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A Phase I, open-label, multi-center study of radiation dosimetry, safety, and tolerability of extended lutetium (177Lu) vipivotide tetraxetan treatment in chemo-naïve adults with metastatic castration-resistant prostate cancer

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Registration date 04/09/2024	**Overall study status** Ongoing	[_] Statistical analysis plan [_] Results
Last Edited 08/10/2024	**Condition category** Cancer	[_] Individual participant data [_] Record updated in last year

Plain English summary of protocol

Background and study aims
This study aims to look at the radiation dose, safety, and tolerability of the study treatment, [177Lu]Lu-PSMA-617 (hereafter referred to as AAA617), in patients with PSMA-positive Metastatic Castration-Resistant Prostate Cancer (mCRPC). This is a subtype of prostate cancer where the disease has spread beyond the prostate gland and affects different parts of the body (referred to as metastases, or metastatic prostate cancer). PSMA is a protein which is highly expressed on prostate cancer cells but has low expression in normal tissues, so is a key indicator of prostate cancer and is targeted in diagnostics.

Who can participate?
Patients with prostate cancer, aged 18 years or older.

What does the study involve?
Participants will undergo Positron Emission Tomography / Computed Tomography (PET/CT) imaging using the diagnostic agent 68Ga-PSMA-11, a radioactive drug which binds to PSMA, which will allow comparison of levels of PSMA. Based on the PET/CT imaging, participants will be grouped into cohorts with normal, moderate, or severe renal (kidney) impairment. All participants in the 3 cohorts will receive AAA617 once every 6 weeks, up to 6 cycles for normal and moderate renal impairment, and 3-6 cycles in severe renal impairment. AAA617 is a radioligand therapy (RLT) drug which binds to the PSMA expressed on prostate cancer cells, releases small levels of radiation, and aims to reduce the cancerous cells. At the end of cycle 6, PET/CT scans will be repeated using 68Ga-PSMA-11 to evaluate changes in PSMA levels following RLT.

What are the possible benefits and risks of participating?
Benefits:
Not provided at time of registration
Risks:
There is a possibility that participants will experience side effects from the study treatments and /or procedures, including radiation from PET/CT scanning, whole body bone scans, and SPECT/CT scans. The risk for patients in this trial will be minimised by compliance with the eligibility criteria and study procedures, close clinical monitoring, and compliance with criteria for treatment dose modification and stopping criteria.
Potential risks include the effects of radiological toxicity, late renal toxicity and bleeding events from blood sampling. There is an inconvenience associated with radioligand therapy as patient must socially distance from others and follow extra hygiene methods for up to 7 days post treatment as per the Therapy Discharge Instructions included in this application.
The safety profile of AAA617 includes fatigue, dry mouth, myelosuppression (including anemia, thrombocytopenia, lymphopenia, leukopenia), nausea, vomiting, and renal adverse effects. Amongst these AEs, renal toxicity and hematotoxicities (myelosuppression) are important identified risks. The kidney is an organ with PSMA-expressing tissues and the primary route of AAA617 excretion. Despite significant radiation exposures that may occur in the kidneys due to renal excretion of AAA617 and expression of PSMA in the kidneys, renal toxicity did not emerge as a significant safety concern in the study. Data from previous VISION study showed patients receiving AAA617 were more likely to have renal events overall, though there appeared to be no difference in the likelihood to experience serious or high-grade events.
Risks of the CT Scan: The patient will receive radiation when CT is done. The radiation received during one exam is the same as 2 -10 years of normal radiation received in everyday life, depending on the body parts included. The physician or technician can explain the procedure and risks in greater detail to the patient and clarify any concerns or questions.
Risks of the MRI scan: Patients may not have an MRI done if they have metal in their body, for example, some hip replacements, hearing aids, pacemakers, bullets, or jewelry that cannot be removed. Patients will be asked to inform the technologist or physician if they have any metal in their body. During the MRI exam, they may feel some heat and hear banging noises but this is normal. Some people may have a ‘closed in’ (claustrophobic) feeling while inside the machine. The injection may make patients feel sick or have pain, warmth, swelling, bruising, a small blood clot, or infection at the injection site. Rarely, they may get a rash or other signs of allergy from the injection or get a rare disease where some of the body parts get scarred. The patient will be asked if they have a history of kidney problems as they may not be able to receive an injection during the MRI exam. The physician or technologist can explain the procedure and risks in greater detail and clarify any concerns or questions.
For tumour biopsies, both archival tissue sample and newly obtained biopsy (if clinically feasible) are acceptable. If a new biopsy is collected the study doctor will inform the participant in detail about the risks since the level of risk will depend upon where the tumour(s) are located and the participants medical condition. In general, having a biopsy can cause pain, swelling, bleeding and /or infection at the site where the biopsy needle penetrates through the skin. An anaesthetic can be used.
The likely risks and side effects of having a biopsy include:
• Minor local bleeding or pain at the needle site
• A swelling under the skin that contains blood
• Sleepiness, shortness of breath, slow heart rate, and low blood pressure.
Unlikely, but serious risks and side effects from having a biopsy include infection. There is also the possibility that having this procedure may shift some cells from the tumour into the surrounding tissues (tissues that come into contact with the biopsy needle). This means that the tumour could spread to that particular area. Participation in the study will not be affected if the procedure is not feasible or a previously collected sample is not available.

There is a very low risk experiencing any of complications during an ECG. The leads on the skin may cause irritation, redness, or burning of the skin when removing the leads. A condom is required for all sexually active male participants to prevent them from fathering a child AND to prevent delivery of study treatment via seminal fluid to their partner.

Where is the study run from?
Novartis Pharmaceuticals UK Limited

When is the study starting and how long is it expected to run for?
June 2024 to November 2027

Who is funding the study?
Novartis Pharmaceuticals UK Limited

Who is the main contact?
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Integrated Research Application System (IRAS)
1009375

Central Portfolio Management System (CPMS)
60777

Protocol serial number
CAAA617A12101

Study information

Scientific Title
A Phase I, open-label, multi-center study of radiation dosimetry, safety, and tolerability of extended lutetium (177Lu) vipivotide tetraxetan treatment in chemo-naïve adults with metastatic castration-resistant prostate cancer

Study objectives
Primary objectives:
1. To assess organ dosimetry of AAA617 following the administration of 7.4 GBq (±10%) for up to 12 cycles in taxane-naïve participants with progressive PSMA-positive mCRPC with normal kidney function or mild renal impairment.
2. To assess the safety of AAA617 following the administration of 7.4 GBq (±10%) for up to 12 cycles in taxane-naïve participants with progressive PSMA-positive mCRPC with normal kidney function or mild renal impairment.
3. To assess the tolerability of AAA617 following the administration of 7.4 GBq (±10%) for up to 12 cycles in taxane-naïve participants with progressive PSMA-positive mCRPC with normal kidney function or mild renal impairment.

Secondary objectives:
1. To assess tumor dosimetry of AAA617 following the administration of 7.4 GBq (±10%) for up to 12 cycles in taxane-naïve participants with progressive PSMA-positive mCRPC with normal kidney function or mild renal impairment;
2. To assess pharmacokinetics (PK) of AAA617.
3. To assess the efficacy of AAA617 with respect to overall response rate (ORR) based on Prostate Cancer Working Group 3 (PCWG3) modified-RECIST 1.1 per local investigator assessment.
4. To assess the efficacy of AAA617 with respect to disease control rate (DCR) based on PCWG3 modified-RECIST 1.1 per local investigator assessment.
5. To assess the efficacy of AAA617 with respect to duration of response (DOR) based on PCWG3 modified-RECIST 1.1 per local investigator assessment.
6. To assess the efficacy of AAA617 with respect to radiographic progression-free survival (rPFS) based on PCWG3 per local investigator assessment.
7. To assess the efficacy of AAA617 with respect to PSA response per PCWG3.

Ethics approval required
Ethics approval required

Ethics approval(s)

Not yet submitted, TBC, ref: 24/SC/0225

Primary study design
Interventional

Study design
Interventional parallel group controlled trial

Study type(s)
Safety

Health condition(s) or problem(s) studied
Metastatic neuroendocrine prostate cancer

Interventions
Prostate cancer is a malignant condition which develops in the prostate gland. When cancer has spread past the prostate into the body, it is called metastatic. Metastatic castration-resistant prostate cancer (mCRPC) is metastatic prostate cancer that has stopped responding to androgen deprivation therapy (ADT). Many prostate cancer cells, including mCRPC, produce a protein on their surface called prostate-specific membrane antigen (PSMA). In normal cells in the prostate there is normally less PSMA protein present on the surface than in cancer cells. This study is for participants who have PSMA (prostate specific membrane antigen) present on the surface of their tumour and who were not exposed to chemotherapy during treatment of mCRPC. This study will look to determine whether up to 12 cycles of radioligand therapy (RLT) referred to as lutetium (177Lu) vipivotide tetraxetan (hereafter identified as AAA617) (also known as the study treatment) is safe and efficient for patients who may benefit from extended treatment. The treatment itself is delivered via a cannula inserted into a vein in your arm and the drug will reach the tumour cells by travelling through the bloodstream. The idea is that the drug has a component that binds to PSMA and therefore delivers the radioactivity to the tumour cells and not healthy tissue. Several studies reported in literature would suggest that treatment with more than 6 cycles would potentiate efficacy. The overall benefit / risk assessment of AAA617 supports the investigation of more than 6 cycles of AAA617 in patients with PSMA-positive prostate cancer. “Dosimetry” refers to the measurement of the absorbed dose of radiation in tumours, organs, or the whole body. Participants will be in the study for 33 months.

Intervention Type
Drug

Phase
Phase I

Drug/device/biological/vaccine name(s)
AAA617 [Lutetium (177Lu) vipivotide tetraxetan], AAA517 [Gallium (68Ga) gozetotide]

Primary outcome(s)
1. Organ dosimetry of AAA617 measured using time activity curves (TACs) and absorbed radiation dose of AAA617 in organs. Absorbed radiation dose to target organs will be calculated by entering the TIAC values for all the source organs in the OLINDA/EXM® or other appropriate software program and adjusting the radiation dose reported by the software for individual weight and organ masses for organs of interest (determined from CT), and red marrow. For dosimetry assessments at Cycle 4, 6, 8, 10, 11, and 12, the individual TACs constructed from

Cycle 1 may be scaled based on the organ activities extracted from one or both SPECT/CT images.
2. Incidence and severity of adverse events (AEs) and serious AEs (SAEs) monitoring throughout the study
3. Tolerability of AAA617 measured by AAA617 dose reductions, interruptions, discontinuations throughout the study

Key secondary outcome(s)
There are no secondary outcome measures

Completion date
12/11/2027

Eligibility

Key inclusion criteria
1. Participants must be adults ≥18 years of age.
2. Participants must have an ECOG performance status ≤1
3. Participants must have histological confirmation of adenocarcinoma of the prostate
4. Participants must be PSMA-positive per gallium (68Ga) gozetotide (also referred to as [68Ga] Ga-PSMA-11 or radiolabeled AAA517 and 68 Ga-PSMA-11) positron emission tomographic–computed tomographic (PET/CT) scans at baseline with at least 1 lesion showing intermediate or high uptake level (PSMA expression score 2 or 3 per PROMISE V2 criteria and no lesions meeting the size criteria as defined in the read rules showing PSMA expression scores 0 or 1 as determined by the central reader
5. Participants must have a castrate level of serum/plasma testosterone (≤50 ng/dL or ≤1.7 nmol /L) either by pharmaceutical or surgical methods
6. Participants must have progressed only once on prior second generation ARPIs (abiraterone, enzalutamide, darolutamide, or apalutamide)

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
Male

Key exclusion criteria
1. Previous treatment with any of the following within 6 months of study enrollment: Strontium89, Samarium-153, Rhenium-186, Rhenium-188, Radium-223, hemi-body irradiation.
2. Any previous radioligand therapy.
3. Prior treatment with cytotoxic chemotherapy for metastatic castration-resistant or metastatic

hormone-sensitive prostate cancer (mHSPC) (e.g., taxanes, platinum, estramustine, vincristine, methotrexate, etc.), immunotherapy or biological therapy [including monoclonal antibodies]. [Note: Taxane exposure (maximum 6 cycles) in the adjuvant or neoadjuvant setting is allowed if 12 months have elapsed since completion of this adjuvant or neoadjuvant therapy. Prior treatment with sipuleucel-T is allowed].
4. Any investigational agents within 42 days prior to the day of the first RLT treatment.

Date of first enrolment
17/11/2024

Date of final enrolment
14/05/2026

Locations

Countries of recruitment
United Kingdom

Switzerland

Study participating centre
-
United Kingdom
-

Sponsor information

Organisation
Novartis Pharmaceuticals UK Limited

Funder(s)

Funder type
Industry

Funder Name
Novartis Pharmaceuticals UK Ltd

Results and Publications

Individual participant data (IPD) sharing plan

All data generated or analysed during this study will be included in the subsequent results publication

IPD sharing plan summary

Published as a supplement to the results publication, Data sharing statement to be made available at a later date