1 Protocol summary

1.1 Summary

Protocol Title:

An International, Prospective, Open-label, Multi-center, Randomized Phase III Study comparing lutetium (^{177}Lu) vipivotide tetraxetan (AAA617) versus observation to delay castration or disease recurrence in adult male patients with prostate-specific membrane antigen (PSMA) positive Oligometastatic Prostate Cancer (OMPC).

Brief Title:

PSMA-DC: An Open-label study comparing lutetium (^{177}Lu) vipivotide tetraxetan (also known as [^{177}Lu]Lu-PSMA-617 or ^{177}Lu-PSMA-617 and hereinafter referred to as AAA617) versus observation in PSMA positive OMPC.

Purpose

To evaluate the efficacy of AAA617 versus observation after Stereotactic Body Radiation Therapy (SBRT), in delaying castration or disease recurrence in adult patients with PSMA positive OMPC with 1 to 5 metastatic lesions detected by PSMA PET using gallium (^{68}Ga) gozetotide or piflufolastat (18F), negative for M1 disease by conventional imaging (CI).

Study Indication /Medical Condition:

Oligometastatic Prostate Cancer (OMPC) by PSMA PET, M1 negative by CI.

Treatment type

Drug

Study type

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Objectives and related endpoints

Objectives	Endpoints
Primary objective	**Endpoint for primary objective**
To evaluate the Blinded Independent Review Committee (BIRC) assessed metastasis free survival (MFS) by conventional imaging in adult participants with OMPC by PSMA Positron Emission Tomography (PET) receiving AAA617 vs observation	MFS is defined as the time from randomization to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., Computed Tomography (CT)/Magnetic Resonance Imaging (MRI) and bone scans) as assessed by BIRC using RECIST 1.1 or death from any cause, whichever occurs first

Objectives	Endpoints
Secondary objectives	**Endpoints for secondary objectives**
Key secondary: To evaluate time to hormonal therapy (TTHT) for castration in adult participants with OMPC by PSMA PET receiving AAA617 vs observation	TTHT is defined as the time from randomization to the time to Androgen Deprivation Therapy (ADT) The type of hormonal therapy will be at the discretion of the Investigator
To evaluate the Investigator assessed MFS by conventional imaging in adult participants with OMPC by PSMA PET receiving AAA617 vs observation	Investigator assessed MFS is defined as the time from randomization to the first evidence of radiographically detectable bone or soft tissue distant metastasis by conventional imaging (i.e., CT/MRI and bone scans) as assessed by Investigator using RECIST 1.1 or death from any cause, whichever occurs first
To evaluate the effect of AAA617 on time to prostate specific antigen (PSA) progression	Time to PSA progression is defined as time from randomization to first PSA progression 1. PSA progression 1 is defined as a rising PSA confirmed on repeated measurement at least 3 weeks later, and at least greater than 25% and ≥2 ng/mL above nadir or baseline, whichever is lower
To evaluate the effect of AAA617 on time to radiographic progression free survival (rPFS) by BIRC and Investigator	rPFS is defined as the time from randomization to first documentation of confirmed radiographic progressive disease by conventional imaging (i.e., CT/MRI and bone scans) using RECIST 1.1 or death due to any cause (whichever occurs first)
To evaluate the effect of AAA617 on time to next therapy (local or systemic)	Time to next therapy is defined as time from randomization to initiation of the next line of anticancer therapy (local or systemic)
To evaluate the effect of AAA617 on 24-month PSA PFS (≥ 0.5 ng/mL)	24-month PSA PFS (≥ 0.5 ng/mL) is defined as PSA PFS at 24 months PSA PFS is defined as the time from date of randomization to the date of first documented PSA progression 2 or death from any cause, whichever occurs first. PSA progression 2 is defined as a PSA concentration above the nadir (or baseline if lower) of ≥ 0.5 ng/mL, confirmed by repeated measurement at least 3 weeks later
To evaluate the impact of AAA617 on the time to symptomatic progression	Time to symptomatic progression is defined as time from randomization to the date of first documented event for any of the following, whichever occurs first. • Development of a symptomatic skeletal event (SSE), • Escalation in cancer-related pain or worsening of disease-related symptoms leading to the initiation of a new systemic anticancer therapy • Development of clinically significant symptoms due to local or regional tumor progression leading to surgery or radiation therapy
To assess the effect of AAA617 on Patient Reported Outcomes (Functional Assessment of Cancer Therapy Prostate (FACT-P), Brief Pain Inventory - Short From (BPI-SF), Functional Assessment of Cancer Therapy-Radionuclide Therapy (FACT-RNT) and European Quality of Life (EuroQoL) 5 Domain 5 Level scale (EQ-5D-5L)	Health-Related Quality of Life (HRQoL) as assessed by FACT-P, BPI-SF, FACT-RNT and EuroQoLEQ-5D-5L

Objectives	Endpoints
To evaluate the effect of AAA617 on time to symptomatic skeletal event (SSE)	Time to SSE (TTSSE) is defined as date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, requirement for radiation therapy to relieve bone pain or death from any cause, whichever occurs first
To evaluate safety and tolerability of AAA617 Common Terminology Criteria for Adverse Events (CTCAE)	Safety: incidence and severity of Adverse Event (AEs) and serious adverse event (SAEs), changes in laboratory values, vital signs and ECGs. Any clinically significant lab, vital signs, ECG abnormalities will be captured as an AE. Tolerability: dose interruptions, reductions and dose intensity
To evaluate the effect of AAA617 on overall survival (OS)	OS is defined as the time from the date of randomization to the date of death due to any cause

Trial Design:

This international, prospective, open-label, multi-center, randomized Phase III study, will enroll adult male participants with OMPC. Approximately 450 eligible participants will be randomized in a 2:1 ratio, to one of the two treatment arms:

Investigational Arm: lutetium (^{177}Lu) vipivotide tetraxetan (AAA617)
Control Arm: observation

All participants with confirmed PSMA-positive OMPC after curative treatment and M0 by CI, will be treated with Stereotactic Body Radiation Therapy (SBRT) to all metastatic lesions before initiation of AAA617 or starting observation.

Brief Summary:

The purpose of this study is to evaluate the efficacy and safety of AAA617 in participants with oligometastatic prostate cancer (OMPC) progressing after definitive therapy to their primary tumor. The data generated from this study will provide evidence for the treatment of AAA617 in early-stage prostate cancer patients to control recurrent tumor from progressing to fatal metastatic disease while preserving quality of life by delaying treatment with ADT.

All participants will be assessed for eligibility and will undergo baseline disease assessments including a mandatory gallium (^{68}Ga) gozetotide (also known as [^{68}Ga]Ga-PSMA-11) or piflufolastat (18F) (also known as[^{18}F]DCFPyL) PET/CT scan and conventional imaging (i.e., CT/MRI and bone scans). Piflufolastat (18F) PET/CT scan will be performed in countries where it is approved. SBRT will be administered to all metastatic Prostate Cancer (PC) lesions after randomization and before the start of treatment with AAA617 or observation.

- The duration of SBRT procedures is approximately 3 weeks.
- For participants randomized to the investigational arm (AAA617), the treatment duration will be up to 4 cycles of AAA617. For participants randomized to the control arm (observation) the treatment duration will end at the last fraction of SBRT administration.
- The visit frequency will be every week 1 and 3 of each of the 4 cycles and every 16 weeks thereafter (for both arms) until first event of disease progression (RECIST 1.1)

- The study duration is approximately 6.5 years.

Treatment of interest

Study participants randomized to the investigational drug will receive a dose of 7.4 GBq (200 mCi) ± 10% of AAA617 which will be administered once every 6 weeks (1 cycle) for a planned 4 cycles. Observational arm participants will not have any treatments other than SBRT. SBRT procedure is standardized for this study.

Number of Participants:

Approximately 450 eligible participants will be randomized in the study.

Key Inclusion criteria

1. Histologically confirmed prostate cancer prior to randomization
2. Participants must have biochemically recurrent disease after definitive treatment to prostate by Radical Prostatectomy ((RP), (alone or with post-operative radiation to prostate bed/pelvic nodes)) or External beam Radiation Therapy (XRT), (prostate alone or prostate with seminal vesicle and/or pelvic nodes) and/or brachytherapy prior to randomization. Biochemical recurrence is defined as: nadir PSA + 2 ng/mL post XRT (if participant received-radiation therapy to intact prostate) and PSA > 0.2 ng/mL and rising post RP (with or without post-operation Radiation Therapy (RT))
3. Participants must have OMPC with ≤5 PSMA-positive metastatic lesions on screening PSMA PET/CT scan (with either gallium (^{68}Ga) gozetotide or piflufolastat (18F)) as visually assessed by BIRC based on the methodology proposed in the Prostate Cancer Molecular Imaging Standardized Evaluation (PROMISE v2) (Seifert et al 2023); for further details, please refer to Section 8.1 and the Imaging Manual. Metastatic lesions may include regional/pelvic lymph nodes (N1), distant lymph nodes (M1a), bone (M1b), lung and others visceral (M1c) **except liver and brain** classified using AJCC 8. When counting the number of oligometastatic lesions, each lesion is counted as distinct metastasis irrespective of its anatomical location (e.g., one pelvic and one extra-pelvic lymph node will be counted as two metastatic lesions)
4. At least 1 PSMA-positive lesion should be a distant metastasis (M1) per AJCC8 classification at screening. For AJCC M staging, PSMA PET information should be used
5. Participants must have a negative conventional imaging for M1 disease at screening.
   Note:
   - For a participant not to be eligible, CI positive M1 lesions should be unequivocal in CI scans, i.e., potentially not attributable to findings thought to represent something other than tumor (e.g., degenerative, or post-traumatic changes or Paget's disease in bone lesions). For conventional imaging assessments, bone lesions must be assessed by bone scan only and soft tissue lesions must be assessed by CT/MRI scans only at screening.
   - Prior knowledge of PSMA PET positivity should not influence the radiologist (reader) in determination of CI positivity. Two different readers will be involved, one reader for PSMA PET scan and one reader for CI: Reader will be blinded to PSMA