash value as a single message. The receiver recalculates the hash value in the received message and checks that the calculated HMAC matches the transmitted HMAC.

Any change in the data or in the hash value results in a mismatch, as it is necessary to know the secret key in order to change the message and reproduce the correct hash value. Therefore, if the original and the calculated hash value match, the message is authenticated.

The pseudonymised numeric identifiers are replaced by other identifiers through an irreversible process, so the result of the process is an anonymised database with no free text.

8.2 Transmission and verification of the database

Only post-anonymised databases may be transferred from the centralised data lake to the blinded analytical study team for study-related analyses. This blinded analytical team will have access only to anonymised and aggregated data; therefore, the dataset must include anonymised data from a minimum of two sites. No member of the blinded analytical study team will have access to any pseudonymised data.

Once the database has been verified and confirmed by the blinded analytical team, Medsavana, as the administrator of the centralised data lake, will execute a process to block the intermediate data stored in the centralised data lake, thereby rendering any reversal of the anonymisation process impossible.

8.3 Patient consent exemption

The data to be used in this study will be obtained directly and retrospectively from the EHRs of the participating hospitals using AI techniques and related disciplines (e.g., NLP, ML). Data for

the study will be extracted by the IT departments of the participating sites. No data that can be used to identify patients directly will be included in this file, as patients' IDs will be presented in a pseudonymised format. These data will also be protected using the security measures described in Annex 4 -Security Measures.

No case report forms will be used in the conduct of this study. The applied methodology involves use of data captured in EHRs during routine clinical practice, including structured and unstructured data. Accordingly, there will be no direct interaction with study patients throughout the conduct of this study.

With respect to the need to collect informed consent from study patients, an exemption of consent will be submitted for consideration to each of the relevant IRBs/IECs due to the following reasons:

1. Data are submitted to the centralised data lake by participating sites in pseudonymised format, and additional information that may allow the data to be re-identified will be kept securely behind a firewall by each site. No member of the study team will be able to access this information. Therefore, patients will not be able to be directly re-identified. See sections Submission process (8.1) and Anonymisation process (8.1.1) for more details.
2. The study involves the use of data already recorded (as of the time of planned extractions) within the EHRs, and therefore, there is no requirement to interact with any patient. This study therefore does not entail any risk associated with participation.
3. The study's objectives are of substantial value to society in relation to the disease studied and the increases in knowledge addressing them are expected to yield.
4. Obtaining informed consent is impractical, considering that relevant data reflect care already rendered (as of the time of planned extraction), will be received in pseudonymised format. Moreover, at least some patients who meet all relevant selection criteria may die before the study initiates, further complicating efforts to obtain consent from next-of-kin (failure to adequately include such patients risk biasing the sample). Collectively, these challenges inform an anticipation of a disproportionately large and impractical effort (of unknown yield) to seek consent relative to the expectation of no risk being associated with "participation" in this study.

For the abovementioned reasons, an exemption of the need to obtain informed consent will be requested by relevant IRBs/IECs, as applicable in each country of interest.

8.4 Institutional review board/IEC

There must be prospective approval of the study protocol, protocol amendments, and other relevant documents from the IRBs/IECs. All correspondence with the IRB/IEC must be retained. Copies of IRB/IEC approvals must be forwarded to the Sponsor.

Before the start of data collection, the study will be presented for review or notification to a national or central IRB or IEC in the designated country, as and if required by local regulations. Additionally, the study will be presented or notified to regional and site IEC/IRBs, as and if required by local laws or regulations and/or hospital policies.

All amendments to the protocol will be subject to the appropriate review and approval process, in accordance with local regulations. At the end of the study, when required by local regulations,

the participating physician or participating site director (or the funding company where necessary) will notify the IRB/IEC of the completion of the study.

8.5 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 the International Society for Pharmacoepidemiology Guidelines for GPP and applicable regulatory requirements, the Helsinki Declaration in its latest edition, and applicable local regulations.

9 Management and reporting of adverse events/adverse reactions

As this is a study based on secondary use of data, safety monitoring and safety reporting, where there is a safety-relevant result, will be provided on an aggregate level only; no reporting on an individual-case level to Novartis is required.

In studies based on secondary use of data with a safety-relevant result, reports of adverse events will be summarised in the study report, i.e., the overall association between an exposure and an outcome will be presented. Relevant findings from the study report will be included in the periodic aggregated regulatory reports submitted to health authorities.

10 Plans of disseminating and communicating study results

Upon study completion and finalisation of the study report, the results of this non-interventional study may be submitted for publication and/or posted in a publicly accessible database of results. Publications will comply with internal Novartis standards and the International Committee of Medical Journal Editors (ICMJE) guidelines.
As applicable for non-interventional post-authorisation safety studies (conducted in the EU or mandated by an EU health authority and conducted outside the EU), the final manuscript will be submitted to the European Medicines Agency, and to the competent authorities of the Member States in which the product is authorised, within 2 weeks after first acceptance for publication.

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12 Annexes

12.1 Annex 1 – List of stand-alone documents

Table 12-1 List of stand-alone documents

Number	Document name/type	Date	Title
None			

12.2 Annex 2 – ENCePP checklist for study protocols

Study title: Understanding drug utilisation, treatment patterns, clinical outcomes, and profile of the patients receiving lutetium (177Lu) vipivotide tetraxetan for the treatment of metastatic prostate cancer: a multicountry, AI-powered registry (PULSE)

EU PAS Register® number: None (Voluntary PASS) **Study reference number (if applicable):** Not Applicable

Section 1: Milestones	**Yes**	**No**	**N/A**	**Section Number**
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	4; 7.1
1.1.2 End of data collection[2]	☒	☐	☐	4; 7.1
1.1.3 Progress report(s)	☐	☐	☒	
1.1.4 Interim report(s)	☒	☐	☐	4; 10
1.1.5 Registration in the EU PAS Register®	☐	☐	☒	
1.1.6 Final report of study results.	☒	☐	☐	4

Comments:

Section 2: Research question	**Yes**	**No**	**N/A**	**Section Number**
2.1 Does the formulation of the research question and objectives clearly explain:	☒	☐	☐	6.1
2.1.1 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)	☒	☐	☐	5; 6.1
2.1.2 The objective(s) of the study?	☒	☐	☐	6.2
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	7.2
2.1.4 Which hypothesis(-es) is (are) to be tested?	☐	☐	☒	
2.1.5 If applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

[1] Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.

[2] Date from which the analytical dataset is completely available.

Section 3: Study design	**Yes**	**No**	**N/A**	**Section Number**
3.1 Is the study design described? (e.g. cohort, case-control, cross-sectional, other design)	☒	☐	☐	7.1
3.2 Does the protocol specify whether the study is based on primary, secondary or combined data collection?	☒	☐	☐	7.4; 7.5
3.3 Does the protocol specify measures of occurrence? (e.g., rate, risk, prevalence)	☒	☐	☐	
3.4 Does the protocol specify measure(s) of association? (e.g. risk, odds ratio, excess risk, rate ratio, hazard ratio, risk/rate difference, number needed to harm (NNH))	☒	☐	☐	6.2; 7.3.2; 7.8
3.5 Does the protocol describe the approach for the collection and reporting of adverse events/adverse reactions? (e.g. adverse events that will not be collected in case of primary data collection)	☒	☐	☐	6.2.2; 7.3.2; 9

Comments:

Section 4: Source and study populations	**Yes**	**No**	**N/A**	**Section Number**
4.1 Is the source population described?	☒	☐	☐	7.2
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period	☒	☐	☐	7.2.1
4.2.2 Age and sex	☒	☐	☐	7.2.3
4.2.3 Country of origin	☒	☐	☐	7.2
4.2.4 Disease/indication	☒	☐	☐	7.2.3
4.2.5 Duration of follow-up	☒	☐	☐	7.2.1
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	7.2; 7.4; 7.5

Comments:

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.1 Does the protocol describe how the study exposure is defined and measured? (e.g. operational details for defining and categorizing exposure, measurement of dose and duration of drug exposure)	☒	☐	☐	7.3.1; 7.3.2; 7.8.1

Section 5: Exposure definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
5.2 Does the protocol address the validity of the exposure measurement? (e.g. precision, accuracy, use of validation sub-study)	☒	☐	☐	7.3.1; 7.5.5.3; 7.8.1
5.3 Is exposure categorized according to time windows?	☒	☐	☐	6.2.1; 7.3.2; 7.8.1
5.4 Is intensity of exposure addressed? (e.g. dose, duration)	☒	☐	☐	6.2.2; 7.3.2; 7.8.1
5.5 Is exposure categorized based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☐	☒	☐	
5.6 Is (are) (an) appropriate comparator(s) identified?	☐	☐	☒	

Comments:

Section 6: Outcome definition and measurement	**Yes**	**No**	**N/A**	**Section Number**
6.1 Does the protocol specify the primary and secondary (if applicable) outcome(s) to be investigated?	☒	☐	☐	7.3.2
6.2 Does the protocol describe how the outcomes are defined and measured?	☒	☐	☐	7.3.2; 7.3.3; 7.8.1
6.3 Does the protocol address the validity of outcome measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, use of validation sub-study)	☒	☐	☐	7.3.2
6.4 Does the protocol describe specific outcomes relevant for Health Technology Assessment? (e.g. HRQoL, QALYs, DALYS, health care services utilisation, burden of disease or treatment, compliance, disease management)	☒	☐	☐	7.3.2; 7.3.3

Comments:

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.1 Does the protocol address ways to measure confounding? (e.g. confounding by indication)	☒	☐	☐	7.3.4; 7.8.1; 7.10

Section 7: Bias	**Yes**	**No**	**N/A**	**Section Number**
7.2 Does the protocol address selection bias? (e.g. healthy user/adherer bias)	☒	☐	☐	7.2; 7.10
7.3 Does the protocol address information bias? (e.g. misclassification of exposure and outcomes, time-related bias)	☒	☐	☐	7.4; 7.5; 7.10

Comments:

Section 8: Effect measure modification	**Yes**	**No**	**N/A**	**Section Number**
8.1 Does the protocol address effect modifiers? (e.g. collection of data on known effect modifiers, subgroup analyses, anticipated direction of effect)	☒	☐	☐	7.3.4

Comments:

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
9.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview)	☒	☐	☐	7.3.1; 7.4; 7.5
9.1.2 Outcomes? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics)	☒	☐	☐	7.3.2; 7.4; 7.5
9.1.3 Covariates and other characteristics?	☒	☐	☐	7.3.4; 7.4; 7.5
9.2 Does the protocol describe the information available from the data source(s) on:				
9.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	7.3.1; 7.4; 7.5
9.2.2 Outcomes? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	7.3.2; 7.4; 7.5
9.2.3 Covariates and other characteristics? (e.g. age, sex, clinical and drug use history, comorbidity, comedications, lifestyle)	☒	☐	☐	7.3.4; 7.4; 7.5
9.3 Is a coding system described for:				
9.3.1 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	7.3.1

Section 9: Data sources	**Yes**	**No**	**N/A**	**Section Number**
9.3.2 Outcomes? (e.g. International Classification of Diseases (ICD), Medical Dictionary for Regulatory Activities (MedDRA))	☒	☐	☐	7.3.2
9.3.3 Covariates and other characteristics?	☒	☐	☐	7.3.4
9.4 Is a linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 10: Analysis plan	**Yes**	**No**	**N/A**	**Section Number**
10.1 Are the statistical methods and the reason for their choice described?	☒	☐	☐	7.3; 7.8
10.2 Is study size and/or statistical precision estimated?	☒	☐	☐	7.6
10.3 Are descriptive analyses included?	☒	☐	☐	7.3; 7.8.1
10.4 Are stratified analyses included?	☒	☐	☐	7.3; 7.8.1
10.5 Does the plan describe methods for analytic control of confounding?	☒	☐	☐	7.8.1
10.6 Does the plan describe methods for analytic control of outcome misclassification?	☒	☐	☐	7.5; 7.8.1
10.7 Does the plan describe methods for handling missing data?	☒	☐	☐	7.3; 7.8
10.8 Are relevant sensitivity analyses described?	☒	☐	☐	7.8.2

Comments:

Section 11: Data management and quality control	**Yes**	**No**	**N/A**	**Section Number**
11.1 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	7.5; 8.1; 8.2; annex 4
11.2 Are methods of quality assurance described?	☒	☐	☐	7.5; 7.9
11.3 Is there a system in place for independent review of study results?	☒	☐	☐	7.5.5

Comments:

Section 12: Limitations	**Yes**	**No**	**N/A**	**Section Number**
12.1 Does the protocol discuss the impact on the study results of:				
12.1.1 Selection bias?	☒	☐	☐	7.5; 7.10
12.1.2 Information bias?	☒	☐	☐	7.5; 7.10
12.1.3 Residual/unmeasured confounding? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods).	☒	☐	☐	7.5; 7.10
12.2 Does the protocol discuss study feasibility? (e.g. study size, anticipated exposure uptake, duration of follow-up in a cohort study, patient recruitment, precision of the estimates)	☒	☐	☐	7.1

Comments:

Section 13: Ethical/data protection issues	**Yes**	**No**	**N/A**	**Section Number**
13.1 Have requirements of Ethics Committee/ Institutional Review Board been described?	☒	☐	☐	8
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☐	☒	
13.3 Have data protection requirements been described?	☒	☐	☐	7.2; 8

Comments:

Section 14: Amendments and deviations	**Yes**	**No**	**N/A**	**Section Number**
14.1 Does the protocol include a section to document amendments and deviations?	☒	☐	☐	3

Comments:

Section 15: Plans for communication of study results	**Yes**	**No**	**N/A**	**Section Number**
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	10
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	10

Comments:

Name of the main author of the protocol: PPD

Date: 26 November 2025

Signature: _____

12.3 Annex 3 – Protocol page signature

Global Medical Affairs, Evidence Generation

Protocol No. CAAA617A02001

Understanding drug utilisation, treatment patterns, clinical outcomes, and profile of the patients receiving lutetium (^{177}Lu) vipivotide tetraxetan for the treatment of metastatic prostate cancer: a multicountry, AI-powered registry (PULSE)

Document type:	Protocol Signature Page Version No. 00 Clean
Referring to:	Protocol content final date on 26 November 2025

Novartis approval signatures for:

Non-interventional Study Protocol CAAA617A02001 v00

Electronic Document Identifier: xxxxxxxxxxxx
Will be available after uploading to NCV.

QPPV delegate	Signature	Date
PPD		
PPD	Signature	Date

Study Statistician	Signature	Date
Medical Lead	Signature	Date
Regulatory Affairs Lead	Signature	Date

Investigator approval signatures for:

Non-interventional Study Protocol CAAA617A02001 v00

Electronic Document Identifier: xxxxxxxxxxxx

Will be available after uploading to NCV.

Investigator signature

I have read the protocol and agree to conduct this non-interventional study in accordance with all stipulations of the protocol, with applicable laws and regulations and in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology, the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines, the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Code of Conduct and with the ethical principles laid down in the Declaration of Helsinki.

Investigator	Signature	Date

Center name and address:

12.4 Annex 4 – Security measures

This section sets out the technical and organisational security measures to be implemented by Medsavana in the performance of data processing activities involved in the study.

a. Logical access control to the systems processing personal data

As a minimum, the following security measures shall be implemented:

Access control:

- Access to systems subject to authentication of authorised personnel.
- The existence of an updated list of users with authorised access to the information systems.
- Prohibition of the use of anonymous or generic accounts, except in justified and limited situations.
- Implementation of an access management system. Access administration should be centralised, and access authorisation should only be granted to authorised personnel, who shall be the only personnel that can grant, alter, or revoke access to systems.
- Segregation of duties in IT systems, which prevents a single individual from accessing, modifying, or using assets without authorisation or detection.
- If outside personnel have access to the resources, they shall be subject to the same security conditions and obligations as in-house personnel.

Identification and authentication:

- Use of passwords with specific security parameters (uppercase, lowercase, numbers, letters and special characters, minimum number of six characters, and expiration once a year), and keeping them unintelligible.
- Use of a procedure for assigning, distributing, and storing passwords that ensures their confidentiality and integrity.

Media management:

- Identification and inventory of the devices processing personal data, as well as of the users accessing them.
- Adoption of measures aimed at preventing subsequent access or recovery of the information contained in the media once it has been decided to dispose of them. To this end, they must be destroyed or completely erased utilizing secure erasure systems. Devices containing personal data should be physically destroyed or the information should be destroyed, deleted or overwritten using techniques that do not allow for the recovery of the original information, rather than using normal erasure or formatting.
- The distribution of media containing personal data that pose a high risk to the rights and freedoms of data subjects shall be carried out after encrypting such data or using any other mechanism that ensures that such information is not accessible or manipulated during transport.

Back-up and continuity of service:

- Documentation of back-up and recovery procedures, which ensure that they are at all times reconstructed to the state they were in at the time of loss or destruction.
- Periodic incremental and daily backups.
- Ensure that systems are operational and that failures are properly reported. Accurate and complete records of backups should be kept.
- The backups should be stored at a remote site, at a sufficient distance to be spared any damage from a disaster at the main site.
- The controls applied to the media at the main site should be extended to the location of the back-up copies.
- A documented and tested Continuity Plan is in place that ensures production, data and services according to the agreed contract/SLA deadlines, and guarantees at least:
    - That the electricity supply installations are adequate for the equipment they are intended to support.
    - That emergency disconnectors are installed near the emergency exits of the rooms where the equipment is located to facilitate quick disconnection in case of an emergency.
    - That, if the main power supply fails, emergency lighting is available.

Developmental testing

- The most significant changes are identified and recorded.
- Changes are planned and tested before implementation.
- The risks and potential impacts of such changes are assessed and subject to a formal approval process.
- Users will have to use different profiles for production and test systems.
- No pre-implementation testing or modification of information systems with personal data shall be carried out with real data. Decoupled data shall be used.
- If deemed necessary, the same security measures must be implemented as in the production environment, and a back-up copy must be made beforehand.
- Segregation of IT test and production environments.

Network security controls

- Use of firewall, router, and VPN-based access controls to protect private service networks and back-end servers.
- Infrastructure security with ad-hoc monitoring.
- Logging of access to host servers, applications, databases, routers, switches, etc.

- The transmission of personal data over public or wireless electronic communications networks shall be carried out under secure protocols.
- Sensitive personal data will be encrypted during transmission using security protocols utilizing strong algorithms and encryption keys.
- There is a limited existence of system administrators.
- Adequate measures are in place to log system administrators' access to the infrastructure.
- Establish mechanisms for recording actions on personal data or logging.

b. Physical access control to facilities and personal data processing areas

At least some of the following security measures have been implemented to prevent physical access to workplaces and data processing centres:

- Access control system.
- Identity reader, magnetic card, or chip card.
- Provision of keys.
- Lock on the door (automatic doors, etc.).
- Alarm system, video, and video surveillance monitors.
- Register of entries and exits from the facilities.
- Location of data centres in secure facilities that provide physical security, redundant power, and infrastructure redundancy.

c. Register of incidents

The following security measures have been implemented:

- Existence of a procedure for notification and management of incidents affecting personal data.
- Existence of a procedure for notification and management of security breaches or violations, and their notification in due time and form to the Data Controller, to comply with the requirements of the regulations.
- Maintenance of a record of incidents/violations.
- Training actions are carried out for employees and other people with access to data, to guarantee adequate data processing under the requirements of the regulations.
- A process of regular verification, evaluation, and assessment of the effectiveness of the technical and organisational measures to ensure the security of the processing has been established, taking into account in particular the risks related to the data processing.

13 Appendices

Revision History

Changes in the current version and high-level summary of changes for all listed previous versions are maintained below.

Version Effective Date	**Reason for Change**	**Summary of Changes**
00 Date 26 November 2025	*Original protocol (New document)*	*Not applicable*