1 Protocol summary

1.1 Description of the study

Protocol Title:

AcTFirst: A phase III, open-label, multi-center, randomized study comparing AAA817+ARPI versus standard of care in adult participants with PSMA-positive metastatic castration resistant prostate cancer.

Brief Title:

AcTFirst: Phase III study comparing AAA817+ARPI versus standard of care in adult participants with PSMA-positive mCRPC.

Purpose:

The purpose of this study is to determine whether [^{225}Ac]Ac-PSMA-617 (AAA817), given for minimum of 2 and up to 6 cycles at a dose of 10 Megabecquerel (MBq) +/- 10%, plus androgen receptor pathway inhibitor (ARPI), improves the radiographic progression free survival (rPFS) by BICR compared to investigator's choice of standard of care (SOC) (ARPI change or taxane-based chemotherapy or [^{177}Lu]Lu-PSMA-617 (AAA617)' in adult participants with PSMA-positive metastatic castration resistant prostate cancer (mCRPC) treated with another ARPI as last treatment and who have not been exposed to a taxane-containing chemotherapy in the mCRPC setting nor having received any prior PSMA-targeting radioligand therapy. Inclusion of the AAA817 monotherapy arm allows for assessment of contribution of ARPI change to AAA817.

Study Indication /Medical Condition:

PSMA-Positive Metastatic Castration Resistant Prostate Cancer

Treatment type:

Drug

Study type:

Interventional

Objectives, Endpoints, and Estimands:

Table 1-1 Objectives and Endpoints

Objective(s)	Endpoint(s)
Primary Objective(s)	**Endpoint(s) for primary objective(s)**
• To determine whether treatment with AAA817+ARPI change prolongs radiographic progression free survival **(rPFS)**, as assessed by Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1, in participants with PSMA-positive mCRPC, treated with another ARPI as last treatment as compared to participants treated with investigator's choice of standard of care (SoC).	• **rPFS** is defined as the time from the date of randomization to the date of first documented radiographic disease progression as assessed by blinded independent central review (BICR) using conventional imaging and Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 criteria or death due to any cause, whichever occurs first.
Secondary Objective(s)	**Endpoint(s) for secondary objective(s)**
• **Key Secondary Objective**: To determine whether treatment with AAA817+ARPI change prolongs overall survival **(OS)** in adult participants with PSMA-positive mCRPC treated with another ARPI as last treatment compared to participants treated with investigator's choice of SoC.	• **Key Secondary Endpoint**: **OS** is defined as the time from the date of randomization to the date of death due to any cause.
• **Key Secondary Objective:** To determine whether treatment with AAA817 prolongs radiographic progression free survival **(rPFS)**, as assessed by Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1, in participants with PSMA-positive mCRPC, treated with another ARPI as last treatment as compared to participants treated with investigator's choice of SoC.	• **Key Secondary Endpoint: rPFS** is defined as the time from the date of randomization to the date of first documented radiographic disease progression as assessed by blinded independent central review (BICR) using conventional imaging and Prostate Cancer Working Group 3 (PCWG3)-modified RECIST v1.1 criteria or death due to any cause, whichever occurs first.
• **Key Secondary Objective:** To determine whether treatment with AAA817 prolongs overall survival (OS) in adult participants with PSMA-positive mCRPC treated with another ARPI as last treatment compared to participants treated with investigator's choice of SoC.	• **Key Secondary Endpoint: OS** is defined as the time from the date of randomization to the date of death due to any cause.
• **Key Secondary Objective**: To determine whether treatment with AAA817+ARPI change prolongs radiographic progression free survival by PSMA PET/CT imaging **(rPFS-PET**) in adult participants with PSMA-positive mCRPC treated with another ARPI as last treatment compared to participants treated with investigator's choice of SoC.	• **Key Secondary Endpoint**: **rPFS-PET** is defined as the time from the date of randomization to the date of first documented radiographic disease progression per RECIP 1.0 as assessed by BICR using PSMA PET/CT or death due to any cause, whichever occurs first (Seifert et al 2023, Gafita et al 2023).
• To evaluate the progression free survival **(PFS)** in the three treatment arms.	• **PFS** is defined as the time from date of randomization to first documented progression by investigator's assessment (radiographic progression according to PCWG3-modified RECIST v1.1 criteria, clinical progression, or PSA progression per PCWG3) or death due to any cause, whichever occurs first.
• To evaluate second progression free survival **(PFS2)** in the three treatment arms.	• **PFS2** is defined as the time from date of randomization to first documented progression on next line of antineoplastic therapy by investigator assessment (radiographic progression according to PCWG3-modified RECIST 1.1, clinical progression, or PSA progression per PCWG3) or death from any cause, whichever occurs first.

Objective(s)	Endpoint(s)
• To evaluate the overall response rate **(ORR)** in the three treatment arms.	• **ORR** is defined as the proportion of participants with best overall response (BOR) of confirmed complete response (CR) or partial response (PR) in soft tissue based on tumor response data per BICR assessment and according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3. Additionally, ORR in soft tissue only according to PCWG3-modified RECIST v1.1 will be analyzed.
• To evaluate the disease control rate (**DCR**) in the three treatment arms.	• **DCR** is defined as the proportion of participants with BOR of confirmed CR, PR, stable disease (SD) or non-CR/non-progressive disease (PD) in soft tissue based on tumor response data per BICR assessment and according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3.
• To evaluate the duration of response (**DoR**) in the three treatment arms.	• **DoR** is defined as the duration of time between the date of first documented response (CR or PR) according to PCWG3-modified RECIST v1.1, in the absence of bone progression as per PCWG3, based on tumor response data per BICR and the date of first documented radiographic progression in soft tissue or death due to any cause, whichever occurs first.
• To evaluate the time to first radiographic soft tissue progression (**TTSTP**) in the three treatment arms.	• **TTSTP** is defined as the time from the date of randomization to the date of radiographic soft tissue progression per soft tissue rules of PCWG3-modified RECIST v1.1 as assessed by BICR.
• To evaluate time to first symptomatic skeletal event (**TTSSE**) in the three treatment arms.	• **TTSSE** is defined as the time from the date of randomization to the date of first new symptomatic pathological bone fracture, spinal cord compression, tumor-related orthopedic surgical intervention, or requirement for radiation therapy to relieve bone pain or death due to any cause, whichever occurs first.
• To evaluate biochemical response as detected by Prostate specific antigen response (**PSA50** and **PSA90**) in the three treatment arms.	• **PSA50 and PSA90** are defined as the proportion of participants who achieved ≥ 50% and ≥ 90% decrease from baseline, respectively, that is confirmed by a second PSA measurement ≥ 4 weeks later.
• To characterize pharmacokinetic profile of AAA817 in participants treated with AAA817+ARPI change or AAA817.	• Time-concentration profiles and PK parameters of AAA817 (e.g. AUC, C_{max}).
• To assess patient reported disease related symptoms and health-related quality of life (HRQoL) in the three treatment arms.	• Change from baseline on FACT-P Prostate Cancer Subscale (PCS). • Time to worsening on the FACT-P total score is defined as the time from randomization to the first occurrence of worsening on the score of at least 10 points decrease from baseline or death due to any cause, whichever occurs first.
• To assess change in patient-reported pain severity in the three treatment arms.	• Time to worsening on the Worst Pain is defined as the time from randomization to the first occurrence of worsening on the Worst Pain item (BPI-SF) of at least 30% compared to baseline or a minimum of a 2-point increase from

Objective(s)	Endpoint(s)
	baseline, or death due to any cause, whichever occurs first.
• To assess the safety and tolerability of AAA817+ARPI change and AAA817.	• Safety endpoints: Incidence and severity of AEs and serious adverse events (SAEs), changes in laboratory values, vital signs, and ECGs. • Tolerability endpoints: dose interruptions/delays, dose reductions, dose discontinuation, dose intensity, and duration of exposure.

Primary Estimand

The primary clinical question of interest is: what is the effect of AAA817+ARPI change (also referred to as AAA817+ARPI or Arm 1) versus investigator's choice of SoC (also referred to as Arm 3) with regard to time to radiographic progression by BICR or death in adult participants with PSMA-positive mCRPC treated with another ARPI as last treatment, regardless of treatment discontinuation for any reason, change in supportive care or start of new anti-neoplastic therapy prior to rPFS event.

The justification for this primary estimand is that it will capture both the effect of the study treatment and the effect of additional medications, mirroring the conditions in clinical practice.

The primary estimand is defined by the following attributes:

1. **Population**: All adult participants with PSMA-positive mCRPC treated with another ARPI as last treatment. Further details about the population are provided in Section 5.
2. **Endpoint**: rPFS is defined as the time from the date of randomization to the date of the first documented radiographic disease progression as assessed per blinded independent central review (BICR) using conventional imaging and PCWG3-modified RECIST v1.1 criteria (Scher et al 2016) or death due to any cause, whichever occurs first. Further details on rPFS are provided in Section 9.3.
3. **Treatments of interest**: The investigational treatment is AAA817+ARPI change regardless of subsequent anti-neoplastic treatment. The control treatment is investigator's choice of SoC, regardless of subsequent anti-neoplastic treatment. Further details on the investigational and control treatments are provided in Section 6.
4. **Intercurrent events:**
   - Discontinuation of study treatment for any reason: Tumor assessment or death data collected irrespective of discontinuation of study treatment reasons will be used for the primary analysis (treatment policy strategy).
   - Change in supportive care: Tumor assessment or death data collected irrespective of change in supportive care will be used for the primary analysis (treatment policy strategy).
   - Start of a new anti-neoplastic therapy (except as allowed per protocol) prior to radiographic progression or death: Tumor assessment or death data collected irrespective of initiation of new anti-neoplastic therapy will be used for the primary analysis (treatment policy strategy).

   Details on how to handle intercurrent events are provided in Section 9.3.3.
5. **Summary measure:** The summary measure is the rPFS hazard ratio (HR) (AAA817+ARPI change versus investigator's choice of SoC) along with 95% confidence

interval, estimated using a Cox proportional hazard model stratified by the randomization stratification factors as obtained via Interactive Response Technology (IRT). Further details on how the summary measure will be tested are provided in Section 9.3.2.

Trial Design:

Approximately 940 eligible participants will be randomized using a ratio of 2:1:2 to receive AAA817+ARPI change (Arm 1), AAA817 (Arm 2) or investigator's choice of SoC, (Arm 3, i.e., change of ARPI or taxane-based chemotherapy or AAA617 monotherapy).

In Arm 3, the number of participants allocated to AAA617 and ARPI change will be approximately 33% each to ensure adequate representation of the different standard of care choices in the control arm. The AAA617 and/or ARPI change options for SoC in the control arm will be closed for screening by the IRT system if and when approximately 33% of participants randomized to the control selected either AAA617 or ARPI change (i.e., approximately 33% for ARPI change and/or approximately 33% for AAA617). The reason for choosing ARPI change as a SoC option will be collected for all participants in IRT. Once the AAA617 and/or ARPI change options for SoC in the control arm are closed by the IRT system, participants may receive the remaining option(s) if randomized to Arm 3.

In Arms 1 and 3, ARPI change is defined as replacing the prior ARPI on which the participants' disease progressed to either abiraterone or enzalutamide. Chemotherapy options in Arm 3 will be either docetaxel or cabazitaxel. Supportive care will be allowed in all arms at the discretion of the investigator, which includes available care for the eligible participant according to best institutional practice for mCRPC treatment, including bone protection agents. Participants are required to maintain castration status and should be continued on ADT if required.

Randomization will be stratified by number of all metastases at baseline (≥ 20 vs. < 20 lesions by PSMA-PET/CT), investigator's choice of SOC in the case the participant is randomized to the control arm (ARPI change vs. chemotherapy vs. AAA617), and prior docetaxel use in the mHSPC setting (Yes vs. No). These stratification factors were chosen based on their predictive and prognostic role and association with rPFS and OS in mCRPC.

For Arms 1 and 2, participants will receive a minimum of 2 and up to 6 doses of AAA817 at 10 Mbq +/- 10% given intravenously every 8 weeks with or without an ARPI respectively (oral enzalutamide or oral abiraterone) as per investigator's choice. Treatment with AAA817 should continue until protocol defined treatment is completed or study treatment discontinuation criteria are met. For Arm 1, treatment with ARPI should continue until protocol defined treatment is completed or study treatment discontinuation criteria are met.

Participants randomized to SoC will be treated with an ARPI change (oral enzalutamide or oral abiraterone) or taxane-based chemotherapy (docetaxel or cabazitaxel) or AAA617 per investigator's choice. Concurrent treatment with ARPI is not permitted with taxane-based chemotherapy or AAA617. SOC treatment should be in accordance with local guidelines and product labels and continue until protocol defined treatment is completed or study treatment discontinuation criteria are met A change from one trade name to another trade name of ARPI is allowed and not considered an ARPI switch when the participant continues receiving the same active ingredient.

In line with published literature, a minimum of six cycles of chemotherapy is recommended unless study treatment discontinuation criteria are met (Oudard et al 2017, Petrylak et al 2021). For all arms, prior ARPIs are allowed to continue until the first dose of study treatment (C1/D1) is initiated.

Imaging intervals for conventional imaging and PSMA PET/CT will be counted from the first dose of any study treatment (Cycle 1/Day 1; C1/D1) for all arms. For Arm 1, AAA817 and ARPI change must be initiated on the same day.

All participants will be monitored for efficacy by conventional imaging every 8 weeks (+/- 7 days) after the first dose of study treatment for the first 24 weeks and then every 12 weeks (+/- 7 days) thereafter until confirmation of radiographic progression per PCWG3-modified RECIST v1.1 by BICR. Additionally, PSMA PET/CT scan will be performed on all participants at screening to confirm eligibility for PSMA-positive disease by BICR. For participants in Arm 1 and Arm 3 (Arm 2 is not included), on-treatment PSMA PET/CT is mandated every 8 weeks (± 7 days) after first dose on study treatment during the first 24 weeks and every 12 weeks (± 7 days) thereafter until confirmation of radiographic progression using conventional imaging per BICR, or until confirmation of radiographic progression using PSMA PET/CT per RECIP 1.0 by BICR, whichever is later. Participants who discontinue for reasons other than radiographic progression per PCWG3-modified RECIST v1.1 by BICR should follow the protocol schedule for conventional and PSMA PET/CT imaging until criteria for discontinuation of imaging assessments are met (Dodd et al 2008).

Safety will be assessed routinely during the study, during the Safety follow-up, Post EOT efficacy follow-up (if applicable), and the long-term follow-up (LTFU) periods.

Crossover is not allowed among study arms.

After completion of study treatment with Arm 1, Arm 2 or Arm 3due to radiographic progression confirmed by BICR, or discontinuation of study treatment for any reason, participants will have an End of Treatment (EoT) visit and enter the post-treatment follow-up: EOT efficacy follow-up (if applicable), 56-day Safety follow-up period, and LTFU period for up to 5 years after last patient entered LTFU.

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Treatment Groups:Investigational Arm: AAA817+ARPI change (Arm 1)

Investigational Arm: AAA817 (Arm 2)

Control arm: Investigator's choice of SoC (ARPI change or taxane-based chemotherapy or AAA617 monotherapy) (Arm 3)

Number of Participants:

Approximately 940 eligible participants will be randomized.

Key Inclusion Criteria:

- Signed informed consent must be obtained prior to participation in the study.
- Participants must be adults ≥ 18 years of age.
- Participants must have an ECOG performance status of 0 to 2.

- Participants must have histological, and/or cytological confirmation of adenocarcinoma of the prostate. Participants with mixed histology (neuroendocrine) are not eligible.
- Participants who have received taxane-based chemotherapy in mHSPC setting are eligible if they are deemed appropriate for chemotherapy,ARPI change, or AAA617 as the next line of therapy in the opinion of the Investigator.
  Note: Participants who have received taxane-based chemotherapy for mCRPC are excluded.
- Participants must have PSMA-PET positive disease using a PSMA imaging agent that is approved as per protocol and are eligible as determined by the sponsor's central reading rules.
- Participant must have been diagnosed with mCRPC with documented progressive disease while on treatment with ARPI in mHSPC or earlier setting as their last treatment (and did not progress on more than one ARPI), based on at least 1 of the following criteria:
  - Serum/plasma PSA progression is defined as 2 increases in PSA measured at least 1 week apart. The minimal start value is 2.0 ng/mL; 1.0 ng/mL is the minimal starting value if confirmed rise in PSA is the only indication of progression as per PCWG3 guidelines.
  - Soft-tissue progression defined [PCWG3-modified RECIST v1.1 (Eisenhauer et al 2009, Scher et al 2016)].
  - Progression of bone disease: 2 new lesions; only positivity on the bone scan defines metastatic disease to bone (PCWG3 criteria Scher et al 2016).
- Participants with deleterious or suspected deleterious germline or somatic homologous recombination repair (HRR) gene-mutated metastatic castration-resistant prostate cancer, as per local testing, may be enrolled if they had prior exposure to PARPi. Note: Candidacy for PARPi therapy is per investigator determination.

Detailed inclusion criteria are provided in Section 5.1.

Key Exclusion Criteria:

- Previous anti-cancer treatment with any approved or investigational radiopharmaceuticals (for example, [^{177}Lu]Lu-PSMA, [^{177}Lu]-DOTA, or Radium-223).
- Previous treatment with any external beam radiotherapy including hemi-body radiation within 6 weeks of randomization (within 2 weeks for radiotherapy of localized metastases).
- Any prior PARP inhibitor or other systemic anticancer therapy administered for metastatic castration-resistant prostate cancer (mCRPC). Any other approved or investigational systemic therapy (including chemotherapy, immunotherapy, biologics, or monoclonal antibodies) is prohibited within 28 days or 5 half-lives (whichever is shorter) before randomization. Note: Prior ARPI administered in the mHSPC setting or earlier may continue until C1D1.
- Baseline xerostomia ≥ Grade 2 based on NCI CTCAE version 5.0.

Detailed exclusion criteria are provided in Section 5.2.